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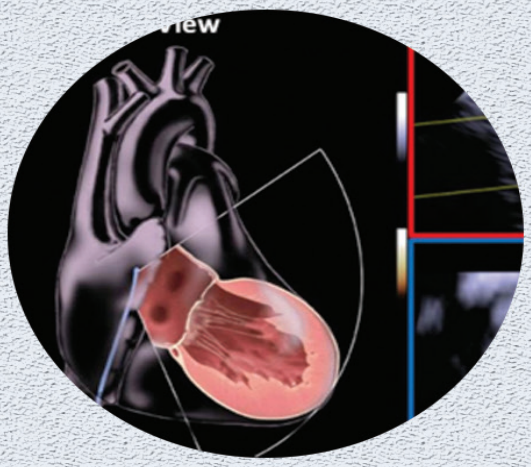

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- Implantation of BIV ICD with Near Zero Contrast Use in Patients with Advanced Renal Insufficiency Using Three Dimensional Electro-anatomical Mapping.
- Comparing Safety and Efficacy of Dabigatran and Factor Xa Inhibitors for Stroke Prevention in Hemophiliacs with Non-Valvular Atrial Fibrillation.
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Editorial

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Issue 4

Volume 12

Dhanunjaya (DJ)Lakkireddy
MD, FACC, FHRS
Editor-in-Chief, JAFIB

Dear Colleagues

Welcome to the first 2020 issue of the Journal of Atrial Fibrillation. The journal enters 12th year of its existence proving to be an important resource in the field of atrial fibrillation. This is the only free open access arrhythmia journal that doesn't charge any fees to publish. We have been blessed with many cold days this winter with a few sub-zero temperature days. The brightest part of this whole ordeal is the Kansas City Chiefs winning the 54th Super Bowl in a convincing way. We are very happy for the team and the City.

Elsewhere around the world, Jeremy Ruskin and team have successfully completed their 25th Annual AF Symposium in Washington DC. I have seen this meeting grow personally over the 18 of these years into somewhat of an institution like nothing else. A lot of amazing science and techniques get their stage, voice and application from this meeting. Over three days of intense learning the what the what of AF from all over the globe gets presented. Congratulations to Jeremy on yet another but landmark year.

The International Symposium on Left Atrial Appendage (ISLAA 2020) concluded its 8th iteration in New York City this past week. This unique educational opportunity show cased the science and technology in LAA management with over 12 live cases and recorded cases from Mt. Sinai, New York City and Arhaus, Denmark.

The current issue of the journal covers several important manuscripts ranging from rheumatic atrial fibrillation predictors in Nepal to sudden cardiac death famous athletes and the lessons learnt. We appreciate your continuous support and look forward to receiving your high quality manuscripts.

Until next issue.

DJ Lakkireddy

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Dofetilide Initiation and Implications of Deviation From the Standard Protocol – A Real World Experience

Tawseef Dar[1], Ghulam Murtaza[2], Bharath Yarlagadda[3], Bader Madoukh[2], Lesley Bravin[4], Venkat Vuddanda[5], Valay Parikh[4], Madhu Reddy[4], Dhanunjaya Lakkireddy[2].

[1]*Department of Nuclear Cardiology, Massachusetts General Hospital, Boston, MA.*
[2]*Kansas City Heart Rhythm Institute & Research Foundation, Overland Park, KS.*
[3]*Division of Cardiology, University of New Mexico, Albuquerque, NM.*
[4]*Division of Cardiovascular Diseases, University of Kansas Hospital & Medical Center, Kansas City, KS.*
[5]*Department of General Internal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Abstract

Background: Manufacturer/federal drug administration (FDA) recommends inpatient initiation of dofetilide with the manufacturer providing an initiation algorithm. The outcomes of algorithm deviation have not been reported outside of clinical trials.

Objective: We sought to perform a chart review of all the patients admitted for inpatient initiation of dofetilide to report on the incidence of protocol deviations and their implications.

Methods: We performed a retrospective review of all patients over a 15-month period who were initiated on dofetilide for the very first time or reinitiated on dofetilide after a break of three months or more at our institution. We assessed data about patients who were given dofetilide without adherence to the protocol (i.e. protocol deviation).

Results: A total of 189 patients were included in the study with a median age of 66 ± 9 years. Mean baseline QTc interval was 436 ± 32 msec, and 61% (116/189) were in atrial fibrillation (AF) at the time of dofetilide initiation. In 9% (17/189) of patients, the drug was discontinued due to intolerance or inefficacy. Therapy in 49% (93/189) of patients was noted to deviate from manufacturer recommended protocol with deviations more than once in some patients during the same hospitalization. Baseline QTc exceeding 440 msec (>500msec in conduction abnormalities) was the most frequent deviation (25%; 47/189).Ventricular tachyarrhythmia occurred in 4% (7/189) of patients, did not differ between patients, and occurred with and without protocol deviations (5% vs 2%; p = 0.27).

Conclusions: In our retrospective study, there were frequent deviations from the manufacturer-recommended algorithm guidelines for dofetilide initation, primarily due to prolonged baseline QTc interval. The impact of these protocol deviations on drug discontinuation was uncertain; however, significant adverse events were higher in the deviation group compared to the group that fully adhered to the protocol. Further multicenter studies are warranted to clarify our findings.

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia. Treatment involves medications to control either the rate while in AF or to pursue a rhythm control strategy to maintain sinus rhythm. Although clinical trials have not revealed a mortality benefit of rhythm control strategy versus rate control strategy [1-3], some patients are extremely symptomatic while in AF and a rhythm control strategy is necessary for these patients. Rhythm control strategy is the current standard of care when rate control is ineffective or patient is symptomatic despite controlled ventricular response[4]. AF leads to negative remodeling of the atria[5] and sinus rhythm restoration, aside from symptomatic improvement, has been show to reverse the process of remodeling and therefore break the vicious circle[6]. In addition, AF, with rates poorly controlled despite use of maximal doses of AV nodal blocking agents, leads to tachycardia-mediated cardiomyopathy and ultimately congestive heart failure (CHF), making rhythm control strategy more suitable, especially in young patients[7]. One study of antiarrhythmic drug (AAD) therapy showed that patients who received dofetilide had a significantly higher probability of remaining in sinus rhythm up to 1 year compared to those who received placebo, even though there was no benefit in all-cause mortality.[8] Sinus rhythm can be restored via pharmacologic or electrical cardioversion and can be maintained with use of AAD. AAD continue to remain the first line maintenance therapy and are often utilized to facilitate conversion from AF to sinus rhythm[9].

Amiodarone is the most potent antiarrhythmic agent but is associated with significant side effects most of which are non-cardiac. Dofetilide, a class III antiarrhythmic agent, blocks rapid component of delayed rectifier potassium current (IKr) inhibitor channels and

Key Words

Dofetilide, Atrial fibrillation, Protocol, Deviation.

Corresponding Author
Dhanunjaya Lakkireddy, MD, FACC, FHRS
Executive Medical Director
The Kansas City Heart Rhythm Institute (KCHRI) @ HCA MidWest
Professor of Medicine, University of Missouri, Columbia, MO
12200, W 106th street, Oveccrland Park Regional Medical Center
Overland Park, KS 66215

is associated with minimal non-cardiac side effects. It increases action potential duration due to delayed repolarization and prolongs QT interval as a result of prolongation of effective and functional refractory period of the His-Purkinje system and the ventricles. Dofetilide is moderately effective in converting AF to sinus rhythm but exhibits 58% efficacy in maintaining sinus rhythm at the end of one year[10]. The package insert pertaining to dofetilide specifies that in patients with supraventricular arrhythmias, the incidence of TdP at dosing <250mcg BID is 0%, at 250mcg BID is 0.3%, at >250-500mcg BID is 0.9%, and at >500mcg is 10.5% . As a result, the FDA, at the time of initial approval of dofetilide in 1999, mandated that dofetilide could only be started in patients after administering the initial 5 doses over three days in the inpatient setting with continuous EKG montitoring.

Furthermore, in July 2011, the FDA released a detailed protocol for initiation of dofetilide suggesting the starting dose and appropriate dosage changes depending on the changes in QTc post initiation and creatinine clearance. The adherence to this protocol and the consequences of deviation are unknown. Outside of the clinical trials involving dofetilide, there is very little data from the real-world experience regarding the frequency of protocol deviations and their outcomes.

Hence, we performed an observational study including patients who were admitted to our hospital for dofetilide initiation with an emphasis on patients whose therapy deviated from the manufacturer recommended protocol.

Methods

Study Population

Upon getting approval from the Institutional Review Board, we performed a retrospective review of all patients, over a 15-month period, who were initiated on dofetilide for the very first time or reinitiated on dofetilide after a break of three months or more at our institution. Patients were included if there was documentation of an EKG with QTc at baseline and two hours after each dose. Patients with long QT syndrome or prior history of cardiopulmonary resuscitation due to any cause were excluded from the study. Every attempt was made to discontinue all prior antiarrhythmics for a period amounting to five half-lives of respective drugs.

Dosing

Patients were dosed as per University of Kansas Hospital Pharmacy protocol for inpatient initiation of dofetilide and the protocol was executed via an electronic order set which is in line with the FDA/manufacturer's recommendations. Doses were mainly based on the initial QTc (or QT interval if heart rate was<60 beats/minute) and creatinine clearance as shown in [Figure 1].

Protocol Deviations

Protocol implementation was overseen by the pharmacy team. Every attempt was made to encourage compliance with the protocol. Any violation of FDA recommended dosing algorithm at any stage was considered a deviation from protocol [Figure 1]. Efforts were made to detect those patients who received dofetilide not in accordance with the protocol.

Data collection and Study outcomes

From the chart review, we collected baseline demographic information, medical history, baseline laboratory blood test results, including creatinine clearance, electrolytes, EKG information pre- and post-dofetilide initiation, direct current cardioversion, and pharmaceutical interventions.

The primary outcome of the study was to evaluate the incidence of deviations from FDA-recommended protocol for inpatient dofetilide initiation in clinical practice. Secondary outcomes included incidence of intolerance/inefficacy leading to drug discontinuation, need for electrical cardioversion, and incidence of ventricular tachyarrhythmia specifically in patients in whom there was a protocol deviation.

Definitions

Drug Intolerance: Symptomatic drug adverse effects including symptomatic proarrhythmias; symptomatic adverse effects eg: headache, dizziness, nausea, back pain, and abdominal pain; laboratory abnormality including QT prolongation but without symptoms leading to physician directed drug discontinuation.

Serious adverse event (SAE): Any ventricular tachyarrhythmia read as Torsades de pointes, ventricular fibrillation, or sustained ventricular tachycardia was classified as a serious adverse event.

Statistical Analysis

Continuous variables are expressed as mean ±standard deviation (SD) if variables are normally distributed, and median (interquartile range) when deviations from normality were present. Categorical variables are expressed as counts and percentages. Categorical variables were compared between the groups using chi-squared test or fisher's exact test. Continuous variables were compared using independent sample t test. A two tailed p value less than 0.05 was considered statistically significant. Binary logistic regression model was used to determine factors related to serious adverse events. Statistical analysis was performed using IBM SPSS Statistics version 23.0 (IBM, Armonk, New York).

Table 1: Demographics and other clinical variables of the overall study population.

Variable	Dofetilide Initiation (Total N=189) n (%)
Demographics	
Female/Male	69 (37%) /120 (63%)
Median age in years ± SD	66 ± 9 (34-86)
Obese (ABW > 40% IBW)	77 (41%)
Medical History	
Hypertension	95 (50 %)
Coronary artery disease	54 (29%)
Ischemic cardiomyopathy	35 (19%)
CHF or EF < 40%	27 (14%)
Creatinine Clearance	
≥ 60 mL/min	164 (87%)
Serum Electrolytes	
Median potassium (range) in mEq/L	4.3 (3.3-5.1)
Median magnesium (range) in mEq/L	1.9 (1.3-2.5)
Electrocardiogram	
Mean baseline QTc (range) in msec ±SD (range)	436 ± 32 (349-530)
In AF or AFl upon initiation	116 (61%)

AF= atrial fibrillation; AFl= atrial flutter; ABW= adjusted body weight; IBW= ideal bodyweight

Table 2: Protocol deviations encountered during Dofetilide loading.

Types of deviations from manufacturer recommended guidelines	No. of patients n (%)
1. Dofetilide initiation with an elevated baseline QTc > 440 msec (or > 500 msec in conduction abnormalities)	47 (25)
2. QTc interval > 500 msec anytime after the 2nd dose without subsequent discontinuation of dofetilide therapy	35(18.5)
3. Increase of QTc interval > 15% above baseline post 1st dose without subsequent dofetilide dose reduction	16 (8.5)
4. Antiarrhythmic drug interaction at time of initiation (patients who were previously on amiodarone or dronedarone and had shorter washout periods than recommended)	13 (7)

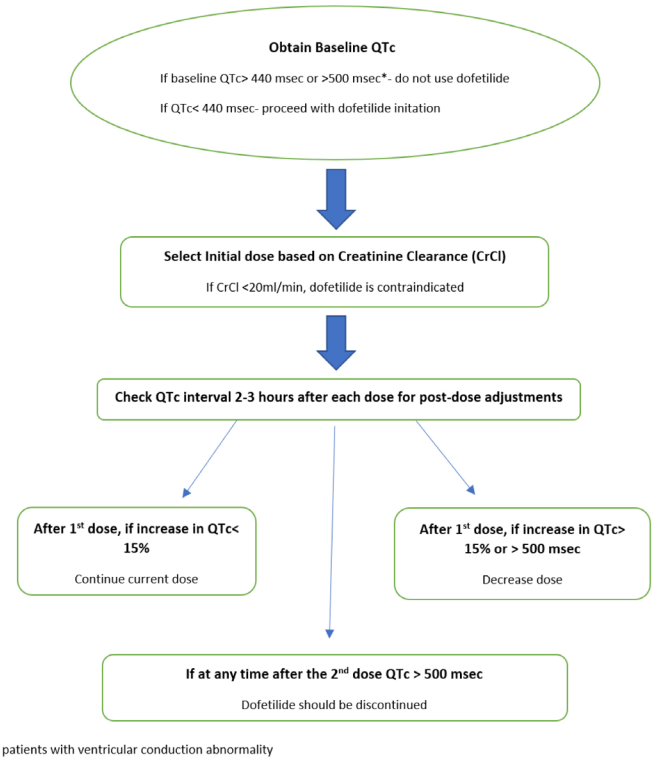

Figure 1: Dofetilide dosing algorithm (FDA approved/ Manufacturer recommended).

Results

Baseline characteristics (AF vs Sinus rhythm)

Baseline characteristics of the 189 patients included in the study are shown in [Table 1]. Mean age was 66 ± 9 years (range 34 – 86 years), and 63 % (n=120/189) were males. Hypertension, coronary artery disease, and cardiomyopathy were seen in 50 % (n=95/189), 29 % (54/189) and 19% (35/1189) of patients, respectively. Severe cardiomyopathy (left ventricular ejection fraction <35%) was seen in 14% (27/189) of patients. The majority of patients (164/189, 87%) had a creatinine clearance ≥ 60 mL/min, calculated using the Cockgroft Gault formula. At the time of dofetilide initiation, 61 % (116/189) were in AF or AFL. Mean baseline QTc interval was 436 ± 32 msec (range 349-530 msec). With regard to the distribution of patients among various QTc intervals, 66% (125/189) of patients had a QTc ≤ 440 msec, 32% (61/189) had a QTc of 441-500 msec, and 2% had a QTc of more than 500 msec at baseline. There was a 19% (35/189) prevalence of a baseline ventricular conduction abnormality.

Table 3: Demographics and clinical characteristics of deviation and non-deviation groups.

Characteristics	Deviation Group (n=93)	No Deviation Group (n=96)	P value
Demographics			
Mean Age	66 ± 8.3	65±9.4	0.12
Gender-Male Female	60 (65%) 33 (35%)	60 (62.5%) 36 (37.5%)	0.68
Comorbidities			
LVEF <40%	15 (16%)	12 (12.5%)	0.42
Heart rate <60 at initiation	20 (16.8%)	3 (4.3%)	0.01
Open heart surgery in last 2 months	1 (0.8%)	0 (0%)	0.447
MI or unstable angina in the past	5 (5%)	0	0.086
AF upon initiation	67 (72 %)	49(51%)	0.054
Creatinine clearance	82 ±17	80±20	0.93
Serious adverse event	4 (4%)	1 (1 %)	0.20
Drug discontinuation rate	12 (13%)	6 (6%)	0.14
QTc interval at discharge in msec	435 ± 26	428± 19	0.66

n (%) or mean ± SD; LVEF= left ventricular ejection fraction; MI= myocardial infarction

Chemical vs electrical cardioversion

Of the 116 patients who presented in AF or AFL, 65% (75/116) required direct current cardioversion while being treated with dofetilide. Overall, 50% (94/189) of patients required electrical cardioversion at some point while in the hospital secondary to AF persistence. At the time of discharge, 11% (20/189) of patients were not in sinus rhythm despite attempts at electrical or chemical cardioversion. In addition, 10% (18/189) were brought back for a repeat attempt at electrical cardioversion 1-2 weeks later, of whom 6% (11/189) had successful electrical cardioversion, with drug discontinuation occurring in 4% (7/189) of patients.

Deviation from protocol

Therapy in 49% (93/189) of patients was noted to deviate from manufacturer-recommended protocol with some of the patients deviating more than once, in different ways, during the same hospitalization. The reasons for deviations are listed in [Table 2]. Baseline QTc exceeding 440 msec (>500msec in patients with conduction abnormalities) was the most frequent deviation (25%; 47/189), followed by QTc interval > 500 msec any time after the second dose without subsequent discontinuation of dofetilide therapy (18.5%; 35/189) [Figure 2].

Dofetilide dosing and QTc prolongation

QTc prolongation (>500msec) was present in 18.5% of patients after getting the second dose, but only two of those patients had persistently prolonged QTc at the completion of loading dose in whom the drug was discontinued. The prolongation of QTc interval >15% occurred in 8.5% of patients after the first dosing but without significant issues

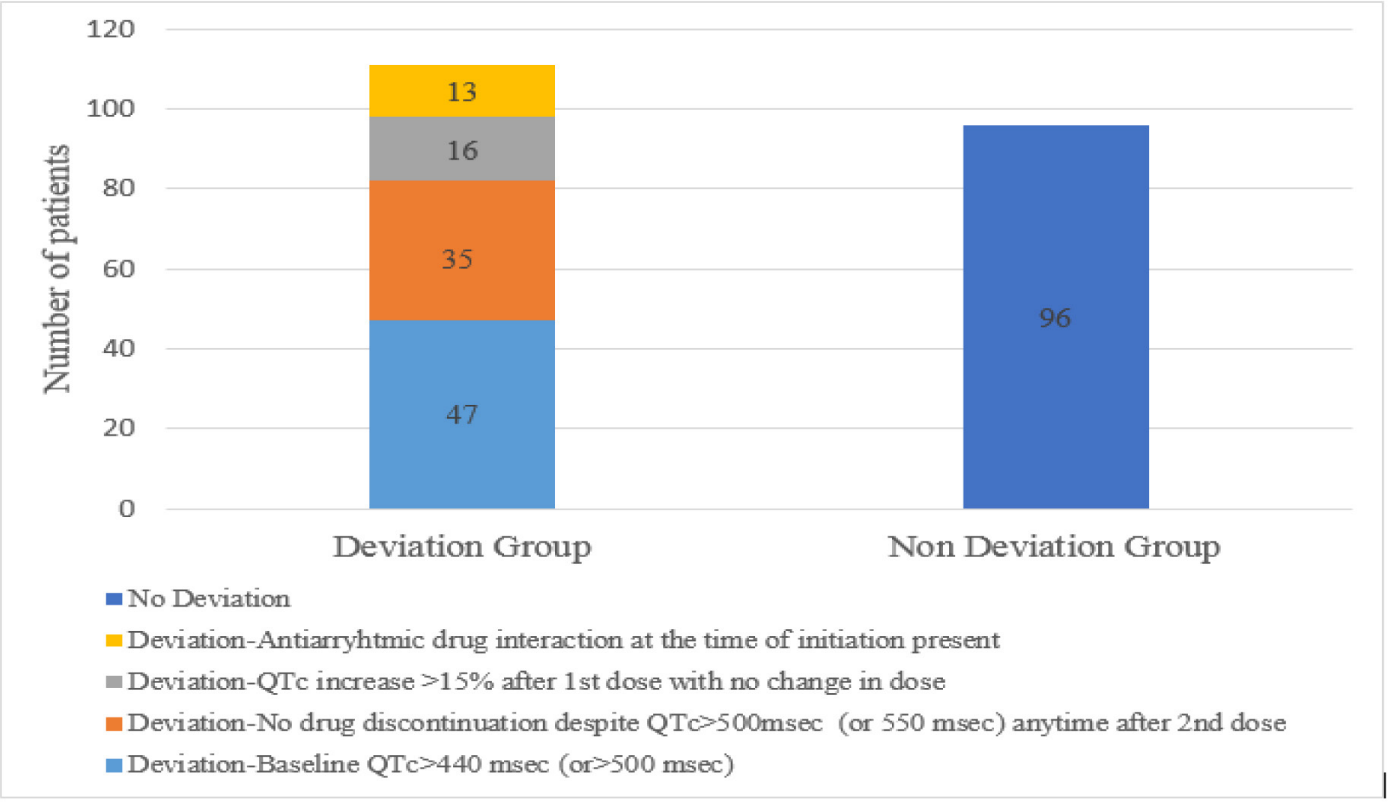

Figure 2: Bar chart diagram showing different types of deviations.

during the subsequent dosing and at time of discharge. None of these patients needed drug discontinuation. Even though 6.5% of patients did not have thorough drug washout from other AADs, there was no significant impact on QTc and/or subsequent clinical outcomes. Post chemical or electrical cardioversion, the QTc intervals at the time of discharge were within the normal limits.

Drug discontinuation and Adverse events (Deviation vs non deviation group)

Overall, dofetilide therapy was discontinued in 9% (18/189) of patients secondary to inefficiency or drug intolerance. The rate of drug discontinuation for "deviation group" was 13% (12/93) vs 6% (6/96) for "non-deviation" group (p= 0.14). A total of 11 patients (torsades de pointes in five following prolonged QTc, non-sustained ventricular tachycardia in two, and QT prolongation without torsades de pointes in four) had drug intolerance leading to drug discontinuation. The overall incidence of SAEs was 2.6% (5/189). The rate of SAE was 4% (4/93) in "deviation group" vs 1% (1/96) in "non-deviation group" (p value = 0.20). One patient in the deviation group had a baseline QTc of 530 msec and developed ventricular fibrillation while being monitored in the hospital. Interestingly, out of 5 patients with SAEs, 4 had QTc>500 milliseconds at one point after the second dose, but only 1 had continued the drug despite such QTc prolongation. There were only two patients who had a baseline QTc >440 msec (including one with baseline QTc >500). Comparison of baseline characteristics of the two groups is shown in [Table 3].

Of note, in patients with severe cardiomyopathy (ejection fraction <35%), deviation was encountered in more than half of the patients (55%, 15/27) with only 1 (3.7%, 1/27) SAE reported.

Discussion

AAD continue to remain the first-line maintenance therapy after cardioversion to sinus rhythm. However, most of the available antiarrhythmic drugs are associated with serious cardiac and/or non-cardiac side effects like arrhythmias, QT prolongation, and liver or lung toxicities. Dofetilide is one of these antiarrhythmic drugs indicated for maintenance of sinus rhythm (Class 1A recommendation) based on reports from several trials like SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) trial[10] and DIAMOND (Danish Investigations on Arrhythmia and Mortality on Dofetilide) study[12]. However, due to risk of dose-dependent QT prolongation and serious arrhythmias, including torsades de pointes, the FDA has mandated that dofetilide initiation take place in the inpatient setting under continuous monitoring following the set protocol per manufacturer [Figure 2]. Despite its favorable side effect profile compared to other antiarrhythmic drugs, dofetilide is still being used as a second or third line drug by most cardiologists [13]. The reason for such practice could be prerequisites like inpatient initiation as well as strict protocol guidelines per manufacturer. Of

note, dofetilide is available in only a few countries outside of the U.S., and the restrictions on its use are different from restrictions in the U.S.

We completed a retrospective review of patients who underwent dofetilide initiation at our center and looked at various parameters during initiation to see how strictly cardiologists were following the manufacturer protocol, and to discern the implications of protocol deviations. We found that almost half of the patients (49%, 93/189) had a deviation from the protocol, and some patients had recurrent deviation during their initiation process.

The most common deviation from the protocol was elevated baseline QTc (>440 msec or >500 msec if ventricular conduction abnormality was present) followed by continuation of the drug despite a measured QTc >500 msec (or>550 msec if ventricular conduction abnormality present) any time after the second dose. The overall incidence of serious arrhythmias was 2.6%, which is the same rate reported in previous studies (SAFIR-D). Similarly, the SAE rate in patients with severe cardiomyopathy is the same as reported in DIAMOND study[12].The mean baseline QTc in most of these patients was 436 msec. There were individual variations in the QTc cut-off values with which each of the prescribers were comfortable. Oftentimes, an accurate QTc interval may be difficult to calculate due to the presenting rhythm of AF and AT, despite correction algorithms based on the rhythm. Unless the QTc is grossly abnormal, borderline QTc intervals above 440 msec may still clinically do well.

The inherent limitations in accurate QTc interval measurement when patients are in AF or AFL may lead to overestimation of QTc. The 440msec cut off may not be valid entirely based on real world experience. Unless the QTc is grossly abnormal, a lot of patients can have dofetilide initiation and subsequent cardioversion to be able to accurately measure QTc. Some of the standard protocol numbers used are mostly arbitrary and supported by historical data. These guidelines should be updated periodically based on real world data. Prospective drug registries can help answer a lot of these questions.

Limitations

Our study was conducted in a single center and was retrospective in nature. The reasons cited by the physicians for drug initiation despite protocol deviation were not reported. Of all the enrolled patients, 39% of patients who had a protocol deviation were in normal sinus rhythm; accurate QTc measurement in these cases would not have been difficult. A larger multi-center registry for dofetilide loading and maintenance would be helpful in better understanding the real-life implications and for better defining the loading parameters and variability in dosing among patients with varying baseline characteristics. Lastly, despite protocols in place to facilitate adherence, some providers did not adhere to the protocol due to personal preference and experience. Methods to emphasize better protocol adherence and documentation are needed.

Acknowledgments

None

Conclusion

Our single center experience with dofetilide initiation showed that deviations from protocols are routinely encountered. However, the implications of most of these deviations on drug discontinuation need further elucidation, and the group that had protocol deviations had significantly more serious adverse events compared to the group that had complete protocol adherence. The protocol for dofetilide initiation may need some revision pending further robust data. Larger multicenter studies are needed to better delineate our findings.

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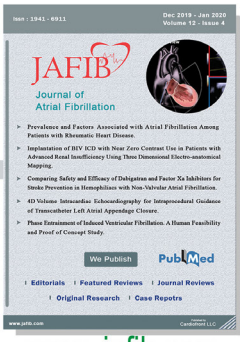

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Avoiding Urinary Catheterization in Patients Undergoing Atrial Fibrillation Catheter Ablation

Andrew B. Lehman[1], Asim S. Ahmed[2], Parin J. Patel[2].

[1]*Marian University College of Osteopathic Medicine, Indianapolis, IN.*
[2]*St Vincent Medical Group, Clinical Cardiac Electrophysiology, Indianapolis, IN.*

Abstract

Purpose: Indwelling urinary catheters are commonly inserted when administering general anesthesia. However, there are significant risks to routine IUC insertion. We compared urinary and other outcomes in a population of patients undergoing atrial fibrillation (AF) ablation with or without IUC.

Methods: This was a single center, retrospective review of patients undergoing AF ablation. Patients were identified by procedure codes and patient health characteristics and outcome data were manually extracted from electronic health records. The primary composite endpoint was 7-day periprocedural urinary outcomes including cystitis, dysuria, hematuria, urethral damage, or urinary retention.

Results: 404 patients were included in the study, 297 with IUC and 107 without IUC. Uncatheterized patients were less likely to have congestive heart failure (CHF) (31.8% vs 43.4%; P = 0.039) and had a shorter procedure length (4.2 vs 4.9 hours; P < 0.001) with less fluid administered (1485 vs 2040 mL; P < 0.001). No urinary complications occurred in the uncatheterized group versus 14 in the catheterized group (P = 0.026). 3 patients in the uncatheterized group developed serious infections versus none in the catheterized group (P = 0.018). There was no incidence of death and no statistically significant difference in readmission in the 30 days after procedure.

Conclusions: There were no urinary complications in 107 patients who received no IUC during AF ablation. Avoiding bladder catheters during AF ablation procedures may lower incidence of adverse urinary complications without adding substantial risk of urinary retention.

Introduction

Atrial fibrillation (AF) ablation is an invasive but highly effective treatment for AF that is superior to medical treatment alone. [1, 2] Standard of care is to place patients under general anesthesia to improve catheter stability and outcomes. [3, 4] Especially during longer cases, large amounts of IV fluid may be administered. To better assess hemodynamic stability and to reduce the risk of urine retention developing during anesthesia, anesthetized patients often undergo indwelling urinary catheterization(IUC).

IUC is a commonly performed procedure in the inpatient setting, but is not risk-free. [5] Common side effects of IUC include cystitis and subsequent complications [6], and mechanical trauma to the genitourinary system, especially in men with Benign Prostatic Hyperplasia (BPH). [5, 7] Risk management strategies include minimizing the time a patient spends catheterized and avoiding IUC in the absence of a clear indication. [8, 9] During medical and surgical procedures that require general anesthesia and IUC, patients often have the urinary catheter removed immediately after the procedure is completed. This has successfully reduced the rates of UTI associated with these procedures. However, it has also resulted in an increase in the rate of acute urinary retention. [10-13] Acute urinary retention may require placement of a urinary catheter and can increase post-procedural length of stay. [14]

At our institution, operators have recently begun to forego IUC in some patients undergoing AF ablation. We hypothesize that avoiding IUC during AF ablation may reduce the overall risk of postoperative urinary complications. This study is a nonrandomized observational study investigating the rates of urinary and other complications in patients who underwent AF ablation with or without IUC.

Methods and Materials

This was a single center, retrospective cohort study of patients undergoing ablation for atrial fibrillation. This study was approved by the Institutional Review Board. Patients were identified by billing code Current Procedural Terminology 93656 (Electrophysiology study and Atrial Fibrillation Ablation) at St. Vincent Hospital in Indianapolis, IN. Patients who underwent the procedure between 3/1/17 and 9/30/18 were eligible for inclusion. All procedures were performed by one of five primary operators, using a wide area, antral, circumferential approach to pulmonary vein isolation. Radiofrequency energy was used for ablation with force sensing ablation catheters with either the NavX Ensite (Abbott, St. Paul, MN) or Carto (Biosense Webster, Diamond Bar, CA) mapping platforms. General anesthesia was used for each ablation.

Patient health characteristics and outcomes data were manually

Key Words

Atrial Fibrillation Ablation Urinary Bladder Catheter

Corresponding Author
Parin J. Patel,
Naab Rd, Suite 400, Indianapolis, IN, 46260

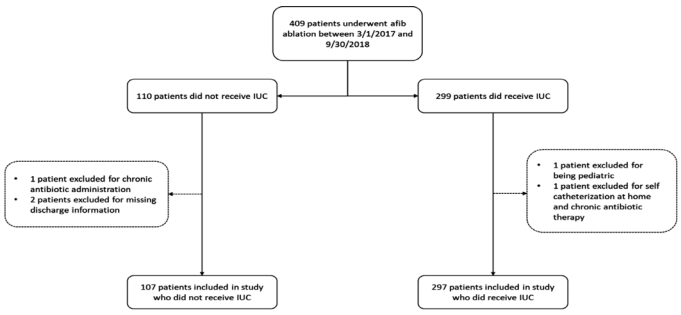

Figure 1: **Patients included and excluded from study.**

extracted from electronic health records (Athena, Athenahealth, Inc., Watertown, MA; and Sunrise, Allscripts Healthcare Solutions, Inc., Chicago, IL). A random sample of 10% of the charts were manually re-reviewed by a second extractor to ensure high degree of ascertainment. Serum creatinine, height, and weight were input using the measurements closest to the date of procedure +/- 30 days. Chronic Kidney Disease was evaluated as any stage of chronic kidney disease. No patients in this study were on dialysis. Other diagnoses were evaluated by presence of appropriate ICD-10 codes in the patient's health records. Recent malignancy/chemo was diagnosed as diagnosis with malignancy and/or ongoing treatment for a malignancy within the 6 months before the procedure. Remote history of malignancy without ongoing treatment was not included. Case duration was reported as room time in and out of the electrophysiology laboratory.

The primary outcome was a composite of the following: urine retention, need for recatheterization, hematuria, dysuria, UTI or other genitourinary (GU) trauma. Urine retention, UTI, hematuria, and penile or urethral pain were considered procedure-related if they occurred in the 7 days after the procedure. Urinary recatheterization was defined as placement of any additional urinary catheter after the initial IUC due to a urinary complication (as opposed to for another procedure or due to rehospitalization). Patients were censored if they were recatheterized for any reason unrelated to the procedure. Other GU trauma was defined as any specific trauma to the genitourinary system secondary to IUC. Outcomes were assessed from the index discharge summary, subsequent call records, appointments notes, and any discharge notes after readmission in the 30 days after the procedure. Secondary outcomes included serious infection, readmission, death, incontinence, incident congestive heart failure, and post-procedural groin complication. Secondary outcomes occurring within 30 days of the procedure were reported. Serious infection was defined as any infection that resulted in readmission. Incident congestive heart failure and post-procedural groin complication were collected separately from 391 of the patients included in the original analysis.

Statistical Analysis

All analyses were conducted using Stata Statistical Software Release 14 (Statcorp, College Station, TX). Data is presented using frequency and mean and standard deviation. Categorical variables were assessed using Fisher's exact test. Continuous variables were assessed using Student's t test. Results were considered significant if they had a $P<0.05$ on two tailed analysis. [10]

Results

409 patients were included in the study, 299 of whom received IUC and 110 of whom received no IUC. 5 patients were excluded as detailed in [Figure 1] and 404 patients were included in final analysis. One patient was censored early due to catheterization unrelated to urinary complications.

Descriptive statistics of the included patient population are described in [Table 1]. Patients who were uncatheterized were less likely to have CHF (31.8% vs 43.4%; P=0.039) and had a higher average BMI (31.7 vs 30.4, P=0.035). Patients who were uncatheterized were also less likely to be on aspirin (12.2% vs 19.3%) and more likely to be on clopidogrel (3.7% vs 1.0%), with an overall P of this association of 0.050. There was no statistically significant difference in proportion of patients with persistent AF in the two groups (30.8% uncatheterized and 39.1% catheterized; P = 0.16).

Intraoperative characteristics are described in [Table 2]. Procedure duration was significantly shorter in uncatheterized patients (4.2 vs 4.9 hours; $p < 0.001$). Total fluid administration was significantly less in uncatheterized patients (1485 vs 2040 mL; $p < 0.001$), and there was only a small amount of urine recorded in either population (overall average 417 mL).

Table 1: **Patient population characteristics.**

Patient Characteristic	No IUC	IUC	P-value
Age (mean)	63.9	62.6	0.214
Male (%)	66.4	64.3	0.725
BMI (mean)	31.7	30.4	0.035
Persistent Afib (%)	30.8	39.1	0.161
Congestive Heart Failure (%)	31.8	43.4	0.039
Coronary Artery Disease (%)	29.0	28.6	1.000
Chronic Kidney Disease (%)	11.2	6.4	0.137
Benign Prostatic Hyperplasia (%)	11.9	12.5	1.000
Prostate Cancer (%)	5.6	4.7	0.752
Diabetes (%)	29.0	19.6	0.056
Chronic UTI (%)	0.9	2.7	0.455
History of Kidney Cancer (%)	0.0	0.3	1.000
Cockcroft-Gault (mean)	107	106	0.743
History of Malignancy/ Chemo (%)	0.9	1.0	1.000
Preop Antiplatelet			0.050
Aspirin (%)	12.2	19.3	
Clopidogrel (%)	3.7	1.0	
Preop Anticoagulant			0.079
Warfarin (%)	17.8	12.2	
Apixiban (%)	62.6	63.5	
Rivaroxiban (%)	13.1	15.9	
Dabigatran (%)	4.7	8.5	

Table 2: Intraoperative patient characteristics.

Intraoperative Characteristic	No IUC	IUC	P-value
Fluid In During Procedure (mL)	1485	2040	<0.001
Fluid Out During Procedure (mL)	326	431	0.080
Case Duration (hours)	4.2	4.9	<0.001
Intraop Complication (%)	2.8	5.1	0.422

Table 3: Results. Urinary outcomes were assessed up to 7 days after AF ablation, secondary outcomes were assessed up to 30 days after AF ablation.

Postop Complications	No IUC (N=107)	IUC (N=297)	P-value
Composite Outcome	0	14	0.026
Urine Retention	0	1	
Urinary Recatheterization	0	4	
UTI	0	5	
Hematuria	0	8	
Penile or Urethral Pain	0	2	
Other GU Trauma	0	3	
Secondary outcomes			
Serious Infection	3	0	0.018
Readmission	7	23	0.831
Death	0	0	
Incontinence	0	0	

Primary and secondary outcomes are described in [Table 3]. No urinary complications occurred in the uncatheterized group versus 14 in the catheterized group (P = 0.026). The most common complications observed were UTI (5 patients) and hematuria (8 patients). 3 patients suffered intraurethral injury during urinary catheter placement, 2 patients reported penile or urethral pain, and 1 patient developed acute urinary retention. 4 patients were recatheterized for urinary complications. Of these, one was the patient who developed acute urinary retention, and the other three were patients with intraurethral injury.

Of the secondary outcomes assessed, 3 patients developed a serious infection requiring hospitalization in the uncatheterized group, versus 0 in the IUC group (P=0.018). There was no statistically significant difference in readmission in the 30 days after procedure. Of readmissions, 3 were those who developed serious infections, 19 were for arrythmia-related issues, 4 for pericarditis or cardiac injury syndrome, 2 issues with anticoagulant use, 1 patient had another cardiac ablation, 1 patient experienced respiratory failure, and one patient had a newly diagnosed brain tumor. The three patients who developed infections suffered from a pneumonia leading to sepsis, acute cholecystitis leading to acute pneumonia, and one patient developed septic shock of unknown origin. There was no observed incidence of death in the 30 days after the procedure in our population. Only 12 out of 391 (3%) patients experienced incident heart failure in the 30 days post procedure; there was no difference in incident HF between the two groups (2.7% v 5.6%, p = 0.10). Only 1 patient required rehospitalization for a groin complication in the bladder catheter group.

Multivariable regression was considered but not performed for this study due to there being zero urinary events in the uncatheterized group and insufficient overall events to ensure statistical validity of a multivariable model.

Discussion

In patients undergoing AF ablation, we compared differences in the rates of urinary and non-urinary outcomes between patients who received IUC for the procedure and those who did not. There was a statistically significant increase in the overall risk of urinary complications in the 7 days postoperatively in patients who received IUC. Urinary catheters are a known means of introducing pathogens into the bladder and can cause mechanical trauma to the urethra during insertion, [5-7] and this finding supports existing data. One of the main risks associated with forgoing IUC in other studies has been urine retention. [15, 16] Urine retention is a urologic emergency, but is typically treated with intermittent urinary catheterization until the patient can successfully void. [17] In the inpatient setting, urine retention can be detected before it becomes emergent, but it may prolong a patient's length of stay. Only one case of urine retention occurred in our study in a catheterized patient. This may be because AF ablation is relatively less traumatic than surgeries that involve manipulation of the viscera and nerve plexuses.

Patients who were catheterized had a significantly higher rate of CHF than patients who were not catheterized. This study was not randomized, and patients with CHF may have received IUC more often to better account for volume status. The higher rate of CHF in catheterized patients may also explain why preoperative aspirin use was higher in this population as well. There were no established criteria for avoiding bladder catheters, and so operator preference and experience, and baseline patient characteristics clearly influenced outcomes. Patients with persistent AF were also slightly more likely to be catheterized in this study, though not statistically significantly so. Because persistent AF ablation may involve ablation in addition to pulmonary vein targets, these procedures can be longer and may involve more fluid administration. This may help explain the difference in average procedure length and fluid administration. Finally, in a post-hoc study of secondary outcomes, incident heart failure and post-procedure groin complications were no different in the two groups.

Inadequate follow-up is a limitation for this study. Procedural complications were ascertained during the index hospitalization, but AF ablation patients are routinely discharged the same day or day after surgery at our institution. After discharge, a patient needed to present to a healthcare facility or lodge a patient call in our system for outcomes to be ascertained. Milder complications, such as dysuria and hematuria, were likely underreported. We found an extremely low rate of UTI after catheter ablation of AF (5/404 = 1%), compared to prior studies (2.9% in Cluckey et al 2019 [18]; 4.7% in Lewandowski et al 2018 [19]). Though the primary composite endpoint was significantly different between those who did or did not have IUC, our study was not powered to see a difference in UTI

alone. It is possible that with appropriate, prospective ascertainment of outcomes, a difference in UTI or readmission can drive significant health care cost savings and reduce patient morbidity.

To address these limitations, we have established a randomized, controlled trial of bladder catheterization during atrial fibrillation ablation (ABCD-AF trial; Avoiding Bladder Catheters During Atrial Fibrillation ablation; clinicaltrails.gov #NCT03635034). We await the results of this trial to better understand the true harm of routine use of bladder catheters during AF ablations.

Conclusion

Avoiding urinary catheterization during AF ablation procedures was associated with a lower incidence of adverse urinary complications in follow up, without adding substantial risk of urinary retention. However, results of this study are confounded by the higher incidence of CHF, persistent AF, longer procedure time, and higher volume of fluid administration intraoperatively in these patients.

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Phase Entrainment of Induced Ventricular Fibrillation: A Human Feasibility and Proof of Concept Study.

Arun V Holden[1], Gordon A Begg[2], Katrina Bounford[2], Berthold Stegemann[3], Muzahir H Tayebjee[2].

[1]*School of Biomedical Sciences, University of Leeds, Leeds, LS2 9JT; UK.*
[2]*West Yorkshire Arrhythmia Service, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX, UK .*
[3]*Medtronic Plc, Bakken Research Center, Endepolsdomein 5, 6229 GW Maastricht, The Netherlands.*

Abstract

Cardioversion and defibrillation by a single high energy shock applied by myocardial or body surface electrodes is painful, causes long term tissue damage, and is associated with worsening long term outcomes, but is almost always required for treatment of ventricular fibrillation .

As a initial step towards developing methods that can terminate ventricular arrhythmias painlessly, we aim to determine if pacing stimuli at a rate of 5/s applied via an implantable cardiac defibrillator (ICD) can modify human ventricular fibrillation.

In 8 patients undergoing defibrillation testing of a new/exchanged intracardiac defibrillator, five seconds of pacing at five stimuli per second was applied during the 10-20 seconds of induced ventricular fibrillation before the defibrillation shock was automatically applied, and the cardiac electrograms recorded and analyzed.

The high frequency pacing did not entrain the ventricular fibrillation, but altered the dominant frequency in all 8 patients, and modulated the phase computed via the Hilbert Transform, in four of the patients.

In this pilot study we demonstrate that high frequency pacing applied via ICD electrodes during VF can alter the dominant frequency and modulate the probability density of the phase of the electrogram of the ventricular fibrillation.

Introduction

Ventricular fibrillation (VF) is a result of high frequency (dominant frequency from 4.0-5.5 Hz, cycle length < 250 ms), irregular, interacting, re-entrant propagation of electrical excitation waves within the ventricular myocardium. This leads to cardiac arrest and death if not treated urgently with defibrillation. The electrical activity of VF may self-terminate [1] or be terminated by a short, large amplitude (5-40 J) electrical shock delivered by an implanted cardioverter defibrillator (ICD) or 120-360 J applied externally. Defibrillation needs to be prompt: in animal studies the threshold for defibrillation increases, and the probability of a successful defibrillation decreases as VF persists [2]. Clinically, between the first 5 and 15 seconds of VF the probablility that a defibrillation shock is successful halves [3]. Defibrillation shocks can produce cell and tissue damage [4]. They are painful, and some patients find the subjective effects of an ICD intolerable. Repeated defibrillation shocks, even when appropriate and successful, are associated with increased morbidity and mortality [5]. Although life style changes and pharmacological agents can reduce the risk of VF, electrical defibrillation is the most effective means of treating VF [6]. There is therefore great interest clinically in the concept of achieving painless defibrillation by using a repetitive sequence of high frequency, low energy, antifibrillation pacing stimuli, rather than a single large defibrillation shock. Defibrillation by high frequency pacing has been achieved in isolated perfusd atrial [7] and ventricular [8] preparations.

Clinically, anti-tachycardia pacing (ATP) is a short sequence of high frequency pacing stimuli, where the pacing interval may be constant (typically 88% of the tachycardia cycle length), or determined by a decreasing fraction of the preceeding cycle length [9]. Implantable cardioverter defibrillators may be routinely programmed to deliver a sequence of ATP once a tachycardia is detected. Atrial ATP is not effective in terminating persistent episodes of atrial fibrillation [10], but can terminate the slower atrial flutter or tachycardia [11]. This has been exploited in reactive ATP, where ATP is applied whenever atrial fibrillation spontaneously transitions to flutter or tachycardia [12]. Terminating these more organised episodes slows the disease progression and leads to a reduced atrial fibrillation burden [13].

ATP is well established for the control of "slow" ventricular tachycardia, with cycle length more than 250 ms [14]. A defibrillation shock may then be applied if the ATP sequence had failed. A role for ATP in VF , however, has not been established.

Downloads from implantable cardiac devices, and intra cardiac recordings during clinical electrophysiological testing in humans, can provide time series data for characterising idiopathic and induced

Key Words
Ventricular Fibrillation, Implantable Cardioverter Defibrillator, High Frequency Pacing, Anti-Tachycardia Pacing.

Corresponding Author
Professor Arun V Holden
School of Biomedical Sciences, University of Leeds, Leeds, LS2 9JT, UK.

VT and VF in humans [15]. During clinical defibrillator testing in the cardiac catheterization laboratory, the 10-30 s of induced VF provides a narrow window for examining any effects of applied perturbations on the recorded VF.

In this percutaneous human pilot study using standard clinical intracardiac defibrillation hardware, within the confines of a hospital cardiac electrophysiology catheter intervention laboratory, the objective was to determine whether the delivery of high frequency pacing at 5/s via intra-myocardial defibrillator leads during VF can alter the quantitative characteristics of the cardiac electrograms (EGMs) during VF.

Methods

This study was registered on ClinicalTrials.gov on 14th December 2015 with the ClinicalTrials.gov registration number: NCT02629445, and received ethics approval from the North West - Greater Manchester West Research Ethics Committee (15/NW/0722). The study protocol was carried out in accordance with the relevant guideslines and regulations of the Leeds General Infirmary, and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each patient.

Consecutive patients undergoing de novo implant, revision, or generator change of trans-venous implantable cardiac defibrillator (ICD) or cardiac resynchronisation defibrillator (CRT-D) devices at the West Yorkshire Arrhythmia Service, Leeds General Infirmary, and who were to undergo planned defibrillation testing as part of their routine medical care, were included in this study [Table 1]. The ICD or CRT-D device and trans-venous leads were implanted according to standard of care. The device pocket was prepared at the left pectoral region. After the pocket was closed, VF was induced from the implanted device using either 2 s of pacing at a rate of 50/s by 8.0 V and 1.5 ms rectangular puses, or a by delivery of a 5 J shock on the T wave. Prior to 50/s pacing VF inductions, the ICD capacitors were charged to intended defibrillation energy to reduce time to the defibrillation shock. VF was induced only once in any one patient.

All patients were implanted with ICD or CRT-D. A programmer was used for programming and interrogation of the implanted device and to induce VF using the electrophysiological testing capabilities

Table 1: Patient Characteristics.

Patient Number	Age	Gender	LV Function	Ischaemia	Device Type	DFT Performed	Induction Type	CS Lead Configuration
1	67	Male	Severe	Y	ICD	N	na	na
2	80	Male	Severe	Y	CRT-D	N	na	LV2-LV3
3	51	Male	Severe	N	ICD	Y	50/s	na
4	73	Male	Severe	Y	CRT-D	Y	50/s	LV1 - Coil
5	54	Female	Moderate	N	CRT-D	Y	T wave shock	LV tip - RVC
6	74	Male	Severe	Y	CRT-D	Y	50/s	LV3-LV4
7	83	Male	Severe	Y	CRT-D	Y	T wave shock	Unknown
8	69	Male	Severe	N	CRT-D	N	50/s	Bipolar
9	73	Male	Moderate	N	CRT-D	Y	50/s	LV3-LV4
10	47	Male	Severe	N	ICD	N	T wave shock	na
11	57	Female	Normal	N	ICD	Y	50/s	na
12	30	Male	Severe	N	ICD	Y	50/s	na
13	29	Female	Severe	N	ICD	N	na	na

The study protocol could not be carried out in patients highlighted in gray. Fibrillation was induced either by 2 s of pacing at a rate of 50/s by 8.0 V and 1.5 ms rectangular pulses, or a by delivery of a 5 J shock on the T wave.

Table 2: Quantitative characteristics of ventricular fibrillation during testing.

Patient	Phase modulation pre-pacing	Phase modulation during pacing	Phase modulation post-pacing	DF pre-pace	DF during pace	DF post-pace
3	0.0241 ± 0.0120	0.0135 ± 0.0103	0.0156 ± 0.0035	5.10 ± 0.14	5.39 ± 0.21	5.28 ± 0.28
4	0.0066 ± 0.0075	0.0082 ± 0.0026	0.0053 ± 0.0030	3.71	4.11	4.09
5	0.0354 ± 0.0208	0.0405 ± 0.0378	0.0474 ± 0.0383	4.35 ± 0.98	4.42 ± 0.21	4.43 ± 0.03
6	0.0148 ± 0.0080	0.0191 ± 0.1175	0.0079 ± 0.0029	5.13 ± 0.58	5.37 ± 0.06	5.50 ± 0.13
8	0.0148 ± 0.0135	0.0133 ± 0.0079	0.0082 ± 0.0020	4.66 ± 0.17	4.91 ± 0.16	4.87 ± 0.46
9	0.0222 ± 0.0179	0.0081 ± 0.0043	0.0087 ± 0.0054	4.87	5.12	4.73 ± 0.20
10	0.0308 ± 0.0221	0.0381 ± 0.0279	0.0200 ± 0.0106	4.95 ± 0.13	5.0	5.80 ± 0.35
12	0.0113 ± 0.0091	0.0631 ± 0.0216	0.0086 ± 0.0063	4.16	4.94 ± 0.04	4.59 ± 0.06
All	0.0200 ± 0.0156	0.0255 ± 0.0249	0.0152 ± 0.0178	4.62 ± 0.49	4.91 ± 0.43	4.91 ± 0.58

Phase modulation = modulation amplitude of probability densities (as in figure 4). DF = Dominant Frequency (Hz)
Data are mean ± standard deviation across all EGM/pseudoECG channels. Where no standard deviation is presented, the same DF value across all channels was obtained.

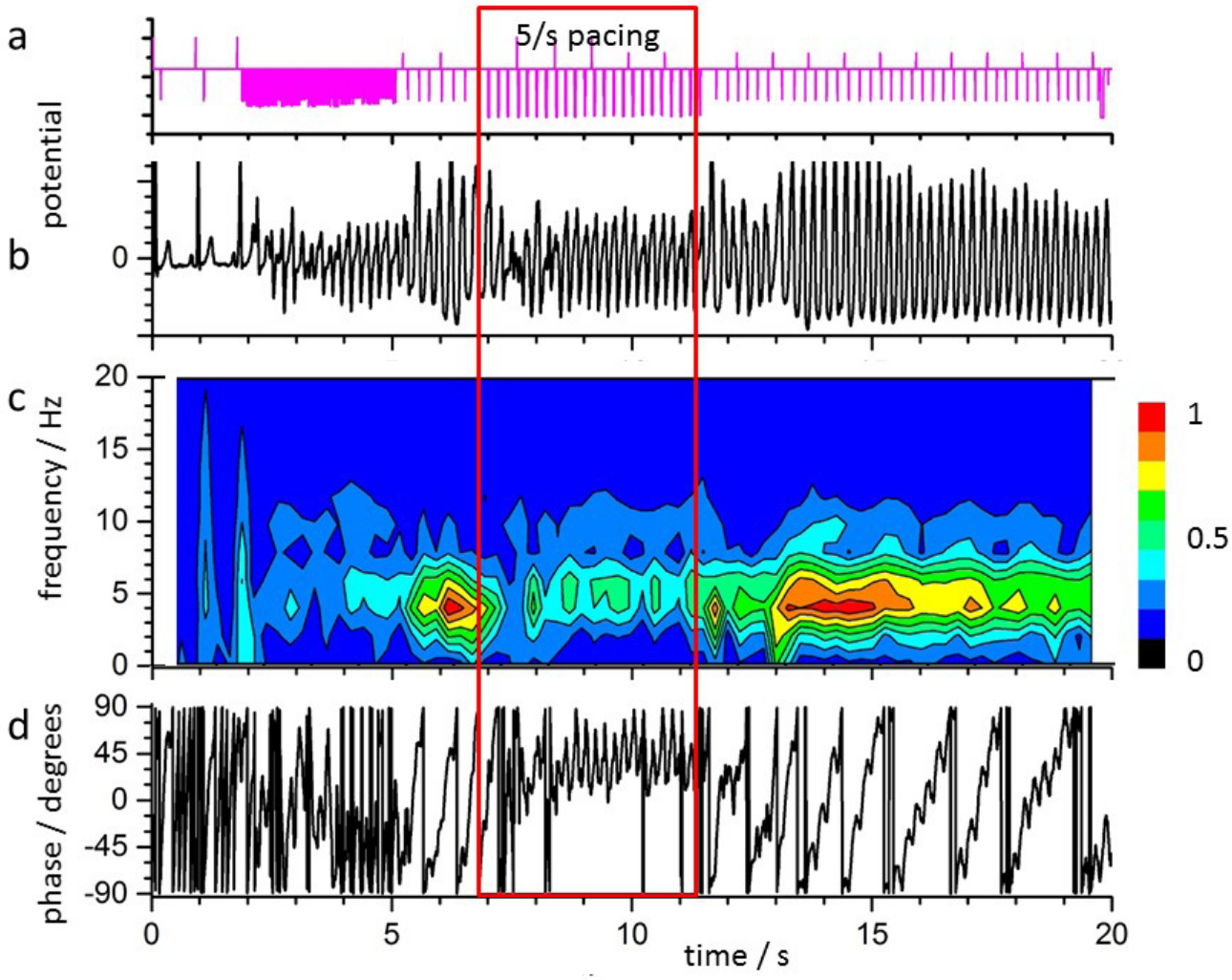

Figure 1: **Sample raw recordings from CRTD/ICD. During a defibrillation test ventricular fibrillation is induced by (A) manually controlled 50/s repetitive stimulation, and, if this fails on the second attempt, by (B) 9 stimuli (8.4 V, 1.5 ms, cycle length 410 ms) followed by a 5 J shock after 400 ms. The 5/s pacing burst is switched on manually after VF has been established for about 5 s. The red lines in A and B mark the defibrillation shock controlled by the ICD algorithm, the green line in B the shock on the T-wave, controlled by the device. (a) is the marker channel (upward stroke atrial signal, downward stroke ventricular signal), (b) the far field EGM - pseudo ECG, (c) EGM1 and (d) EGM2. A is from patient 8, B from patient 5.**

of the implanted defibrillator. A breakout box was connected to the programmer and provided access to analogue signals that were continuously telemetered from the device. The breakout box provided analogue signals for the device marker information, the far field ECG was derived from the implant, and two EGM channels were derived from the right and/or left ventricular lead system. The EGM source and source sensitivity were selected on the programmer, depending on the lead system and EGM signal amplitude. Analog signals were digitized at 22 bit amplitude resolution and 500 samples/s using standard data recording equipment.

Once VF was induced, repetitive 5/s pacing was delivered from the RV tip or an LV electrode for approximately 4-5 s at a cycle length of 200 ms, at maximum output of 1.5 ms pulse width and 8.0 V. The pacing frequency was selected as it was within the range of dominant frequencies characteristic of human ventricular fibrillation and faster than the frequencies used in anti-tachycardia pacing [15]. EGMs were recorded from the RV coil and the atrial electrode for the right ventricle, and between the two LV electrodes adjacent to the LV stimulation electrodes for the left ventricle. Each patient only underwent one defibrillation test.

Data were converted from its proprietary poly5 (TMSI Porti) format and exported as .csv files, which were analysed (Short Term Fourier Transform, Hilbert Transform for phase) and plotted. Prior to analysis, the signals were low pass filtered with a 45Hz cut off and high pass filtered with a 1Hz cut off. We performed a Hilbert transformation analysis [16]. If v(t) and p(t), both of the same duration, are the recorded EGM and a 5Hz cosine phase locked to the repetitive pacing signal, and v~(t) and p~(t) are their Hilbert transforms, the

phase was calculated from equation 1:

$$\text{phase} = \arctan\{(v\bullet \tilde{p} - \tilde{v}\bullet p)/(v\bullet p + \tilde{v}\bullet \tilde{p})(t)\}. \quad (1)$$

Dominant frequency and phase values were calculated during VF before, during and after the pacing intervention. The differences in dominant frequency and phase were quantified.

The phase, computed using the Hilbert transform from equation 1 as demonstrated in [Figure 2D], is bounded and distributed between, -90˚ and +90˚. If there is no relation between the EGM and the reference signal, the phase will be uniformly distributed, with the probability density histogram fluctuating randomly about a constant value of 1/180˚. Modulation of the probability density histogram is used as an indicator of a phase entrainment by the high frequency pacing intervention of the EGM during ventricular fibrillation. The modulation of the probability density histogram was quantified using the amplitude of a single cycle of a cosine fitted to the histogram.

Data is represented as mean ± standard deviation unless otherwise stated.

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

Thirteen patients were enrolled. Eight patients underwent the pacing protocol with defibrillation testing . Defibrillation testing could not be performed for clinical reasons in the five excluded patients. The baseline characteristics of the patients studied and the devices which were implanted are shown in [Table 1].

50/s stimulation induced sustained VF in 6 of the 8 patients. In the remaining 2 patients, sustained VF was initiated by a low energy shock synchronised to the T wave. The interval between initiation of VF until defibrillation shock delivery from the implanted device was < 20.4 s (18.03 ±2.3s) , giving 6.79±1.03 s of VF before pacing, 4.87±0.834 s of VF during 5 /s pacing and 6.38±2.13 s of VF after pacing (see Supplementary data).

The magnitude of the EGMs during ventricular fibrillation, either as the peak-peak amplitude of the three EGM signals, as in [Figure 1B,C,D] and [Figure 2B], or as the root-mean-square amplitude/ Hz of their frequency spectra, did not change during high rate high output ventricular pacing intervention . A clear reduction in amplitude was only observed in one patient (see Supplementary Figures).

The amplitude Fourier spectra of the EGMs during the VF before, during and after pacing have the harmonic structure characteristic of a repetitive waveform, with a single, large, dominant frequency (DF) component and smaller peaks at integer multiples of this DF [Figure 3A]. In all eight patients the high frequency pacing increased the

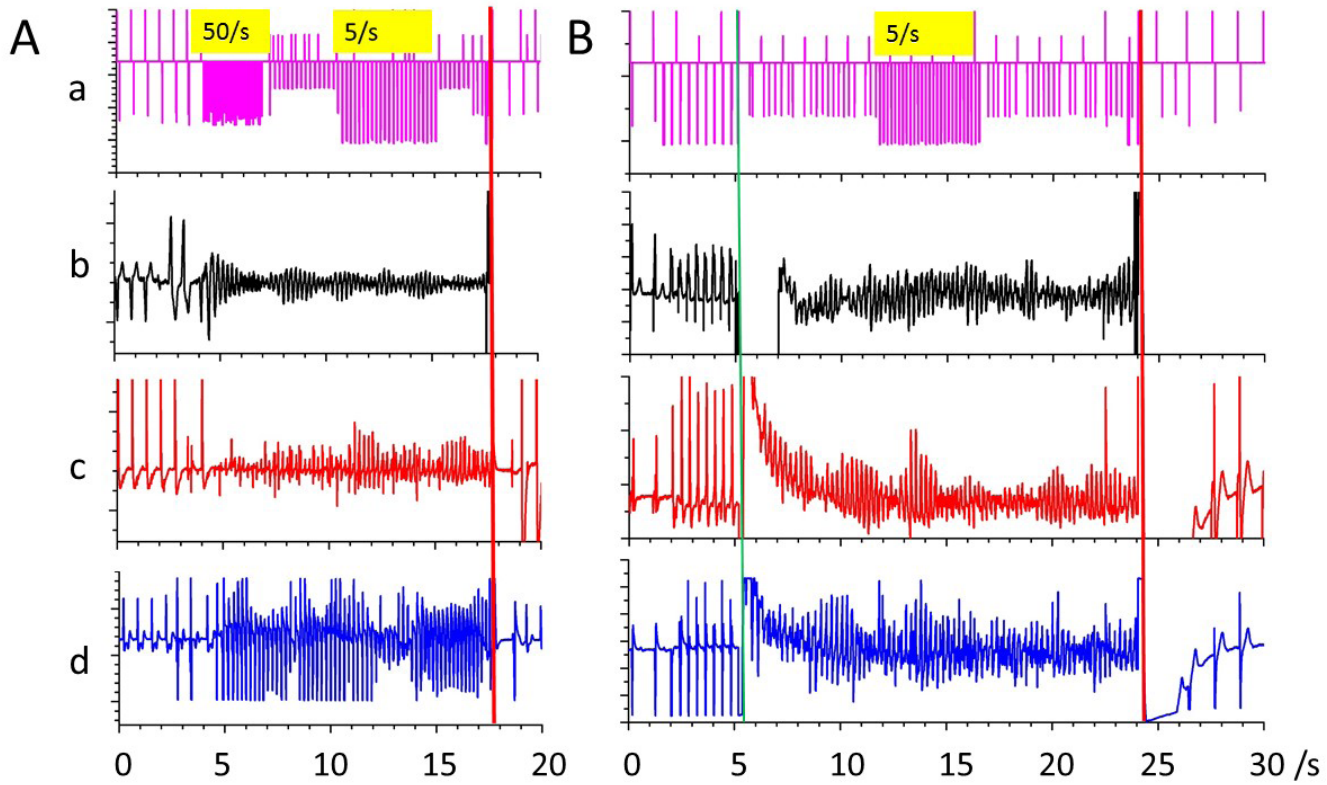

Figure 2: **Characterization of ECG surrogate during ventricular fibrillation induced by 50/s pacing: (a) marker channel; (b) the far field EGM - pseudo ECG (low-pass filtered to 45 Hz, zero-meaned and normalised); (c) Chrono-spectrum of pseudo ECG, the normalized root mean square amplitude of the spectrum is colour coded with a linearly mapped colour look-up table. (d) Phase angle of ECG surrogate, estimated by equation (1). The red box outlines the period of pacing at 5/s Data from patient 12.**

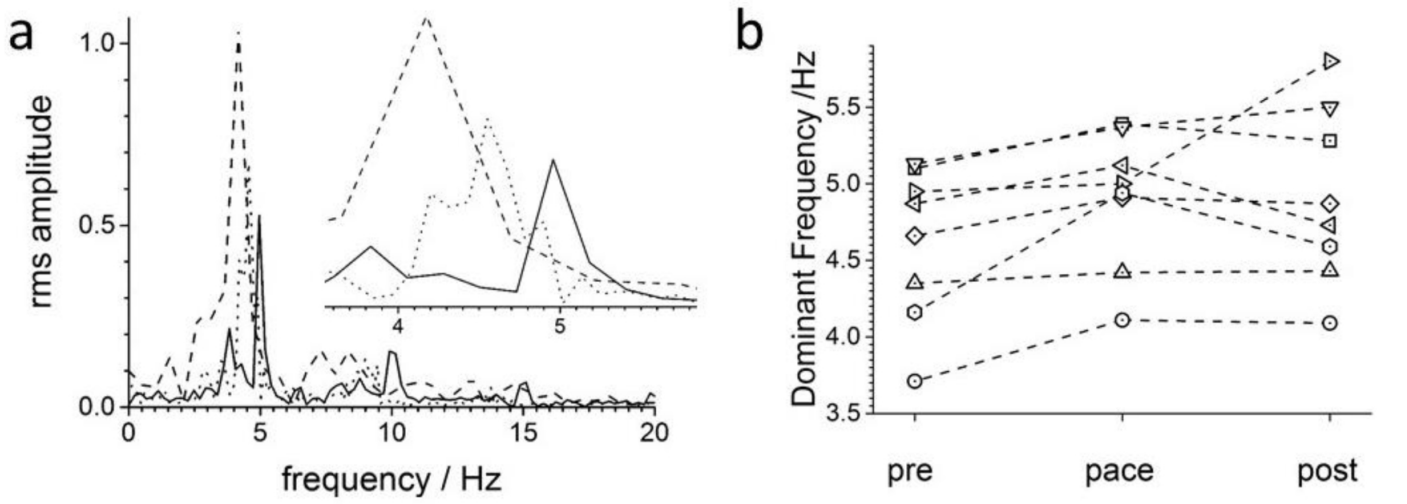

Figure 3: **Dominant frequencies of cardiac electrograms during induced ventricular fibrillation: (a) normalised rms amplitude spectra of initial VF (black) that is followed by 5 s of 5 /s pacing (red) then VF (blue) before automated defibrillation. Patient 12. Frequency scale expanded in inset. (b) dominant frequencies of VF electrogram before (pre), during (pace) and after (post) pacing at 5 /s. Numbers adjacent to each plot correspond to patient number as in table 1.**

DF of the ventricular fibrillation EGM, from from 4.6 ± 0.47 to 4.9 ± 0.41 - see data in [Table 2]. The increase of the dominant frequency was maintained throughout the rest of the episode until the VF was defibrillated [Figure 3B]. The DF change from 4.6 ± 0.48 to 4.9 ± 0.58 Hz from the pre- to post-pacing intervals.

Estimated probability density histograms are illustrated in [Figure 4A-4D]. During pacing [Figure 4C] there is clear modulation of the probability density. [Figure 4E] shows an increase in the amplitude of the modulation of the probability density histogram in 4 of the 8 patients.

The quantitative characteristics of the dominant frequency and phase are presented in [Table 2].

Discussion

VF is sustained by irregular, multiple re-entrant wave trains that are propagating in the excitable myocardial tissue, with a velocity of 0.2-0.7 m/s and have a rate of ~5/s [17]. During clinical VF there can be about 10 re-entrant sources [18] that generate propagating wavefronts The waves are composed of irregular action potentials, that spread into tissue that has recovered its excitability, by local circuit currents.

The tissue into which the depolarising wavefronts of the action potential propagate at any instant in time will be smoothly crumpled, curved sheets, of variable width, each ahead of a propagating wavefront, and behind the repolarisation waveback of the preceeding propagating wave, or a boundary of the tissue. These irregular, moving, writhing narrow sheets form the recovered excitable tissue that can be influenced by electrical stimuli or shocks. The electrical stimulation alters the spatio-temporal pattern of propagation, by altering the cell membrane potentials, tissue excitability , or exciting new action potentials, If the excited cells form a compact, sufficiently large volume of tissue, activity can propagate and capture surrounding myocardium.

The theory of nonlinear waves in excitable media provides an understanding of the spatio-temporal structures and dynamics of the electrical activity driving VF, and how they are modified by anisotropic propagation and heterogeneities [19]. Optical mapping in vitro experiments can give a two dimensional, surface view of re-entrant arrhythmia, and when combined with simultaneous high resolution ultrasound imaging the associated three dimensional scroll wave mechanical filament has been recorded in animal hearts [20]. Bidomain theory [21] provides an approach to how stimulation from electrodes in or near the heart can excite and pace the myocardium, or defibrillate via the induction of virtual electrodes [22]. These theories have been used to design [23] and test methods to produce defibrillation by repetitive trains of small amplitude electrical stimuli, numerically [24, 25] , in vitro, on cell cultured preparations and isolated perfused hearts, and in acute animal preparations [8, 26 -27].

The physical rationale for defibrillation by low amplitude repetitive pacing is that if VF is driven by interacting, multiple re-entrant waves, then progressive elimination of these re-entrant waves or rotors will terminate fibrillation [21,25]. If an isolated rotor is idealized as a pinned or a meandering free stable spiral or scroll wave in a two and three-dimensional excitable medium [28], then repetitive perturbations can unpin it and also produce a drift in the position of the core, or filament, of the wave. Repetitive, appropriately timed stimulation would act to gently push the core out of the medium [23].

A few bursts of far field repetitive stimulation of ~10% defibrillation single shock amplitude have been shown to be able to terminate re-entry in an isolated canine heart [26].

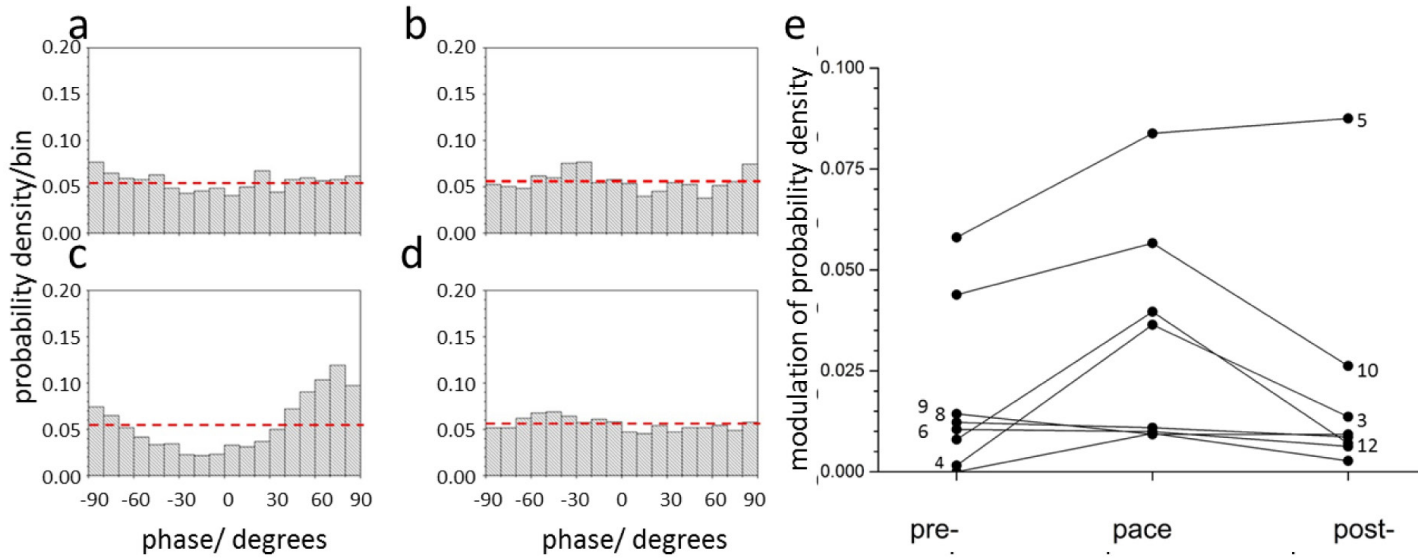

Figure 4: **Estimated probability density histograms for phase relative to 5Hz cosine, calculated by equation (1), during induced fibrillation (a) during 50/s pacing induction (b) before 5/s pacing (c) during 5/s pacing and (d) after 5/s pacing and before defibrillation shock. The red dashed line is the density predicted on the assumption that there is no relation between the cardiac electrogram during fibrillation and the 5/s pacing signal (it is 1/18 as the bins are 10° wide). Patient 12 channel b. (e) Modulation amplitude of the probability densities (pre) before pacing, (pace) during 5/s pacing and (post) after 5/s pacing and before defibrillation shock. Numbers adjacent to each plot correspond to patient number as in table 1.**

Although the possible mathematical, physical and biophysical mechanisms of defibrillation can be dissected in isolation in animal and tissue model systems, and the isolated perfused human heart [29] mechanisms for clinical defibrillation need to be studied and tested in human hearts, as the quantitative details of propagation phenomena are species specific, and in vivo, as cardiac excitability and propagation are influenced by sympathetic activity .

In this first in human study, we have demonstrated that 5/s high frequency high output pacing intervention applied via ICD electrodes during VF can alter the quantitative characteristics of the VF electrograms. These changes with time, of frequency, phase and amplitudes imply that the spatio-temporal pattern of activity, or the propagating activity, that produces ventricular fibrillation have been modified by the pacing stimuli. In these experiments the VF before and after the pacing act as the controls, and the VF during the pacing as the test.

There is an apparent increase in the DF from before pacing to during pacing ([Figure 3B, [Table 2]). This higher DF can be maintained post pacing. However, the increase in DF may not be produced by the pacing itself, but result from the evolution of the properties of VF with time since its initiation, as seen in unpertubed, induced VF [17]. Since the duration of the pre-, during and post-pacing VF recordings are short, the spectral estimates have a low resolution and consistency (few degrees of freedom). However, the values in [Figure 3B] are consistent with:

• the range of DF in optical recordings of evoked VFevoked episodes in isolated perfused human hearts , from 5.4 to 6.8 Hz [27],

• the increase in the global mean DF of the cardiac electrograms reported between 1 and 30 s during induced episodes of VF in vivo, from 3.9 ± 0.8 to 5.9± 1.0 Hz [30]

• and the increase in DF, at a rate of rate of 0.018 ± 0.005 Hz/s during VF induced by burst pacing reported during open chest surgery using a 256 electrode epicardial sock [30].

The modulation of the estimated probability density histograms ([Figure 4], [Table 2]) for the phase is only observed during the 5 /s pacing, and is a reversible effect of the 5 /s pacing. Modulation is observed in the far field ECG channel, and both recorded EGM channels of [Figure 1], in 4 of the 8 patients.The EGMs for each of these channels is the potential between two adjacent electrodes on the ICD leads. In a mono-domain and bi-domain models of the heart this would be modelled by a weighted integral of the spatio-temporal activity. Any change in the EGMs produced by the pacing could be produced by changes in both, or either of, the temporal and spatial activity during VF.

The 3D spatio-temporal pattern of activity during clinical VF has not been observed. In isolated, perfused hearts, the epicardial surface pattern of excitation during VF (with phase singularities identified as the intersection of a reentrant vortex filament with the surface) are consistent with VF resulting from multiple reentrant vortices [17-19]. The re-entrant waves propagate into tissue that has recovered its excitability. Numerical modelling of the evolution of VF following initiation of a single scroll wave by an S1S2 protocol shows that during the first 30 s of induced VF there are multiple, irregular re-entrant waves with fluctuations in the number of vortex filaments, which range between 5-20 (mean~11) [31]. During VF there are thin, moving, sheet-like volumes of tissue that have recovered excitability, and are ahead of and about to be invaded by the propagating wave-front surfaces. Parts of this spatio-temporal excitable gap that are close to the active electrodes may be excited by the pacing stimuli,

either sub-threshold, or initiating action potentials that propagate and capture a surrounding volume. A changed distribution of excitability in the excitable gap and/or partial capture would account for the modulation of phase probability density and increase in DF shown in [Figure 3-4].

The high frequency pacing burst did not terminate the VF in any of the subjects, but phase entrainment of the cardiac electrograms was produced. The phase entrainment reflects a decrease in the complexity, or increase in the orderliness of the VF, simplifying VF to a process closer to a high frequency VT. The ability of high frequency periodic stimuli to modify the spatio-temporal patterns of the electrical activity that produces VF raises the possibility of modifying VF to a VT that can then be terminated by an appropriately timed, repetitive sequences of pulses.

Study Limitations

The number of leads for pacing and sensing, and their positioning, is determined by the implanted device, and is not designed to be optimal for capturing myocardium. Multiple or long line elctrodes that provide wide area, surface stimulation of the ventricule would be more effective [32]. In order to minimise the duration of VF, and therefore risk to the patient, stimulation was not prolonged beyond five seconds, and there was only one test per patient, to allow the defibrillation shock to be applied within 10 seconds. The effects of repeated and prolonged stimulation could be investigated in animal or in vitro experiments.

The principal limitation of this proof of concept study is the small number of participants, hence the paucity of statistical analysis. Defibrillation testing is now no longer routinely undertaken, and therefore it would be difficult to increase patient numbers.

Disclosure of Financial upport and Conflicts of Interest

MHT has received research grants from Medtronic, Abbott, Biosense Webster and Boehringer Ingelheim. GAB received research fellowship funding from St. Jude Medical (now Abbott). BS is a Senior Research Scientist at Medtronic Bakken Research Centre. AVH, KB declare no competing interests.

Conclusion

In this first in human study, we have demonstrated that a high frequency (5/s) high pacing intervention can modify VF, presumably by exciting or possibly by capturing parts of the myocardium in the excitable gap of VF. Harnessing this has potentially useful implications in extending the delivery of painless pacing from slow and fast VT to VF. Such development could be approached by incorporating data acquired during invasive clinical ventricular electrophysiological investigation and mapping (illustrative examples) with computational simulations (repeated experiemnts within the same ventricular geometry, or over populations of geometries) [33].

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Thromboembolic Outcomes of Different Anticoagulation Strategies for Patients with Atrial Fibrillation in the Setting of Hypertrophic Cardiomyopathy: A Systematic Review

Matthew R. Lozier[1], Alexandra M. Sanchez[1], John J. Lee[2], Elie M. Donath[1], Vicente E. Font[3], Esteban Escolar[2].

[1]*University of Miami at Holy Cross Hospital, Division of Internal Medicine, Fort Lauderdale, FL, USA.*
[2]*Columbia University at Mount Sinai Medical Center, Division of Cardiology, Miami Beach, FL, USA.*
[3]*Jim Moran Heart and Vascular Center at Holy Cross Hospital, Division of Cardiology, Fort Lauderdale, FL, USA.*

Abstract

Objective: Limited data is available assessing the efficacy and safety of different anticoagulation (AC) strategies for prevention of thromboembolic events, major bleeding, and all-cause mortality in patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF). In this systematic review, we conducted a literature search to examine the possible association between different AC strategies and prevention of these adverse outcomes.

Methods: Scientific databases (PubMed, EMBASE, and Scopus) were searched using relevant medical subject headings and keywords to retrieve studies published through September of 2019. Studies assessing the outcomes of interest in patients with HCM and AF receiving AC versus no AC as well as direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) were selected.

Results: This review identified 14 observational studies evaluating thromboembolic events by AC strategies in 8,479 participants with concomitant HCM and AF. The use of AC was associated with a lower pooled incidence rate of total thromboembolic events at 9.5% (112 events in 1,175 patients) compared to 22.1% with no AC (108 events in 489 patients). In addition, the use of DOACs was associated with a lower pooled incidence rate of thromboembolic events at 4.7% (169 events in 3,576 patients) compared to 8.7% with VKAs (281 events in 3,239 patients). Furthermore, the use of DOACs compared to VKAs was associated with a lower pooled incidence rate of major bleeding and all-cause mortality at 3.8% (136 events in 3,576 patients) versus 6.8% (220 events in 3,239 patients) and 4.1% (124 events in 3,008 patients) versus 16.1% (384 events in 2,380 patients), respectively.

Conclusions: AC of patients with concomitant HCM and AF was associated with a lower incidence of thromboembolic events when compared to antiplatelet therapy or no treatment. Treatment with DOACs was also associated with a lower incidence of thromboembolic events, major bleeding, and all-cause mortality when compared to VKAs.

Introduction

Patients with hypertrophic cardiomyopathy (HCM) can range from asymptomatic to a multiplicity of clinical presentations and associated comorbidities.[1-3] Atrial fibrillation (AF) is the most common sustained arrhythmia diagnosed in patients with HCM, occurring in approximately 20-30% of this subpopulation.[4-6] Patients with concomitant AF and HCM tend to have more symptoms and are at an increased risk of stroke, transient ischemic attack, or systemic embolism compared to patients with either condition alone.[7] These findings suggest that both aggressive screening of HCM patients and prophylactic anticoagulation (AC) for all individuals diagnosed with concomitant AF are likely to have a significant prognostic impact on thromboembolic outcomes.[1,4,5,8] Within this subpopulation, AC therapy with a vitamin K antagonist (VKA), such as warfarin, is a Class I recommendation in several guidelines over antiplatelet therapy or no treatment.[9,10] Alternatively, there are no data to suggest that direct oral anticoagulants (DOACs), including a direct thrombin inhibitor or factor Xa inhibitors, cannot be used.[9,10] It is worth noting that these recommendations are based mainly on expert consensus and several relatively small observational studies as there are currently no prospective randomized controlled trials (RCTs) on the subject to date.[1,5,7,11-21]

The aim of this study was to systematically review the literature and objectively quantify the risk associated with different AC strategies in this particular population of interest. This encompasses both a comparison of AC versus no AC and subsequently DOACs versus VKAs for thromboembolic events in patients with concomitant HCM and AF. When available for comparison, major bleeding and all-cause mortality will also be analyzed by the different treatment strategies.

Key Words

Hypertrophic cardiomyopathy, Atrial fibrillation, Vitamin K antagonist, Direct oral anticoagulant, Anticoagulation, Thromboembolism, Major bleeding, All-cause mortality.

Corresponding Author
Matthew R. Lozier,
Holy Cross Hospital, 4725 N Federal Hwy, Fort Lauderdale, FL, 33308.

Methods

Literature Search Strategy

Table 1: Characteristics of the individual studies included in the meta-analysis for thromboembolic events (AC vs. No AC).

First Author	Year	Journal	Country	Design	Age (Years)	Female (%)	[a]HCM & AF (n)	[b]AC (n)	[c]No AC (n)	Follow-Up (Years)
[14]Higashikawa et al.	1997	Jpn Circ J	Japan	[d]SC Cohort	55.5 ± 7.8	36.8	19	7	12	7.9 ± 4.6
[15]Doi et al.	2001	J Cardiol	Japan	SC Cohort	51.0 ± 14.0	31.9	22	10	12	6.7 ± 4.8
[2]Olivotto et al.	2001	Circulation	USA, Italy	[e]MC Cohort	45.0 ± 20.0	39.0	107	59	48	9.1 ± 6.4
[7]Maron et al.	2002	JACC	USA, Italy	MC Cohort	46.0 ± 20.0	39.0	190	82	108	7.0 ± 7.0
[17]Inoue et al.	2006	Circ J	Japan	SC Cohort	66.6 ± 10.3	35.2	25	16	9	2.0 ± 0.4
[4]Guttmann et al.	2015	Eur J Heart Fail	UK, Spain, Greece, Italy	MC Cohort	49.0 ± 16.4	36.1	600	471	129	5.9 ± 5.0
[16]Haruki et al.	2016	Stroke	Japan	SC Cohort	51.0 ± 15.6	37.1	162	84	78	10.7 ± 7.5
[18]Lee et al.	2017	Heart	South Korea	SC Cohort	62.0 ± 11.0	32.0	70	53	17	5.5 ± 2.0
[19]Rowin et al.	2017	Circulation	USA	SC Cohort	57.0 ± 14.0	33.0	299	233	66	4.8 ± 3.4
[20]Tsuda et al.	2019	Heart Rhythm	Japan	SC Cohort	71.0 ± 10.0	29.1	170	160	10	2.4 ± 0.9

[a]HCM & AF indicates the number of patients (n) with both HCM and AF from the individual study; [b]AC indicates the number of patients with both HCM and AF from the individual study that received anticoagulation; [c]No AC indicates the number of patients with both HCM and AF from the individual study that did not receive anticoagulation; [d]SC indicates a single-center study design; [e]MC indicates a multi-center study design.

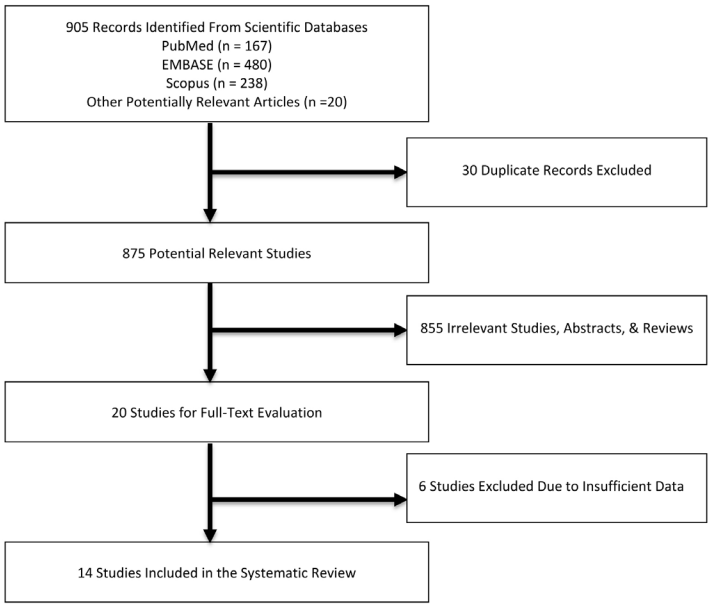

Figure 1: PRISMA flow diagram of the systematic review literature search.

Scientific databases including PubMed, EMBASE, and Scopus were searched through September of 2019 using the terms "hypertrophic cardiomyopathy" AND "atrial fibrillation" AND "stroke." All sets included Medical Subject Heading (MeSH) and free-text terms. No language restrictions were applied. Additionally, relevant publications cited in these studies were assessed to increase the sensitivity of the search. The methodology and presentation of the review are based on the PRISMA guidelines.[22]

Inclusion/Exclusion Criteria & Quality Assessment

Inclusion criteria of interest were: 1) human observational studies in peer-reviewed journals, 2) participants aging ≥ 18 years old, and 3) studies that reported data on thromboembolic events in patients with concomitant HCM and AF receiving AC versus no AC or DOACs versus VKAs. While reporting data on major bleeding or all-cause mortality was not part of the inclusion criteria for this systematic review, these outcomes were compared between the different AC strategies when available. For the comparisons of AC versus no AC or DOACs versus VKAs, thromboembolic events were excluded if they occurred in association with or prior to the initial episode of AF as there was no opportunity for a treatment strategy to be chosen. For the comparison of DOACs versus VKAs, patients were excluded if the etiology of AF was related to valvular causes.

Duplicate publications, irrelevant articles, abstracts, reviews, editorials, and letters were excluded. Two reviewers (MRL and AMS) assessed the titles and abstracts of the identified studies. If the reviewers had inconsistent ideas about an article, it was re-evaluated by a third party (JJL). We also avoided selecting overlapping data by analyzing author names and hospitals in which patients were followed up. Quality assessment was done using Joanna Briggs Institute critical appraisal tool.[23] In addition, the level of evidence for individual studies was assessed using the Oxford Centre of Evidence-Based Medicine – Level of Evidence document (in which a designation of 1A represents the highest level of evidence relative to 5 being the lowest). All studies included in this systematic review received the designation 2b for level of evidence which indicates a well-designed cohort study or low-medium quality RCT. A protocol for this review was submitted and accepted online through the PROSPERO website under the registration number CRD42019127534.

Data Extraction

Critical data extraction was done by MRL; then, the data were entered in Microsoft Office Excel 2016 (Microsoft Corp, Redmon, Washington, USA) and subsequently compared with the original data collected by AMS and JJL to assure the accuracy of the extraction process. The extracted data for each individual study included the following information: first author's last name, journal/year of publication, country, study design, follow-up duration, sample size of the study population, age of the study population, percentage of female patients, sample size of patients with concomitant HCM and AF within the study population, numbers of patients from this subpopulation receiving AC versus no AC or DOACs versus VKAs, and study results (thromboembolic events, major bleeding, and all-cause mortality). Eligible studies for the comparison of AC versus

Table 2: Characteristics of the individual studies included in the meta-analysis for thromboembolic events, major bleeding, and mortality (NOACs vs. VKAs).

First Author	Year	Journal	Country	Design	Age (Years)	Female (%)	[a]HCM & AF (n)	[b]VKA (n)	[c]NOAC (n)	Follow-Up (Years)
[11]Noseworthy et al.	2016	JACC	USA	[d]MC Cohort	67.0 ± 13.3	34.6	1427	859	568	0.56
[12]Dominguez et al.	2017	Int J Card	Spain	MC Cohort	61.6 ± 12.7	34.6	532	433	99	5.25
[13]Jung et al.	2019	Chest	Korea	MC Cohort	69.0 ± 10.9	44.0	2459	955	1504	1.33 ± 1.33
[14]Lee et al.	2019	Stroke	Korea	[e]PB Cohort	67.3 ± 11.2	41.0	2397	1405	992	1.60 ± 1.40

[a]HCM & AF indicates the number of patients (n) with both HCM and AF from the individual study; [b]VKA indicates the number of patients with both HCM and AF from the individual study that received vitamin K antagonists for anticoagulation; [c]NOAC indicates the number of patients with both HCM and AF from the individual study that received non-vitamin K oral anticoagulants; [d]MC indicates a multi-center study design; and [e]PB indicates population-based study design.

no AC and DOACs versus VKAs are qualitatively summarized in [Table 1] and [Table 2], respectively. Due to heterogeneity in baseline characteristics, HCM types, and AC strategies utilized across the included studies, it was not feasible to run a meta-analysis for the outcomes assessed.

Classifications of HCM, AF, and AC Strategies Received

The classification of HCM was variable within the individual full-text studies analyzed. Noseworthy et al., Jung et al., and Lee et al. defined HCM utilizing claims for diagnostic codes (International Classification of Disease, Tenth Revision; ICD-10). The study by Lee et al. also required patients to be registered in the rare intractable disease program where the criteria for HCM was verified by echocardiography. A previous study by Choi et al. demonstrated that the combination of ICD-10 codes and RID codes showed a positive predictive value (PPV) for HCM of 100%.[24] A study by Dominguez et al. utilized a different approach and defined HCM as a maximum LV wall thickness ≥ 15 mm unexplained solely by loading conditions. HCM patients with any type of non-valvular AF (i.e. paroxysmal, persistent, long-standing persistent, and permanent) were included as long as those patients were also diagnosed with HCM based on the above criteria.

For the outcome of thromboembolic events in patients receiving AC versus no AC, participants who received any type of AC during the study period were classified into the AC category. Participants who did not receive any type of AC during the study period or received antiplatelet agents without AC were classified into the no AC category. For the outcome of thromboembolic events in patients receiving DOACs versus VKAs, participants who received apixaban, dabigatran, edoxaban, or rivaroxaban during the study period were classified into the DOACs category and those who received acenocoumarol or warfarin were classified into the VKAs category.

Study Endpoint

There were two primary endpoints of interest. The first primary endpoint assessed the incidence of thromboembolic events in patients with concomitant HCM and AF who received AC versus no AC. The second primary endpoint assessed the incidence of thromboembolic events in patients with concomitant HCM and AF who received DOACs versus VKAs. As stated above, major bleeding and all-cause mortality were also assessed when available for the different AC strategies; however, these two outcomes were not part of the inclusion criteria for this systematic review.

Definitions of Outcomes Assessed

An ischemic stroke was defined as a focal neurological deficit of sudden onset as diagnosed by a neurologist, lasting greater than 24 hours, and caused by ischemia. A transient ischemic attack was defined as a focal neurological deficit of sudden onset as diagnosed by a neurologist and lasting less than 24 hours. A systemic embolic event was defined as thromboembolism outside of the brain to the heart, eyes, lungs, kidneys, spleen, or limbs. Major bleeding was defined as a decrease in hemoglobin level of at least 2 g/dL and/or hemorrhage leading to an unscheduled visit to a healthcare center or requiring a temporary interruption of AC therapy. All-cause mortality was defined as any death event that occurred during the study period.

Results

Study Selection

The above search strategy yielded 905 publications. Following the exclusion of duplicate and irrelevant records, fourteen papers with a total of 8,479 patients met the inclusion criteria for this systematic review (Refer to [Figure 1]). [1,5,7,11-21] All 14 studies reported data on thromboembolic events such as strokes, transient ischemic attacks, or systemic emboli in patients with concomitant HCM and AF.

Baseline Characteristics

Of the 14 articles retrieved, ten (seven single-center and 3 multi-center observational cohorts) provided data on thromboembolic events in patients with HCM and AF receiving AC (n = 1,175) versus no AC (n = 489). [1,5,7,15-21] The mean age of this population was 54.2 ± 15.6 years old (35.7% females) and the mean duration of follow-up was 6.1 ± 4.7 years. Two of the 10 studies also included data on thromboembolic events in patients who were receiving antiplatelet agents (but no AC).[2,18] Notably, 3 of the 10 studies included data on thromboembolic events occurring before a documented episode of AF - these were not included in the extracted data. Study characteristics are provided in [Table 1].

The remaining four of the 14 retrieved articles provided data on thromboembolic events in patients with HCM and AF receiving DOACs (n = 3,576) versus VKAs (n = 3,239).[11-14] All four studies were propensity-matched observational cohorts. Within the DOAC arm, 874 patients received apixaban, 1,025 patients received dabigatran, 280 patients received edoxaban, and 1,397 patients received rivaroxaban. Within the VKA arm, 433 patients received acenocoumarol and 2,806 patients received warfarin. The mean age of this specific population was 67.4 ± 11.6 years old (40.2% females) and the mean duration of follow-up was 1.57 ± 0.97 years. While major bleeding was reported for all four studies, all-cause mortality

was only reported in three (of the four studies). Study characteristics for these four trials are provided in [Table 2].

Thromboembolic Events (AC versus No AC)

Notably, all ten studies examined for this endpoint were post hoc subgroup analyses of larger cohorts.[1,5,7,15-21] In patients with HCM and AF, the use of AC was associated with a lower pooled incidence rate of total thromboembolic events at 9.5% (112 events in 1,175 patients) compared to 22.1% with no AC (108 events in 489 patients). Eight of the ten studies included in this portion of the analysis reported a lower incidence rate of thromboembolic events in patients receiving AC versus no AC, as expected (refer to [Table 1]). The remaining two studies by Higashikawa et al. and Inoue et al. had a small number of patients that met the inclusion criteria and produced contradictory results with a higher incidence rate of thromboembolic events in patients receiving AC versus no AC. Further analysis of these two studies as well as the studies by Lee et al. and Maron et al. revealed sub-therapeutic international normalized ratios (INRs) at or near the time of certain thromboembolic events in patients classified as receiving AC (Higashikawa et al. 5/6 events; Inoue et al. 5/5 events; Lee et al. 3/6 events, and Maron et al. 9/15 events). Removal of these 22 data points from the current study would result in an even more pronounced difference in the incidence of thromboembolic events in patients receiving AC at 7.8% (90 events in 1,153 patients) versus no AC at 22.1% (108 events in 489 patients).

Thromboembolic Events (DOACs versus VKAs)

As mentioned, this portion of the analysis included four propensity-matched cohorts.[11-14] The use of DOACs in patients with HCM and AF was associated with a lower pooled incidence rate of thromboembolic events at 4.7% (169 events in 3,576 patients) compared to 8.7% with VKAs (281 events in 3,239 patients). In 2016, Noseworthy et al. were the first to compare the two AC strategies and identified a relatively small difference in incidence rate of 3.3% with DOACs (19 events in 568 patients) compared to 4.2% with VKAs (36 events in 859 patients). Since then, three more studies have continued to demonstrate an even more impressive efficacy profile for DOACs relative to VKAs (refer to [Table 2]).

Major Bleeding (DOACs versus VKAs)

The use of DOACs in patients with HCM and AF was associated with a lower pooled incidence rate of major bleeding at 3.8% (136 events in 3,576 patients) compared to 6.8% with VKAs (220 events in 3,239 patients). The study performed by Noseworthy et al. in 2016 demonstrated a minor difference in the incidence rate of major bleeding at 2.3% with DOACs (13 events in 568 patients) compared to 3.0% with VKAs (26 events in 859 patients). Subsequent studies demonstrated slightly larger differences in incidence rates of major bleeding between the AC strategies, also favoring DOACs over VKAs (refer to [Table 2]).

All-Cause Mortality (DOACs versus VKAs)

The use of DOACs in patients with HCM and AF was associated with a lower pooled incidence rate of all-cause mortality at 4.1% (124 events in 3,008 patients) compared to 16.1% with VKAs (384 events in 2,380 patients). One study in particular, performed by Dominguez et al. in 2017 demonstrated an outsized difference in the incidence rate of all-cause mortality at 2.0% with DOACs (2 events in 99 patients) compared to 24.7% with VKAs (107 events in 433 patients). More recent studies demonstrate similar results favoring DOACs over VKAs (refer to [Table 2]) on this endpoint.

Discussion

Experts concur that patients with concomitant HCM and AF are at high risk for strokes, transient ischemic attacks, and systemic embolic events. While this is a valid concern, there is a limited pool of data and no RCTs to provide guidance regarding the value of prophylactic AC, as opposed to no AC. Due to this paucity of evidence and erring on the side of thromboembolic event prevention, AC is recommended within the current guidelines for all patients with concomitant HCM and AF. This systematic review sought to assess the validity of this recommendation and also to compare DOACs to VKAs for superiority between the two available AC options. Importantly, we firmly establish that treatment of patients with AC was associated with a lower incidence rate of thromboembolic events compared to no AC (Refer to [Figure 2A]), and that treatment with DOACs was associated with lower incidence rates of thromboembolic events, major bleeding, and all-cause mortality when compared to VKAs (Refer to [Figure 2B-2D]).

Prevalence and predictors of AF

The estimated prevalence of AF (thought to be 20-30%) in patients with HCM appears to be approximately five times higher than in the age-matched general population.[2] The main pathophysiologic process thought to drive the increased incidence of AF includes hypertrophy and impaired relaxation of the myocardiocytes of the left ventricle.[25] This ultimately leads to some degree of diastolic dysfunction, compromised blood flow, and increased atrial pressure in nearly all patients with HCM.[25] In addition, mitral regurgitation, usually in the setting of outflow tract obstruction, can also cause irregularities in the normal hemodynamics.[5] With these additional stressors placed on the atria, HCM patients are prone to developing AF.

Prevalence and predictors of thromboembolic events

The prevalence of thromboembolic events in patients with HCM and AF is estimated to be approximately 27%.[2] Furthermore, HCM patients that develop AF demonstrated more than a seventeen-fold increased likelihood of developing thromboembolic events when compared to HCM patients in sinus rhythm.[2] While there is a limited pool of data examining the clinical profile of HCM patients experiencing these thromboembolic events and the determinants of an occurrence, previous studies suggest left atrial diameter, left atrial volume, and age as potential predictors.[1,5,6,7] However, due to study heterogeneity and lack of patient-level data, predictive models for development of thromboembolic events in HCM patients with AF are low-yield. Future studies on the topic with propensity-matched baseline characteristics and similar AF burden will help clinicians delineate which individuals are at increased susceptibility for these adverse outcomes.

Unexplained events with prophylactic AC

This study also raises the important consideration that prophylactic

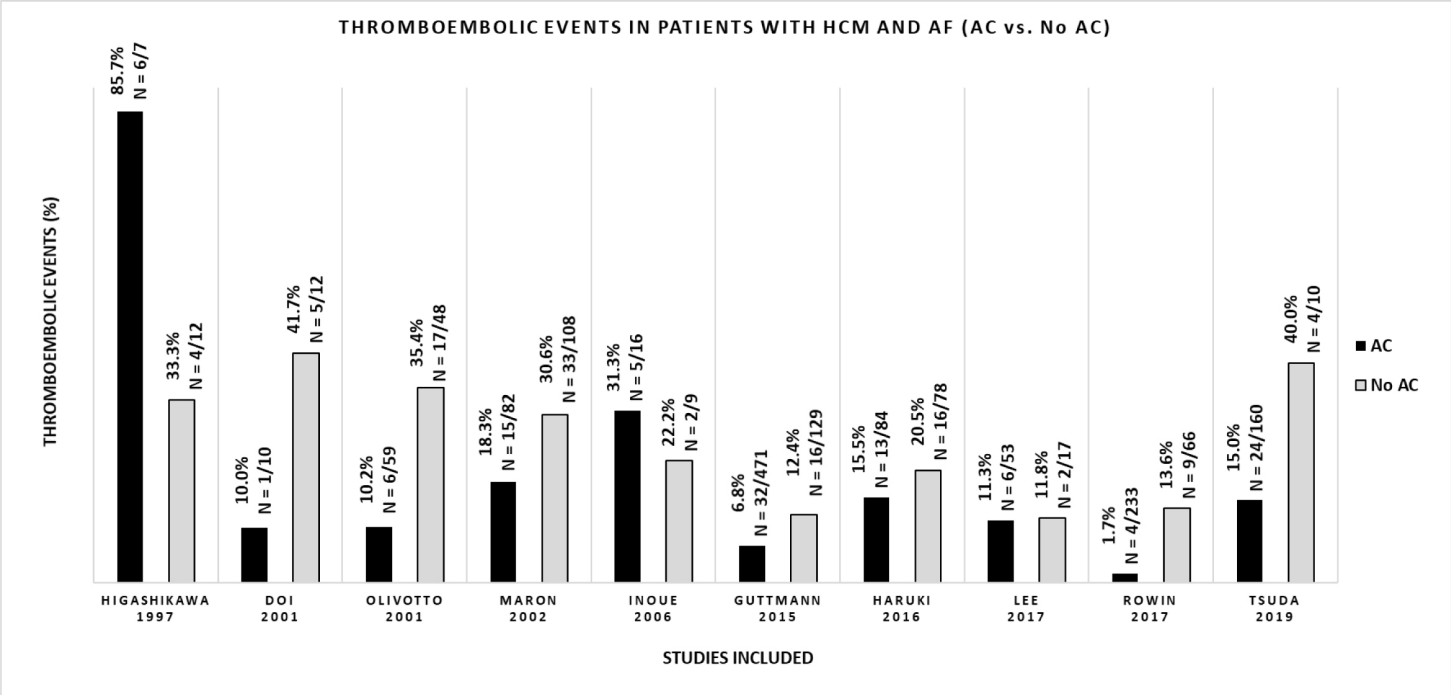

Figure 2A: Percentage of thromboembolic events in patients with HCM and AF who were treated with AC vs. no AC in the individual studies included in this systematic review.

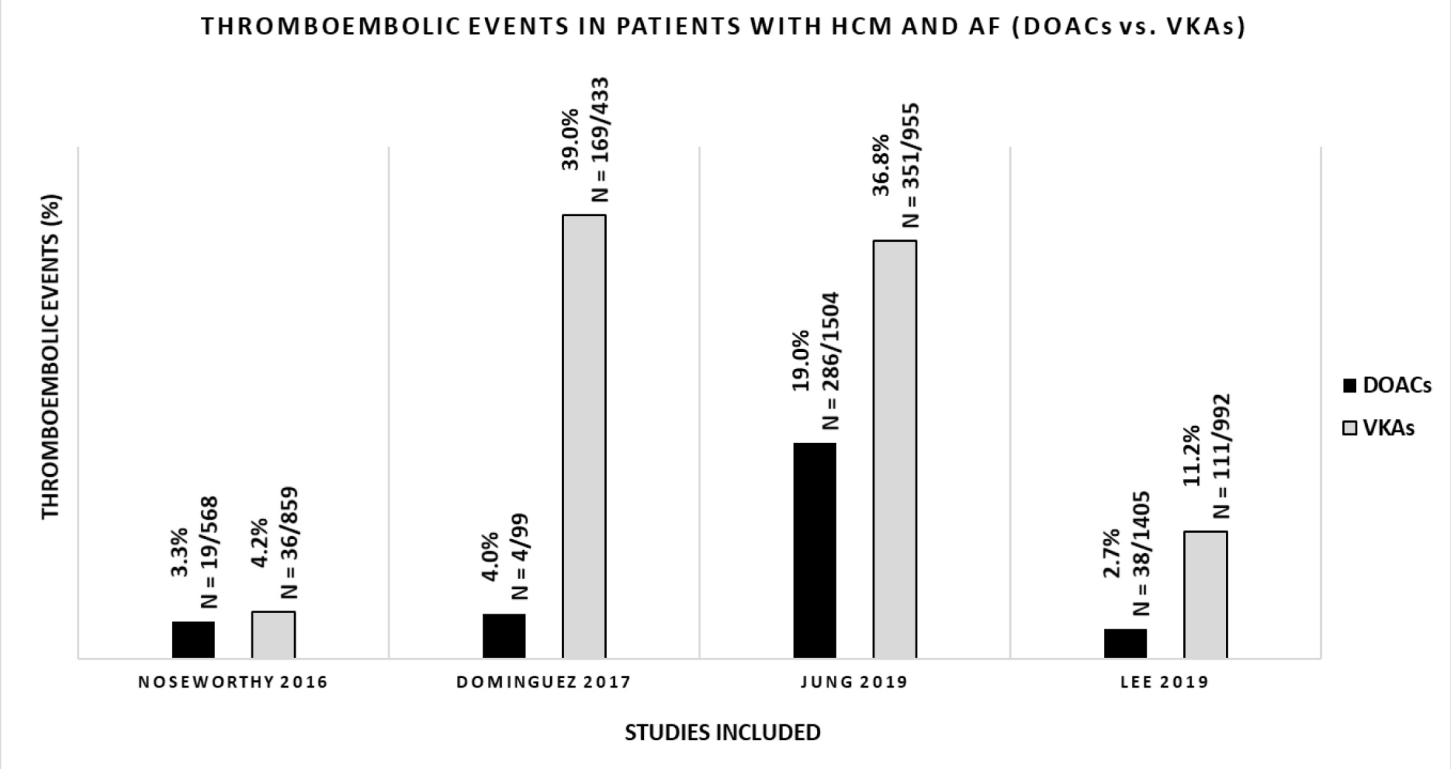

Figure 2B: Percentage of thromboembolic events in patients with HCM and AF who were treated with DOACs vs. VKAs in the individual studies included in this systematic review.

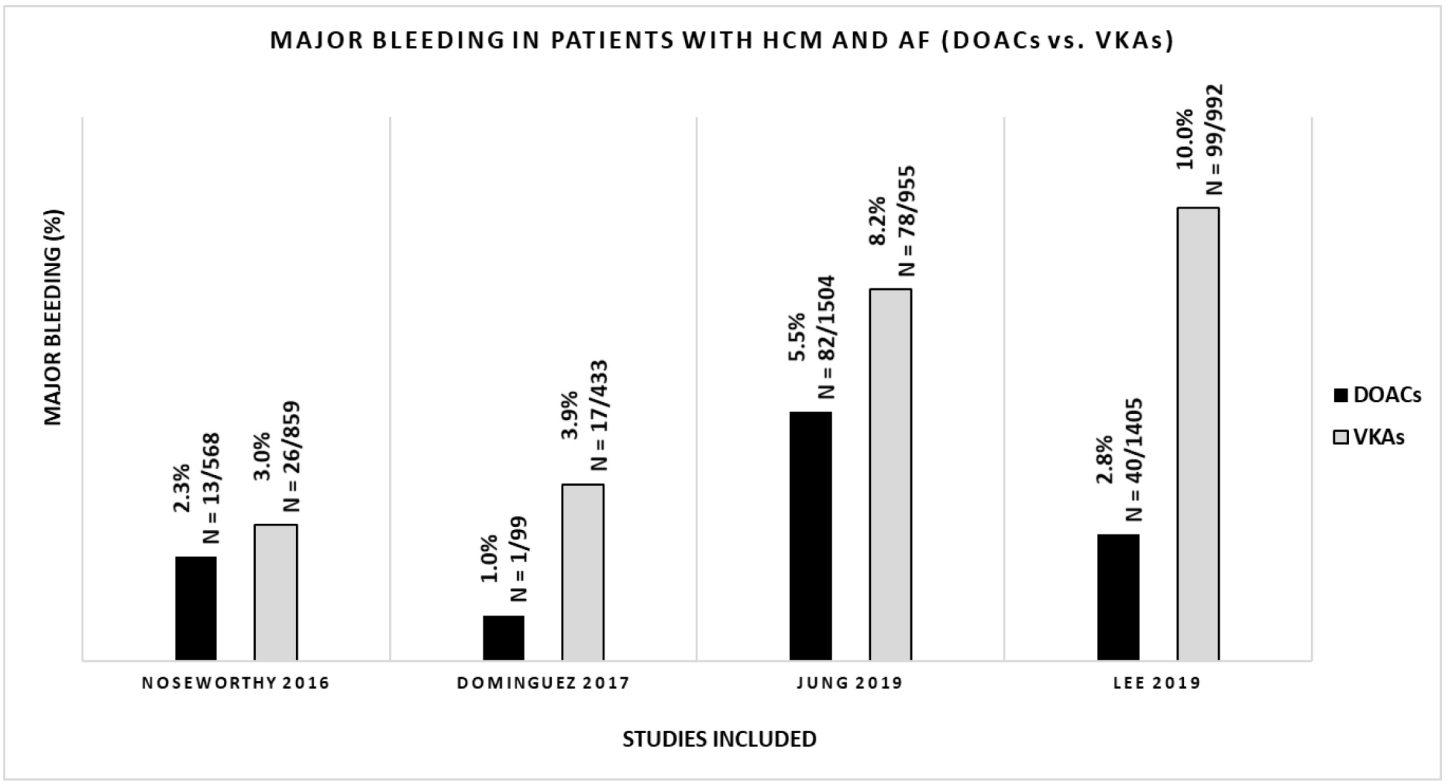

Figure 2C: Percentage of major bleeding events in patients with HCM and AF who were treated with DOACs vs. VKAs in the individual studies included in this systematic review.

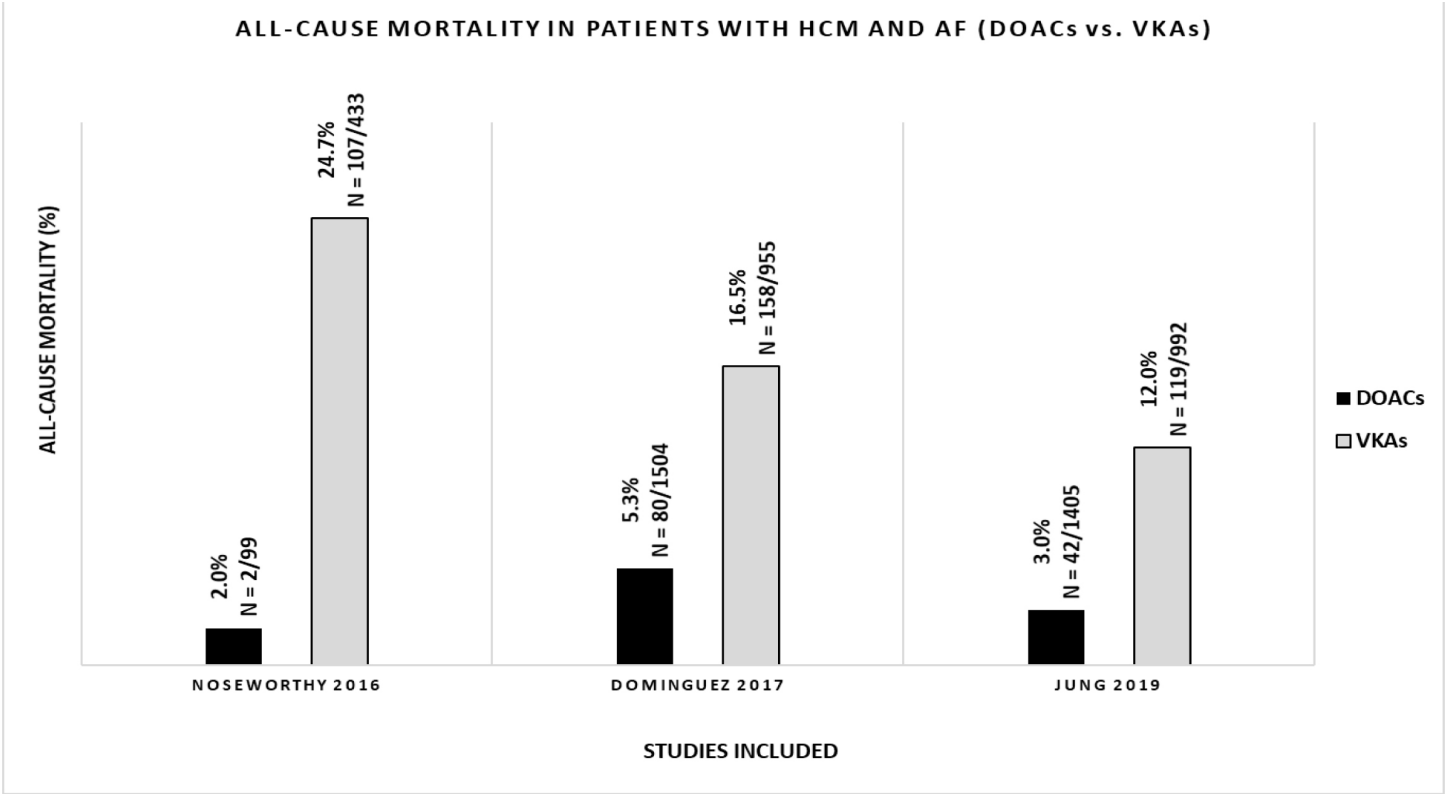

Figure 2D: Percentage of all-cause mortality events in patients with HCM and AF who were treated with DOACs vs. VKAs in the individual studies included in this systematic review.

treatment with AC in this population should not be considered an absolute guardrail against thromboembolic outcomes. Inadequate medication compliance or physician dosing and/or sub-therapeutic INRs in patients taking VKAs could contribute to this, as noted above. However, there were still patients with thromboembolic events from these individual studies that had therapeutic INRs on VKAs at or near the time of thromboembolic events (additionally thromboembolic events occurred in patients receiving appropriate doses of DOACs).

It has been hypothesized that thrombogenesis of the endothelium may be enhanced due to outflow tract obstruction in patients with HCM.[25] This is a possible contributing factor for some of these unexplained events. Another proposed theory suggests thrombosis-inducing anti-cardiolipin antibody is produced by some cell lines of HCM patients when AF occurs.[26] Other pathophysiological factors such as blood stagnation in patients with "end-stage phase" HCM have been implicated.[27] While left ventricular remodeling in children with HCM involves progression of marked wall thickening, the changes seen in some adults can have paradoxically the opposite effect with wall thinning associated with the development of left ventricular cavity enlargement, systolic dysfunction, and eventually congestive heart failure.[28-30] This gradual change in structure of the heart is thought to be the result of extensive myocardiocyte apoptosis and massive replacement fibrosis leading to impaired function and contractility.[27] Standard treatments have not been shown to influence this "end-stage phase" morphologic evolutionary process which may contribute to worse thromboembolic outcomes in HCM patients, especially in the setting of AF. In addition, another study demonstrated that the combination of AF and basal outflow tract obstruction resulting from systolic anterior motion of the mitral valve leaflet can prevent forward flow of blood and possibly contribute to adverse thromboembolic events.[5] This same study eluded to the fact that patients with obstructive HCM may rely on left atrial contraction for left ventricular filling more than non-obstructive patients, and that these same obstructive individuals may be more prone to blood stagnation and development of thrombi.[5]

Utilization of CHA_2DS_2-VASc score

While AC is generally recommended to prevent strokes in the setting of AF with CHA_2DS_2-VASc score ≥ 2, this tool has not been validated in patients with HCM.[1,8] This is due to the many clinical and mechanistic differences inherent to HCM patients.[1,8] Just one study in this systematic review evaluated the utility of this risk stratification tool.[19] Lee et al. found that among HCM patients with AF - those who experienced strokes had a significantly higher CHA_2DS_2-VASc score compared to those who did not have a stroke (5.6 ± 1.7 versus 3.0 ± 1.7, p = 0.002). Interestingly, all patients within this study that had strokes also had CHA_2DS_2-VASc scores greater than two. Inoue et al. recommended modifying the CHA2DS2 -VASc score by adding one point for the presence of HCM as it is an independent risk factor for stroke. A subsequent letter published by Joung et al. in 2019 recommended that HCM be considered as falling into the C criterion of the CHA2 DS2 -VASc score as this cardiac condition typifies heart failure with preserved ejection fraction.[31] While this would be a simple and practical approach to a well-known scoring tool, a HCM population that by itself has a 22.1% incidence of thromboembolic events also supports lifelong anticoagulation without further risk stratification. Future studies further assessing the utility of this adjusted risk stratification tool in this complex subpopulation of HCM patients are warranted, since the statistical weight has not been calculated and validated.

Limitations

Multiple limitations were encountered during this systematic review. First and foremost, this study is based on observational data, with most of the included articles being post hoc subgroup analyses with unmatched cohorts for the AC versus no AC endpoint of thromboembolic events. Potential biases are likely to be greater in these types of studies when compared to RCTs. Second, factors that may predispose patients to thromboembolic events were highly variable and sometimes unable to be accounted for within the individual studies analyzed in this systematic review. These predisposing factors include, but are not limited to, atrial size/stretch, left ventricular outflow tract obstruction, left ventricular mid-cavity obstruction, location predominant/type of hypertrophic cardiomyopathy, history of obstructive sleep apnea or hypertension, diastolic dysfunction, age, or CHA2DS2 VASc score. Moreover, some patients may have been receiving sub-therapeutic doses of VKAs or non-compliant with VKAs and DOACs during the time period that the data was collected. These factors as well as the addition of antiplatelet agents to AC may skew results.

Conclusion

While a relatively small percentage of the HCM population with AF is affected by thromboembolic events, the severity and disabling nature of these events are worth targeting and attempting to eliminate entirely. As we continue in pursuit of optimizing healthcare for HCM patients, implementing evidence-based medicine to improve clinical outcomes, quality of life, and patient satisfaction remain the primary goal. Our study lends additional support to the existing literature that AC is warranted in all patients with concomitant HCM and AF. Furthermore, this is the first systematic review to suggest that DOACs are associated with a lower incidence of thromboembolic events, major bleeding, and all-cause mortality when compared to VKAs. RCTs with larger sample sizes are warranted to help practicing cardiologists further delineate the association of these adverse outcomes and different AC strategies within this complex subpopulation of patients.

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4D Volume Intracardiac Echocardiography for Intraprocedural Guidance of Transcatheter Left Atrial Appendage Closure.

Houman Khalili[1], Marquand Patton[1], Haider Al Taii[2], Priya Bansal[2], Matthew Brady[3], Jeanellil Taylor[3], Arati Gurung[3], Brijeshwar Maini[1,2].

[1]*Tenet Healthcare Corporation, Delray Beach, FL.*
[2]*Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL.*
[3]*Siemens Healthineers, Malvern, PA.*

Abstract

Background: Fluoroscopy and transesophageal echocardiography (TEE) are used to guide transcatheter left atrial appendage (LAA) closure in patients with atrial fibrillation to prevent thromboembolic events. This study examines whether real-time three-dimensional volume ICE guidance (4D volume ICE) can be used as an alternative to TEE during LAA closure (LAAC).

Methods and Results: Fifteen patients with atrial fibrillation (AF), who had high risk for stroke and contraindication for long-term warfarin therapy, were enrolled in the study. The WATCHMAN device was used for transcatheter LAAC under fluoroscopy. LAA and device sizing was performed using TEE and volume ICE guidance from the right heart. Intraprocedural ICE measurements were consistent with TEE; LAA maximal width and depth, and maximal diameter of the implanted device were moderately correlated (Pearson's coefficient: 0.63, 0.65, and 0.71 respectively; $p<0.05$) with good agreement (bias: -0.03 cm, -0.07 cm, and 0.003 cm respectively). The average imaging success rate, defined by the number of patients with all the required intraprocedural measurements, was 67% for ICE and 100% for TEE. The WATCHMAN device was successfully implanted in all patients with a device to patient ratio of 1:33.

Conclusions: 4D volume ICE can be used as an intraprocedural sizing and guidance tool for transcatheter LAAC with measurements comparable to TEE. Challenging patient characteristics significantly degrade the diagnostic image quality when imaging from the right heart. Standardized workflow with proper patient selection and optimal preprocedural planning may improve the diagnostic quality of volume ICE guidance for transcatheter LAAC procedure.

Introduction

Standard intraprocedural guidance for transcatheter left atrial appendage closure (LAAC) employs a multi-modality integrated approach combining fluoroscopy for guiding the delivery system, and transesophageal echocardiography (TEE) for intracardiac characterization to guide device selection and monitor procedural complications[1–6]. Successful implantation of the device is confirmed with contrast-enhanced fluoroscopy and color Doppler flow imaging on TEE. TEE is the current gold standard for procedural guidance but requires general endotracheal anesthesia (GETA) to avoid patient motion and discomfort during the procedure[6]. General anesthesia, however, is associated with pulmonary complications and patient discomfort due to endotracheal intubation[7,8]. Intraprocedural LAAC guidance under local anesthesia or conscious sedation might help mitigate these GETA-related disadvantages and has motivated multiple clinical studies, including a systematic review[9] and a meta-analysis[10], which have established intracardiac echocardiography (ICE) as a safe and feasible alternative to TEE[4,7,8,11–20].

ICE guidance for LAAC can be provided by placing the catheter, introduced via a femoral venous access, either on the right atrium[11,12,14–16], the right ventricular outflow tract[14], coronary sinus[15], or the left atrium[13,16–20]. Comparatively superior image quality and thus diagnostically optimal guidance for LAAC procedure are obtained with the left atrial ICE approach. This however requires a transseptal access to advance the catheter from the right atrium into the left atrium, either via the same transseptal puncture used for device delivery[17,18] or via a second puncture[8,13]. The residual transseptal shunt is shown to be clinically acceptable for ICE guidance when using 8Fr or 10Fr catheters. While the 2D ICE can provide adequate intraprocedural guidance, the real-time three-dimensional (3D) volume ICE (i.e. 4D volume ICE) can improve characterization of the LAA anatomy and its complex 3D morphology compared to 2D ICE[21,22]. The volumetric acquisition in real-time and in 3D allows the 4D volume ICE technology to reduce the need to acquire images from different anatomical locations wherein the coronal plane allows planar assessment of the LAA anatomy, facilitates spatial orientation, and provides circumferential peri-valvular as well as peri-device flow assessment using Color Doppler.

The primary drawback of the previous generation of 4D ICE was

Key Words

LAA Closure, WATCHMAN, TEE, ICE.

Corresponding Author
Brijeshwar Maini, MD, FACC
Clinical Professor of Medicine, Florida Atlantic University
Regional Medical Director of Transcatheter Therapies
Tenet Healthcare Corporation
4205 W. Atlantic Ave, Suite 201B Delray Beach, FL 33445

a smaller field of view with limited echo views. The new generation of 4D volume ICE offers a larger imaging volume of 90˚ x 50˚ with multiplanar reformatted (MPR) echo views for anatomical landmarks and procedural guidance including sizing (see Supplemental Video 1). We hypothesize that the additional MPR echo views and the anatomical landmarks from the larger imaging volume provide optimal LAAC intraprocedural guidance similar to TEE. This study reports our early clinical experience of using the enhanced 4D volume ICE system for intraprocedural imaging guidance of LAAC with WATCHMANTM (Boston Scientific, Natick, MA), and examines the performance of right sided ICE for LAAC guidance in comparison to TEE.

Methods

Patients with permanent or paroxysmal atrial fibrillation, $CHADS_2$-VASc > 2, and contraindication to long-term warfarin therapy were recruited for study participation. Pre-procedural TEE assessment was performed one week to a month prior to the procedure date to rule out the presence of intracardiac thrombus and to assess the dimensions and morphology of the LAA for transcatheter LAAC suitability; patients with LAA thrombus or pericardial effusion were excluded. Participants provided written informed consent prior to enrollment. The study was approved by the institutional review board (DEL16036). Patients were evaluated for the presence of pericardial effusion and thrombus using both TEE and ICE prior to the procedure.

WATCHMAN System and Protocol

The WATCHMAN system consists of a delivery sheath with a pre-packaged occluder. The occluder size was selected based on the maximal diameter of the LAA orifice following the manufacturer guidelines, and using the maximal length of the LAA measured on echocardiogram [Figure 1]. Intraprocedural measurements of the LAA width and depth were acquired on both ICE and TEE per protocol. Both ICE and TEE were used to assess for any procedural complications prior to insertion of the device delivery sheath. Under fluoroscopy and echocardiography, a Baylis wire and the device delivery sheath were introduced through the right femoral vein for transseptal puncture. The delivery sheath was subsequently placed into the LAA and the device was deployed after "the tug test" under both ICE and TEE. Success of the WATCHMAN implantation was evaluated via imaging measurements of the device diameter for proper positioning and compression, and color Doppler flow assessment for any peri-WATCHMAN leak. The WATCHMAN occluder was released after confirmation of a successful implantation or removed and replaced with a corrected size until a successful implantation was confirmed. The device per patient ratio was thus calculated as the total number of WATCHMAN selected divided by the total number of WATCHMAN successfully implanted. The manufacturer clinical specialist was present for each of the LAAC procedure.

Intraprocedural Imaging Guidance

Intraprocedural LAAC guidance was provided simultaneously with ICE and TEE via 2D and 4D visualization, 2D and 3D measurements, and color Doppler flow imaging. TEE was performed under general anesthesia using the Z6M transesophageal transducer probe connected to an echocardiogram. ICE was performed by introducing a 12.5Fr ICE catheter into the left femoral vein via a 14Fr delivery sheath and advanced into the right atrium via the inferior vena cava [Figure 2A]. The entire procedure was performed by placing the ICE catheter in the right side of the heart; the ICE catheter was placed in the right atrium and advanced into the right ventricle (RV) or the right ventricular outflow tract (RVOT) in patients where image quality was degraded due to challenging characteristics such as enlargement of the atrial chambers or the inter-atrial septum. The sterile ICE catheter was connected to a second echocardiogram via a SwiftLinkTM adaptor. The intraprocedural ICE workflow constituted acquisition of a reference frame, known as the "home view" wherein the right atrium, the tricuspid regurgitation, and the right ventricle are visualized for reference [Figure 2B]. The inferior and posterior portion of the interatrial septum were visualized for transseptal puncture guidance ([Figure 2C] and Supplemental Video 2) followed by left atrial characterization including the LAA sizing for device selection [Figure 1]. Lastly, the selected device was deployed into the LAA followed by a tug test to ensure proper positioning and compression, under contrast-enhanced fluoroscopy before releasing the device [Figure 2D].

Intraprocedural Volume ICE Workflow

The LAA and the WATCHMAN device were characterized from multiple viewing angles, akin to TEE, by methodically orienting the multiplanar images reconstructed from the volume images[23]. Every effort was made to obtain the equivalent views on the 4D volume ICE that correspond to the requisite angles 0˚, 45˚, 90˚, and 135˚. A step-by-step description of a typical 4D volume ICE workflow for acquiring the four equivalent views of TEE is given below:

Table 1: Patient baseline and procedural characteristics

Baseline Characteristics	Mean ± SD or Number
Age (years)	75.6 ± 10
Number of patients	15 (4 female; 27%)
Body Mass Index (kg/m2)	28 ± 4
Indication for Exam	
Permanent atrial fibrillation	12/15 (80%)
Paroxysmal atrial fibrillation	3/15 (20%)
$CHADS_2$-VASc Score	4.6 ± 1
Procedure time (min)	102 ± 25
Fluoroscopy time (min)	16.07 ± 7*
Fluoroscopy dose (mGy)	858 ± 792*
Contrast Agent (ml)	
Visipaque	2/15 (80-190)
ISOVUE-300	13/15 (75-175)
WATCHMANTM Device	
21 mm	2/15 (13%)
24 mm	3/15 (20%)
27 mm	7/15 (47%)
30 mm	2/15 (13%)
33 mm	1/15 (7%)
Device per patient	20/15 (1.33)
Overestimation	3
Underestimation	2
Imaging Measurement Success Rate for ICE	10/15 (67% overall)
LAA Width	14/15 (93%)
LAA Depth	12/15 (80%)
Device Diameter	11/15 (73%)

ICE = Intracardiac Echocardiography; LAA = Left atrial appendage; SD = Standard deviation; *Outlier removed

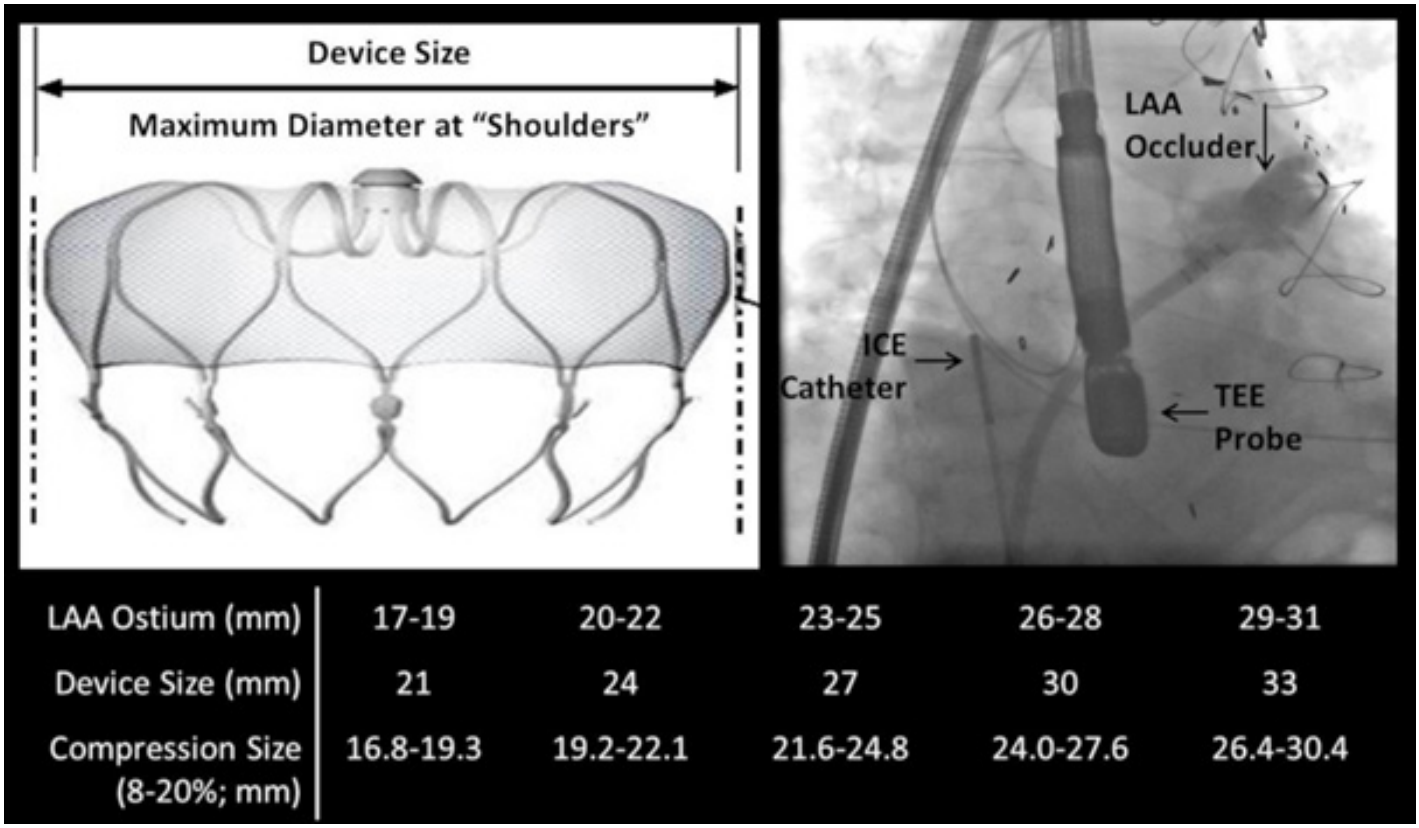

Figure 1: **Device selection criteria for LAA closure. The physical device size is defined as the maximum "shoulder-to-shoulder" diameter of the device and is selected using the manufacturer's guidelines based on the LAA ostium width measured on TEE, ICE or angiogram (left illustration with permission from Boston Scientific). Post deployment, adequate compression of the device is measured.**

Step 1: With the ICE catheter tip placed in the middle right atrium, via the inferior vena cava, the ICE catheter can be rotated clockwise to visualize the LAA or the device.

Step 2: Once a 2D image visualizing the largest diameter of the LAA or the device is acquired, the imaging is 'suspended' or put 'on freeze'; this allows the operator to methodically rotate the corresponding planar lines on the MPR planes to view the LAA or the device at any angle of interest e.g. at TEE-equivalent 0˚.

Step 3: With the planar tools locked orthogonally, the adjacent green plane becomes the TEE-equivalent 90˚ view.

Step 4: Rotating these 0˚ and 90˚ views clockwise by 45˚ will then generate the imaging planes at 45˚ and 135˚ respectively.

On both TEE and ICE, the LAA orifice width was measured on the coronal plane along the short axis (SAX) and the long axis (LAX) ([Figure 3]; A: TEE, B: ICE), and on the non-coronal plane ([Figure 3]; C: TEE, D: ICE). The LAA depth was measured from the center of the orifice to the apex of the appendage [Figure 3C-D]. The size of the compressed device was measured on both ICE and TEE [Figure 4]; A: TEE, B: ICE) targeting an average compression of 8% to 20% relative to its physical dimension. Color Doppler was used for peri-device leak assessment on both TEE [Figure 4C] and ICE [Figure 4D] and Supplemental Video 3). All the required measurements were acquired from multiple angles including the 2D orthogonal planes reconstructed from the 3D volumes. The ICE measurements were performed prior to the TEE measurements in the last 12 patients to avoid measurement bias. The manufacturer clinical specialist was present for ICE imaging for each of the procedure; TEE was performed by a separate operator.

Measurements and Statistical Analysis

The LAAC procedure duration was calculated from the time of the first groin puncture for venous access to the time when the device delivery sheath was removed. The diagnostic fluoroscopy duration, the air karma radiation dose, and the total procedure duration were analyzed for each of the 15 patients, and accounted for the combined TEE and ICE guidance. Three intraprocedural imaging measurements were required for a successful LAAC guidance: the LAA orifice maximal width, the LAA maximal depth, and the device maximal diameter post implantation. Failure to acquire any of these three measurements was counted against the success rate of the imaging modality for guiding LAAC procedures. The average imaging success rate of TEE and ICE for LAAC guidance was defined by the number of patients with all three intraprocedural measurements. The imaging success rate was calculated for each of the three measurement variables.

The maximal orifice width and depth of the LAA and the maximal diameter of the implanted device were compared between TEE and

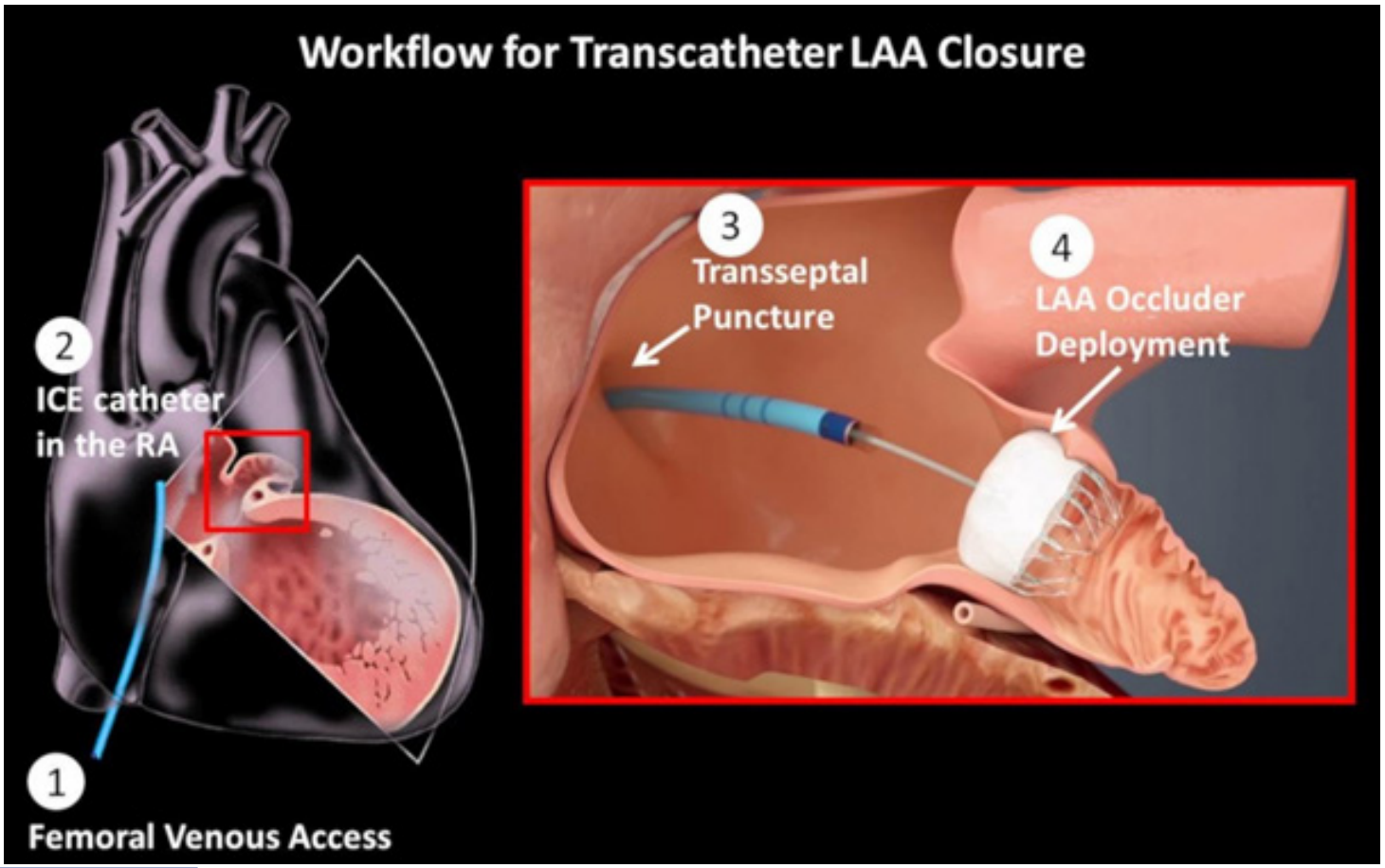

Figure 2A: 2A: LAAC workflow illustration using 4D Volume ICE guidance. The ICE catheter is introduced via a femoral venous access into the right atrium (RA). Under echo guidance, a Baylis wire is used for interatrial transseptal puncture for delivery of the occluder device into the LAA under fluoroscopy (right illustration with permission from Boston Scientific).

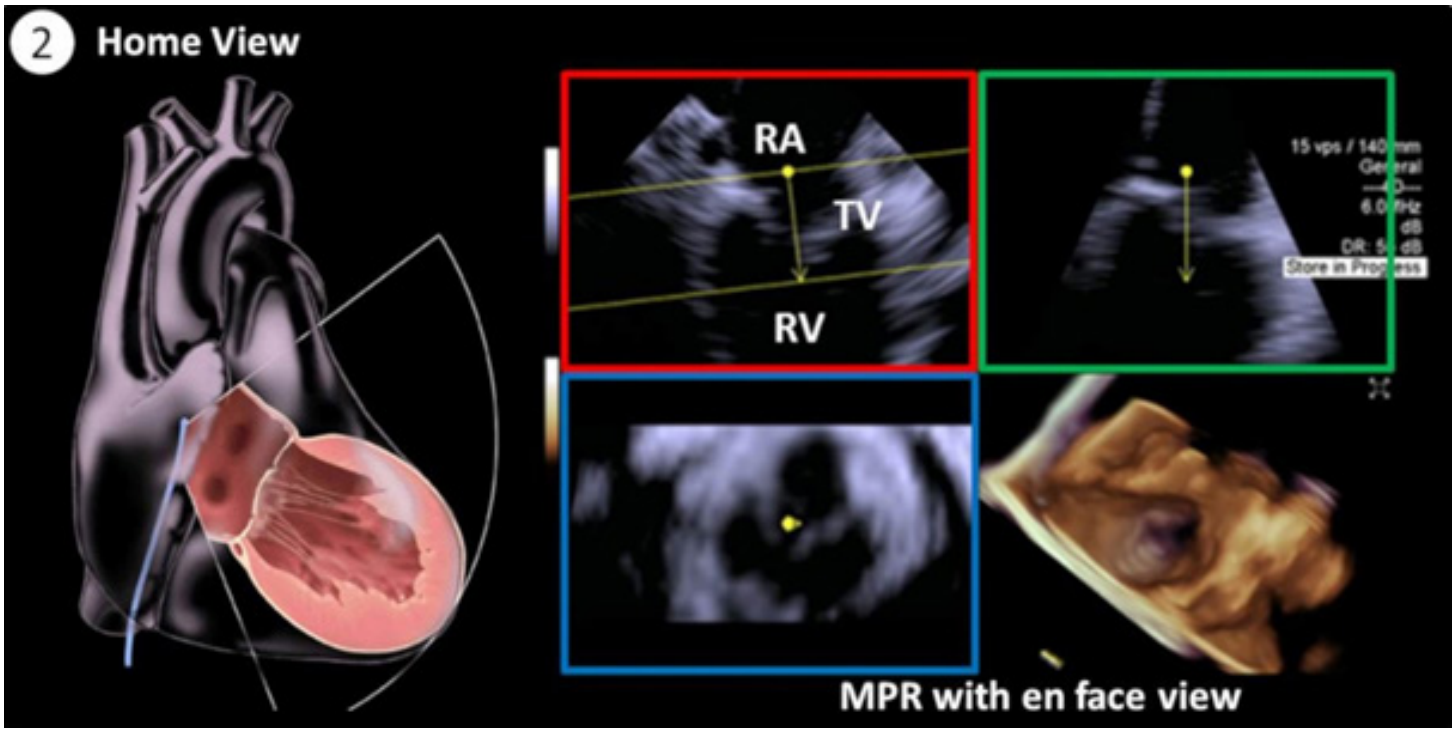

Figure 2B: 2B: Home View. With the ICE catheter positioned in the right atrium, the anatomical landmarks are visualized to establish spatial orientation (see Supplemental Video 1): a Home View consists of the right atrium (RA), the tricuspid valve (TV), and the right ventricle (RV). The catheter probe is swept to assess for any contraindications in this view and orthogonal multiplanar reformatted (MPR) planes.

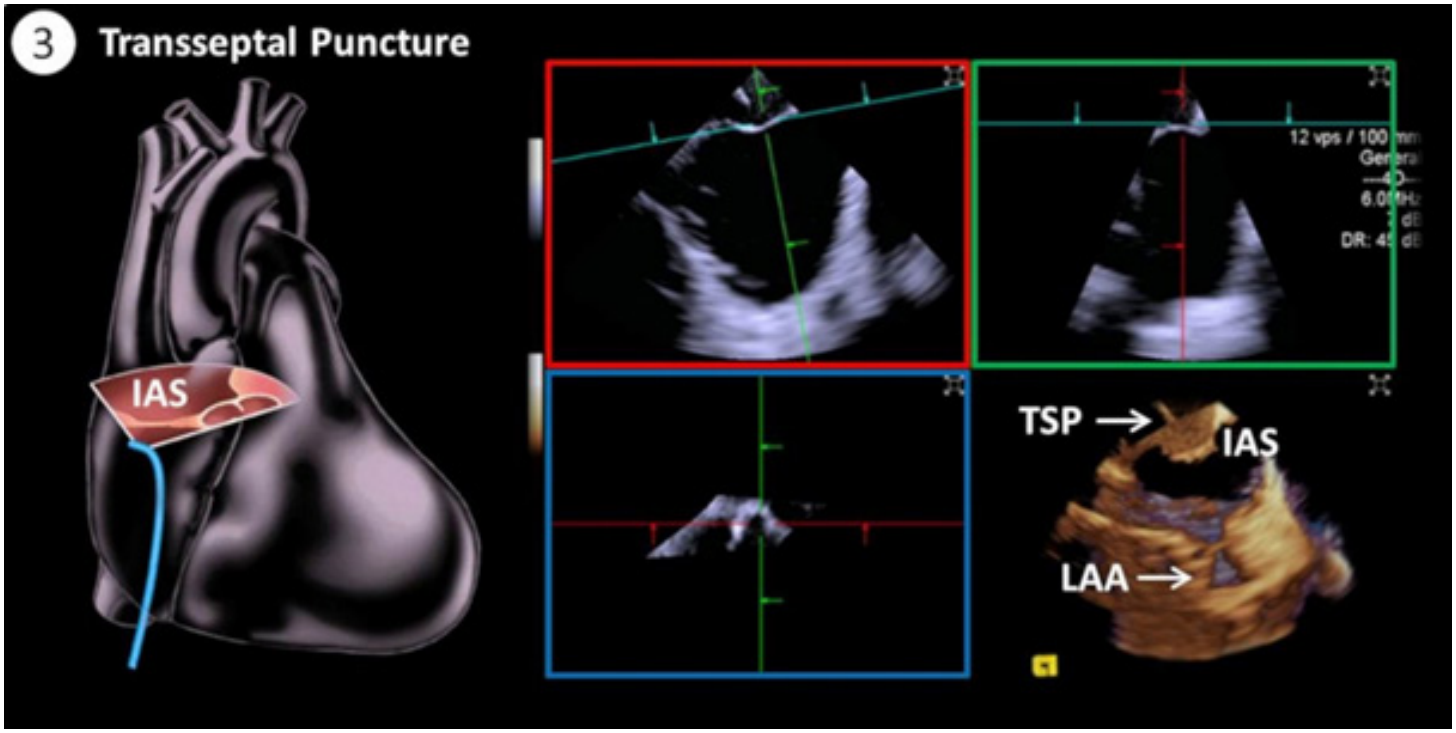

Figure 2C:	2C: Transseptal Puncture. ICE from the right heart is used to visualize the interatrial septum (IAS) to guide the Baylis wire for a transseptal puncture. 4D ICE MPR and en face views can be used for TSP guidance (see Supplemental Video 2).

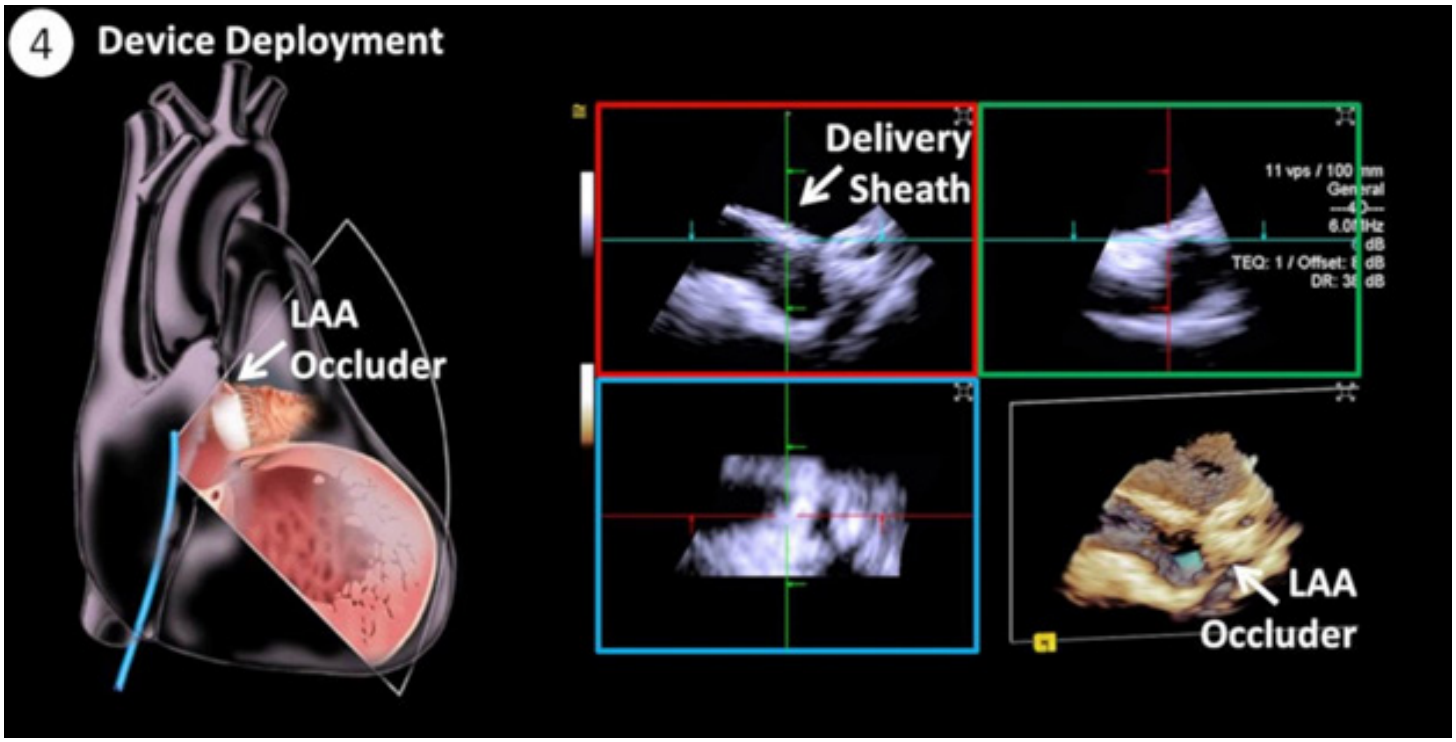

Figure 2D:	2D: Device Deployment. Under fluoroscopy, the WATCHMAN LAA occluder device is deployed via a delivery sheath which can be visualized under ICE (See Supplemental Video 3) and TEE. The compression measurement of the occluder is taken on multiple views to determine adequate device positioning and seal following the manufacturer's guidelines for device release.

ICE. The degree of correlation was calculated using the Pearson correlation coefficient (r) and the degree of agreement between the two modalities was assessed using the Bland-Altman method; two standard deviations were used to calculate the 95% limits of agreement and a normality test was performed. Statistical significance was considered at a p-value (p) of less than 0.05. Multiple measurements of the LAA orifice width and depth, and the device diameter post implantation were acquired from 2D images only. The Grubb's test was used to detect outliers. All statistical analyses were conducted using Minitab (version 18, Pennsylvania, USA).

Results

From March 2018 through February 2019, 18 consecutive patients were recruited; 15 patients agreed to participate in the study. Atrial fibrillation was paroxysmal in two patients and permanent in 13 patients (87%) with a $CHADS_2$-VASc score of 4.6±1. All 15 patients (age 78.6±8 years, BMI 28±4 kg/m2, 4 female) underwent successful WATCHMAN implantation [Table 1]. No major adverse cardiac events were observed during the procedures.

Procedural Characteristics

TEE was used for preprocedural LAAC planning. The LAAC procedure was performed under fluoroscopy with a mean air karma radiation dose of 858±792 mGy and a mean diagnostic fluoroscopic duration of 16±7 minutes; the air karma radiation dose for the first patient in the study was 10523 mGy which was detected as an outlier and removed from the mean dose calculation [Table 1]. Visipaque (80 ml to 190 ml) contrast was used in 2 patients whereas ISOVUE-300 (75-175 ml) was used in 13 patients to assess proper positioning of WATCHMAN for adequate LAA occlusion. The average procedure duration was 102±25 minutes.

The WATCHMAN device size varied among the patients from 21 mm to 33 mm with the most common size of 27 mm (47%; [Table 1]).

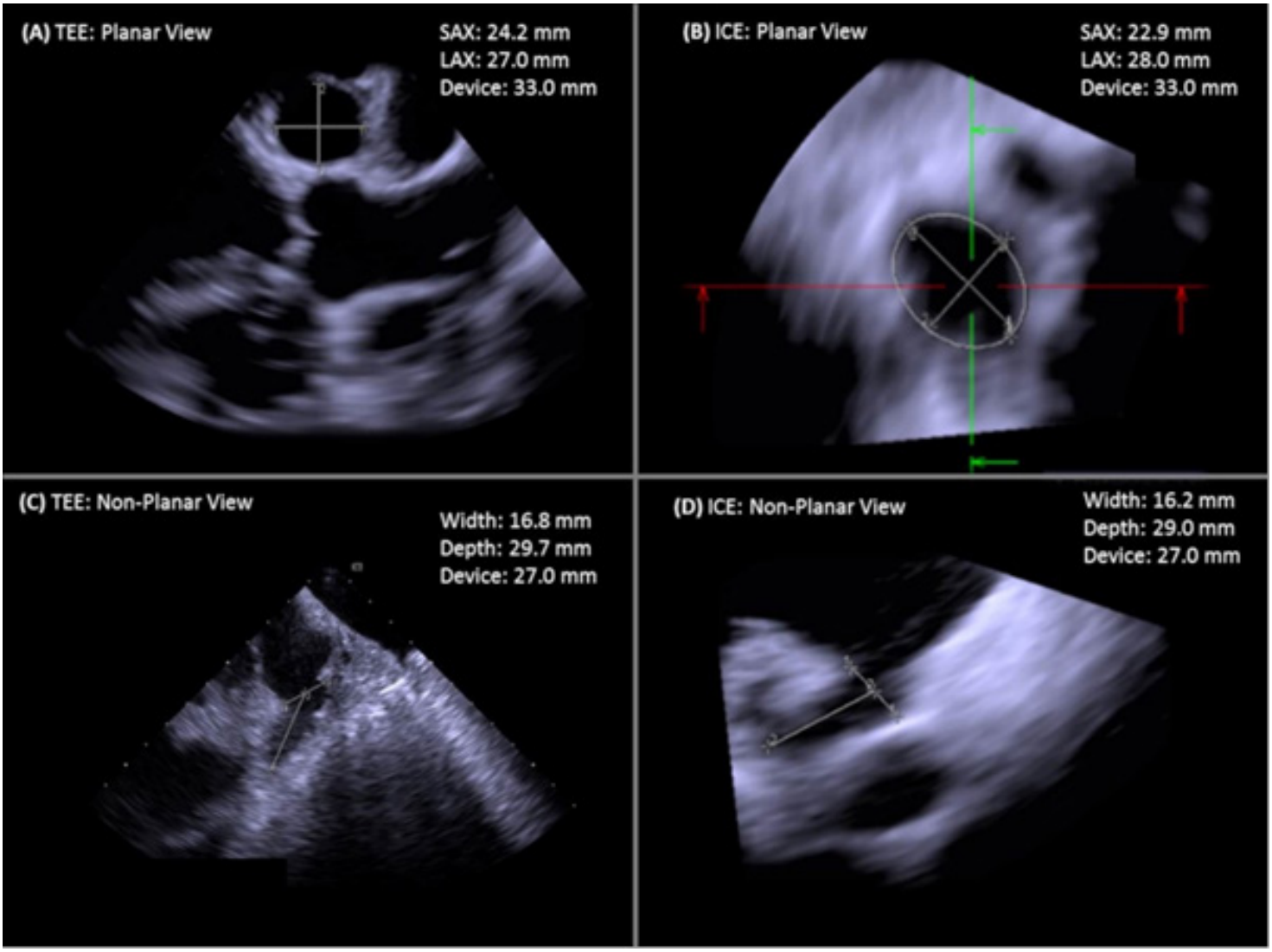

Figure 3: LAA Sizing. LAA orifice width and depth are measured on multiple views on both TEE and ICE using planar (A and B; SAX: short axis, and LAX: long axis) and non-planar (C and D) views, to determine the maximal LAA sizing for device selection per the manufacturer's guidelines.

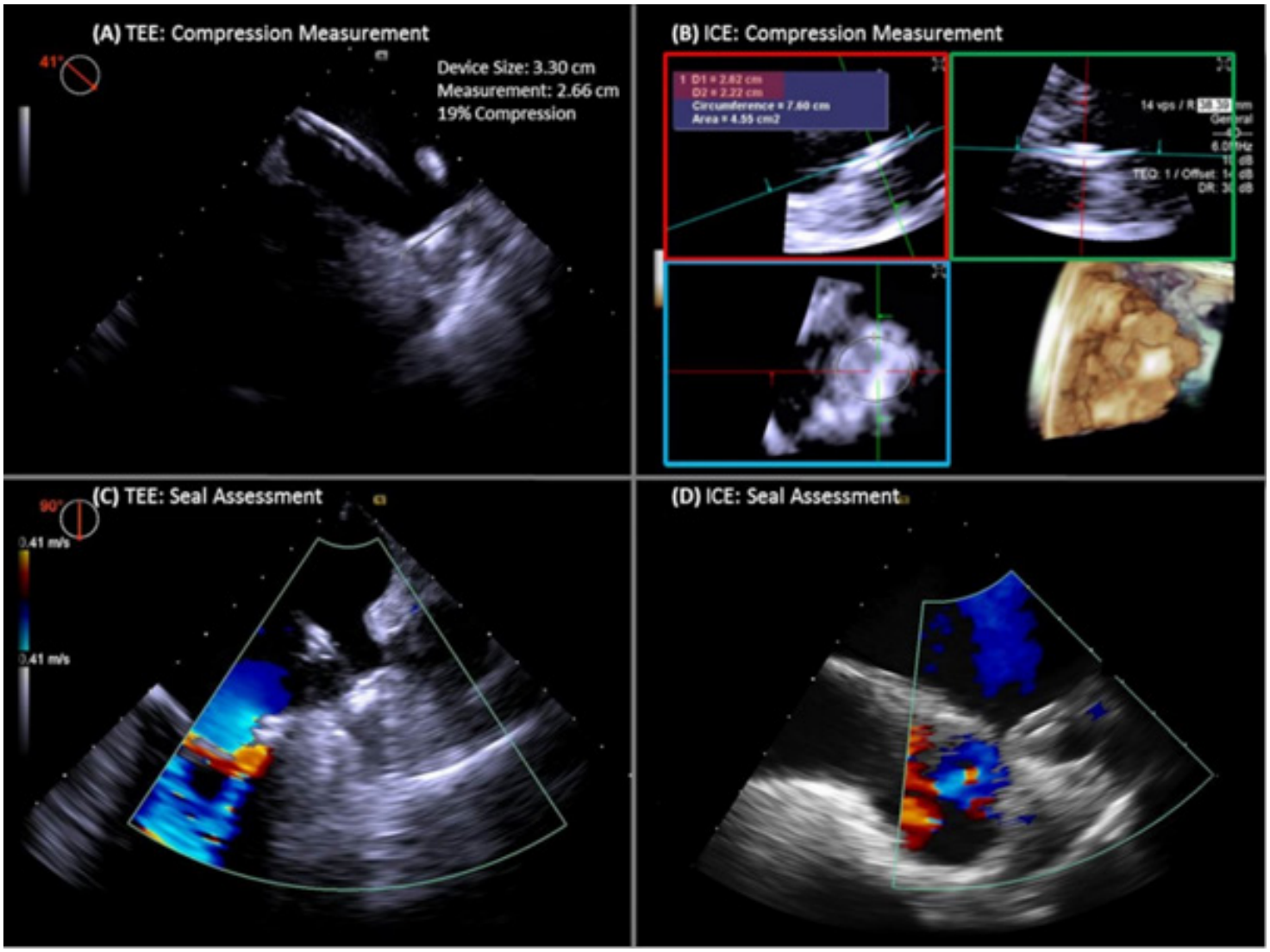

Figure 4: **Compression Measurement. The device release criteria is followed to ensure adequate positioning, anchoring, sizing, and seal. Compression measurements are taken on both TEE (A) and ICE (B) to determine the adequate compression rate. Tug test is performed for adequate anchoring prior to device release, and Color Doppler flow is used to assess for peri-device leak (C and D; see Supplemental Video 3).**

The average device to patient ratio was 1.33 (20/15; the initial device size was overestimated in 3 patients and underestimated in 2 patients). Intraprocedural imaging guidance for LAAC was provided with TEE and volume ICE; the ICE catheter was positioned in the right atrium for all the 15 patients. The LAA orifice width was successfully measured with volume ICE imaging from the right heart in 14 out of 15 patients (93%). The LAA depth was successfully measured in 12 out of 15 patients (80%), and the diameter of the implanted device was successfully measured in 11 out of 15 patients (73%). On average, the three required measurements were successfully acquired with right sided ICE in 10 out of 15 patients (67%); the success rate for TEE was 100% for all the three measurement variables. The 5 patients with the missing measurements had challenging intracardiac morphology such as thickened interatrial septum or atrial hypertrophy that caused significant signal attenuation, or had highly calcified intracardiac tissues with previously implanted artificial valves that caused significant artifacts rendering the ICE image quality diagnostically insufficient.

Intraprocedural Measurements

ICE measurements were consistent with TEE [Figures 3-4, Figure 5A]. The LAA orifice maximal width was 2.35±0.4 cm with TEE versus 2.41±0.5 with ICE (a 3% discrepancy in LAA sizing). The LAA maximal depth was 3.14±0.7 cm with TEE versus 3.14±0.6 cm with ICE. TEE and ICE measurements of the LAA orifice maximal width and the LAA maximal depth were moderately correlated (r = 0.63 and 0.65 respectively, both significant at $p<0.05$) with a systematic bias of -0.03 cm [-0.78, 0.72], and -0.07 cm [-1.32, 1.19] respectively ([Figure 5B-C] respectively). The device maximal diameter or compression with TEE was 2.23±0.3 cm with an average compression rate of 15% compared to 2.27±0.3 cm with an average compression rate of 14% with volume ICE (a 2% discrepancy in device sizing); moderate correlation (r = 0.71, $p<0.05$) with a systematic bias of 0.008 cm [-0.24, 0.25] was observed [Figure 5D]. The procedure duration, including the diagnostic fluoroscopy duration was randomly distributed over the course of the study [Figure 6] and comparable to

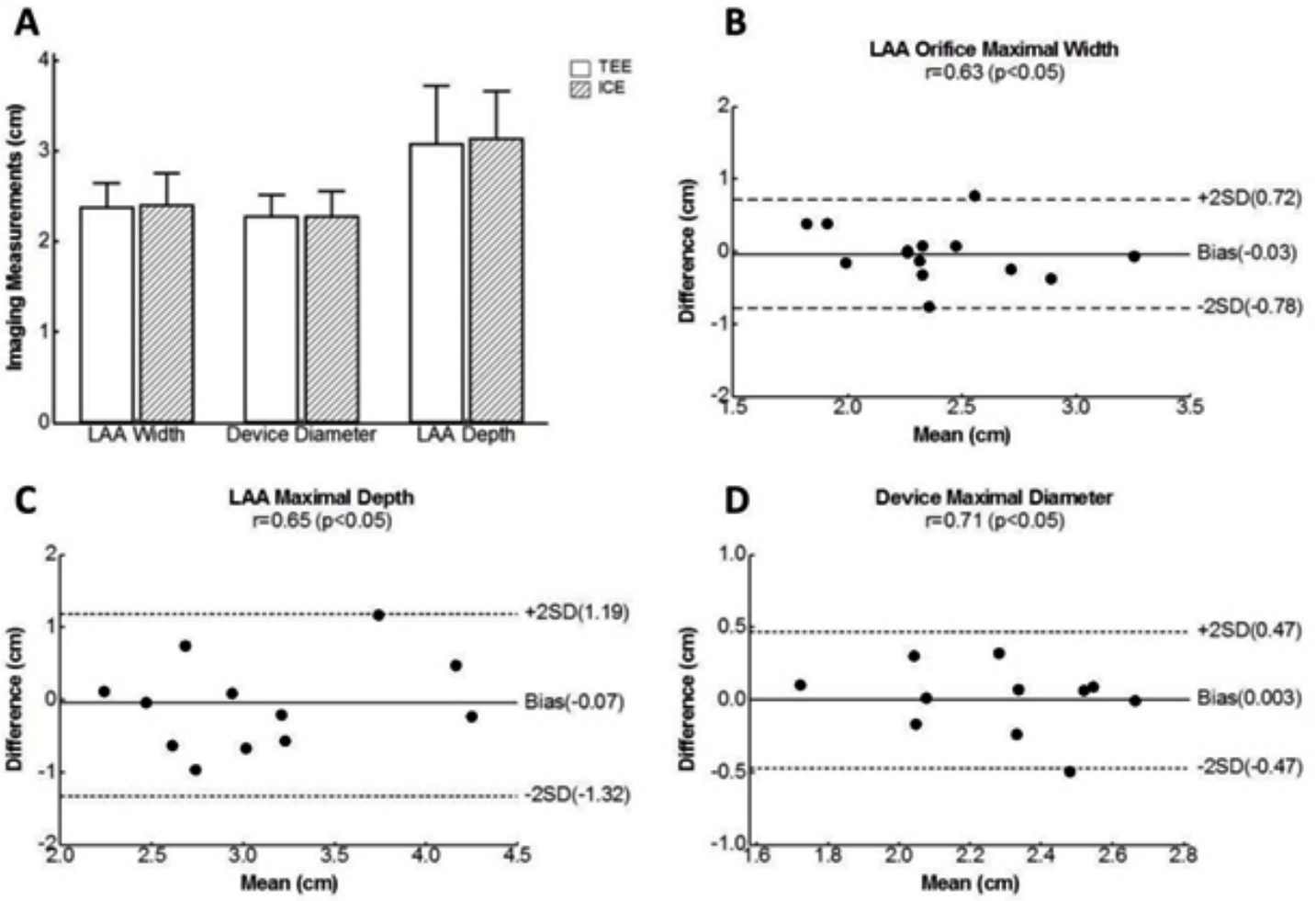

Figure 5: **Correlation and Agreement Analysis. TEE and ICE measurements of LAA maximal width and depth, and the device maximal diameter (A) were moderately correlated with good agreement (B, C and D respectively); r = Pearson's correlation coefficient; SD = Standard deviation; 2SD was used to calculated the 95% limits of agreement.**

values reported in literature[7,8,11,13,17–19].

Discussion

The main finding of this study is that volume ICE from right heart can be used for intraprocedural sizing and guidance for transcatheter LAAC with measurements comparable to TEE. Proper patient selection, however, is essential for imaging success given the LAA distance from the right atrium and challenging patient characteristics such as interatrial hypertrophy or enlarged left atrium with calcific tissues that can impair the diagnostic image quality.

Procedural Outcome

Our study adds to the growing body of literature establishing transcatheter left atrial appendage closure as a standard alternative to anticoagulation therapy for prevention of thromboembolic events in patients with atrial fibrillation. Atrial fibrillation accounts for 20% of all strokes, and LAA remains the primary source of thromboembolism in 90% of the patients with atrial fibrillation[1]. This has motivated the development and advancement of mechanical devices for transcatheter occlusion of the LAA. The WATCHMAN system is the only transcatheter device approved by the United States Food and Drug Administration (FDA) for LAAC. Transcatheter LAAC has shown to reduce risk of thromboembolic events such as stroke and systemic embolism comparable to warfarin[24,25]. LAA was successfully occluded with the WATCHMAN device, with adequate positioning and implantation of the device confirmed by contrast-enhanced fluoroscopy, TEE and ICE. Color Doppler was adequately used on both TEE and ICE for peri-WATCHMAN leak assessment on all 15 patients; no significant leak was observed.

An average of 1.33 WATCHMAN devices was deployed per patient in this study which is comparable to 1.8 devices per patient reported in the first half of the PROTECT AF study[24], 1.38 reported in the post-FDA approval study[25], 1.1 reported in the LAAC study using TEE and 2D ICE[11,16], and 1.25 reported in the LAAC study using TEE and 3D computed tomography (CT) image guidance aided with 3D LAA prototyping for LAAC planning[4]. In the latter study, patient-specific 3D prints of LAA were reconstructed from its preprocedural 3D CT image and used for device selection by test-fitting the WATCHMAN device, ex-vivo, in situations

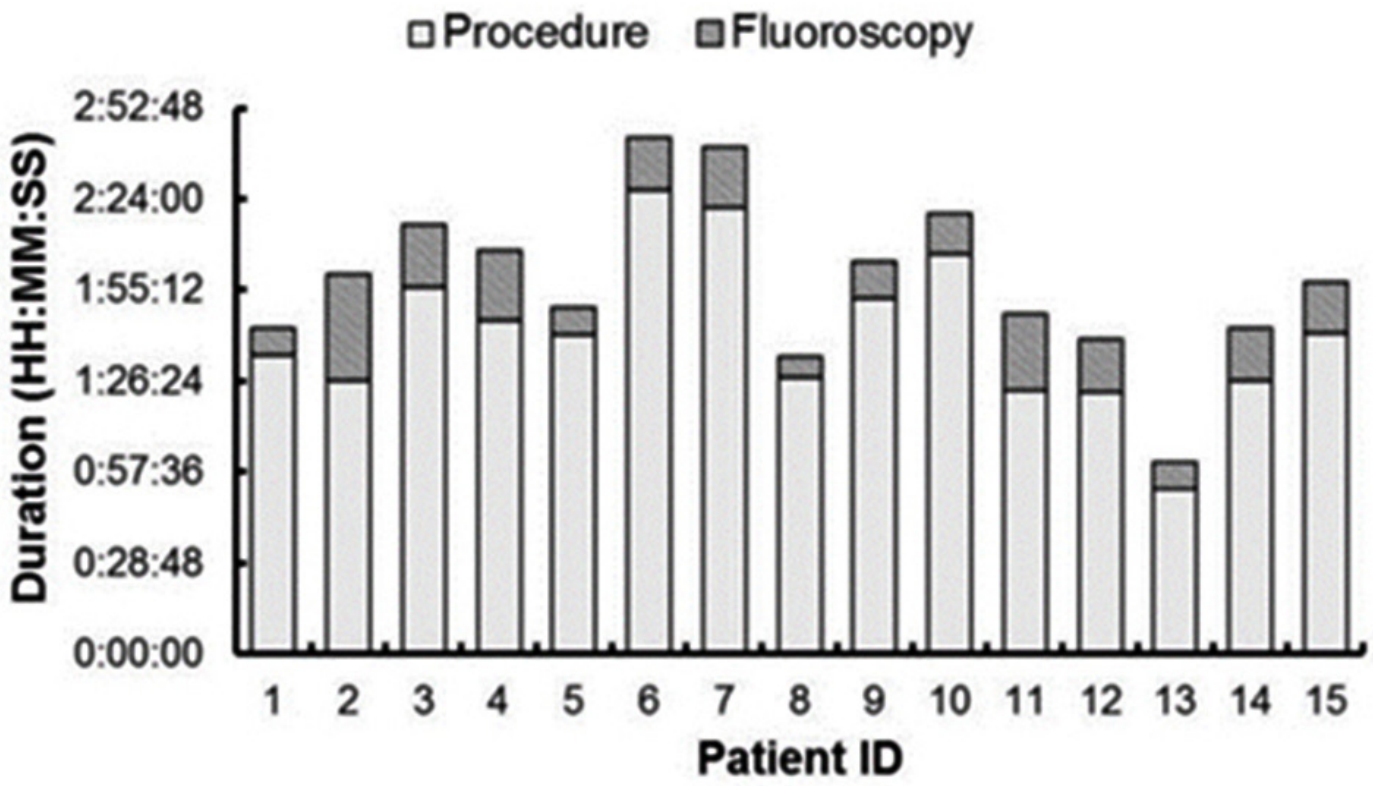

Figure 6: **Procedural Characteristics. On average, the procedure duration (white) and the diagnostic fluoroscopy duration (stacked striped) were randomly distributed and comparable to reported values.**

where the LAA ostium was ambiguous. The supplemental 3D printing for LAAC planning combined with 3D CT guidance for WATCHMAN implantation was shown to reduce the procedure duration to 48 minutes (±11) by providing accurate sizing. With the increasing role of 3D printing in the preprocedural planning of a wide range of structural heart interventions, low-cost options for rapid 3D prototyping have emgerged[26]. This is beneficial for LAAC planning given the complex morphology of the LAA[17,26], and could potentially benefit intraprocedural ICE guidance.

Our data demonstrated the feasibility of right sided 4D volume ICE guidance for LAAC, avoiding procedural complications associated without the need for transseptal access. Identifying the anatomical landmarks, e.g. the Aortic Valve, facilitates spatial orientation and confidence in catheter navigation. We found that certain intracardiac tissue characteristics could significantly affect the diagnostic image quality. Imaging of the LAA from the right atrium or right ventricle demands a larger imaging depth requiring the ultrasound signal to travel through the interatrial septum. Larger attenuation in the presence of highly muscular or fibrous interatrial septum or fossa ovalis can greatly reduce the diagnostic image quality of LAA. Atrial hypertrophy or enlargement can have a similar effect on the image quality as observed in this study and previously reported by Matsuo et al[16]. The image quality becomes diagnostically insufficient in the presence of acoustic shadowing and reverberation artifacts caused by highly calcified cardiac tissues such as a calcific aortic valve or annular calcification, or in the presence of mechanical or bioprosthetic valves. Imaging from the right ventricular outflow tract, the left atrium, the coronary sinus, or the proximal pulmonary allows optimal visualization of the LAA although with a steeper learning curve[9,14]. These alternatives were not attempted in this study since the objective was to evaluate the performance of ICE guidance from the right heart for LAAC in comparison to TEE.

Intraprocedural Measurements

Intraprocedural TEE and ICE measurements of the maximal width and depth of the LAA, and the compressed WATCHMAN diameter showed moderate correlation and good agreement. Overall, volume ICE tends to overestimate the LAA dimensions compared to TEE similar to the findings reported by Matsuo et al. (2016)[16]. Likewise, Wang et al. (2016) also reported LAA undersizing by TEE compared to 3D CT and showed 3D CT guided LAAC to be more accurate, safe, and faster than TEE or fluoroscopy alone[4]. In this study, every effort was made to emulate the TEE equivalent views on 4D volume ICE by utilizing its MPR feature. It should also be noted that In TEE the intracardiac anatomy and the intracardiac device are

imaged from outside the heart, i.e. from the esophagus, and the heart may be rotated with respect to the viewing angle on TEE. On the contrary, the cardiac rotation becomes inconsequential in ICE since the intracardiac anatomy and the intracardiac device are imaged from within the heart with the ICE angulation adjusted for. Fluoroscopy was used to guide device delivery and implantation throughout the study.

The diagnostic fluoroscopy time in our study was 16.07±7 minutes which is comparable to the fluoroscopy durations reported in similar studies (9.8±4.5 minutes[17]; 25±11 minutes[11]; and 30.4±17 minutes[19]). Because the new ICE catheter used in this study is larger than the previous generation (12.5Fr versus 8Fr for 2D ICE and 10Fr for 3D ICE), additional fluoroscopy was performed for precautionary purposes. This also explains the high air karma radiation dose of 10523 mGy observed in the very first case of the study. Similarly, the total procedure time in this study was 102±25 minutes, which is longer than 42±13 minutes reported in a study evaluating a dual-imaging guidance[14], and 65.8±15 minutes reported in a left atrial ICE guidance[19] but shorter than 103±33 minutes reported in a 2D ICE guided LAAC study[11]. This variability in procedure time, fluoroscopy time, and fluoroscopy dose indicates that the procedural characteristics are dependent on study settings, operator experience, and unique patient characteristics.

Clinical Implications

The primary benefit of 4D volume ICE imaging guidance for transcatheter LAAC is the possibility to avoid the use of GETA during LAAC and the possibility to expand LAAC care to patients with contraindications to GETA and TEE[27]. A recent case study by Perez et al. (2019) demonstrated successful provision of transcatheter LAAC care to a patient with apixaban-associated gastrointestinal bleeding; the procedure was guided with 4D volume ICE under conscious sedation[27]. Furthermore, procedures with GETA are often associated with masked neurological complications, pulmonary complications related to endotracheal intubation such as airway injury during intubation or post-intubation pneumonia, longer procedure time, higher personnel costs related to the need for an anesthesiologist, and importantly prolonged recovery time for the patient[7,28]. ICE guidance under conscious sedation can avoid GETA related complications, reduce patient discomfort and recovery time, and improve procedural efficiencies by reducing resource utilization[6,27,28]. Although the intraprocedural measurements with volume ICE were comparable to TEE, ICE characterization of the LAA from the right atrium did not have the same diagnostic confidence of TEE in 33% of the patients. While TEE guidance was required for LAAC in these patients, the finding that the diagnostic quality of right sided volume ICE was similar to TEE in the remaining 67% of the patients is suggestive of the possibility that LAAC can be performed without the need for TEE and hence without GETA. Furthermore, right sided ICE guidance avoids transseptal advancement of the ICE catheter into the left atrium and reduces risks for procedural complications.

We believe that proper patient selection, based on their intracardiac anatomical complexity, might help select appropriate imaging modality and optimal catheter placement for adequate intraprocedural guidance. Given the superior diagnostic quality of left sided ICE demonstrated by multiple studies, a direct comparison between the left sided and the right sided volume ICE intraprocedural guidance might help formulate workflow guidelines and standardize LAAC procedures while accounting for unique patient characteristics. In our study, efforts were made to standardize the volume ICE workflow in relation to the established TEE protocol. A workflow integrating preprocedural selection of the imaging modality, either right sided ICE or left sided ICE or TEE or 3D CT, for intraprocedural LAAC guidance may facilitate staff scheduling, e.g. between an echocardiologist and the anesthesiologist, and optimize resource allocation, e.g. TEE versus ICE, or CT angiography versus fluoroscopy. Preprocedural planning using CT might be beneficial in simplifying the LAAC workflow using 4D volume ICE with comparable 3D coronal measurements. The present study did not use CT for preprocedural planning. Preprocedural planning may also be supplemented with 3D LAA prototyping for ex-vivo¬ simulation of the LAAC procedure, particularly in patients where right sided ICE characterization of the LAA may be non-diagnostic. 3D LAAC simulation may contribute to reducing the learning curve associated with ICE guidance particularly by facilitating catheter placement and identifying anatomical landmarks for spatial orientation during the procedure.

Study Limitation

Our study is limited by its small sample size. Larger multi-center and randomized studies are needed to expand our understanding of the benefits and challenges of volume ICE intraprocedural guidance for different structural heart procedures, and in comparison, to different imaging modalities such as 3D CT. The intraprocedural measurements required for LAAC guidance were obtained on 2D multiplanar images; future studies should focus on the accuracy and feasibility of 3D imaging measurements. Our study did not have a control group. Proper patient selection for success of volume ICE guidance for LAAC needs to be investigated. Cost due to the one-time usage of the catheter is a primary concern. A recent study comparing procedural and cost considerations between 2D ICE and TEE showed that the total hospital charges for ICE with local anesthesia were similar to TEE with GETA but with significantly lower professional fees for ICE by avoiding high technical fees associated with TEE, anesthesia and recovery rooms[28]. Studies evaluating both the clinical impact, including knowledge gain and workflow efficiency, and the financial impact of volume ICE substitution for TEE would be highly relevant.

Clinical Perspectives

This study was the first to evaluate the clinical feasibility of wide-angled (90° x 50°) 4D volume ICE for intraprocedural guidance of LAAC. TEE is the current gold standard but requires GETA whereas ICE can be performed under conscious sedation and presents an alternative for patients with contraindications to GETA or TEE. This study demonstrated the feasibility of right sided ICE guidance for LAAC, without the need for a transseptal access and with measurements comparable to TEE. Larger prospective studies with proper patient selection, optimized preprocedural guidance, and standardized workflow should be performed to determine the clinical efficacy and outcome of volume ICE guidance for LAAC in

comparison to TEE.

Conclusion

4D volume ICE imaging from the right atrium or ventricle circumvents the need for a transseptal access for providing intraprocedural imaging guidance during LAAC; multiple MPR echo views and anatomical landmarks help optimize the LAAC procedural guidance but suffer from non-diagnostic image quality in the presence of challenging patient characteristics. Standardized workflow based on proper patient selection and optimal preprocedural preparation, including adequate training to reduce the learning curve, may improve the imaging success rate of volume ICE guidance from the right heart for transcatheter LAAC procedure. This is promising for patients who have contraindications for TEE or intolerance to anesthesia necessitating a TEE alternative for intraprocedural LAAC guidance.

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Comparing Safety and Efficacy of Dabigatran and Factor Xa Inhibitors for Stroke Prevention in Hemophiliacs with Non-Valvular Atrial Fibrillation

Safeera Khan[1], Ratna Krishnaswamy[1], Bilal Haider Malik[1], Muhammad Islam[1], Deepti Gupta[1], Shrawan Kumar Mandal[1], Ian H. Rutkofsky[1, 2]

[1]*California Institute of Behavioral Neurosciences and Psychology, Fairfield, California, USA.*
[2]*Mercer University, Macon GA, USA.*

Abstract

Background: Atrial fibrillation, a progressively rising global health problem, is also rising in Hemophiliacs due to an increase in life expectancy in them. While treating Hemophiliacs with AF, deciding eligibility, choosing the anticoagulant based on risk-benefit ratio are tough decisions for physicians to make. This review paper aims to explore and compare existing studies, reviews and consensus papers to assess the safety of different Novel Oral Anticoagulants (NOACS) in this population.

Methods: Thorough literature search was conducted on Pubmed using Atrial Fibrillation, Hemophilia A, Oral anticoagulants, stroke prevention, Dabigatran, factor Xa inhibitors as keywords separately and in combinations. Papers in English language only from the past 5 years were selected for review. After removing duplicate results, 80 papers were selected and after applying different exclusion criteria and according to relevance, 40 papers were finalized for review.

Results: The keywords AF, Stroke prevention, oral anticoagulants, Hemophilia a, Factor Xa inhibitors and Dabigatran gave 24899, 13619, 8964, 3503, 2850, 2799 results, respectively. Combination keywords also showed some papers and out of short-listed 80 relevant papers 35 were finalized. Reviewing and analyzing these papers revealed no clinical trials in hemophiliacs with AF in the past 5 years and 5 clinical trials comparing NOACs with Warfarin in general population. Rest were systematic reviews, consensus papers and meta-analyses on management in this group. A few compared these drugs for AF in the general population but not specifically in Hemophiliacs and others. consensus papers developed suggestions for management and showed that NOACs are superior to Warfarin but need individual evaluation in Hemophiliacs with AF.

Conclusions: Patients with Hemophilia can also have thrombo-embolism despite their bleeding tendency and NOACs are a better option in them because of less need for monitoring, no food interactions and fewer drug interactions. This comparative review emphasized the need for more work to develop proper guidelines for thrombo-prophylaxis management in this specific group.

Introduction

Global prevalence of Atrial Fibrillation (AF) was estimated to be 33.5 million in 2010 making up 0.5 % of the world population and is constantly rising [1]. In the United States, the estimates are around 2.7 to 6.1 million and are expected to rise to 12.1 million by 2030 [2] and in Europe, the expected rise is 17.9 million by 2060 [3]. AF is more common in adults more than 65 years of age but can occur in young patients as well. In the US 9% of people older than 65 have AF and 2% of people less than 65 are affected by it [4]. Such prevalence rate and the need for long term management of stroke and the complications related to it pose a huge burden on the healthcare system. United States spends approximately 26 billion dollars annually on managing AF and its related complications [2, 4] and has approximately 750,000 hospitalizations each year and estimated mortality of 130,000 deaths per year [5].

Key Words

Atrial fibrillation, Hemophilia A, Warfarin, NOACs.

Corresponding Author
Safeera Khan.

AF is one the most commonly diagnosed and persistent arrhythmia globally which predisposes patients to unexpected, sudden and often fatal thrombo-embolic neurological events, increasing the risk of ischemic stroke 5-fold [6]. Preventing these complications is important to decrease the overall disease burden and so anticoagulants are considered after risk stratification through CHADS 2 scoring [7]. Oral anticoagulants also have a risk of unexpected bleeding including severe episodes [8]. Warfarin, a Vit. K antagonist, remained the gold standard anticoagulant to prevent embolic stroke [9] but needed strict monitoring of INR to keep it in the therapeutic range (2-3) and failed to do so may lead to increased bleeding risk[9]. Dabigatran, a direct thrombin inhibitor was the first direct oral anticoagulant which needed less monitoring as compared to Warfarin. Later newer anticoagulants factor Xa inhibitors were added which also needed less monitoring as compared to Warfarin.

Several trials compared the efficacy and the safety of the new oral anticoagulants with Warfarin and proved the newer drugs to be as effective as Warfarin and superior in decreasing the intracranial bleeding episodes and needing less frequent monitoring [10]. Non-K

inhibitor anti-coagulants are being compared against each other for efficacy and safety to prevent complications in AF and not much data is available about challenging scenario about the choice of an anticoagulant when the patient has a predisposition to bleeding because of hereditary and acquired bleeding disorders yet needing anticoagulation based on CHADS 2 scoring. Attaining a balance in anticoagulation and bleeding episodes is a tough target and hence safety profile of the anticoagulants is important in order to prevent the patient from an ischemic stroke while avoiding hemorrhagic stroke and other major bleeding episodes. Hemophilia A is one such hereditary condition having limited information about safety of newer anticoagulants. It is an X-linked recessive condition with low levels of clotting factor VIII predisposing a person to excessive bleeding [11]. Owing to recent advances like CFC (Coagulation Factor Concentrates), life expectancy is increased but so are the complications which arise as a person ages like AF. The prevalence of AF was found to be as high as 0.84% in a cross-sectional survey from 14 Hemophilia centers in Europe [12].This value is similar to the prevalence of AF in general population [13] and increases with increasing age as it does in general population with 0.2 % in less than 60 years old hemophilia patients and reaches up to 3.4% in hemophiliacs more than 60 years of age [12].

Comparison of efficacy and safety profile of these two groups of non-Vit K anticoagulants can help in the better assessment of the scenario and in deciding the anticoagulant to be used in patients with bleeding tendencies without disturbing the delicate balance between preventing ischemic stroke and a chance of causing hemorrhagic stroke. Dabigatran had been in use already in hemophiliacs with AF, considering antidote was available and now with FDA approving the antidote for Rivaroxaban, this provides clinicians with more options of anticoagulants and this review article aims to assess their safety in the scenario.

Methods

Research Strategy

Research was conducted to identify studies analyzing and assessing safety profile of newer anticoagulants in setting of AF with inherited bleeding disorders, specifically Hemophilia. PubMed was used as our main database to find the relevant articles. Keywords which were used for the search were Atrial fibrillation, Oral anticoagulants, Hemophilia A, Stroke prevention, Dabigatran, and factor Xa inhibitors. MeSH keywords Atrial fibrillation, Hemophilia and Dabigatran were also used for search.

Table 1: No. of research articles for the searched Keywords.

Keywords / Combination of keywords	Database	No. of results
Atrial Fibrillation	PubMed	24899
Stroke prevention	PubMed	13619
Oral anticoagulants	PubMed	8964
Factor Xa inhibitors	PubMed	3503
Hemophilia a	PubMed	2850
Dabigatran	PubMed	2794
Atrial fibrillation AND Hemophilia a	PubMed	17
Hemophilia a AND anticoagulation	PubMed	10
Stroke prevention AND Hemophilia a	PubMed	4

Search results

Atrial fibrillation yielded 10146 research articles, Using the keyword Hemophilia A yielded 2850 research papers, Oral anticoagulants yielded up 8964 research papers and Factor Xa inhibitors yielded total number of 3503. A combination of keywords Atrial fibrillation and Oral anticoagulants gave a total of 3953 research papers, Atrial fibrillation and stroke prevention yielded 3847 papers, Atrial fibrillation and Hemophilia A yielded 17 research papers. Atrial fibrillation, anti coagulation and Hemophilia a gave 10 articles and Stroke prevention with Hemophilia a gave 4 research papers. Out of these results a total of 80 articles relevant to the research question were selected. After applying inclusion and exclusion criteria, duplicate papers were removed and finally a total of 35 articles were selected for review. A few relevant research papers about mechanism of actions, published before past 5 years from references of selected papers were also included.

Inclusion/Exclusion criteria

Peer-reviewed, full-text research papers from past 5 years were included in the review. All selected articles were in English language and no global or geographical considerations were given. Any non peer- reviewed and duplicate papers were excluded from finally selected articles.

Results

Out of 35 finalized papers, there were no controlled clinical trials

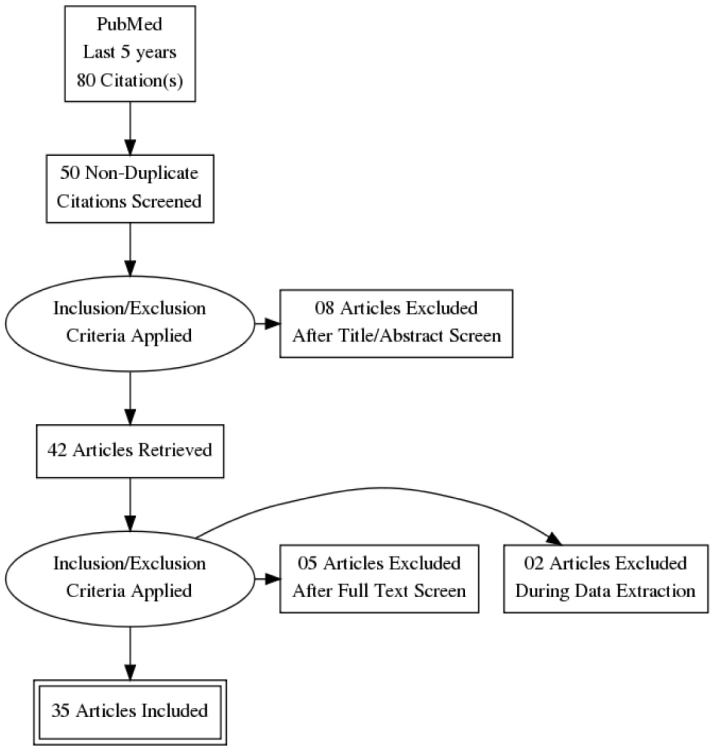

Figure 1: PRISMA FLOW diagram showing the process of selection of research papers

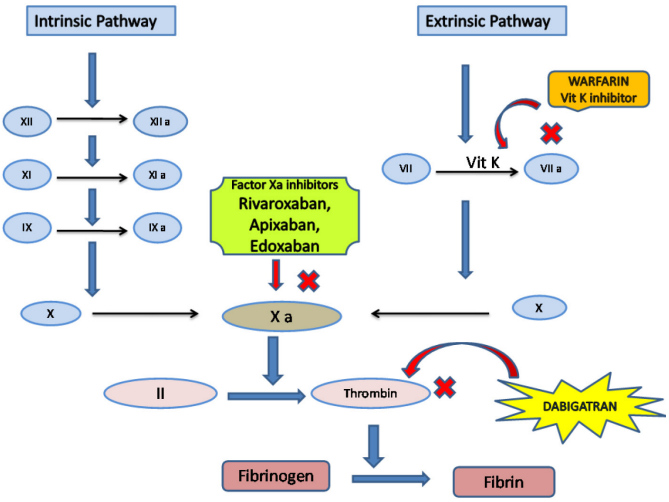

Figure 2: Site of action of Warfarin, Dabigatran and Factor Xa inhibitors

in Hemophiliacs population with AF but a few case studies showed up. A total of 5 clinical trials comparing the newer anticoagulants in general population with AF were included for review of their findings and indirect comparisons of these drugs, most of which showed superiority of NOACS over Warfarin. One retrospective cross-sectional study evaluating prevalence of AF in Hemophiliacs was included which showed increase in AF with increasing age. Anticoagulation is under-prescribed in these patients. Two meta-analyses were included which indirectly compared clinical trials comparing NOACS with Warfarin. One of them had compared 3 clinical trials with 42,411 patients on NOACs and 29,272 patients on Warfarin and showed that NOACs are superior in efficacy in preventing stroke and safety in terms of prevention of major bleed specially Intracranial bleed, Rivaroxaban showed increased GI bleeding. Rest were review articles and consensus papers about managing thrombo-embolism in hemophiliacs with AF and other conditions needing anticoagulation. Results of these systematic reviews and consensus papers showed that depending on severity of Hemophilia and risk-benefit assessment, anti-coagulation can be started and NOACs were a preferable choice although final choice of anticoagulant depends on patient's individual evaluation.

Discussion

Both Intrinsic and extrinsic pathways of normal coagulation cascade involve a number of different clotting factors and have different triggers to get activated but later converge and have a common pathway. Intrinsic pathway is triggered by direct damage to the blood vessels and activates a series of coagulation factors whereas extrinsic is triggered by damage to the tissue which in turn activates Factor VII. Both pathways converge at a point where Factor X is activated which leads to the formation of Thrombin or activated Factor II and at the end fibrinogen is converted to fibrin. Certain co-factors are mandatory for the process to complete like Vit. K, Ca++, etc. Deficiency in some of these factors may be the cause of different inherited bleeding disorders making the person more prone to the bleeding episodes, and some risk factors may increase the chances of thrombo-embolism and may have serious consequences of its own therefore needing prophylaxis with anticoagulants. When these both conditions co-exist using anticoagulation needs more vigilant and conscious approach.

Mechanism of action and pharmacological properties of oral anticoagulants

Warfarin had been the main oral anticoagulant for around 50 years since 1945 and had been effective. It acts as Vit K inhibitor, so inhibits all the steps which are catalyzed by Vit. K. While using Warfarin it was very important to keep in mind the delicate balance which had to be maintained to avoid any bleeding episodes for which purpose INR monitoring was necessary and needed to be in between 2-3. INR can easily be affected by dietary and drug interactions so needed frequent monitoring. Dabigatran was introduced long after Warfarin in 2010 and has a different mechanism of action. It acted at the later stage of the coagulation cascade, as a thrombin inhibitor as shown in [Figure 2], so it affected both intrinsic and extrinsic pathway. It had an advantage of less need for monitoring of INR as compared to Warfarin. It was first among the NOAC's, the latest oral anticoagulants added to treat pro-thrombotic conditions are Factor Xa inhibitors inhibiting the activated Factor Xa both in free form and attached to the pro-thrombin complex. Considering its important site of action in the coagulation cascade it also affected both intrinsic and extrinsic pathways. It is a group of medications out of which frequently used drugs include Rivaroxaban, Apixaban etc. Rivaroxaban was approved in 2011. The problem remained that in case of any need of urgent or immediate reversal, they had no antidotes available, until an antidote for Dabigatran, Idarucizumab was approved and recently in 2018 an antidote for Rivaroxaban and Apixaban has been approved. Pharmacological properties of fXa inhibitors differed in many ways from earlier anti-coagulants as they targeted a specific factor instead of multiple factors and have a rapid onset of action and their bioavailability is also better in comparison to Warfarin [13]. Owing to this mechanism of action there is no effect of dietary intake on Vit.K inhibitors as it is on Warfarin and so a fixed dose is a convenience which a patient gets with them and along with these, they have fewer drug interactions [14]. Because their pharmacokinetics and pharmacodynamic properties depend on the dose given, they have a predictable response after a fixed dose is administered and so need lesser monitoring [15].

When to start anticoagulation in Hemophiliacs with AF: Is CHADS2 VAS and HAS-BLED scoring enough?

Atrial fibrillation may cause intra-cardiac thrombus formation due to stasis and can cause thrombo-embolic stroke which may be life- threatening. Atrial fibrillation may be asymptomatic and this complication can be its first presentation, therefore screening and diagnosing it in time is important to prevent stroke. This is done by risk assessment for stroke through CHADS2 or CHADS VAS scoring and then prophylactic treatment is initiated in the form of oral anticoagulant based on the risk stratification and approved guidelines for general population. Hemophilia patients have now increased life expectancy owing to recent advances like the use of Recombinant FVIII in management but so are the conditions which are more prevalent in old age, this makes Atrial fibrillation to rise

Table 2: Some of the studies/papers included in review.

Author/Year	Country	Treatment	Focus of study	Type of study	Findings	Summary
De Koning et al, 2017	Utrecht, The Netherlands	Oral anticoagulants	Thrombin generation in Hemophiliacs	Cross-sectional study	They concluded that patients with severe hemophilia had similar haemostatic ability as compared to patients who had a normal range INR and approximately one third of mild to moderate hemophilia had even better haemostatic ability than patients using Warfarin with normal INR.	Anti coagulation therapy needs to be an option for patients who have non-severe hemophilia with AF and need more research in this field which may help in the near future where treatment option can be guided by ETP.
Murray et al, 2018	Santiago, Chile	Oral anticoagulants	Atrial fibrillation in Hemophiliacs	Case report	Factor VIII levels can alter with the changing time and can keep changing the risk-benefit assessment.	This case study suggests and sheds light on importance of individual risk-benefit assessment in hemophiliac patients with AF as risk factors and benefits of oral anticoagulants may vary especially in hemophilia A carriers where change in FVIII levels alters bleeding risk.
Martin & Key, 2016	North Carolina, USA	Oral anticoagulants	Anti coagulation in patients with inherited bleeding disorders	Case-review series	Evidence based Management guidelines aren't available for this specific population.	Anticoagulation in hemophiliacs needed to be considered based on the individual risk of bleeding in these patients if the risk of thrombotic events is high. Strategies to used oral anticoagulants were discussed to manage venous thrombotic disease, atrial fibrillation in inherited bleeding disorders and atherothrombotic disease were discussed.
Lip et al, 2014	UK/Denmark	Oral anticoagulants	Indirect comparison between Rivaroxaban, apixaban and dabigatran	Systemetic review	Dabigatran 110 mg and Apixaban were found to be equally safe as no significant differences were found. In comparison of Dabigatran 110 mg and Rivaroxaban, Dabigatran was associated with less major bleeding and intra cranial bleeding episodes.	In this indirect comparison between apixaban, Rivaroxaban and two doses of Dabigatran, they were found to be equally efficacious in preventing thrombotic stroke, although Dabigatran 110 mg was slightly more superior in preventing stroke. Dabigatran at lower dose of 110 mg and apixaban were safer as they had less episodes of major intracranial bleed. More accurate results will be obtained only when direct comparison is done between both groups of newer OACs.
Schutgens et al, 2016	North Carolina, USA	Oral anticoagulants	Suggestions for anticoagulation in inherited bleeding disorders	Letter to the editor	Not enough clinical data was found and whatever work is available has smaller sample size.	Owing to the lack of clinical trials on larger cohorts giving us not enough examples from clinical settings, anticoagulation in hemophiliacs is a complex matter. Suggestions are made to serve as a guide to manage these patients and more clinical data is needed about safety and efficacy of anticoagulants and need implementation of certain measures.
Shutgens et al, 2014 **ADVANCE working group**	Europe (14 hemophilia centers)	Oral anticoagulation in Hemophilia	To review anticoagulant prescribing practices in hemophiliacs	Cross-sectional study	Atrial fibrillation (AF) is a common health problem in the general population, but data on prevalence or management in patients with haemophilia (PWH) are lacking. The aims of this study were to analyse the prevalence of AF and risk factors for stroke using a cross-sectional pan-European design and to document current anticoagulation practice. The ADVANCE Working Group consists of members from 14 European haemophilia centres.	Hemophilia's prevalence increases as the patient ages and is fairly common in mild Hemophilia. And the percentage of patients receiving any type of anticoagulation is only 33 %. CHADS2 VAS2 scoring may overestimate the stroke risk in this population and HAS BLED score may underestimate the risk of bleeding so both are not reliable enough in Hemophiliacs with AF. Oral anticoagulation with any oral anticoagulant may be considered in patients with high risk of stroke if FVII levels are adequate.
Lee et al, 2018	Japan/ Taiwan	Rivaroxaban and Warfarin	Safety of low dose Rivaroxaban compared to Warfarin in Asian population.	Cohort study	In Asian population, Rivaroxaban had lower risk of thrombo-embolism than Warfarin.	Both low doses of Rivaroxaban were associated with a lower risk of ischemic stroke/ systemic embolism, intracranial hemorrhage, gastrointestinal bleeding, all major bleeding, and all-cause mortality compared with Warfarin in Asian NVAF patients. The 15 mg Rivaroxaban dose was associated with a lower risk of acute myocardial infarction compared to Warfarin.
Ruff et al, 2014	Boston, USA	Oral anticoagulants	Comparison of oral anticoagulant NOACs with Warfarin	Meta-analysis of RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI	A total of 42,411 participants received a NOAC and 29,272 participants received Warfarin. NOACs significantly reduced stroke or systemic embolic events by 19% compared with Vit K inhibitor, Warfarin. New oral anticoagulants also significantly reduced intracranial hemorrhage but Rivaroxaban was associated with increased gastrointestinal bleeding.	This was the first meta analysis which included phase 3 clinical trials about stroke prevention in AF by of all four new oral anticoagulants. Newer anticoagulants have better efficacy in terms of stroke prevention and safety in terms of less intracranial hemorrhage and mortality and better risk-benefit profile than Warfarin. Only type of systemic bleeding which occurred more than Warfarin was Gastrointestinal bleeding.

Villines et al, 2019	USA (Department of Military health system)	Oral anticoagulants	Atrial fibrillation	Retrospective cohort study	Patients using Dabigatran demonstrated similar risk of ischemic stroke but less risk of hemorrhagic stroke compared to the patients using Rivaroxaban and for other major bleeding episodes in individual component sites, Dabigatran comparatively had lower risk of major intracranial bleed but risk was similar for major bleed at extra cranial sites. For comparison of Apixaban and Dabigatran both had similar risk of ischemic stroke but the risk of major intra cranial bleed could not be assessed due to low number of events but risk was same for extra cranial sites.	In the cohorts comparing Dabigatran and Rivaroxaban , Dabigatran had less bleeding risk but similar efficacy in stroke prevention. While comparison between Dabigatran and Apixaban no statistically significant conclusions were drawn because of small sample size.
Gremmal et al, 2018	Austria	Use of oral anticoagulants in high risk population	To review use of NOACs in high risk population	Consensus paper	This consensus reviewed properties and use in a number of high risk populations like Chronic kidney disease, old age patients.	NOACs have a superior safety profile than Vit K inhibitors but it's important to consider dose reduction criteria and their contraindications to have proper risk-benefit assessment and outcome

in hemophiliacs as well [16]. These patients already have a bleeding tendency and whether they need anticoagulation is an important question which is frequently encountered while managing such patients. Despite the defect in clotting in hemophiliacs they still have other risk factors to develop thrombotic cardiovascular diseases [17]. Another study evaluating the risk factors for cardiovascular diseases between hemophiliacs and non hemophiliac controls although showed that controls have slightly higher incidence but as result was not statistically significant so recommended that they should be evaluated on individual basis [18]. Even with the use of recombinant FVIII there is still a risk of thrombosis in mild and moderate hemophilia, severe cases are somewhat protected though may still have a chance of thrombo-embolism [19]. Reducing the risk of stroke in patients with Atrial fibrillation depends on attaining an optimal risk and benefit balance which means estimating the risk of developing stroke due to thrombo-embolism by CHADS 2 OR CHADS2 VAS and then estimating the risk of bleeding secondary to using oral anti-coagulant by HAS-BLED score [20]. But will the same risk-benefit assessment criteria and guidelines give an idea about anticoagulation in Hemophiliacs with AF as they have increased propensity to bleed. There are very few trials addressing anticoagulation for AF in this specific population or group of patients and currently, no proper guidelines for risk assessment and management are developed as yet and only few expert consensuses developed to address this knowledge gap are available and serve as a guide to physicians [21, 16]. Since the bleeding risk is high,an approach is devised in the form of an algorithm [16].

Normally patients are stratified for risk according to CHADS2-VAS scoring and HAS-BLED or FVIII levels, and then a score of >3 or equal to 3 is used to start prophylactic anticoagulation. But no cut off value was available for Hemophiliacs with AF and so one such consensus was developed and it was suggested to be >2 or equal to 2 and the level of Factor VIII to be lowered from 30% to 20% [22], and it's recommended not to start anticoagulation if this level is below 20% [22]. However, this threshold should still be evaluated according to the particular patient who is under consideration [20].

The case report and literature analysis by Murray et al focused on a female patient, a hemophilia carrier, and highlighted that every case of hemophilia with Atrial fibrillation should be evaluated individually depending on their individual risk-benefit evaluation. They emphasized that as levels of Factor VIII in females may vary with time and can change the risk-benefit balance and assessment so any hemophilia A carrier with low factor VIII levels may have a decreased risk of bleeding [20] so an individual assessment will give a better idea about when to start and what to consider for anticoagulation.

During individual assessment, the primary consideration while making a decision is the bleeding phenotype of the patient, which is whether the patient bleeds spontaneously, whether bleeding occurs due to an initiating stimulus like trauma and how severely a patient bleeds [23]. Developing inhibitory antibodies in Hemophiliac is frequently encountered complication .The hemophilia patients who don't have an inhibitor generally respond well to clotting factor replacement, thus making it easier to control or prevent severe bleeding [23]. On the other hand, patients who have inhibitors have a less predictable response. It was shown by some studies that around 10% to 20% of bleeding episodes with inhibitors were not responsive at all or responded partially to a bypassing agent [24, 25]. This evaluation can serve as a guide in assessing the risk-benefit ratio of a hemophiliac patient and whether the patient needs a thrombo-prophylaxis in Atrial fibrillation or not.

Regarding whether to start thrombo-prophylaxis in hemophilia, De Koning and colleagues suggested/concluded in their literature review that approximately one third patients with non-severe hemophilia had a significantly better haemostatic potential than the patients who were on Vit K inhibitors with therapeutic INR whereas patients with severe hemophilia had equally comparable haemostatic potential to the patients with therapeutic INR, which showed that a considerable number of patients with non-severe hemophilia should be considered for thrombo-prophylaxis [26].

Maintaining balance between anticoagulation and bleeding risks in bleeding prone population/ischemic stroke vs hemor-

rhagic stroke

As the main complication of inherited bleeding disorders like Hemophilia is spontaneous or post-traumatic bleeding, they are somewhat protected from thrombosis but both arterial and venous thrombosis do occur occasionally, so they may need anticoagulation as the situation arise and also consideration is needed to start prophylactic anti-coagulants as the need can be comparable to general population like in the presence of AF [23] where the complication can be more serious. But with tendency of increased bleeding and taking oral anti-coagulant can have their own risk of bleeding if INR fluctuates or if medication is affected by dietary intakes or drug-drug interactions as was the case in Warfarin where regular monitoring was needed, but with the new direct oral anticoagulants, there is an increased safety profile, as proven by many studies especially considering intra-cerebral hemorrhage [27].

In general population, all DOACS were considered safer than Warfarin and as effective as it is but there isn't much evidence as not many trials have been done specifically in hemophiliacs so a literature review and review of different consensus done earlier can help us in analyzing and comparing the effectiveness and safety of DOACS in hemophiliacs. Although Rivaroxaban and Apixaban are proven to be superior and safer to Warfarin in patients with AF, they still do have a chance of increased bleeding as in all anti-coagulants [28]. It was suggested that instead of using Warfarin, it will be safer in order to prevent a major bleeding episode by prescribing Rivaroxaban, a factor Xa inhibitor at a lower dose of 10 mg daily [22] but in such patients, anti-coagulation is to be considered if a factor VIII level is more than 20%.

In hemophiliacs, if oral anti-coagulants have to be used it is comfortable to use them when trough FVII/FIX and vWF activity levels are >30% and are maintained on that but still a final decision has to be taken after a thorough individual evaluation but in patients with severe hemophilia where the factor activity level is at times even <1%, anti-thrombotic therapy is avoided as bleeding tendency is already very high especially if no clotting factor therapy is ongoing [23]. A multicenter study involving 33 hemophilia patients from 20 European hemophilia centers showed that bleeding occurred in 1 out of 3 hemophilia patients on oral anticoagulant who was not taking prophylactic treatment with clotting factors alongside to maintain factor 8 trough level above 0.2 IU L -1, and this questions the safety of the drugs in this group despite being safe in general population and may need detailed assessment and prophylactic clotting factors before starting their use [12].

Lower doses of Rivaroxaban were proven to be safer than Warfarin as they were associated with lower risk of ischemic stroke and systemic embolism in one of the studies conducted in Asian NVAF patients [29]. Newer anti-coagulant agents reduced the risk of Intracranial hemorrhage by half approximately having a risk ratio of 0.44, 95% CI in a study [30].

Best drug in maintaining optimal balance

While choosing an anticoagulant for patients who have a high risk of bleeding and inherited bleeding disorders, among all available oral anticoagulant options, considerations should be given to the bleeding risk with each medicine, its reversibility and half-life. Agents with shorter half-life are preferred in patients with bleeding disorders as they are easy to reverse. Warfarin and Dabigatran were frequently used because of the availability of available antidotes [23]. Factor Xa inhibitors were not used in this category of patients as they had no available antidote but recently with approval of antidote of Rivaroxaban and increased safety of FXa inhibitors as compared to Warfarin, they also should be an agent of choice. The issue which arises here now is which agent to choose among Dabigatran and Factor Xa inhibitors.

Table 3: Comparison of Pharmacological Properties of thrombin inhibitors and Factor Xa inhibitors

Characteristics	Thrombin Inhibitors		Factor Xa Inhibitors	
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Thrombin Inhibition	Factor Xa inhibition	Factor Xa inhibition	Factor Xa inhibition
Available doses	75 mg, 150 mg	2.5 mg, 10 mg, 15 mg, 20 mg	2.5 mg, 5 mg	15 mg, 30 mg, 60 mg
Food Interaction	None	None To be taken with food only for higher doses (20 mg)	None	None
Route of Elimination	Renal	Renal & Hepatic	Renal & Hepatic	Renal & Hepatic
Bioavailability	6.2 %	80 %	50 %	62 %
Half –life (Normal Renal function)	12-14 hrs	5-9 hrs Increase with old age	12hrs	10-14 hrs
Renal impairment with AF				
Mild (>50ml/min)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Moderate (15-50 ml/min)	Reduce dose (75 mg/day when below 30ml/min)	15 mg/day	Reduced dose (2.5 mg/day)	Reduced dose (30 mg/day)
Severe (<15 ml/min)	Avoid use	Avoid use	Reduced dose (2.5mg) if on dialysis	Avoid use Below
Hepatic Impairment Mild	None	None	None	None
Severe		Avoid use	Not recommended	Not Recommended

Considering the high-risk Warfarin has, NOACs are definitely a safer option; Vit K antagonists have more adverse events because of their narrow therapeutic margin and many drug and food interactions. It is considered a leading cause of ER presentations/hospitalizations in the elderly due to its adverse effects [31]. Not many clinical trials are done to assess the safety and efficacy in hemophiliacs with AF, so by comparing the clinical trials in other high risk population and assessing which medications are safer than Warfarin and relative to each other and comparing reviews, consensus and meta-analysis about such scenario, we can indirectly compare the safety and efficacy of such medication. Rivaroxaban was found to be superior to Warfarin in many high risk populations in a review by Diener et al, by comparing the results of ROCKET_AF trial and were found to be consistent in these populations [32]. The EXPAND study conducted in Japan showed low dose of Rivaroxaban in non valvular Atrial fibrillation to have lesser incidence of stroke, and serious bleeding than it's higher dose and Warfarin [33].

The elderly population is a high risk population, whose thrombo-embolic risk is higher than general population using CHADS VASc score which makes age an important factor in scoring, but anticoagulation is not commonly used as needed and anti-platelet agents without anticoagulants are not of much benefit in the elderly but are more prone to cause major bleeding episode [34]. This high-risk group tests the ability of the medication's safety considering the different co-morbidities, the poly-pharmacy in them and the interactions those medications may have as AF is common in the ageing population. With the increased life expectancy in hemophiliacs and the increasing AF in this population, consideration of the medicine which is safe in the ageing population can be considered in this population as well. NOAC's are considered a safer option in the elderly population because of their short half-life and predictable pharmacokinetics and less need for monitoring as Warfarin and the trials showing the decreased chances of intracranial hemorrhage. A meta-analysis by Ruff et al showed these results about their safety and efficacy in 29000 patients over the age 75 [35].

Renal impairment is a condition which is not uncommon in patients with AF, in ageing population and patients with hemophilia. NOAC's have renal route of excretion and so is one of the main limitations when they need to be prescribed to CRF population. Consideration of GFR is important while deciding the oral anticoagulant which needs to be greater than 30 ml/min for prescribing NOACs. An expert Consensus document preferred using Anti Xa inhibitors instead of Vit K Inhibitors with GFR rate ranging from 15-30 ml/min, they were found to have an upper hand in terms of safety in patients with renal impairment as compared to Vit K inhibitors [36]. 20 mg rivaroxaban is superior in efficacy to Warfarin but even low dose of Rivaroxaban at 15 mg was also proven equally efficacious in another study done in Japanese population [29] which can be used in patients with compromised renal functions or even in Hemophiliacs or with both.

In a retrospective study by Villines et al, patients with Dabigatran were compared to Rivaroxaban and to Apixaban separately but the sample size of Apixaban was not statistically significant but for comparison of Dabigatran and Rivaroxaban showed that Dabigatran was associated with less major bleeding events than Rivaroxaban although the rates of thrombo-embolic rate were not different in both of them. So in terms of efficacy both were comparable but in safety from a major bleed Rivaroxaban was found to be superior in this study [37].

The results of one of the studies in which Patients with NVAF of >65 years were selected which were recently started on these medications, showed that there was no difference in thrombo-embolic stroke in patients on Rivaroxaban or Dabigatran but an increase in Intra cranial hemorrhage and major bleeding episode risk in the cohort taking Rivaroxaban compared to the one taking Dabigatran [38]. The results of both of these studies were somewhat similar to the results of a few other recent studies like a meta-analysis of different studies by Li et al which also showed that Rivaroxaban, a thrombin inhibitor and Apixaban, a factor Xa inhibitor were comparable in efficacy with Rivaroxaban, another factor Xa inhibitor, but both were better in safety as they were associated with lesser episodes of major bleeding than Rivroxaban [39]. A meta-analyses of 7 studies by Providencia et al concluded that none among both groups Factor Xa and thrombin inhibitors are better in all parameters, one group may be better than other in one thing and may be inferior in other one [40] and hence decision should be taken on individual patient's risk-benefit ratio which is even more important in Hemophiliacs. In those cases where Vit K inhibitors cannot be prescribed, Apixaban was found to be safer alternative [34]. A Consensus report by Gremmel et al also recommended to assess each patient individually for the need of anticoagulation, as except for severe Hemophilia, others may not be protected enough against thrombo-embolism [41], so the decision of specific drug also needs to take in account the specific conditions and co-morbidities of patient. Considering all these limitations, the option of Left Atrial Appendage closure can also be considered and needs to be studied in this group as it may help us to avoid the oral anticoagulants altogether in this group while still preventing thrombosis. A meta-analysis of PROTECT AF and Prevail trial showed similar chances of having ischemic stroke but decreased chances of hemorrhagic stroke as compared to Warfarin [42].

Limitations

While searching for the literature, there were not many clinical trials or studies which were conducted in the Hemophiliacs with AF, the ones which were available were in general population. Most of the papers specifically in the concerned population were the consensus recommendations based on clinical cases or indirect comparisons of different studies. There were no literature/guidelines found about risk assessment in this population group and the risk assessment criteria like CHADs and HAS-BLED score cannot be applied to this population group, making the decision of prophylactic anticoagulation more difficult. Actual comparison between these drugs in this specific population was difficult and conclusions were drawn based on literature available and their properties in general population or clinical case reviews. More clinical trials are needed to study these drugs in hemophiliacs with AF.

Conclusion

NOAC's although considered a better option in general public

have not been studied for efficacy and safety in Hemophiliacs with AF. Hemophilia patients despite having a bleeding risk and decreased tendency for thrombosis may still have thrombosis in pro-thrombotic conditions like Atrial fibrillation. This makes it clear that these patients also have the need for prophylactic anticoagulation as the complication is more serious, but the unreliability of risk assessment scores in this group of patients also needs to be considered. Warfarin was in use for decades for prophylaxis and had been effective in preventing thrombo-embolic stroke but needed frequent monitoring of INR and had frequent drug and food interactions which may make it difficult for these patients. NOACs having different site of action are not dependant on food intake, and the need of less monitoring of INR make it a better option in hemophiliacs with AF having a predictable response, but they may still need clotting factors alongside to prevent major bleeding event, depending on individual assessment. As these conclusions are drawn from research about thrombo-prophylaxis on various other vulnerable groups, more studies are needed to extrapolate these effects in this group. Among NOACs, as shown in different trials / meta-analysis, Dabigatran and Apixaban were shown to be better than Rivaroxaban in having fewer episodes of major intra-cranial bleeding episodes but have the same efficacy in preventing strokes. In case of co-existing CRF since all NOACs have renal route of excretion as well need dose adjustment and need to be decided based on eGFR. Apixaban was the one which could be prescribed in GFR even between 15- 30. There still is a huge gap in knowledge and there is need for more clinical trials in this specific population as not much is available and there is a need to develop proper guidelines about using oral anti-coagulants in Atrial fibrillation with Hemophilia and Inherited coagulation disorders. Considering all these limitations, options like Left Atrial Appendage (LAA) occlusion device therapy may be considered and studied further in this group as a treatment option to avoid long term anti-coagulation in this vulnerable population having high risk of bleeding.

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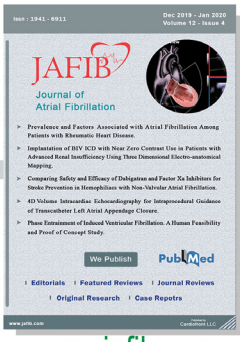

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Implantation of BIV ICD with Near Zero Contrast Use in Patients with Advanced Renal Insufficiency Using Three Dimensional Electro-anatomical Mapping.

Adel Mina[1], Bradley Knight, Nicholas Warnecke[1].

[1]*UnityPoint Health Methodist Invasive Cardiology/Clinical Cardiac Electrophysiology Peoria, Illinois.*

Abstract

Background: Biventricular (BIV) ICD implantations are traditionally performed using contrast and fluoroscopic guidance. Contrast use in patient with advanced renal disease can cause deterioration of renal function and even lead to dialysis.

Objective: To evaluate the feasibility of utilizing 3 D mapping technique in reducing or eliminating contrast use in patient with advanced renal disease.

Methods and Results: The study consisted of 30 consecutive adult patients, in which BIV implantation was accomplished in advanced renal disease (stage III and IV GFR 15 to 59) by electroanatomical 3D mapping (EAM).

Acute procedural success was 96% and only one patient LV lead implantation was unsuccessful due to unsuitable anatomy.

47 % of patients had BIV ICD implantation with zero contrast. Average contrast exposure for the group was 4.3 ml only. Average ratio of contrast use to GFR (glomerular filtration rate) was only 0.1. Improved mean GFR was observed from 42 to 50 post procedure (P value<0.01), and continued to improve to 48 at 3 and 6 month (P value<0.01) and improvement decreased to 45 and 44 beyond 6 month and 1 year (P value NS). There was no single case of contrast induced acute renal insufficiency (CI-ARI) due to minimal use of contrast.

69 % of the patients experienced an improvement in their functional class. A decrease in QRS duration was seen from 159 to 136 milliseconds (86% of patients had improved QRS duration); P value = <0.001. The average pre procedure ejection fraction (EF) for the group was 23%. The average EF post procedure for the group was 35%; P values = <0.001 (72% of patient had EF improvement).

93% of patient had either EF and/or GFR improvement suggesting substantial clinical benefit from the procedure.

There was no minor or major complications.

Conclusions: Implantation of BiV ICD using EAM with near zero contrast is feasible, safe and effective in patients with moderate to severe renal insufficiency. There is an added renal protection and benefit from procedure in this group of patients.

Introduction

The use of fluoroscopy has long proven itself as an invaluable tool in many cardiovascular procedures such as pacemaker and defibrillator implantation. More specifically, fluoroscopy aids in defining anatomical structures, navigation through those anatomical structures of the heart and allows for accurate fixation of the leads within the chambers of the heart.[1,2,3]

One prime example for the use of fluoroscopy arises with implantation of biventricular devices for resynchronization therapy. During the procedure, fluoroscopy helps to locate the ostium of the coronary sinus thereby allowing access for the LV lead. [4]

However, there is a variable degree of variance from person to person in regards to the anatomical location of the ostium. Likewise, it can be difficult to accurately define the anatomy within the heart. It is this variance that often lends itself to prolonged fluoroscopy times related to anatomical complexity. Furthermore, the fluoroscopy only provides a 2D view of catheter movement and position within the heart at times making it difficult to adequately position catheters. These limitations only increase the complexity of the case and leads to greater radiation and contrast exposure to the patient.

We have shown in our prior study the feasibility of 3 D mapping to reduce fluoroscopy and contrast use in patient with normal renal function. [1] However, there is no study to our knowledge that evaluated the feasibility of EAM in BIV ICD implantation in patients with advanced renal disease largely because of increased threat for of CI-AKI in those patients. This makes the utility of implantation of CRT device in patients with advanced renal disease limited and restricted and in most cases not even offered for fear of needing dialysis post procedure.

Aim of study

To evaluate the feasibility of EAM in reducing contrast exposure during implantation of BIV ICD or CRT device in patients with advanced renal disease.

Key Words

BiV ICD, Near Zero Contrast, Advanced renal disease, Three dimensional Electro-anatomical Mapping.

Corresponding Author
Adel Mina,
112 NE Crescent Avenue Peoria Illinois 61606

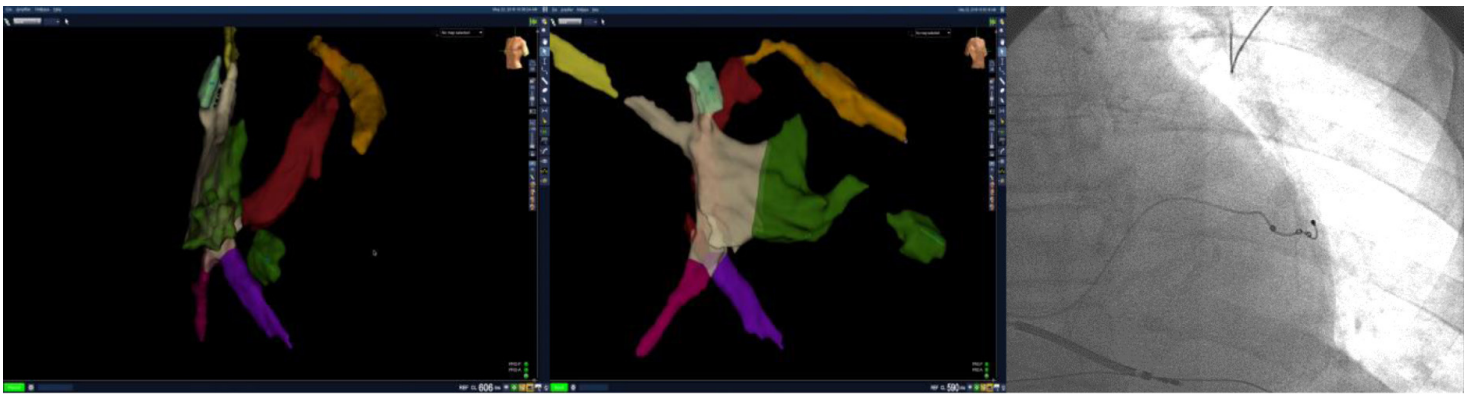

Figure 1: EAM of the coronary sinus veins with segmentation of the heart chambers and coronary venous branches using different colors (LAO and RAO projections)

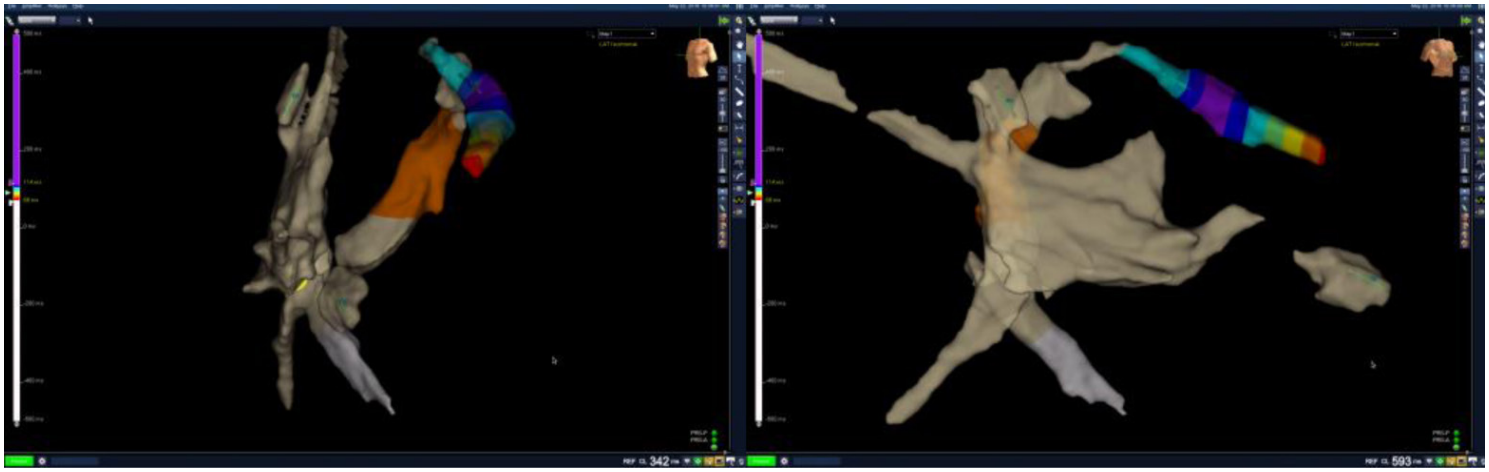

Figure 2: EAM of the coronary sinus veins with activation mapping showing the latest delay marked by the purple color at the mid left lateral branch. With fluoroscopy showing lead position in LAO 15 degree projection .

Table 1: Baseline characteristics for patients.

Age	Average 70	(55-86)		
Gender	24 Male 6 Female			
Indication	LBBB (23)	RBBB (2)	RV pacing (1)	IVCD (4)
GFR	Average 41 (19-56)			
EF	23 (9-35)			
QRSD	158 (120-207)			
Functional class	25(class III), 4(class II)1(class IV)			
CKD stage	3(stage 4), 26 (stage 3)			

Methods

A retrospective analysis was performed on the last 30 consecutive cases where 3D-EAM was employed for BIV ICD implantation in patients with chronic renal disease. Chronic renal disease being defined as a patient whose GFR was 15 to 59 ml/min at baseline (n = 30). The technique employed for the implantations has been outlined below in step-like fashion.

Qualitative baseline data was obtained which included procedure indication, age, gender, functional class of heart failure, GFR pre, QRS duration pre, and ejection fraction pre for group.

Procedure outcome data was also collected and included total procedure time, total fluoroscopy time, total contrast used, GFR pre/post , QRS duration pre/post , and ejection fraction pre/post [Table 2]. Furthermore, GFR was monitored at time of implant, 0-1 month, 1-3 months, 3-6 months, 6-12 months and >12months [Figure 2]

Averages for these categories were then calculated for the group [Table 1,2].

Procedure for Near Zero contrast implantation of BIV ICD

1- Procedures were performed under monitored anesthesia care. Ultrasound (Sonosite) left axillary venous micropuncture access was done eliminating need for fluoroscopy or contrast during these steps.

2- A Deflectable Quad 6 Fr EP catheter was advanced via the left axillary vein into the right atrium, right ventricle and into the CS while obtaining anatomy of the cardiac chambers using Ensite or precision St Jude/Abbott 3D mapping system [Figure 1]

Table 2: Procedural outcome .

Cases	GFR Pre	Post GFR 0-1mo	Post GFR 1-3 mo	Post GFR 3-6 mo	Post GFR 6-12 mo	Post GFR >12 mo	EF pre	EF post	Contrast (ml)	Ratio of contrast to GFR	Fluoroscopy time(min)	QRS pre (ms)	QRS post (ms)	Functional Class Pre	Functional Class Post	CKD Stage	Total Procedure Time (mins)
Case 1	33	33	39	27	27	41	25	25	0	0.00	0.3	151	122	2	1	3	61
Case 2	19	29	24	29	30	29	15	35	0	0.00	2.4	160	120	3	3	4	86
Case 3	46	48	47	47	39	45	22	22	0	0.00	6.2	152	144	3	3	3	146
Case 4	27	37	31	31	31	21	34	35	6	0.22	5.5	187	148	3	3	4	129
Case 5	50	56	56	56	56	56	30	40	0	0.00	3.11	159	129	3	1	3	103
Case 6	47	56	56	45	45	59	25	25	10	0.21	16.6	158	138	3	2	3	81
Case 7	40	40	31	44	25	28	30	47	0	0.00	1.22	153	118	2	1	3	81
Case 8	34	30	30	30	29	27	22	50	0	0.00	2.3	180	144	3	2	3	98
Case 9	45	46	54	54	57	77	23	45	4	0.09	19.5	174	159	4	2	3	198
Case 10	34	50	37	54	60	44	29	60	5	0.15	9.1	140	124	3	2	3	113
Case 11	28	32	32	32	35	32	35	45	0	0.00	12.3	197	125	3	3	4	132
Case 12	45	51	51	51	36	36	25	35	5	0.11	4.8	139	123	3	2	3	111
Case 13	46	52	58	43	31	37	13	21	10	0.22	5.1	132	144	3	3	3	86
Case 14	38	45	45	45	44	41	25	40	0	0.00	4.7	151	121	3	2	3	99
Case 15	47	68	68	68	64	65	15	15	0	0.00	1.9	183	153	3	1	3	123
Case 16	47	66	52	50	52	46	30	45	2	0.04	12.3	135	118	3	1	3	106
Case 17	47	61	57	49	49	46	30	25	8	0.17	12.3	165	142	3	1	3	120
Case 18	49	57	66	58	58	48	30	35	15	0.31	11.7	180	134	3	2	3	135
Case 19	44	56	50	58	53	44	15	26	3	0.07	5.1	118	110	3	3	3	70
Case 20	46	56	56	56	46	49	9	10	0	0.00	13.4	126	135	3	2	3	213
Case 21	39	33	33	33	34	29	30	45	3	0.08	13	150	112	3	2	3	195
Case 22	45	44	44	55	61	61	35	65	0	0.00	3.5	148	111	3	1	3	95
Case 23	45	45	44	44	50	41	20	30	24	0.53	7	188	126	2	1	3	95
Case 24	48	45	45	45	45	45	20	40	0	0.00	5.1	207	197	3	1	3	96
Case 25	41	57	45	47	43	37	10	LV lead not placed	3	0.07	18.4	170	170	3	3	3	153
Case 26	43	53	71	71	45	45	20	15	12	0.28	6.9	156	151	3	3	3	105
Case 27	39	60	48	42	39	39	30	45	4	0.10	14.22	159	162	2	1	3	97
Case 28	43	67	67	67	57	47	25	45	0	0.00	2.1	123	124	3	3	3	87
Case 29	47	60	41	44	46	41	10	32	0	0.00	2.3	180	137	3	1	3	77
Case 30	49	68	58	58	58	58	19	25	15	0.31	14.2	134	121	3	2	3	115
AVERAGE	41.70	50.03	47.87	47.77	44.83	43.80	23.37	35.28	4.30	0.10	7.89	158.50	135.40	2.90	1.93	3.10	113.53

3- The RV lead was then advanced under EAM into the RV, the bipolar electrodes of the lead were attached to alligator clips in one terminal, and to the EP box in the other terminal and was displayed on the EP monitor. Care was taken not to apply more than usual mild pressure during advancement of any catheters or leads. R wave amplitude was monitored during advancement and a threshold of 5 mV or more was used as adequate marker for good endocardial lead contact.

Appropriate apical lead position was confirmed by EKG RV Pacing configuration or by limited fluoroscopy.

A snap shot fluoroscopy which was usually done after helix deployment to confirm adequate slack and helix deployment.

4. Likewise, RA lead advanced under EAM in the right atrium, parked in place to be later placed in the appendage at the end of LV lead implantation after peeling of left ventricular lead sheath.

5- An EP deflectable Quad 4 fr. catheter (St Jude INQUIRY) was advanced as a unit with the guiding coronary sinus (CS) sheath into the 9 fr. sheath and into the right atrium under EAM, alternatively the 6 Fr deflectable EP catheters were used.

Care was given to allow 3-5 cms of the EP catheter out of the sheath during advancement to avoid sheath trauma to the veins or the heart. The coronary sinus was subsequently cannulated under EAM as well as EGM guidance. This step was facilitated by the prior EAM of the coronary sinus. The 4 fr. EP catheter was advanced further towards the lateral border of the heart which acted as a support to advance the outer guiding sheath.

If during advancement of the EP catheter one of the branches of the lateral veins were cannulated we used this opportunity to advance the outer sheath at the os of that vein for later insertion of the coronary sinus lead through the guiding sheath.

6- The outer sheath was then advanced over the 4 fr EP catheter to the outer third of the coronary sinus and the 4 fr. EP catheter was then removed.

7- The LV lead was subsequently advanced through the outer guiding sheath with the BMW wire as one unit, BMW wire was protruding 2-3 cm outside the lead and a slight bend was previously shaped into the wire to allow for sub-selection of the target vein.

This was done also under EAM with the lead likewise connected

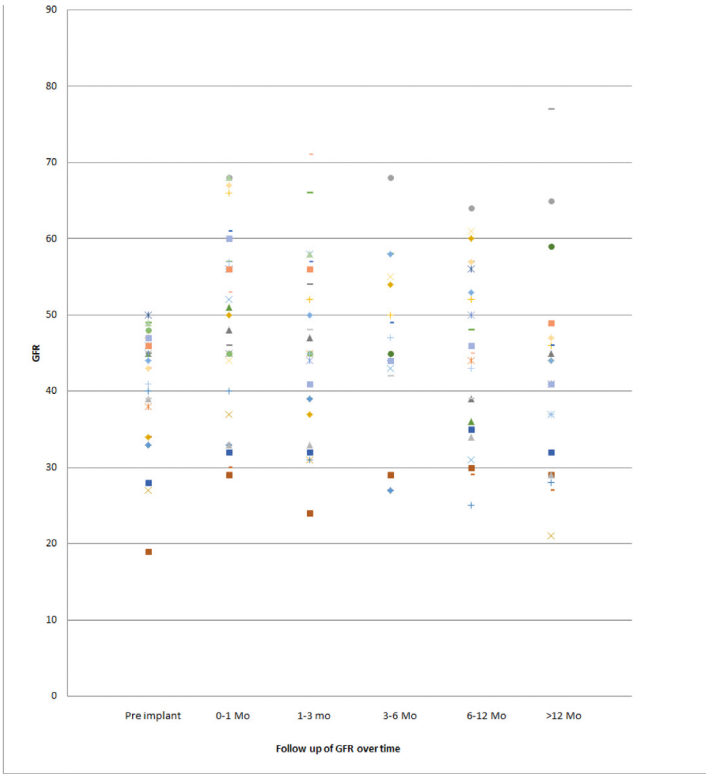

Figure 3: **Pre and post procedure GFR presented for the 30 patients in the NZC group notice the remarkable improvement post procedure first 6 months.**

to the connecting box via standard alligator clips. The lead with the BMW wire was used as one unit to try to cannulate the target vein if any resistance was felt the unit was withdrawn back to sheath to straighten the lead and another attempt is made till target vein was cannulated.

The targeted vein was previously identified from prior coronary venous road map. If map is not available careful various manipulations of lead, wire, subselective sheaths inserted with the 4 fr EP catheter were usually sufficient to subselect a branch.

Selection is preferred in the lateral and posterior aspect of the LV . Also, basal or mid segments of the LV were achieved in all cases. If multiple branches were cannulated we usually chose the more lateral branch with more LV to RV separation, alternatively the branch with the latest LV activation is chosen to maximize CRT benefit to patients [Figure 1]. We also used the multipolar Quatro (St Jude) LV lead in most cases to help with multiple configurations in case of diaphragmatic pacing or high thresholds. We also used the multi-pacing device option if there are more than 2 good thresholds available.

8- Limited Fluoroscopic exposure was done usually snap shot in RAO and LAO to assess if the three leads have adequate slack and if the helix of the atrial and right ventricular leads were properly deployed. It also confirms that all lead positions are adequate. Adding or removing of slack if needed was done at this stage.

9- Pacing optimization was done in multiple vectors and VV timing optimization done to choose the narrowest QRSd or the most delayed portion of the LV.

10- Patients with more difficult anatomy limited fluoroscopy and contrast was needed to overcome difficulty in the usual traditional way.

Results

The study consisted of 30 consecutive adult patients, in which BIV implantation was accomplished in advanced renal disease (stage III and IV GFR 15 to 59) by EAM. Acute procedural success was 96% and only one patient LV lead implantation was unsuccessful due to unsuitable anatomy.

There were no major or minor complications amongst the group. There were no changes in lead performance in all devices during follow up.

47% of patient had there BIV ICD implantation with zero contrast. Average contrast exposure for the group was 4.3 ml. Average ratio of contrast use to GFR (glomerular filtration rate) was only 0.1. Improved mean GFR was observed from 42 to 50 post procedure (P value <0.01), continued to improve to 48 at 3 and 6 months (65% of patients had GFR improvement at 3 months) (p value <0.01) and improvement decreased to 45 and 44 beyond 6 month and 1 year (P value NS). There was no single case of contrast induced acute renal insufficiency (CI-ARI) due to minimal use of contrast.

Sixty nine percent of the patients experienced an improvement in their functional class. Furthermore, a decrease in QRS duration was seen from 159 to 136 milliseconds P value= <0.001 (86% of patients had improved QRS duration). The average pre procedure EF for the group was 23%. The average EF post procedure for the NZC group was 35% P values = <0.001 (72% of patient had EF improvement).

One hundred percent of the patients who had BiV implanted experienced GFR improvement, QRS improvement and/or EF improvement [Figure 4] of which 93% had either EF and/or GFR improvement suggesting substantial clinical benefit from the procedure.

62% of patients with improved EF had a concomitant improvement of GFR. We also noted that all 7 patients with EF < 20 had a significant improvement of GFR suggesting even more benefit in those patients with severely reduced EF due to improvement of cardio renal syndrome.

Total fluoroscopy exposure was minimal with an average fluoroscopy time of 7.9 minutes.

Discussion

Cardiac resynchronization therapy (CRT) with an implantable cardioverter-defibrillator (ICD) plays an important role in reducing heart failure morbidity and improving survival in patients with severe left ventricular (LV) dysfunction, intraventricular conduction

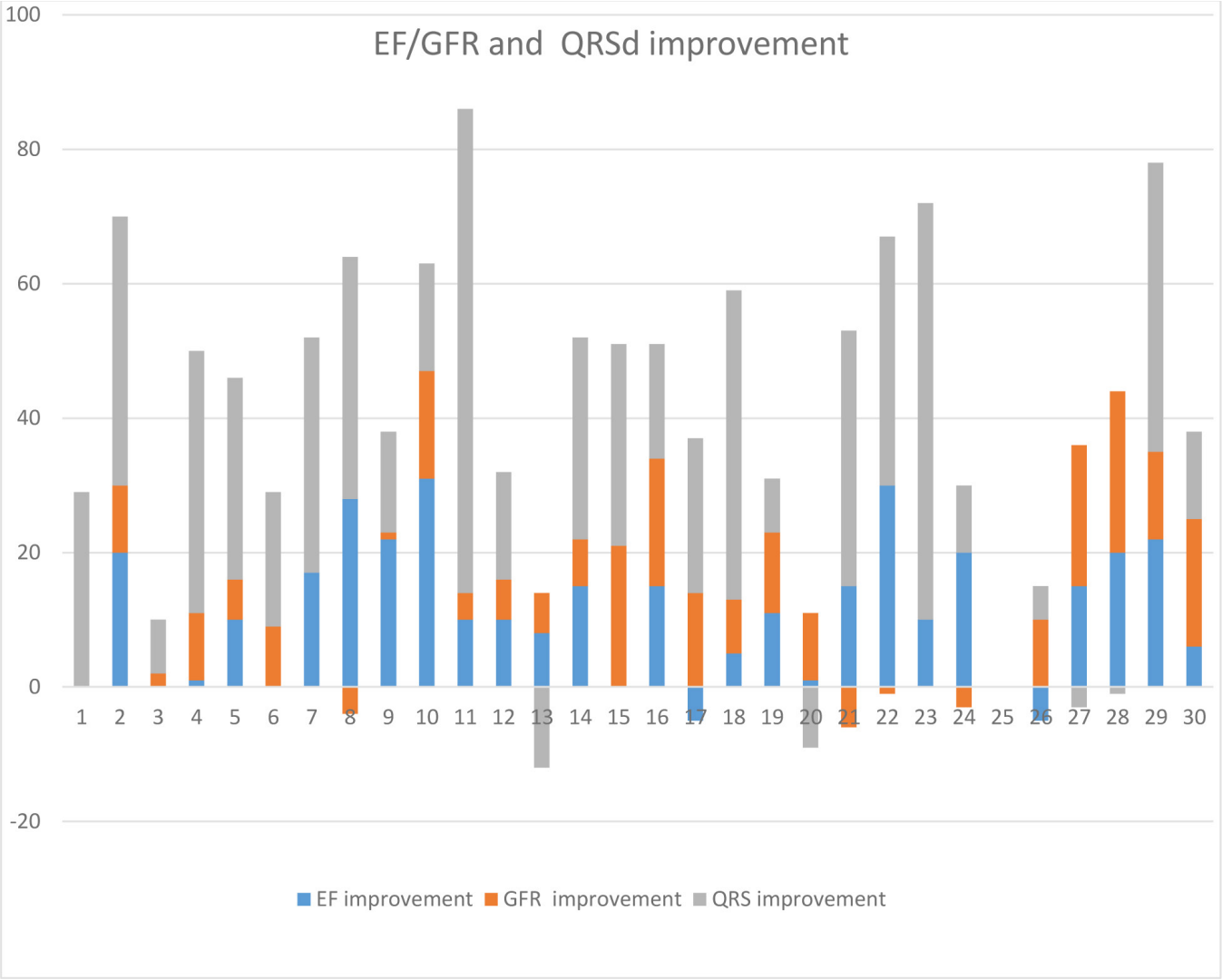

Figure 4: **Diagram showing EF improvement, GFR Improvement and QRS improvement post procedure.**

delay, and heart failure symptoms despite optimal medical therapy. However, there are still significant limitations to this therapy. For one, biventricular device implantation may be associated with significant radiation and contrast exposure. In addition, approximately 30% of patients do not experience improvements in heart failure symptoms or LV function with CRT [5].

However, the number of BIV ICD implantations is increasing due to inclusion of class II and class I ischemic patients with LBBB as indications. Patients undergoing these procedures can be exposed to a significant amount of radiation and contrast. Some patients also undergo multiple procedures further adding to their cumulative radiation and contrast exposure.

For the most part, the use of 3D EAM for identifying anatomical structures of the heart had been relegated to EP studies and ablations. [6, 14] As the technology continues to advance, its applications are growing. The technology has advanced enough allowing Naurizio Del Greco and colleagues to demonstrate feasibility of electroanatomical mapping in the implantation of a CRT-ICD device. [2] These findings were replicated by our prior cohort study demonstrating the safety and feasibility of EAM in BIV ICD implantation. [1]

Another area driving the push for implementation of electroanatomical 3D mapping involves the subset of patients in which fluoroscopy or contrast exposure poses too high of a risk or is even contraindicated. These subsets include the pediatric patient, those patients who are pregnant and patients with advanced renal disease.

Jason Payne MD and colleagues demonstrated the use of electroanatomical mapping in the implantation of pacemaker in a pregnant patient.[7]

Individuals with chronic kidney disease or near end stage kidney disease represent another high risk population. In this population exposure to contrast may induce further renal damage and possibly lead to dialysis. Celik and his colleagues identified independent

predictors for CI-AKI as low ventricular ejection fraction, e-GFR < 60ml/min and contrast volume (CV)-e-GFR ratio of greater than 2 in patients undergoing primary PCI.[8] Furthermore, contrast volume to GFR ratio of 3.9 has been specified to predict CIN development with 71% sensitivity and 80% specificity in patients undergoing TAVI.[9]

CI-AKI is a serious and frequent procedural complication of CRT-D implantation with a significant negative influence on long-term survival [10]. The risk of CI-AKI with CRT implantations is substantial. Data on CI-AKI in patients undergoing cardiac resynchronization therapy is limited.

Of the data available the TRUST CRT trial showed that among the 98 subjects of the trial, 10 patients (10.2 %) developed CI-AKI after CRT-D implantation.[7] In patients with glomerular filtration rate (GFR) <60 mL/min/1.73 m2 on admission, the incidence of CI-AKI was almost two-fold (15.4 %) higher than in subjects with GFR ≥60 (8.3 %). CRT-D recipients with CI-AKI had significantly higher mortality rate (50.0 %) compared to those without CI-AKI (17.0 %) during 30 months of follow-up. [11]

Furthermore, Cowburn et al. demonstrated 14 % occurrence of contrast-induced nephropathy defined as at least 25 % increase in serum creatinine from the baseline within 48 h after contrast exposure during CRT implantation. [10]

According to CIN (contrast induced nephropathy)Consensus Working Panel from 2006, CIN is responsible for approximately 11 % of hospital-acquired renal failure cases [9] Thus, these findings coming mainly from registries, where coronary angiograms and PCI were the leading causes of CI-AKI, are similar to the incidence of CI-AKI demonstrated in CRT recipients.[12]

Gregory A. Tester et al were able to demonstrate this in their large subject population (Eight hundred and twenty-two subjects) in which patients were divided based on the amount of procedural contrast used into tertile 1 (<55 mL, 257 patients), tertile 2 (55–94 mL, 261 patients), and tertile 3 (≥95 mL, 304 patients). Contrast-induced nephropathy occurred in 5.4% of patients in tertile 1, 5.4% in tertile 2 and 11.8% in tertile 3 (P = 0.004). Among the tertiles, lead positioning was optimal in 95, 80 and 66%, respectively (P < 0.0001). In this study most patients had kidney function baseline GFR 57 ± 21 mL/min. [13]

It is therefore expected that CIN would be even more substantiated with patients with poor renal function.

We have shown in prior study the feasibility of 3 D mapping to reduce fluoroscopy use in patients with normal renal function. However, there is no study to our knowledge that evaluated the feasibility of EAM in BIV ICD implantation in patients with advanced renal disease largely because of increased threat for of CI-AKI in those patients. Making the utility of implantation of CRT device in patients with advanced renal disease restricted and in most cases not even offered for fear of needing dialysis post procedure. In our paper we were able to substantially reduce contrast exposure to minimal with an average contrast volume to GFR ratio of 0.10 and maximum ratio of 0.2 which is well below the ratio of 2 at which CI-AKI is observed in other studies.

This is the first study to demonstrate feasibility of EAM in near elimination of contrast use during BIV implantation in patients with advanced renal disease. A population in which the risk for contrast induced nephropathy is substantial as described above. Despite the added steps of EAM there was a favorable procedure time which may be attributed to the facilitation of 3 D mapping to navigate leads in target sites rather than 2 D fluoroscopy technology, also the use of Quadripolar leads in selected cases may have eliminated some time when diaphragmatic stimulation or high thresholds were encountered.

Study Limitation

We do recognize a number of limitations to our study which includes small, non-randomized study, performed by a single operator who has experience in use of EAM techniques during catheter ablation and have performed various ablations including atrial fibrillation, ventricular tachycardia without use of fluoroscopy. Given small sample size statistical power is not very high as well. With that being said, we do report a strategy for zero contrast implantation of BiV device that can be utilized in experienced centers with EAM to safely implant BiV ICD in patients with renal disease.

Uncontrollable variables such as patient anatomy and underlying patient comorbidities influence outcomes as well and are much more difficult to control for. Further ongoing studies evaluating feasibility, efficacy and safety will need to be performed.

Another set of limitations involve the EAM system itself. The technology is fairly expensive and would require capital cost for those centers where the EAM system is not available. The EAM system itself also requires technical expertise to drive the EAM system along with experience level of lab personnel. Both of which could lead to added costs, procedure times.

Although there is added cost to the procedure there may be a potential for cost saving overall if we factor the decreased hospital stay, improved renal function and the delay of early dialysis in this patient population with this technique. Cowburn PJ et al showed that the mean length of hospital stay post-procedure in patients developing contrast nephropathy was 19+/-18 (SD) days versus 4+/-5 days for those patients with stable renal function post CRT implantation [10].

Disclosures

No financial disclosures.

Conclusion

Further studies will be needed to evaluate safety and efficacy of this technique on a broader patient population.

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Prevalence and Factors Associated with Atrial Fibrillation Among Patients with Rheumatic Heart Disease

Sahadeb Prasad Dhungana[1], Rajesh Nepal[1], Rinku Ghimire[2].

[1]*Associate Professor of Cardiology, Nobel Medical College Teaching Hospital, Biratnagar, Nepal.*
[2]*Lecturer, Department of Pharmacology, Nobel Medical College Teaching Hospital, Biratnagar, Nepal.*

Abstract

Introduction: Rheumatic heart disease (RHD) is one of the common causes of atrial fibrillation (AF) and is associated with significant morbidity and mortality. There is a lack of data on the prevalence of AF and factors associated with increased risk of AF in patients with RHD from Nepal.

Methods: A total of 120 patients who received care at Nobel Medical College Teaching Hospital from January 2018 to February 2019 with a diagnosis of RHD with AF were enrolled. Demographic information, relevant clinical and laboratory parameters and predisposing conditions for AF were obtained from a structured questionnaire designed.

Results: The prevalence of AF was 120 (36.3%) out of 330 cases of RHD screened. The male to female ratio was 32:88. The mean age was 50.2 (range 22-80) years. Prevalence was slightly more in females (36.9%) as compared to males (34.7 %). The prevalence of AF in patients with predominant mitral stenosis (MS) was 66.6% and less in patients with predominant mitral regurgitation (MR) (16.6%). The prevalence of AF in cases of MS with mitral valve area (MVA) < 1.5 cm2 was 76.2% as compared to 23.7% in cases with MVA > 1.5 cm2. Mitral valve (MV) was the most commonly affected valve (83.3%) followed by the aortic valve (10%). Both mitral and aortic valves were involved in 6.6% of patients. Majority of patients (97.5%) had enlarged left atrium (>40mm), reduced estimated glomerular filtration rate (eGFR) of <90 ml/min (85.8%). Patients of RHD with AF were complicated with decreased left ventricular (LV) systolic function (67.5%), pulmonary artery hypertension (52.5%), left atrial clot (9.1%), stroke (8.3%), and peripheral embolism (2.5%).

Conclusions: AF is a common rhythm disorder in patients with RHD. Prevalence of AF is common in females, increases with age, increasing LA size, increased severity of MS and decreased level of eGFR.

Introduction

Rheumatic heart disease (RHD) is one of the common types of structural heart disease and carries significant morbidity and mortality [1]. Although uncommon in developed countries, RHD is still a public health problem in developing countries like Nepal and is associated with a higher incidence of AF.

The association between AF and RHD is well established. The presence of RHD was a strong predictor of the development of AF [2]. Although information regarding the overall prevalence of AF in various cardiac conditions and its predictors are available from studies done in different countries, there is a paucity of data among patients with RHD in particular. The knowledge of factors associated with increased risk of AF in patients with RHD is important for its prevention and to reduce morbidity and mortality. Hence, this study will give insight into the prevalence of AF and various factors associated with AF in patients with RHD.

Key Words

Atrial fibrillation, Prevalence, Rheumatic heart disease, Risk factors.

Corresponding Author
Dr. Sahadeb Prasad Dhungana
Nobel Medical College Teaching Hospital,
Biratnagar, Nepal

Methods and Materials

This is an observational cross-sectional study. The diagnosis of RHD was based on the basis of clinical history, examination, and echocardiography. The patients were classified as in sinus rhythm or AF based on (ECG). AF is defined as an irregularly irregular heart rate without detectable 'a' wave along with f wave on 12 lead ECG. A total of 330 patients of RHD with age >15 years who received care at the cardiology unit of the Department of Internal Medicine, Nobel Medical College Teaching Hospital were screened for AF on a consecutive basis. Focused history and examination were performed to note demographic profile and co-morbid conditions. Echocardiographic parameters like different valves' involvement, its severity, mitral valve area, left atrial size, left ventricular (LV) size, LV function was assessed.

Echocardiography

Transthoracic echocardiogram (GE, Vivid E95, and Chicago, USA) was performed with use of 2D, M-mode, doppler modalities. Images were taken from the parasternal long axis, parasternal short axis, apical four chambers, and apical five-chamber views. The mitral valve area (MVA) was quantified based on planimetry and pressure half time (PHT) methods. Mitral stenosis (MS) was classified as mild for valve area between 1.6–2.0 cm2, moderate for 1.1–1.5 cm2, and severe for ≤1.0 cm2. Mitral and aortic regurgitation were evaluated

using quantitative methods. Aortic stenosis (AS) was diagnosed based on the presence of commissural fusion of the aortic leaflets. Valve area was assessed using planimetry and pressure gradient across the valve.

Statistical Analysis

Data were entered in Microsoft excel 2007 and converted into IBM SPSS data editor, version 20. Continuous and categorical variables were presented as mean, percentage and interquartile range wherever found necessary. The tabular presentation was made for necessary variables.

Results

The prevalence of AF was 120 (36.3%) out of 330 cases (238 females and 92 males) of RHD screened. The male to female ratio was 32:88. The mean age was 50.2 (range 22-80) years. The prevalence of AF was more in the age group of 30-60 yrs (81.6%) and the prevalence was slightly more in females (36.9%) as compared to males (34.7%). Among all patients, 10 (8.3%) were current smoker and 6 (5%) had a history of significant alcohol consumption. Mean hemoglobin (Hb) was 12.9 gm/dl (range 8.3-18.7) with 43(35.8%) patients having anemia (Hb <12gm/dl). Mean body mass index (BMI) was 21.39 (range 13.8-33.7) kg/m2 with 24 (20%) having BMI <18kg/m2. Majority 103 (85.8%) had reduced eGFR of <90 ml/min. Baseline characteristics of patients with RHD and AF have been illustrated in [Table 1].

Table 1: Baseline characteristics of patients with atrial fibrillation (n= 120)

Characteristics	Number
Male: female	32:88
Mean age in years (Range)	50.2 (22-80)
Smoker	10 (8.3%)
Alcohol use	6 (5%)
Education level and employment	
No education	95 (79.1%)
Primary education	25 (20.8%)
Currently employed	12 (10%)
Mean body mass index in kg/m2 (Range)	21.39 (13.8-33.7)
Mean systolic blood pressure in mmHg (Range)	107.5 (80-150)
Mean diastolic blood pressure in mmHg (Range)	72.2 (60-100)
Mean hemoglobin (gm/dl) (Range)	12.9 (8.3-18.7)
Mean eGFR (ml/min)	69.5 (26.1-125)
Mean heart rate (BPM)	93.74 (50-160)
Heart rate (BPM) < 100	77 (64.1%)
≥100	43 (35.8%)
Prior history of rheumatic fever	12 (10%)
Coronary artery disease	2 (1.6%)
Drugs use pattern	
Antithrombotics	
Aspirin	70 (58.3%)
OACs	46 (38.3%)
None	4 (3.3%)
For rate control	
Beta-blockers	70 (58.3%)
Calcium channels blockers	46 (38.3%)
Digoxin	10 (8.3%)
Diuretics	94 (78.3%)
Penicillin prophylaxis	30 (25%)

eGFR: Estimated glomerular filtration rate, BPM: Beat per minute, OACs: Oral anticoagulants

The mitral valve was the most commonly affected valve (83.3%) followed by the aortic valve (10%). Both mitral and aortic valves were involved in 6.6% of patients. The primary Tricuspid valve was involved in 4.1% and secondary Tricuspid regurgitation was present in 52.4% cases. The prevalence of AF in patients with predominant MS was 66.6% and less in patients with predominant MR (16.6%) as shown in [Table 2]. The prevalence of AF in cases of MS with mitral valve area ≤ 1.5 cm2 was 76.2% as compared to 23.7% in cases of MS with MVA > 1.5 cm2. Majority of patients (97.5%) had enlarged left atrium (>40mm), reduced estimated glomerular filtration rate (eGFR) of <90 ml/min (85.8%). Distribution of different characteristics and risk factors in patients with AF has been illustrated in [Table 3].

Patients of RHD with AF were complicated with decreased LV systolic function (67.5%), pulmonary artery hypertension (52.5%), left atrial clot (9.1%), stroke (8.3%), and peripheral embolism (2.5%) as shown in [Table 4].

Discussion

RHD is one of the common causes of AF and associated with significant morbidity and mortality [3]. Thus, the estimation of the burden of AF and factors associated with AF is important for its prevention and control. Various studies have reported the prevalence of AF in patients with RHD which ranges from 13.9% to 43 % [3,4,5,6]. In our study, we observed a significant burden of AF (36.3%) in patients with RHD.

In low to middle-income countries, RHD, particularly mitral stenosis is the common cause of AF and it is more common in women than men [7]. Similarly, in our study, we observed an increased prevalence of AF in female patients.

There is an independent association of AF with age, LA size and MS among patients with RHD. [4] Although the average age of patients with RHD developing AF in developing countries is 15 to 20 years earlier than patients in western countries [8]. In the present study, the highest incidence of AF was found in the age group of 31 to 60 years.

LA size and severity of MS were reported as the risk factors of AF in a retrospective cohort of patients of RHD with MS [9]. The occurrence of AF is known to correlate with LA size, and the incidence of AF rises from 3% when the left atrial diameter is < 40mm to 54% if the left atrial diameter is > 40 mm [10]. In our patients with RHD, 97.5%

Table 2: Patterns of valve involvement (n=120)

Valves	Number
Mitral valve	100 (83.3%)
Predominant MS	80 (66.6%)
Predominant MR	20 (16.6%)
Aortic valve	12 (10%)
Predominant AS	8 (6.6%)
Predominant AR	4 (3.3%)
Mitral +Aortic valve	8 (6.6%)
Tricuspid Valve (primary)	5 (4.1%)
Tricuspid Valve (Secondary)	63 (52.5%)

MS: Mitral stenosis, MR: Mitral regurgitation, AS Aortic stenosis, AR: Aortic regurgitation

of patients with AF had an LA size of more than 40mm.

Several studies in patients with various cardiovascular diseases reported an increased incidence of AF with a decreasing threshold of eGFR [11, 12, 13]. We observed an increased prevalence of AF among patients with RHD with a decreasing level of eGFR since 85.7% of our patients had eGFR of less than 90 ml/min.

Although chronic anemia is an independent predictor of death and hospitalizations in elderly patients with HF, coronary artery disease or AF, [14] it has not been shown to be associated with an increased incidence of new-onset AF [15]. Similarly, we did not find any relationship between blood hemoglobin levels and the prevalence of AF in our patients with RHD.

Although Zafar N et al [16] could not find an association between AF and the severity of MS, there is an association between the severity of MS and burden of AF as reported by Keren et al [17] and Sharma SK [6] . In our study, we found that the prevalence of AF increased with moderate to severe MS compared to mild MS. The observed association of AF with the severity of MS may have clinical implications for AF prevention offering percutaneous transvenous mitral commissurotomy (PTMC) for mild to moderate MS in the prevention of AF.

Table 3: Distribution of different characteristics and risk factors in patients with Atrial Fibrillation

Characteristics	Number
Female	88 (73.3%)
Male	32 (26.6%)
Age (in years)	
≤ 30	3 (2.5%)
31-40	28 (23.3%)
41-50	34 (28.3%)
51-60	36 (30%)
61-70	12 (10%)
≥70	7 (5.8%)
Body mass index (kg/m2)	
<18	24 (20%)
18-23	63 (52.5%)
>23	33 (27.5%)
eGFR (ml/min)	
<50	23 (19.1%)
50-90	80 (66.6%)
>90	17 (14.1%)
Blood Hemoglobin (gm/dl)	
<10	6 (5%)
10-12	37 (30.8%)
>12	77 (64.1%)
LA diameter (mm)	
<40	3 (2.5%)
41-50	42 (35%)
>50	75 (62.5%)
LVEF (%)	
<40	19 (15.8%)
40-55	62 (51.6)
>55	39 (32.5%)
MVA (cm2)	
<1	30 (25%)
1-1.5	31 (25.8%)
1.6-2	19 (15.8%)

eGFR: Estimated glomerular filtration rate, LA: Left atrium, LVEF: Left ventricular ejection fraction, MVA: Mitral valve area

Table 4: Complications of atrial fibrillation in patients with rheumatic heart disease

Complications	Number
LV systolic dysfunction (LVEF <55%)	81 (67.5%)
Pulmonary artery hypertension	63 (52.5%)
LA/LAA clot	11 (9.1%)
Stroke	10 (8.3%)
RV dysfunction	6 (5%)
Peripheral embolism	3 (2.5%)

LV: left ventricular, LVEF: left ventricular ejection fraction, LA: Left atrium, LAA: Left atrial appendage, RV: Right ventricle

Limitations

This study lacks data on a control group which would have provided an important contrast and helped to adjust the variables. This is a single-center study in a limited number of patients that may influence the estimation of the prevalence of AF and its determinants in patients with RHD. The prevalence of AF was documented based on ECG that was done at the time of enrollment thus paroxysmal AF may have been missed.

Disclosure

The authors declare no conflict of interest.

Conclusion

AF is a common rhythm disorder in patients with RHD. Prevalence of AF is common in females, increases with age, increasing LA size, increased severity of MS and decreasing the level of eGFR. AF increases the risk of left ventricular dysfunction, pulmonary hypertension, and systemic thromboembolism.

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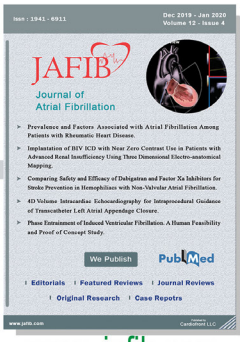

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Hemoptysis After Cryoablation For Atrial Fibrillation

Narendra Kumar[1], Madhan Kumar Ranganathan[2], Shaimaa Mustafa[3], Carl Timmermans[4].

[1]*Dept. Of Cardiology, Manchester University NHS Foundation Trust.Oxford Road, Manchester, M13 9WL, UK .*
[2]*BronxCare Health System, Bronx, New York,NY 10457 USA .*
[3]*Assistant professor of cardiovascular medicine, Benha University, faculty of Medicine, Egypt.*
[4]*Department of Cardiology, Maastricht University Medical Centre, and Cardiovascular Research Institute Maastricht (CARIM), the Netherlands.*

Abstract

Aim: Cryoballoon is a widely used tool for ablation for atrial fibrillation (AF). There are several complications after cryoablation. This paper assesses the incidence rate and severity of hemoptysis after cryo ablation for AF.

Methods: For current systemic review and meta-analysis, literature has been reviewed from 2008 to 2019 focusing on the incidence of hemoptysis after cryoballoon ablation for atrial fibrillation catheter ablation in PubMed, Cochrane library and EMBASE databases.

Results: This meta-analysis included 3534 patients from 20 studies; of mean age 54.0 ± 10.9 years. All patients had cryoballoon ablation for paroxysmal or persistent AF refractory to treatment and follow up duration for 8.2 ± 5.9 months with mean procedure duration of 153.4± 65.4 minutes. The mean cryoablation duration was 869.4 ± 148 sec with mean temperature of -59.7 ± 5.1°C and a total of 109 patients (3.08%) had hemoptysis which was mild in the majority of cases (76.1%), mild to moderate in 20.2% and severe in only 3.7%. Hemoptysis onset was at 29.0 ± 56.5 day with median of 7 days, range (2 hours to 210 days). In 11 studies hemoptysis occurred early in 51 patients (95% CI for I^2 was 0.0% to 0.0, P =0.95, I^2 was 0.0%), but in 9 studies, hemoptysis occurred late in 58 patients (95% CI for I^2 was 0.0% to 0.0, P =0.96, I^2 was 0.0%).

Conclusions: Mild hemoptysis is experienced by significant number of cryoballoon AF ablation patients and severe type in 3.5 % attributed to significantly lower temperature in inferior pulmonary veins and is more often associated with bigger cryoballoon.

Introduction

Catheter ablation is an effective treatment for atrial fibrillation (AF), and pulmonary vein (PV) isolation is considered the cornerstone of all AF ablation strategies. In recent years, balloon-based ablation has emerged as an encouraging alternative to RF ablation and is equally effective for PV isolation in patients with paroxysmal and persistent AF [(1)]. There are several reasons for this. The acute and long-term safety and efficacy associated with cryoablation appears comparable to that of radiofrequency ablation in patients with both paroxysmal and persistent types of AF. Moreover, cryoablation offers a milder learning curve, shorter ablation duration and overall procedure time and simultaneously avoiding costly electroanatomical mapping technologies. Lastly, with the recent advent of the second-generation cryoballoon, the effectiveness of cryoablation has further improved dramatically [(2)].

It is important to evaluate procedure-related complications described to date, to understand its mechanism and to take steps to minimize their occurrence. Complications of cryoenergy ablation may be due to damage of structures close to the application site, resulting in phrenic nerve (PN) paralysis, gastroparesis, atrioesophageal fistula, or esophageal lesions as collateral cryoablation damage. Until now few authors reported on hemoptysis after cryoballoon ablation but without regular follow-up or a definite etiology. Cryoablation causes vascular injury through multiple factors, including ice formation within the vasculature. The ice during expansion causes the formation of tears, clefts, leakages, and stasis postreperfusion. The interruption of vascular integrity is the reason for intramyocardial hemorrhage as well as for hemoptysis associated with cryoinjury to the lung tissue. A few reports on the effects of freezing have described acute lung injury due to cytokine release in about 35% of animal subjects [(3)].

Key Words

Cryoballoon, Atrial fibrillation, Hemoptysis, Complication, Temperature, Frozen lung.

Corresponding Author
Dr. Narendra Kumar.
Dept. Of Cardiology, Manchester University NHS Foundation Trust.
Oxford Road, Manchester, M13 9WL, UK

Methods

For this current systemic review and meta-analysis, Literature has been reviewed from January 2008 to March 2019 focusing on the incidence of hemoptysis after cryoballoon ablation for AF ablation in PubMed, Cochrane library and EMBASE databases. Data were analyzed using MedCalc software (MedCalc Software, Mariakerke, Belgium) to perform meta-analysis to provide a numerical estimate of the overall effect of interest from separate but similar studies. Total fixed and random effects were calculated.

Statistical analysis

Data were analyzed using MedCalc software (MedCalc Software, Mariakerke, Belgium). Descriptive statistics were computed for different variables. Qualitative data were presented as number and percentages. Mean ± SD, median, range were calculated for quantitative variables. Meta-analysis was performed to provide a numerical estimate of the overall effect of interest from separate but similar studies. Total fixed and random effects were calculated. To assess heterogeneity, Cochran's Q test and I^2 statistic were calculated, Cochran's Q test with low P-values indicates presence of heterogeneity. I^2 statistic, is the percentage of observed total variation across studies that is due to real heterogeneity rather than chance. The results of the different studies, with 95% CI, and the overall effect (under the fixed and random effects model) with 95% CI are illustrated in a graph called "forest plot" [23].

Continuous variables are expressed as mean ± standard deviation and were compared with the Mann Whitney U-test as appropriate. The significance level was set at $p < 0.05$. The systemic review was conducted according to PRISMA guidelines.

Study selection criteria

Total of 125 studies were included through database and 43 studies were excluded as duplicate or irrelevant references. Further, a total of 59 studies were excluded by screening, and 3 more study

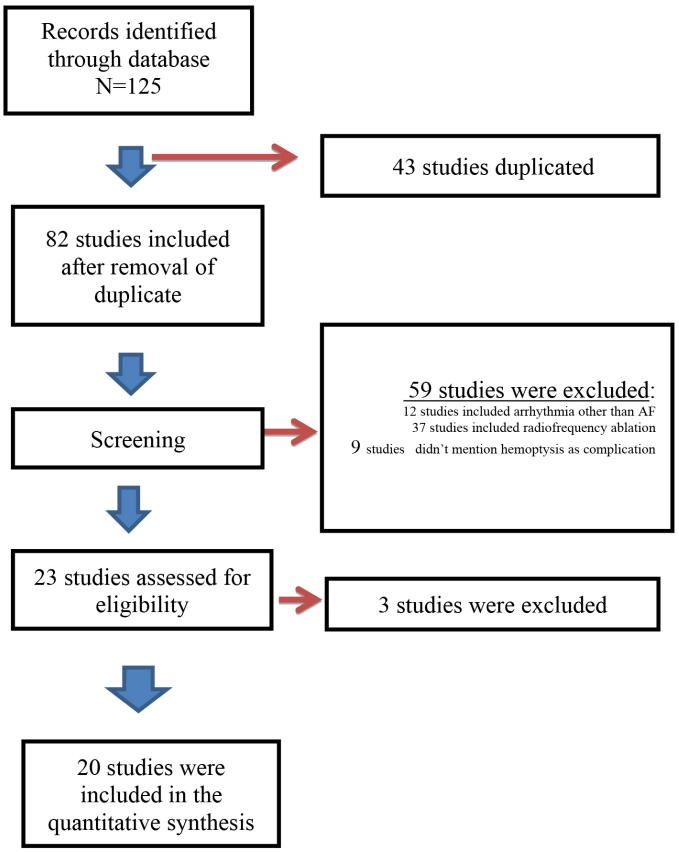


Figure 1: Overview of the manuscripts selected for the systemic review and meta-analysis.

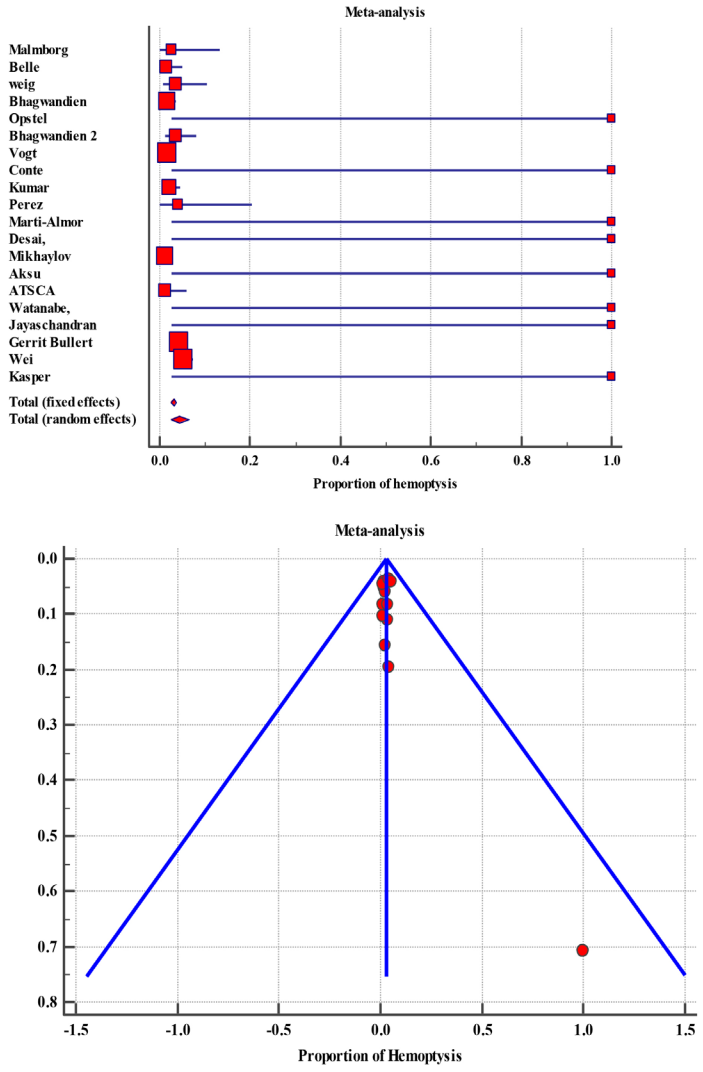


Figure 2: Meta-analysis of proportion and Forest plot for the proportions of hemoptysis incidence

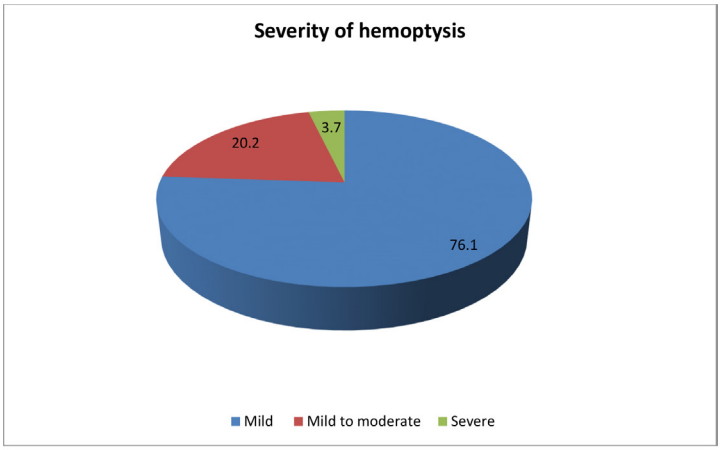
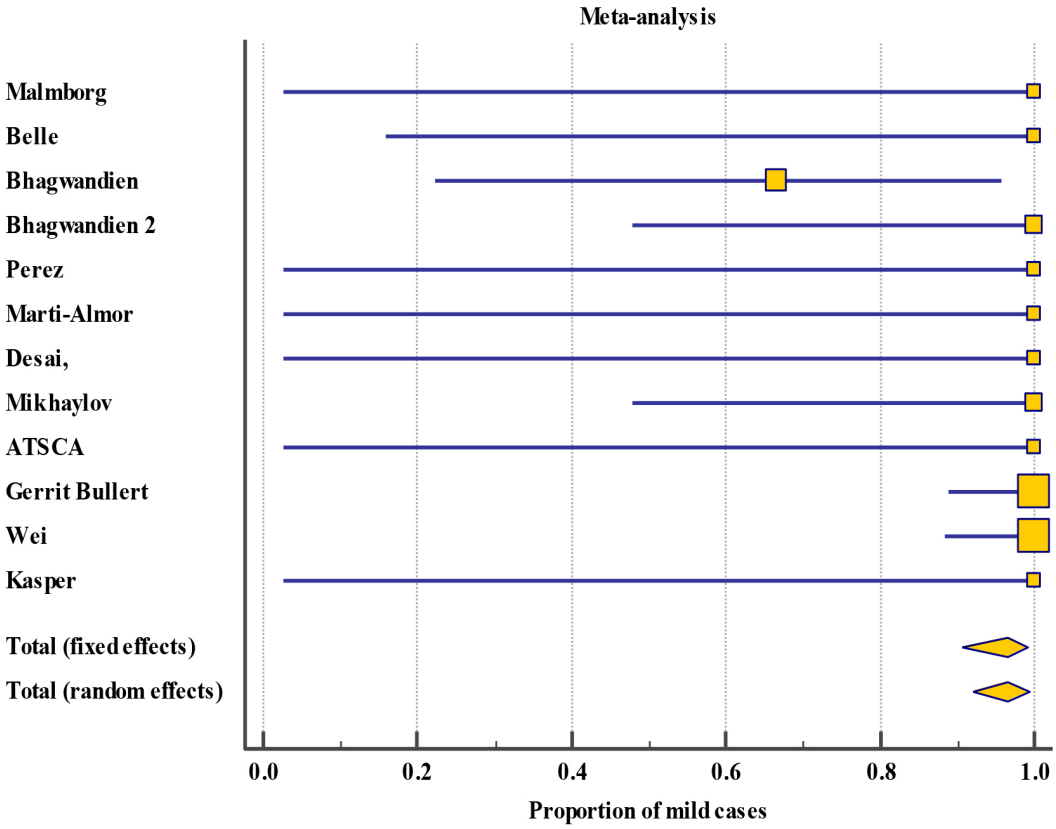


Figure 3: Severity of hemoptysis



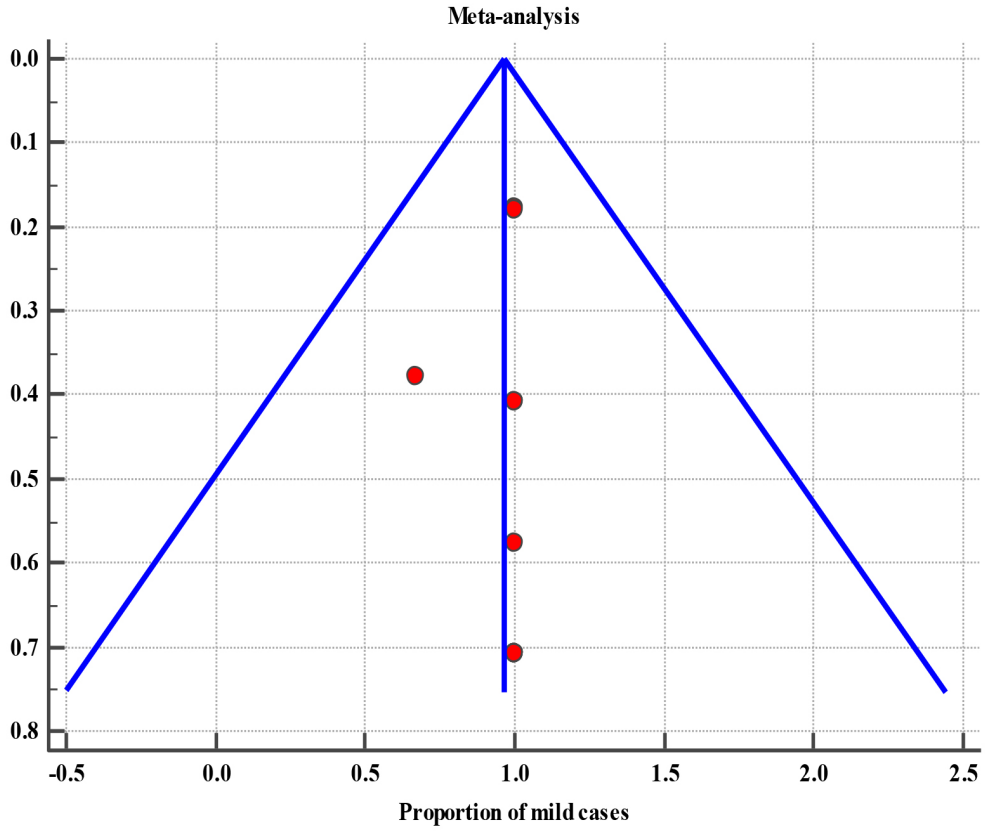
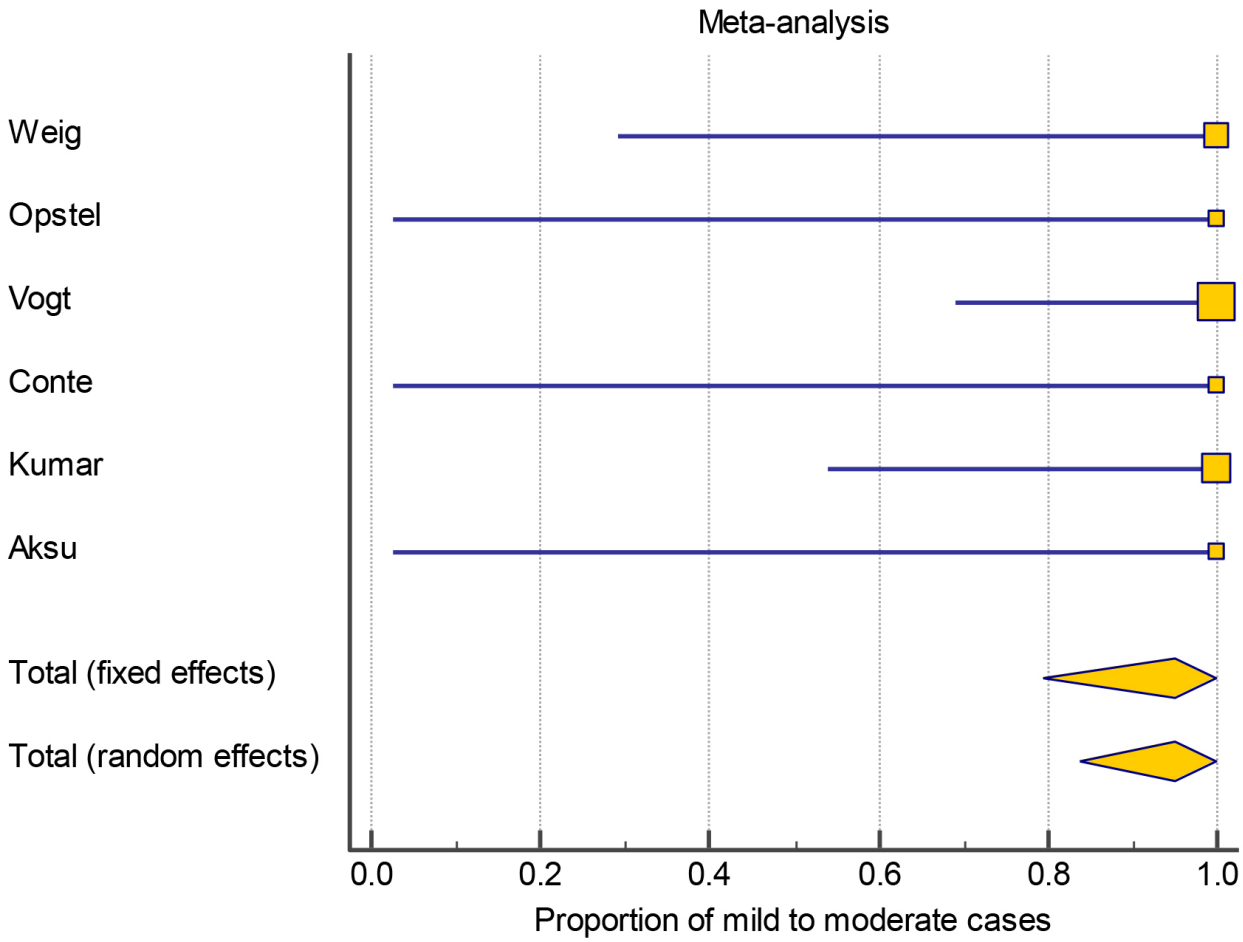


Figure 4: Meta-analysis and Forest plot for the proportions of mild hemoptysis



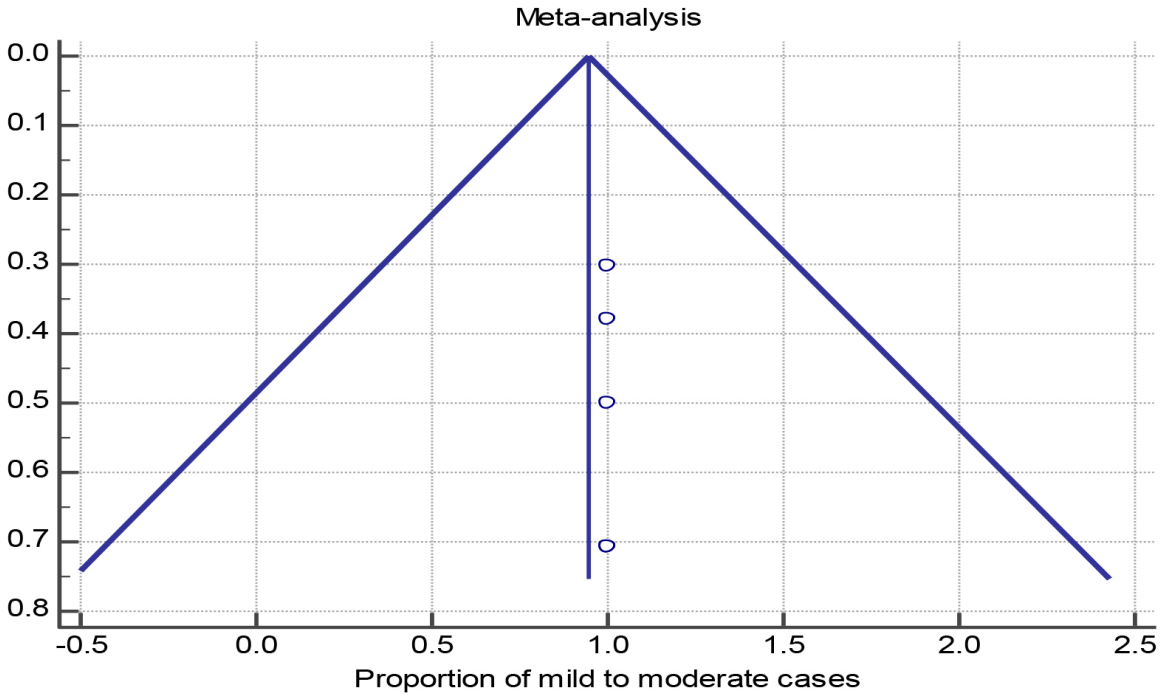


Figure 5: Meta-analysis and Forest plot for the proportions of mild to moderate hemoptysis

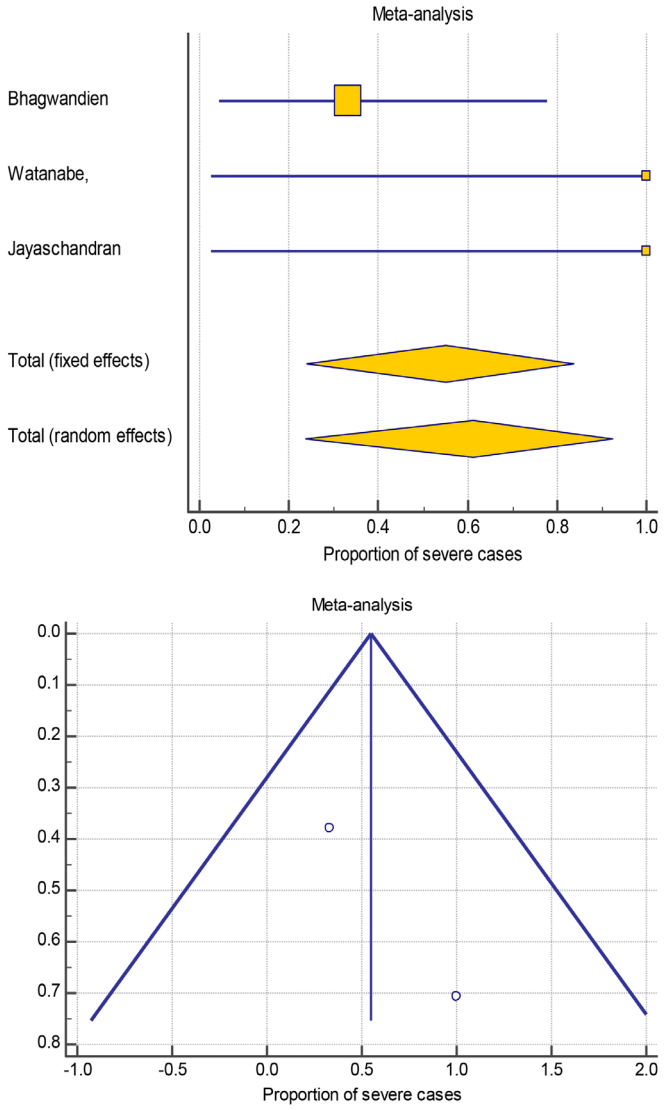


Figure 6: **Meta-analysis and Forest plot for the proportions of severe hemoptysis**

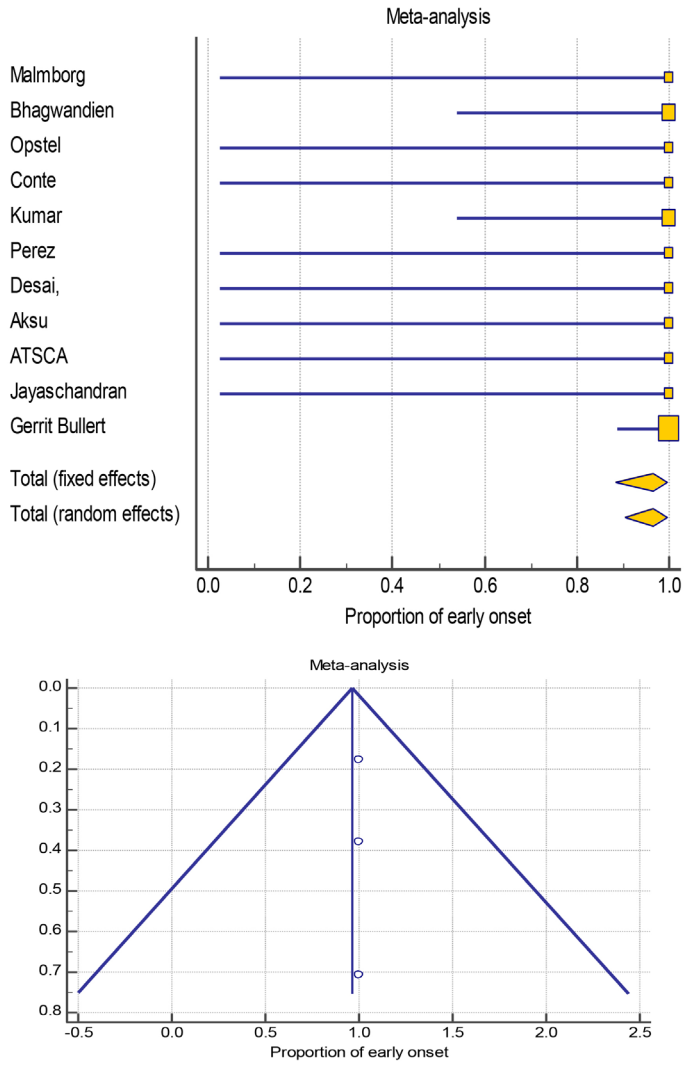


Figure 7: **Meta-analyses and Forest plot for the proportions of early onset hemoptysis**

by eligibility, so the final number of the studies included in the quantitative synthesis were 21 studies as shown in [Figure 1] and 11. Of the 20 studies that were included in the meta-analysis, 8 studies were prospective while 2 were retrospective. The other 8 studies were case studies, with last 2 being surveys.

Study population

From 20 studies, a total of 3,534 patients of mean age 54.0 ± 10.9 years had balloon cryoablation for paroxysmal or persistent AF with follow up duration for 8.2 ± 5.9 month. The mean procedure duration was 153.4 ± 65.4 minutes, mean cryoballoon ablation duration was 869.4 ± 148 seconds and mean temperature was -59.7 ± 5.1 °C.

Incidence and severity of hemoptysis

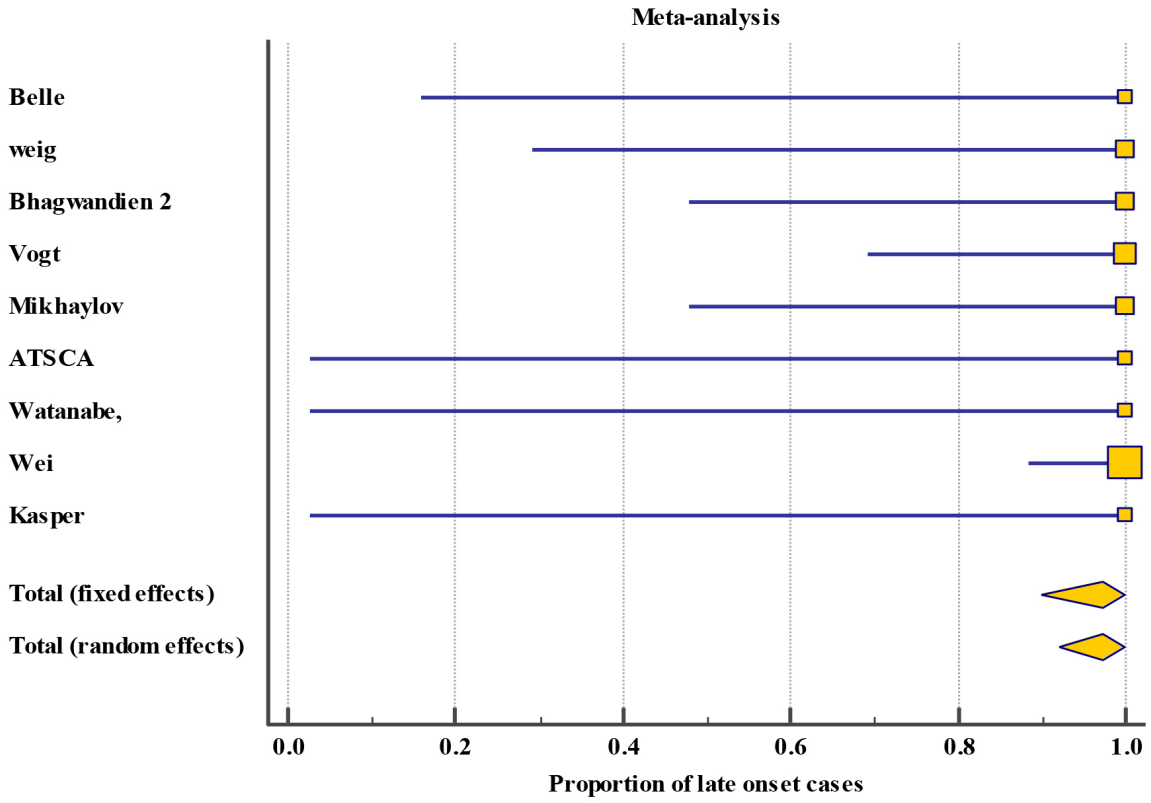
Out of 3,534 patients included in the study; 109 patients 3.08% developed hemoptysis (95% CI for I^2 was 69.3 to 86.5, P < 0.001, I^2 was 79.7%) as shown in [Figure 2]. Hemoptysis was mild in the majority of cases i.e. 77%, and mild to moderate in 19.5% and severe in only 3.5% as shown in [Figure 3].

[Figure 4] shows that a total of 12 studies revealed mild hemoptysis in 83 patients (95% CI for I^2 was 0.0 to 55.8 %, P =0.50, I^2 was 0.0%). [Figure 5] shows that a total of 6 studies demonstrated mild to moderate hemoptysis in 22 patients (95% CI for I^2 was 0.0 to 0.0 %, P =0.97, I^2 was 0.0%). [Figure 6] shows that 4 studies demonstrated severe hemoptysis in 4 patients (95% CI for I^2 was 0.0 to 97.7%, P =0.227, I^2 was 32.4%).

Moreover, on doing detailed analysis further, bigger cryoballoon was associated higher incidence of hemoptysis as seen in supplementary file.

Onset of hemoptysis

The onset of hemoptysis was at the day 29.0 ± 56.5 after cryoablation with median of 7 days, and range of 2 hours to 210 days. Considering



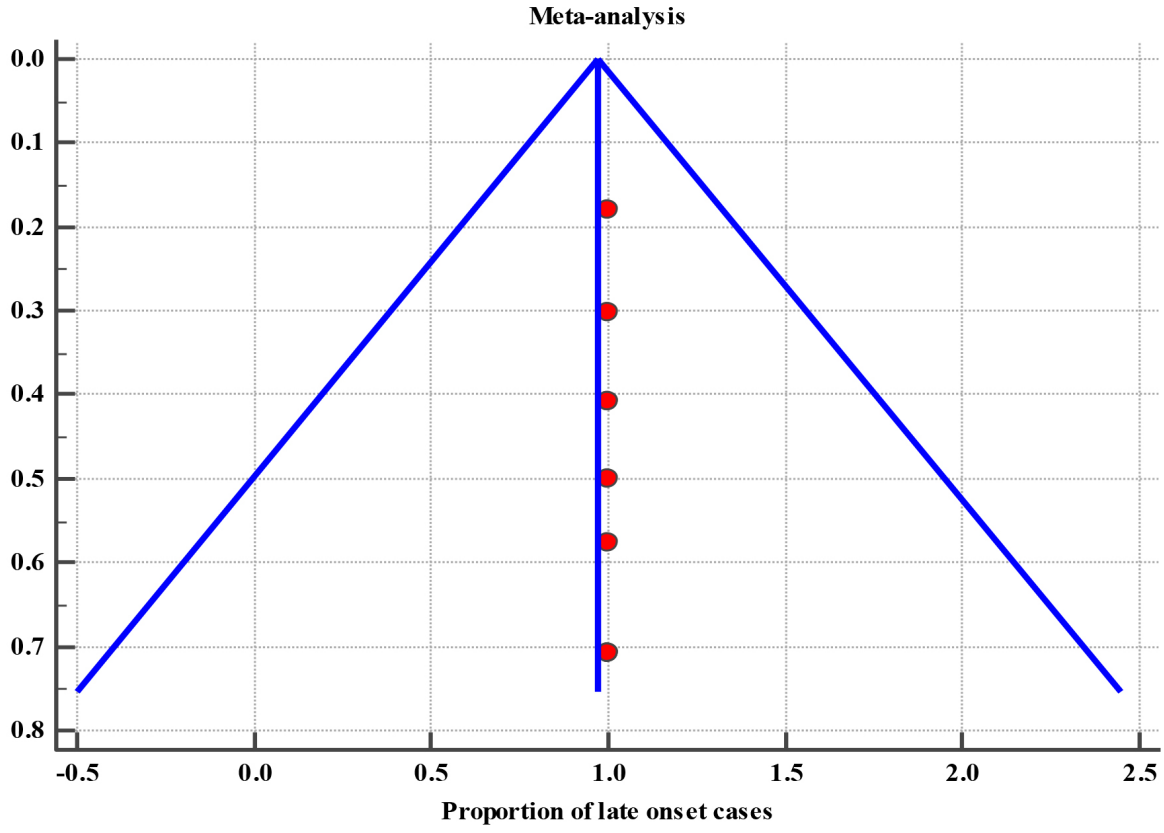


Figure 8: Meta-analysis and Forest plot for the proportions of late onset hemoptysis

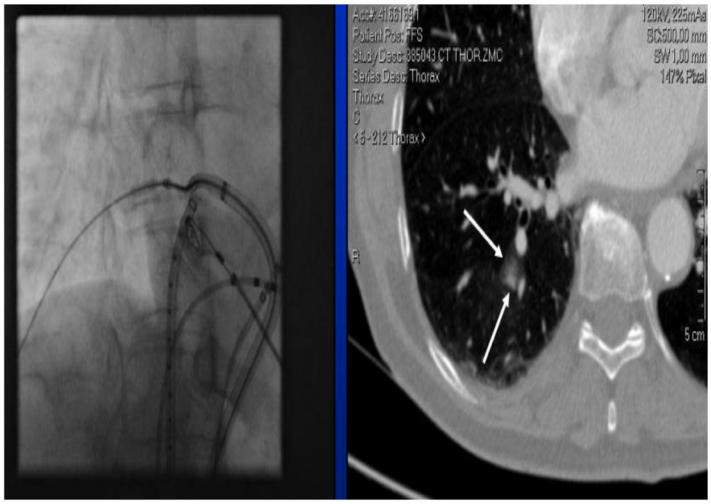


Figure 9: a)The deep position of the guide wire in the Right inferior pulmonary vein during intra procedural fluoroscopy. b) ground glass opacification seen on computed tomography scan.

Potential mechanism of hemoptysis:

- **Extremely low nadir temperatures (–60°C or lower):** lower nadir temperature during CB application (–66°C vs –45°C) showed increased bronchial mucosal oedema, erythema and inflammation in post-ablation bronchoscopy.
- **Deep seating of the CB:** collateral thermal injury of the bronchial tree
- **PV stenosis and obstruction:** induce lung circulatory stagnation and pulmonary artery dysfunction. this stagnation causes ischemia of the lung. this ischemia leads to overgrowth and abnormal development of the bronchial artery, which eventually dominates the ischemic lung and causes congestion in the lung because blood cannot flow to the left atrium. Finally, this rapidly developed fragile artery induces hemoptysis

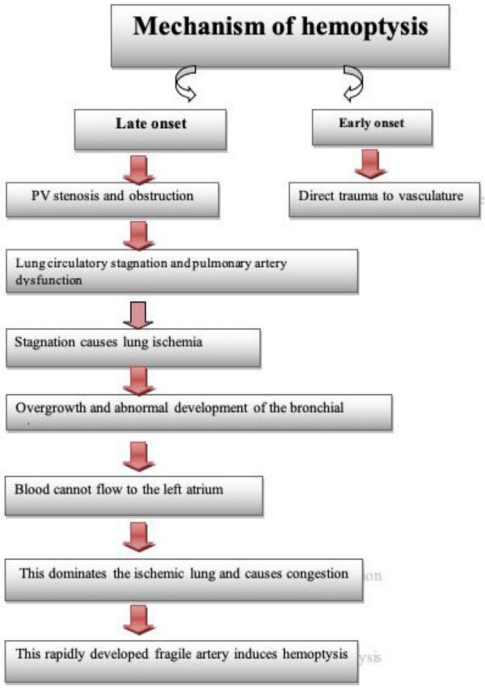


Figure 10: The potential mechanism for hemoptysis

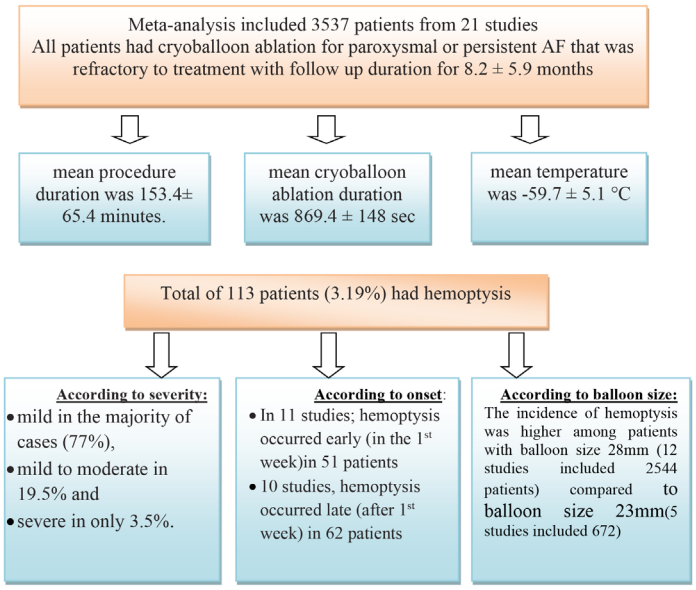


Figure 11: Central illustration for hemoptysis after cryoballoon ablation for atrial fibrillation.

the median of 7 days, the hemoptysis onset was classified into

1) early onset: starting in the 1st week and
2) late onset: starting after 1st week.

As per [Figure 7], a total of 11 studies revealed hemoptysis occurred in 51 patients within the 1st week of procedure (95% CI for I^2 was 0.0 to 0.0%, P =0.95, I^2 was 0.0%). However, [Figure 8] shows that 9 studies with 58 patients developed late hemoptysis (after 1 week of procedure) (95% CI for I^2 was 0.0 to 0.0%, P =0.96, I^2 was 0.0%).

Discussion

Hemoptysis has been reported sporadically by different authors following cryoablation of AF with varying incidence. The present paper emphasizes the association between hemoptysis and cryoballoon ablation of AF which is attributable to significantly lower temperature in inferior PVs. Transient interruption of vascular integrity, perhaps within the pulmonary capillary system due to cryoinjury, has been postulated as the reason for hemoptysis. Very low freezing temperature (which always is associated with good isolation) is the etiology for hemorrhagic infarction and the hemoptysis [9,17]. A possible mechanism might be that a complete isolation with very low freezing temperatures causes cryo-injury to the adjacent tissues and vasculature as summarized in [Figure 10]. Based on the evidence till date, both the clinical symptoms and findings appear to be self-limiting, with gradual resolution over time [10-14]. No evidence has shown that these cases are associated with catastrophic complications, such as the formation of a fistula [3]. Bronchial erosion can also be detected during bronchoscopy [15-16]. Moreover, an argument against direct trauma is the fact that in some cases it took several hours to days for the hemoptysis to become clinically overt. When causing a vascular rupture through instrumentation, bleeding would be expected to occur immediately and is usually severe. PV ablation might cause vascular damage in the pulmonary capillary tissue caused by a pressure rise when no collateral circulation is present. Meanwhile, it might be wise to limit the number of occlusions, or to shorten the occlusion time to a minimal duration [9]. But mechanisms leading to

complications have not been studied in details and the underlying mechanism, onset and severity were different in clinical trials as we can see from previous experience [18-21]. Below are several important studies who reported hemoptysis after cryoballoon ablation of AF.

Weig et al investigated 82 patients with paroxysmal AF who underwent single big cryoballoon technique for PV isolation and were followed up for 5 months. In 3 patients with a minimum temperature of −56°C and −59°C at a rather small left inferior and right inferior PV, respectively, a CT documented frozen lung complication, leading to coughing and hemoptysis for a maximum of one week. This complication forced them to stop post interventional anticoagulation [7].

In a series of 359 cryoballoon ablations, Bhagwandien et al [8] discovered clinically important hemoptysis requiring readmission in 2 patients. In the first patient the guiding wire was very distal in one of the veins and exceptional low freezing temperatures (-55° c) were recorded in the left inferior PV. Four additional patients complained of hemoptysis at the 3-month follow-up visit, which resolved after temporary cessation of anticoagulation. The authors concluded that hemoptysis can occur after cryoballoon ablation when a stringent anticoagulation regimen is adhered to, and when occlusion is associated with very low freezing temperatures. The authors further observed that PV isolation using a cryoballoon on 142 patients with AF was associated with hemoptysis in 4% of the patients. [9]

Vogt et al conducted a prospective observational study involved 605 consecutively enrolled patients with symptomatic paroxysmal AF (n = 579) or persistent AF. After 24 months. Hemoptysis with hematoma or edema around PVs was observed in 10 cases, all of which healed within 10 days. Patients remained free of hemoptysis during the follow-up period. [10]

Recently, Wei et al observed that 30 patients developed hemoptysis after second generation cryoballoon ablation, and it was compared with a matched control group. PV isolation was performed with 28-mm balloon using single 3-minute freeze technique. A shorter distance between left superior PV (LSPV) and left main bronchus (LMB) was associated with hemoptysis, whereas no significant difference in the distance between right superior PV (RSPV) and right main bronchus (RMB) was found between groups. LMB-LSPV distance as an independent predictor of hemoptysis (odd ratio 2.676; 95% CI 1.121–4.843, P < 0.001). A cutoff value ≤ 9.5 mm predicted hemoptysis after cryoballoon ablation with 93.8% sensitivity and 75.0% specificity [22].

Conclusion

Physicians must keep hemoptysis in mind with other complications during and after Cryoballoon ablation for AF. It has maximum incidence during and up to few days after procedure and is independent of other complications like phrenic nerve paralysis, gastroparesis. Dexterity of PV location does not influence the incidence. A high degree of suspicion is necessary to avoid misleading diagnostic procedures and to allow proper and prompt management.

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Sudden Cardiac Death in Famous Athletes, Lessons Learned, Heterogeneity in Expert Recommendations and Pitfalls of Contemporary Screening Strategies

Trenton Bickel[1], Prasad Gunasekaran[1], Ghulam Murtaza[2], Rakesh Gopinathannair[2], Sampath Gunda[3], Dhanunjaya Lakkireddy[2]

[1]*Division of Cardiovascular Disease, University of Kansas Hospital and Medical Center, Kansas City, Kansas.*
[2]*The Kansas City Heart Rhythm Institute & Research Foundation, Overland Park, Kansas.*
[3]*Division of Cardiology, University of Michigan, Ann Arbor, Michigan.*

Abstract

Sudden cardiac death (SCD) in competitive athletes, though relatively uncommon, invariably leads to controversy. Specific limitations of an extensive screening process include lack of robust evidence to support prevention of SCD, poor cost-effectiveness and uncertain downstream implications of a positive screening test. An emerging body of evidence points to enhanced neurologically intact survival to hospital discharge when automated external defibrillators (AEDs) are used in a timely manner following sudden cardiac arrest (SCA). A viable alternative to an expansive screening process could be a robust secondary prevention system comprising of improvements in AED availability, stringent enforcement of CPR training in athletes and trainers to provide timely and effective resuscitation to reduce death following SCA. This strategy could widen the window to diagnose and treat the underlying etiology and prevent recurrence of SCA while also offering financial feasibility. Restricting athletes from competitive sports is a difficult decision for physicians owing to a lack of well-defined cutoffs for acceptable and prohibitive risk from pathology predisposing to SCD, especially in the absence of a protective medico-legal framework. In this review, we highlight a few cases that generated intense scrutiny by the public, media and medical professionals about the efficacy, feasibility and pitfalls of the existing screening process to diagnose cardiovascular pathology predisposing to SCD. Furthermore, contrasting approaches to screening, diagnosis and downstream workup protocols between the European Society of Cardiology and the American Heart Association are analyzed.

Introduction

Athletes have traditionally been known to exhibit an exorbitant level of physical fitness and excellent cardiac health. Contrary to the general belief that they are relatively well protected from cardiac pathology, a diverse array of cardiac conditions have come to the fore of media attention by virtue of sudden unexpected deaths of celebrated athletes. SCD is defined as unexpected death due to a cardiac etiology occurring within 1 hour of symptom onset, most commonly from a lethal ventricular arrhythmia in individuals without a known potentially fatal condition.[1] This paper focuses on highlighting the conditions which are uncommon but carry a significant risk of SCD in young athletes, the incidence of SCD, available screening techniques and the pitfalls of contemporary screening for athletes with conditions predisposing to SCD. Our report emphasizes on delays in the recognition of sudden cardiac arrest (SCA), timely and effective delivery of cardiopulmonary resuscitation (CPR), and concurrent use of automated external defibrillators (AED) and their efficacy as a safety net once SCA has occurred. Often, SCA is the sentinel manifestation of these underlying conditions when individuals are subject to rigorous physical activity.

The highest incidence of SCD in young athletes is among those participating in sports like basketball, football, track, and soccer.[2] Triggers such as extreme physical exertion coupled with a substrate like underlying structural heart disease constitutes the pathologic basis of SCD in athletes.[1, 3] An age cutoff of 35 years delineates young from older athletes.[4] Hypertrophic cardiomyopathy (HCM) is reportedly the leading cause of sudden cardiac death in the younger age while atherosclerotic coronary artery disease predominate the older age group.[5, 6] Controversies have predominated aspects regarding modalities of screening, their cost-effectiveness, downstream efficacy and implications of testing for pathological entities predisposing to SCD.

We present cases highlighting SCD in famous athletes who gathered considerable public attention after their demise [Table 1]. These cases were influential in the study of SCD in athletes and were recommended by the American Sports Medicine Institute, American Medical Society for Sports Medicine, and the American College of

Key Words

Atrial fibrillation, Sudden cardiac death, Sudden cardiac arrest.

Corresponding Author
Dhanunjaya Lakkireddy, MD, FACC, FHRS
Executive Medical Director
The Kansas City Heart Rhythm Institute (KCHRI) HCA Midwest
Overland Park, Kansas

Sports Medicine.

Sudden Cardiac Death in Professional Athletes

Upon Reggie Lewis was a professional basketball player selected in the first round of the 1987 draft by the Boston Celtics and went on to become the league's leading scorer. He underwent a treadmill test which was reportedly unremarkable, days prior to a near-syncopal event during a playoff game in 1993 against the Charlotte Hornets. He continued through the game without subsequent events. Subsequent cardiac assessment revealed conflicting reports with a team of eminent cardiologists suggesting ventricular tachycardia (VT) from hypertrophic cardiomyopathy (HCM) and strongly advised against further participation in competitive sports. In contrast, a different cardiologist suggested neurocardiogenic syncope which and reinstate privileges to continue competitive sports. Amidst conflicting reports, Reggie Lewis resumed light workouts and Lewis succumbed to SCD at age 27 years during an off-season practice game. Autopsy revealed dilated cardiomyopathy with extensive myocardial scarring and normal coronary arteries. The complicated dynamics of this case generated immense media attention on the heterogeneity among experts and the need for aggressive risk assessment in trained athletes.

Hank Gathers from the Loyola Marymount University was college basketball's leading scorer and a candidate for the player of the year for the 1988-89 season. Moments after he dazzled the crows with a two-handed dunk, Gathers had a sudden cardiac arrest in the first half of the game against the Portland Pilots. He was pronounced dead less than two hours later. Notably, the AED was not present courtside, leading to a fatal delay in recognition and definitive treatment of VT. Autopsy reports revealed idiopathic cardiomyopathy with residual interstitial myocarditis.

Table 1: Famous Athletes, Causes of Sudden Cardiac Death and Underlying Genetic Mechanisms

Athlete	Diagnosis	Incidence	Common Mutation
Reggie Lewis	HCM	1 in 500	Cardiac myosin binding protein C, β-myosin heavy chain, Troponin I, T, α-tropomyosin
Marc Vivien Foe	HCM	1 in 500	
Miklos Feher	HCM	1 in 500	
Zena Ray Upshaw	HCM	1 in 500	
Nick Knapp	HCM	1 in 500	
Hank Gathers	Idiopathic		N/A
Antonio Puerta	ARVD	1 in 2500 - 5000	Plakophilin-2, Desmoglein-2, Desmoplakin, Desmocollin-2
Wes Leonard	DCM	0.57 in 100,000 (≤18 years)	Titin, β-myosin heavy chain, α-myosin, myopalladin, troponin T
Flo Hyman	Marfans Syndrome	1 in 5000	Fibrillin-1, TGF-β receptor 1, 2
Sergei Grinkov	Myocardial infarction	12.9 per 1000 (30 - 34 years)	PLA-2 variant
Alexander Dale Oen	Myocardial infarction	12.9 per 1000 (30- 34 years)	
Darryl Kile	Myocardial infarction	12.9 per 1000 (30-34 years)	
Pete Maravich	Absent LMCA	Rare	N/A
Jim Fixx	Myocardial infarction	600 in 100,000	N/A

HCM = hypertrophic obstructive cardiomyopathy; ARVD = arrhythmogenic right ventricular dysplasia; DCM = dilated cardiomyopathy; CMN = cystic medial necrosis; MS = marfan syndrome; MI = myocardial infarction; PLA = platelet antigen gene; LMCA = left main coronary artery

The deaths of Marc Vivien Foe, Miklos Feher, and Antonio Puerta within 3 years (2004-2007) prompted Fédération Internationale de Football Association (FIFA) to enforce screening of players at all levels before competitions. Presence of AEDs and sideline medical teams with specialized training in cardiopulmonary resuscitation (CPR) were made mandatory at every professional soccer stadium in the world. In 2013, FIFA mandated the availability of at least 1 AED at the sideline of all FIFA matches. FIFA also introduced consolidated medical emergency bags containing AEDs and airway equipment to sideline medical emergency teams at the 2014 world cup in Brazil. More recently, FIFA has launched the FIFA Sudden Death Registry in 2014 to identify potential delays in recognition and enforce timely definitive therapy for SCA during football events.

Marc Vivien Foe played in the 1994 and 2002 World cups, won 2 African championships with Cameroon and also won the French league title in 1998 and 2002. On June 26, 2003, Foe was playing for Cameroon in a semi-final match for the FIFA Confederations Cup against Colombia when he was noted to have SCA and subsequent CPR for 45 minutes before death was declared. Autopsy results revealed HCM with resultant VT as the likely cause of death.

Miklos Feher, a Hungarian soccer player who played for Benfica based out of Lisbon, earned top division totals of 80 games and 27 goals along with international credentials of 7 goals in 25 games. On January 25, 2004, after he helped create the game winning goal in the 25th minute following which he suffered a fatal SCA followed by prolonged CPR. His autopsy also revealed HCM and resultant VT as the likely cause of death which was not recognized on prior routine medical examinations.

Antonio Puerta played for Sevilla football club in Spain, helping them achieve an astounding 5 titles in 15 months. At age 22 years, Puerta suffered a SCA, 35 minutes into a game against Getafe.

Table 2: Limitations of Cardiovascular Screening Tests.

Test	Diagnosis	Limitations
History and physical examination	Congenital aortic stenosis	Low specificity for SCD
	CAD risk factors in older athletes	
	Family history of SCD	
2D Echocardiography	HCM	$400 – 2000/study 1:500 HCM = $250,000 per case False (+) and (-)
	Valvular heart disease	
	Aortic root dilatation	
	Coronary artery anomalies	
Coronary arteriography	Congenital coronary artery anomalies	Invasive test
		Increased associated risks
MRI	Arrhythmogenic right ventricular dysplasia	Expense and availability
12 Lead EKG	Hypertrophic cardiomyopathy	Low specificity
	Coronary anomalies	
	Long QT syndrome	

Puerta regained consciousness, was substituted and had another SCA in the locker room. Despite timely CPR, he was subsequently placed on life support before being declared dead on August 28, 2007. The autopsy report identified the cause of death as arrhythmogenic right ventricular dysplasia but his prior medical examinations were unremarkable, even in the prior 3 weeks leading to his demise.

Wes Leonard was a 16 year-old basketball player for Fennville High School in Michigan. He was a standout athlete and a three year starter in basketball and football. On March 3, 2011, in overtime of the last game of the regular season, he made the game winning basket to achieve a 20-0 record. His teammates lifted him into the air and as soon as he was put down he collapsed to the court gasping for air. His presentation was misconstrued for heat exhaustion and his colleagues attempted to cool him down with ice and cool cloths. Ironically, the on-site medical personnel attached the AED from school to his chest and the device was non-functional owing to depletion of battery life, thereby resulting in ineffective CPR and subsequent death. Forensic pathology revealed dilated cardiomyopathy from either a genetic defect or due to prior undetected viral myocarditis which was again not detected on prior exams. Following his death, Leonard's mother Jocelyn became an advocate for CPR/AED training drills which resulted in the placement and routine maintenance of AEDs at all schools in Michigan.

Table 3: Comparison of U.S. And European Guidelines for Preparticipation Screening for Competitive Sports

Condition	[1]U.S. Recommendations	[2]European Recommendations
HCM	[a] Exclude from most sports	[a] Exclude from most sports
Genotype + Phenotype -	No data to exclude	Participation only in noncompetitive or leisure-time sporting activities
Marfan Syndrome	[b] Restricted to class IA & IIA sports	[c] Exclude from all sports
Long QT Syndrome	≥470ms (men); ≥480ms (women)	≥440ms for men; ≥460ms (women)
	Restriction to low intensity sports	Exclude from all sports
Genotype + Phenotype -	No exclusion	Discouraged participation in sports
	LQT1 genotype: refrain from competitive swimming	
Brugada Syndrome	Restriction to low intensity sports	Exclude from all sports
Genotype + Phenotype -	No exclusion	Exclude from all sports
Ventricular pre-excitation	[d] Asymptomatic: EPS not mandatory	Asymptomatic: EPS mandatory
(WPW Syndrome)	Symptomatic: EPS required	Symptomatic: EPS mandatory
	Return after RFA: 4 weeks	Return after RFA: 3 months
PVC	No restriction unless PVCs increase with exercise, then restriction to low intensity sports	
NSVT	No CV disease: No exclusion	No CV disease: No exclusion
	CV disease: restricted to low intensity sports	CV disease: restricted to recreational sports
ICD	Exclude from competitive sports	
	Exception: sports without associated risk of trauma to the device	
Screening	[3]Medical history + physical exam	[4]12 lead ECG + medical history + physical exam
Perform screening	Physician volunteers	Sports medicine physicians
	Healthcare workers	
Authority for disqualification	High school or college officials	Sports medicine physician

[1] 36th Bethesda Conference; [2] European Society of Cardiology Conference; [3] U.S. strategy for high school and collegiate athletes; [4]Italian screening model
[a] Exceptions: low static and low dynamic intensity sports such as golf; [b] Class IA & IIA: low and moderate static/low dynamic competitive sports. Cannot have one or more of following: aortic root dilatation ≥40mm in adults or more than 2 SDs from the mean for body surface in children, moderate to severe mitral regurgitation, family history of dissection or sudden death in Marfan relative; [c] Independent of aortic root dimension; [d] EPS advisable in moderate or high level competitive sports
CV - cardiovascular; ECG - electrocardiogram; EPS - electrophysiologic study; HCM - hypertrophic cardiomyopathy; ICD - implantable cardioverter-defibrillator; LQTS - long QT syndrome; NSVT – non-sustained ventricular tachycardia; PVC - premature ventricular complex; RFA - radiofrequency ablation; WPW - Wolff Parkinson white syndrome

Flo Hyman, a world class professional volleyball player was a silver-medalist for the United States in the 1984 Olympics, three time All-American champion and was also rated 69th greatest female athlete of the century by Sports illustrated in 1999. On January 24, 1986, she was substituted out of a game in Japan and suffered SCA while on the bench, resulting in SCD at age 31. Autopsy reports demonstrated an aortic dissection from undiagnosed Marfan syndrome. Her death prompted more research and attention to a disease that less extensively characterized in the 1980s. Multiple examinations by professional medical personnel were unremarkable for signs of Marfan's syndrome except for her height which one would expect with Olympians.

Sergei Grinkov was a pair skater with his wife Ekaterina Gordeeva. He won the Olympic championship in 1988 and 1994 and also four world championships. Amidst training with his wife in Lake Placid, New York in 1995 for the Stars on Ice tour, he suffered SCA. The etiology was a lethal myocardial infarction at a young age of 28. Autopsy showed a near-complete occlusion of the left anterior descending and diagonal arteries. He was discovered to have a genetic platelet antigen-2 (PLA-2) polymorphism which predisposes one to arterial thrombi. His father was noted to have prematurely died from a heart attack at age 40.

"Pistol" Pete Maravich, college basketball's all-time leading scorer with 3,667 points, was named the greatest college basketball player of all time by ESPN in 2005. Having excelled for Louisiana State University and 3 different NBA teams, he was named one of the 50 Greatest Players in NBA History in 1996. He was one of the youngest players inducted into the Naismith Memorial Basketball Hall of Fame. In January 1988, he suffered SCA at a promotional game at a church gymnasium in California, minutes following appearance on a national radio show. He was pronounced dead at the hospital at age 40 years. The coroner's reported the absence of a left coronary artery and chronic myocardial fibrosis due to ischemia from a single right coronary artery supplying his entire heart. None of his previous medical examinations raised suspicion of cardiovascular defects and his long successful stint in sports was remarkable considering the limited survival of patients with the underlying pathology.

Jim Fixx was the author of the New York Times best-selling book The Complete Book of Running which sold over a million copies. He advocated that regardless of diet or genetic susceptibility, an individual would not suffer a fatal heart attack if they were a non-smoker and

Table 4: Survival Outcomes in Studies Evaluating the Efficacy of Automated Electrical Defibrillators in Out-of-the Hospital Cardiac Arrest

Investigator	Study Design	Sample Size	Study Comparison	Outcomes
Hansen et al.[29]	Retrospective (CARES Registry)	N = 4,961	Impact of providing focused training for BS and FRs on survival in OHCA	BS resuscitation had higher survival rates: EMS (CPR + Defibrillation)= 15.2% BS (CPR + Defibrillation)= 33.6% BS CPR + FR Defibrillation= 24.2% FR CPR + Defibrillation= 25.2%
Berdowski et al.[26]	Retrospective	N = 2,833	Onsite vs. dispatched AED on time to defibrillation and NIS to discharge	Onsite AED: 4.1 min, NIS 49.6% Dispatched AED: 8.5 min, NIS 17.2%
Blom et al.[28]	Retrospective	N = 6,133	Is NIS after OHCA due to AED use in those with initial shockable rhtyhms?	NIS: 29.1% (no AED) vs. 41.4% (with AED)
Capucci et al.[32]	Prospective	N = 3,366	AED use by FR vs. EMS on survival to discharge	Survival : FR (41.4%) vs. EMS: 5.9%
Ringh et al.[33]	Retrospective	N = 474	Defibrillation by FR vs. EMS on 1-month survival	1-month survival: FR with public AEDs (70%) vs. EMS 31%
Lijovic et al.[34]	Retrospective (Victorian Ambulance Cardiac Arrest Registry)	N = 2,270	AED use by BS vs. EMS on survival to discharge	Survival to discharge: 45% (BS) vs. 31% (EMS)
Nakahara et al.[19]	Retrospective (Japanese Nationwide OHCA Registry)	N = 167,912	Defibrillation by FR vs. EMS on NIS to discharge	NIS: 40.7% (BS) vs. 15% (EMS)
Hallstrom et al.[31]	Prospective, randomized public access defibrillation trial	N = 3,413	CPR only vs. CPR+AED by trained laypersons on survival to discharge following OHCA	23.4% (CPR+AED) vs. 14% (CPR only)
Agerskov et al.[25]	Retrospective (Mobile Emergency Care Unit and the Danish Cardiac Arrest Registry)	N = 521	30-day survival for AED application before and after EMS arrival	AED before EMS (64%) vs. after EMS arrival (37%); 15% OHCAs occurred within 100m of AED but only 3.8% had AED use
Weisfeldt et al.[35]	Prospective population based cohort study	N = 13,769	AED vs. no AED use before EMS arrival on survival to discharge	Survival: no AED (9%) vs. AED only (24%) vs. AED+shock (38%)
Eckstein et al.[27]	Prospective, longitudinal and observational study	N = 59	Impact of public access AED on survival to diacharge	Public access AED use = 69% NIS to discharge.

AED = automated external defibrillator; BS = bystander; CARES =Cardiac Arrest Registry to Enhance Survival; CPR = cardiopulmonary resuscitation; EMS = emergency medical services; FR = first responder; NIS = neurologically intact survival; OHCA = outside of hospital cardiac arrest

exercised sufficiently. Fixx popularized running and was considered the face of America's fitness revolution. Prior to embarking on a fitness journey, he was a heavy smoker and weighed over 220 pounds and had a familial history of premature myocardial infarctions. By the time his first book was published he had lost 60-70 pounds and quit smoking. On July 20, 1984, Fixx was on a daily run when he suffered SCA from a fatal heart attack at age 52 years. Ironically, his demise triggered a debate on the benefits of physical exercise and life expectancy. Autopsy reports showed critical occlusions in all 3 coronary arteries, diffuse atherosclerosis of the aorta and peripheral arteries and at least 3 myocardial infarctions in the weeks prior to death. He exhibited no angina symptoms and was noted to run 10 miles a day.

Zena Ray "Zeke" Upshaw was American professional basketball player who played in the D league after going undrafted in the NBA. In the final game of the regular reason, he collapsed and was taken to the near hospital. He passed away 2 days later and autopsy showed hypertrophic cardiomyopathy as the cause of SCD. His death raised questions regarding failure of the NBA to have proper policies and procedures in place to detect players who could potentially suffer SCD.

Alexander Dale Oen was a Norwegian swimmer who was the first male from his country to win a Gold medal at a major international long course championship. He collapsed while taking a shower at training camp. His teammates found him and started CPR, however he was pronounced dead upon arriving to the hospital. Cause of death was myocardial infarction from underlying severe atherosclerotic disease, and resultant triple vessel disease with up to 90% occlusion.

Darryl Kile was an American Major League baseball starting pitcher for the St. Louis Cardinals and in June 2002, he was missing from pre-game warmups and personnel found him dead on his hotel bed. Cause of death was myocardial infarction at the age of 33 and an autopsy performed showed 90% occlusion in two coronary arteries.

Nick Knapp, a college basketball player for Northwestern in 1994, was one of the lucky ones who survived a sudden cardiac arrest. While playing a preseason pickup game in Peoria, Nick collapsed. Luckily, Nick's dad, certified CPR instructor, along with an off-duty firefighter, happened to be at the scene and started CPR until paramedics arrived shortly afterwards. After 3 rounds of shock via defibrillator, he gained return of spontaneous circulation. He was diagnosed with hypertrophic cardiomyopathy afterwards. His case underscores the importance of CPR training and awareness among the general public.

Lastly, Omar Carter, a 25-year old during a semi-professional basketball game, on July 2013 suddenly collapsed and suffered a 13-minute SCA. He laid there for 13 minutes waiting for someone to start CPR until paramedics arrived. Fortunately, he survived. To show his gratitude and increase awareness regarding sudden cardiac arrest, CPR and AEDs, he has started a foundation called 'Omar

Carter Foundation' which so far has helped teach CPR to more than 15,000 people. His goal is to teach 1 million people bystander CPR so people aren't afraid to step in and start resuscitation if they witness a sudden cardiac arrest until paramedics arrive. His foundation also works to identify locations for AED devices along with community outreach.

The superlative physical fitness of athletes and the success in their careers often leads people to believe they are protected from heart disease. Contrary to this belief, there is often considerable discussion regarding the adequacy and efficacy of contemporary screening modalities in a special population such as athletes. The initial manifestation of underlying undetected heart disease pathology as SCD and the paucity of symptoms often associated with these conditions often pose a diagnostic challenge to cardiologists. There remain several clinically pertinent questions: Whom to screen? How to screen? Do we screen for all possible genetic and developmental pathological entities? How effective are our contemporary detection techniques? Does early detection lead to change in practice? Is it ethical to recommend refrainment from sports if such a condition is detected? How cost effective are our strategies? The relatively low incidence of these conditions has imposed heavy reliance on expert consensus rather than randomized research evidence.

Difference in Screening and Workup Protocols between the European Society of Cardiology and the American Heart Association

Continuous Professional societies like European Society of Cardiology (ESC) and the American Heart Association (AHA) have presented clinicians with recommendations and a body of evidence to guide screening of athletes.[7, 8] The European recommendations is based upon a well validated screening model derived from the Italian guidelines called COCIS providing data spanning 25 years.[9] The efficacy of the nationwide systematic preparticipation athletic screening introduced in Italy in 1982 is underscored by a staggering 89% reduction in SCD among athletes (driven by reduction in SCD from cardiomyopathies) as compared to the unscreened non-athletic general population.[10, 11] The American Heart Association does not have a screening program on a national level as in Italy or Israel and is heavily reliant on a 14-point history and physical examination model alone.[12] Both these guidelines are similar in multiple regards but a strikingly aggressive nature of screening, further workup of individuals identified on screening and also restriction from competitive sports in noted with the European guidelines.[8, 13] Contrasting recommendations from both professional societies elucidated in [Table 3] are to be noted.[13]

The Italian Approach

Contemporary literature suggests a more stringent and aggressive screening and diagnostic approach in Europe with a body of evidence emanating from an Italian screening model introduced in 1982, which mandates annual history and physical examinations coupled with a 12-lead EKG at the Center of Sports Medicine in Padua.[13] Over a span of 26 years, this model has elicited a staggering 89% reduction in SCD among screened athletes while the incidence has remained static in unscreened individuals, thereby leading to endorsement of this model by the International Olympic Committee medical commission and the ESC.[13] Similar efficacious results were noted in identification of subclinical HCM in young athletes despite the absence of echocardiography as a diagnostic tool, clearly reinstating the robust and well-validated nature of this screening model.[11] Of note, the Italian government mandates procurement of an eligibility certificate in all individuals willing to participate in competitive sports after a rigorous screening process and an annual medical assessment.[14] None of the other European countries and the U.S. advocate for this requirement. In the U.S., there is no law which requires medical clearance prior to participation in school and college level competitive sports. Moreover, the screening process is exclusively conducted by sports medicine specialists as opposed to the U.S where the process is conducted by physician volunteers and other allied medical professionals which could potentially offer room for errors.

Limitations of an Expansive Screening Process and Heterogeneity in Outcomes Following Adoption of Electrocardiograms as a Routine Screening Tool

Presently, the screening process recommended by the ACC/AHA for prescreening of young healthy individuals of age 12-25 years does not include a 12-lead EKG.[15] Evidence suggesting beneficial results remains isolated to the Italian screening model. Data from U.S. investigating this effect has shown lack of beneficial results with routine utilization of EKG as a screening tool.[16, 17] Similar strategies adopted in Israel have demonstrated no reduction in the incidence of SCD among athletes.[16] Differences in the pre-participation screening timeframes between studies from Italy and Israel could explain the discrepant findings (2 years [Italy] vs. 12 years [Israel]). Coincidentally, incidence of SCD in elite athletes in both studies had a high incidence of SCD in the 2-years prior to adoption of EKG as a routine mandatory screening tool (Italy: 3.6 per 100,000 person-years; Israel: 8.4 per 100,000 person-years). However, the Italian approach reported a significant reduction from 3.6 per 100,000 person-years with a 2-year pre-enforcement period to 0.4 per 100,000 person-years at the end of follow-up. In contrast, results from Israel noted a non-significant reduction in SCD from 2.6 per 100,000 person-years in a much longer 12-year pre-enforcement period to 1.1 per 100,000 person-years 12–years after adopting mandatory screening with EKGs. Interestingly, if the same 2-year pre-participation period similar to the Italian approach was analyzed in Israel, the same study demonstrated a significant reduction in SCD from 8.4 to 1.1 per 100,000 person-years. This raises doubts whether the perceived lack of benefit noted by the Israeli experience is merely from a large yearly non-linear variation in SCD incidence with a lower pre-enforcement incidence rate due to averaging SCD incidence over a longer 12-year period as opposed to a 2-year period than a true lack of benefit from EKG screening enforcement. The persistently low incidence of SCD over 3 decades of follow-up after the adoption of mandatory screening in Italy further lends credence to EKG as an effective screening tool. However, similar results were not replicated in studies involving the U.S.[15]

Firstly, the incidence of SCD among athletes remains considerably low at 1 in 200 000 in young athletes under 35 years of age.[4] With the lack of incremental value of EKG and echocardiography in detection and subsequent prevention of SCD in athletes, even with

the best of screening tests which provides a specificity approaching 100%, approximately 2000 athletes would need to be screened to successfully identify one true positive result which limits financial feasibility.[18] Recent literature elicits a cost-effectiveness ratio of $42,900/life-year saved with mandatory EKG screening in contrast to history and physical alone which provides higher a cost-effectiveness ratio of $76,100/life-year saved when compared to no screening.[19] These statistics demonstrate potential for an enormous financial burden on the healthcare system of the U.S. with inclusion of EKGs to the screening process. The lack of cost-effectiveness of adding EKG to history and physical versus the latter alone has been well demonstrated [20-22] and these findings were mainly driven by the high rate of false-positive results.

HCM is the most common cause of SCD in athletes with an estimated prevalence of 1:500 with a strong genetic component comprising of >1500 specific mutations and >11 involved genes.[23] Comprehensive screening of genetic abnormalities lacks feasibility and poses financial constraints when performed on a routine basis. In addition, the natural course of genotype-positive phenotype-negative individuals is variable in terms of phenotypic expression to overt HCM. [24] Data from screening of asymptomatic athletes in Italy has shown that routine mandatory echocardiography showed no incremental value over history, physical examination and 12-lead EKG in the detection of HCM. [11]

Automated External Defibrillators: A Potential Solution to Improve Survival Outcomes from Sudden Cardiac Arrest?

Previously published literature suggests 67% survival from sudden cardiac arrest (SCA) if immediate by-stander CPR, defibrillation and advanced cardiac life support (ACLS) were concurrently initiated within a minute of SCA.[25] These results were reinforced by Berdowski et al who demonstrated a 3.9-fold higher neurologically intact survival rate with onsite AED use for initial shockable rhythms.[26] The AHA has reported that up to 40% of out-of-the hospital SCAs are treated by lay public and only 60% are familiar with CPR.[27] Randomized trial evidence from the public access defibrillation trial has shown that volunteers trained in CPR administration coupled with AED use substantially improved survival following SCA in public places without compromise in neurological function.[28] [Table 4] elucidates a summary of evidence suggesting enhanced outcomes following early use of AED to treat shockable rhythms. These results reinforce that timely AED use and effective CPR by well-trained individuals could translate into better survival outcomes. However, among out-of-the hospital SCAs, only 20% occur in public places while approximately 80% occur at home.[28] Extensive implantation of AED units and improving availability of trained personnel could improve outcomes in only approximately 20% of this subset, thereby limiting extrapolation to SCA occurring at home which unfortunately happens to be the major fraction among this subset.

However, in the relatively narrow spectrum of training fields and stadiums where athletes reach near-maximal limits of physical exertion, the substantial body of evidence depicting enhanced survival outcomes following SCA with early use of AEDs could be applicable. Prevalence of SCA in older spectators, coaches and officials is up to 80% of SCA cases in NCAA division I college sporting venues, the rest being accounted for by students and athletes.[29,30] Importantly, survival to discharge was reported in 67% of these cases.[30] The prevalence of at least one AED in NCAA colleges, most commonly in the training room, is estimated at 90% in division I but only in 77% and 81% in divisions II-III, respectively, which is clearly suboptimal.[31] Division I colleges were also noted to have twice the median number of AEDs in comparison to lower divisions, thereby eliciting a disparity in the AED penetrance.[31] Increasing availability of AEDs across training locations, diversification of personnel to be trained in CPR (including athletes themselves, athletic faculty, emergency responders, security guards, and the common person), formulation and coordination of response plans, periodic monitoring of AED function and quality control of these interventions could potentially reduce death from SCA, specifically pertaining to athletes. Successful resuscitation after SCA could provide an opportunity to retrospectively identify, treat and prevent recurrence of SCA resulting from disease entities which have missed detection by the screening process.

Contrasting Approaches between Europe and America for Restrictions and Disqualification from Competitive Sports

In Italy, the decision to restrict or disqualify athletes from competitive sports once diagnosed with a condition with high risk for SCD is exclusively vested with the sports medicine physician. In addition, there is presence of a legal framework which gives the physician the authority to disqualify athletes from participation in sports which could be lethal. However, in the U.S., the Physician can only recommend but not restrict or disqualify athletes from participation. The ultimate authority remains a shared responsibility between the athlete and the educational institution, thereby shifting the autonomy to the individual and institution under question. Moreover, restriction from competitive sports, even if diagnosed with structural heart disease with high risk for SCD, is considered violation of personal freedom. In the absence of federal laws to uphold decisions made by specialized physicians on restriction and disqualification, the legal liabilities remain high and decision-making becomes more conservative in the U.S.

Conclusion

SCD in athletes, despite its low incidence, remains highly publicized. Contemporary evidence highlights multiple similarities in the screening process between Europe and the United States. Striking differences which are to be noted are the inclusion of 12-lead EKGs in the routine screening process and the shift in autonomy towards the sports medicine physician with regards to restriction from competitive sports in confirmed cases of increased risk for SCD in Europe. A more expansive screening process would entail a less-evidence based approach and a higher financial burden on the health system. An alternative to an expansive screening process could be a robust secondary prevention system comprising of widespread availability of AEDs and improving the penetration of CPR training in athletes themselves and athletic trainers to provide timely and effective resuscitation to reduce death following SCA. This strategy could provide a feasible and financially viable diagnostic and therapeutic window to address the underlying etiology for SCA and to prevent further occurrence of SCD. The decision to restrict athletes from competitive sports in the setting of high risk for SCD

remains a challenge since there exists a dubious distinction between acceptable and prohibitive risk for SCD in this elite subgroup. The lack of a protective medico-legal framework and pertinent social repercussions associated with disqualification further impose a challenging situation on the sports physicians in the U.S, thereby contributing to a conservative approach. Further evidence could possibly help streamline the existing process.

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Dr. Dhanunjaya Lakkireddy, MD, F.A.C.C, FHRS

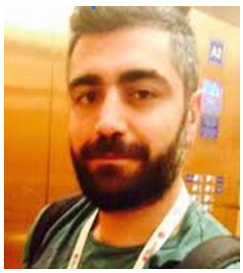
A board certified electrophysiology expert and practices at Mid-America Cardiology and The University of Kansas Hospital Clinics in Kansas City, KS, USA

Dr. Dogac Oksen, MD

Dogac Oksen, MD is clinical cardiologist and investigator, currently working at Istanbul University Institute of Cardiology, Istanbul, Turkey. He has achieved Doctor of Medicine degree at Cerrahpasa Medical Faculty. His scientific focuses are interventional cardiology, arrhythmia cardiac electrophysiology and catheter based treatment of arrhythmias

Dr. Mattias Duytschaever, MD

Department of Cardiology, Sint-Jan Hospital Bruges; Ruddershove 10, 8000 Bruges, Belgium

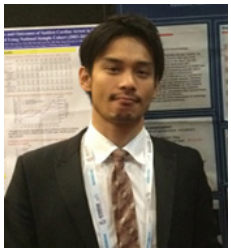


Dr. Tolga Aksu, FESC, FEHRA

He is an Associate Professor of Cardiology. He is working Department of Cardiology and Director of Clinical Electrophysiology at the Kocaeli Derince Education and Research Hospital in Turkey. Dr. Aksu clinically interested in invasive electrophysiology, device implantation and catheter ablation therapies. Special interest areas are Atrial fibrillation and cardioneuroablation. Dr. Aksu has published more than 100 national and international scientific publications. Also, He is in Editorial Board of some international academical journals.

Dr. George Louridas, MD

Emeritus Professor of Cardiology, Aristotle University, Thessaloniki Greece, Director of Cardiac Catheterization Laboratory, AHEPA Hospital (1983-2006), Director of Department of Cardiology, AHEPA Hospital (1996-2006).



Dr. Kyoichiro Yazaki, MD

Affiliation: Ogikubo Hospital, Department of Cardiology,Cardiovascular Center, Tokyo, Japan.
Clinical research of electrophysiology, catheter ablation, and Device therapy are of my interests

Dr. Ashraf Alqaqa, MD, FACC

Dr. Farhad Farokhi received his medical degree from the Kansas City University of Medicine & Biosciences. He finished his internal medicine residency at the Grandview Hospital in Dayton, OH. He currently holds board certification in Cardiovascular Disease and Clinical Cardiac Electrophysiology from the American Osteopathic Board of Internal Medicine, Internal Medicine from the American Osteopathic Board of Internal Medicine, and Echocardiography from the American Society of Echocardiography. Dr. Farokhi's clinical interests include Atrial Fibrillation, Catheter Ablation, Ventricular Arrhythmia, and Left Atrial Appendage Closure (LARIAT).

Dr. Hickey

Dr. Hickey is an Associate Professor of Nursing at Columbia University Medical Center and holds a joint appointment in the Division of Cardiology (electrophysiology) as both a family and adult nurse practitioner. Her interdisciplinary research, clinical practice and scholarship is focused in the areas of cardiac genetics, the clinical care of those with chronic cardiac conditions and arrhythmias, and the prevention of sudden cardiac death. Her current grant awards include a R01 from the National Institute of Nursing Research (iHEART) focusing on arrhythmia telehealth monitoring in those with atrial fibrillation, her newly awarded (multiple-PI) P30 award with Dr. Suzanne Bakken is focusing on improving symptom self-management for underserved populations with or at risk for chronic health conditions.

Dr. Andres Enriquez, MD

Dr. Enriquez received his medical degree from the Universidad de Concepcion, in Chile. He specialized in Internal Medicine, Cardiology and Cardiac Electrophysiology at Pontificia Universidad Catolica de Chile in Santiago.

Between 2013 and 2015 he moved to Canada to continue his electrophysiology training at Queen's University, Kingston, Ontario.

He currently resides in Philadelphia with her wife Karen and is a second-year fellow in the Advanced Clinical Electrophysiology program at the Hospital of the University of Pennsylvania, under the mentorship of Dr. Francis Marchlinski.

Dr. Enriquez interests include electrocardiology, clinical electorphysiology catheter ablation and cardiac devices.

Dr. Ryan Dean White. MD

Dr. Ryan Dean White, MD, medical degree from the University of Missouri and currently training in internal medicine at Indiana University School of Medicine in Indianapolis, Indiana.

Dr. James R Edgerton, MD, FACC, FACS, FHRS

The Heart Hospital

Dr. Jackson J. Liang, MD

Clinical Cardiac Electrophysiology Fellow
Hospital of the University of Pennsylvania

Dr. Gianluca Rigatelli, MD, PhD, EBIR, FACP, FACC, FESC, FSCAI, Vice-Director

Cardiovascular Diagnosis and Endoluminal Interventions
Director, Section of Adult Congenital Heart Interventions
Rovigo General Hospital, Viale Tre Martiri
45100 Rovigo, Italy