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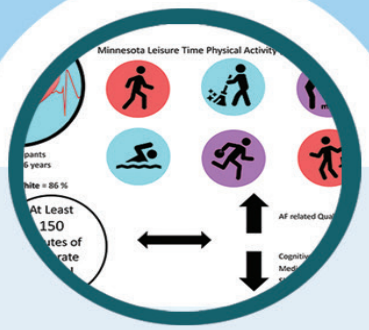

Journal of Atrial Fibrillation

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Editorial

Journal of Atrial Fibrillation

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Battling the Second Wave of COVID...

Journal of Atrial Fibrillation (JAFIB)

Feb - Mar 2021

Issue 5

Volume 13

Dear Colleagues

Our sincere condolences to those who lost their loved ones to the second wave of COVID sweeping across the world. Just about as the world was about to get a break from ayearlong carnage that this tricky microbe has caused, we are seeing incredibly discouraging news from India and other places. We cannot underestimate the ability of this virus to mutate and continue to infect humanity. As the vaccination program gets a solid footing, we should continue our efforts to enforce appropriate social distancing, masking, and disinfection practices. The Center for Disease Control should exert some restrain in lifting the masking requirements in public places. There is a significant misinformation prevalent that is deterring people from embracing the COVID vaccination. Please educate your patients, family, friends, and neighbors to get vaccinated and change the course of this deadly pestilence.

In this issue of the journal, we have a wide range of manuscripts covering the value head up tilt table tests in determining the need for pacemakers to understanding device embolization during left atrial appendage occlusion. Another interesting paper on using myocardial strain indices using intracardiac echocardiography opens several opportunities to study the intraprocedural aspects of myocardial strain and arrhythmic conditions. The impact of exercise on atrial fibrillation in elderly patients and the accompanying editorial are a must read.

We have now adopted a new manuscript management system, and this has significantly improved the workflow and the review process. We want to thank you for your continued support of the journal. Very soon I will be stepping down as the Editor-in-Chief of the journal and my replacement will be announced soon. I once again thank you all for the opportunity to work with many of you on the editorial board. Thank you.

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

Sincerely
DJ Lakkireddy

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Original Research
Journal of Atrial Fibrillation

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Left Atrial Appendage Occlusion Device Embolization (The LAAODE Study): Understanding the Timing and Clinical Consequences from a Worldwide Experience

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Abstract

Background: Left atrial appendage occlusion device embolization (LAAODE) is rare but can have substantial implications on patient morbidity and mortality. Hence, we sought to perform an analysis to understand the timing and clinical consequences of LAAODE.

Methods: A comprehensive search of PubMed and Web of Science databases for LAAODE cases was performed from October 2nd, 2014 to November 1st, 2017. Prior to that, we included published LAAODE cases until October 1st, 2014 reported in the systematic review by A minian et al.

Results: 103 LAAODE cases including Amplatzer cardiac plug (N=59), Watchman (N=31), Amulet (N=11), LAmbre (N=1) and Watchman FLX (N=1) were included. The estimated incidence of device embolization was 2% (103/5,000). LAAODE occurred more commonly in the postoperative period compared with intraoperative (61% vs. 39%). The most common location for embolization was the descending aorta 30% (31/103) and left atrium 24% (25/103) followed by left ventricle 20% (21/103). Majority of cases 75% (77/103) were retrieved percutaneously. Surgical retrieval occurred most commonly for devices embolized to the left ventricle, mitral apparatus and descending aorta. Major complications were significantly higher with postoperative LAAODE compared with intraoperative (44.4% vs. 22.5%, p=0.03).

Conclusion: LAAODE is common with a reported incidence of 2% in our study. Post-operative device embolization occurred more frequently and was associated with a higher rate of complications than intraoperative device embolizations. Understanding the timings and clinical sequelae of DE can aid physicians with post procedural follow-up and also in the selection of patients for these procedures.

Key Words:
Left Atrial Appendage Closure Device, Embolization, Atrial Fibrillation, Watchman, Amplatzer Cardiac Plug, Amulet

Disclosures:
All of the others except for GM, KA, SPS, TD, BY, SL, JG and MT are consultants to either Abbott or Boston Scientific.

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Introduction

Percutaneous left atrial appendage closure (LAAC) has emerged as a suitable alternative for stroke prevention in non-valvular atrial fibrillation (AF) patients considered poor candidates for long – term oral anticoagulation[1]. Despite its efficacy, LAAC is not devoid of complications and can be associated with increased patient morbidity and mortality[2,3]. Pericardial effusion, device embolization (DE), and device thrombosis are some of the complications that are infrequently associated with LAAC. Amongst these, DE is poorly understood with a reported incidence of <4%[4]. Left atrial appendage (LAA) to device size mismatch and operator experience are believed to be the most common causes for DE[5]. Currently, there is limited patient-level data regarding the clinical outcomes of patients who experience DE. We therefore sought to perform a retrospective analysis of LAAC DE cases from a worldwide multi-center experience to further understand the timing and clinical consequences of DE.

Methods

Search strategy

We searched PubMed and Web of Science databases for eligible studies from October 2nd, 2014 to November 1st, 2017. We used the following search terms: Left atrial appendage closure, LAA closure, LAA occlusion, LAA, Watchman, Amplatzer Cardiac Plug, Amulet, Wavecrest and LAmbre. We also included the cases of LAAC DE published in the systematic review by Aminian et al (search conducted until October 1st, 2014) (5). All the corresponding authors of the cases of DE obtained through our search were contacted to obtain patient–level data regarding the respective cases and additional unpublished cases of LAAO DE that occurred during the time period.

Study selection

Studies reporting at least one case of LAAC DE and any new unreported cases of DE from the search described above were included in our analysis. Editorial comments, review articles, studies reporting DE with PLAATO device and any reported or unreported cases which were also included in a larger study or trial were excluded. We only included studies involving human subjects and published in the English language.

Data extractions and quality appraisal

Two investigators (GM and MT) independently performed the literature search and screened all titles and full text versions of all the relevant studies that met study inclusion criteria. The data from the individual studies were extracted using a standardized protocol and data extraction form by two independent investigators (GM and MT). Caution was taken to make sure that there was no duplication of cases in prior studies.

Definitions

- Intraoperative device embolization: Event occurred during the procedure.
- Acute device embolization: Event diagnosed postoperatively within 24 hours.
- Subacute device embolization: Event diagnosed postoperatively after 24 hours but < 1 week
- Delayed device embolization: Event diagnosed any time after 1 week post-procedure.
- Major complication: DE that required (i) any cardiac intervention or surgery, (ii) resulted in damage to the surrounding cardiovascular structures, (iii) precipitated symptoms of angina, stroke, congestive heart failure, limb ischemia or heart block or (iv) resulted in the death of a patient.
- Minor complication: any other complication that did not meet the above criteria was considered minor complication.
- Percutaneous retrieval: was defined as device retrieval through a peripheral vascular access without any surgical cut-down.
- Surgical retrieval: was defined as any surgical technique that was used to retrieve the embolized device.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) if normally distributed, and median ± Interquartile range (IQR) 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 nonparametric test (Kruskal-Wallis Test). A two tailed p value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 23.0 (IBM, Armonk, New York).

Table 1: Baseline characteristics and timing of device embolization

Variable	Total N= 103	ACP N=59	Watchman N=31	Amulet N=11	p-value
Age (years) (IQR)	75 (68-80)	75 (68-80)	68 (56.5-73)	77 (74.5-85.5)	0.15
Female (%)	14 (13.6%)	8 (13.5%)	2 (6.4%)	4 (36%)	0.13
LAA size (mm) (IQR)	20.3 (18.5-24.2)	22.8 (18.8-25)	17 ± 2.0 (17-20.5)	21.1 (18.5-21.7)	0.3
Device Size (mm) (IQR)	26 (24-28)	26 (24-28)	24 (21-27)	28 (25-31)	0.6
$CHADS_2$ (IQR)	4 (3-5)	4 (3-5)	4 (3-4.5)	3 (3-5.5)	0.9
HAS-BLED (IQR)	3.0 (3-4)	3 (3-4)	4 (2.5-4)	3 (2.5-4)	0.9
Intraoperative DE	40 (39 %)	29 (49%)	8 (25.8%)	3 (27%)	0.06
Post-operative DE	63 (61 %)	30 (51%)	23 (74.2 %)	8 (73%)	0.06
Acute Subacute Delayed	32 (50.8%) 9 (14.3%) 22 (34.9%)	15 (50%) 5 (16.7%) 10 (33.3%)	10 (43.5 %) 3 (13%) 10 (43.5%)	6 (75%) 1 (12.5%) 1 (12.5%)	

ACP=amplatzer cardiac plug; IQR=interquartile range; DE= device embolization

Figure 2A: **Comparison of intraoperative and postoperative device embolizations**

Variable	Intraoperative embolization N= 40	Postoperative embolization Total N= 63	Acute N= 32	Subacute N= 9	Delayed N= 22	P-value
Complications	9 (22.5%)	28 (44.4)	12 (37.5%)	4 (44.4%)	12 (54.5%)	0.034
Surgery	3 (33%)	23 (82%)	7 (58%)	4 (100%)	12 (100%)	
Stroke/ TIA	2 (22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Myocardial infarction	1 (11%)	2 (7%)	2 (17%)	0 (0%)	0 (0%)	
Cardiogenic shock	1 (11%)	2 (7%)	1 (8%)	0 (0%)	1 (8%)	
Valvular damage	3 (33%)	2 (7%)	1 (8%)	0 (0%)	1 (8%)	
Limb ischemia	0 (0%)	1 (4%)	1 (8%	0 (0%)	0 (0%)	
Internal bleeding	2 (22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Death	1 (11%)	7 (25%)	2 (17%)	1 (25%)	4 (33%)	

TIA = transient ischemic attack
*P - Value for intraoperative vs postoperative embolization
Note:Intraoperative refers to diagnosis of device embolization while still in the procedure; Postoperative refers to diagnosis of device embolization in the postoperative period and is further subdivided into Acute (within 24 hours of the procedure), Subacute (24 hours to 1 week after the procedure), Delayed (>1 week after the procedure)

Results

Search results and data synthesis

A total of 414 studies were identified during the initial literature search. Each study's abstract was reviewed individually and screened based on study inclusion/exclusion criteria. Of these, 362 reports were excluded because of review articles (N=114), exclusive use of either the Lariat device (N=46), the PLAATO device (N=26), studies with no reported cases of DE (N=160) or duplicate studies (N=4). Finally, 64 studies reporting 93 cases were included. Patient-level data, as well as another 10 unreported cases of DE, were obtained from the individual corresponding authors of the included studies. 103 cases of DE were included in the final analysis (Figure 1).

Study baseline characteristics

A total of 103 cases of DE occurred from an estimated 5,000 percutaneous endocardial LAAC procedures done up until that point with an incidence of about 2%. Of these, 57% (N=59/103) occurred with Amplatzer Cardiac Plug (ACP), 30% (N=31/103) with Watchman (WM) and 11% (N=11/103) with Amulet device. One case each was reported with the investigational LAmbre and Watchman FLX devices (6,7). The median device size (IQR) in each group (ACP, WM, and Amulet) was 26 mm (IQR 24-28 mm), 24 mm (IQR 21-27 mm), and 28mm (IQR 25-31 mm), respectively. The median CHADS2 score was 4 (IQR 3-5) in ACP, 3 (IQR 3-4.5) in WM and 3 (IQR 3-5.5) in Amulet group. Median HAS-BLED scores were 3 (IQR 3-4), 3 (IQR 2.5-4), 3 (IQR 2.5-4) in each group, respectively. Other baseline characteristics of the study cohort are demonstrated in Table 1.

Timing of device embolization and complications

DE occurred more commonly in the post-operative period than intraoperative period (61% vs 39 %, p=0.06). Among ACP devices, intraoperative embolization was reported in 49% (n=29/59) and post-operative in 51% (N=30/59) of cases. DE with WM and Amulet occurred predominantly in the postoperative period (74.2%; N=23/31 and 73%; N=8/11) with only 25.8 % (N=8/31) and 27% (N=3/11) occurring intraoperatively (Table 1).

In one case, DE was found on routine 6-month transesophageal echocardiography (TEE)[6]. Uncomplicated DE occurred in 62% (64/103) and complicated DE occurred in 36% (37/103) of patients. Death occurred in 8 cases (8%). Bailout surgery to retrieve the device was needed in 25.2% (26/103) of cases. Of all the complicated DEs, 75.7% (28/37) were reported to have occurred in post-operative period and 24.3% (9/37) in the intraoperative period (p=0.02) (Table 2B). The rate of major adverse events (including death) was significantly higher in patients who had postoperative DE compared with those who had intraoperative DE (44.4%; n=28/63 vs 22.5%; n=9/40: p=0.034). Furthermore, the rate of surgical intervention was 7.5% (3/40) for intraoperative DE vs 38% (23/63) for post-operative DE (p=0.016) (Table 2A)

Site of device embolization and complications

The most common site for embolization was the left atrium (LA) (22.5%, n=9/40) for intraoperative cases and the descending aorta/abdominal aorta (19.7%, n=12/61) for post-operative cases (Table 3). In general, devices embolized to left ventricle (LV) and mitral valve apparatus were more likely to get complicated in comparison to other sites of embolization (p=0.002) (Table 2B). Furthermore, devices embolized to LV and mitral valve apparatus were more likely to require surgical intervention compared to other sites (p= 0.0074). LA embolization had a 94% chance of being snared percutaneously. Overall, the trend for surgical requirement increased dramatically if the embolized device was found in the LV/left ventricular outflow tract (LVOT)/mitral valve apparatus (44.4%, n=12/27) compared to the aorta or iliac bifurcation (13.7%, n=4/29), or the left atrium (6%, n=1/17) (p=0.0074). (Table 4)

Embolization site, mode of retrieval and complications with each device type

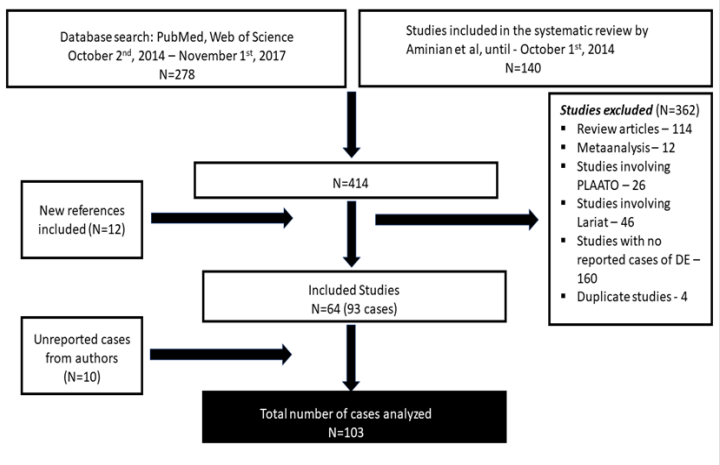

Figure 1: **Search criteria and flow diagram describing the process of case selection**

Figure 2B: Comparison of complicated and uncomplicated embolizations

Variable	Complicated embolizations N= 37	Uncomplicated embolizations N= 64	P- value
Intraoperative diagnosis	9 (24%)	31 (48.4%)	0.02
Postoperative diagnosis	28 (76%)	33 (51.6%)	0.02
Acute (within 24 hours)	12 (33%)	20 (31.2%)	0.37
Subacute (within 1 week)	4(11%)	4 (6.3%)	
Delayed (after 1 week)	12 (32%)	9 (14.1%)	
Device type			0.31
Amplatzer cardiac plug	19 (51%)	40 (62.5%)	
Watchman	12 (32.4%)	17 (26.7%)	
Amulet	6 (16%)	5 (7.8%)	
Watchman FLX	0	1 (1.5%)	
LAmbre	0	1 (1.5%)	
Site of embolization			0.002
Left atrium	2 (5.4%)	15 (23.4%)	
Left ventricle	12 (32.4%)	7 (11%)	
Left ventricular cavity	7 (19%)	4 (6.2%)	
Left ventricular outflow tract	5 (13.5%)	3 (4.7%)	
Mitral valve apparatus	4 (11%)	3 (4.7%)	
Aorta	6 (16.2%)	22 (34.4%)	
Ascending aorta/ arch of aorta	1 (2.7%)	5 (7.8%)	
Descending/ abdominal aorta	3 (8%)	14 (21.8%)	
Aorta/ iliac bifurcation	2 (5.4%)	3 (4.7%)	

The most common sites of DE (both intraoperative and postoperative) for the ACP was the LA (25%, n=15/59) and for the Watchman device was the descending aorta/abdominal aorta (38.7%, n=12/31). (Table 3)

The mode of retrieval was predominantly percutaneous snaring for each device type. Specifically, 78% (46/59) of ACP, 67.7% (21/31) of WM and 72.7% (8/11) of Amulet DE were successfully snared percutaneously. Only 2 cases described internal bleeding during percutaneous snaring and both of them involved WM devices which embolized intraoperatively. All other successful percutaneous retrievals were uneventful. The need for surgical intervention was most frequent with WM device (32.2%, n=10/31) followed by Amulet device (27.3%, n=3/11) and the ACP device (22%, n=13/59) (Table 3). Patients who required surgical intervention had a higher incidence of prolonged hospitalization and mortality. Of 26 cases that required surgical retrieval, 38.4% (n=10/26) had major complications which included severe valvular damage (n=6) and death (n= 6).

Impact of LAA morphology on device embolizations

Conclusions regarding morphology and its impact, if any, on DE cannot be drawn as the morphology of the LAA was not reported in majority of the cases (68%, n=70/103). Among those reported, cauliflower morphology was reported in 14 cases followed by chicken wing in 9, cactus in 6 and windsock in 4.

Acute leaks

Acute leak was reported in 8.7 % (n=9/103) of patients. Out of these 9 patients, 7 belonged to the ACP (3) and Amulet groups (4), one belonged to WM group and one belonged to LAmbre. Six out of these nine patients had postoperative (acute) DE and three had intraoperative DE.

Operator reported reasons for device embolization

Out of 21 device-LAA mismatches, device oversizing was reported in 4 patients, device undersizing was reported in 7 patients and in the remaining 10 patients, the mismatch was not specifically defined.

Discussion

This is the largest reported series of DE with LAAO to date. The main findings of this systematic review are: 1) the incidence of DE is 2% in our series; 2) DE occurred more frequently in the postoperative period and was associated with higher risk of serious complications, need for surgical retrieval and mortality compared with intraoperative DE; 3) operator reported device/LAA size mismatch is the most commonly identified factor associated with DE.

Earlier studies have reported that DE are more commonly observed intra-procedurally (5). On the contrary, in our study we found that more DE occurred post-procedurally. More than 50% of cases were recognized within the first 24 hours and 35% cases after one week. Embolized devices were found within the LA if recognized early and in the LV, LVOT, or aorta if found late.

Table 3: Mode of retrieval with site of device embolization

Site of Embolization Total N= 73		Need for surgery N=26*	Percutaneous snaring N=75*	p-value
LEFT ATRIUM	**17**	**1**	**16**	**0.0074**
Intraoperative cases 9		**1**	**8**	
Post-operative cases 8		**0**	**8**	
LEFT VENTRICLE	**20**	**8**	**12**	
Left ventricular cavity 13		**6**	**7**	
Intraoperative cases 7		**1**	**6**	
Post-operative cases 6		**4**	**2**	
Left ventricular outflow tract (LVOT) 7		**2**	**5**	
Intraoperative cases 1		**0**	**1**	
Post-operative cases 6		**2**	**4**	
MITRAL VALVE APPARATUS	**7**	**4**	**3**	
Intraoperative cases 3		**2**	**1**	
Post-operative cases 4		**2**	**2**	
AORTA	**29**	**4**	**25**	
Ascending aorta/Arch of aorta 6		**1**	**5**	
Intraoperative cases 2		**0**	**2**	
Post-operative cases 4		**1**	**3**	
Descending aorta/Abdominal Aorta 18		**3**	**15**	
Intraoperative cases 5		**0**	**5**	
Post-operative cases 13		**3**	**10**	
Aortic/Iliac bifurcation 5		**0**	**5**	
Intraoperative cases 3		**0**	**3**	
Post-operative cases 2		**0**	**2**	

The numbers from different tables might not add since the data in different patients is missing
* This number is higher since the data about site of embolization is not mentioned in some cases

Table 4: Comparison of different device types

Variable	ACP N=59	WM N=31	Amulet N=11	P-Value
Intraoperative embolizations	29 (49.2%)	8(25.8%)	3 (27.3%)	0.066
Site of Embolization				
Left atrium	08	01	0	
Left ventricle	06	01	0	
Descending aorta/Abdominal aorta	02	3	0	
Arch of aorta/Ascending aorta	02	0	0	
Aortic bifurcation/Iliac bifurcation	02	0	1	
Mitral valve apparatus	02	0	1	
Left ventricular outflow tract (LVOT)	0	0	0	
Unknown	07	03	1	
Postoperative embolization	30 (50.8)	23 (74.2%)	8 (72.7%)	
Site of Embolization				
Left atrium	7	1	0	
Left ventricular outflow tract (LVOT)	4	1	1	
Ascending aorta/Arch of aorta	1	1	1	
Descending aorta/Abdominal aorta	3	9	0	
Aortic/Iliac bifurcation	0	1	1	
Mitral valve apparatus	3	0	1	
Left ventricular cavity	5	0	1	
Unknown	7	10	3	
Complications	19 (32.2%)	12 (38.7%)	6 (54.5%)	0.35
Surgery	13	10	3	
Valvular damage		1	1	
Internal bleeding	0	2 (while PC snaring)	0	
Stroke/TIA	2	0	0	
Myocardial infarction	2	0	1	
Cardiogenic shock	1	0	2	
Limb ischemia	0	0	1	
Death	7	1	0	
Retrieval process				0.568
Surgery	13 (22%)	10 (32.2%)	3 (27.3%)	
Percutaneous snaring	46 (78%)	21 (67.8%)	8 (72.7%)	
Compression factor (IQR)	14.1% (11.3-24.5%)	19% (14.1-19%)	23% (19.8-30.9%)	

ACP=amplatzer cardiac plug; WM=watchman; PC=percutaneous snaring; IQR= interquartile range

The rate of major complications (including death) was significantly higher in postoperative DE cases compared to intraoperative DE. The need for surgical intervention and the rate of mortality significantly increased with LAAO DE occurring later from the time of deployment. All the complicated embolizations (100%, n=12/12) diagnosed more than 1 week after the procedure required surgical intervention and 33% of these resulted in mortality. This may relate to the fact that over time, the embolized device migrates out of the LAA and LA towards the mitral valve apparatus and LVOT. Devices in the LV are more likely to be trapped by the valves (mitral or aortic), both before and during the process of retrieval, requiring open surgical removal in most of the cases. Also, delay in recognition of LAAO DE prevents any prompt action until patient's condition deteriorates and this can lead to increases in morbidity and mortality. Embolized ACP devices tended to locate in the LA (both intra and postoperatively) and also were less likely to require surgical intervention. This could perhaps be related to the design and structure of the device preventing it from going through the MV. In our study, we found that DE to LV and mitral valve apparatus were more likely to get complicated in comparison to other sites of embolization and were also more likely to require surgical intervention compared to other sites.

Table 5: Clinical characteristics and outcomes of patients with complicated surgical interventions

Clinical variables	Device type/timing	Outcome
Acute severe MR due to entrapment of the device in the anterior mitral apparatus and mitral chordae rupture, was noted with the presence of a flail anterior leaflet. Also, the device caused dynamic obstruction of the LVOT, all leading to cardiogenic shock. Emergent surgery was planned.	ACP device, diagnosed after 30 days post procedure, $CHADS_2$ score 8 HASBLED score 4	Death
Aortic cusps damage. Aortic valve replacement and pacemaker implantation	WM, Intraprocedural	Prolonged hospitalization
Acute heart failure secondary to mitral valvular damage	ACP, Post-operative within 24 hours HASBLED score 3	Prolonged hospitalization (18 days)
Surgery with reconstruction of mitral valve	ACP, Intraoperative , $CHADS_2$ score 4 HASBLED score 3	Prolonged hospitalization (13 days)
MR leading to hemodynamic instability	Amulet, Intraoperative, $CHADS_2$ score 6 HASBLED score 4	Prolonged hospitalization
Surgical intervention	ACP, Post-operative	Death
Surgical intervention	ACP, Post-operative	Death
Ruptured mitral chordae tendinae/ severe MR	WM, $CHADS_2$ score 4 HASBLED score 4, Post-operative	Death
Hybrid surgical trans apical retrieval of the device but developed MOF	ACP	Death
Device dislocated one day after intervention and was caught in the mitral valve; Patient was transferred to University hospital of Bonn, device was removed and patient successfully operated; However, died of bleeding complications 6 days after the operation	ACP, Post-operative, $CHADS_2$ score 3 HASBLED score 3	Death

ACP=amplatzer cardiac plug; MR=mitral regurgitation; LVOT=left ventricular outflow tract; MOF=multiorgan failure

The goals of this study are to make operators aware of the timings, outcomes and complications involved with LAAODE. We highlighted the temporal and spatial association of LAAODE with clinical outcomes. An operator should maintain a high index of suspicion for LAAO DE for early recognition and mitigation of a complicated course. It is possible that a proportion of the post-operative DE occur within the first 24 hours but are only detected later during routine follow-up or when a patient becomes symptomatic. Routinely performing transthoracic echocardiography (TTE) within the first 24 hours (as early as 3-4 hours) following a procedure may help to identify and possibly minimize the complications of an acute DE. In our experience these devices are difficult to locate on Xray due to the lack of radiopaque materials in their construction. Future generation devices should include radiopaque materials to facilitate Xray localization. Due to the reported lag between time of actual embolization and time of diagnosis in some cases, consideration should be given to performing a TTE before the routine 1 month follow-up to identify any DE (6). Patient education regarding symptoms and signs of DE (unusual palpitations, congestive heart failure decompensation/ shortness of breath, stroke/transient ischemic attack, limb ischemia) could also play an important role in early diagnosis. Early recognition is key in minimizing morbidity and mortality associated with DE.

Study limitations

Out study is limited by all the issues related to its retrospective observational nature. In addition, the rhythm at the time of embolization was not reported by the authors. Another limitation is residual confounding. Lastly, heterogeneities between operators, institutions and device specific variables could influence the LAAODE rates.

Conclusion

DE with percutaneous LAA occlusion is common with a reported incidence of 2% in our review. DE occurred more frequently in the postoperative period and was associated with higher risk of serious complications, need for surgical retrieval and mortality compared to intraoperative embolization.

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ICE-Derived Left Atrial and Left Ventricular Endocardial and Myocardial Speckle Tracking Strain Patterns in Atrial Fibrillation at the Time of Radiofrequency Ablation

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Abstract

OBJECTIVES Intracrdiac echocardiography (ICE) has excellent imaging resolution and border recognition which increase strain measurement accuracy.We hypothesized that left atrial(LA) substrate and functional impairment can be detected by measuring LA strain deformation in patients with persistent and paroxysmal atrial fibrillation(AF), as compared to those with no AF. Strain deformation changes in LA and left ventricle(LV) can alsobe assessed post-ablation to determine its effect.

METHODS ICE-derived speckle tracking strain(STS) was prospectively performed in 96 patients, including 62 patients with AF(31 persistent and 31 paroxysmal AF) pre-/post-ablation, and 34 patients with no AF.We measuredmajorstrain parameters including longitudinal segmental (endo/myocardial) "average peak overall strain of all segments"(PkAll), peak strain rate(SR), and different time-to-peak strainin LA and LV images.

RESULTS At baseline, persistent AF patients had significantly lower ($p<0.01$) LA endocardial (4.3±2.5 vs. 20.3±8.9 and 25.5±12.9 %) and myocardial PkAll(4.4±2.6 vs. 15.7±7.2 and 20.9±9.2 %), endocardial(0.9±0.4 vs. 1.8±0.7and 2.2±0.6 1/s) and myocardial peak SR (0.7±0.4 vs. 1.5±0.6 and 1.9±0.5 1/s), as compared to paroxysmal AF and no AF patients. After successful ablation, endo-/myocardial LA PkAll and peak SR were significantly improved, most dramatically in patients with persistent AF. LV endocardial/myocardial strain and SR also improved in AF patients post-ablation.

CONCLUSION LA longitudinal strain(%)/SR(1/s) parameters in AF patients are more abnormal than those with no AF, suggesting LA substrate/functional damage. AF ablation improved LA strains/SRbut with values in paroxysmal > persistent AF suggesting background LA damage in persistent AF.

Introduction

Speckle tracking strain (STS) is a unitless measurement of dimensional or deformational change. Using image-processing algorithms for routine 2-dimensional digital echocardiographic images, small stable myocardial footprints, or speckles, generated by ultrasound-myocardial tissue interactions are identified within a defined region of interest. Tracked frame-to-frame over the cardiac cycle, distances between speckles or their spatiotemporal displacement (regional strain velocity vectors) provide non-Doppler information about global and segmental myocardial deformation.[1-2] Left atrial (LA) and ventricular (LV) STS echocardiography has been used for the assessment of LA and LV function and deformation.[3-7] In contrast to LA "strain" assessed with tissue Doppler imaging by transthoracic echocardiography (TTE)[8] which is Doppler angle-dependent, STS is basically angle-independent, and thus less susceptible to the limitations of Doppler echocardiographic assessment of strain.[9-10] To challenge STS being angle-independent, one study using TTE with comparison of longitudinal peak systolic strain in standard four-chamber apical, parasternal, subcostal and off-axis apical imag-

Key Words:
Atrial Fibrillation, Catheter Ablation, Intracardiac Echocardiography, Speckle Tracking Strain Imaging.

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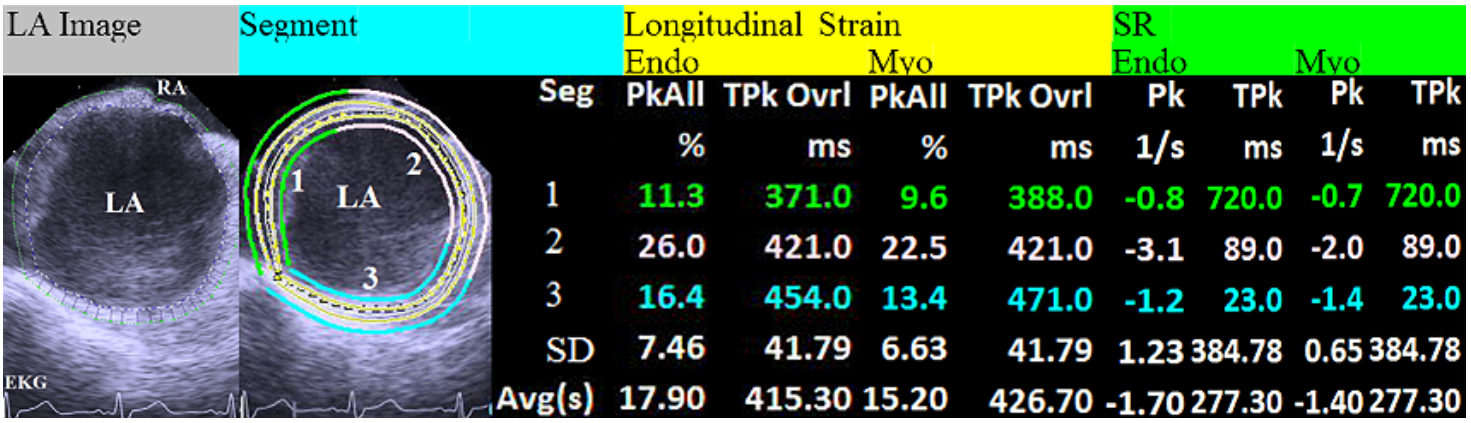


	Longitudinal Strain Endo		Longitudinal Strain Myo		SR Endo		SR Myo	
Seg	PkAll %	TPk Ovrl ms	PkAll %	TPk Ovrl ms	Pk 1/s	TPk ms	Pk 1/s	TPk ms
1	11.3	371.0	9.6	388.0	-0.8	720.0	-0.7	720.0
2	26.0	421.0	22.5	421.0	-3.1	89.0	-2.0	89.0
3	16.4	454.0	13.4	471.0	-1.2	23.0	-1.4	23.0
SD	7.46	41.79	6.63	41.79	1.23	384.78	0.65	384.78
Avg(s)	17.90	415.30	15.20	426.70	-1.70	277.30	-1.40	277.30

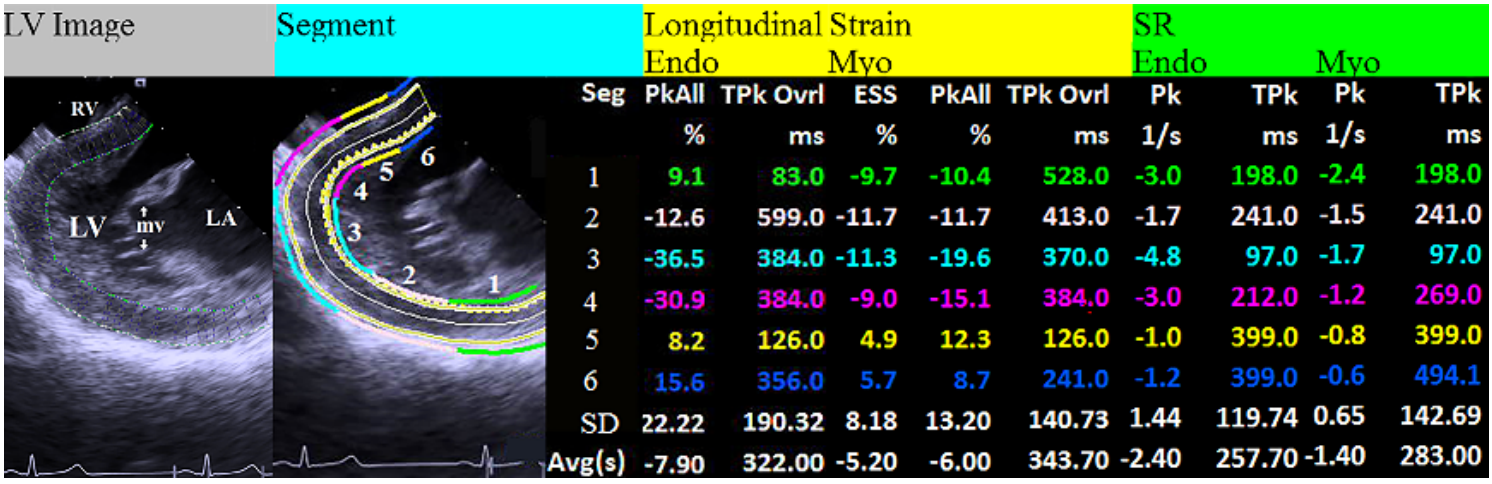
Figure 1: **ICE-derived LA image and LA strain analysis in a patient (male age 62) with paroxysmal AF. The LA image was obtained with the ICE transducer placed at the junction of the RA and superior vena cava with light clockwise rotation from LV inflow into the LA view; LA strain analysis is performed for the 3-segment (Seg) including LA roof/anterior lateral wall (Seg 1, representated by green line), medial/interatrial septal wall (Seg 2, white line) and posterior annulus wall (Seg 3, with blue line) (supplemental video clip S2);**

Longitudinal endocardial and myocardial strains were analyzed with the average overall peak value of all segments "Avg(s)" adopted for further statistical analysis including peak overall strain (PkAll), overall time-to-peak strain (TPkOvrl), peak (Pk) and time-to-peak systolic (TPk) strain rate (SR) parameters. Endo=endocardium; Myo=myocardium; SD=standard deviation.

ing views reported that TTE-derived longitudinal peak strain values were modestly dependent on angle of insonation and target depth.[11] However, based on their methodology the study may emphasizethat STS echocardiography needs standard imaging views with higher ultrasonic resolution and measurement reproducibility, rather than angle and depth dependence. LA/LV STS has become a research-based measurement that relates to LA and LV deformation and has been described to be altered in patients with atrial fibrillation (AF)[12-13] and many other pathophysiological conditions [1-2,5-7]. At present, STS software designed and provided for LA and LV STS measurements and imaging views are designed for use by TTE. As compared to TTE, intracardiac echocardiography (ICE) can provide better views for LA and LV imaging with improved resolution and border recognition.[14-15] We hypothesized that ICE-derived LA and LV STS measurements may provide accurate quantitative evaluation of myocardial and endocardial deformations which compares deformation to original length, such as longitudinal strain and allows for discrimination between normal active myocardial segmental deformation versus passive displacement of a dysfunctional myocardial segment due to adjacent segment tethering and global cardiac motion.The aim of this study was to determine: A) the effect of AF on LA strain and strain rate; and B) the effect of radiofrequency (RF) AF ablation on LA and LV strain and strain rate measurements.

Methods

This was a prospective ICE STS study. The study population of total 96 patients comprised 62 patients with AF and 34 patients with no-AF with relatively normal cardiac structure undergoing first RF AF ablation procedure at the Hospital of the University of Pennsylvania, Philadelphia or the Sir Run Run Shaw Hospital of the Zheji-



	Longitudinal Strain Endo			Longitudinal Strain Myo			SR Endo		SR Myo	
Seg	PkAll %	TPk Ovrl ms	ESS %	PkAll %	TPk Ovrl ms		Pk 1/s	TPk ms	Pk 1/s	TPk ms
1	9.1	83.0	-9.7	-10.4	528.0		-3.0	198.0	-2.4	198.0
2	-12.6	599.0	-11.7	-11.7	413.0		-1.7	241.0	-1.5	241.0
3	-36.5	384.0	-11.3	-19.6	370.0		-4.8	97.0	-1.7	97.0
4	-30.9	384.0	-9.0	-15.1	384.0		-3.0	212.0	-1.2	269.0
5	8.2	126.0	4.9	12.3	126.0		-1.0	399.0	-0.8	399.0
6	15.6	356.0	5.7	8.7	241.0		-1.2	399.0	-0.6	494.1
SD	22.22	190.32	8.18	13.20	140.73		1.44	119.74	0.65	142.69
Avg(s)	-7.90	322.00	-5.20	-6.00	343.70		-2.40	257.70	-1.40	283.00

Figure 2: **ICE-derived LV image and LV strain analysis in a patient (female, age 70) with paroxysmal AF. The LV longitudinal image was obtained with the ICE transducer placed in the RV; LV strain analysis is performed for the 6-segment (Seg) including LV posterior (Seg 1, green line), inferolateral (Seg 2, white line), anterolateral apical (Seg 3, azure line), septal apical (Seg 4, pink line), mid septal (Seg 5, yellow line) and basal septal wall (Seg 6, blue line)(supplemental video clip S3).**

Longitudinal endocardial and myocardial strains were analyzed with the average overall peak value of all segments "Avg(s)" adopted for further statistical analysis including peak over strain (PkAll), overall time-to-peak strain (TPkOvrl), end systolic strain (ESS, myocardial), peak (Pk) and time-to-peak systolic (TPk) strain rate (SR) parameters.
Endo= endocardium; Myo= myocardium; SD=standard deviation.

Table 1: Clinical Characteristics.

Group	Persistent AF 1 (n-=31)	Paroxysmal AF 2 (n-=31)	no AF 3 (n-=34)	p Value		
				1 vs. 2	1 vs. 3	2 vs. 3
Age, yrs	64±8	62±8	54±13	NS	0.01	0.01
Male (%)	25 (81)	23 (74)	23 (68)	NS	NS	NS
Body surface area, m²	1.98±0.23	2.08±0.18	1.99±0.18	NS	NS	NS
Heart rate, beats/min	75±15	65±13	74±10	0.04	NS	0.03
SBP, mmHg	122±11	120±9	120±11	NS	NS	NS
DBP, mmHg	73±10	67±8	66±9	0.04	0.03	NS
No heart disease (%)	6 (19)	13 (42)	15 (44)	NS	0.04	NS
Hypertension (%)	21 (68)	14 (45)	14 (41)	NS	0.04	NS
Other (%)	4 (13)	4 (13)	5 (15)	NS	NS	NS
Echocardiographic variables						
LAIDs, cm	4.9±0.4	4.4±0.3	4.3±0.3	0.01	0.01	NS
LAEF, %	39±17	60±13	68±12	0.01	0.01	NS
LAEV, ml	49±20	57±16	68±21	NS	0.01	NS
LVIDd, cm	5.0±0.5	4.8±0.4	4.8±0.5	NS	NS	NS
LVEF, %	54±9	58±6	56±8	NS	NS	NS
E, cm/s	70±11	61±11	72±13	0.02	NS	0.04
E/e'	9.4±2.5	8.2±2.8	8.7±3.6	NS	NS	NS
PASP, mmHg	30±5	28±5	25±6	NS	0.02	NS

DBP and SBP=diastolic and systolic blood pressure; E=transmitral early diastolic Doppler flow velocity; e'=early diastolic tissue Doppler velocity sampling at posterolateral miitral annulus; LAEF=left atrial ejection fraction; LAEV=LA emptying volume; LAIDs=LA inner dimension at end-systole; LVIDd=left ventricular inner dimension at end-diastole; PASP=pulmonary artery systolic pressure.

ang University, Hangzhou, China. These patients underwent detailed ICE imaging as part of their procedures. All patients gave written informed consent in accordance with the institutional guidelines of each of the University Health Systems. Patients with previous TTE study or baseline ICE studies with moderate or severe mitral regurgitation and/or LV ejection fraction (EF) lower than 30% were excluded from this study.

ICE Study

ICE imaging was performed using a Siemens SC-2000 machine and an intracardiac ultrasound catheter with 8 or 10 Fr (Biosense, Siemens-Acuson, Mountain view, CA) advanced through the femoral vein into right atrium (RA) and right ventricle (RV). As previously described [14,16] at baseline tricuspid regurgitation was assessed for estimation of pulmonary artery systolic pressure (PASP) in the RV inflow and outflow view. LA diameter and mitral inflow peak (E and/or A) velocity, LA EF and emptying volume (LAEV) were measured in the LV mitral inflow view. Posterolateral mitral annual early diastolic (e') peak velocity was measured using Doppler tissue imaging(supplemental figure S1). The peak velocity E or E/A, and E/e' were calculated for assessing diastolic function and estimating LV filling pressure[17]. LV end-diastolic and end-systolic volume, stroke volume, LVEF and LV cardiac output (CO) were assessed in the LV long-axis view with the ICE transducer placed in the RV.

ICE STS Measurements

The LA and LV STS were measured using SC2000_eSie VVI (Siemens, Mountain View, CA) for analysis of endo- and myocardial layer strain parameters including segmental longitudinal (endo- and myocardial) "average peak overall strain of all segments" (PkAll), peak end-systolic strain (ESS), overall time-to-peak strain (TPkOvrl), peak strain rate (SR), and time-to-peak systolic SR (TPk), in the LA and LV longitudinal chamber views. The ICE transducer was first positioned at the high RA just adjacent to the junction of the LA roof and superior limbus as the key location to obtain LA longitudinal view for LA STS measurements (Figure 1). After obtaining mitral inflow view, the transducer is then rotated slightly clock wise to obtain the above-mentioned LA view for STS measurements. This image consistently includes the posterior mitral annulus and adjacent LA wall instead of the mitral valve inflow structures. The anatomic reference of this LA view for LA STS analysis included three segments: LA roof (with superior limbus)/anterior lateral wall, medial/interatrial septal wall and posterior annulus wall(Figure 1 and supplemental video clip S2). With the transducer positioned within the RV, LV longitudinal with mitral inflow view was obtained. The anatomic reference of this LV view for LV STS study included six segments: LV posterior wall, inferolateral wall, anterolateral apical (with its papillary muscle), septal apical, and mid and basal septal segments(Figure 2 and supplemental video clip S3). To avoid the foreshortening of the LV apex the ICE transducer was advanced along the interventricular septum to as near the RV apex as possible. Each LA STS parameter was measured, defined as the average STS measurement of the three segments of the LA imaging view. Each LV STS parameter was measured, defined as the average STS measurement of the six segments of the LV long-axis view. The absolute values of averaged STS measurements were adopted for statistical analysis. Image acquisition was performed with frame rate of 50-90 fps (acoustic clip capture with extended R-R) to ensure high quality. The LA and LV endocardial borders were traced manually and the epicardial borders were created by automated recognition with 5 mm for the LA wall thickness and 10 mm for the LV wall thickness. Based on the actual ICE imaging measurements of the wall thickness, manual correction and visual tracking accuracy of wall thickness and wall contour movement during cardiac cycles were performed in each case.LV papillary muscles were not included in the region of interest.

RF Ablation for Pulmonary Vein Isolation

Multipolar catheters were placed at the lateral RA and in the coronary sinus. Dual transseptal catheterization with ICE imaging guidance was performed to position a multipolar mapping catheter (Lasso™ or PentaRay) and a mapping/ablation catheter (Biosense Webster, Irvine or Diamond Bar, CA, USA) within the LA using standard techniques. Pulmonary vein (PV) isolation was performed at the LA/antral PV junction using previously described techniques.[18-19] All patients received isoproterenol infusion (up to 6 to 20 μg/min) and/or adenosine bolus (up to 12 to 18 mg), in an attempt to provoke PV reconnection and non-PV triggers following PV isolation. Non-PV triggers were routinely targeted by focal ablation unless from superior vena caval or posterior LA origin in which case isolation was also performed. Acute ablation success was defined as the inability to demonstrate reconnected PVs or AF triggers from

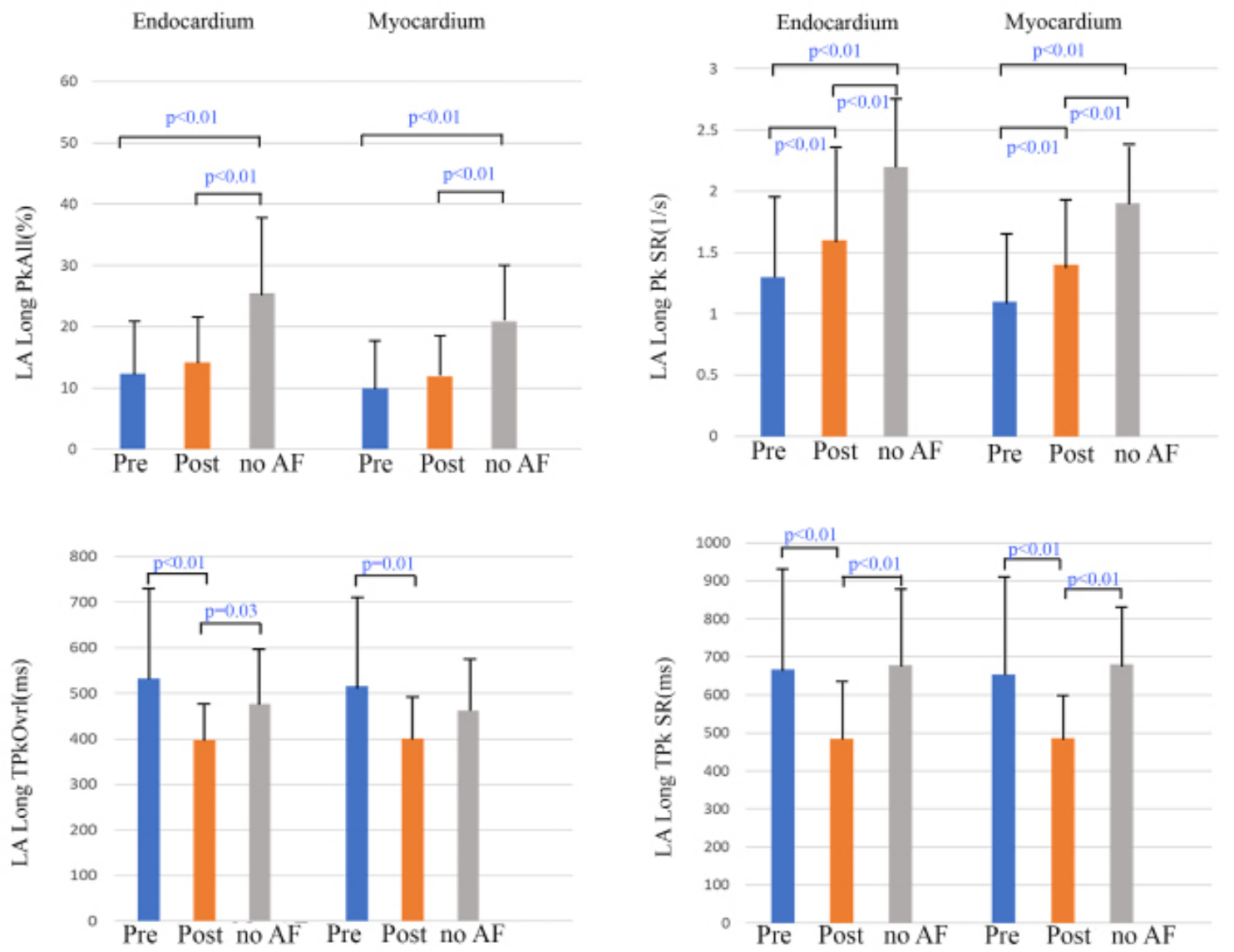


Figure 3: **ICE-derived LA STS Measurements (the bars expressed as mean + 1 SD) Pre- and Post-RF ablation in AF Versus Baseline in no AF Patients. LA STS measurements pre-RF ablation in AF group (1+2) as compared to no AF group at baseline, showed similar results as the no-AF versus persistent AF group 1, including significantly lower LA longitudinal (Long) endocardial and myocardial PkAll and peak (Pk) SR, but not the endo-/myocardial TPkOvrl and TPk SR parameters. LA PkAll (%) was only mildly increased, and only Longendo- and myocardial Pk SR (1/s) reached significantly post-RF ablation. However, there were significantly shortening of the LA Long endocardialand myocardial TPkOvrl and TPk SR in AF patients post-RF ablation.**

AF=atrial fibrillation;ICE=intracardiac echocardiography; LA=left atrium;PkAll=average peak overall strain of all segment; RF=radiofrequency; SR=strain rate; STS=speckle tracking strain; TPk=time-to-peak; TPkOvrl=overall time-to-peak strain.

non-PVs sources in response to isoproterenol (and/or adenosine) and following cardioversion of induced AF during isoproterenol administrationat the end of ablation procedure.

Statistical Analysis: The values were expressed as mean±SD. Categorical data were summarized as frequencies and percentages. Differences in clinical and echocardiographic variables between groups were evaluated using unpaired or paired Student t test, and/or Wilcoxon signed-rank test (if the differences between pairs of observations are severely non-normally distributed)[20] as appropriate. For categories variables, the chi-square test is used. Intra- and interobserver variations (%) were expressed as $Mean_{difference}/Mean_{both\ measurements}$ x 100 $\pm SD_{difference}/Mean_{both\ measurements}$ x 100.[21-22] All statistical tests are 2-sided, and a p value <0.05 is considered significant.

Results

Patient Characteristics and Treatment of AF

The study population included 96 patients divided into three groups: Group 1 - persistent AF (n=31), Group 2 - paroxysmal AF (n=31) and Group 3 - no AF (n=34, in which 27 with PVCs and 7 with supraventricular tachycardias of non-LA origin). Baseline characteristics of the study groups are presented in Table 1. Patients in Group 1 had a slightly higher age and PASP, a higher incidence of hypertension, more dilated LA inner dimension at end-systole

Table 2: ICE LA STS Measurements Pre- and Post-RF Ablation in AF Versus Pre-RF Ablation in No AF Groups

Group	Persistent AF 1		Paroxysmal AF 2		no AF 3	p Value		
						1 vs. 2	1 vs. 3	2 vs. 3
	Pre	Post	Pre	Post	Pre	Pre	Pre	Pre
Longitudinal Strain								
Endo PkAll, %	4.3±2.5	8.0±4.8*	20.3±8.9	20.5±7.	25.5±12.9	0.001	0.001	NS
TPkOvrl, ms	432±171	418±101	632±252	379±65*	476±128	0.02	NS	NS
MyoPkAll, %	4.4±2.6	6.5±3.2*	15.7±7.2	17.3±6.0	20.9±9.2	0.001	0.001	NS
TPkOvrl, ms	433±168	422±118	599±221	380±68*	462±113	NS	NS	NS
Longitudinal SR								
Endo SR Pk, 1/s	0.9±0.4	1.2±0.5*	1.8±0.7	2.1±0.8	2.2±0.6	0.001	0.001	0.04
TPk, ms	488±203	483±151	846±306	487±159*	678±209	0.001	0.01	NS
Myo SR Pk, 1/s	0.7±0.4	1.0±0.4*	1.5±0.6	1.8±0.6	1.9±0.5	0.001	0.001	0.04
TPk, ms	515±179	480±126	795±304	494±124*	680±162	0.003	0.01	NS

*P ≤0.02 Post-RF vs. Pre-RF in AF group 1 or 2; NS = statistically no significance.
Endo=endocardium; Myo=myocardium; Pk=peak; PkAll=average peak overall strain of all segment; SR=strain rate; TPk=time-to-peak; TPkOvrl=overall time-to-peak strain.

(LAIDs) and lower LAEF/LAEV as compared to Group 2 and 3 patients at baseline.There were no significant differences between 3 groups regarding sex, body surface area, systolic blood pressure, LV inner dimension at end-diastole, LVEF and E/e' parameters. There were significant differences among the Group 1/2 and Group 3 patients regarding resting heart rate, diastolic blood pressure and mitral peak flow velocity E, but all the average values of these parameters were within their normal and mildly variant ranges.

At the end of the procedure Group 1 and 2 AF patients had acute ablation success and remained in sinus rhythm, as indicated by PV isolation and no inducible non-PV triggers in response to isoproterenol and/or adenosine and following cardioversion of induced AF at the end of ablation procedure. No patient had acute PV stenosis (based on ICE PV ostial flow velocity measurement <100 cm/s), embolic events or pericardial effusion with cardiac tamponade at the time of procedure.

LA STS Measurements Pre-RF Ablation in AF and No-AF Patients at Baseline

When comparing the LA STS measurements pre-RF ablation between AF patients in Group 1 and Group 2 (Table 2), patients with persistent AF(Group 1) had significantly lower LA longitudinal endocardial PkAll (4.3±2.5 vs. 20.3±8.9 %) and myocardial PkAll (4.4±2.6 vs. 15.7±7.2 %), LA longitudinal endocardial peak SR (0.9±0.4 vs. 1.8±0.7 1/s) and myocardial peak SR (0.7±0.4 vs. 1.5±0.6 1/s)(all p<0.05), whereas patients with paroxysmal AF in Group 2 had significantly longer LA longitudinal endocardial TPkOvrl (632±252 vs. 432±171ms)and myocardial TPkOvrl (599±221 vs. 433±168ms), LA longitudinal endocardial TPk SR(846±306 vs. 488±203ms) and myocardial TPk SR (795±304 vs. 515±197ms) (all p<0.05)pre-RF ablation.

In comparing LA STS measurements pre-RF ablation between patients of AF Group1, 2 and Group 3 at baseline, patients with persistent AF (Group 1) had the lowest LA longitudinal endocardial PkAll (4.3±2.5 vs. 25.5±12.9 %) and myocardial PkAll (4.4±2.6 vs. 20.9±9.2 %), LA longitudinal endocardial peak SR (0.9±0.4 vs. 2.2±0.6 1/s) and myocardial peak SR (0.7±0.4 vs. 1.9±0.5 1/s)(all p<0.05).Strain and SR parameters for paroxy smal AF(Group 2) pre-RF ablation, where modestly lower as compared to non-AF Group 3 at baseline, only lower endocardial(1.8±0.7 vs. 2.2±0.6 1/s) and myocardial SR (1.5±0.6 vs. 1.9±0.5 1/s) reached statistical significance (p<0.01).

LA STS measurements pre-RF ablation in AF Group (1 + 2)as compared to no AF Group 3 at baseline, showed similar results as the persistent AF Group 1,including significantly lower LA longitudinal endocardial and myocardial PkAll and peak SR, but not the endo-/myo-cardial TPkOvrl and SRTPk (Figure 3).

Changes in LA STS Measurements Post-AF Ablation

Although patients with persistent AF (Group 1) had lowest strain and SR measurements pre-RF, improved LA endo/myocardial PkAll (%) and peak SR (1/s)were observed post successful RF ablation (Table 2).In general, patients with AF (Group 1 + 2)had an increase of all LA strain and SR parameters with the endo-(1.3±0.7 vs. 1.6±0.8 1/s) and myocardial Pk SR (1.1±0.6 vs. 1.4±0.6 1/s)reaching significant differences (p<0.01) post-RF ablation (Figure 3). These changes were coincident with a significant increase in LAEF (50±17 vs. 56±12%) and LACO (3344±1400 vs. 4557±1476 ml/min) post-RF.However, the increased values in AF patients post-RF were still significantly lower (p<0.01) than values in no-AF patients at baseline (Figure 3).

There were significant reductions of LA endo-(532±216 vs. 398±83 ms) and myocardial TPkOvrl (516±208 vs. 401±92ms), and LA endo-(667±286 vs. 485±155 ms)and myocardial SR TPk (653±272 vs. 487±126 ms)(all p ≤ 0.01) post-RF ablation(Figure3). The differences in shortening of the TPkOvrl(ms) and SR TPk (ms) post-RF ablation reached significance in paroxysmal AF Group 2 but not the persistent AF Group 1(Table 2).

LV STS Measurements Pre- and Post-AF Ablation

LV STS measurements pre- and post-RF ablation are listed in Table 3. Pre-RF ablation patients with persistent AF(Group 1) had significantly lower LV longitudinal endo- (10.9±4.5 vs. 15.8±5.4 %),

Table 3: ICE LV STS Measurements Pre- and Post-RF Ablation in AF Groups.

Group	Persistent AF 1		Paroxysmal AF 2		AF 1+2	
	Pre	Post	Pre	Post	Pre	Post
Longitudinal Strain						
Endo PkAll, %	10.9±4.8†	16.2±5.4	18.6±6.6*	13.6±5.9	15.8±6.7*	13.1±5.4‡
TPkOvrl, ms	399±84	389±85‡	430±95	340±42*	414±92	364±64*
Myo ESS, %	7.1±3.4†	8.2±3.3‡	9.8±3.5	11.0±4.7	8.5±3.6	9.7±4.1*
PkAll, %	8.5±3.6	9.2±3.9‡	10.6±4.2	12.4±4.7	9.5±3.9	10.8±4.6*
TPkOvrl, ms	384±77	359±65	431±93	342±45*	408±90	351±55*
Longitudinal Strain Rate						
Endo SR Pk, 1/s	1.5±0.6	1.7±0.6‡	2.0±0.6	2.2±0.5	1.7±0.6	2.0±0.6
TPk, ms	228±91	212±68	253±68	192±55*	240±82	202±62*
Myo SR Pk, 1/s	1.1±0.4	1.2±0.4‡	1.4±0.5	1.6±0.4	1.2±0.5	1.4±0.4
TPk, ms	224±76	198±69	251±68	198±47*	238±74	198±58*

*p≤0.04: Post- versus Pre-RF in AF Group or AF Group 1+2;
†p<0.04 Pre-RF: AF Group1 versus AF Group 2; ‡p<0.04 Post-RF:AF Group 1 versus AF Group 2.
Abbreviations as in Table 2; ESS=peak end-systolic strain.

myocardial GLS PkAll (7.6±3.7 vs. 10.6±4.0 %), endocardial PkAll (10.9±4.8 vs. 16.2±5.4 %) and myocardial ESS (7.1±3.4 vs. 9.8±3.5 %) as compared to those with paroxysmal AF(Group 2). Patients with AF (Group 1+2) after successful ablation had significant increase in endo- and myocardial strain (%) and the TPkOverl/SR TPk (ms) shortened (Table 3). These improvements were coincident with a demonstrated increase in LVEF (39±17 vs. 51±12%) and LV CO (3566±1788 vs. 4302±1551 ml/min) (p<0.05).

Intra- and Inter-observer Variation

Intra- and inter-observer (between JR and SC) variations for ICE-derived LA (n=20 measurements) and LV (n=23 measurements) strain parameters were assessed in 20 patients. The intra- and interobserver variations of major LA/LV longitudinal endo- and myocardial strain parameters were listed in Table 4. The intra-observer variations for LA strains were measured from 11±7 to 21±14%; and for LV strains, from 10±6 to 16±12%. The interobserver variations for LA strains were measured from 16±11 to 59±34%; and for LV strains, from 13±10 to 28±20%.

Discussion

Novel therapeutic options such as RF catheter ablation techniques and transcatheter closure of the LA appendage or replacement of cardiac valves for severe regurgitation demand advanced imaging to maximize patient safety and procedural outcomes. ICE provides excellent imaging views and resolution for evaluation of cardiac structure and function. ICE has become a valuable and useful imaging tool during interventional electrophysiological procedures.[14] In addition to our previously developed ICE-derived RV myocardial strain deformation patterns in arrhythmogenic cardiomyopathy[23], this is the first prospectively 2D ICE-derived LA and LV STS evaluation, to our knowledge, in AF patientspre and post-ablation procedure.

Lower LA STS Values at Baseline Can Identify Background LA Damage in AF Patients

Our findings demonstrate that at baseline LA longitudinal endocardial and myocardial average segmental PkAll strain (%)and peak SR (1/s)in patients with AF were significantly lower (average 52 and 42%, respectively) pre-RF ablation than those without AF using ICE-derived 2D STS. Lower PkAll and peak SR values were more marked in the persistent AF patients (81 and 61%, respectively) than the paroxysmal AF patients (22 and 20%). In this study, patients with AF were older age than those without AF. Patients with persistent AF had slightly larger LAIDs and lower LAEF/LAEV than those of paroxysmal AF and no AF patients. ICE derived E/e' measurements (average <12 or 15) did not show a higher likelihood of increased LV filling pressure in the AF group.[17] Based on evidence of only a mildly enlarged LA and normal PASP measurements, the AF group patients in this study probably represented a less advanced cardiac disease state. The modestly elevated PASP measurements especially in the persistent AF patients,probably still reflects more structural abnormalities as compared to without AF patients with a comparably dilated LA (p=0.02). LA dilation and myocardial fibrosis causing LA dysfunction and electromechanical conduction delay characterize the substrate for AF.[24-25] Lower LA strain and SR measurements indicate LA substrate damage during remodeling coincident with LA dilation and increase in fibrosis in patients with AF. Our findings of lower LA strain and SR especially with persistent AF,may reflect LA substrate and functional damage with fibrosis(stiffness) rather than just LA dilation[26]. A reduced LA reservoir strain (during LV systole) has been also shown to correlate with LA wall fibrosis determined by delayed-enhancement magnetic resonance imaging in patients with AF.[27-28] Therefore, findings of lower strain and SR parameters pre-RF AF ablation in this study suggests their sensitivity in the identification of LA substrate changes due to AF.

Limited Improvement of LA Strain and SR in AF Patients afterAblation

This study showed that patients in both AF Groups demonstrated an increase in strain and SR parameters post-RF. Of note, LA endo-/myocardialstrain and SR parameters significantly increased (p ≤ 0.02) after successful RF ablation in the persistent AF patients. This might be attributed to change in heart rhythm from AF to the sinus in the patients with persistent AF. However, these values although significantly increased from baseline are still significantly lower than those of paroxysmal AF and Non-AF patients, indicating more LA substrate and functional damage in persistent AF patients. TTE intra-LA vector flow mapping and tracking study revealed that successful AF catheter ablation slightly improves but does not reverse impaired LA intra-flow and mechanics after 3- and 6-month follow-up.[13] Whether the pathophysiological mechanism for the changes observed relates to LA dyssynchrony and heterogeneous deformation remains to be further studied.[23]

Shortening in LA Time to Peak Strain and SR (ms) after AF ablation

The LA STS measurements of paroxysmal AF pre-RF ablation showed longer LA segmental longitudinal endo- and myocardial TPkOvrl (ms) and TPk SR (ms) than those of persistent AF. Never-

Table 4: Intra- and Inter-Observer Variation for LA and LV STS Parameters.

Variation	Intraobserver %		Interobserver %	
	LA	LV	LA	LV
Longitudinal Strain				
Endo PkAll	13±7	15±7	59±34	28±20
TPkOvrl	19±15	10±6	23±18	15±14
MyoPkAll	11±7	16±9	43±35	28±22
TPkOvrl	21±14	12±8	29±23	13±10
Longitudinal SR				
Endo SR Pk	19±14	15±15	16±11	22±19
Myo SR Pk	19±11	10±9	19±14	18±15

Abbreviations as in Table 2

theless, immediately after RF ablation these longitudinal endo- and myocardial TPkOvrl and TPk SR were significantly shortened.A shortened and improved LA longitudinal endo- and myocardial TPkOvrl and SR TPk (ms) in the paroxysmal AF patients post RF ablation may reflect mild and reversible changes due to LA functional abnormalities from the AF. However, maintenance of a shortened time to peak strain and SR (ms) in the persistent AF patients post-RF ablation correlates with the maintenance of sinus rhythm and efficacy of RF catheter ablation. In addition, the changes in segmental atrial velocity and the magnitude and the rate of myocardial deformation during the cardiac cycle should also be considered.[29-30] Whether a prolongation or shortening of the time to peak strain and SR (ms) is related to LA changes in dimension, anatomic/electrophysiological function and/or extent of fibrosis needs to be further studied.

Improvement in LV STS Post-RF Ablation for AF

Our study demonstrated that the patients with AF, especially persistent AF had reduced LV EF and lower LV longitudinal endo- and myocardial strain (%) and SR (1/s) parameters pre-RF AF ablation. The AF may lead to adverse cardiac remodeling and may be primarily responsible for the development of a cardiomyopathy.[31-32] However, our results showed that the majority of the LV longitudinal endo- and myocardial strain and SR parameters were improved immediately post acutely successful ablation as compared to results immediately pre-RF ablation. This may be a benign interaction between improvement of reservoir and contractile atrial and LV function immediately after ablation. These results suggest that careful assessment of individual changes in LVEF and STS parameters may provide critical prognostic and diagnostic value immediately after restoration of sinus rhythm.

Study Limitations

This was a dual-center, prospective study using ICE imaging with a selected group of patients with AF undergoing first RF ablation procedure. ICE as an invasive catheter-based technique is not indicated for use in normal subjects. We selected a group of patients without AF but with PVCs and other arrhythmias of non-LA origin undergoing first RF ablation procedure, who had STS measurements at baseline as the reference population. The sample size was relatively small and patients with moderate or severe mitral regurgitation were excluded. The STS measurements in this study were obtained from a specific view of the LA and LV using 2D-ICE imaging. STS measurements from multiple views may increase its diagnostic value for more complicated structural heart disease, such as ischemic and nonischemic dilated cardiomyopathy. However, our results of STS measurements at pre-RF ablation have indicated that average segmental endo- and myocardial peak LA strain (%) and peak SR (1/s) parameters can clearly differentiate different severity of LA substrate and functional damage between the persistent and paroxysmal AF groups. Our findings also demonstrated that LA strain (%) and SR (1/s) did improve especially in the persistent AF patients post-RF ablation and furthermore, the majority of LV STS parameters were improved after acutely successful ablation. However, the LA strain values did not return to those observed in no AF patients, suggesting background LA damage.

The results of intraobserver and interobserver variations indicated that intraobserver variations were smaller (than interobserver variations) and acceptable as compared to the marked changes of STS measurements in patients with AF. At present, our ICE-derived STS measurements may not exactly compare with the other techniques especially using different strain software packages since a higher variability and reproducibility of segmental/regional strain measurement has been shown among 7 different vendors.[33-34] Finally, STS echocardiography is a novel clinical technique which needs further development and study to confirm reproducibility of strain measurements and other factors that can influence measurements. Nevertheless, our results support these STS parameters as a potential marker of LA substrate and functional damage and an adjunctive measure of the mechanical effects that the LA sustains from AF.

Conclusion

ICE-derived speckle tracking LA longitudinal strain and SR parameters in AF patients, especially with persistent AF were significantly lower than those with no-AF patients, suggesting LA substrate and functional damage. AF ablation did improve those LA strain/SR parameters, especially in persistent AF patients, but still with lower values suggesting background LA damage. The majority of LV strain and SR were improved with successful ablation for AF.

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Catheter Ablation for Hospitalized Atrial FibrillationPatients with Reduced Systolic Function:Analysis of Inpatient Mortality, Resource Utilization and Complications

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Abstract

Background: Randomized trials have shown improvement in hard clinical end points when catheter ablation (CA) is employed as a management strategy for certain atrial fibrillation (AF) patients with heart failure and reduced ejection fraction (HFrEF). Limited data, however, exist in this realm outside the controlled clinical trial settings. We sought to determine real-world data on mortality and complications after utilization of CA in such patients.

Methods and Results: Data were derived from National Inpatient Sample from January 2008 to August 2015. Patients were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. Baseline characteristics and outcomes were compared among HFrEF and AF patients undergoing CA or not. Propensity matching was done to mitigate selection bias and balance confounding variables. Various CA related complications were assessed. Logistic regression was done to determine predictors of mortality in our study cohort. A total of 2,569,919 patients were analyzed and a total of 7773 patients underwent CA. Mortality was significantly better in CA group in both unmatched (1.2% vs. 4.9%, p < 0.01) and propensity matched cohorts (1.2% vs. 3.6%, p < 0.01). Overall complication rate was 10.2% in CA cohort and primarily driven by cardiac and neurological etiologies. In regression analysis, CA remained a strong predictor of reduced mortality (OR 0.301, 95% CI 0.184-0.494).

Conclusion: CA is associated with improved mortality in admitted AF patients with concomitant HFrEF. Overall complication rate after CA was modest at 10.2%.Consideration can be given to the utilization of this therapeutic modality in hospitalized AF patients with concomitant HFrEF.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice [1]. AF and congestive heart failure (CHF) frequently co-exist due to similar predisposing risk factors and ability of one to perpetuate the other [2,3]. AF is associated with increased CHF hospitalizations, stroke and all-cause mortality [4,5,6]. Various randomized trials conducted in last two decades have shown efficacy of catheter ablation (CA) for AF in HF and reduced ejection fraction (HFrEF) patients with respect to hard clinical end-points of mortality and CHF hospitalizations [7,8]. With the result of these trials, it is expected that the volume of CA would continue to grow for management of AF and HFrEF patients. It is therefore imperative that data be sought from real world settings with respect to mortality and complications associated with CA in AF and HFrEF patients. Till to date, studies utilizing national databases for assessing aforementioned outcomes did not discriminate based on HF status of the patient [9,10,11,12]. We, therefore, utilized National Inpatient Sample (NIS) to assess contemporary trends in mortality and complications associated with CA in AF and HFrEF patients.

Key Words

Atrial fibrillation; Heart failure with reduced ejection fraction; Catheter ablation; Outcomes; National sample

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Methods

We conducted analysis on National Inpatient Sample (NIS)from January 2008 to August 2015. NIS is part of Healthcare Resource and Utilization Project (HCUP) and made possible by a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is derived from all States and utilized for computing national estimates of healthcare utilization, cost and outcome [13]. NIS is compiled annually and the data can be used for analysis of disease trends overtime. Institutional Review Board approval and informed consents were not required for this study given the de-identified nature of the NIS dataset and

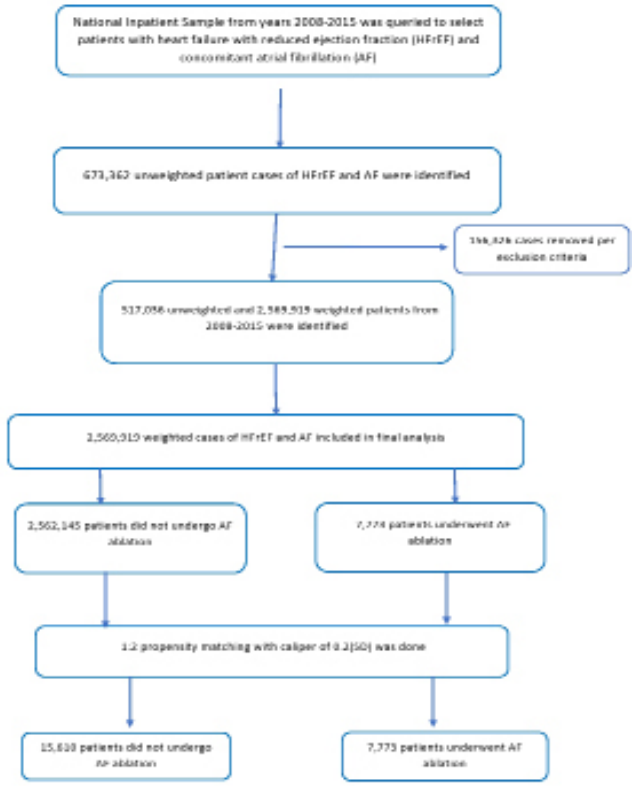

Figure 1: Flow sheet of patient selection.

public availability.

We analyzed NIS data from January 2008 to August 2015 using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. Patient under 18 years of age were excluded. Inclusion criteria included patients with HFrEF and AF. Cases with concurrent diagnostic codes for atrial flutter, supraventricular tachycardia, ventricular tachycardia, other premature beats, cardiac dysrhythmia, Wolf-Parkinson-White syndrome, atrioventricular nodal tachycardia and open surgical ablation were excluded. Age was divided into three groups, <65, 65-74 and ≥75. $CHAD_2VASC_2$ score was calculated. Complications associated with ablation were subsequently assessed. Please see figure 1 for flow sheet of patient selection.

Baseline characteristics of patients under going ablation versus not along with hospital out comes were derived. Length of stay and mean

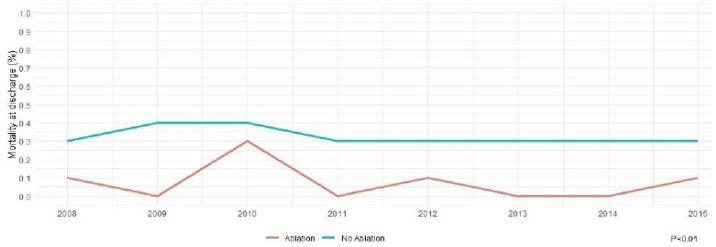

Figure 2: Trends in mortality in heart failure with reduced ejection fraction and atrial fibrillation patients vs. not over the study years

Table 1: Baseline characteristics of the study population stratified on the basis of AF ablation versus not

Variable no. (%)	No Ablation (n=2562145)	Ablation (n=7773)	All patients with Afib† andHFrEF‡ (n=2569919)	P value
Age (mean [SD]) years	76.2(11.6)	69.6(12)	76.2(11.6)	<0.01
Age <65	415112(16.5%)	2504(33.1%)	417616(16.50%)	<0.01
65-74	521723(20.7%)	2088(27.6%)	523811(20.70%)	<0.01
¬≥75	1584144(62.8%)	2980(39.4%)	1587124(62.80%)	<0.01
Female	1068414(41.70%)	2635(33.90%)	1069086(41.60%)	<0.01
$CHAD_2VASC_2$ score (Median, IQR)	4(2)	3(2)	4(2)	
Race				
Caucasian	1896153(80.2%)	5801(83.7%)	1901954(80.20%)	<0.01
African American	254526(10.8%)	597(8.6%)	255123(10.80%)	
Hispanics	120305(5.1%)	319(4.6%)	120624(5.10%)	
Asian or Pacific Islander	33809(1.4%)	45(0.6%)	33854(1.40%)	
Native American	10747(0.5%)	31(0.4%)	10778(0.50%)	
AHRQ§Medical comorbidity				
Alcohol abuse	72809(2.8%)	211(2.7%)	73020(2.80%)	0.49
Anemia	34472(1.3%)	54(0.7%)	34526(1.30%)	<0.01
Chronic pulmonary disease	858847(33.5%)	2098(27.0%)	860945(33.50%)	<0.01
Coagulopathy	208605(8.1%)	492(6.3%)	209097(8.10%)	<0.01
Diabetes	218960(8.5%)	378(4.9%)	219338(8.50%)	<0.01
Hypertension	1745998(68.1%)	5075(65.3%)	1751073(68.10%)	<0.01
Fluid and electrolyte disorders	895405(34.9%)	1904(24.5%)	897309(34.9%)	<0.01
Liver disease	69092(2.7%)	133(1.7%)	69225(2.70%)	<0.01
Neurological disorders	205974(8.0%)	324(4.2%)	206298(8.0%)	<0.01
Peripheral vascular disorders	354809(13.8%)	843(10.8%)	355652(13.8%)	<0.01
Renal failure	996522(38.9%)	2458(31.6%)	998980(38.9%)	<0.01
History of stroke	226751(8.9%)	498(6.4%)	227249(8.80%)	<0.01
Valvular Disease	273245(10.7%)	131(1.7%)	273376(10.60%)	<0.01
Hospital Location				
Rural	304736(11.9%)	303(3.9%)	305039(11.90%)	<0.01
Urban Non-teaching	943247(36.8%)	1746(22.5%)	944993(36.80%)	
Urban Teaching	1314162(51.3%)	5725(73.6%)	1319887(51.40%)	
Bed size of the hospital				
small	345854(13.5%)	611(7.9%)	346465(13.5%)	<0.01
medium	667961(26.1%)	1506(19.4%)	669467(26.1%)	
large	1548331(60.4%)	5656(72.8%)	1553987(60.5%)	
Region				
Northeast	568435(22.2%)	1722(22.2%)	570157(22.2%)	<0.01
Midwest	666681(26.0%)	1913(24.6%)	668594(26.0%)	
South	930343(36.3%)	3024(38.9%)	933367(36.3%)	
West	396686(15.5%)	1115(14.3%)	397801(15.5%)	
Median household income percentile				
0–25th	722541(28.7%)	2038(26.5%)	724579(28.7%)	<0.01
26–50th	677852(27.0%)	2183(28.4%)	680035(27.0%)	
51–75th	615639(24.5%)	1897(24.7%)	617536(24.5%)	
76–100th	498023(19.8%)	1573(20.5%)	499596(19.8%)	

†Atrial Fibrillation; ‡Heart Failure with reduced Ejection Fraction;§Agency for healthcare research and quality

Table 2: Hospital encounter outcomes and resource utilization of the study cohort

Variables no. (%)	No Ablation (n=2562145)	Ablation (n=7773)	All patients with Afib† and HFrEF‡ (n=2569919)	P value
Died at discharge	124674(4.9%)	91(1.2%)	124765(4.9%)	<0.01
<65	11280(2.7%)	10(0.4%)	11290(2.7%)	<0.01
65-74	21181(4.1%)	31(1.5%)	21212(4.1%)	<0.01
>/=75	90688(5.7%)	49(1.6%)	90737(5.7%)	<0.01
Discharge Disposition of surviving patients				
Routine/self-care	1026629(42.1%)	5420(70.5%)	1032049(42.2%)	<0.01
Short-term hospital	69374(2.8%)	54(0.7%)	69428(2.8%)	
Another type of facility	735372(30.2%)	980(12.8%)	736352(30.1%)	
Home Health Care	589475(24.2%)	1219(15.9%)	590694(24.2%)	
Resource utilization, Mean (SD)				
Length of stay, mean (SD), days	6.1(5.7)	6.2(6.4)	6.1(5.8)	<0.01
Cost of hospitalization-mean (SD), $	46370(69554)	92327 (90984)	46516(69680)	<0.01

†Atrial Fibrillation; ‡Heart Failure with reduced Ejection Fraction

cost of stay (inflation adjusted) were subsequently calculated.

For missing values imputation, multiple iterations of Markov Chain Monte Carlo (MCMC) method were used. To account for potential confounding factors and selection bias, a propensity score-matching model was developed using logistic regression to derive two matched groups for comparative outcomes analysis. Given larger non-ablation group and to minimize case loss, a nearest neighbor 1:2 variable ratio, parallel, balanced propensity-matching model was made using a caliper width of 0.2. Descriptive statistics were presented as frequencies with percentages for categorical variables and as means with standard deviations for continuous variables. Baseline characteristics were compared using a Pearson$\chi 2$ test and Fisher's exact test for categorical variables and independent samples t-test for continuous variables.

Logistic regression was performed to estimate odds ratios (ORs) with 95% confidence intervals (CIs) to determine predictors formortality in our cohort. Initially, binomial logistic regression model was used to identify variables from demographic data (table 1) that were significantly associated with patient mortality (P value < 0.10). These variables were then subsequently utilized in a multiple logistic regression model to identify predictors of mortality. A type I error rate of <0.05 was considered statistically significant. All statistical analyses were performed using statistical package for social science (SPSS) version 26 (IBM Corp) and R 3.5 for propensity matching. All analyses were done on a weighted sample.

Results

A total of 2,569,919 patients with AF and HFrEF were identified from NIS dataset. Out of these, about 7,773 patients underwent AF ablation. Baseline characteristics of the study population are shown in table 1. Patients undergoing ablation tend to be younger when compared to patients not undergoing ablation (69.6 vs. 76.2 years, p < 0.01). 41.6% of the study cohort constituted female patients and ablation was performed in 34% of them. Median $CHAD_2VASC_2$ score was 4(2) for the non-ablation group and 3(2) for the ablation group.

Table 2 illustrates outcomes and resource utilization of our study cohort based on raw unmatched data. A total of 124,765 (4.9%) patients in our study died at discharge. Mortality was significantly lower in the ablation group compared to no ablation group in both unmatched (1.2% vs. 4.9%, p < 0.01) and propensity matched groups (1.2% vs. 3.6%, p < 0.01). Please see table 3 for detailed outcomes after propensity matching. Mortality trend remained low and stable over study years in both ablation and no ablation group (figure 2). There had been a steady increased trend in mean cost for hospital stay over study years in both groups (figure 3).

Overall, 10.2% patients had at least one complication associated with CA (table 4). Complications associated with ablation included stroke (1.8%), myocardial infarction (3.6%), need for percutaneous coronary intervention (0.7%), cardiogenic shock (2.3%),cardiac tamponade (0.7%), vascular complications (0.7%),septic shock (0.7). The incidence of per icardiocentesis was 0.7% in our ablation cohort.

Mortality predictors for AF patients with HFrEF are shown in figure 4. Advanced age (OR 1.027, 95% CI 1.026-1.029), chronic pulmonary disease (OR1.108, 95% CI 1.077-1.139), coagulopathy (OR1.797, 95% CI1.729-1.867), fluid and electrolyte disorders (OR2.242, 95% CI2.182-2.303),peripheral vascular disease (OR 1.128, 95% CI 1.088-1.17), valvular heart disease (OR 1.157, 95% CI 1.111-1.204) and renal failure (OR1.302, 95% CI1.267-1.338) were associated with increased mortality while ablation was independently associated with lower mortality in our cohort (OR0.301, 95% CI 0.184-0.494).

Discussion

The main findings of current study include: (1) AF patients with HFrEF tended to have low mortality if they undergo ablation in both unmatched (1.2% vs. 4.9%, p < 0.01) and propensity matched cohorts (1.2% vs. 3.6%, p < 0.01). (2) CA was an independent predictor of reduced mortality in adjusted mortality analysis. (3) Approximately 10.2% patients had at least one procedure related complication with cardiac and neurologic complications being the most frequent in our cohort.

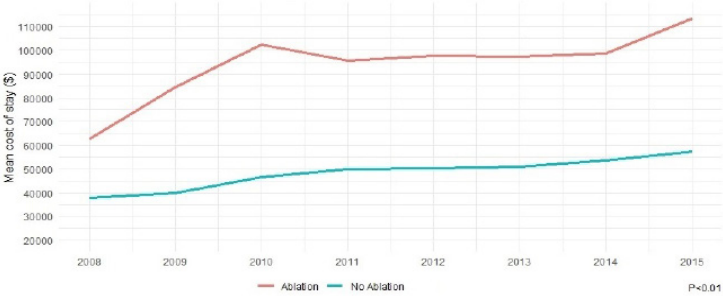

Figure 3: Trends in mean cost of stay in heart failure with reduced ejection fraction and atrial fibrillation patients undergoing ablation vs. not over the study years

Table 3: Outcomes and resource utilization of the study cohort after 1:2 propensity matching

Variables	No Ablation (n=15610)	Ablation (n=7773)	All patients with Afib† andHFrEF‡ (n=2569919)	P value
Died at discharge	565(3.6%)	91(1.2%)	656(2.8%)	<0.01
<65	139(2.5%)	10(0.4%)	149(1.9%)	<0.01
65-74	84(2.4%)	31(1.5%)	115(2.0%)	<0.01
≥75	338(5.4%)	49(1.6%)	387(4.2%)	<0.01
Discharge Disposition of surviving patients				
Routine/self-care	8374(55.7%)	5420(70.5%)	13794(60.7%)	<0.01
Short-term hospital	484(3.2%)	54(0.7%)	538(2.4%)	
Another type of facility	3127(20.8%)	980(12.8%)	4107(18.1%)	
Home Health Care	2998(19.9%)	1219(15.9%)	4217(18.6%)	
Resource utilization, Mean (SD)				
Length of stay, mean (SD), days	5.9(6.6)	6.4(6.9)	6.0(6.7)	<0.01
Cost of hospitalization-mean (SD), $	47,900 (100,799)	93,535(92,919)	63,071(100,572)	0.04

†Atrial Fibrillation; ‡Heart Failure with reduced Ejection Fraction

AF and CHF frequently co-exist and the prevalence of CHF is reported to be 42% in AF patients [14]. AF is associated with frequent hospitalizations and mortality in CHF patients [4,5,6]. Several trails have reported improvement in hard clinical end points of mortality and hospitalizations in AF patients with concomitant HfrEF if CA was employed as part of therapeutic modality [7,8]. In the AATAC study [7], 203 patients with persistent AF and HFrEF were randomized to get either amiodarone or CA. At the end of follow-up, CA was found to be superior to amiodarone in maintain sinus rhythm and improving left ventricular ejection fraction (LVEF). The study also showed 45% relative risk reduction for unplanned hospitalizations and 56% relative risk reduction for mortality in CA patients when compared to amiodarone group. More recently, CASTLE AF [8] enrolled patients with paroxysmal and persistent AF and concomitant HFrEF to either CA or medical therapy with rate or rhythm control. The primary end-point taken in this trial was a composite of all-cause mortality or CHF hospitalizations. At the end of 37 months follow up, primary end point occurred in few patients who underwent CA compared to medical therapy (HR 0.62, 95% CI 0.43-0.87). In our real world analysis of AF patients with HFrEF, we have demonstrated significant improvement in mortality in patients in whom CA was employed as a therapeutic strategy for management of AF. The significant reduction in mortality was uniform in both matched and unmatched cohort. Additionally, in our adjusted mortality analysis, CA was found to independently predict improved mortality in our cohort (OR 0.301, 95% CI 0.184-0.494). Of note, due to limitation of NIS dataset, CA assessment was only done while patients are admitted to inpatient settings. These patients are speculated to be sicker when compared to their counterparts who get elective CA procedure as an outpatient and were the ones primarily enrolled in aforementioned trials. It is pertinent to point here that even in these sick patients, CA was associated with improved survival at discharge suggesting that due consideration should be given to this therapeutic modality for management of such patients.

In our study, about 10.2% patients sustained procedure related complications after CA ablation. In a study by Tripathi et al [12] on recent contemporary trends of CA in AF patients, the overall complication rate was reported at 5.46%. It is pertinent to point out that Tripathi et al. utilized all AF patients for their analysis and did not discriminate based on HFrEF status. Patients admitted with AF and concomitant HFrEF are particularly on the sickest end of spectrum in their disease process. The high complication rate of 10.2% in our study cohort probably reflected variable degree of institution experience in performing CA in these sickest patients. Our study also showed increased rate of myocardial infarction (3.6%) and cardiogenic shock (2.3%) in study population. Some degree of tropon in elevation is frequently encountered post ablation due to localized myocardial necrosis consequent to creation of lesion sets [15], however, about 0.7% patients in our cohort did undergo coronary stenting indicative of type I myocardial infarction. Strong index of suspicion is therefore warranted for timely detection of these key cardiovascular complications as that may result in improved outcomes. In our cohort, about 0.7% patients were found to be septic during the particular hospitalization in which CA was performed. Sepsis typically is a late complication of CA and usually occurs within 30-days of procedure as demonstrated by recent study from Cheng et al. [16] and that may explain relatively low rate of this complication during our patients index hospitalization. The rate of vascular complications was 0.7% and that was similar to reports from earlier studies [12]. Stroke happened in approximately 1.8% of our patients when compared to 1% of patients in Tripathi et al. study [12]. AF perpetuates thrombus formation due to stasis of blood and it is speculated that HFrEF may accentuate this response by promoting further stagnation of blood. It is therefore advised that close attention should be paid to anti-coagulation regimen and activating clotting times during the CA procedure to minimize the risk of strokes in AF patients with concomitant HFrEF.

Limitations

Our study has following key limitations: (1) NIS is an

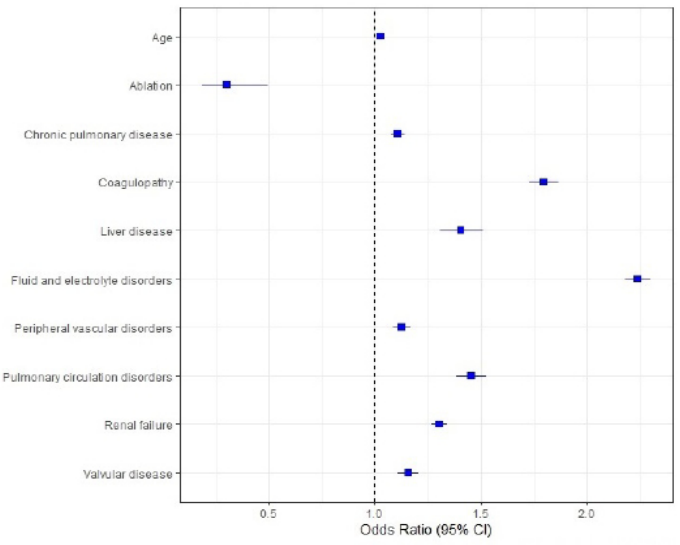

Figure 4: Predictors of mortality in patients with heart failure and reduced ejection fraction and atrial fibrillation

Table 4: Complications in AF ablation patients stratified on the basis of gender

Variableno. (%)	All complications (n=7773)	Men (n=5135)	Women (n=2637)	P value
At least one complication	788(10.2%)	555(10.8%)	233(8.8%)	<0.01
Iatrogenic cardiac complications	121(1.6%)	90(1.80%)	31(1.20%)	0.05
Stroke	138(1.8%)	63(1.20%)	75(2.80%)	<0.01
Vascular complications	55(0.7%)	30(0.6%)	25(0.9%)	0.07
Pneumothorax	21(0.3%)	11(0.2%)	10(0.4%)	0.18
Post-operative respiratory failure	30(0.4%)	20(0.4%)	10(0.4%)	0.94
Need for pericardiocentesis	57(0.7%)	28(0.5%)	29(1.1%)	0.02
Cardiac tamponade	57(0.7%)	28(0.5%)	29(1.1%)	0.07
Cardiogenic shock	181(2.30%)	151(2.90%	30(1.10%	<0.01
Septic shock	54(0.7%)	44(0.9%)	10(0.4%)	0.02
Myocardial infarction	277(3.6%)	204(4.0%)	73(2.8%)	<0.01
Percutaneous coronary intervention	53(0.7%)	44(0.9%)	9(0.3%)	<0.01
Pulmonary embolism	44(0.6%)	29(0.6%)	15(0.6%)	0.98

administrative claim-based database that uses ICD-9-CM codes for diagnosis that may be subject to error. However, the hard clinical end point of mortality and procedure code for ablation are less prone to error. Additionally, HCUP quality control measures are routinely performed on NIS dataset to ensure continued reliability and validity [13]. (2) NIS collects data on inpatient discharges and do not reflect on outpatient related encounters. Currently, most AF ablations are done as an elective outpatient procedure and these patients are relatively less sick and expected to have lower mortality and complication rate when compared to our sample of admitted AF patients. Nonetheless, our study reflects real word data on outcomes in these sickest hospitalized AF patients after CA and largely representative of United States population sample. (3) Several patient related factors such as type and duration of AF, cardiac parameters such as chamber dimensions and ejection fraction and procedure related factors such as type of lesions performed (pulmonary vein isolation alone or in combination with left atrial roof and floor lines etc.) and type of energy used to create lesion sets could not be ascertained from present data set. (4) NIS does not collect longitudinal data on patients so long term follow up could not be assessed. To the same end, certain specific CA complications such as development of an atrio-esophageal fistula occurs weeks to months after the procedure and unfortunately the incidence of this complication could not be studied from NIS.

Conclusion

In this large nationally representative sample of United States population, we demonstrated that CA is associated with reduced mortality in AF patients with HFrEF in both matched and unmatched cohorts. The complication rate was 10.2% and primarily were cardiac and neurological in origin.

Link for Supplementary Content

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Impact of Afterload-Integrated Diastolic Index on Prognosis in Elderly Patients With Heart Failure With Preserved Ejection Fraction With and Without Atrial Fibrillation

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Abstract

Objects: We aimed to clarify the differences in the significance of the ratio of diastolic elastance (Ed) to arterial elastance (Ea), [Ed/Ea=(E/e')/(0.9×systolic blood pressure)], an afterload-integrated diastolic index that reflects left atrial pressure overload, on prognosis between patients with heart failure with preserved ejection fraction (HFpEF) with and without atrial fibrillation (AF).

Methods: We studied 552 HFpEF patients hospitalized for acute decompensated heart failure (sinus rhythm/AF:352/200). Blood testing and transthoracic echocardiography were performed before discharge. Primary endpoint was all-cause mortality after discharge.

Results: During a median follow-up of 508 days, 88 patients (sinus rhythm/AF: 54/34) had all-cause mortality. In the subgroup with sinus rhythm, but not AF, Ed/Ea was significantly higher in patients with than without all-cause mortality. In a multivariate Cox hazard analysis, Ed/Ea was significantly associated with all-cause mortality independent of N-terminal pro-brain natriuretic peptide level in patients with sinus rhythm, but not with AF.

Conclusions: Ed/Ea provided lesser important information for predicting all-cause mortality in HFpEF patients with AF than with sinus rhythm. The prognostic risk factors may differ between elderly HFpEF patients with and without AF.

Introduction

Assessment of diastolic function using a combination of several indices based on the recommendations for left ventricular (LV) diastolic evaluation by echocardiography is useful for estimating the prognosis of patients with heart failure with preserved ejection fraction (HFpEF) [1-3]. Patients with HFpEF have an increased left atrial volume (LAV), an index of LA volume overload, and an increased E/e', an index of LA pressure overload [4-6]. E/e' is correlated with invasive LV filling pressure and adequate reproducibility even in patients with atrial fibrillation (AF) [7].

Key Words

Atrial Fibrillation, Diastolic Function, Left Atrial Overload, NT-proB-NP

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LV diastolic elastance (Ed) is expressed as (E/e')/stroke volume (SV)[8] or (E/e')/LV end-diastolic volume [9]. Arterial elastance (Ea) is calculated as (0.9 × systolic blood pressure)/SV [8]. We previously reported the ratio of Ed to Ea as a novel index of the LV diastolic function relative to afterload, which can be calculated as (E/e')/(0.9 × systolic blood pressure) where the Ed is (E/e')/SV [10,11]. Ed/Ea is positively correlated with pulmonary capillary wedge pressure and exhibits an LA pressure relative to the systemic pressure[12]. Thus, the Ed/Ea ratio may be an index reflecting the left-sided heart function including the atrio-ventriculo-arterial interaction under a preserved LV ejection fraction. We recently reported that Ed/Ea may be a useful independent determinant of all-cause mortality in elderly patients with HFpEF[13]. This study aimed to clarify the differences in the role of Ed/Ea on prognosis in patients with HFpEF with and without AF.

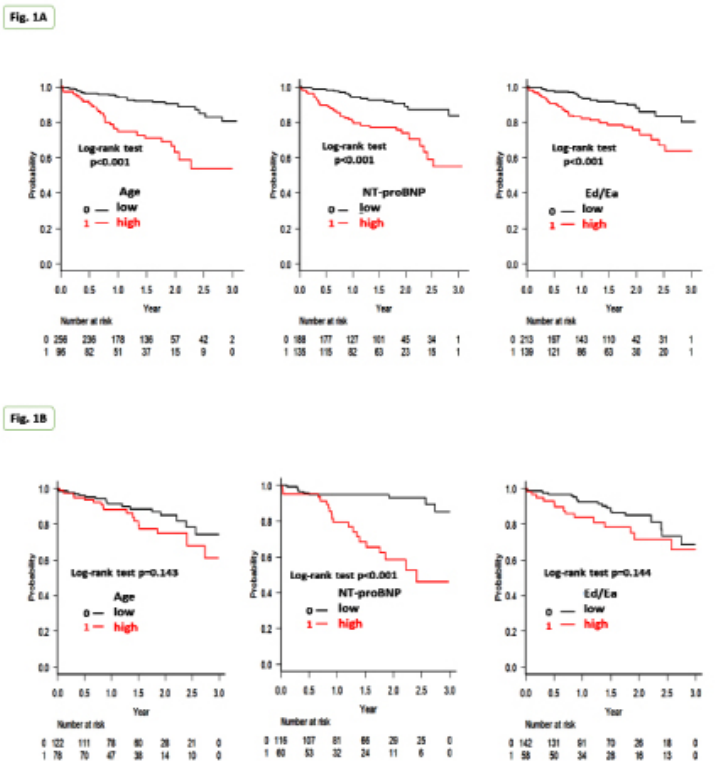

Figure 1: **Kaplan–Meier survival curve analysis of patients with heart failure with preserved ejection fraction. (A) Patients with sinus rhythm: Age >86 years, N-terminal pro-brain natriuretic peptide (NT-proBNP) >1,220 pg/mL, and ratio of diastolic elastance (Ed)/arterial elastance (Ea) >0.132 were significant factors for all-cause mortality. (B) Patients with atrial fibrillation: NT-proBNP > 2,081 pg/mL, but not Age >84 years or Ed/Ea >0.144, was a significant factor for all-cause mortality.**

Methods

Study subjects

Of 637 patients with prognostic data recruited from the Prospective Multicenter Observational Study of Patients with Heart Failure with Preserved Ejection Fraction (PURSUIT HFpEF) registry, we excluded 85 with missing or poor echocardiographic data. Therefore, we enrolled 552 patients (LV ejection fraction ≥50%; men/women, 255/297; sinus/AF 352/200; mean age, 81 years) at discharge during the index hospitalization for HF. The PURSUIT HFpEF registry is a prospective, multicenter observational registry in which collaborating hospitals in the Osaka region of Japan record clinical, echocardiographic, and outcome data of patients with HFpEF (UMIN-CTR ID: UMIN000021831) [6,14]. This registry is managed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee of each participating hospital and all participants provided written informed consent.

Echocardiography and laboratory testing

Transthoracic echocardiography was performed when patients were in a stable condition before discharge. Echocardiographic measurements were obtained according to American Society of Echocardiography (ASE) or European Society of Echocardiography guidelines [1,15]. Volumetry was standardized using the modified Simpson's method and the index was calculated as LAV divided by the body surface area. As a marker of LA pressure overload for estimating LV diastolic function, we examined afterload-integrated Ed/Ea [(E/e')/(0.9 × systolic blood pressure)] [6,11,16]. As relative markers of LAV overload, we evaluated LAVI and the ratio of stroke volume (SV) to LAV [12]. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and albumin levels, hemoglobin concentration, and estimated glomerular filtration rate (eGFR) were also examined when patients were stable before discharge.

Follow-up/clinical outcome

After discharge, all patients were followed-up at each hospital. Survival data were obtained by dedicated coordinators and investigators through direct contact with patients and their physicians at the hospital, in an outpatient setting, via telephone interview with their families, or by mail. The primary endpoint of this study was all-cause mortality.

Statistical analysis

Continuous variables are expressed as means ± standard deviations, whereas categorical variables are presented as frequencies and

Table 1: **Clinical characteristics before discharge in patients with heart failure with preserved ejection fraction with and without all-cause mortality**

	Sinus rhythm		P value (- vs. +)	Atrial fibrillation		P value (- vs. +)
	All-cause mortality			All-cause mortality		
	- (n = 298)	+ (n = 54)		- (n = 166)	+ (n = 34)	
Age, years	79 ± 10	86 ± 8	<0.001	82 ± 7	84 ± 7	0.043
Male sex, n (%)	132 (44)	22(41)	0.628	84 (51)	17 (50)	0.949
Systolic blood pressure, mmHg	122 ± 17	123 ± 20	0.713	116 ± 16	116 ± 17	0.879
Diastolic blood pressure, mmHg	65 ± 11	66 ± 11	0.819	66 ± 12	64 ± 11	0.411
Heart rate, bpm	70 ± 12	73 ± 14	0.217	72 ± 15	75 ± 14	0.254
Coronary artery disease, n (%)	65 (22)	12 (22)	0.946	31 (19)	10 (29)	0.157
Diabetes mellitus, n (%)	107 (36)	20 (37)	0.873	58(35)	9 (26)	0.341
Dyslipidemia, n (%)	138 (46)	18 (33)	0.077	65 (39)	13 (38)	0.920
Hypertension, n (%)	256 (86)	50 (93)	0.261	147 (89)	24 (71)	0.007
N-terminal pro-brain natriuretic peptide, pg/mL	2,479 ± 5,566	4,842 ± 13,163	0.034	1,995 ± 3,003	3,826 ± 2,817	0.002
Echocardiographic data						
LAD, mm	42 ± 7	41 ± 8	0.797	48 ± 9	48 ± 7	0.656
LAVI, mL/m²	48 ± 21	57 ± 32	0.014	62 ± 26	61 ± 20	0.768
SV/LAV	0.80 ± 0.37	0.78 ± 0.56	0.709	0.56 ± 0.31	0.56 ± 0.28	0.926
LVEF, %	60 ± 8	59 ± 9	0.269	61 ± 7	61 ± 7	0.789
Ed/Ea	0.125 ± 0.052	0.150 ± 0.057	0.001	0.125 ± 0.045	0.141 ± 0.054	0.071
Medications						
Beta-blockers, n (%)	159 (53)	29 (54)	0.962	93 (56)	22 (65)	0.420
Calcium-channel blockers, n (%)	167 (56)	32 (59)	0.661	75 (45)	16 (47)	0.841
Diuretics, n (%)	238 (80)	44 (81)	0.784	147 (89)	32 (94)	0.335
RAAS inhibitors, n (%)	212 (71)	39 (72)	0.871	132 (80)	25 (74)	0.438
Statins, n (%)	108 (36)	19 (35)	0.881	50 (30)	10 (29)	0.934

Values are mean ± standard deviation or number (%).
LAD, left atrial diameter; LAVI, left atrial volume index; SV, stroke volume; LAV, left atrial volume; LVEF, left ventricular ejection fraction; Ed, diastolic elastance; Ea, arterial elastance.

Table 2: Analytical data of prognostic factors for all-cause mortality in patients with heart failure with preserved ejection fraction showing sinus rhythm

			Cox hazard analysis					
	ROC curve analysis		Univariate			Multivariate		
	Cutoff point	AUC	Ratio	95% CI	P value	Ratio	95% CI	P value
Age	86 years	0.721	3.812	2.228-6.523	<0.001	3.491	1.948-6.257	<0.001
Sex	-	-	0.919	0.533-1.582	0.761	1.191	0.659-2.149	0.562
NT-proBNP	1,220 pg/mL	0.681	3.322	1.859-5.936	<0.001	2.755	1.512-5.021	<0.001
LAVI	46 mL/m^2	0.578	1.407	0.804-2.46	0.231	0.884	0.485-1.612	0.689
Ed/Ea	0.132	0.642	2.517	1.456-4.351	<0.001	1.835	1.019-3.305	0.043

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; LAVI, left atrial volume index; Ed, diastolic elastance; Ea, arterial elastance.

percentages. Differences in categorical variables between the groups were assessed using chi-square tests, while those in continuous variables were assessed using Student's t- or Welch's t-tests, as appropriate. Correlations were assessed using Pearson or Spearman coefficients and p-values were examined using regression analysis. Cutoff points of prognostic factors for all-cause mortality were evaluated using receiver operating characteristic (ROC) curve analysis. Survival curves were estimated using the Kaplan–Meier survival analysis and the groups were compared using log-rank test. The Cox hazard ratio was evaluated in univariate and multivariate analyses. P-values <0.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical and laboratory characteristics of patients with HFpEF

During a median follow-up of 508 days, 88 patients (sinus rhythm/AF 54/34) had all-cause mortality. We observed significant differences between patients showing sinus rhythm with and without all-cause mortality in terms of age (p<0.001) and serum NT-proBNP level(p=0.034) (Table 1). We observed no significant differences in medications or the incidence of hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease between the two groups. In contrast, the incidence of hypertension was significantly lower in AF patients with than without all-cause mortality. We observed no significant differences in age, NT-proBNP level, incidence of coronary artery disease, diabetes mellitus and dyslipidemia, or medication use between AF patients with and without all-cause mortality.

With respect to echocardiographic parameters, LAVI (p=0.014) and Ed/Ea (p=0.001)—but not SV/LAV, or LV ejection fraction—at discharge differed significantly between patients with and without all-cause mortality showing sinus rhythm (Table 1). In contrast, patients with AF showed no significant differences in LAVI and Ed/Ea between those with and without all-cause mortality (Table 1). Although the data are not shown, the deceleration time of the E wave, septal e', lateral e', and E/A did not differ significantly between the groups.

In patients with sinus rhythm, the NT-proBNP log-transformed level was modestly correlated with echocardiographic indices such as LAVI (r=0.244, p<0.001), SV/LAV (r=0.224, p<0.001), and Ed/Ea (r=0.182, p<0.001). In contrast, the NT-proBNP log-transformed level was more modestly correlated with LAVI (r=0.203, p=0.011) and Ed/Ea (r=0.148, p=0.049) in those with AF. Evaluations of the correlations between the indices of LA pressure and volume overload showed that Ed/Ea was modestly correlated with LAVI in patients with sinus rhythm (r=0.231, p<0.001), but not with AF (r=0.009, p=0.905).

Prognostic analysis

The areas under the curve and cutoff points of each parameter were evaluated in ROC curve analysis for the prediction of all-cause mortality. The cutoff point for age was lower but those of NT-proBNP, Ed/Ea and LAVI were higher in patients with AF than those with sinus rhythm (Tables 2, 3). Although NT-proBNP level was a significant prognostic factor in patients with sinus rhythm (p<0.001) or AF (p<0.001) by Kaplan–Meier survival analysis, age (p<0.001) and Ed/Ea (p<0.001) were significant only in those with sinus rhythm (Figure 1). Although not shown, Ed/Ea was a modest prognostic factor even in patients with AF, when the prognosis was evaluated for the first year after enrollment by Kaplan-Meier survival analysis (p=0.050). In a multivariate Cox hazard analysis, Ed/Ea and NT-proBNP were independent predictors of prognosis in sinus rhythm after adjusting for age, sex, and LAVI (Table 2). However, NT-proBNP, but not Ed/Ea, was independently associated with prognosis in AF patients after adjusting for age and sex (Table 3).

Differences in clinical characteristics between patients with and without AF

Although we observed no differences in all-cause mortality, age, and male sex between patients with and without AF, systolic blood pressure (p<0.001) was significantly lower and albumin level (p=0.008) and hemoglobin concentration (p<0.001) were significantly higher in patients with AF as compared to those in patients without AF (Table 4). In echocardiographic findings, the indices of LA volume overload such as left atrial dimension, LAVI, and SV/LAV differed significantly between patients with and without AF (p<0.001 for all).

Table 3: Analytical data of prognostic factors for all-cause mortality in patients with heart failure with preserve dejection fraction showing atrial fibrillation

			Cox hazard analysis					
	ROC curve analysis		Univariate			Multivariate		
	Cutoff point	AUC	Ratio	95% CI	P value	Ratio	95% CI	P value
Age	84 years	0.600	1.646	0.839-3.227	0.146	1.108	0.488-2.511	0.806
Sex	-	-	0.956	0.488-1.875	0.897	1.009	0.463-2.193	0.982
NT-proBNP	2,081 pg/mL	0.755	5.545	2.514-12.23	<0.001	5.651	2.374-13.45	<0.001
LAVI	55 mL/m^2	0.528	0.897	0.436-1.845	0.767	0.916	0.422-1.986	0.825
Ed/Ea	0.144	0.589	1.659	0.835-3.298	0.148	1.388	0.622-3.094	0.423

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; LAVI, left atrial volume index; Ed, diastolic elastance; Ea, arterial elastance.

Table 4: Differences in patient characteristics with and without atrial fibrillation

	Atrial fibrillation		P value (- vs. +)
	- (n = 352)	+ (n = 200)	
All-cause death, n (%)	54 (15)	34 (17)	0.608
Age, years	81 ± 10	82 ± 7	0.057
Male sex, n (%)	154 (44)	101 (51)	0.126
Systolic blood pressure, mmHg	122 ± 18	116 ± 16	<0.001
Diastolic blood pressure, mmHg	65 ± 11	66 ± 12	0.825
Heart rate, bpm	71 ± 13	73 ± 15	0.075
Laboratory data			
Albumin, g/dL	3.4 ± 0.5	3.5 ± 0.4	0.008
eGFR, mL/min/1.73 m²	42.2 ± 20.8	43.4 ± 15.2	0.507
Hemoglobin, g/dL	11.1 ± 1.9	11.8 ± 2.0	<0.001
N-terminal pro-brain natriuretic peptide, pg/mL	2,860 ± 7,392	2,296 ± 3,050	0.335
Echocardiographic data			
LAD, mm	42 ± 7	48 ± 9	<0.001
LAVI, mL/m²	50 ± 23	62 ± 25	<0.001
SV/LAV	0.79 ± 0.40	0.56 ± 0.31	<0.001
LVEF, %	60 ± 8	61 ± 7	0.235
Ed/Ea	0.129 ± 0.053	0.127 ± 0.047	0.652

Values are mean ± standard deviation.
eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LAVI, left atrial volume index; SV, stroke volume; LAV, left atrial volume; LVEF, left ventricular ejection fraction; Ed, diastolic elastance; Ea, arterial elastance.

However, the indices of LA pressure overload such as Ed/Ea did not differ between the two groups. The incidence of coronary artery disease, hypertension, diabetes mellitus and dyslipidemia was not significantly different between the two groups (data not shown).

Discussion

The Ed/Ea, an afterload-integrated diastolic index that reflects LA pressure overload, provided lesser additional prognostic information to the serum NT-proBNP level for predicting all-cause mortality in HFpEF patients with AF than in those without AF. The prognostic risk factors may differ between elderly HFpEF patients with and without AF.

Since albumin level and hemoglobin concentration were significantly higher, and systolic blood pressure was significantly lower in patients with AF than those in patients without AF, volume reducing therapy may be more prominent in patients with AF than that of those without AF at recruitment. This issue would be related to the lack of difference in all-cause mortality between patients with and without AF. As a matter of cause, the indices of LA volume overload were significantly higher in patients with AF than those in patients without AF.

Notably, we observed no significant differences in the indices of LA pressure overload such as Ed/Ea between the patients with and without AF, and between AF patients with and without all-cause mortality. In patients with AF, the variability of the LA enlargement could bring a compensatory mechanism to maintain LA pressure. Accordingly, further increase in LA volume may not elevate LA pressure when the hemodynamic state worsens after enrollment in patients with AF. In other words,the alterations of LA pressure overload accompanying with hemodynamic changes would be different between the patients with and without AF. Therefore, indices of LA pressure overload such as Ed/Ea would be less prominent as a determinant factor of prognosis in patients with AF. Furthermore, LV diastolic dysfunction may be already related to the occurrence of AF per se in HFpEF patients with AF.The prognostic role of LA pressure overload resulting from LV diastolic dysfunction, was offset in the patients with AF, but not without AF, resulting in less prognostic role of Ed/Ea in patients with AF. These issues were reflected in the higher cutoffs of NT-proBNP and LAVI for prognosis in patients with AF than in those in patients without AF. Because there was a significant difference in the incidence of hypertension between AF patients with and without all-cause mortality, but not between those showing sinus rhythm with and without all-cause mortality, the genesis of death may differ between HFpEF patients with and without AF. Thromboembolic events may be important in the causes of death in patients with AF.

Limitations

We examined all-cause mortality rather than cardiac death because the determination of cardiac death can be difficult in elderly patients. One must pay attention to measure E/e' by echocardiography in patients with AF [14]. The factors affecting the reproducibility of echocardiographic measurements included the ratio of preceding to pre-preceding cycle length and heart rate during image acquisition. The mean heart rate in our AF patients was 73 beats/min, which is optimal for guideline recommendation of cycle lengths equivalent to a heart rate range of 60–80 beats/min.

Conclusions

The Ed/Ea [(E/e')/(0.9 × systolic blood pressure)], an afterload-integrated diastolic index that reflects LA pressure overload, provided lesser important information for evaluating all-cause mortality in HFpEF patients with AF than with sinus rhythm. The prognostic risk factors may differ between elderly HFpEF patients with and without AF.

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Same-Day Versus Next-Day Discharge Strategies for Left Atrial Ablation Procedures: A Parallel, Intra-Institutional Comparison of Safety and Feasibility

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Abstract

Background: Head-to-head comparative data for the postoperative care of patients undergoing left atrial ablation procedures are lacking.

Objective: We sought to investigate complication and readmission rates between patients undergoing same-day (SD) or next-day (ND) discharges for ablative procedures in the left atrium, primarily atrial fibrillation (AF).

Methods: Two electrophysiology centers simultaneously perform left atrial ablations with differing discharge strategies. We identified all patients who underwent left atrial ablation from August 2017 to August 2019 (n = 409) undergoing either SD (n = 210) or ND (n = 199) discharge protocols. We analyzed any clinical events that resulted in procedural abortion, extended hospitalization, or readmission within 72 hours.

Results: The primary endpoint of complication and readmission rate was similar between SD and ND discharge (14.3% vs 12.6%, p = 0.665). Rates of complications categorized as major (2.4% vs 3.0%, p = 0. 776) and minor (11.9% vs 9.5%, p = 0.524) were also similar. Multivariable regression modeling revealed no significant correlation between discharge strategy and complication/readmission occurrence (OR 1.565 [0.754 – 3.248], p = 0.23), but a positive association of hypertension and procedure duration (OR 3.428 [1.436 – 8.184], p = 0.006) and (OR 1.01 [1 – 1.019], p = 0.046) respectively.

Conclusions: Left atrial ablation complication and readmission rates were similar between SD and ND discharge practices. Hypertension and procedural duration were associated with increased complication rates irrespective of discharge strategy. These data, which represent the first side-by-side comparison of discharge strategy, suggests same-day discharge is safe and feasible for left atrial ablation procedures.

Introduction

Catheter ablation for atrial fibrillation (AF) has established superiority to medical therapy for the long-term maintenance of sinus rhythm and improvement in quality of life. Catheter ablation for AF and left atrial flutter (LAFL) is emerging as the most common ablation procedure performed in the U.S. with exponential growth observed in the past decade.[3,4] Despite the high frequency, there is little consensus on the postoperative management for these procedures. The standard remains inpatient admission and overnight monitoring. However, many practices have begun exploring alternative discharge strategies including outpatient AF ablation. [5] While it would be more efficient and cost-effective to adopt a same-day discharge strategy for these types of procedures, concerns due to longer procedure times, left atrial lesion delivery, and heparinization have rendered the appropriate discharge strategy controversial.

There have been limited published data regarding same-day discharge for AF ablation procedures – with the majority consisting of historical case control studies or simple descriptive studies of clinical experience. Prior studies have either used non-randomized patient preference [6], historical control after institutional discharge strategy implementation[7,8], or observational longitudinal descriptions [9-11].

With two high-volume electrophysiology centers simultaneously performing left atrial ablation differing primarily in post-procedure discharge strategies, we found a unique opportunity to compare outcomes between same-day (SD) and next-day (ND) post-ablation discharge with little variability to ablation strategy, operator experience, or patient factors. We analyzed acute outcomes of AF ablation and other left atrial ablation procedures in terms of complications and

Key Words
Atrial Fibrillation, Left Atrial, Ablation, Complications, Hospitalization, Discharge Strategy

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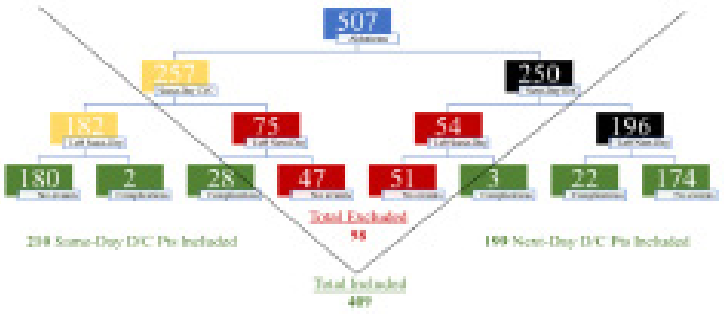

Figure 1: **Schematic Outline of Patient Classification According to Predetermined Discharge Protocol and Actuality.**

*507 total ablations (blue) were performed between sites with 182 out of 257 anticipated same-day (yellow) and 196 out of 250 anticipated next-day(black) discharges proceeding according to plan. 75 patients in the same-day group and 54 in the next-day group did not discharge according to plan (red), some uneventful and others experiencing complications. Patients with deviation from anticipated discharge protocol and no events were excluded from additional analysis (red) while those discharging according to anticipated strategy plus those that deviated and experienced a complication were further analyzed (green). Abbreviations: D/C = Discharge, Pts = Patients.

readmission rates to assess,in a temporally-parallelformat, the safety and feasibility of SD versus ND discharge strategy.

Methods

Consecutive patients undergoing AF, LAFL, or left atrial tachycardia ablationsinvolving transseptal puncture at two high-volume centers within the Emory Healthcare systembetween August 2017 and August 2019 were analyzed. Discharge strategy consisted of general practice guidelines within each hospital and were defined as: 1. ND, consisting of routine overnight stay in a telemetry floor with subsequent discharge the following morning after clinical assessment and groin check; and 2. SD, consisting of discharge after 2-4 hours of bedrest, clinical exam, and groin check. Ablation procedures followed accepted practice guidelines and consisted of predominantly cryo-ablation for paroxysmal AF and radiofrequency (RF) for persistent AF. Ultrasound either by intra-cardiac echo (ICE) or trans-esophageal echo (TEE) was used in the majority of cases and general anesthesia was used according to physician discretion.To specifically compare discharge practices, analysis excluded those who deviated from the institutional discharge strategy, but a separate intention to treat analysis was performed as well. The study was approved by the Emory Institutional Review Board.

All routine demographic data including gender, age, and body mass index as well as routine medical history was evaluated. Specificbaseline arrhythmia characteristics were also noted, including AF subtype (paroxysmal, persistent, or permanent) and history of cardioversion or prior ablation. Procedural characteristics were also analyzed including anesthesia type, ablation type and location, procedure duration, and hemostasis method use.

The primary endpoint was defined as any clinical event that resulted in procedural abortion, a longer hospital stay than anticipated at either center, or readmission within 72 hours. Individual complications were categorized by type and classified as major or minor based on their clinical significance. Major complications included stroke, tamponade, phrenic nerve palsy, sinus node dysfunction, and esophageal perforation. Minor complications included access site issues, pericarditis, simple effusion, unstable labs or vitals, incomplete studies, and a few others.

Statistical methods

Differences between groups were subjected to the Student's t test or Wilcoxon rank sum test for normally and non-normally distributed continuous data, respectively, or the Fisher's exact test for categorical variables. A 2-tailed P <.05 was considered significant. Continuous data are presented as mean ± standard deviation. We also performed multivariable regression to identify independent predictors of complications among the cohortthat included discharge strategy in an a priori fashion, as well as variables found to be associated with complications in univariateanalysis (p<0.05) as covariates. All analyses

Table 1: **Demographic, Clinical, and Procedural Characteristic Comparison by Discharge Strategy.**

	Same-Day (210)	Next-Day (199)	P
Age	64.7 (11.1)	63.14 (10.9)	0.273
Gender (F)	31.9% (67)	32.7% (65)	0.916
Body Mass Index	29.06 (5.27)	31.11 (6.3)	<0.001
Arrhythmia Type			0.019
Permanent Afib	0.5% (1)	0% (0)	
Persistent Afib	31.9% (67)	45.7% (91)	
Paroxysmal Afib	61% (128)	48.7% (97)	
Other	6.7% (14)	5.5% (11)	
Hypertension	56.7% (119)	67.3% (134)	0.032
Hyperlipidemia	38.6% (81)	40.7% (81)	0.686
Structural (Valvular, Congenital)	18.1% (38)	13.6% (27)	0.226
Congestive Heart Failure	14.8% (31)	26.6% (53)	0.003
Ejection Fraction (%)	54.46 (8.35)	50.97 (11.12)	0.003
Coronary Artery Disease	11% (23)	15.6% (31)	0.19
Diabetes Mellitus	10.5% (22)	19.6% (39)	0.012
Cerebrovascular Accident	11.4% (24)	7.5% (15)	0.238
Chronic Kidney/End-stage Renal Disease	7.1% (15)	5.5% (11)	0.548
Obstructive Sleep Apnea	21.4% (45)	29.6% (59)	0.069
Chronic Obstructive Pulmonary Disease	2.4% (5)	4% (8)	0.406
Prior Ablation	34.3% (72)	31.2% (62)	0.528
Prior Direct Current Cardioversion	47.1% (99)	54.0% (107)	0.167
Ablation Type			<0.001
PVI Only	23.7% (49)	33.7% (67)	
PVI +	63.3% (131)	46.2% (92)	
Non-PVI	10.6% (22)	6.5% (13)	
Convergent	0.5% (1)	13.1% (26)	
Other	1.9% (4)	0.5% (1)	
Sedation Type			<0.001
Moderate Sedation	78.8% (164)	55.1% (109)	
General Anesthesia	21.2% (44)	44.9% (89)	
Hemostasis Type			<0.001
Manual	68.6% (144)	97.5% (194)	
Device	31.4% (66)	2.5% (5)	
Procedure Duration (hours:min)	2:14 (0:36)	2:09 (0:31)	0.181
Ablation Duration (min)	41.4 (40.7)	40.3 (27.9)	0.404
Cryo Lesions [#]	8 (8, 8)	8 (7, 9)	0.025
RF time (min)	13.7 (13)	22.4 (23)	0.062
RF Lesions [#]	18.5 (9, 34.25)	16 (7.75, 30.25)	0.145
Power [watts]	59.5 (18.719)	56.84 (23.369)	0.788

Abbreviations: Non-PVI=ablation excluding pulmonary vein isolation; PVI=pulmonary vein isolation; PVI+=pulmonary vein isolation plus additional lesion set; RF=radiofrequency

Table 2: Demographic, Clinical, and Procedural Characteristic Comparison by Complication Occurrence.

	Complication (55)	No Complication (354)	P
Age	66.16 (10.39)	63.57 (11.11)	0.109
Gender (F)	43.64% (24)	30.51% (108)	0.063
Body Mass Index	31.49 (6.62)	29.83 (5.73)	0.040
Arrhythmia Type			0.483
Permanent Afib	0% (0)	0.28% (1)	
Persistent Afib	47.27% (26)	37.29% (132)	
Paroxysmal Afib	49.09% (27)	55.93% (198)	
Other	3.64% (2)	6.5% (23)	
Hypertension	76.36% (42)	59.6% (211)	0.017
Hyperlipidemia	43.64% (24)	38.98% (138)	0.554
Structural (Valvular, Congenital)	21.82% (12)	14.97% (53)	0.232
Congestive Heart Failure	30.91% (17)	18.93% (67)	0.049
Ejection Fraction (%)	51.82 (11.91)	52.85 (9.65)	0.397
Coronary Artery Disease	5.45% (3)	14.45% (51)	0.085
Diabetes Mellitus	21.82% (12)	13.84% (49)	0.152
Cerebrovascular Accident	9.09% (5)	9.6% (34)	1
Chronic Kidney/End-stage Renal Disease	12.73% (7)	5.37% (19)	0.066
Obstructive Sleep Apnea	21.82% (12)	25.99% (92)	0.618
Chronic Obstructive Pulmonary Disease	5.45% (3)	2.82% (10)	0.406
Prior Ablation	36.4% (20)	32.2% (114)	0.540
Prior Direct Current Cardioversion	52.7% (29)	50.1% (177)	0.773
Ablation Type			0.020
PVI Only	17% (9)	30.3% (107)	
PVI +	52.8% (28)	55.2% (195)	
Non-PVI	13.2% (7)	7.9% (28)	
Convergent	15.1% (8)	5.4% (19)	
Other	1.9% (1)	1.1% (4)	
Sedation Type			0.042
Moderate Sedation	54.72% (29)	69.12% (244)	
General Anesthesia	45.28% (24)	30.88% (109)	
Hemostasis Type			0.088
Manual	90.91% (50)	81.36% (288)	
Device	9.09% (5)	18.64% (66)	
Procedure Duration (hours:min)	2:26 (0:45)	2:10 (0:32)	0.025
Ablation Duration (min)	47.43 (37.17)	39.3 (27.08)	0.541
Cryo Lesions [#]	8 (7, 9)	8 (8, 9)	0.303
RF time (min)	21.81 (17.35)	20.7 (22.47)	0.484
RF Lesions [#]	22.5 (12, 30.25)	17 (9, 34)	0.206
Power [watts]	53.23 (19.77)	58.56 (22.13)	0.198

Results of the univariate predictors of complications during left atrial ablations. Univariate predictors identified were body mass index, hypertension, congestive heart failure, ablation type, sedation type, and procedure duration. Abbreviations: Non-PVI=ablation excluding pulmonary vein isolation; PVI=pulmonary vein isolation; PVI+=pulmonary vein isolation plus additional lesion set; RF=radiofrequency

were performed using IBM SPSS ver. 26 (2019; IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp).

Results

Patient Population

A total of 507 patients underwent left atrial ablation involving transseptal puncture between the two centers. 257 patients were ablated under the SD discharge protocol and of these patients 182 discharged SD according to planwhile 75 deviated from the discharge strategy. 250 patients were ablated under the ND discharge protocol and 196 discharged asplanned after overnight monitoring while 54 deviated from the discharge strategy. There were a total of 98 patients excluded from the following data analysis due to deviations from the protocol not due to complication (e.g. patient preference, time of day, transportation). Therefore, a total of 409 patients undergoing atrial ablation were included for comparison of 210 SD discharge patients and 199 ND discharge patients (Figure 1)

Clinical and Procedural Characteristics between Discharge Strategy Cohorts

The average age and gender between the 210 SD and 199 ND discharge patients were similar as were rates of most medical comorbidities and prior ablations or cardio versions. A few statistically significant differences were found between cohorts with ND patients having higher body mass index (31.11% vs 29.06%, p = <0.001) and rates of hypertension (67.3% vs. 56.7%, p = 0.032), diabetes (19.6% vs. 10.5%, p = 0.012), and congestive heart failure (CHF) (26.6% vs 14.8%, p = 0.003) associated with lower ejection fractions (50.97 vs. 54.46, p = 0.003) than their SD counterparts. While AF accounted for over 90% of arrhythmia type in either group, SD patients had higher rates of paroxysmal (61% vs. 48.7%) and lower rates of persistent (31.9% vs. 45.7%) AF which contributed to a significant difference (p = 0.019). Overall procedure and ablation duration were similar between discharge strategies as were RF time, lesion number, and power. SD patients were more likely to undergo pulmonary vein isolation (PVI) plus additional lesion sets (63.3% vs. 46.2%) under moderate sedation (78.8% vs. 55.1%) with aid of a hemostasis device (31.4% vs. 2.5%). ND patients underwent more convergent ablations in combination with cardiothoracic surgery (13.1% vs. 0.5%) and lone PVI procedures (33.7% vs. 23.7%) that more often involved general anesthesia (44.9% vs. 21.2%) and manual pressure hemostasis (97.5% vs. 68.6%).

Univariate Predictors of Complication and Readmission

Several univariate predictors of complications and readmission were identified in the cohort. As seen in Table 2, patients with higher body mass index (31.49 vs 29.83, p = 0.040), rates of hypertension (76.36% vs 59.6%, p = 0.017), and CHF (30.91% vs. 18.93%, p = 0.049) were more likely to have complications or be readmitted within 72 hours. Procedure duration was significantly longer in those with complications (2:26 +/- 0:45 vs. 2:10 +/- 0:32, p = 0.25), in addition,ablation type (p = 0.020) and sedation type (p = 0.042) varied significantly. A higher percentage of patients with complications underwent convergent (15.1% vs 5.4%) and non-PVI (13.2% vs. 7.9%)ablations while a lower percentage with complications underwentPVI only (17% vs. 30.3%) procedures. General anesthesia (45.28% vs. 30.88%) was more commonly used among patients with complications than moderate sedation (54.72% vs. 69.12%). All other factors such as average age, gender breakdown, medical comorbidities, and technical procedural aspectswere similar between those with and without experiencing complications.

Overall Complication and Readmission Rates

Among the 409 patients that analyzed, 55 (13.5%) experienced

Table 3: Overall Complication Rates of Transseptal Ablations Stratified by Discharge Policy

	Total (n = 409)	Same-Day (n = 210)	Next-Day (n = 199)	P-level
Overall Complication Rate	13.45% (55)	14.3% (30)	12.6% (25)	0.665
Major	2.69% (11)	2.38% (5)	3.01% (6)	0.776
Cardiac Tamponade	0.98% (4)	0.95% (2)	1.01% (2)	
Phrenic Nerve Palsy	0.73% (3)	0.48% (1)	1.01% (2)	
Cerebrovascular Accident	0.45% (2)	0.95% (2)	0% (0)	
Sinus Node Dysfunction	0.45% (2)	0% (0)	1.01% (2)	
Esophageal Perforation	0% (0)	0% (0)	0% (0)	
Minor	10.76% (44)	11.90% (25)	9.55% (19)	0.524
Unstable Vitals or Labs	4.65% (19)	5.71% (12)	3.52% (7)	
Access Site Comp.	2.93% (12)	3.33% (7)	2.51% (5)	
Anatomic Diff. / Thrombus	0.98% (4)	0.95% (2)	1.01% (2)	
Significant Pericarditis	0.73% (3)	0.95% (2)	0.50% (1)	
Simple Effusion	0.45% (2)	0.48% (1)	0.50% (1)	
Other (pain, urinary retention)	0.98% (4)	0.48% (1)	1.51% (3)	

Complications rates among the same-day and next-day cohorts. Both the major and minor complication rates were found to be similar among the groups. Abbreviations: Comp.=Complication; Diff.=difficulty

complication or readmission within 72 hours. Complications were classified as minor (n=44, 10.8%))and major (n=11, 2.7%) events. No statistically significant differences were found between either discharge strategy when comparing readmission, major, or minor complication groups. (Table 3) Major complications included 4 (0.98%) cases of cardiac tamponade involving drain placement, 3 (0.73%) cases of persistent phrenic nerve palsy at follow-up, 2 (0.45%) post-procedure thromboembolic strokes causing mild deficits, and 2 (0.45%) cases of sinus node dysfunction requiring either temporary or permanent pacemaker insertion. Minor complications were more prevalent with the leading problems involving unstable vitals/labs and access site difficulties. A total of 19 (4.7%) cases necessitated additional monitoring or medical intervention for hemodynamic instability such as hypotension or tachycardia or laboratory abnormality such as anemia or acute kidney injury. Furthermore, 12 (2.93%) patients experienced bleeding or mild hematoma/bruising from their access site post-operatively. There were no cases of pseudo aneurysm formation or retroperitoneal bleeding. Additional minor complications involved rates < 1% for incomplete procedures due to findings of atrial thrombus or difficulty with transseptal access, clinically significant pericarditis or small pericardial effusions, and other problems such as uncontrolled pain or urinary retention prompting additional monitoring.

Of all patients, 2 were readmitted within 72 hours of same-day discharge (0.95%) - onefor chest pain found to be pericarditis and another for syncope deemed a vasovagal event although with findings of a small pericardial effusion. A separate intention-to-treat analysis including those patients deviating from the hospital-defined discharge strategy was also performed for overall complication/readmission rates and yielded no statistically significant differences (p = 0.546).

Multivariable Regression Analysis

Multivariable regression modeling was performed to further evaluate the relationship of baseline clinical or procedural characteristics found to be significant predictors of complications with univariate analysis. Discharge strategy was also included in this analysis. Results are outlined in Table 4 with univariate predictors of CHF, body mass index, ablation type, and sedation type not found to be associated with complications in multivariate analysis. The presence of hypertension (odds ratio of 3.428 [1.436 - 8.184]) and procedure duration (odds ratio of 1.01 [1 – 1.019]) was significantly associated with increased rates of complication in our regression model. Finally, our regression model showed no effect of discharge strategyon complication rate(odds ratio at 1.565 [0.754 – 3.248)].

Discussion

Our analysis using an intra-institutional comparison of SD versus ND discharge strategy represents a unique and more robust form of analyzing complication and readmission rates for patients undergoing left atrial ablation procedures. Our data indicate two important findings. First, there was no significant difference in complication rates or readmission ratesamong SD or ND discharge strategy when used as a general hospital-based approach. We feel this adds strength to the limited but growing evidence in favor of SD discharges for most AF and left atrial ablative procedures. Comparable rates of major complications are reported in large reviews[12-16] and, while there is limited data from the U.S., other countries' analyses introduced above reveal a lack of significant difference in these rates when patients are kept overnight. When examining a variable such as time of discharge, the importance of selection bias cannot be overstated, as those who do well would tend to have physicians choose to send the patient home sooner, and those in whom there was clinical concern would be expected to be monitored longer. This is why we chose to exclude those who deviated from the general discharge policy at the two comparator clinical sites. Importantly, when we chose to include the deviations from each site as an intention to treat, we continued to observe a non-significant difference in complication rate.

Secondly, multivariate analysis showed hypertension and procedure duration, not discharge strategy as inepedentpredictors of our primary endpoint. There were unavoidable differences in our patient demographic between the SD and ND hospitals that warrant mention and could confound our findings. Namely, a higher incidence of persistent AF, CHF, general anesthesia, and convergent/hybrid surgical procedures were observed in the ND cohort. Of these, procedure type, CHF, and sedation type were associated in univariate analysis with higher complication. However, multivariate analysis including these variables only identified hypertension and duration of procedure as significant predictors of complication. Gender has been identified as a risk marker for complication in other studies not examining discharge strategy for AF.[17-20] In our analysis we found a trend (P=0.06) toward higher univariate risk for complication, but this variable did not meet clinical significance. Other risk markers as outlined in Table 2 are congruent with prior published studies.[21]

Conclusions

Complication and readmission rates among two high-volume medical centers within the same healthcare system adhering to either SD or ND discharge strategy do not significantly differ for left atrial ablation procedures. These data support a growing body of evidence in favor of SD discharge for this common procedure and the need for a prospective randomized trial.

Table 4: Multivariable model of predictors of complications for Atrial Fibrillation Ablation.

	Beta Coefficient	Odds Ratio (95% CI)	P-Level
Discharge Strategy (Same-Day vs. Next-Day)	0.448	1.565 (0.754 - 3.248)	0.230
Congestive Heart Failure	0.514	1.671 (0.809 - 3.453)	0.165
Hypertension	1.232	3.428 (1.436 - 8.184)	0.006
Body Mass Index	0.015	1.015 (0.957 - 1.076)	0.619
Ablation Type (Compared to PVI only)			0.380
PVI+	0.488	1.628 (0.644 - 4.118)	0.303
Non-PVI	0.852	2.344 (0.594 - 9.249)	0.224
Convergent	1.295	3.652 (0.979 - 13.625)	0.054
Other*	-18.269	0 (0 - .)	0.999
Sedation Type (General vs Conscious)	0.543	1.721 (0.807 - 3.672)	0.160
Procedure Duration (per min)	0.01	1.01 (1 - 1.019)	0.046

Results of the multivariable regression model of predictors of complication after atrial fibrillation ablation. Independent predictors in the model include hypertension (HTN), as well as procedure duration. *Because there were vert few patients in this group, the odds ratio and confidence interval are less meaningful. Abbreviations: CI=confidence interval; Non-PVI=ablation excluding pulmonary vein isolation; PVI=pulmonary vein isolation; PVI+=pulmonary vein isolation plus additional lesion set

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Incidence of Cancer Treatment Induced Arrhythmia Associated with Immune Checkpoint Inhibitors

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Abstract

Background: Cancer treatment induced arrhythmia (CTIA) is a well-recognized form of cardiotoxicity associated with chemotherapy. Immune checkpoint inhibitors (ICI) have been associated with important forms of cardiotoxicity, including myocarditis. However, the incidence of CTIA associated with ICI has not been well characterized.

Methods: We reviewed all patients treated with ICIs at our institution from Jan. 2010 to Oct. 2015. CTIA was defined as a new diagnosis of clinically relevant arrhythmia within 6 months after ICI initiation.

Results: During the study period, 268 patients were treated with immune checkpoint inhibitors, of whom 190 received monotherapy with ipilimumab (n=114), nivolumab (n=52) or pembrolizumab (n=24) and 78 received combination therapy: ipilimumab & nivolumab (n=37), ipilimumab & pembrolizumab (n=39) and nivolumab & pembrolizumab (n=2). Four patients (1.5%) developed CTIA. Of these, 3 patients developed a new diagnosis of atrial fibrillation (AF), one of whom required cardioversion. In 2 cases of new-onset AF, significant provoking factors were present in addition to ICI therapy including thyrotoxicosis in one and metabolic disarray in another. Six patients (2.2%) with a pre-existing diagnosis of paroxysmal AF experienced episodes within 6 months of initiating ICI therapy. None of the arrhythmic events were associated with known or suspected myocarditis.

Conclusion: The incidence of arrhythmic complications associated with immune checkpoint inhibitors appears to be very low (~1.5%). Patients with a pre-existing diagnosis of AF may be at-risk of recurrence during ICI treatment and should be monitored accordingly. These data suggest that from an arrhythmia perspective, ICIs appear to be very safe and well-tolerated.

Introduction

Immune checkpoint in hibitors (ICI) are a relatively new class of anti-neoplastic systemic agents that have gained significant importance as a novel class of cancer therapy and have revolutionized the treatment of a large number of cancers[1-3]. In addition, the use of these agents has been advocated as safer than traditional cytotoxic chemotherapeutic drugs and has been advocated and approved for maintenance therapy,unlike other forms of chemotherapy, in a number of malignancies including lung cancer[4]. The use of ICIs is therefore expected to increase overtime and will be introduced in different regions of the world. Identifying ICI related toxicities regardless of their frequency, is therefore of high significance.

Key Words

Atrial Fibrillation; Chemotherapy; Immune Checkpoint Inhibitors; Cardiooncology

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Immune checkpoint inhibitors target a range of co-stimulatory signaling molecules on T lymphocytes and antigen presenting cells, including cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1/ligand-1 (PD-1/PD-L1)[5-7]. ICIs have been associated with the development of immune-related adverse events (irAEs), which can target various organ systems[6]. Cardiovascular manifestations of ICI-associated toxicity take several forms including myocarditis, pericardial disease and vasculitis[6,8,9]. Cancer treatment induced arrhythmia (CTIA) is a well-recognized form of toxicity occurring in the setting of chemotherapy [10,11] and several forms of CTIA have been reported in association with ICIs, including atrial and ventricular tachyarrhythmias and symptomatic bradycardia, including complete heart block [5,8]. Arrhythmic events associated with ICIs have mostly been reported to occur in the setting of myocarditis [5]; however, risk factors for the development of arrhythmias associated with ICIs have not been well-characterized. Therefore, we sought to describe the incidence of, risk factors for, and clinical outcomes associated with CTIA during ICI therapy.

	with CTIA (n= 4)	without CTIA (n= 264)	p
Age (years)	71.5 ± 6.5	66.8 ± 12.6	0.11
Male gender	4 (100)	172 (65)	0.30
Hypertension	3 (75)	157 (60)	0.65
Diabetes Mellitus	2 (50)	54 (21)	0.19
Congestive Heart Failure	2 (50)	27 (10)	0.06
Coronary Artery Disease	2 (50)	90 (34)	0.61
Obstructive Sleep Apnea	0	24 (9.1)	1.00

Table 1: **Baseline characteristics stratified by the presence of cancer treatment induced arrhythmia (CTIA)**

*Data are presented as mean ± standard deviation or n (%)

Methods

The protocol for this study was approved by the Emory University Institutional Review Board. We retrospectively reviewed all patients receiving de novo treatment with ICIs at Emory Healthcare/Winship Cancer Center from January 2010 to October 2015. Inpatient and outpatient electronic medical records (EMR) and pharmacy orders were queried to identify first-time orders for the following ICIs: ipilimumab, nivolumab and pembrolizumab. Four additional ICIs have been approved since the period of our study but were not included in this analysis. The end date for this analysis corresponds to the transition from International Classification of Diseases (ICD) 9 to ICD 10, which occurred in conjunction with changes to the EMR and pharmacy systems at our institution. Therefore, all analyses were performed using ICD-9 for consistency.

Electronic medical record databases were queried to identify cases of CTIA associated with ICIs. CTIA was defined as a new diagnosis (either billing code diagnosis or new inclusion of a diagnosis code in the medical problem list) for any of the following occurring up to 6 months after the initiation of immune checkpoint inhibitor therapy: atrial fibrillation/atrial flutter (AF), supraventricular tachycardia (SVT), sustained ventricular arrhythmias, sinus node dysfunction/sinoatrial node dysfunction, 2nd degree atrioventricular (AV) block, 3rd degree AV block, complete heart block and any symptomatic arrhythmia requiring treatment (i.e. change in medical therapy, cardioversion/defibrillation, need for catheter ablation or pacemaker/defibrillator implantation). Asymptomatic sinus bradycardia and sinus tachycardia and premature atrial and/or ventricular beats not requiring treatment were not included in the CTIA definition. A combination of billing codes and medical problem list queries, manual chart review and review of available electrocardiograms (ECGs) was used to identify cases of CTIA.

Only new arrhythmia diagnoses were included in the definition of CTIA. Patients with a pre-existing diagnosis of arrhythmia, present prior to the initiation of ICI therapy, were not included in the primary endpoint. However, data were collected on recurrences of arrhythmias among patients with pre-existing diagnoses to report separately from the primary endpoint. Baseline demographics and clinical covariates known to be associated with the development of arrhythmias (hypertension, diabetes mellitus, congestive heart failure, coronary artery disease and obstructive sleep apnea) were ascertained by EMR query, ICD-9 billing codes and manual chart review. Relevant clinic notes and results of cardiovascular testing were reviewed to identify known or suspect cases of my ocarditis.

Statistical Analysis

The primary endpoint for this analysis was the incidence of CTIA at 6 months after initiation of ICI therapy. Continuous variables are presented as mean ±standard deviation (SD) and categorical variables are presented as frequencies and percentages. Comparisons between groups were tested using the Fisher's exact test, Chi-squared test, or T-test, as appropriate. A two-tailed $p < 0.05$ was considered significant. All statistical analyses were performed using Statistica® (Statsoft, Tulsa, OK).

Results

During the period of interest,268 patients were treated with immune checkpoint inhibitors, of whom 190 received mono therapy with ipilimumab (n=114), nivolumab (n=52) or pembrolizumab (n=24). Seventy-eight patients received combination therapy with ipilimumab & nivolumab (n=37), ipilimumab & pembrolizumab (n=39) and nivolumab & pembrolizumab (n=2). Across the entire cohort, at the time of ICI initiation, mean age was 60.9 ± 12.5 years, 66% were male and comorbidities included hypertension (60%), diabetes (21%), coronary artery disease (34%), congestive heart failure (11%) and sleep apnea (9%).

By 6 months following initiation of ICI therapy, 4 patients (1.5%) met the primary endpoint definition for CTIA. The Table presents baseline characteristics, stratified by the presence of CTIA. Patients with CTIA tended to be older and were numerically more likely to be male and have a history of hypertension, although differences were not significant. All 4 cases of CTIA involved ipilimumab, two of which also included concomitant nivolumab therapy. No cases were identified with pembrolizumab.

A brief summary of the clinical features of the 4 CTIA cases follows:

1. 78-year-old male with history of hypertension developed symptomatic atrial fibrillation with rapid ventricular response (AF with RVR) approximately 5 months after initiating ipilimumab for metastatic melanoma. He was initially treated with transesophageal echocardiogram (TEE)-guided cardioversion and discharged home with anticoagulation and an increased dose of beta blockers, which he had previously been taking for hypertension. He presented again in AF with RVR 48 hours after the first discharge. During the second admission, he was loaded on amiodarone and again underwent cardioversion

2. 68-year-old male with hypertension and diabetes being treated with concomitant ipilimumab and nivolumab for metastatic melanoma was admitted for diabetic ketoacidosis (DKA) approximately 2 months after initiating combination ICI therapy. During hospitalization, while on an insulin drip, he developed self-limited AF which resolved spontaneously after about 48 hours as metabolic abnormalities and volume status were corrected. No additional therapy for AF was required.

3. 66-year-old male with hypertension being treated with concomitant ipilimumab and nivolumab for metastatic melanoma presented with AF with RVR approximately 6 weeks after initiating combination ICI therapy. Evaluation was notable for hyperthyroidism,

felt to possibly be drug-induced toxicity from the ICIs. Thyroid stimulating hormone level was markedly suppressed at 0.01 mU/L, with elevated levels of T3 and free T4. Hyperthyroidism was treated with methimazole and steroids and AF with RVR controlled with beta blockers. Anticoagulation was not started due to recurrent gastrointestinal bleeding from metastatic duodenal melanoma.

4. 74-year-old male with diabetes and extensive cardiac history including 3 prior ablations for atrial fibrillation was being treated with ipilimumab for metastatic melanoma. Approximately 3 months after initiating ICI therapy, he presented with increased fatigue and dizziness with sinus bradycardia (heart rates in the high 40s to low 50s at rest). He had been maintained on beta blockers for many years given the history of AF and previously, sinus rates had been adequate despite beta blocker therapy. Given concern that sinus bradycardia may be contributing to his symptoms, the dose of beta blocker was halved. Despite the history of atrial fibrillation, because sinus node dysfunction had not been documented prior to ICI therapy, and the dose of beta blocker was reduced, this event was included in the definition of CTIA.

None of the CTIA cases required stopping treatment with the ICIs. In addition to the 4 cases meeting the primary endpoint definition of CTIA, 6 additional patients with a history of paroxysmal atrial fibrillation developed episodes of AF within 6 months after beginning ICI therapy. These cases were not included in the CTIA definition given the pre-existing arrhythmia diagnosis. None of the cases of CTIA, or cases of recurrent AF in those with a pre-existing diagnosis of atrial fibrillation, were associated with known or suspected myocarditis.

Discussion

Our data demonstrate that the incidence of arrhythmic complications associated with immune checkpoint inhibitors appears to be very low. Only 4 cases (1.5%) in the cohort met the primary endpoint definition of CTIA occurring within 6 months of ICI treatment and in most instances, the arrhythmias could be managed in a relatively straightforward manner. None of the cases required stopping ICI therapy. Patients with a pre-existing diagnosis of atrial fibrillation may be at-risk of recurrence during ICI treatment and should be monitored accordingly. Importantly, none of the arrhythmia events in this cohort were associated with suspected myocarditis. These data add to the available literature on the cardiovascular safety profile of ICIs and suggest that from an arrhythmia perspective, ICIs appear to be very safe and well-tolerated.

Even among the CTIA cases in this cohort, in two instances there were significant additional factors which likely predisposed to the onset of arrhythmia, including significant metabolic abnormalities from DKA in one case and thyrotoxicosis in the other. In the case of sinus node dysfunction, although the need to reduce the dose of beta blocker therapy, strictly speaking, met our definition for CTIA, the clinical importance of this event is likely minimal.

Although much has been written about cardiovascular toxicities associated with ICIs, relatively little is known specifically about arrhythmic events. Although it has been suggested that most arrhythmic events associated with ICIs occur in the setting of myocarditis [5], this association has not been well-characterized and none of the arrhythmic events in our cohort occurred in the setting of suspected myocarditis. Atrial fibrillation is the arrhythmia most commonly associated with ICIs. In an analysis of the World Health Organization Vigi Base, a global database of individual case safety reports, arrhythmic adverse events due to atrial arrhythmias were significantly more common in association with ICIs compared to non-ICIs (0.71 vs. 0.42%) [8]. In contrast, adverse events related to other arrhythmic complications (ventricular arrhythmias, prolonged QT interval/Torsade de pointes and conduction system disorders) were not significantly different between ICIs and non-ICIs. Among recent clinical trials of newer ICIs, in the PACIFIC trialwith durvalumab for non-small-cell lung cancer (n=473 patients in the ICI arm), atrial arrhythmias occurred in 4 patients in the ICI arm and none in the placebo arm [5,12]. In the DETERMINE study of tremelimumab for mesothelioma (n=382 patients in the ICI arm), atrial arrhythmias occurred in 13 patients in the ICI arm and 7 in the placebo arm[5,13]. In aggregate, our data are consistent with prior reports which show that although atrial arrhythmias can occur during ICI therapy, the incidence appears to be quite low (~1-3% across studies).

The incidence of atrial arrhythmias associated with ICIs appears comparable to the incidence associated with others forms of chemotherapy. Atrial arrhythmias have been reported to occur within the first 6 months of treatment in about 3% of patients treated with other forms of chemotherapy including anthracyclines, monoclonal antibodies and tyrosine kinase inhibitors [11].

Less is known about the incidence of arrhythmic complications other than atrial arrhythmias associated with ICIs. Other than the one case of mild sinus node dysfunction which necessitated a reduction in beta blocker dose, we did not identify any other cases of symptomatic brady-arrhythmias in this study. Case reports have identified complete heart block associated with ICI therapy, typically in the setting of myocarditis [14,15], which may be reversible with cessation of ICI treatment [16]. However, beyond individual case reports, our study is among the limited datasets to systematically look for cases of heart block and brady-arrhythmias in the setting of ICI therapy and suggests that the incidence of this complication is very low.

Limitations

Several important limitations of our work should be noted. First, due to the transition from ICD-9 to 10 and associated changes in medical diagnosis and billing codes, our cohort includes only the 3 original immune checkpoint inhibitors approved for use and not any of the agents approved subsequently. Second, because we used billing codes and medical problem lists in our EMR to identify cases of CTIA, arrhythmic events that were managed outside our health system during ICI treatment may have been missed. Third, data on left ventricle ejection fraction were only available for a small number of patients in the cohort (n=30) and were not systematically obtained. Therefore, we cannot comment on the association between ejection fraction and risk for CTIA with ICIs. Finally, some arrhythmic events are asymptomatic and do not come to clinical attention but may have important prognostic and treatment implications, such as anticoagulation for subclinical atrial fibrillation. Our study only looked at clinically apparent arrhythmias and did not use any form of continuous rhythm monitoring to look for subclinical events.

Conclusions

The incidence of new-onset arrhythmias during the first 6 months after immune checkpoint inhibitor therapy appears to be very low (~1.5%) and most of the arrhythmias were relatively easily managed from a clinical perspective. Patients with a pre-existing diagnosis of atrial fibrillation may be at-risk of developing recurrences during ICI treatment and should be monitored accordingly. Importantly, none of the arrhythmias noted in this cohort occurred in the setting of suspected myocarditis. These data suggest that ICIs have an excellent safety profile from an arrhythmia perspective.

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Abstract

Background: Recent trials found poor temporal relationship between atrial fibrillation (AF) episodes and strokes. Thus, stroke in AF patients probably involves more mechanisms than cardiac embolism. We compared factors of inflammation, thrombosis and platelet reactivity between left (LA) and right atria (RA) and femoral vein (FV) in patients with AF.

Methods: Blood samples were collected from patients undergoing AF-ablation from the FV, RA and LA for neutrophil to lymphocyte ratio (NLR), immature platelet fraction (IPF) and count (IPC), CD40 ligand, P-selectin and E-Selectin. IPF was measured by an autoanalyzer; CD40 ligand, P-selectin, and E-Selectin were measured by ELISA and NLR was calculated from complete blood counts.

Results: Sixty-seven patients were included (age 65±10y, 63% male, CHA_2DS_2-VASc score 2.8±1.8, LA volume index 40±24 mL/m², 63% paroxysmal AF). There was no difference between FV, RA and LA regarding NLR and CD40 ligand. Factors associated with platelets activity: P-selectin, IPC and IPF% were higher in RA vs LA (60.3 IQR 49.0-76.4 ng/ml vs. 59.3 IQR 49.0-74.7, respectively, p=0.03 for P-selectin, 7.5 IQR 5.2-10 10^3/µL vs. 7.1 IQR 5-9.8, p<0.01 for IPC, and 3.6 IQR 2.7-5.0 % vs. 3.6 IQR 2.6-4.8, p<0.01 for IPF%). Similar trends were for E-selectin (41.2 IQR 31.1-51.2 ng/mL vs. 38.7 IQR 27.9-50.4 p=0.09). Similar significant differences were found in patients with CHA_2DS_2-VASC≥2 but not in patients with low score.

Conclusions: Patients with AF, especially those with CHA_2DS_2-VASc≥2, have higher markers of thrombogenicity in RA compared to LA. There was no difference in inflammatory properties between the atria.

Introduction

Atrial fibrillation (AF) confers a 3-6 fold increase in the risk of ischemic stroke, depending on CHA_2DS_2-VASc score[1]. Emerging evidence shows that temporal relationship between subclinical AF and stroke occurs only in a minority of patientsand that strokes often occur without subclinical AF detected within 30 days before the event[2,3]. Thus, stroke in patients with AF probably involves other mechanisms in addition to cardiac embolism. AF might simply be a marker of stroke risk — possibly indicating myocardial fibrosis or hypertrophy, thrombogenic tendency and platelet hyper-reactivity, as well as a pro-inflammatory state[3]. Although in patients with AF, thrombi often originate in the left atrial appendage, anatomical considerations alone cannot completely explain the higher frequency of thrombi in the left heart chambers.

Immature or Reticulated platelets (RPs) are hyper-reactive platelets that are larger platelets with higher dense granules content and contain more RNA compared with mature platelets [4,5]. They are associated with thrombotic propensity and have a greater predilection for thrombus formation. Increased levels of RPs are associated with arterial thrombotic events including acute coronary syndrome and acute stroke[6–8]. Measuring the level of RPs is technically difficult. Recently, an automated assay - immature platelet fraction (IPF) - was introduced and correlates directly with reticulated platelets level[9].

Other markers associated with plateletshyper-reactivity, thrombogenicity and inflammation are markers expressed by platelets such asthe platelet glycoproteins P-selectin (CD62), CD 40 ligand and E-selectin expressed by endothelial cells[10–13]. P-selectin and CD 40

Key Words:
Atrial Fibrillation, Thrombosis, Inflammation, Platelet Activation, P-Selectin, IPF, Neutrophil To Lymphocyte Ratio, Left Atrium.

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ligand are glycoproteins translocatedto the surface of platelets upon activation, and then cleaved and released into the circulation. They promote platelets activation, aggregation and thrombus formation[14,15]. E-selectin is an endothelial surface molecule that acts as an adhesion molecule. E-selectinis enhanced as a result of endothelial activation.High E-selectin levels are found in patients with AF[6,13]. Another marker that was recently correlated with thromboembolic events and stroke in non-valvular AF is the neutrophil-to-lymphocyte ratio (NLR)[16,17]. NLR is an inflammatory marker that has been correlated with atherosclerosis and coronary cardiac events[18] and was shown to be an independent risk factor for spontaneous echo contrast of LA appendage and LA thrombus formation[17,19].

There is limited data to suggest that there is chamber specific platelet activation that could explain, in part, the propensity for LA thrombus formation in patients with AF[10,12,20]. It is still unclear whether there is any difference between right and left atria regarding platelets activation.

The aim of this study is to examine whether inflammatory markers, such as NLR, C-reactive protein (CRP) and CD40 ligand, and/or pro-thrombogenic markers (such as P-selectin,E-selectin and CD-40) differ between systemic circulation and both atria or between LA and RA, thereby potentially explain the higher proportion of stroke in AF patients.

Methods

We enrolled consecutivepatients withAF who underwent ablation as per European guidelines indications- pulmonary vein isolation and substrate ablation as needed[1]. All patients were enrolled during the index hospitalization for the ablation. The study was approved by the ethical review board of our institution (Institutional Helsinki Board) and all subjects provided written informed consent. The study was registered in the Ministry of Health website of clinical trials.

We excluded patients with chronic hemato-oncologic diseases, anemia (hemoglobin < 10 g/dL), or thrombocytopenia (platelet level < 100 K/μL) or any other condition that could affect blood count. Any patient with acute coronary syndrome or an acute infectious or inflammatory disease was excluded as well.

Three blood samples of 5 cc were drawn from each patient during the ablation procedure: one sample from peripheral vein was taken from the femoral vein (FV); one sample was taken from the RA; and a third sample was taken from the LA immediately after trans-septal puncture and prior to the administration of intravenous Heparin. From each sample (three per patient), we measured NLR, IPF, CRP, CD40 ligand, P-selectin and E-selectin.IPF assessment was performed by automated analyzer (Sysmex XN-3000, Sysmex America Inc. Mundelein, Illinois) that uses fluorescent dyes containing polymethine and xazine. This system discriminates between mature and immature platelets and reports the immature platelet fraction[9]. Plasma level of soluble P selectin, E selectin and CD40 ligand were analyzed using enzyme-linked immuno-adsorbent assay (Human P selectin Quantkine ELISA DPSE00, Human E selectin Quantkine ELISA DSLE00 and Human CD 40 Ligand Quantkine ELISA DCDL 40, R&D systems, Minneapolis).

Statistical analysis of continuous variables between the groups was conducted using student paired t-test for normal distributed variables or Wilcoxon rank test for non-normal distribution as appropriate. Categorical variables were compared by a chi-square ($x2$) test. Data are presented as mean ± SD for normally distributed continuous variables, as median with interquartile range (IQR) for continuous variables that are not normally distributed, and as frequency (%) for categorical variables. Statistical significance was accepted at p <0.05. All analyses were performed with the SPSS version 22 statistical software (IBM Inc. Chicago, Illinois).

Results

Baseline patients' characteristics

Sixty-seven patients who underwent AF ablation wereenrolled in this study.Table 1 describes baseline clinical and echocardiographic characteristics. Mean age was 65.1 ± 10.3 years and 42 (62.7%) were men. Forty-twopatients (62,7 %) had paroxysmal AF and 25 (37.3%) had persistent AF. MeanCHA_2DS_2-VAScscorewas 2.8± 1.8, with 19 patients (28%) having low score and inherent differences in baseline co-morbidities accordingly (Table 1).

Regarding medical treatment, patients with CHA_2DS_2-VASc≥2 were treated more with statins and angiotensin converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) than patients with CHA_2DS_2-VASc<2: 28(58.2%) vs. 5 (26.3%) and 36 (75.0%) vs. 6 (31.6%) respectively (p=0.02 and p=0.001). There was no difference regarding antithrombotic therapy, including aspirin, clopidogrel, ticagrelor or prasugrel. Almost all patients in our cohort -65 (97.0%) - were treated with anticoagulation according to their CHA_2DS_2-VAScscore. (Table 1)

Regarding echocardiographic characteristics of the cohort: mean measurements of ejection fraction (EF) were55.3 ± 9.1 %, LA diameter 43.1± 5.6 mm, LA volume 79.5±26.4 mL and indexed to body surface 40.1± 23.9 mL/m2. Patients with CHA_2DS_2-VASc≥2 had higher estimated pulmonary artery wedge pressure (36.3 ±9.4 mmHg vs. 29.7 ±8.8, respectively; p<0.05). There was no difference in LA diameter, volume and indexed volume to body surface area (Table 1).

Platelets reactivity and inflammatory markers

Platelet activation was evaluated by soluble P-selectins,IPF and CD40 ligand levelsand activated endothelium was evaluated by soluble E-selectinlevel (Table 2). Soluble P-selectin mean levels were significantly higher in the RA compared to LA (60.3 IQR 49.0-76.4 ng/ml vs. 59.3 IQR 49.0-74.7 ng/ml, respectively, p=0.03). CD40 ligand levels did not differ between RA and LA. There was also a trend towards higher soluble E-selectin levels in the RA vs LA (41.2 IQR 31.1-51.2 ng/ml vs. 38.7 IQR 27.9-50.4 ng/ml, respectively, p=0.09) (Table 2). No difference was found in soluble P-selectin, E-selectin and CD40 levels between peripheral blood and both atria.

The level of immature platelet counts (IPC) was higher in the RA compared to LA, 7.5 IQR 5.2-10.0103/μL vs. 7.1 IQR 5.0-9.8 103/μL (p <0.01) and 8.2±4.2 103/μL in RA vs. 7.9±4.1 103/μL in LA

Table 1: Patients'baseline characteristics

	All Patients (N=67)	$CHA_2Ds_2VASC<2$ (N= 19)	$CHA_2DS_2VASC≥2$ (N= 48)	P value
Clinical Characteristics				
Age (years)	65.1 ± 10.3	55.1± 9.2	69.1±7.8	<0.01
Male Gender (%)	42 (62.7)	16 (84.2)	26 (61.9)	0.02
Diabetes Mellitus (%)	22 (32.8)	1 (5.3)	21 (43.8)	<0.01
Hypertension (%)	47 (70.1)	5 (26.3)	42 (62.7)	<0.01
Dyslipidemia (%)	40 (59.7)	7 (36.8)	33 (68.8)	0.02
Smoker (%) *	6 (9.0)	2 (10.50	4 (8.3)	1.00
Ischemic heart disease (%) *	13 (19.4)	0 (0)	4 (27.1)	0.01
Cerebrovascular disease (%) *	6 (9.0)	0 (0)	6 (12.5)	0.17
Peripheral arterial disease (%) *	5 (7.5)	0 (0)	5 (10.4)	0.31
Congestive Heart Failure (%) *	12 (17.9)	1 (5.3)	11 (22.9)	0.16
Chronic renal failure (%)	4 (6.0)	0 (0)	4 (8.3)	0.57
$CHAD_2$-$VASC_2$ Score	2.8 ± 1.8	0.6 ± 0.5	3.6±1.3	<0.001
Arrhythmia Type - Paroxysmal AF (%)	42 (62.7)	14 (73.7)	28 (58.3)	0.24
Persistent AF (%)	25 (37.3)	5 (26.3)	20 (41.7)	
Medical Treatment				
Aspirin (%) *	7 (10.4)	2 (10.5)	5 (10.4)	1.0
Other anti-aggregation (Clopidogrel, Ticagrelor, Prasugrel) (%) *	2 (3.0)	0 (0)	2 (4.2)	1.0
Statins (%)	33 (49.3)	5 (26.3)	28 (58.3)	0.02
ACE-I/ARB (%)	42 (62.7)	6 (31.6)	36 (75.0)	0.001
Beta Blockers (%)	42 (62.7)	12 (63.2)	30 (62.5)	0.96
Anticoagulation (Apixaban, Rivaroxaban, Dabigatran) (%)	65 (97.0)	17 (89.4)	48 (100)	0.16
Antiarrhythmic (%)				
Ic (Propafenone, Fecanide)	11 (16.4)	5 (26.3)	6 (12.5)	
III (Sotalol)	2 (3.0)	0 (0)	2 (4.2)	0.49
III (Amiodarone, Dronaderone)	32 (47.8)	7 (36.8)	25 (52.1)	
Echocardiographic Characteristics				
Ejection Fraction (%)	55.3 ± 9.1	55.8 ± 5.8	55.1±10.1	0.73
LVEDd (mm)	47.4 ± 5.3	48.4 ± 5.3	47.0 ± 5.3	0.33
LVESd (mm)	32.1 ± 5.6	32.7 ± 5.0	31.9 ± 5.9	0.56
Diastolic Dysfunction grade – 0 (%)	19 (28.4)	9 (47.4)	10 (20.8)	0.118
1 (%)	7 (10.4)	1 (5.3)	6 (12.5)	
2 (%)	16 (23.90	2(10.5)	14 (29.2)	
3 (%)	3 (4.5)	0 (0)	3 (6.3)	
Left Atrial Diameter (mm)	43.1 ± 5.9	42.9 ± 6.6	43.1 ± 5.8	0.90
Left Atrial Area (cm^2)	24.4 ± 5.3	22.7 ± 4.8	25.0 ± 5.4	0.14
Left Atrial Volume (mL)	79.5 ± 26.4	73.6 ± 28.8	81.2 ± 25.8	0.46
Left Arial Volume Index (mL/m^2)	40.1 ± 23. 9	35.7 ± 12.5	41.3 ± 14.2	0.26
Right Atrial Area (cm^2)	19.2 ± 5.5	18.9 ± 4.1	19.3 ± 6.0	0.77
Right Atrial Volume (mL)	48.8 ± 23.4	49.7 ± 16.6	48.6 ± 25.1	0.88
Right Arial Volume Index (mL/m^2)	24.4 ± 10.9	25.0 ± 6.7	24.2 ± 11.8	0.82
Estimated Pulmonary Arterial Pressure (mmHg)	34.7 ± 9.6	29.7 ± 8.8	36.3 ± 9.4	0.03

* By Fisher Exact Test

Abbriviations: LVEDd= left ventricular end diastolic diameter, LVESd=left ventricular end systolic diameter, AF= atrial fibrillation, CHA2DS2-VASc score =score for atrial fibrillation stroke risk that includes congestive heart failure, hypertension, age above 65 or 75, diabetes, previous stroke, vascular disease history and female sex, ACE-I= angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker.

(p=0.05). IPF% (immature platelets fraction) was higher in the RA compared to LA as well, 3.6 IQR 2.7-5.0 % vs. 3.6 IQR 2.6-4.8 % (p<0.01) and 4.4±2.9 % in RA vs. 4.1±2.5 % in LA(p=0.04).

Inflammatory markers were evaluated by NLR and CRP (Table 2). There was no difference between RA and LA regarding NLR. However, CRP was lower in the LA vs. RA (2.6 IQR 1.3-5.0 mg/dL, 5.2 mg/dL, p<0.05).

Platelets and inflammatory markers according to CHA_2DS_2-VASc score

We examined separately patients with CHA_2DS_2-VASc≥2 and CHA_2DS_2-VASc<2 (Table 3); patients with low CHA_2DS_2-VASc score had no differences in platelet activation markerssuch as soluble P-selectin, IPF% or soluble E-selectin (Table 3). However, patients with CHA2DS2-VASc≥2 had higher levels of IPF% and soluble P-selectinin the RA compared with the LA (3.6 IQR 2.7-9.6 % vs. 3.5 IQR 2.7-5.2 % (p<0.01) and 69.3 IQR 48.5-79.1 ng/mL vs. 59.3. IQR 49.0-75.6 ng/mL (p<0.05), respectively). There was also a trend towards higher soluble E-selectin levels in the RA vs LA in this group of patients. No difference was found between RA and LA regarding NLR in both groups with either CHA_2DS_2-VASc≥2 and CHA_2DS_2-VASc<2(Table 3).

Discussion

The main findings of our study are that in patients with AF, markers of platelet activation are higher in the RA compared with the LA, while most inflammatory markers do not differ between the atria. These differences are especially pronounced in patients with CHA_2DS_2-VASc≥2.

In this study we examined three microparticles related to platelets reactivity. P-selectin is an important protein in recruitment and aggregation of platelets and is an important marker of activated platelets [21]. Soluble P-selectin is a remnant marker of activated pro-thrombotic platelets.Thus, soluble levels of P-selectin correlate with expressed P-selectin within plateletmembrane[15,21]. Activated platelets also release CD40 ligand. CD40/CD40 ligandactivation results in expression of many pro-inflammatory and pro-thrombotic factors, including IL-1, IL6, and TNF-α and correlatewith pro-thrombotic states such as cerebrovascular ischemia[21]. Another glycoprotein related to thrombogenicity of platelets is E-selectin. E-selectin is expressed on endothelial cells and is related to activated leukocytes; it is also secreted from intracellular granules and is measurable in soluble form. E-selectin has been shown to be an important factor in neutrophil trafficking and platelets recruitment and therefore hasan important key role in thrombus formation. [21,22]

Previous studies showed that platelets of patients with AFare more pro-thrombotic compared to non-AF patients[23]. Patients with AF have higher levels of pro-thrombotic markers such as P-selectin, CD40 and mean platelets volume[11,24–26].

Table 2: A comparison of platelet and inflammatory markers between peripheral vein and both atria

	Right Atria	Left Atria	P value (left vs. right atria)
WBC (103/µL)	6.0 (4.9-7.8)	6.1 (5.0-7.8)	0.70
Neutrophils(103/µL)	3.8 (2.7-5.6)	3.7 (2.8-5.7)	0.70
Lymphocytes (103/µL)	1.6 (1.2-2.1)	1.6 (1.3-2.0)	0.45
Neutrophils (%)	63.6 (55.8-68.9)	63.9 (56.8-68.8)	0.52
Lymphocytes (%)	25.5 (21.6-31.1)	25.5 (21.6-32.3)	0.72
Platelets (103/µL)	195.5 (160.5-229.0)	194.0 (163.3-234.0)	0.99
IPC (103/µL)	7.5 (5.2-10.0)	7.1(5.0-9.8)	<0.01
IPF (%)	3.6 (2.7-5.0)	3.6 (2.6-4.8)	<0.01
NLR (ratio)	2.5 (1.9-3.2)	2.5 (1.7-3.2)	0.37
CRP (mg/dL)	2.7 (1.5-5.2)	2.6 (1.3-5.0)	<0.01
Soluble P-Selectin (ng/mL)	60.3 (49.0-76.4)	59.3 (49.0-74.7)	0.03
Soluble E-Selectin(ng/mL)	41.2 (31.1-51.2)	38.7 (27.9-50.4)	0.09
CD-40 ligand (pg/mL)	512.5 (371.9-746.9)	500.0 (362.5-843.8)	0.72

Abbreviations: WBC= white blood count; NLR= neutrophils to lymphocytes ratio; CRP= C reactive protein; IPF= immature platelets fraction, IPC=immature platelets count.

Thrombogenicity of the LAwas shown to be induced by AF and to return to baseline after return to sinus rhythm[27]; however, the reason why thrombi are more prevalent inthe LA is still an unanswered question. Temporal relationship between subclinical AF and stroke occurs only in a minority of patientsand strokes often occur without subclinical AF detected within 30 days before the event[3,23]. Thus, debate still exists whether thrombus formationis related only to the stunning ofthe atria during and post AF or there are anatomical differences between the atria that cause propensity of LA thrombus (fibrosis, hypertrophy, etc.). Possibly,there are other alternativemechanisms related to cell activation, such as in situ thrombogenic tendency or platelet hyper-reactivity or a pro-inflammatory state that is associated with both AF and stroke[10,28].

There is conflicting evidence regarding the propensity of the LA to form thrombi. Some studiesimply that platelets are more activated within the LA. Unexpectedly, other studies suggest the contrary- that there are more pro-thrombotic factors,including elevated platelet activation markers, in the RA, as was shown in our study.

Yamamoto et al. have shown that the coagulation system is more activated in the LAin patients with mitral stenosis[29]. Willoughby et al. reportedelevated P-selectinlevels and elevated ADP-induced platelet aggregation within LA compared to RA in patients who underwent pulmonary vein isolation ablation for AF[10]. Lim et al.reportedhigher platelet activation (assessed by P-selectin levels) in patients with AF compared with anon-AF group, and an increase in thrombin generation in the LA compared with peripheral blood in patients with AF[27].

In contrast to these studies, Schultz et al. did not show any differences between P-selectin, CD 40 or endothelial markers in the right and the left atria in patients with either AF or supra-ventricular tachycardias[30]. Jesel et al. also did not show any atrial specific differences in the levels of pro-coagulant factors, including platelet derived microparticles.They did show, however, that endothelial-derived microparticles, tissue factor activity and collagen-induced platelet aggregation were slightly elevatedin the RA of patients with a history of AF[31]. Park et al. also did not show any differences between right and left atria regarding pro-thrombotic factors, such as E-selectin, in patients with valvular AF[32]. Additionally, Akar et al. showedin AF patients (spontaneously or following atrial pacing), thatP-selectin levels were elevated in the coronary sinus compared to the peripheral blood. They also showed increased local thrombin generation in the coronary sinus, decreased nitric oxide production and no change in in flammatory markers.This study suggests increased pro-thrombotic characteristics of platelets especially in the RA, although sampling from the left side of the heartwas not performed[20].

In our study we compared directly thrombogenic and inflammatory markersin RA vs. LA and also vs.peripheral blood in AF patients. Our results imply that thrombogenicityis higher in the RA than the LA in the setting of AF.We found an increase in platelet activation markers in the RA, as reflected by elevated P-selectin, E-selectin,IPC and IPF levels in the RA vs. LA, especially in patients with CHA_2DS_2-VASc≥2. In contrast, we did not find any significant difference between the atria in markers of inflammatory process (CD40 ligand, NLR or CRP levels).

Recently the approach to pathophysiology of AF focuses on atrial cardiomyopathy as the process leading to atrial dysfunction. The fibrillation of atrium is a symptom of this pathology. AF can affect both atria in atrial cardiomyopathy in patients with AF which is not related to rheumatic heart disease[33]. Bilge et al. showed that atrial thrombi are formed in the right atrium as well as in the left side in patients with non-valvular AF, as compared with valvular AF[34].Other echocardiographic studies have also shown thrombi formation in the RA as well as in LA[32-35]. In a study by Shahin et al. RA dysfunction was demonstrated in addition to left sided atrial dysfunction[35].

Another explanation could stem from the role of the lungs in this process: However, because the lungs are capable of absorbing microthrombi without any clinical significance, as opposed to the left system, the resulting neurological and peripheral consequence of the left side emboli are well expressed [36–39]. This explanation suggests that thrombi are formed in the right side of the heart as well as in the left side, with higher thrombogenicity in the RA, but with less clinical consequences. This is probably the reason for the higher soluble P-selectin in RA versus LA found in our study; soluble P-selectin is created by proteolytic degradation of P-selectin on platelets. It was higher in RA either due to secretion from higher IPF in RA (as stated above) or due to more protein sequestration in the lungs. Because of the scarce data available regarding the function and the role of RA in patients with AF, the data from our study that suggest that RA has thrombogenic properties, has a novel additive value to understandingthis controversial subject.

Platelets are removed from the circulation in the reticuloendothelial system after a short lifespan of 8-10 days. Much information exists regarding mechanisms of platelets activation. But less is knownabout the clearance of cells and their death [40]. Platelets undergo a

Table 3: A comparison of platelet and inflammatory markers between atria according to CHA_2DS_2-VASc Score

	CHA_2DS_2-VASc≥2 (N=48)			CHA_2DS_2-VASc<2 (N=19)		
	Right Atria	Left Atria	P value	Right Atria	Left Atria	P value
WBC(10^3/μL)	6.4 (5.2-8.3)	6.4 (5.3-8.2)	0.93	5.9 (4.8-6.8)	6.1	0.5
Neutrophils (10^3/μL)	4.1 (2.8-5.7)	4.0 (2.8-5.9)	0.99	3.5 (2.5-4.7)	3.5 (2.4-4.5)	0.5
Lymphocytes (10^3/μL)	1.6 (1.2-1.9)	1.6 (1.1-2.0)	0.73	1.7 (1.4-2.1)	1.6 (1.4-2.0)	0.4
Neutrophils (%)	64.0 (58.2-70.2)	64.2 (57,7-70.3)	0.74	60.6 (54.2-67.6)	60.3 (54.1-68.0)	0.4
Lymphocytes (%)	24.8 (18.9-30.5)	25.1 (18.5-31.0)	0.98	26.1 (23.7-36.3)	27.4 (23.0-35.6)	0.5
Platelets (103/μL)	192.5 (159.5-233.0)	193.0 (160.8-232.0)	0.72	207.0 (161.3-229.0)	197.5 (162.0-237.3)	0.8
IPC (103/μL)	7.4 (5.3-9.6)	7.0 (5.3-9.6)	0.02	7.9 (4.8-10.5)	7.3 (4.1-10.4)	0.08
IPF (%)	3.6 (2.7-9.6)	3.5 (2.7-5.2)	0.01	3.6 (2.5-4.7)	3.8 (4.1-10.4)	0.1
NLR (ratio)	2.5 (1.9-3.6)	2.6 (1.8-3.7)	0.5	2.3 (1.5-2.7)	2.5 (1.6-2.8)	0.5
CRP (mg/dL)	3.0 (1.6-5.5)	2.6 (1.6-5.5)	0.01	2.4 (1.0-5.0)	2.2(0.9-4.6)	0.08
Soluble P-Selectin (ng/mL)	69.3 (48.5-79.1)	59.3(49.0-75.6)	0.04	58.5 (49.8-69.8)	56.8 (40.1-74.3)	0.4
Soluble E-Selectin(ng/mL)	43.6 (30.5-52.8)	39.6(28.0-51.5)	0.08	40.0 (31.2-46.7)	37.4 (27.5-45.7)	0.8
CD-40 ligand (pg/mL)	512.5 (362.5-825.0)	500.0 (333.3-850.0)	0.4	512.5 (377.1-581.3)	496.9 (406.3-828.1)	0.4

Abbreviations: WBC= white blood count; NLR= neutrophils to lymphocytes ratio; CRP= C reactive protein; IPF= immature platelets fraction.IPC=immature platelets count.

process that is similar to intrinsic apoptosis in the liverthrough Ashwell-Morrell receptor (AMR) [41].Therefore, following this process of apoptosis the venous blood return from the liver likely contains more young platelets. The higher levels of IPF and IPC that we have found in the RA probably reflect the venous blood circulation after the apoptosis process of 'old' platelets, contributing to the higher proportion of immature platelets in the RA.According to this theory, it is notsurprising to find more young platelets in the RA and pulmonary vasculature.

In this study we found a small difference towards higher level of CRP in the RA compared to LA. CRP is produced in the liver and is distributed to the rest of the circulation through the venous return to the heart [42].This is probably the reason for the difference between the two atria. In our opinion, this difference is too small to have any clinical significance.

Limitations: One of the limitations of the study is the non-relevance of the FV blood samples regarding thrombogenic factors. Given the sheaths (7F) were already introduced and blood was collected from the FV through the sheaths, it is possible that some of the observed values of the FV are due to introduction of potentially thrombogenic material into the vasculature. Anotherlimitation of the study is the lack of a control group of non-AF patients, in order to better understand the role of AF in these LA-RA differences. However, the above-mentioned previous studies did not find any differences between the atria in non-AF patients[30]. Another limitation is a non-uniform rhythm of the cohort during AF ablation: some patients underwent the procedure in sinus rhythm, others were in AF, and some patients started the procedure in AF and converted to sinus.

Conclusions

We found higher markers of thrombogenicity and platelet activation in the right compared to the left atrium in patients with AF. The results were even more pronounced in patients with CHA_2DS_2-VASc≥2.There does not appear to be a gradient of inflammatory properties between the two atria in these patients. These findings set the basis for further investigation to explain the higher stroke risk in AF patients.

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Factors Associated with Moderate Physical Activity Among Older Adults with Atrial Fibrillation

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Abstract

Objective: Engaging patients with atrial fibrillation (AF) in moderate-intensity physical activity has been encouraged by published guidelines. We examined factors associated with engagement in moderate physical activity among older adults with AF.

Methods: Data are from the SAGE (Systematic Assessment of Geriatric Elements)-AF study. Older adults (≥65 years) with AF and a CHA_2DS_2-VASc≥2were recruited from several clinics in Massachusetts and Georgia between 2015 and 2018. The Minnesota Leisure Time Physical Activity questionnaire was used to assess whether participants engaged in moderate-intensity physical activity (i.e. at least 150 minutes of moderate exercise). Logistic regression was utilized to examine the sociodemographic and clinical characteristics and geriatric elements associated with engaging in moderate-intensity physical activity.

Results: Participants were on average 76 years old and 48% were women. Approximately one-half (52%)of study participants engaged in moderate-intensity physical activity. Morbid obesity (adjusted OR [aOR]=0.41, 90%CI=0.23-0.73), medical history of renal disease (aOR=aOR=0.68,90%CI= 0.48-0.96), slow gait speed (aOR=0.44,90%CI=0.32-0.60), cognitive impairment (aOR=0.74, 90%CI=0.56-0.97), and social isolation (aOR=0.58, 90%CI= 0.40-0.84) were independently associated with a lower likelihood, while higher AF related quality of life score (aOR=1.64, 90%CI=1.25-2.16) a greater likelihood, of meeting recommended levels of moderate physical activity.

Conclusions: Nearly one-half of older adults with NVAF did not engage in moderate-intensity exercise. Clinicians should identify older patients with NVAF who are less likely to engage in physical activity and develop tailored interventions to promote regular physical activity.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an estimated prevalence of at least 33.5 million worldwide.[1] AF markedly decreases quality of life and increases the risk of stroke, heart failure, dementia, and death.[2-7] Lifestyle interventions, including participation in regular exercise and risk factor management, have been shown to benefit older patients with AF by decreasing their symptoms and improving their quality of life.[8-10]

Key Words:
Atrial fibrillation, Physical Activity, Moderate Exercise.

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Widely disseminated guidelines by national agencies encourage moderate - intensity physical activity in patients with AF yet advocate against chronic excessive endurance exercise among middle-age and older adults with AF.[11] Patients with AF who engage in moderate-intensity physical activity have a lower risk of CVD mortality compared with those who are inactive and moderate exercise has been shown to result in a lower risk of CVD mortality than strenuous exercise.[12] In addition, moderate-intensity physical activity has been shown to enhance quality of life, exercise capacity, and the ability to perform activities of daily living among adults with AF.[13] However, little is known about the extent of engagement in moderate exercise or the factors that may promote or hinder engagement in moderate exercise among older adults with AF. Understanding these facilitators or barriers would help clinicians identify patients with AF who are less likely to meet recommended levels of physical activity and develop tailored interventions to promote moderate-intensity physical activity in these individuals.

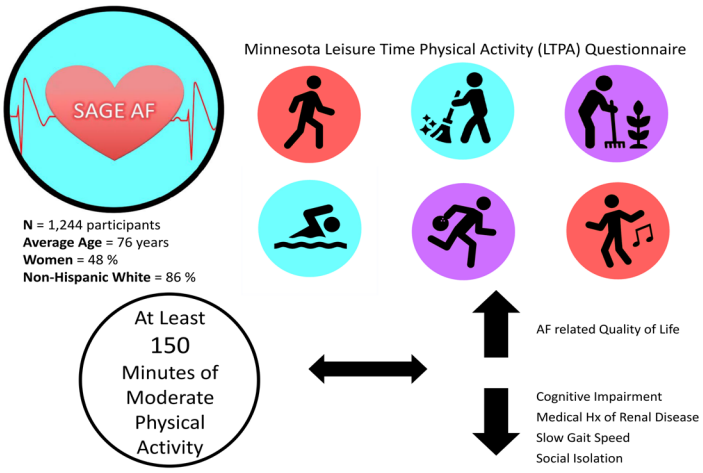

Figure 1: **Minnesota Leisure Time Physical Activity (LTPA) Questionnaire**

Using data from a large contemporary cohort, the Systematic Assessment of Geriatric Elements (SAGE)-AF study,[14,15] we examined the sociodemographic, geriatric, clinical, and patient reported elements associated with meeting recommended levels of moderate physical exercise.

Methods

Study Population

The data used for this cross-sectional analysis were derived from the prospective cohort study, Systematic Assessment of Geriatric Elements (SAGE) in AF.[14,15] Participants were recruited from multiple primary care and specialty care clinics in Massachusetts and Georgia between 2015 and 2018. Participants included were 65 years and older, diagnosed with NVAF, and had a CHA_2DS_2-VASc≥2 [16]. Patients with contraindications to oral anticoagulation, or on anticoagulation therapy for conditions other than AF, those with impaired decision making who were unable to provide written consent, or were non-English speakers were excluded. The Institutional Review Boards at the University of Massachusetts Medical School, Boston University, and Mercer University approved this study. Participants were enrolled into this observational study after providing written informed consent.

Measurement of Physical Activity

The Minnesota Leisure-Time Physical Activity (MLTPA) questionnaire was used to evaluate self-reported level of physical activity and was completed at the time of study enrollment.[17,18] The MLTPA questionnaire asks participants to self-report whether they haveper formed the following moderate activities during the prior 2 weeks: (1) walking at af airly brisk pace for exercise, (2) moderately strenuous household chores (i.e., scrubbing, vacuuming), (3)moderately strenuous outdoor chores (i.e., mowing or raking lawn, working in the garden), (4) dancing, (5) bowling, or (6) any regular exercise program other than walking such as stretching, strengthening exercises, or swimming. The questionnaire assesses the frequency (how many times) and duration (in minutes) participants spend doing each reported activity. The total duration of moderate exercise that participants engaged in on a weekly basis was calculated by adding the number of minutes that participants reported having performed each of the activities mentioned previously. The total number of minutes of moderate exercise was then categorized as a binary variable (yes/no) for engaging in at least 150 minutes of moderate exercise on a weekly basis or meeting recommendations for moderate-intensity physical activity. Existing AF guidelines recommend that patients with AF engage in moderate-intensity physical activity, however do not focus on the duration (time)[11]; we utilized the recommended category, by AHA/ACC guidelines, of moderate exercise in minutes for all apparently healthy adults (at least 150 minutes of moderate exercise).[19]

Clinical and Geriatric Elements

Trained research staff collected data through the conduct of in-person interviews and through the review of participants' medical records. Trained study staff used standard methods to review participants' medical charts and abstract sociodemographic and clinical data including age, sex, race, marital status, and level of education. Clinical factors included body mass index (BMI; overweight, obese, morbidly obese), anticoagulant therapy, type of AF, time since AF diagnosis, calculated stroke and bleeding risk scores, medical history, and relevant laboratory findings.

We used the Cardiovascular Health Survey (CHS) frailty scale to assess frailty among study participants.[20]Gait speed was assessed using the time to walk 15 feet.[21] Social isolation was assessed using the Social Support Scale and Social Network Scale.[22] Participants' cognitive function was assessed using the Montreal Cognitive Assessment Battery (MoCA) with a score≤23 classified as being cognitively impaired.[23] The Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder Scale (GAD7) were used to examine the presence of depressive and anxiety symptoms, respectively.[24,25] Occurrence of falls in the past 6 months, and sensory deficits, including visual and hearing impairments, were self-reported by participants. AF related quality of life was assessed using the Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire and OAC treatment satisfaction was assessed using the Anticoagulation Treatment Satisfaction (ACTS) scale.[26,27]

Statistical Analysis

We compared those who met the recommended number of minutes of moderate exercise (≥150 minutes) to those who did not (<150 minutes) according to participants' baseline sociodemographic, clinical, and psychosocial characteristics. We used chi-square tests to examine between group differences for categorical variables and unpaired t-tests for continuous variables.

Logistic regression as used to determine the factors associated with meeting the working definition of moderate exercise. We adjusted for groups of variables based on their clinical relevance as well as their level of significance ($p<0.05$) in their independent association with engagement in moderate physical activity. In Model 1, we examined the association of socio-demographic and clinical variables with participation in moderate exercise. In Mode l 2, we additionally controlled for geriatric elements (i.e., gait speed, falls in past 6 months, cognitive impairment, social isolation, depression, anxiety, and visual

Table 1: Baseline Socio-demographic and Clinical Characteristics of Participants According to Self-Reported Moderate Physical Activity: SAGE-AFStudy

Baseline Characteristics	Moderate Physical Activity		
	Yes (n=652)	No (n=592)	P-value
Socio-demographics			
Age, years, (M, SD)	75 (7)	77 (7)	<0.001
Female (%)	299 (46)	308 (52)	0.03
Married (%)	394 (62)	300 (51)	<0.01
Non-Hispanic White (%)	571 (88)	485 (82)	<0.01
College graduate or more (%)	317 (50)	210 (36)	<0.001
Clinical			
Mean Body Mass Index (kg/m^2) (SD)	29 (6)	31 (7)	<0.001
Body Mass Index (kg/m^2)			
Normal (<25)	133 (20)	113 (19)	<0.001
Overweight (25-29.9)	250 (38)	186 (32)	
Obese (30-39.9)	237 (36)	231 (39)	
Morbidly Obese (≥40)	31 (5)	60 (10)	
Type of AF (%)			
Paroxysmal	403 (62)	338 (57)	0.06
Persistent	157 (24)	152 (26)	
Permanent	28 (4)	45 (8)	
Left Ventricular Ejection Fraction	56 (11)	53 (14)	<0.01
Time since AF Diagnosis, mean, years (SD)	5 (4)	6 (4)	0.16
On OAC (%)	559 (86)	505 (85%)	0.83
Medical History (%)			
Alcohol Use	227 (35)	157 (27)	<0.01
Anemia	186 (29)	205 (35)	<0.01
Asthma/COPD	141 (22)	175 (30)	<0.01
Diabetes	156 (24)	190 (32)	<0.01
Heart Failure	192 (29)	271 (46)	<0.001
Hypertension	576 (88)	546 (92)	0.02
Major Bleeding	118 (18)	126 (21)	0.16
Myocardial Infarction	107 (16)	135 (23)	<0.01
Peripheral vascular disease	76 (12)	103 (17)	<0.01
Renal Disease	146 (22)	210 (35)	<0.001
Stroke/TIA	52 (8)	70 (12)	0.03
Hemoglobin	13 (2)	13 (2)	<0.01
Risk Scores (M, SD)			
CHA_2DS_2-VASc	4 (2)	5 (2)	<0.001
HAS-BLED	3 (1)	3 (1)	<0.01

Abbreviations; DOAC: Direct Oral Anticoagulant; TIA: Transient Ischemic Attack; COPD: Chronic Obstructive Pulmonary Disease; CHA2DS2-VASc: Stroke risk assessment; HAS-BLED: Bleeding risk assessment

impairment) that may influence meeting the recommended minutes of moderate exercise. In Model 3, we further controlled for a patient reported element, namely AFEQT. All statistical analyses were conducted using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 1,244 participants were included in this study. Participants were on average 76 years old, nearly half were women, and three-fifths did not graduate from college. The average body mass index of participants was 30 kg/m2. Approximately 14 % of the study sample were frail and 60 % had paroxysmal AF. Slightly over one-half of study participants (52%) engaged in moderate-intensity physical activity.

Factors Associated with Moderate Physical Activity

Women, those who were obese and morbidly obese, and those who had a history of anemia, asthma/COPD, diabetes, heart failure, hypertension, myocardial infarction, peripheral vascular disease, and renal disease were less likely to meet the recommended level of physical activity than respective comparison groups (Table 1). In addition, participants who were cognitively impaired, were socially isolated, had symptoms of anxiety and depression, experienced a fall in the past 6 months, were visually impaired, current smokers, and those with a lower AFEQT score were less likely to meet the working definition of moderate exercise than respective comparison groups(Table 2).

On the other hand, married participants, non-Hispanic whites, those with a college degree or higher, participants with a history of alcohol use and stroke/TIA, and those that were robust (not frail) and had a normal gait speed were more likely to engage in moderate-intensity physical activity (Tables 1and 2).

In our fully adjusted regression models, morbidly obese participants were 60 % less likely than participants with a normal BMI to engage in moderate activity (Table 3; adjusted OR [aOR]= 0.41; 95% CI= 0.23-0.73). Participants with slow gait speed (aOR= 0.44; 95% CI= 0.32-0.60),a medical history of renal disease(aOR= 0.68,90% CI= 0.48-0.96), who were cognitively impaired (aOR=0.74; 95% CI= 0.56-0.97), and participants with low social support (aOR=0.58; 95% CI= 0.40-0.84)were significantly less likely to meet the recommended level of physical activity than respective comparison group after adjusting for other potentially confounding variables (Table 3).Participants with a high AF related quality of life (AFEQT score >80) were two-thirds more likely to meet the recommended level of physical activity after adjusting for other covariates (Table 3).

Discussion

In our large cohort of older adults with NVAF, slightly more than one-half met current recommendations for participation in moderate physical activity. We showed that morbid obesity, slow gait speed, a medical history of renal disease, cognitive impairment, and social isolation were associated with a lower likelihood of engaging in moderate-intensity physical activity, while participants with a higher health related quality of life were more likely to meet these recommendations.

Extent of Engagement in Moderate Physical Activity

In our cohort, nearly half of older adults with AF reported that they did not engage in moderate-intensity physical activity. We postulate that patients' inability to engage in activity may be playing an important role with failing to meet these recommendations. SAGE-AF participants are older adults with a number and variety of comorbidities who may not have yet adapted to their condition and may be discouraged or reluctant to engage in various physical activities. In a study assessing quality of life among 161 patients with

Table 2: Baseline Psychosocial, Geriatric, and Patient Reported Characteristics ofParticipants According to Self-Reported Moderate Physical Activity: SAGE-AF Study

Baseline Characteristics	Moderate Physical Activity		
	Yes (n=652)	No (n=592)	P-value
Psychosocial and Geriatric			
Gait Speed (%)			
Normal	539 (83)	347 (59)	<0.001
Slow	111 (17)	245 (41)	
Frailty (%)			
Notfrail	391 (60)	22 (4)	<0.001
Pre-frail	248 (38)	411 (69)	
Frail	13 (2)	159 (27)	
Cognitive Impairment (MOCA≤23) (%)	229 (35)	299 (51)	<0.001
Social Isolation (%)	60 (9)	96 (16)	<0.001
Depression (PHQ9 ≥ 5) (%)	143 (22)	210 (36)	<0.001
Anxiety (GAD-7 ≥5) (%)	131 (20)	160 (27)	<0.01
Fall in Past 6 months (%)	126 (19)	144 (24)	0.03
Sensory Deficits (%)			
Visual Impairment	193 (30)	235 (40)	<0.001
Hearing Impairment	243 (37)	208 (35)	0.45
Patient Reported Outcomes			
AFEQT			
Score (M, SD)	84 (16)	76 (19)	<0.001
ACTS (M, SD)			
Burden Score	17 (6)	17 (6)	0.76
Benefit Score	11 (4)	10 (4)	<0.001
TTR (warfarin), mean, time (SD)	0.5 (0.4)	0.5 (0.4)	0.34
Health Behavior			
Current smoker (%)	15 (2)	20 (3)	0.14

Abbreviations; MOCA: Montreal Cognitive Assessment; PHQ9: Patient Health Questionnaire 9; GAD7: Generalized Anxiety Disorder; AFEQT: Atrial Fibrillation Effect on Quality of Life; ACTS: Anticoagulation Treatment Satisfaction; TTR: Time in Therapeutic Range

AF, approximately 90 % indicated that their condition affected their ability to perform regular daily activities.[28] In addition, patients with AF maybe misinformed about their ability to exercise, or even the guideline recommendations of engaging in moderate-intensity physical exercise and avoidance of chronic excess endurance exercise[11]. Older adults with AF may also lack information about how to be physically active while coping with other comorbidities, which may explain the large proportion of individuals in the present study who failed to report regular engagement in moderate physical activity. Therefore, healthcare providers should develop tailored interventions to improve the extent of engagement in moderate physical activity.

Factors Associated with Moderate Physical Activity

To the best of our knowledge, no previous study has examined factors associated with moderate physical activity among older adults with AF. In our study, morbidly obese participants with NVAF were less likely to engage in moderate-intensity physical activity than participants with a normal BMI. Prior studies in healthy individuals have shown that the higher the BMI, the greater the limitation in physical activity observed.[29,30] In addition, due to the various complications of obesity, including in spiratory muscle fatigue and restrictive ventilation, exercise can be very difficult in severely obese patients.[31-34] Therefore, clinicians need to play a crucial role in encouraging morbidly obese patients with AF to engage in some form of physical activity which would also result in the further benefit of weight loss in this high-risk population.

Slow gait speed and social isolation were associated with a lower likelihood of participating in moderate physical activity. Both gait speed and social isolation have been shown to be associated with longer time spent being sedentary, loss of capacity for daily living activities, and reduced time spent in objective physical activity.[35,36] It has been previously shown that healthy adults with high walking speed were more likely to meet recommended levels of physical exercise.[35] Also, interpersonal interactions and social participation were independently associated with physical performance among older adults. Social disengagement and decrease interpersonal interactions were associated with poor physical performance[37]. Health care providers should encourage social engagement and interpersonal interactions through participation in community fitness programs, such as group walks in neighborhoods, and in peer-delivered physical activity interventions which has been shown to increase physical activity behavior.[38]

In the present study, participants who were cognitively impaired were less likely to meet current recommendations for moderate exercise. We postulate that physicians may be more skeptical to engage cognitively impaired adults in their treatment as well as inform them about the importance of incorporating regular moderate exercise into their daily routines.

Participants with a medical history of renal disease were associated with a lower likelihood of participating in moderate exercise. In fact, reduced physical activity and sedentary lifestyle are common in patients with renal disease.[39] Due to the strikingly low physical activity among patients with chronic kidney disease (CKD),[40] detailed exercise guidelines for CKD patients have been published. Patients with CKD are recommended to engage in specific types of exercise and structured activities including strength, flexibility, and aerobic activities. [41] Health care providers should encourage AF patients with CKD to engage in these structured activities to the extent of meeting the recommended intensity of moderate physical activity.

Our study also showed that participants with high AF related quality of life were more likely to report being engaged in moderate activity than those with a low AF related quality of life. Indeed, in the prior study of 161 patients with symptomatic AF, improvement of AF-related symptoms and quality of life improved the physical health index among those who underwent catheter ablation [28]

Our findings have clinical relevance in managing older adults with AF. Since only one-half of older adults with AF reported participating in moderate exercise, health care providers need to encourage patients to partake in regular physical activity and inform them about the health benefits this may provide. In addition, health care providers should identify any physical function or social barriers, including obesity and social isolation, that may hinder meeting the recommended levels of physical activity. Identifying and addressing these "modifiable" factors may help in increasing the proportion of

Table 3: Factors Associated with Self-Reported Moderate Physical Activity: SAGE-AFStudy

	Model 1 Adjusted OR (95 % CI)	Model 2 Adjusted OR (95 % CI)	Model 3 Adjusted OR (95 % CI)
Socio-demographic			
Age (yrs)			
65-74	Ref.	Ref.	Ref.
75-84	0.71 (0.51, 0.97)	0.74 (0.53, 1.03)	0.73 (0.52, 1.02)
85+	0.51 (0.33, 0.79)	0.66 (0.42, 1.05)	0.63 (0.40, 1.00)
Sex (Female vs Male)	0.81 (0.60, 1.10)	0.88 (0.64, 1.21)	0.91 (0.66, 1.25)
Married (No vs Yes)	0.89 (0.69, 1.16)	0.97 (0.74, 1.27)	0.97 (0.74, 1.28)
Non-Hispanic White (Yes vs No)	1.25 (0.88, 1.78)	0.92 (0.63, 1.34)	0.90 (0.61, 1.32)
College Graduate (Yes vs No)	1.36 (1.06, 1.74)	1.19 (0.92, 1.55)	1.16 (0.89, 1.51)
Clinical			
Body Mass Index (BMI), kg/m²			
Normal	Ref.	Ref.	Ref.
Overweight	0.90 (0.64, 1.27)	0.88 (0.62, 1.25)	0.86 (0.60, 1.23)
Obese	0.72 (0.51, 1.02)	0.70 (0.49, 1.00)	0.71 (0.50, 1.02)
Morbidly Obese	0.35 (0.20, 0.61)	0.39 (0.22, 0.70)	0.41 (0.23, 0.73)
Type of AF (%)			
Paroxysmal	Ref.	Ref.	Ref.
Persistent	0.98 (0.73, 1.31)	0.99 (0.74, 1.34)	1.04 (0.77, 1.30)
Permanent	0.69 (0.41, 1.17)	0.61 (0.36, 1.04)	0.65 (0.38, 1.11)
Medical History			
Alcohol Use	1.32 (0.97, 1.78)	1.16 (0.85, 1.59)	1.12 (0.81, 1.54)
Anemia	1.03 (0.78, 1.35)	1.08 (0.82, 1.44)	1.07 (0.81, 1.42)
Asthma/COPD	0.82 (0.62, 1.10)	0.86 (0.64, 1.16)	0.91 (0.67, 1.22)
Diabetes	0.95 (0.69, 1.31)	1.01 (0.72, 1.41)	0.99 (0.71, 1.38)
Heart Failure	0.69 (0.51, 0.94)	0.79 (0.57, 1.09)	0.83 (0.60, 1.15)
Hypertension	0.91 (0.60, 1.39)	0.99 (0.63, 1.53)	0.95 (0.61, 1.48)
Myocardial Infarction	0.78 (0.55, 1.10)	0.73 (0.51, 1.04)	0.72 (0.51, 1.03)
Peripheral vascular disease	0.78 (0.54, 1.14)	0.79 (0.53, 1.16)	0.78 (0.53, 1.14)
Renal Disease	0.76 (0.54, 1.06)	0.71 (0.50, 1.00)	0.68 (0.48, 0.96)
Stroke/TIA	0.78 (0.48, 1.25)	0.83 (0.50, 1.35)	0.78 (0.48, 1.29)
Risk Scores			
CHA_2DS_2-VASc	1.05 (0.90, 1.22)	1.08 (0.92, 1.27)	1.09 (0.93, 1.28)
HAS-BLED	0.94 (0.79, 1.11)	0.98 (0.82, 1.17)	1.00 (0.84, 1.20)
Geriatric Elements			
Gait Speed			
Normal		Ref.	Ref.
Slow		0.45 (0.33, 0.61)	0.44 (0.32, 0.60)
Cognitive Impairment (MOCA)		0.75 (0.57, 0.99)	0.74 (0.56, 0.97)
Social Isolation		0.55 (0.38, 0.81)	0.58 (0.40, 0.84)
Depression (PHQ-9 ≥ 5)		0.68 (0.49, 0.94)	0.76 (0.55, 1.05)
Anxiety (GAD-7 ≥5)		0.85 (0.61, 1.20)	0.93 (0.66, 1.31)
Fall in the Past 6 months		0.92 (0.68, 1.24)	0.96 (0.71, 1.30)
Visual Impairment		0.82 (0.63, 1.07)	0.85 (0.65, 1.12)
Patient Reported Outcome			
AFEQT >80			1.64 (1.25, 2.16)

Model 1: Adjusting for sociodemographic and clinical factors and smoking status; Model 2: M1 + Geriatric Elements; Model 3: Model 1 + Model 2 + patient reported outcomes; Abbreviations:TIA: Transient Ischemic Attack; CHA2DS2-VASc: Stroke risk assessment; HAS-BLED: Bleeding risk assessment; MOCA: Montreal Cognitive Assessment; PHQ-9: Patient Health Questionnaire 9; GAD-7: Generalized Anxiety Disorder; AFEQT: Atrial Fibrillation Effect on Quality of Life.

those engaging in moderate exercise. Lifestyle counseling, including risk factor modification, and patient-centered communication should also be the focus of health care providers in order to improve engagement among older adults with AF.

Study Strengths and Limitations

Our study has several strengths and limitations. First, we included a large and diverse cohort of older adults with NVAF. Second, this study is unique in examining the impact of various geriatric elements, as well as patient reported elements such as AFEQT,that may influence physical activity. Third, we used the Minnesota Leisure Time Physical Activity (LTPA) Questionnaire, a validated questionnaire, to assess physical activity. Alimitation of the present study, however, is that physical activity was self-reported. Subjective methods of physical activity assessments among healthy adults tend to overestimate actual participation in physical activity compared with objective methods of assessment[42] In addition, our study participants are mostly non-Hispanic whites which limits the generalizability of our findings to other study populations. Finally, no causal inferences can be made, and we cannot determine the directionality of the associations since this analysis was cross-sectional in design.

Conclusions

A considerable proportion of older adults with NVAF did not report being engaged in moderate physical activity. Participants who were morbidly obese, cognitively impaired, had a slow gait speed, had a medical history of renal disease, and were socially isolated were less likely, while those with a higher AFEQT score were more likely, to meet these activity recommendations. Our findings provide information for healthcare providers to assessfactors that influence the engagement of older men and women with NVAF in moderate - intensity physical activity and reinforces the need for sustained efforts by healthcare providers to ensure better engagement of their older patients in regular moderate-intensity physical activity which may reduce patient's symptoms of AF and improve their quality of life.

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Editorial

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Physical Inactivity Among Older Adults with Atrial Fibrillation: Prime Time to Get Active!

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Editorial

Atrial fibrillation (AF) affects more than 3 million Americans, with estimated prevalence of nearly 10% in 65 years and older[1]. The prevalence of the disease increases steeplyin the elderly, affecting nearly 12% in 75–84 years, and approximately 1/3 in 80 years or older. The current estimated global burden of the disease is more than 33.5 million[2]. With increasing disease incidence by approximately 5 million each year worldwide, there is urgent need to identify and address associated risk factors [3]. In the recent CABANA trial, with over 2100 patients, the median Atrial Fibrillation Effect on Quality of Life (AFEQT) score was just 63 (Interquartile 25-75%: 48-80) suggesting more than 75% of the patients were moderate to severely symptomatic affecting their quality of life[4]. The toll of AF in overall health and quality of life that it poses cannot be overemphasized.

Over the last two decades, our understanding on AF has much advanced and a number of risk factors have been identified[1,5]. While some risk factors are non-modifiable such as age, male gender, single or polygenic (heritable or de-novo) inheritance, important modifiable risk factors have also been identified. In addition to metabolic syndrome, obesity, sleep apnea, hypertension, chronic kidney disease, diabetes mellitus, cigarette smoking, and depression, physical inactivity has been identified among the most potent modifiable risk factor[1,6]. In a CARDIO-FIT study, Pathak et al have shown that a tailored exercise program designed for age and physical ability involving combination of aerobic and resistance/strength exercises for progressive fitness, every METs gained from baseline was associated with 9% decline in risk of AF recurrence[7]. Hence the role of risk factors management including structured moderate physical activity and weight loss cannot be over stated.

In this issue of JAFIB, Mehawej, J et al report onfactors associated with lower levels of moderate intensity physical activity in acohort of elderly patients.Assessing physical activity in real life is challenging as it is associated with inaccuracies and often exaggerated due to recall bias. A strength of the study is the use of the Minnesota Leisure Time Physical Activity questionnaireto assess the level of physical activity[8]. This instrument has been validated and correlates positivelywith level of cardiorespiratory fitness[9].The use of the Cardiovascular Health Study frailty scale is another strength of the study. This instrument was developed based on the Cardiovascular Health Study, where frailty phenotype (defined as presence of ≥ 3: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity) was independently predictive of incident falls, worsening mobility, hospitalization and deaths (adjusted HR: 1.29–2.24)[10]. Depending on the tool of assessment, prevalence of frailty has been described in up to 75% of the elderly patients with AF[11]. Evaluating frailty in patients with AF is important as it has been associated with increased mortality, higher symptom burden, poor success to ablation therapies, and higher incidence of bleeding on oral anticoagulation[11,12].

Another strength of this study is the gender makeup of the population, withnearly 50% of the study participants being women.While the age adjusted prevalence of AF in US has been reported to be 0.9% in females compared to 2.4% in male, female gender has been underrepresented in the majority of major clinical trials[13]. In theCABANA trial assessing the effect of catheter ablation vs medical therapy on quality of life in AF patients, only 37% of the subjects were female[4]. Similarly, in the HUNT study,assessing the physical activity and cardiovascular outcome in AF patients, only 31% were females[14]. The Cardiovascular Health Study whichassessed the physical activity and incidence of AF in older adults had better female participation, about 56%. In that study women had lower rate of participation in recommended physical activity and were older compared to males[14,15]. It is important to highlight that the level of physical activity can have gender specific impacts on outcome. In a recent meta-analysis, women were shown to benefit from all level of physical activities, whereas in males, up to moderate physical activity was beneficial but vigorous activities were associated with higher incidence of AF[16].

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As in most trials, African American, Asian American and Hispanics are underrepresented in this study also. With little data, the true incidence and prevalence of the disease in these population is hard to ascertain. Despite higher prevalence of known risk factors as hypertension, obesity, diabetes in African Americans and Hispanics, the incidence of AF may be lower in these population although these populations are underrepresented in majority of trials and population-based studies[1]. In The Cardiovascular Health Study assessing physical activity and incidence of AF in older population, only 17% of the participants were nonwhite15. Even in the Multiethnic Study of Atherosclerosis (MESA), only 42.9% of the participants were non-white highlighting the disparity in representing these population, with AF incidence of 3.4% over a median follow-up of 5.3 years[17].

Too many Americans are sedentary. In a Center for Disease Control (CDC) survey from 2014, nearly 27% of individuals between ages 65-74 years old and nearly 35% aged ≥75 years old were physically inactive or reported no physical activity outside of their work18. In current study by Mehawej, J et al, the results are even more sobering as nearly 50% of the adults above 65 years are engaged in less than the recommended physical activity. Regardless, both of these studies highlight the importance of exercise as a readily available tool that is highly effective in improving AF outcomes yetis much underutilized. In the same CDC survey, as the number of chronic diseases, identified as stroke, coronary heart disease, arthritis, cancer (excluding skin cancer), chronic obstructive pulmonary disease (COPD) and depression burden increased, the level of physical activity was more limited[18]. Besides the CDC identified risk factors for reduced physical activity in elderly population, the investigators have identified factors pertaining to elderly AF patients that includes morbid obesity, renal disease, slow gait speed, cognitive impairment and social isolation.

As in any cross-sectional study, it is a limitation that direction ofcause-and-effectcannot be determined and relationships may be complex. Obesity has been associated with poor self-esteem, depression, and social isolation which in turn likely limit the much-needed physical activity in these patients and perpetuate obesity and its related complications[19]. On the other hand, there is increasing evidence that depression and physical inactivity interact in both directions leading to poor cardiovascular health outcomes[20].

This study has clearly identify that physical inactivity is rampant in elderly patients with AF. How to improve this?In patients with multiple forms of cardiovascular disease including acute myocardial infraction, congestive heart failure, coronary artery bypass and open-heart surgery, cardiac rehabilitation programs with graded exercise are safe and effective. A number of smaller studies have showncardiac rehabilitation in patient with AF is also safe and effective in improving cardiovascular outcomes[7,21,22]. Asevidence builds of the safety and efficacy of moderate intensity physical activity in patients withAF, it is prime time to institute it in our practice. Increasing awareness of potential benefits of physical activity in this population is critical. Adults who remain physically activein their mid-life are likely to remain active and have better health outcomes later in their life so promoting these activities in early or mid-adulthood will have a lasting impact in our growing elderly population[23]. As shown by Pathak R et al, aggressive risk factors reduction such as weight loss, moderate intensity physical activity, blood pressure, lipid and sleep disorder managementwereassociated with long term arrhythmia free survival[24]. Programs designed to engage individuals at community level such as community fitness programs, peer delivered physical activity, neighborhood group walks programs can be effective to encourage physical activity and break social isolation to improve cardiovascular health outcomes[25,26]. Also, similar programs to increase awareness and incorporateroutine scheduled physical activities in long term care facilities can benefit substantial elders as approximately 6% of the US population get help or live in some form of assisted or long-term care facilities.

It has been reported that excessive endurance activities can lead to increased incidence of AF. But how much should we be concerned about urging increasing activity, given the evidence that "excessive endurance exercise" can worsen AF? In Finnish veteran orienteers with history ofhigh endurance activity (an average military training history of 36 years),the incidence of lone AF was 5.3% compared to control of 0.9%and those between the age of 63-70 years had anincidence of 6.6%[27]. In a study of elderly Norwegian men between the age of 65-90 years with history of long-term endurance sport (average 33 years of systematic endurance training, in average competed 17cross-county ski races)had 6% (95% CI: 0.8-11.1) added risk compared to general population of the similar age group[28]. These vigorous activities included long range cycling, marathon running and high endurance sports, are not applicable to most of our elderly patients[29]. Several studies have shown a U-shaped response with the intensity of physical activity and increased risk of AF when cumulative hours of vigorous endurance sports activity are >1500-2000 hours or >5 hours per week[30-32]. Very few elderly patients areengaging in these high levels of endurance activity. While recognizing this impact is important for the tiny minority of AF patients who run marathons or involve in high endurance activity, for the vast majority of our patients, helping them get off the couch and get moving is one of the most important interventions we can offer.

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Why is the Tilt Table Test Still Useful to Define who Should or Should Not Get A Pacemaker with Vasovagal Syncope?

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Abstract

The the tilt table test (TTT) has been used identify appropriate candidates for pacing in the majority of randomized trials. However, in recent years, it has been claimed—based largely on International Study on Syncope of Uncertain Etiology (ISSUE) studies—that the TTT demonstrates only a weak correlation with the mechanism documented by implantable loop recorder (ILR) at the time of syncope and thus confounds the correct diagnosis. Thus, cardiac pacing was supported in patients with recurrent vasovagal syncope (VVS) in whom clinically relevant asystole had been documented by ILR. In the present Editorial, we tried to discuss potential role of TTT in diagnostic workflow of VVS based on current data.

Introduction

Vasovagal syncope (VVS) is a clinical condition related to brady cardia (cardioinhibitory response) and/or hypotension (vasodepressor response), likely mediated by parasympathetic activation and sympathetic inhibition. Although clinical presentation is usually associated with a situational, isolated and/or self-limited event, in some cases, VVS might be recurrent, unpredictable and debilitating. There is still no specific medical therapy has been proven widely effective. For a long time, evidence of severe cardioinhibition on the tilt table test (TTT) in association with VVS has been used to offer permanent pacing to combat bradycardia/asystole [1]. However, its value has been debated. The temporal causative association of bradycardia with syncope by using TTT may help identify which patient could benefit from pacing but the timing and type of pacing in lieu of blood pressure changes may be critical. This brief review discusses randomized pacing trials in VVS and what we have learned about selection of patients for pacing benefit.

Trials of Pacing in Vasovagal Syncope

The first randomized controlled trial compared pacing with medication or no treatment (VPS I) was published in 1999 and were followed by 2 others (VASIS and SYDIT) including patients with documented evidence of severe cardioinhibition by TTT [2-4]. Although those studies demonstrated very encouraging results, following 2 trials (VPS II and SYNPACE) compared pacing "off" and "on" showed no pacing benefit [5,6]. As an important point, a rate-drop response pacemaker was implanted in all those studies. Although there is a trend in favour of active pacing in prolonging the time to first recurrence, especially for those patients who had had an asystolic response during TTT, a high percentage of patients with recurrent tilt-induced VVS continued to have syncopal relapses despite active cardiac pacing in SYNPACE trial [6]. Inefficacy of active pacing in preventing syncopal recurrence and placebo effect of inactive pacing were considered the main causes of negative results of pacemaker implantation by authors. However, in these two double-blind trials, patient selection failed to include documented evidence of severe cardioinhibition (Table 1).

In recent years, it has been claimed—based largely on International Study on Syncope of Uncertain Etiology (ISSUE) studies—that the TTT demonstrates only aweak correlation with the mechanism documented by implantable loop recorder (ILR) at the time of syncope and thus confounds thecorrect diagnosis [7-9]. Thus, cardiac pacing was supported in patients with recurrent vasovagal syncope (VVS) in whom clinically relevant asystole had been documented by ILR [10].Furthermore, some groups have argued that TTT for the workup of syncope should be abolished because the TTT fails to establish an explicit cause of syncope [11].

The double-blinded, randomized ISSUE-3 trial showed that dual-chamber rate-drop response cardiac pacing was effective in reducing the recurrence of syncope in patients ≥40 years with severe asystolic VVS documented by ILR, with the risk of syncope recurrence reduced from 57 % to 25 % (P=0.039) [8].To investigate the role of TTT response in predicting syncopal recurrence in the ISSUE-3 population, patients

Key Words
Atrial fibrillation,Vasovagal syncope, Cardioinhibition

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Table 1: Summary of Randomized Trials Evaluating the Utility of Pacing in Vasovagal Syncope*

Trial	PM	Age for inclusion/ mean age	Case number	TTT	ILR	Type	Results	Limitation
VPS I[1]	**RDR**	**>18 / 43**	**27 in PM 27 in CT**	**HR <60 bpm or HR <70 bpm (≤2 mcg/min isoproterenol) HR <80 bpm (>2 mcg/min isoproterenol)**	**(-)**	**NB PM vs CT**	**Presyncope was similar 84% relative risk reduction in syncope**	**Placebo effect Early termination Baseline difference between groups**
VASIS[2]	RDR	>40 or <40 in refractory syncope/ 64 in PM 56 in CT	19 in PM 23 in CT	VASIS type 2A or type 2B	(-)	NB PM vs CT	Syncope 5% in PM 61% in CT	Placebo effect Mean age was higher in PM group 64 vs 56
SYDIT[3]	RDR	> 35 / 58	46 in PM 47 in CT	HR <60 bpm	(-)	NB PM vs atenolol	Syncope 4.3% in PM 25.5% in MT	Mean age was higher in PM group 61 vs 55 Study was stopped early
VPS II[4]	RDR	>19/ 50	52 in ODO 48 in DDD	HRXBP <6000/min X mmHg	(-)	DB Pacing on vs off	Syncope 40% in ODO 31% in DDD (no difference)	Each center used its own HUT protocol
SYNCPACE[5]	RDR	>18/ 52	16 in pace on 13 in pace off	(+) TTT response	(-)	DB Pacing on vs off		Study was stopped early due to VPS II
ISSUE 2[6]	RDR	>30/ 66	47 in pacing 50 in CT	88% TTT response was not an inclusion criterion	(+)	NB PM vs CT	Syncope 5% in pacing 41% in CT	Old age Typical presentation for VVS was seen in 41% No prodrome in 50%
ISSUE 3[7]	RDR	≥40/ 63	38 in pace on 39 in pace off	87% TTT response was not an inclusion criterion	(+)	DB	Syncope 57% in pacing off 25% in pacing on (P=0.039)	Typical presentation for VVS in only 47% of cases Uncertain presentation in 53%
ISSUE 3 sub-analysis[8]	RDR	≥40/ 62	76 in TTT (4) 60 in TTT (-)		(+)	DB	Syncope 31% in TTT (+) 4% in TTT (-)	Typical presentation for VVS in only 52% of cases Atypical ILR response in 28%
INVASY[12]	CLS	>18/ 58	2:1 DDD-CLS (17 patients) to DDI ratio (9 patients)	Type 2A or 2B	(-)	SB DDD vs DDI	Syncope 0% in DDD 44% in DDI (no difference)	Study was stopped early Variable follow up time
Russo V[13]	CLS	>40/ 53	50 patients Crossover	Type 2B	(-)	SB CLS on vs off	Syncope 2% during CLS on 16% during CLS on	Carryover effect
SPAIN[11]	CLS	≥40/ 56	DDD → DDI (21 patients) vs DDI → DDD (25 patients)	A HR <40 bpm for at least 10s or >3 s pause	(-)	DB	Syncope 8.7% in DDD 46% in DDI (37% absolute risk reduction)	A >50% reduction in syncope frequency was selected as the primary efficacy outcome

BP, blood pressure; CLS, closed loop stimulation; CT, conventional treatment; DB, double-blind; HR, heart rate; ILR, implantable loop recorder; INVASY, Inotropy Controlled Pacing in Vasovagal Syncope; ISSUE, Third International Study on Syncope of Uncertain Etiology; MT, medical treatment; NB, non-blinded; PM, pacemaker; RDR, rate drop response; SB, single-blind; SPAIN, Closed Loop Stimulation for Neuromediated Syncope; SYNPACE, the vasovagal Syncope and Pacing Trial; SYDIT, SyncopeDiagnosisandTreatment; TTT, tilt table test; VASIS, vasovagal syncope international study; VPS, the North American Vasovagal Pacemaker Study; VVS, vasovagal syncope.
*SyncopeUnit Project (SUP) trialsareexcluded in theanalysisbecausethepatientswithcarotidsinussyncopewerealsoincluded in thesestudies.

with asystole documented by ILR who received a pacemaker were divided into 2 groups: TTT was positivein 26 and negative in 26[9]. Although authors defined that patients with TTT (+) and TTT (-) had similar characteristics, patients were older at the time of first syncope in the TTT (-) group (48 vs 42). This older age in TTT (-) group is inconsistent with the classical presentation of VVS in which the first syncope episode typically occurs before the age of 40 years[4]. Furthermore, typical vasovagal presentation was also lower in TTT (-) group (42% vs 58%). Syncope recurred in 8 TTT (+) and in 1 TTT (-) patients (P=0.004). At multivariable analysis, TTT (+) and total number of events were the only independent predictor of syncope recurrence.

On the contrary, double-blinded, randomized SPAIN trial supported the clinical utility of TTT in VVS population [12]. Patients were aged ≥40 with TTT confirmed cardioinhibitory response: bradycardia <40 bpm during >10 s or asystole >3 s, as per the Vasovagal Syncope International Study classification were included in the study. Mean age was 56.30 ± 10.63 years and significantly younger than ISSUE population. Only 8.7% of 46 patients who received dual-chamber pacing with closed loop stimulation suffered syncopal events, compared to 46% randomized to the sham DDI mode with an relative risk reduction of 89% and an absolute risk reduction of 37% ($p < 0.0001$). High clinical efficacy of closed loop stimulation system was compatible with previous single-blind randomized controlled trials [13,14].

How should We Interpret Disparateresults of Pacing Studies?

Considering older age, atypical presentation with no or subtle prodrome, and lack of recognizable triggers of cases in ISSUE 3, we can speculate that positive effect of pacing in TTT (-) cases might be

associated with non-reflex nature of syncope, and may have had sinus node dysfunction. TTTdemonstrated true reflex syncope cases, but pacing support with rate-drop response pacemaker, even at faster rates, may be too little and too late to counteract reflex arc and prevent the event. Thus, beside patient's characteristic and sinus node dysfunction, pacing method (closed loop stimulation vs. rate-drop response) might be another plausible explanation for the different results between SPAIN and ISSUE 3. Furthermore, SPAIN trial did not select patients on relative absence of prodrome or predominant vasodepressor response in contrast to ISSUE-3.

In a recently published study, by using TTT, Dijk et al [15] revealed that cardioinhibition is observed in 91% of patients at a median time of 58 seconds before syncope episode. Furthermore, at the onset of cardioinhibition, median heart rate was at 98 bpm higher than baseline. Cardioinhibition thus initially only represented a reduction of the corrective heart rate increase. At the time of syncope, stroke volume had a strong negative effect on blood pressure, total peripheral resistance a lesser negative effect, while heart rate had increased (all $p<0.001$). Thus, by detecting local impedance in the right ventricle which may relate to contractility, closed loop stimulation may evaluate autonomic function and improve the timing for onset of pacing. Also, the effect of cardiac pacingin asystolicTTT (+) patients who did not achieve the end point ofan ILR event documentation was not studied in the ISSUE III trial. Theoretically, these patients couldhave a better outcome with a pacemaker.

Although ISSUE trials suggest that among patients with ILR documented asystole during VVS, pacing efficacy was primarily of value in those individuals without evident vasodepressor susceptibility, it is not possible to quantify how much vasodepression and cardioinhibition contribute to cerebral hypoperfusion with ILR. By using TTT with continuous electroencephalographic monitoring, temporal relationships of vasodepression and cardioinhibitionmight be determined [15]. If asystole starts after the onset of syncope or within 3 s of syncope, it cannot be the main cause of syncope. Thus,we can avoid pacing without benefit by defining the timing of syncope.However, one plausible confounder contributing to the less than predictable nature of clinical response to pacemaker is the relative contribution of vasodepression and cardioinhibition at different times in a given patient may be variable.

Guidelines

Although many of the treatment recommendations were grossly similar between the European and U.S. guidelines, there were key differences noted in recommendations for patients with syncope [10, 16]. Both guidelines recommend pacemaker implantation for patients with recurrent reflex syncope older than age 40 years and evidence of symptomatic pauses for at least 3 s, or asymptomatic pauses for at least 6 s [10,16]. However, spontaneous asystole in patients with reflex syncope received a slightly different class of recommendation in the U.S. guidelines (Class IIb) when compared with the European guidelines (Class IIa) [10,16].

Although each of the guidelines define reflex syncope encompassing VVS, carotid sinus syndrome (hypersensitivity), and situational syncope, the European guidelines also describe adenosine-sensitive syncope in which the patients often present without prodrome, have a structurally normal heart, normal ECG, and a negative response to TTT [10,16]. Thus, the European guidelines also provide Class IIb recommendations for pacing in patients older than age 40 years with tilt-induced asystolic response and frequent unpredictable recurrent syncope, and in patients with clinical features of adenosine-sensitive syncope, without direct parallel U.S. recommendations [10, 16]. The subtlest change in the European guidelines was related to TTT. Recommendation of TTT dropped from I B to IIa B–and the diagnostic criteria indication falled from I to IIa. In addition, its lack of ability to direct management is maintained [16]. Application of TTT was still considered useful for assessing vasodepressor component, differential diagnosis of epilepsy and psychogenic pseudosyncope.

The Existing Knowledge Gaps

Despite existence of randomized controlled trials outlined above, there is still several knowledge gaps. The exact mechanism of VVS and underlying hemodynamics need further studies.A well-performed TTT may clarify pathophysiology of VVS by demonstrating the temporal relationship among vasodepression, loss of consciousness, and cardioinhibition [17].

By using an algorithm to predict VVS during TTT based on the simultaneous analysis of heart rate and beat-to-beat systolic blood pressure, a sensitivity of 97.6% and a specificity of 88.2% might be achieved in VVS [18]. The data is scarce whetherpacing is useful for those under the age of 40 years with recurrent VVS associated with severe bradycardia and/or asystole or not. We need more data which patients with VVS over 40 years of age may more benefit from pacing. It should be investigated whether TTT combined with ILR monitoring may provide better insights to select the best candidates for pacing in VVS. Finally, the best pacing algorithm and how it is it best to programme the pacemaker for better success in VVS patients need further investigation.

Preliminary results of the double-blind, randomized, and placebo-controlled BIOSync trial (NCT02324920) was presented at the European Society of Cardiology Congress 2020 [19,20]. The trial conducted across 24 sites in Europe and Canada with a medium follow-up of 11.2 months. When comparing the CLS-paced group versus the control group, syncope recurrence rate and the combined rate of syncope and/or pre-syncopewere reduced by 77% and by 56% in a medium follow-up of 11.2 months.Although the use of TTT to select patients with severe recurrent VVS for cardiac pacing was controversial until this study, the positive results of this trial demonstrate that asystolic response to HUT is a valuable criterion for cardiac pacing.

As an emerging therapy, catheter ablation of cardiac of ganglionic plexi (cardioneuroablation) provided promising observational data in patients with cardioinhibitory type VVS and vagally mediated bradycardia [21-26]. In all cohorts related cardioneuroablation, VVS cases were included in the study according to TTT results. Furthermore, we recently demonstrated that TTT seems as a valuable diagnostic tool not only to select suitable candidates and but also toevaluate success of cardioneuroablation [24]. Fifty-one consecutive patientswith VVS were included in the study. After confirmation of >3 s asystoleon TTT, all

patients underwent cardioneuroablation. TTT was repeated 1 and 6 months after cardioneuroablation.The main outcome measures were recurrence of syncopeepisode and positive response on TTT. Repeated TTTs were negative in 44 (86.2%)patients. When patients with recurrent syncope were excluded, vasodepressor response was seen in three casesand cardioinhibitory response in one case, respectively. Cardioneuroablationcaused significant and durable shorteningof RR interval in all cases. This effect was significantly higher in patients without positive TTT responses.

Conclusions

TTT can be helpful to predict outcome of pacing with respect to syncope recurrence which can lead physicians away from implantation of an ineffective rate drop responsepacemakers in this scenario. It may also demonstrate the patients who benefit from dual-chamber closed loop stimulation pacing.

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Predictors of Acute Atrial Fibrillation and Flutter Hospitalization across 7 U.S. Emergency Departments: A Prospective Study

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Abstract

Introduction: International rates of hospitalization for atrial fibrillation and flutter (AFF) from the emergency department (ED) vary widely without clear evidence to guide the identification of high-risk patients requiring inpatient management. We sought to determine (1) variation in hospital admission and (2) modifiable factors associated with hospitalization of AFF patients within a U.S. integrated health system.

Methods: This multicenter prospective observational study of health plan members with symptomatic AFF was conducted using convenience sampling in 7 urban community EDs from 05/2011 to 08/2012. Prospective data collection included presenting symptoms, characteristics of atrial dysrhythmia, ED physician impression of hemodynamic instability, comorbid diagnoses, ED management, and ED discharge rhythm. All centers had full-time on-call cardiology consultation available. Additional variables were extracted from the electronic health record. We identified factors associated with hospitalization and included predictors in a multivariate Poisson Generalized Estimating Equations regression model to estimate adjusted relative risks while accounting for clustering by physician.

Results: Among 1,942 eligible AFF patients, 1,074 (55.3%) were discharged home and 868 (44.7%) were hospitalized. Hospitalization rates ranged from 37.4% to 60.4% across medical centers. After adjustment, modifiable factors associated with increased hospital admission from the ED included non-sinus rhythm at ED discharge, no attempted cardioversion, and heart rate reduction.

Discussion: Within an integrated health system, we found significant variation in AFF hospitalization rates and identified several modifiable factors associated with hospital admission. Standardizing treatment goals that specifically address best practices for ED rate reduction and rhythm control may reduce hospitalizations.

Key Words:

Atrial Fibrillation, Atrial Flutter, Predictors Of Hospitalization, Variation, Heart Rate, Electric Cardioversion, Emergency Medicine

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Introduction

Atrial fibrillation (AF) and flutter (AFL) (combined: AFF) impair quality of life, heighten the risk of ischemic stroke, and complicate the course of congestive heart failure.[1-5] These age-related atrial dysrhythmi as are growing in prevalence with the aging of the U.S. population and the increasing prevalence of chronic heart disease.[6] In

the coming years, the substantial public health and economic burden associated with AFF will only rise. Driven primarily by hospitalizations, the annual health care costs exceed $6 billion in the U.S.,[7] and have continued to increase for this population.

While AFF is the same disease globally, hospitalization rates of emergency department (ED) patients with AFF vary dramatically between countries, ranging from approximately 25% in the U.K. to nearly 70% in the U.S. with geographical variations.[8] Even within countries, inter-facility hospitalization can vary widely, ranging from 3% to 97% within one Canadian province.[9] The degree to which physician experience, medical treatments, and ED factors contribute to the variation in AFF hospitalization is poorly understood.[9,10] A study by Lin et al. found that one-fifth of variation in U.S. hospitalizations from 2006-2011 was due to the hospital site and not hospital characteristics, suggesting that institution-specific practice culture contributes significantly to variance in ED hospitalization for AF.[11] Further contributing to the variation in hospitalization is the lack of international multidisciplinary consensus guidelines for AFF care for ED providers to call upon.[12-14] Several studies have developed scoring tools to risk-stratify patients to identify who would benefit from admission, includingTrOPs-BAC (Troponin, Other acute ED diagnosis, Pulmonary disease, Bleeding risk, Age> 75yo and evidence of Cardiac failure) and RED-AF (Risk Estimator Decision aid for Atrial Fibrillation) risk stratification scoring systems.[15,16] However, no single risk stratification instrument has been widely adopted by emergency providers.

Given the variation in AFF hospitalization and the need to better identify modifiable management factors, we undertook a multicenter, prospective observational study within an integrated healthcare system in the western U.S. to evaluate AFF hospitalization practice patterns.We expected that patient-level factors leading to variations in AFF hospitalization rates would be more evident within a single system. We also examined hospital- and physician-level predictors of hospitalization. As follow-up care is more easily coordinated within an integrated care system, thereby facilitating home discharge from the ED, we hypothesized that hospitalization would be lower than the U.S. western average (57%) in this setting and would primarily vary at the patient-level by patient case-mix,[8] with hospitalization associated with higher acuity patients and failure to achieve rate and rhythm control more than with physician or hospital variables.

Methods

Study Design, Setting, and Population

This analysis was part of a larger prospective multicenter observational study, TAFFY (Treatment of AFF in emergencY medicine) conducted in 7 Kaiser Permanente Northern California (KPNC) urban community EDs between May 2011 and August 2012.[2] These urban community EDs are part of a large integrated healthcare system providing comprehensive medical care to health plan members who are highly representative of the demographic diversity of the surrounding and statewide population and represent approximately 33% of the population in areas served.[17]

Study hospitals are non-rural urban community hospitals with a trauma designation at the time of Level III or less. Annual census ranged from 25,000 to 85,000, and inpatient bed capacity ranged from 116 to 340. Several medical centers were affiliated teaching facilities for emergency medicine (n=3) and internal medicine residency training programs (n=2), and one was a primary teaching facility for internal medicine. All hospitals allowed short-term (<24 hours) inpatient observational status. Three had an outpatient short-term clinical decision area, two of which were managed by hospitalists and one by emergency physicians. All 7 medical centers had an intensive care unit that provided cardiac care, and on-call cardiology was available to the ED around the clock. Each medical center in the system uses a comprehensive, integrated electronic health record (EHR; Epic, Verona, WI), which includes inpatient, outpatient, emergency, pharmacy, laboratory, and imaging data.[18] Additionally, all centers had around-the-clock pharmacy services available for the dispensing of medications on site and the involvement of a pharmacy-led, telephone-based anticoagulation service for close follow-up and serial monitoring.[19]

Hospitalization decisions were made by residency-trained and board-certified (or board-prepared) emergency medicine and hospitalist faculty (not residents). During the study period, No policies were in place at the participating medical centers during the study period to govern the hospitalization decision-making or overall management of patients with AFF. Patient care was left entirely to the discretion of the treating physicians.[2]

Prospective study enrollment was undertaken via convenience sampling by treating ED physicians using either a two-page paper sheet or an electronic template.[20] Adult (≥18 years) KPNC health plan members in the ED with electrocardiographically-confirmed nonvalvular AFF were eligible for enrollment if their atrial dysrhythmia was either symptomatic (including newly diagnosed) or treated in the ED. Patients were ineligible for the study if they transferred in from another ED, were receiving palliative-only comfort care, had

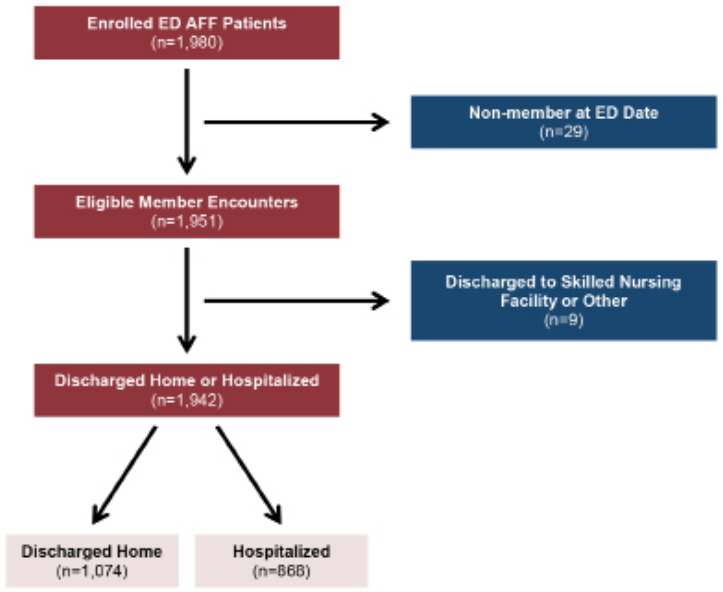

Figure 1: Derivation of Hospitalization Study Cohort from TAFFY Study Cohort

ED, Emergency department; AFF, atrial fibrillation or flutter

Table 1: Demographics of emergency department patients with atrial fibrillation or flutter, stratified by hospitalization.

Patient Characteristics	Total, n=1,942	Hospitalized, n=868 (44.7%)*	Discharge to Home, n=1,074 (55.3%)*	P-value†
Age at ED Visit, years				
Mean (SD)	70.7 (13.8)	74.3 (12.7)	67.9 (14.0)	<0.0001
Categorical				
< 45	72 (3.7)	13 (1.5)	59 (5.5)	<0.0001
45-64	526 (27.1)	183 (21.1)	343 (31.9)	
65-74	493 (25.4)	201 (23.2)	292 (27.2)	
≥ 75	851 (43.8)	471 (54.3)	380 (35.4)	
Female Sex	985 (50.7)	456 (52.5)	529 (49.3)	0.16
Race				<0.01
Asian	144 (7.4)	76 (8.8)	68 (6.3)	
Black/African American	161 (8.3)	88 (10.1)	73 (6.8)	
White/European	1,566 (80.6)	675 (77.8)	891 (83.0)	
Other/Unknown	71 (3.7)	29 (3.3)	42 (3.9)	
Low Socioeconomic Status[a]	335 (17.3)	172 (19.8)	163 (15.2)	<0.01

ED, emergency department
* n (%) except where noted
† P-values from chi-square likelihood ratio tests for all categorical comparisons. For comparison of means of continuous variables, Student t-tests are reported.
a Socioeconomic status defined by census tract (see text for details).

an implanted cardiac pacemaker/defibrillator, or had just been resuscitated from cardiac arrest. For this analysis, those discharged to another facility outside of the healthcare systemwere excluded to assure complete capture of the outcome. This practice was uncommon in this setting.

To assess for selection bias, we undertook monthly manual chart review audits at each medical center to identify cases that were TAFFY eligible but had not been enrolled. We compared the enrolled population with the missed eligible population to assess for selection bias. Physician abstractors were trained on data collection by the principal investigator, who also answered questions and arbitrated coding questions until consensuswas achieved. Although we collected prospective data on each eligible ED AFF episode, only a patient's first enrollment was included in this analysis.

The study was approved by the KPNC Institutional Review Board. Waiver of informed consent was obtained due to the observational nature of the study.

Measurements

Data Elements

Variables collected prospectively included presenting symptoms, characterization of the atrial dysrhythmia, ED provider impression of hemodynamic instability, comorbid diagnoses, ED management (e.g. intravenous rate reduction medications [calcium or beta blocker] or digoxin needed to manage rapid ventricular response, attempted cardioversion [pharmacologic and/or electrical], failed cardioversion attempt, failure of restoration of sinus rhythm in the ED, formal cardiology consultation), and ED discharge rhythm. At the time of ED enrollment, we identified other active conditions that may have triggered the AFF onset or exacerbation, including pulmonary processes, systemic infections, hypovolemia, toxins, and other potential triggers.[21]

Additional variables extracted from the EHR included demographics, stroke risk (ATRIA [Anticoagulation and Risk Factors in Atrial Fibrillation][22, 23] stroke risk score ≥7 and CHA_2DS_2-VASc[24] score ≥2]), bleeding risk (HAS-BLED[25] score ≥3), Charlson Comorbidity Index (CCI), acuity of presentation defined by the Emergency Severity Index for triage (resuscitative, emergent/urgent, or non-urgent),[26] heart rate greater than 100 at disposition, first systolic blood pressure, and abnormal cardiac markers (elevated troponin >99th percentile, elevated B-type natriuretic peptide >500 mg/dL).Given findings from a prior study, hospital site, time of ED evaluations (weekday/weekend of ED visit, early morning [00:01-7:59], working hours [8:00-17:00], and evening [17:00-24:00]) and ED length of stay (hours), were also included as possible predictors.[27] We also measured census tract-level socioeconomic status (SES) from census data, where residence in a tract with ≥20% of households in poverty or ≥25% of residents who did not graduate high school was categorized as low SES.

Additionally, we calculated two risk stratification scores as possible predictors of hospitalization. The TrOPs-BAC score is a simplified pragmatic instrument that predicts 30-day mortality for AF patients in the ED.[15] The RED-AF risk score predicts the absolute risk of 30-day adverse events following an ED evaluation.[16] Both scores were modified slightly to accommodate the collection of data from the EHR.

Two physicians reviewed all hospital admitting diagnoses from the EHR to determine if AFF was the primary reason for admission, or if admission was likely triggered by another process (BK, DRV). Consensus was achieved through discussion between the two physicians.

Provider and Hospital Characteristics

We extracted demographic and clinical variables from the health system's databases on ED provider characteristics, including gender and years of experience using age as a proxy. Hospital factors extracted included total number of ED visits per year and the number of ED beds, teaching status, and specialty of residency teaching.

Outcome

Our primary study outcome was hospital admission, including short-term admissions (<24 hrs) to an observation unit or clinical decision area.

Statistical Analyses

We compared characteristics between those hospitalized and not hospitalized using likelihood ratio exact chi-square tests for categorical variables and t-tests or Wilcoxon rank sum tests for continuous variables. We used ANOVA to identify significant differences in unadjusted hospitalization rates between medical centers, and we calculated the intra class correlation coefficient to determine the strength of correlations due to nesting of patient under physician and physician under the medical center. As hospitalization was a relatively

Table 2: Comorbidities and scores of emergency department patients with atrial fibrillation or flutter (AFF), stratified by hospitalization.

Patient Characteristics	Total, n=1,942	Hospitalized, n=868 (44.7%)*	Discharge to Home, n=1,074 (55.3%)*	P-value†
Comorbidities and Scores				
History of AFF	996 (51.3)	397 (45.7)	599 (55.8)	<0.0001
On Anticoagulation				
No	1,478 (76.1)	656 (75.6)	822 (76.5)	0.62
Yes	464 (23.9)	212 (24.4)	252 (23.5)	
CharlsonScore[a]				
Mean (SD)	1.8 (2.2)	2.5 (2.4)	1.3 (1.9)	<0.0001
Median (IQR)	1 (0-3)	2 (0-4)	0 (0-2)	
Categorical				
0	774 (39.9)	229 (26.4)	545 (50.7)	
1	347 (17.9)	155 (17.9)	192 (17.9)	
2	265 (13.7)	130 (15.0)	135 (12.6)	<0.0001
3+	556 (28.6)	354 (40.8)	202 (18.8)	
ATRIA Risk Score [28-30]				
Mean (SD)	8.3 (6.0)	10.0 (5.9)	6.8 (5.7)	<0.0001
Median (IQR)	7.0 (3-12)	11 (5-14)	6 (2-11)	
Categorical				
0-5 (Low)	749 (38.6)	233 (26.8)	516 (48.0)	
6 (Medium)	151 (7.8)	53 (6.1)	98 (9.1)	<0.0001
≥7 (High)	1,042 (53.7)	582 (67.1)	460 (42.8)	
CHA_2DS_2-Vasc Risk Score [31]				
Mean (SD)	2.9 (1.7)	3.4 (1.6)	2.5 (1.7)	<0.0001
Median (IQR)	3 (2-4)	4 (2-4)	2 (1-4)	
Categorical				
0-1 (Low)	459 (23.6)	114 (13.13)	345 (23.1)	
2-4 (Medium)	1150 (59.2)	551 (63.5)	599 (55.8)	
≥5 (High)	333 (17.2)	203 (23.4)	130 (12.1)	
HAS-BLED Risk Score [32]				
Mean (SD)	2.1 (1.6)	2.7 (1.5)	1.6 (1.4)	<0.0001
Median (IQR)	2 (1-3)	3 (2-4)	1 (1-2)	
Categorical				
0-1 (Low)	790 (40.7)	207 (23.8)	583 (54.3)	<0.0001
2-3 (Medium)	772 (39.7)	404 (46.5)	368 (34.3)	
≥3 (High)	380 (19.6)	257 (29.6)	123 (11.5)	
RED-AF Score[20]				
Mean (SD)	128.4 (36.8)	133.2 (37.1)	124.5 (36.1)	<0.0001
Median (IQR)	126 (103-153)	132 (108-159)	124 (98-147)	
TrOPs-BAC[18]				
Mean (SD)	2.1 (1.4)	2.7 (1.4)	1.5 (1.3)	<0.0001
Median (IQR)	2 (1-3)	3 (2-4)	1 (0-2)	

ED, emergency department
* n (%) except where noted
† P-values from chi-square likelihood ratio tests for all categorical comparisons. For comparison of means of continuous variables, Student t-tests are reported.
aCharlson Score: 87 cohort members did not have a Charlson score because they had no encounters with the health system in the year prior to their enrollment. 39 of these were hospitalized, while 48 were not. There was no difference in missing Charlson scores between the hospitalized and non-hospitalized groups, p-value 0.98.

common outcome, we used a Poisson regression to estimate relative risks instead of a logistic model to estimate odds ratios. A Generalized Estimating Equations (GEE) model was chosen to generate estimates of associations between potential predictors and hospitalization as we were interested in population-level estimates, not individual patient-level estimates. While the interclass correlation was low for clustering by facility and physician, we explored adjusting for clustering by including provider as a random effect in these models. The non-clustered and clustered model results were nearly identical, thus a random effects model is presented in this manuscript. Due to a large amount of crossover between facilities by ED physicians, adjusting for hospital clustering using hospital as a random effect in a GEE Poisson mixed model was not possible (models didn't converge). Therefore, we included hospital as a fixed effect in the final models to examine differences in hospital admission rates after adjusting for patient characteristics. We reviewed QIC and QICu statistics to determine which independent variables to include in our final parsimonious model after reviewing associations between independent variables and the outcome in univariate models.

Thus, a Generalized Estimating Equations Poisson model estimating relative risks of hospitalization was selected with provider as a random effect and medical center as a fixed effect as our final model. Due to the co-linearity of stroke risk (ATRIA[22,23,28] and CHA_2DS_2-VASc[24]) and bleeding risk (HAS-BLED[25]) stratification scores, only ATRIA was included in the final model.

To further understand the difference in relative risk among patients with and without cardioversion and with failed vs successful cardioversion, we calculated the linear combinations of symptom group coefficients to generate estimates of hospitalization. All analyses were conducted using SAS statistical software, version 9.4 (Cary, N.C.).

Results

During the study period, 241 unique providers enrolled patients. The mean provider age was 40.8 years (SD 8.1) in 2011 with 37.3% (n=90) female (Supplement Table 1). The mean number of years since medical school graduation was 12.5 (SD 8.3).

Among 2,849 identified eligible patients,1,980 (69.5%) were enrolled by the treating ED physicians in the parent TAFFY study (Figure 1). Enrolled and non-enrolled patients were comparable in terms of age, sex, comorbidity, and stroke risk scores[29], except that enrolled patients were more likely to have a history of prior AFF as reported elsewhere.[21]

Adult (≥18 years) health plan members in the ED with electrocardiographically-confirmed nonvalvular AF/FL were eligible for enrollment if their atrial dysrhythmia was either symptomatic (including newly diagnosed) or treated in the ED. Patients were ineligible for the study if they transferred in from another ED, were receiving palliative-only comfort care, had an implanted cardiac pacemaker/defibrillator, or had just been resuscitated from cardiac arrest.

Overall, the mean patient age was 70. 7years (SD 13.8) and 985 (50.7%) were female. Characteristics of the cohort by hospitalization

Table 3: Presenting characteristics and treatment of emergency department patients with atrial fibrillation or flutter (AFF), stratified by hospitalization.

Patient Characteristics	Total, n=1,942	Hospitalized, n=868 (44.7%)*	Discharge to home, n=1,074 (55.3%)*	P-value
Rhythm Characteristics				
Diagnosis				
Atrial Fibrillation	1,615 (83.2)	742 (85.5)	873 (81.3)	0.04
Atrial Flutter (isolated)	256 (13.2)	101 (11.6)	155 (14.4)	
Both	71 (3.7)	25 (2.9)	46 (4.3)	
Recent-Onset of Rhythm-Related Symptoms (<48 hours)				
Yes	915 (47.1)	277 (31.9)	638 (59.4)	<0.0001
No/Unclear	1,027 (52.9)	591 (68.1)	436 (40.6)	
Clinical Impression of Stability				
Stable	1796 (92.5)	738 (85.0)	1058 (98.5)	<0.0001
Unstable	146 (7.5)	130 (15.0)	16 (1.5)	
QRS Interval ≥ 0.12 seconds	201 (10.4)	126 (14.5)	75 (7.0)	<0.0001
Secondary AFF[a]	448 (23.1)	313 (36.1)	135 (12.6)	<0.0001
Management Variables[b]				
Attempted Cardioversion				
No	1,629 (83.9)	822 (94.7)	807 (75.1)	<0.0001
Yes	313 (16.1)	46 (5.3)	267 (24.9)	
Pharmacological Only[c]	75 (24.0)	14 (30.4)	61 (22.9)	0.38
Electrical Only	195 (62.3)	28 (60.9)	167 (62.6)	
Both	43 (13.7)	4 (8.7)	39 (14.6)	
ED Consultation with Cardiologist	688 (35.4)	220 (25.4)	468 (43.6)	<0.0001
Sinus Rhythm at Discharge	679 (35.0)	132 (15.2)	547 (50.9)	<0.0001
Encounter Characteristics				
Triage				
Level 1: Resuscitative	18 (0.9)	17 (2.0)	1 (0.1)	<0.0001
Level 2: Emergent	1,140 (58.7)	527 (60.7)	613 (57.1)	
Level 3: Urgent	775 (40.0)	322 (37.1)	453 (42.2)	
Level 4: Non-Urgent	9 (0.5)	2 (0.2)	7 (0.6)	
Brought in by ambulance	587 (30.2)	370 (42.6)	217 (20.2)	<0.0001
ED length of stay (hours), mean (SD)	5.3 (3.7)	5.9 (3.4)	4.9 (3.9)	<0.0001

ED, emergency department
* n (%) except where noted
† P-values from chi-square likelihood ratio tests for all categorical comparisons. For comparison of means of continuous variables, Student t-tests are reported.
[a] Secondary AFF: A trigger or cause of AFF, such as sepsis.
[b] ED Management: patients may have had more than one treatment and may be included in more than one treatment in this section.
[c] Pharmacologic cardioversion included the following medications: amiodarone, dofetilide, flecanide, ibutilide, magnesium, procainamide, propafenone, quinidine, and vernakalant. Physicians had the option to indicate if amiodarone was used for pharmacologic cardioversion or rate control. Amiodarone use may be included in both locations.

outcome are described in Tables 1, 2, and 3 (and in greater detail in Supplemental Table 2). The majority of patients were discharged home (55.3%; n=1,074). Hospitalization varied from 37.4% to 60.4% between medical centers in this integrated care system (Supplemental Figure 1). The attributes and hospitalization rates for each of the 7 hospitals are available in the supplement (Supplemental Table 3). Intraclass correlation coefficient estimates indicated that 1.2% of the variability in hospitalization was attributable to providers, while 2.7% was attributable to medical centers, and neither interclass correlation coefficient was significant.

Among those admitted, 15.0% were considered unstable by the physician compared to 1.5% among those discharged home (p<0.001) (Table 3). Mean CCI was 2.5 (SD 2.4) among those hospitalized and 1.3 (SD 1.9) among those discharged home (p <0.0001), while anticoagulation status between the two groups was comparable with about one-quarter of patients on prescribed anticoagulant medications(p=0.62) (Table 2).A minority of patients underwent cardioversion attempts for AFF in the ED:313 (16.1% of patients enrolled). Of these,75 (24.0%) received pharmacologic only, 195 (62.3%) electrical only, and 43 (13.7%) received both(Table 3). Attempted cardioversion varied significantly between medical centers, ranging five-fold between the lowest (5.1%) and highest (27.6%) cardioverting EDs. Among the 1,461 patients(75.2%) who received intravenous rate reduction medications, 26.6% received beta-blockers, 57.8% received calcium channel blockers, and 8.2% received both of these therapies. A small proportion of patients received digoxin, amiodarone, or a combination of these medications in addition to a calcium channel or beta blocker.

Inthe adjusted Poisson regression model(Table 4),anincreased risk of hospitalizationwas associated most strongly with failure of sinus rhythm restoration by the time of ED discharge, noattempted cardioversion, treatment at hospital G, physician impression of instability,last ED heart rate >100, andno prior history ofAFF (all RR >1.3).

Other significant predictors with a smaller relative risk (RR ≤ 1.3) included Black/African American race,QRS interval > 0.12seconds, CCI ≥ 3, a 1 point increase in TrOPS-BACS Score, triage level as emergent, arrival by ambulance, no ED consultation with a cardiologist, a 1 hour increase in ED length of stay, and treatment at hospital E. Stroke risk(ATRIA Stroke Risk Score) and patient agewere not associated with hospitalization in the fully-adjusted model(Table 4).Differences in characteristics bet ween hospitals G and A included ED census (G: second lowest at 34,869 vs A: second highest at 81,342) and teaching hospital status (G: no vs A: yes).

To explore the impact of cardioversion and rhythm outcome on hospitalization in the adjusted model, we used linear combinations and found that patients with attempted cardioversion who remained in AFF at discharge (n=55) had a non-significant RR for hospitalization of 1.23 (95% CI: 0.88-1.72), whereas those in AFF at discharge without attempted cardioversion had a RR for hospitalization of 1.93 (95% CI: 1.65-2.25). In patients where cardioversion was attempted and the patient left the ED in sinus rhythm, the RR of hospitalization decreased to 0.64 (95% CI: 0.50-0.81).

Discussion

In this multicenter prospective cohort study of recent-onset AFF patients, we found variation in hospitalization rates similar to other sites.[8, 30] In our study, there was almost a two-fold difference in hospitalization proportions. However, the overall mean hospitalization

Table 4: Patient characteristics and facilities associated with hospitalization for AFF from a modified Poisson regression with provider as random effect.

Patient Characteristics	Univariate Models		Adjusted Model	
	RR	95% CI	RR	95% CI
Female (ref: Male)	1.08	0.98, 1.19	1.01	0.92, 1.11
Age at ED Visit (ref: Age <45)				
45-64	1.96	1.17, 3.29	1.31	0.82, 2.09
65-74	2.30	1.35, 3.89	0.91	0.55, 1.51
≥ 75	3.10	1.87, 5.12	0.86	0.52, 1.41
Race (ref: White)				
Black/African American	1.26	1.07, 1.48	1.18	1.02, 1.36
Asian	1.17	1.01, 1.36	1.13	0.96, 1.34
Other/Unknown	0.94	0.73, 1.22	1.05	0.85, 1.28
Low Socioeconomic Status (ref: Not Low)	1.19	1.05, 1.35		
QRS interval > 0.12 seconds (ref: ≤ 0.12 seconds or missing)	1.46	1.30, 1.65	1.13	1.01, 1.27
Rhythm Characteristics (ref: Paroxysmal)				
Chronic	1.70	1.48, 1.96		
Unclear	1.86	1.67, 2.08		
Physician Impression of Instability (ref: Stable)	2.23	2.05, 2.43	1.44	1.30, 1.60
No Prior History of AFF (ref: Prior History)	1.25	1.13, 1.40	1.41	1.29, 1.54
Onset Was Not Recent/Clear (ref:Recent/Clear)	1.91	1.66, 2.20		
Secondary AFF (ref:Primary)	1.87	1.69, 2.06	1.09	0.98, 1.21
AFF Rhythm at Discharge (ref: Sinus Rhythm)	2.97	2.50, 3.53	1.93	1.65, 2.25
Risk Scores				
Charlson Score (ref: 0)				
1	1.50	1.29, 1.73	1.10	0.96, 1.26
2	1.66	1.40, 1.96	1.11	0.96, 1.28
≥ 3	2.15	1.90, 2.43	1.27	1.13, 1.44
ATRIA Score [28-30] (ref: Low: 0-6)				
6 (Medium)	1.12	0.87, 1.43	1.13	0.86, 1.49
≥ 7 (High)	1.79	1.59, 2.01	1.24	1.00, 1.54
CHA_2DS_2-VASc [31] (ref: <2)				
2-4 (Medium)	1.92	1.59, 2.32		
5-9 (High)	2.44	2.02-2.95		
HAS-BLED[32] (ref: <2)				
2-3 (Medium)	1.98	1.71, 2.29		
≥3 (High)	2.57	2.25, 2.95		
RED-AF Score[20] (10 Point Increase)	1.04	1.02, 1.05		
TrOPs-BAC Score [18](1 Point Increase)	1.34	1.30, 1.39	1.17	1.10, 1.24
Triage Level (ref: Non-Emergent and Urgent)				
Emergent	1.12	0.99, 1.26	1.27	1.16, 1.40
Resuscitative	2.22	1.90, 2.61	1.17	0.86, 1.58
Last ED Heart Rate > 100 (ref: <100)	2.24	2.04, 2.46	1.44	1.31, 1.57
Arrival by ambulance (ref: No)	1.73	1.56, 1.90	1.30	1.19, 1.41
Rate Control Medications (ref: No Rate Reduction Medications)				
Any Digoxin Rate Reduction	1.77	1.49, 2.11	0.93	0.83, 1.05
Non-Digoxin Rate Reduction	1.14	0.99, 1.31	1.12	0.94, 1.34
No Attempted Cardioversion (ref: Attempted Cardioversion)	3.40	2.56, 4.51	1.57	1.23, 2.00
No ED Consultation with Cardiologist (ref: Cardiology Consult)	1.63	1.42, 1.88	1.23	1.10, 1.37
ED Length of Stay (1 Hour Increase)	1.04	1.02, 1.05	1.03	1.01, 1.04
Facilities [ref: A (low)]				
B	1.0	0.78, 1.29	0.98	0.80, 1.21
C	1.05	0.87, 1.27	1.13	0.97, 1.32
D	1.22	1.00, 1.50	1.05	0.88, 1.26
E	1.25	1.04, 1.50	1.26	1.09, 1.47
F	1.47	1.18, 1.82	1.18	0.95, 1.47
G	1.61	1.35, 1.92	1.44	1.22, 1.71

AFF: Atrial fibrillation or flutter; ED: Emergency department.
Shaded variables were not included in the final adjusted model

rates (44.7%) were lower in this healthcare system compared to the Western region of the U.S. (57%) as well as the entire U.S.(70%). Secondly, we found statistically significant predictors of increased hospitalization including any prior AFF episode, a failure to return to sinus rhythm by the time of disposition, no attempted cardioversion, a physician's impression of an unstable patient, and a final heart rate greater than 100beats per min at time of disposition. Of these, the factors over which the ED physician may exert some control to reduce hospitalization include rhythm control (that is, *effective* cardioversion) and adequate reduction of heart rate.

In our study, effective rhythm control was associated with ED discharge to home in the adjusted model, a finding that makes clinical sense and has been demonstrated in the literature.[29, 31] Patients with any cardioversion attempted during an ED stay were less likely to be hospitalized than those without attempted cardioversion, regardless of rhythm at the time of ED discharge after adjusting for other variables. Furthermore, we found that even if the patient remained in AFF at discharge, a cardioversion attempt reduced the risk of hospitalization compared to those without cardioversion (RR 1.23 vs 1.56).

ED patients with a rapid ventricular response to their AFF often have complaints of palpitations and symptoms of left ventricular dysfunction such as shortness of breath and exercise intolerance. Controlling the rapid ventricular response from 150 to 100 beats per minute, for example, improves ventricular function and often reduces symptoms sufficiently to allow discharge home. Sinus restoration is an even more effective means of AFF symptom resolution, as it solves the primary problem that triggered the ED visit. Failure to achieve a sustained reduction in the rapid ventricular response, therefore, is one of the leading reasons ED patients require hospitalization.[31, 32]

The relationship between optimizing rate and rhythm control of ED patients with AFF and their subsequent hospitalization has been demonstrated in a variety of clinical settings where the implementation of ED AFF treatment pathways has resulted in safe and sizable reductions in hospitalization.[33-35] Shared among these successful

ED models of care are simple, standardized approaches to improve rhythm and rate control, including the early use of oral rate reduction medications. Empowering providers to actively manage these patients with such pathways could increase home discharges as well as decrease variation in hospitalization.

Across the U.S. there are significant regional differences, with ED AFF hospitalizations ranging from 73% in the Northeast and South to 55% in the West.[8, 30] In neighboring Ontario, Canada, one finds a 10-fold difference in AF hospitalization between the top and bottom decile of 154 EDs,[9, 10] as well as wide variation in management among institutions.[9, 10, 36-39] Another study comparing differences between the management of AF in Canada and the U.S. reasoned that the latter's more complex medical system heavily contributed to its increased hospitalizations.[37] Piccino et al. hypothesized that "differences in the financial incentives (and disincentives) for hospitals to admit low-risk patients in the U.S. and Canada may contribute to the variation in hospitalization." Unlike many parts of the U.S. however, our health system is integrated and allows greater access to timely follow-up; thus, our study likely represents the most optimal conditions in the U.S. for an outpatient disposition.

This hypothesis may be valid as integrated health systems do not directly benefit from hospitalization as a path to optimizing a members' health. Instead, supporting outpatient management by facilitating timely follow-up care with a primary care physician or anticoagulation management service, can lower the threshold for safely discharging a patient home. For example, clinicians in this integrated health system were provided point-of-care clinical decision support for patients with pulmonary embolism in a controlled pragmatic study. The intervention increased home discharges by 11.3% and had no effect on 5-day return visits related to pulmonary embolism or 30-day major adverse outcomes.[40] At facilities where such integrated care is unavailable, the threshold to admit may be lower than to discharge home, as obtaining follow-up care can be an additional burden in the time-pressured setting of the ED.

A study by Rozen et al.showed a steady surge in the absolute numbers of ED visits for AF resulting in an overallincreasein hospitalizations and, correspondingly, the cost to the healthcare system.[30] Without a dramatic shift in how hospital systems manage the transitions of care and improved management guidelines for providers with patients with AF, there is unlikely to be any change in hospitalization volumes. Cultural differences within settings can be difficult to overcome unless sweeping changes are made throughout a system, from the ED, inpatient and outpatient services, to the pharmacy. Similar to how the care of ST-elevation myocardial infarctions was entirely transformed with door-to-balloon time standards[41] and now emergency medical services (EMS)-to-balloon time, perhaps the same may need to occur for a transformation in comprehensive AF care.

Until recently, the professional society guidelines on the approach to patients with AF have offered divergent recommendations on management.[42-45] Moreover,several of these guidelines have undergone frequent updates over a short period of time,[12] making it more difficult for providers to stay current. However, in the past few years, there has been a shift towards multidisciplinary panels seeking to guide ED providers on AF management. Canada has been a leading force on ED-specific guidelines,[14, 45-47] and much can be learned by their unifiedfront. Further studies will be needed to determine whether such guidelines make an impact on ED management, hospitalization, and subsequent clinical outcomes.

Facility-specific variation abounds inthe U.S., as each hospital system can be a unique entity with its own variety of observation units, consultant availability, outpatient follow-up care, as well as provider practice variations. These variations can make it more challenging to implement widespread practice changes; in fact, it could be that changes need to occursystem by system, each designing their own tailor-made plan that may also include protocols facilitating discharge of new-onset AF patients. Society guidelines and web-based applications(e.g. healthdecision.org) can nevertheless provide hospitals templates of clinical pathways that can be customized for unique systems.[48, 49] Other opportunities to increase professional guideline uptake may include the integration of clinical decision support tools into EHR systems.[40, 50]

Limitations

Our study population was a convenience sample and may be subject to selection bias despite representativeness of the greater population on measured variables. The data are from 2011-2012 and practice patterns may have evolved in the subsequent years. The study sample was relatively small, which accounts for the moderate confidence intervals, and thus we might fail to detect associations of smaller magnitude. Our data also did not account for ED recidivism. Due to the limited number of hospitals involved, their characteristics could not be assessed as predictors; the hospitals were, however, similar in their basic capacity and function. Our study was conducted in a large integrated health care system in California which may limitthe generalizability of our results to other geographic locations and practice settings. However, this dataset allowed for clinical data with a high degree of internal validity—features that cannot be found in claims-based datasets. As integrated health systems tend to have fewer system-level differences (e.g., one primary insurance program, a unified EHR, a means for facilitating follow-up), variations in an integrated health system are likely conservative estimates.

Conclusions

While hospitalization rates of AFF patients vary among medical centers within a single integrated healthcare system, there are modifiable factors that could decrease hospitalizations.Physician management decisions could be improved by standardizing treatment goals that specifically address best practices for ED rate reduction and rhythm control.

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Pulmonary Vein Isolation Followed by AV node Ablation and CRT-P Implantation with out Fluoroscopy in a Super Morbidly Obese Patient: A Case Report

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Abstract

We present the first ever reported case of a super morbidly obese patient (BMI > 60) with drug refractory, symptomatic persistent atrial fibrillation who underwent an uncomplicated, but unsuccessfulPVI ablation procedure and subsequently underwent AV node ablation and cardiac resynchronization therapy – pacemaker (CRT-P) insertion using a zero fluoroscopy technique. This case demonstrates the following two critical points: (1) difficulties in the treatment of massively obese patients with arrhythmias1; (2) increased use of fluorolessprocedures[2-4].

Introduction

It has been observed that obesity has become a global pandemic and more so in United States. In the US, 48% of all Americans are obese (body mass index of > 30 kg/m^2) and 12% are super obese [5]. Super obese or Class III patients are defined as having a BMI of Greater than 40 kg/m^2 [6]. We describe a SANS FLUORO (zero fluoroscopy) ablation of a super morbidly obese patient with longstanding, persistent AF that was unsuccessful, followed by fluoroless successful AV node ablation and CRT-P implantation.

Case Report

49 year oldsuper morbidly obese gentleman (BMI 60.3 kg/m^2, 213.2 kg or 469 lbs) with longstanding persistent atrial fibrillation, hospitalized multiple times with AF with uncontrolled rates and HFpEF (Heart Failure with preserved Ejection Fraction of 40%) who had had multiple unsuccessful cardioversions despite being placed on amiodarone. Other medical problems included: hypertension, obstructive sleep apnea, and history of non-compliance. The patient described severe dyspnea on exertion with debilitation to the point that he was mostly bed bound using a urinal and bedside commode. His left atrium was moderately dilated at 4.6 cm^2.

Key Words:
Atrial Fibrillation Ablation, Obesity, Fluoroless procedures.

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On his 4th admission with exacerbation of HFpEF as well as AF with uncontrolled rates (figure1), heart catheterization revealed only non-obstructive coronary artery disease. Due to hisrelatively young age, we initially attempted a rhythm control strategy with Pulmonary Vein Isolation (PVI). PVI was performed in his bariatric bed as the table would not support his weight. Additionally, portable C arm was not used as it would not fit beneath the bed and images would be sub-standard.The bed was placed in the EP lab, and the Abbott Precision system was used. The patient was intubated for airway protection. Three sheaths were placed in the right groin without complication. A 3-D electro-anatomic impedance-based map of the RA was generated using a coronary sinus catheterwhereas the RA was mapped with the HD Grid multi-spline catheter. The LA map was compared to a previous chest CTA to ensure that all veins were accounted for. An intracardiac echocardiography (ICE) catheter was extensively utilized to visualize RA, SVC, transseptal puncture, left atrial ablation and pericardial space to ensure safety.We also used an irrigated force sensing ablation catheter to improve safety and efficacy (45 W anteriorly and 40 W posteriorly). Despite pulmonary vein isolation, posterior wall isolation, mitral and cavo-tricuspid isthmus ablation, and complex fractionated atrial electrogram ablations (CAFÉ) (figure 2); restoration of sinus rhythm even with cardioversion x2 with 720 J (simultaneous use of 2 external cardiac defibrillators in biphasic mode) was unsuccessful.

His symptoms improved and his AF rates were controlled in the 80s on amiodarone 400 mg twice daily. Due to neurologic side effects, amiodarone was discontinued which led to re-hospitalization with AF rates to the 140s only 2 weeks later. At this point, it was

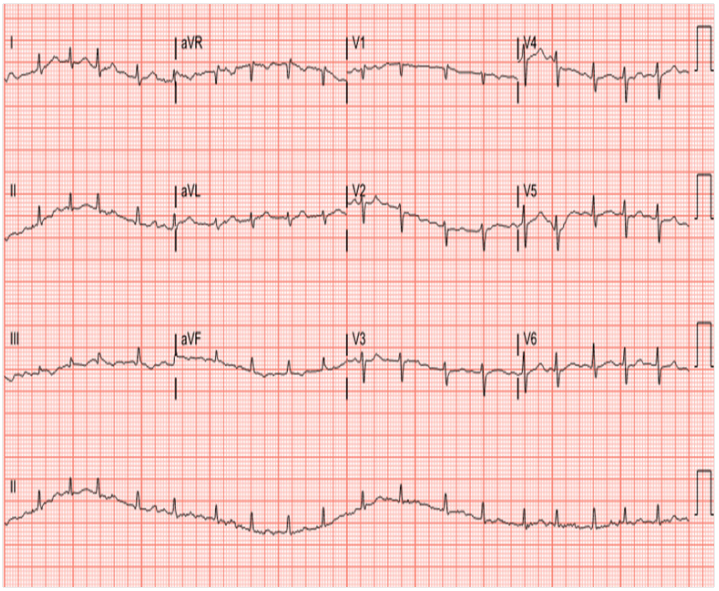

Figure:1 ECG revealing Atrial Fibrillation with rates in the 120s and diffuse non-specific ECG changes

decided that AV node ablation and pacemaker would be the last resort treatment.

The patient underwent a completely fluoroless CRT-P insertion under general anesthesia as well as AV node ablation utilizing a single left subclavian access (figure 3).[3] D electroanatomic mapping with the Abbott Precision system was utilized to generate a detailed map of the right atrium, right ventricle, and coronary sinus with branches. The RV lead was visualized using alligator clips that connected to the mapping system. Injury current was also used to confirm satisfactory placement of active fixation screw in the low septum. The CS sheath was advanced over the ablation catheter deep in the vein. The Biotronik Vision wire with inwithin the CS lead both of which are visible on the 3D map utilizing double alligator clips to guide the lead successfully into a previously mapped lateral CS branch. There were no complications with access or lead placement (figure 4). RV threshold was 0.5 V @ 0.5 msec and LV threshold was 2.5 V @ 0.5 msec (Figure 5). The following day he was able to ambulate around the unit for the first time and at his 2 week follow up, he had lost 11.4 kg (25 lbs) (Figure 6). After 7 months, the EF has recovered to 60% and he has not required hospitalization.

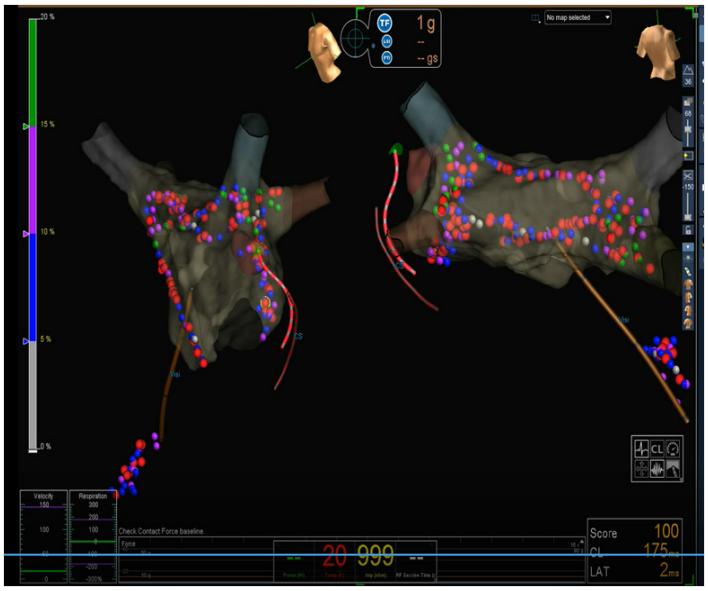

Figure:2 AP and PA view of Electro Anatomic Map of ablation lesions with CS catheter and Vizigo sheath. Impedance scale is shown on the left. Red lesions denote that Lesion Severity Index of > 4.5

Discussion

This case is important because it outlines 2 distinct issues: management of atrial arrhythmias in super morbid obese patients and the concept of fluoroless procedures. It is well known that obese patients with or without sleep apnea suffer from an increased rate of atrial arrhythmias and HFpEF[5-8]. Initially, consideration was given to portable C arm use, but this would have delivered uninterpretable images and prohibitive amounts of X-ray radiation exposure to the patient and the staff (at least 2-4 times normal amounts) due to body habitus[9]. Additionally, a single stick approach decreased the risk of complications and overall case time length[10].

Improvements in 3 dimensional mapping systems have demonstrated capabilities of providing the necessary visual information needed to perform various ablations, especially atrial flutter and atrial fibrillation[11].As obesity rates are continuing to rise, these patients will become commonplace in everyday practice. Finally, recent studies have shown that obesity may have a deleterious effect on long term ablation success rates[12]. This is a particular case that would have been either unsuccessful or extremely technically challenging if reliance on traditional fluoroscopic techniques had been utilized. As a matter of caution, higher level of intracardiac echocardiography skills, very detailed 3 D mapping and low threshold to use fluoroscopy if absolutely needed for safety is important in fluoroless procedures. This case illustrates safety and feasibility of fluoroless procedures in all patients but especially super morbidly patients.

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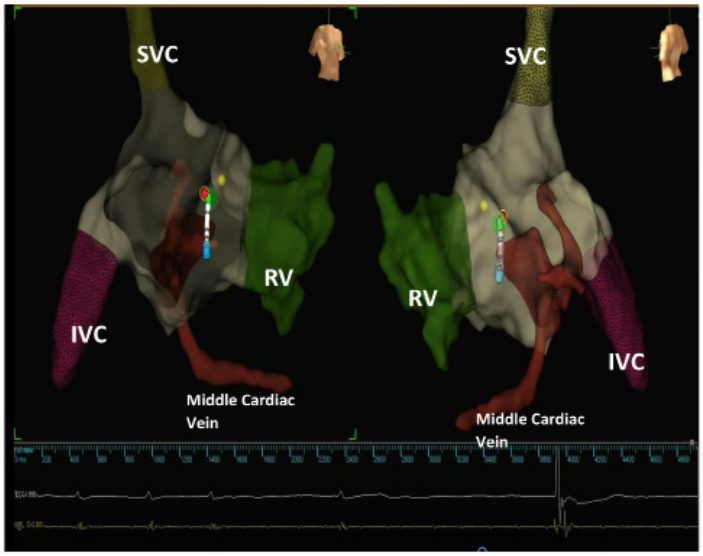

Figure:3 Fluoroless Ablation of AV node with resulting paced rhythm. Left view is RAO with cutaway revealing the os of the coronary sinus as well. Yellow dot denotes the His position and Red dot denotes ablation lesion.

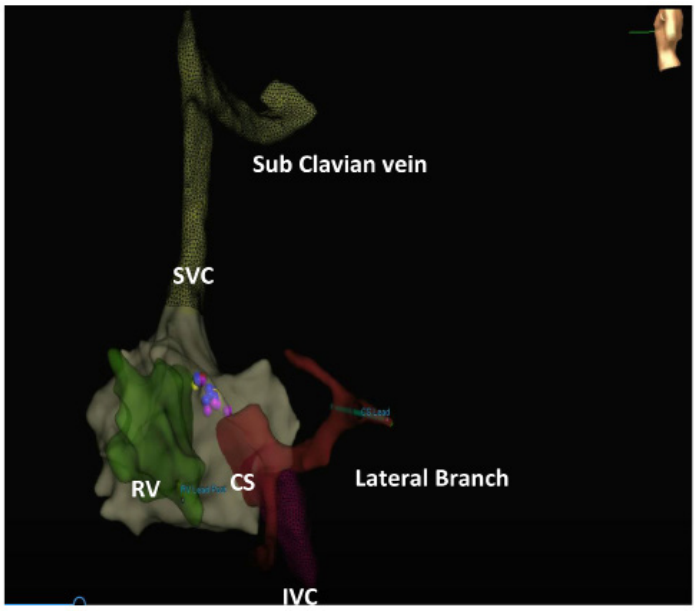

Figure:4 Left lateral projection of RV lead, CS lead and ablation lesions. SVC, IVC and middle cardiac vein is also well visualized.

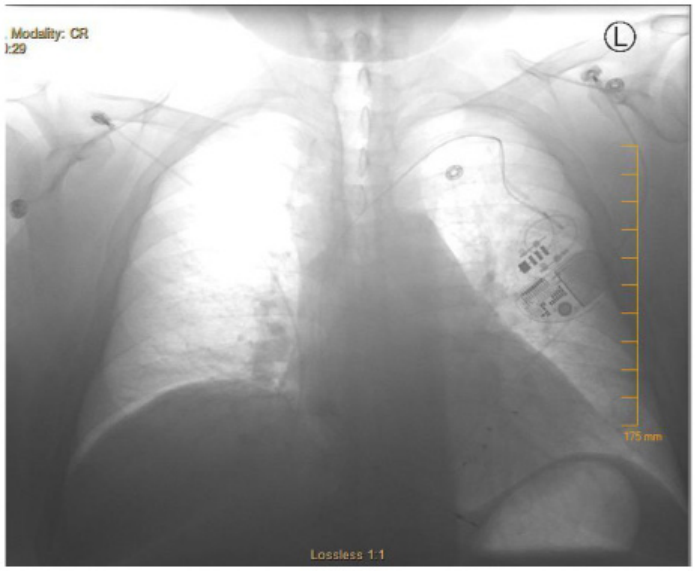

Figure:5 Post CRT-P chest radiograph that is under exposed to reveal lead positions

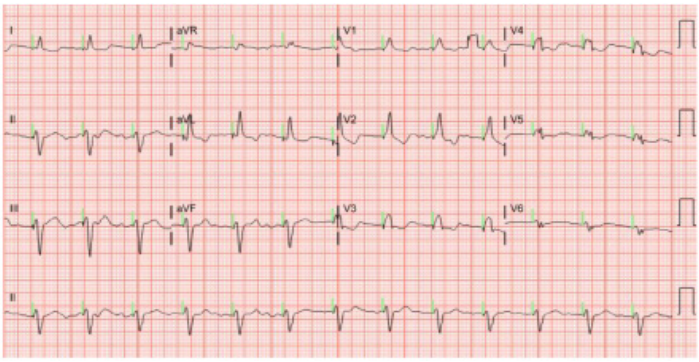

Figure:6 Post CRT-P ECG revealing a completely paced rhythm at 80 bpm

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Subcutaneouscardiac Rhythm Monitors: A Comprehensive Review

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Abstract

Subcutaneous loop recorders (SCRMs) are subcutaneous electronic devices which have revolutionized the field of arrhythmia detection. They have become increasingly appealing due to advances such as miniaturization of device, longer battery life, bluetooth capabilities and relatively simple implantation technique without the need for complex surgical suites. They can be implanted in the office, patient bedside without the need to go to the operating room. One of the most common indications for their implantation is detection of atrial fibrillation (AF) after a cryptogenic stroke. They have also been utilized for assessing the success of rhythm control strategies such post pulmonary venous isolation. More recently studies have assessed the utility of SCRMs for detecting silent AF in at risk populations such as patients with sleep apnea or those on hemodialys is. In this paper, we review the evolution of SCRMs, the clinical studies assessing their value for different indications, their role incurrent clinical practice and future avenues in the era of smart wearable devices like apple watch etc.

Introduction

Healthcare providers frequently use electrocardiography (ECG) and 24-48-hour external Holter monitorsto detectcardiac arrhythmias. Devices like event monitors, mobile telemetry monitors or external loop recorders increase the odds of detecting arrhythmias by further prolonging the duration of monitoring[1].Subcutaneouscardiac rhythm monitors (SCRMs) or subcutaneous loop recorders (ILRs) are small electronic devices that have been increasingly used to monitor cardiac rhythm for prolonged durations. Common indications for SCRM sinclude detection of occult atrial fibrillation (AF) in patients with a stroke of uncertain etiology, otherwise called cryptogenic stroke, monitoring success of rhythm control strategy in the management of AF,[2] arrhythmia detection in patients with unexplained syncope and in patients with infrequent but disabling palpitations. In this article, we review the current literature on SCRMs and future avenues for research.

Evolution of SCRMs:

Subcutaneous cardiac monitoring devices with a continuous cardiac rhythm monitoring capability for an extended time period were initially developed in the 1990s. The development of the cardiac monitoring devices started with the original cardiac monitor that was a pacemaker-size device (53 x 60 x 8 mm or 26 cubic centimeters) with two electrodes on the device can (Figure 1a, Cardiac Monitor, Model 1033[3], Medtronic, Minneapolis, MN). In late 1990s and early 2000s, a set of downsized subcutaneous cardiac monitors with additional capabilities, such as increased battery longevity, larger memory capacity for stored electrograms and events, MR-conditional and remote monitoring emerged. Medtronic Reveal, Medtronic Reveal Plus, Medtronic Reveal DX, Medtronic Reveal XT, St. Jude Medical Confirm, Biotronik Biomonitor, Biotronik Biomonitor 2, Boston Scientific LUX-Dx and Transoma Sleuthare some such examples that revolutionized the long-term clinical management of the patients receiving cardiac monitors with a streamlined outpatient implant procedure and accurate and reliable detection of arrhythmic events during the monitoring duration (Figure 1B).

The currently used cardiac monitors are further miniaturized (1.2 – 1.9cc) with an "insertable" mechanism for implantation by uniquely designed insertions tools. The insertion takes only a few minutes, and patients can be continuously monitored, with device data uploading to the remote care network for remote review by clinicians. The insertable cardiac devices are MR-conditional and last more than 2 years once inserted. Figure 2 illustrates the currently available "insertable" cardiac monitors with respective insertion tools and transmitters. The basic

Key Words
Subcutaneous Cardiac Rhythm Monitors, Loop Recorder, Atrial Fibrillation, Cryptogenic Stroke

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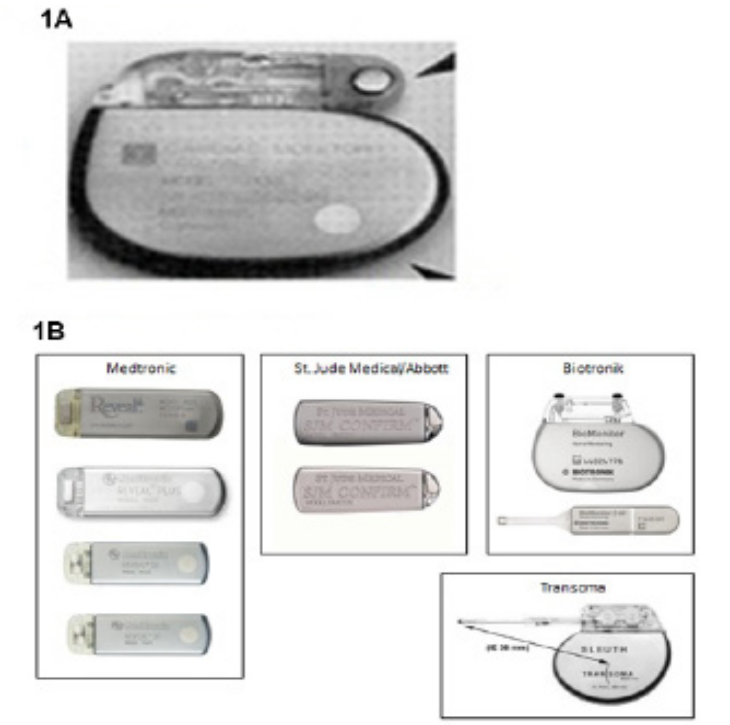

Figure 1A & 1B: **Evolution of SCRMs., 1A : Evolution of SCRMs., 1B : Various implantable cardiac monitors.**

operation of the typical cardiac monitor is illustrated in Figure 3. Similar to other cardiac subcutaneous devices, cardiac electrograms recorded from bipolarly configured electrodes located at each end of the device (typically >35mm) are amplified and filtered through analog circuitry. Based on electrogram analysis, rhythm adjudication will log and store the events of interest (e.g., pause, bradycardia, tachycardia, AF) in the device's memory. Stored episodes and electrograms will be transmitted to the device manufactures' remote care network at a scheduled time interval or instantaneously via either radiofrequency based bedside monitor (Medtronic and Biotronik) or low energy Bluetooth based wireless communication using patient's smartphone (Abbott/St. Jude Medical Confirm Rx/Boston Scientific Lux-Dx/ Medtronic Linq II).

Available SCRMs:

SCRMs, also called insertable cardiac monitors (ICMs),[3] appeal to healthcare providers and patients alike due to the recent advances in miniaturization and remote monitoring4. Latest SCRMs are

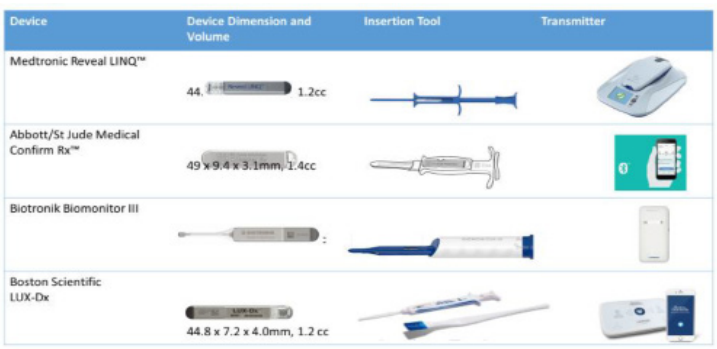

Figure 2: **Currently available SCRMs in the United States.**

"injectable" devices implanted with the help of 'kits' supplied by the manufacturer with battery liferanging from 2-4 years. The devices are small, inconspicuous and do not interfere with daily activities. As opposed to those with external monitors, patients with SCRMs don't have to take any precautions while swimming or bathing. SCRMs are more patient friendly and suitable for patients with allergy to electrode material used in external monitors. All devices are MRI compatible. The currently approved indications for ILR implantation are listed in Table 1.

Reveal-XT (Medtronic, Minneapolis, USA) was one of the earliest commercially launched SCRMs that had a separate memory for automatic recordings and patient activated recordings. It has now been replaced in clinical practice with the Reveal-LINQ SCRM, which is currently the smallest SCRM available on the market. The device and recordings are monitored using "CARELINK" remote monitoring. The battery life is about 3 years and the patients are given hotspots like pacemaker remote monitoring boxes which can be plugged next to their bed-stand for wireless monitoring and transmission.

Confirm RX (Abbott St Jude Medical, Minneapolis, USA) is another device currently on the market5. The battery life for this device is estimated at 2 years. It is monitored remotely by the "MERLIN" system. Patients can send symptom recordings through an app on the smartphone. Patients who do not have a smartphone are provided a dummy smartphone with the app by the manufacturer. Biomonitor 3 (Biotronic SE & Co, Berlin, Germany) is a recently launched SCRMdevice6. It is the company's third generation device. It is the biggest in size compared to all SCRMs and has the longest battery life of about 4 years. The "SMART" algorithm allows to save the first, longest and the last episode of every arrhythmia and is monitored by "HOME MONITORING" system provided for remote monitoring. These patients get a hotspot which can be kept next to the patient's bed-stand for wireless transmissions. Patients can also record symptoms and check device status with a smartphone app.

Although there are numerous SCRMs available, there are no published studies that compare them. However, performing such studies is challenging given the need for a large sample size and associated costs.

Linq II (Medtronic, Minneapolis, USA) is one of the latest devices available claiming 4.5 years of longevity. It also has the lowest published rate of false positive AF (4.7%)[7]. It can also detect PVCs which could

Table 1: **Current indications for subcutaneous loop recorders**

Recommended indications: **1. Patients with cryptogenic stroke in whom reasonable workup including electrocardiogram, Holter and mobile telemetry monitors, routine transthoracic and/or transesophageal echocardiograms, carotid duplex and hypercoagulable workup has not revealed a diagnosis** **2. Patients with unexplained syncope which is too infrequent to be caught on a Holter or event monitor**
Reasonable indications: **1. Patients with palpitations that are too infrequent to be caught on a Holter or event monitor and cardiac arrhythmia is strongly suspected based on clinical presentation** **2. Patients with atrial fibrillation who undergo ablation to monitor for recurrence**
Other indications where more data are needed: **1. Patients at high risk for arrhythmias like those with sleep apnea, hemodialysis or history of cardiac especially mitral valve surgeries** **2. Patients with stroke where a cause has been identified already for example those with patent foramen ovale**

Table 2: Studies evaluating role of subcutaneous loop recorders in patients with cryptogenic stroke

Study name	Year	Number of patients (n)	Arrhythmia characteristics	Median follow up	Outcome
Glotzer et al (MOST trial)	2003	312	Patients with PPM detected AR≥220 bpm for at least 5 min	27 months	HR for death or non-fatal stroke 2.79 (95% CI 1.51-5.15, p=0.001)
Dion et al	2010	24	Patients with CS with AF ≥30 sec	14.5 months	No patient had significant AF during fu
Healey et al (ASSERT trial)	2012	2580	PPM or ICD detected AR ≥190 bpm for at least 6 min	2.5 years	HR for ischemic stroke or systemic embolism 2.49 (95% CI 1.28-4.85, p=0.007)
Etgen et al	2013	22	Patients with CS and AF duration≥6 minutes	1 year	27.3% patients had AF during fu
Cotter et al	2013	51	Patients with CS and AF≥ 2 min	229± 116 days	25.5% patients had AF during fu
Ritter et al	2013	60	Patients with CS and AF≥ 2 min	1 year	17% patients had AF during fu
Rojo-Martinez et al	2013	101	Patients with CS and AF≥ 2 min	281±212 days	33.7% patients had AF during fu
Christensen et al (SURPRISE study)	2014	85	Patients with CS and AF≥ 2 min	569±310 days	16.1% patients had AF during fu
Sanna et al (CRYSTAL-AF trial)	2014	221	Patients with CS and AF≥ 30 sec	1 year	12.4% patients had AF during fu
Brachman et al (CRYSTAL-AF trial)	2016	221	Patients with CS and AF≥ 30 sec	3 years	30.0% patients had AF during fu
Toni et al (SAFFO study)	2016	424	Patients with athero-embolic or lacunar stroke	1 year	Ongoing with results expected in 2021

HR – hazard ratio, CI – confidence interval, AF – atrial fibrillation, CS – cryptogenic stroke
Bpm – beats per minute, Min – minutes, Fu – follow up

be helpful in detecting high-risk patients. Patients can utilize their smartphones for the mobile application to transfer data, log their symptoms and to monitor device status[8]. Patients who do not want to or cannot use mobile phones, there is a Bluetooth home communicator as an alternative for transferring data. It is also the first device with an option for remote programming which might help reducing patient office visits.

Lux-Dx (Boston Scientific, Marlborough, Massachusetts)is also one of the latest entries into the SCRM market[9]. It features a dual-stage algorithm to automatically detect and verify data before sending it. It also features remote programming like Linq II so that cardiologists can make adjustments to the device without calling the patients into the office. Bench testing for the device showed 53% reduction in false posiitves. It claims around 3 years of battery life.

Implant considerations:

Manufacturers supply an insertion kit which contains the device, a blade and an insertion tool. The device is usually inserted in the third to fifth intercostal space, just to the left of sternal border. The device can be either implanted vertically and parallel to the sternum, or at a 45° angle to the sternum10. The diagonal approach can maximize the output signal as this would be parallel to both atrial and ventricular depolarization vectors[2]. Other implantation sites reported include left axillary location or a horizontal implant in the sixth or seventh intercostal space.

The supplies are arranged on a Mayo stand prior to implantation (Figure 4). Pre-procedure antibiotics can be given, especially in higher risk patients like those with immunosuppression. The parasternal region between 3rd and 5th intercostal space is identified and shaved. Full aseptic precautions are employed to minimize pocket infections. After washing hands thoroughly as in the caseof any device implant, the implanting provider wears a sterile gown and gloves. The previously identified area is cleaned with betadine or chlorhexidine and patient is covered with a sterile drape. Only a small area of chest should remain exposed where SCRM is to be inserted. Usually 5-10 ml of 2% lidocaine is given subcutaneously for local anesthesia. Lidocaine with epinephrine is also useful reduce risk of skin bleeding as many of these patients could be on anti-coagulation. Using less amount oflocal anesthetic will cause patient discomfort but a large amount candampen the initial output signals. A pocket is made with the blade and SCRM is inserted with the help of insertion tool. The technique for insertion differs slightly between different SCRM brands. The pocket should be of accurate size to avoid device movement which causes artifactif pocket is bigger, and risk for erosion is higher when pocket is smaller. Once the SCRMhas been inserted, it should be checked for good signal strength by connecting it wirelessly to the remote monitor. This is an important step to reduce false detections. If signal is unsatisfactory, then the device can be adjusted or re-implanted for better signal strength. Once adequacy of signal is verified (usually R waves more than 0.3 mV), the incision can be closed with absorbable suture. Though skin staple is used in some institutes, this appears to be less preferred. Skin glue or dermabond is also being used in some centers which avoids suture removal or staple removal later. Finally, a medium sized band-aid or transparent bandage is applied. The procedure takes about 20-30 minutes. A trained technician explains the monitoring techniqueand safety precautions to the patient and the family. Pain control strategy is individualized but most patients do well with 3-5 days of acetaminophen or non-steroidal medications. It is recommended to keep the insertion site dry for a week, until patients come back to the clinic for a site check. The site should be checked visually for any signs of infection like erythema or drainage. If the insertion site is healed, then the staples or non-absorbable sutures are removed.

SCRMs wereinitially implanted predominantly by electrophysiologists, though non-invasive and invasive cardiologists, and general practitioners have been implanting them increasingly. In some organizations, nurses, and advanced practice practitionersimplant SCRM with significant cost reductions[11,12]. SCRMs were initially implanted in the hospital setting only, mostly in the electrophysiology lab. Current data suggests that SCRMs can be safely implanted even in the office setting. In a non-randomized study (Reveal LINQ In-Office) performed by Rogers et al, SCRM implantation in a non-hospital setting was performed in 65 patients with low complication rate and only 3% of patients requiring device explant[13]. The same authors then conducted a randomized study of 521 patients RIO-2 (Reveal LINQ In-Office-2) and showed that the overall complication rates were similar in patients who underwent SCRM implant in hospital versus office environment[14]. In this study, the implanting providers described

Table 3: Guidelines for current indications for SCRM implantation

Condition / Guideline	Class	Level of Evidence	Recommendations
Atrial Fibrillation			
2019 AHA/ACC/ HRS Atrial fibrillation guidelines	I	B-NR	In patients with cardiac subcutaneous electronic devices (pacemakers or implanted cardioverter-defibrillators), the presence of recorded atrial high-rate episodes (AHREs) should prompt further evaluation to document clinically relevant to AF to guide treatment decisions (S7.12-1-S7.12-5).
	IIa*	B-R	In patients with cryptogenic stroke (i.e., stroke of unknown cause) in whom external ambulatory monitoring is inconclusive, implantation of SCRM (loop recorder) is reasonable to optimize detection of silent AF (S7.12-6).
2020 ESC Atrial Fibrillation guidelines	IIa	B	In selected stroke patients (elderly, CV risk factors, indices of LA remodelling etc), additional ECG monitoring by long-term non-invasive ECG monitor insertable cardiac monitors should be considered, to document AF.
Syncope			
2009 ESC syncope Guidelines	I	B	SCRM is indicated in an early phase evaluation in patients with recurrent syncope of uncertain origin, absence of high risk criteria and a high likelihood of recurrence within the battery longevity of the device
	I	B	SCRM is indicated in High risk patients in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment.
	IIa	B	SCRM should be considered to assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain reflex syncope presenting with frequent or traumatic syncopal episodes.
Cryptogenic Stroke			
Canadian Stroke Best Practice Recommendations: Acute Inpatient Stroke Care Guidelines, Update 2015		C S B P R Evidence Level B	Prolonged cardiac monitoring (up to 30 days) is recommended to assess for paroxysmal atrial fibrillation if cardioembolic mechanism suspected and no evidence of atrial fibrillation on 24-48 hour ECG monitoring
Ventricular arrhythmia / Sudden Cardiac death			
ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death	I	B	SCRMs are useful in patients with sporadic symptoms suspected to be related to arrhythmias such as syncope when a symptom-rhythm correlation cannot be established by conventional diagnostic techniques
	I	C-EO	The choice of a specific cardiac monitor should be determined on the basis of the frequency and nature of syncope events
	IIa	B-R	To evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology, an subcutaneous cardiac monitor can be useful.

the office location to be 'very convenient' and associated with less delays. The patients also had a 'positive experience' more often in the office setting.

SCRMs for cryptogenic stroke:

Stroke is one of the leading causes of morbidity and mortality in the United States[15]. Patients are deemed to have acryptogenic stroke if a cause is not readily identified after routine initial workup.[16] Almost a third of all ischemic strokes are ultimately labelled as cryptogenic and almost a quarter are associated with occult AF[17]. AF remains subclinical in majority of patients and can be missed by rhythm monitoring for short duration. Detection of occult AF and subsequent initiation of anticoagulation can significantly reduce the risk of a recurrent stroke[18,19].

One of the first observational study to evaluate the role of SCRMs in patients with cryptogenic stroke was performed by Dion et al. who prospectively enrolled 24 patients aged≤75 years who had a cryptogenic stroke within the previous 4 months[20]. No sustained arrhythmias were detected after a follow up of 14 months. The major limitation of the study was its small sample size. In contrast,Etgen et al. found subclinical AF of ≥ 6 minutes duration in 17 (27%) of the 65 patients with cryptogenic stroke after one year of monitoring[21]. Cotter et al studied 51 patients with cryptogenic strokeand found subclinical AF in a quarter (25.5%) of patients after a mean follow up of 8 months with median time to detection 48 days[22]. Several other investigators found that SCRMs detected AF of ≥2 minutes duration in 17%-33% of patients with cryptogenic stroke[23–25] with detection times ranging from 60-109 days.

The first randomized study to assess the utility of SCRMs in patients with cryptogenic stroke was the CRYSTAL-AF (Cryptogenic Stroke and Underlying AF) study[23]. This study randomized 441 patients aged ≥40 years to either SCRM implantation or conventional monitoring strategy. After a mean follow up of 6 months, AF was detected in 8.9% in patients with SCRM compared to 1.4% of patients with conventional strategy (hazard ratio (HR) 6.4, 95% confidence interval (CI) 1.9 to 21.7, p<0.001). After 12 months, AF was detected in 12.4% of patients with SCRM versus 2% of the patients with control group (HR 7.3, 95% CI 2.6 to 20.8, p<0.001). The median time for detection was 84 days in the SCRM group. About 79% of these patients had asymptomatic AF which is higher than 60-70% reported prevalence of asymptomatic AF[24,25].The device was found to be safe with only 5 (2.4%) device infections needing explant and 96.6% of patients still had the SCRM inserted after 12 months. Potential reasons for the lower 1-year detection rate in this study compared to the prior observational studies could be the younger age of the study population and lower prevalence of hypertension. Significant differences in detection of subclinical AFpersisted at 3 years (30.0% with SCRM vs 3.0% in control arm, HR 8.8, 95% CI 3.5 to 22.2, p<0.001)[26]. In a recent study, Milstein et al analyzed data from 343 consecutive patients who underwent SCRM implantation for cryptogenic stroke[27]. During first 30 days, only 5% of the patients had AF compared to 21% patients at 1 year. Hence, the authors proposed directly proceeding with SCRM implant prior to hospital discharge in patients with cryptogenic stroke.

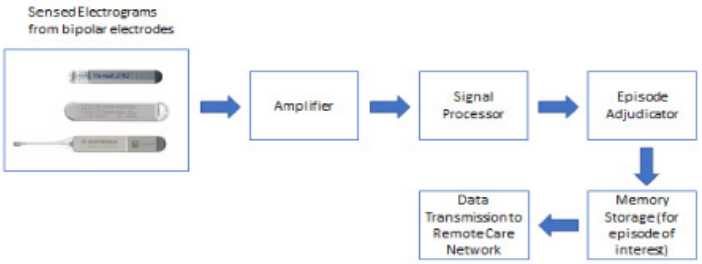

Figure 3: Basic operation of SCRMs

Table 4: Advantages and Disadvantages of different modes on cardiac rhythm monitoring

	Advantages	Disadvantages	Indications
Holter Monitoring	*Low Cost *Continuous monitoring	Limited to 24-48h (<2 weeks) Intrusive *No remote monitoring capability	*Daily/near daily symptoms *Analysis of AHRE burden *Assessment of PVC burden * Diagnosis of inappropriate sinus tachycardia
Event Recorders	*Relatively longer duration – upto 1 month. *Comfortable – intermittent use	*Intermittent monitoring limited to events. *No record of asymptomatic events or arrhythmia *Disabling symptoms or loss of consciousness precludes device activation by the patient. *Selective sequence recording	*3-4episodes/month *Assessment of cardiac etiology of syncope or palpitations.
External loop recorder	*Relatively longer duration – upto 1 month. *Automatic event detection. No patient activation required.	*Device storage is limiting *Selective sequence recording	*3-4episodes/month *Assessment of cardiac etiology of syncope or palpitations.
Subcutaneous cardiac rhythm monitor	*Duration upto 4.5 years *Automatic event detection. No patient activation required.	*Relatively more expensive *Minimally invasive surgery involved. *Selective sequence recording	*Monthly symptoms (Infrequent) * Cryptogenic stroke – assessment for AF. * AHRE burden analysis
Commercially available devices (Smartwatches/ Fitness bands)	*Widely available and non-intrusive *Real time user alerts	*Lack of sufficient validation data on performance. *False positive / clinically insignificant alerts to user contributes to undue anxiety.	*Assessment of cardiac etiology of syncope or palpitations. * AHRE burden analysis * Diagnosis of inappropriate sinus tachycardia

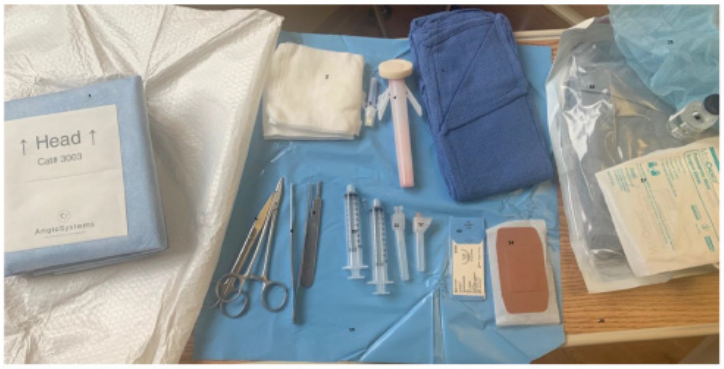

Figure 4: Equipment needed for implantation

Legend:
1 Sterile patient drape
2 4x4 gauze pieces
3 Skin glue
4 Chlorhexidine prep
5 Sterile towels
6 Medium scissors
7 Needle holder
8 Forceps
9 Blade holder
10 10 ml syringes x2
11 22 gauge needle to draw anesthetic
12 26 gauge needle to inject anesthetic
13 Silk suture
14 Skin bandage
15 surgeon hat
16 Surgeon sterile gown
17 Sterile gloves
18 2% Lidocaine with/out epinephrine
19 Sterile drape for tabletop
20 Mayo stand

A meta-analysis of 16 studies, 3 randomized and 13 observational, found significantly higher odds of AF detection with SCRM compared to conventional strategy (OR 4.54, 95% CI 2.92 to 7.06, p <0.00001). Another meta-analysis of 11 studies (a mix of randomized, observational and registry data) also found a 5.7-fold increased detection of AF in patients with SCRM compared to conventional monitoring in patients with cryptogenic stroke[28]. A large multicenter, randomized, controlled, open label trial, Detection of Silent AF after Ischemic Stroke (SAFFO) is currently enrolling patients ≥65 years of age with ischemic or lacunar stroke and randomizing to SCRM versus standard monitoring[29].

Furthermore, available data suggests that device detected atrial high rate events (AHREs) are associated with excess risk of thromboembolism and stroke. One of the first studies to suggest this was a subgroup analysis of MOST (Atrial Diagnostics Ancillary Study of the Mode Selection) study which randomized patients with sinus node dysfunction to either DDDR versus VVIR pacing modes[30]. In the study, AHREs defined as atrial rate >220 beats per minute (bpm) lasting ≥5 minutes wereassociated with a 6-fold increased risk of AF and a more than 2-fold increase in both total mortality and stroke[31]. Similarly, in the ASSERT study (Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial),atrial tachyarrhythmias defined as atrial rates (AR)>190 bpm for ≥6 minutes were associated with a 5.5-fold increased risk of AF and more than 2-fold risk of ischemic stroke or systemic embolism[32].

While a number of consensus groups and professional societies recommend prolonged cardiac rhythm monitoring of patients with cryptogenic stroke, they do not recommend a duration. SCRMs have not yet been included as a standard recommended procedure in any of these guidelines. The most recent 2017 ISHNE/HRS guideline on ambulatory ECG monitoring and the 2020 ESC/EHRA/ESO guidelines for management of AF favor extended cardiac rhythm monitoring though they do not specify the duration for monitoring[33,34]. The only guideline that suggests a duration of monitoring is the 2014 AHA/ASA guideline on prevention of stroke in patients with prior stroke or TIA which recommends 30-day cardiac rhythm monitoring within first 6 months of index event[35]. However, large outcome studies are needed to confirm or refute the benefit of SCRMs in patients with cryptogenic stroke. Whether detection of AF in patients with cryptogenic stroke leads to reduction in incidence of future strokes remains to be seen. Additionally, more studies are needed to address the potential concern for increased bleeding as more patients are started on anticoagulation after detection of a brief subclinical AF episode.

SCRMs for AF detection in patients at risk of AF other than those with cryptogenic stroke:

AF, is the most common cardiac arrhythmiaand35SCRMs have been increasingly used in patients at high risk for AF, other than patients with cryptogenic stroke. Multiple studies have found AF even in patients with TIA or stroke from a known cause. Among patients with any stroke, Rabinstein et al. found AF in 14% patients with 3-week ambulatory ECG monitoring while Grond et al in a larger study of 1135 patients with any stroke or a TIA reported silent AF in 4.3% after 72-hour Holter monitoring[36,37]. The ongoing STROKE-AF (Stroke of Known Cause and Underlying AF) is a multicenter, randomized

Table 5: Future areas of research in the field of subcutaneouscardiac rhythm monitors

1. Threshold duration for SCRM- detected atrial fibrillation to initiate anticoagulation which will maximize the benefit to risk ratio
2. Determining whether patients who have other identified risk factors for stroke on initial workup will benefit from SCRM implant to look for occult atrial fibrillation
3. Improving the SCRM algorithms to reduce the burden of false readings
4. Determining whether administration of antibiotics pre-implant is cost effective in reducing device infections
5. Determining the optimal site of implant for best possible signal and concomitantly reducing false readings
6. Determining the optimal amount of local anesthetic and post implant pain control strategies
7. Cost-effectiveness of SCRMs in patients with different indications for best selection of patients
8. Implantation of SCRM for detection of arrhythmias in high-risk populations

controlled trial that aims to compare detection of AF using an SCRM versus standard therapy in patients with a recent stroke presumed to be due to large vessel cervical or intracranial atherosclerosis, or small vessel disease[38].

The ongoing LOOP study will shed light on the clinical impact of SCRM on stroke reduction by screening patients for occult AF and initiating anticoagulation[39]. In the recently published sub-study analysis of 597 patients enrolled in the LOOP study,[40] AF was found in 35% of patients after 40 months with cumulative incidence for episodes lasting ≥6 minutes, ≥5.5 hours and ≥24 hours being 33.8%, 16.1% and 5.7% respectively. Notably, despite the high prevalence of AF, overall burden was low at 0.13% , only 16% of patients progressedto having 24 hour episodes and the vast majority (90%) remained asymptomatic[41]. SCRMs have also been used to monitor the success of rhythm control strategy in patients undergoing percutaneous or surgical ablation and can be particularly important when making decisions regarding cessation of anticoagulation[42–44].

SCRMs for unexplained syncope:

Syncope accounts for about 1-2% of emergency department visits and 6% of hospital admissions with an annual cost of $1.7 billion in the United States alone[45]. Various guidelines have been published for evaluation and management of patients presenting with syncope[46]. An unexplained syncope is defined as syncope for which the cause is undetermined after a thorough history, physical examination including orthostatic vital signs and ECG[47]. SCRMs have been shown to be important diagnostic tools for evaluation of unexplained syncope particularly when a dysrhythmia is suspected. One of the first randomized studies to evaluate the role of SCRMs in patients with syncope was the RAST (Randomized Assessment of Syncope Trial) study which randomized 60 patients to SCRM versus conventional monitoring[48]. After a mean follow up of 10.5 months, SCRMgroupwas significantly more likely to have a diagnosis (55% in SCRM vs 19% in conventional group). Theinvestigators alsodemonstrated that prolonged monitoring with SCRM was more cost effective than conventional monitoring[49]. Similarly, Edvardsson et al.in a study of 650 patients with unexplained syncopereported that 78% of patients (n=170) who had recurrent episode (only 218 of 650 pts) had received a diagnosis from ICRM and 51% of those patients received pacemaker[50]. In another study, patients in the SCRM-guided strategy who underwent permanent pacemaker implantation were 57% less likely to have a syncopal spell during follow up[51]. A number of other investigators have demonstrated similar success of SCRM guided strategy in identifying prolonged pauses or asystole needing pacemaker even in those with alternative diagnosis such as postural orthostatic tachycardia syndrome (POTS).[52,53] Current guidelines on the indications for SCRM implantation are listed in Table 3.

SCRMs for infrequent palpitations:

Palpitations are one of the most common reasons for visit to the primary care physician or emergency department[54]. They can be infrequent, sometimes with patients being symptom free for months. Such infrequent episodes may be missed by traditional ambulatory ECG monitors. For a select group of patients with disabling episodes of palpitations that have been missed by Holter and event monitors, SCRM implantation can be considered[55]. However, there are no published studiesregarding use of SCRMs in such patients.

SCRMs for detection of arrhythmias in other high-risk patients:

Dodeja et al retrospectively studied 22 patients with adult congenital heart disease who underwent SCRM implantation[56]. SCRM findings resulted in change in management in 41% of the patients with one-third of events being asymptomatic. In another study evaluating the role of SCRMs inpatients with adult congenital heart disease, SCRMs led to a diagnosis in 59% of the patients with median time to diagnosis being 4.5months[57]. Patients on hemodialysis have also been found to be at high risk of arrhythmias which can be detected with SCRMs[58].In a study of patients on hemodialysis, SCRMs shed light on the causes of sudden death demonstrating the burden of silent arrhythmias in this population[59].A recent study showed the possible benefit of SCRMs in patients with congestive heart failure; 43% of patients hadSCRM guided therapeutic changes[60]. Another group at risk for arrhythmias is patients who have sleep apnea with 20% of patients found to have occult AF[61].

Studies comparingSCRMs and other modes of monitoring:

In the prospective ABACUS (Assessing Arrhythmia Burden After Catheter Ablation for AF Using an Subcutaneous Loop Recorder), Kapa et al demonstrated the superiority of SCRM indetermining the success of AF ablation62. After one year, 60% patients were found to have AF by SCRM compared to 31%with conventional monitoring. In contrast, Podd et al. demonstrated that SCRMis inferior to a permanent pacemaker set at ODO mode(monitoring only) for detecting AG following ablation[63]. Pacemaker group had significantly more AF detection rate (97% vs 55%, p<0.001) and positive predictive value (100% vs 58%, p = 0.03) compared to the SCRM group. In a recently published study, Mamchur et al studied 53 patients with AF were randomized to an SCRM or a noninvasive ambulatory ECG monitoring device[64]. The diagnostic value was comparable between the two groups with no additional diagnostic information after 2 weeks of monitoring. However, the SCRM group was only monitored for 3 months which was a major limitation of this study as detection rates continues to rise with longer monitoring. In a sub-analysis of the LOOP study, various other rhythm monitoring strategies were compared to SCRM and were found to be more sensitive in patients who were older, men and those with higher NT-proBNP values[65]. The diagnostic yield increased with increased number of duration, dispersion and number of screenings. The advantages and disadvantages

of SCRMs compared to other modes of rhythm monitoring are listed in Table 4.

Safety:

SCRMs are associated with low complication rates overall and most complications occur within a few days of implantation. In a study of 540 patients, overall complication rate was 3.3% with majority being implant site infection and implant site pain leading to explant or pocket revision66. In the CRYSTAL-AF study, overall explant rate at 12 months was 3.4% with infection, pain and inflammation at the insertion site being the most common adverse events[23].

Data Management:

While SCRMs provide an invaluable source of diagnostic data, they also can easily overwhelm the staff who have to manage this data. The precise management of SCRM data and alerts is imperative to reduce alarm fatigue and data overload (which can lead to missed abnormal rhythms). There are 2 essential parts to manage SCRM data – the first being how the device is programmed at implant and subsequent visits (based on patient specific needs) and the second is how the alerts are programmed on the websites.

Keeping all alerts and detection criteria for all diagnosis on for all patients can significantly increase the unnecessary data that is received. This can contribute to increased workload burden to the clinic staff and create alarm fatigue. Prior to turning on any alert or detection criteria for a patient, the clinician should always ask the question, "is this going to prompt clinical action for this patient?" If the answer is no, then it is likely that turning that alert on or detection criteria would not provide any contribution to that patient's care and in fact could increase alarm fatigue potentially leading to a true arrhythmia being missed.

The other recommendation to alert management is disabling non-critical alerts. For example, symptomatic episodes that do not coincide with a detected episode and AF in patients with known AF and on anticoagulation. Instead of getting alerted for each episode (which could be hundreds), for these patients it may be better plan to review those episodes and the overall burden every 31 days. If the clinician is constantly reviewing multiple episodes at this time and once again, no clinical action is taken, it is recommended to program the device more aggressively. For example, if the patient has known AF and has had multiple episodes of 6 minutes which have not prompted any change in therapy, consider programming the device to record episodes of AF if they last greater than 6 hours or if the average ventricular rate is 100 bpm or greater.

The most important way to manage data overload is minimizing inappropriate detections. These are most commonly caused by undersensing, oversensing, or when the algorithm misinterprets the rhythm (i.e. calls sinus rhythm with PACs AF).

Frequent undersensing commonly leads to numerous false episodes of pauses and bradycardia. When there are frequent false pause and brady episodes due to undersensing, consider increasing the sensitivity and increasing the detection criteria (i.e. for pause change from 3 sec to 4.5 sec or bradycardia change from 4 beats to 8 beats).

For those practices that have difficulty managing their SCRM data, an option to consider is investment in a software platform or 3rd party vendor to outsource the data management. Some companies provide both the software platform, others provide just the service component, while some provide both as well as allow for a hybrid model to allow the customer to choose how much and which patients they want manged by them. Examples of these vendors include PaceArt Optima (Medtronic), Scottcare, Geneva, Muse, and Pace Mate to name a few. The benefit of using some over the other is that some provide a service component.

Future areas of research:

SCRMs are relatively new in the realm of cardiology compared to other monitoring devices. Table 4 lists the areas for future research with SCRMs. Ischemic strokes can happen even after AF detection and initiation of anticoagulation. In the SURPRISE study, SCRMs detected AFin 18 out of the 85 patients with cryptogenic stroke[67]. However, there were 4 recurrent strokes with 3 of those in patients with diagnosed AF despite being on oral anticoagulation. In the CRYSTAL-AF study after 12 months follow up, even though the rate of use of oral anticoagulants was 14.7% in the ICM group versus 6% in the control group, 7.1% of the patients with SCRMs had a recurrent stroke versus 9.1% patients in the control group[23]. It is therefore obvious that AF is not the sole cause of stroke in a proportion of patients with cryptogenic stroke and SCRM detected AF. Patients who had an ischemic stroke and a positive finding of PFO on echocardiography pose a unique challenge to the clinician to determine whether to close the PFO or evaluate for occultAFor both. A recent study by Scacciatella et al found that SCRMs detectedAF≥5 minutes in a significant number of patients (14.3%) who underwent PFO closure68. There are no published guidelines in this respect.We propose consideration for SCRM implantation and monitoring for at least 6 months before closing the PFO though this approach has not been tested.

False positive readings are an area of huge concern due to the huge burden on device clinics and significant healthcare cost associated with this. In a recent study, the false positive detection rate was found to be 46-86% depending upon indication for implantation, with higher false positive rates for SCRMs implanted for cryptogenic stroke and syncope compared to those implanted for AF surveillance[69]. In the ABACUS study, false positive detection rate for AF with SCRM was 51%[62]. The false positive rate was found to be 31% in the DISCERN study where 50 patients with prior known AF were monitored with SCRM[70]. It is likely that this false positive detection rate is higher in real world practice and can expose patients to excess risk of bleeding from unwarranted anticoagulation. Manufacturers should continue to work on improving algorithms for detection and improving the overall sensitivity and specificity of the devices to address this concern for "data overload"[71]. Triaging the incoming data remains one of the biggest challenges in managing patients with an SCRM. Another related area is reliability of data transmission to a central portal for physician review.

Whether there is a learning curve to implanting an SCRM has also not been studied. The value of peri-implant antibiotics, the optimal amount of anesthetic that should be used during implant and the best regimens for postoperative pain control have not been studied. Another area that needs further study is the optimal site and orientation of implant as different implant sites can have difference in output signals from atrium and ventricle and hence limit sensitivity and/or specificity. The cost effectiveness of SCRMs in various settings also needs to be evaluated so those patients with the most possible benefit

can be selected.

Finally, SCRMs face increasing competition from newer small wearable devices like Apple Watch with Kardiaband (Alivecor Inc) and Fitbit (Fitbit Inc)[72]. Apple watch was found to be better than Fitbit in detecting AF in one study of 40 patients who underwent cardiac surgery[73]. Wasseerlauf et al compared Apple watch with SCRM for detection of AF in 24 patients with prior history of AF[74]. The sensitivity of the watch compared to SCRM was 97.5% with positive predictive value of 40%. However, 3 of the 18 patients with AF>1 hour had AF only when watch was not being worn thus showing the limitation of wearable devices compared to SCRM. In the large Apple Heart Study recruited >400,000 patients, 34% of the patients who returned ECG patches usable for analysis had AF with 84% positive predictive value and no reports of serious app-related adverse events[75]. The future areas of research are listed in Table 5.

Conclusion:

SCRMs facilitate improved arrhythmia detection in patients with unexplained syncope, AF detection in cryptogenic stroke and have become an important part of cardiac diagnostic armamentarium. Technologic advances like device miniaturization and prolonged battery life, decreasing costsand ease of implantation have resulted in increasing use of SCRMs. Future research should focus on improving diagnostic accuracy by minimizingfalse positive detections and defining appropriate patient selection criteria in this era of Apple watch and other smart wearable devices.

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Screening for Atrial Fibrillation in Community and Primary Care Settings: A Scoping Review

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Abstract

Background: Atrial Fibrillation (AF) is the most common tachyarrhythmia and is associated with increased risk of stroke, morbidity and mortality. AF is responsible for up to a quarter of all strokes and is often asymptomatic until a stroke occurs.Screening for AF is a valuable approach to reduce the burden of stroke in the population.

Objectives:The motivation for this review was to synthesise and appraise the evidence for screening for AF in the community. The aims of this scoping review are 1). To describe the prevalence of newly diagnosed AF in screening programmes 2). Identify which techniques/ tools are employed for AF screening 3). To describe the setting and personnel involved in screening for AF.

Eligibility Criteria: All forms of AF screening in adults (≥18 years) in primary and community care settings.

Methods: This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping reviews (PRISMA-ScR).

Results:Fifty-nine papers were included; most were cross-sectional studies (n=41) and RCTs (n=7). Prevalence of AF ranged from 0-34.5%. Screening tools and techniques included the 12-lead ECG (n=33), the 1-lead ECG smartphone based Alivecor® (n=14) and pulse palpation (n=12). Studies were undertaken in community settings (n=30) or in urban/rural primary care (n=28). Personnel collecting research data were in the main members of the research team (n=31), GPs (n=16), practice nurses (n=10), participants (n=8) and pharmacists (n=4).

Conclusion: Prevalence of AF increased with advancing age. AF screening should target individuals at greatest risk of the condition including older adults ≥65 years of age. Emerging novel technologies may increase the accessibility of AF screening in community and home settings. There is a need for high quality research to investigate AF prevalence and establish accuracy and validity for traditional versus novel screening tools used to screen for AF.

Introduction

Atrial fibrillation (AF) is the most common, sustained, progressive tachyarrhythmia worldwide and is associated with increased risk of stroke, systemic embolism and increased morbidity and mortality[1, 2]. AF is associated with higher morbidity and mortality rates than other cardiac arrhythmias[3]. AF represents a significant public health problem that places a burden on health resources and constitutes a public health challenge with high comorbidity [5]. The most frequent co-morbidities associated with AF are hypertension, diabetes mellitus, congestive heart failure, ischaemic heart disease and valvular heart disease[4]. Male gender is an established risk factor for AF however due to greater longevity in females the prevalence across both genders is equivalent [4]. The clinical presentation of AF varies significantly in severity and type[4]. Symptoms are often related to tachycardia and can include palpitations, dizziness, chest pain and dyspnoea[5]. However, symptoms can be non-specific or absent. Thus, up to one third of AF cases are not recognised because they are asymptomatic and have silent or subclinical AF [4].

The global prevalence of AF was 191.3 rate per 100,000 in 2013[4] with approximately 1-3% of the population affected [5]. Both the prevalence and incidence of AF increase markedly with advancing age[5] with reports of AF prevalence of 4.2% in people aged 60-69 years of age[6]. Hence, due to an ageing population the prevalence of AF is increasing; it is predicted that AF will affect 6-12 million people in the USA by 2050 and 17.9 million people across Europe by the year 2060[7]. However, it can be argued that the true prevalence of AF is unknown. This may be due to a lack of, or limited access to screening for AF and the fact that AF is often asymptomatic or silent[4]. AF often remains

Key Words

Atrial fibrillation, Opportunistic screening, Systematic screening, Arrhythmia, Community, Primary Care,

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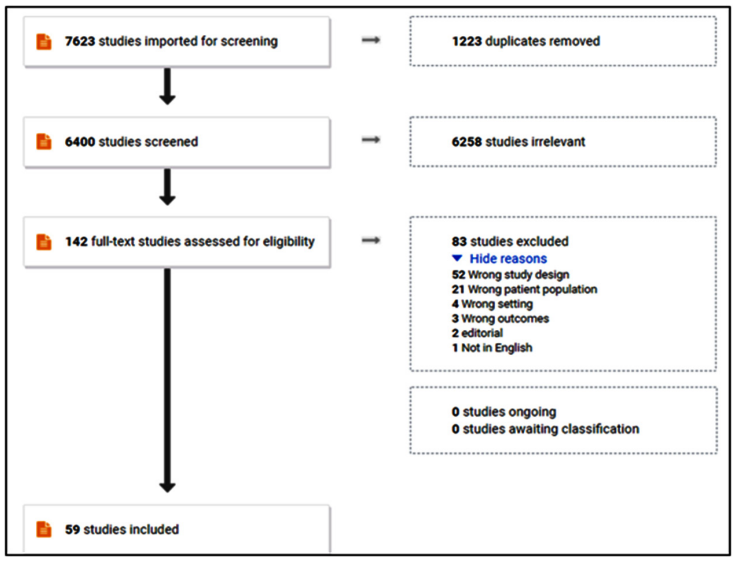

Figure 1: **PRISMA Flowchart.**

undiagnosed and untreated which can lead to devastating outcomes. AF is associated with increased risk of systemic embolism and stroke, in fact AF is found in one third of all ischaemic strokes[7].Early identification of AF allows for early antithrombotic treatment which can reduce the incidence of stroke and premature death in patients with AF[2]. AF is also associated with significant morbidity, as measured by disability-adjusted life years [7]. Screening for AF is recommended in European guidelines in all patients >65 years of age[8]. The main rationale for AF screening is to prevent stroke in the population by identifying those with the condition and allowing for early anticoagulation treatment and thus prevent ischaemic events and reduce morbidity and mortality [4]. Opportunistic screening is defined as a screening programme that uses a health care professional to check for AF during routine consultations. Whilst systematic screening is defined as a programme where all people above a certain age or who reach set criteria are invited to attend a location for screening[9]. Various clinical techniques can be employed to screen for AF including pulse palpation and 12 lead ECG with expert interpretation[10]. The advent of novel technologies including devices such as portable smartphone ECGs and photoplethysmography are emerging which, will make AF screening more accessible in community and homesettings. However, currently the most effective method of screening for AF remains unclear and given the diverse approaches to AF screening and the tools and techniques employed there is a need to review the current evidence-base[10]. The scoping review did not aim to assess technical or statistical aspects of existing and novel technologies for AF screening. Rather, the motivation for this review is to explore the breadth and extent of the literature, synthesise, appraise the evidence for screening for AF in community settings and inform future research. Therefore, a scoping review methodology was chosen. The aims of this scoping review are 1). To describe the prevalence of newly diagnosed AF in screening programmes 2). Identify which clinical techniques/ tools are employed for screening for AF 3). To describe the setting and health professionals involved in screening for AF in community and primary care settings.

Methods

Protocol

We performed a scoping review in a structured manner, to synthesise the available evidence. We followed the methodology of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping reviews (PRISMA-ScR)[11].

Eligibility Criteria

Inclusion Criteria: Research articles published between the years 2000-2020 and written in the English language. The search timeframe was chosen to ensure currency of the evidence in relation to the tools used in AF screening. All forms of screening for new diagnosis of AF in adults (≥18 years) in primary and community care settings were included.

Exclusion Criteria: Studies not in the English language and those out with the period under investigation. Systematic reviews, meta- analyses, reports, pilot studies or unpublished studies were excluded. Participants must not have had a previous AF diagnosis. Studies that consisted of follow-ups for patients that had obtained treatment for AF, studies where AF screening was conducted in an acute/hospital setting, studies where AF was identified post stroke/surgical intervention, studies where AF was diagnosed after a period of monitoring were all excluded.

Information Sources

We carried out a systematic search of databasesincluding Scopus, Google Scholar, Pubmed, Science Direct, Medline and Embase. A grey literature search of the literature was conducted. The literature searches took place in April 2020.

Search Strategy

We used a population, intervention, and outcomes-based approach to identify our search strategy. The population under investigation were people with AF, the intervention was opportunistic or systemic screening and the outcomes were the prevalence of AF, screening tools used, and the setting and health professionals involved in screening for AF. The search commenced on 2nd of April 2020. The databases included were Pubmed (02.04.2020), Scopus (02.04.2020), Google Scholar (06.04.2020), Science Direct (09.04.2020), Medline (09.04.2020) and Embase (10.04.2020). The last search took place on 28.04.2020. This final search included papers identified through reference lists of included papers. All papers were imported into Covidence and duplicates were removed.

The search used the mesh terms generated from the PICO question

Table 1: **Keywords used for the literature search .**

Population	Intervention	Outcome
Atrial Fibrillation Or Cardiac abnormality Or Cardiac arrhythmia Or Uncoordinated atria contractions Or Vascular Disease	Opportunistic Screening Or Systematic Screening Or Pulse palpation Or ECG Rhythm Strip Or Smartphone ECG 12- ECG	Diagnosed AF Or Identifying AF

Table 2: Boolean Operators employed

1 :EXP atrial fibrillation
2 :Cardiac* Abnormality/
3 :EXP arrhythmia*
4 :Uncoordinated atria contraction adj3
5 :Vascular Disease/
6 :1 or 2 or 3 or 4 or 5
7 :EXP opportunistic* screen*
8 :EXP systematic* screen*
9 :pulse palpation
10 :ECG rhythm strip
11 :12* lead ecg
12 :smartphone ecg
13 :7 or 8 or 9 or 10 or 11 or 12
14: diagnose* atrial fibrillation adj3
15: identify* atrial fibrillation adj3
16: 14 or 15
17: 6 and 13 and 16

to identify studies (table 1). The Boolean operators used are detailed in table 2.

Selection of Sources of evidence

The systematic review management system Covidence was used for the study selection process (www.covidence.org). The review was carried out in four stages: import references, title and abstract screening, full text screening and extraction. On import into Covidence, duplicate papers were automatically removed. Two authors independently screened all titles and abstracts (EC, CMcI, CMacG), any disagreement on papers were discussed between authors until consensus was reached. In phase two,potentially eligible articles were reviewed in full text and any disagreements were resolved between co-authors (EC, CMcI, CMacG).

Data Charting Process

One author (EC) extracted data using a standardised data extraction form in Excel and a second author (CMcI, CMacG) then independently verified the extracted data. The data extraction form was based on JBI guidelines on data extraction for scoping reviews[12].

The following study characteristics were extracted: year of publication, country, setting, study design, participant recruitment, screening tool, data collectors, screening type, eligibility criteria, sample size, gender, risk factors, number of participants with new AF diagnosis, prevalence of AF.

Critical Appraisal of Individual Sources of Evidence

We undertook a narrative synthesis of the research literature assessing systematically and comprehensively the results of each study, highlighting important characteristics of the included studies without quality assessment or extensive data synthesis [13].

Results

We included 59 studies. A PRISMA flow chart (see figure 1) displays the flow of papers and reasons for exclusion.

Studies were conducted across 22 different countries. The majority of studies were conducted in the USA (n=10), the UK (n=7), Italy (n=5), Hong Kong (n=5), Spain (n=4) and Sweden (n=4), other countries included Australia (n=3), Ireland (n=3), Germany (2), Norway (n=2), China (n=2), Canada (n=2) Denmark (n=1), New Zealand (n=1),

Table 3: Country of research, age, sample size and prevalence of newly diagnosed AF in the research studies

Study	Location	Age	No. of Participants	AF Prevalence %
Perez et al., 2019[37]	USA	Not reported	415787	Not reported
Yan et al., 2018[26]	Hong Kong	Not reported	217	34.50%
Lau et al., 2013[43]	Australia	>/65	109	27.80%
Soliman et al., 2010[44]	USA	21-74	3257	18%
Heckbert et al., 2018[34]	USA	>/57	1415	17.50%
Ghazal et al., 2018[27]	Sweden	70-74	324	15.40%
Engdahk et al., 2013[26]	Sweden	75-76	848	14.30%
Wiesel Abraham and Messineo 2013[45]	USA	>/65	139	13.43%
Walker et al., 2014[27, 46]	New Zealand	>/65	121	12.40%
Svennberg et al., 2015[27]	Sweden	75-76	7173	12.30%
Cunha et al., 2020[26]	Portugal	>/40	205	11.20%
Salvatori et al., 2015[25]	Italy	>/65	304	11%
Kearley et al., 2014[47]	UK	>75	999	11%
Clua-Espuny et al., 2013[48]	Spain	>60	1043	10.90%
Smyth et al., 2016[49]	Ireland	>/65	7262	10.90%
Bury et al., 2015[11]	Ireland	>/70	566	10.30%
Scalvini et al., 2011[50]	Italy	Not reported	1719	9.70%
Scalvini et al., 2005[51]	Italy	Not reported	7516	9.60%
Hobbs et al., 2005[24]	UK	>/65	14802	8.08%
Gonzalez Blanco et al., 2017[52]	Spain	>/65	6990	7.90%
Loehr et al., 2019[53]	USA	Not reported	2434	7.15%
Baber et al., 2010[33]	USA	>/45	26917	6.77%
Lowres et al., 2014[54]	Australia	>/65	1000	6.70%
Morgan and Mant 2002[35]	UK	>/65	1538	5.30%
Huang et al., 2018[32]	China	>/80	1038	5.30%
Turakhia et al., 2015[55]	USA	>/55	75	5.30%
Grubb et al., 2019[23]	UK	>/65	1805	5.10%
Jaakkola et al., 2017[22]	Finland	>/75	215	4.90%
Wiesel and Salomone 2017[56]	USA	>/65	11	4.90%
Berge et al., 2018[6]	Norway	63-65	3706	4.50%
Rhys Azhar and Foster 2013[57]	UK	>/65	573	4%
Godin et al., 2019[23]	Canada	>/65	7585	4%
Orchard et al., 2016[58]	Australia	>/65	972	3.80%
Kaassenbrood et al., 2016[59]	Netherlands	>60	9450	3.70%
Bacchini et al., 2019[2]	Italy	>/50	3071	3.20%
Ostgren et al., 2004[60]	Sweden	>/40	1739	3.20%
Schnabel et al., 2012[61]	Germany	34-74	5000	3.20%
Frewn et al., 2013 [21]	Ireland	>/50	4902	3%
Habizadehet et al., 2004[31]	Iran	>50	463	2.80%
Quinn et al., 2018[62]	Canada	>/65	2054	2.70%
Steinhubl et al., 2018[63]	USA	>/65	2054	2.70%
Chan et al., 2016[19]	Hong Kong	>/65	1013	2.60%
Halcox et al., 2017[64]	USA	>65	1001	2.50%
Chan et al., 2018[30]	Hong Kong	>50	11574	2.40%
Suzuki et al., 2015[23]	Japan	40-90	12410	2.40%
Benito et al., 2015[5]	Spain	>/65	928	1.83%
Omboni and Verberk 2015[36]	Italy	>/18	220	1.80%
Chan et al., 2017[29]	Hong Kong	>/18	1322	1.80%
Fitzmaurice et al., 2007[10]	UK	>/64	14802	1.60%
Soni et al., 2018[22]	India	>40	2100	1.60%

Yap, Pin and Ong 2007[21]	China	>/55	1839	1.50%
Chan et al., 2017[28]	Hong Kong	>/65	5969	1.20%
Hald et al., 2016[20]	Denmark	>/65	970	1.03%
Gill et al., 2011[19]	UK	Not reported	5408	0.95%
Berge et al., 2018[4]	Norway	>65	1510	0.90%
Dewhurst et al., 2012[14]	Tanzania	>70	2232	0.67%
Brunner et al., 2017[18]	Germany	>18	7159	0.66%
Rodriguez-Captain 2017[65]	Spain	Not reported	13179	0.40%
Muthalay et al., 2018[14]	Uganda	>18	856	0%

Finland (n=1), Japan (n=1), India (n=1), Tanzania (n=1), Netherlands (n=1), Uganda (n=1), Portugal (n=1),Iran (n=1) (table 2).

Setting

The majority of studies were undertaken in community settings (n=30) or in urban/rural primary care (n=28). Only one study used multiple different settings.

Study Design

Of the 59 studies included there were n=41 cross sectional studies, n=7 randomised controlled trials,n=6 longitudinal studies, n=2 observational cohort studies, n=1 pseudo longitudinal study n=1 parallel arm cluster controlled study and n=1 prospective pragmatic study.

Prevalence of newly diagnosed AF

The mean prevalence rate of AF across the 59 studies was 6.2%. The prevalence of newly diagnosed AFwas wide ranging across the studies at 0-34.5%. African and Asian countries showed the lowest prevalence; in the African studies the prevalence ranged from 0-0.67%[14, 15]. A low prevalence of AF was also observed in a UK study that screened minority ethnic groups(0.95%)[16]. Studies conducted in Asian countries generally showed lower prevalence figures ranging from 1.2-5.3%[17-25] with the exception of one study based in Hong Kong where the prevalence of AF was 34.5% (26). Participants in this study were recruited directly from Cardiology clinics. European and American countries showed the highest prevalence rates. In Europe, studies conducted in Sweden reported the highest prevalence rates of AF ranging from 12.3-15.4%(27-29)(Table 2).

Screening tool

A range of tools were used to screen for AF; the majority of studies used the 12 lead ECG (n=33), the 1 lead ECG- smartphone based Alivecor® (n=14) and pulse palpation (n=12), other tools employed included the 7 lead (n=1) and 3 lead ECG (n=1), 1 lead handheld portable ECG (Zenicor®) (n=4), 1 lead CardioCard® (n=1), 1 lead Cardio-A Palm® ECG (n=1), 1 lead MyDiagnostick® (n=1), 1 lead Omron monitor® (n=1), 1 lead HeartCheck® (n=1). Thirty-one studies used only one tool, twenty-three studies used two tools, four studies used three tools and one study used five tools.Several studies employed more than one screening tool; thirty one groups used one tool, twenty two groups used two tools, four groups used three tools and one group used four tools (31(1) +22(2) + 4(3) +4 = 91) (table 3).

Data Collectors

In the majority of studies the personnel collecting the research data were members of the research team (n=31), this was followed by GPs (n=16), practice nurses (n=10), participants themselves (n=8), pharmacists (n=4), trained non-medical volunteers (n=4), cardiac nurse (=2), health care worker (n=1) and Clinical Events Adjudication Committee (n=1). In some studies, multiple personnel were involved in data collection. Cardiologists reviewed ECG readings in 31 studies.

Screening Type

The majority of studies employed systematic screening (n=29) and opportunistic screening (n=26), four studies used both opportunistic and systematic screening.

Discussion

We report the findings of a scoping review, a form of structured evidence collation, used to address a broad research question[12].The objective of this scoping review was to broadly synthesise and appraise the evidence for screening for AF in community settings. More specifically, we set out to describe the prevalence of newly diagnosed AF in screening programmes, identify which clinical techniques/ tools are employed for screening for AF and to describe the setting and health professionals currently involved in screening for AF in community and primary care settings.

Prevalence of AF

The mean prevalence rate of AF across the 59 studies was 6.2%, however the prevalence of newly diagnosed AF was wide ranging from 0-34.5% across the studies and therefore the mean prevalence should be interpreted with caution. The highest prevalence for AF was reported in a Hong Kong based study (34.5%) (27). This study used a novel method of AF screening using an iPhone camera to detect and analyse photoplethysmographic signals from the face by extracting subtle beat to beat variations of skin colour that reflect the cardiac pulsatile signal [27]. However, participants in this study were recruited directly from cardiology services, which, is likely to have inflated the prevalence of AF given the population under investigation.There is a high chance of selection bias in this study given the methodological approaches employed. The lowest prevalence of AF was 0%; this low prevalence was reported following a screening programme set in community health fairs, targeting eight villages in rural Uganda [14]. Residents of Nyakabare Parish were invited to free community health fairs and 856 (47.2%) adults in the area attended.The patients underwent a 10 second seated ECG recording using a portable ECG machine (CardioCard Digital ECG Box®)[14]. The authors conclude that AF appears to be less prevalent in rural Uganda than in developed countries and this may be due to genetic and/or environmental factors or related to survivorship bias. However, the profile of the population under investigation was

Table 4: Prevalence AF Risk Factors

Risk Factors	Range (%)
Hx of Hypertension	4.5-100%
Hx of Diabetes Mellitus	2.3- 45.9%
Hx of Tia/Stroke	1-18.9%
Hx of Heart Disease	1.1-50.7%
Hx of Smoking	2.7-50.9%
Hx of Heart Failure	0.3- 32%

Table 5: Summary of the Data Collection Tool employed in the Research Studies

Data Collection Tool	Study	Total
12-lead ECG	Brunner et al., 2017, Baber et al., 2010, Berge et al., 2018, Chan et al., 2016, Dewhurst et al., 2012, Frewn et al., 2013, Ghazal et al., 2018, Godin et al., 2019, Habibzadehet et al., 2004, Salvatori et al., 2015, Chan et al., 2017, Clua-Espuny et al., 2001, Fiztmaurice et al., 2007, Engdahk et al., 2013, Gill et al., 2011, Blanco et al., 2017, Hald et al., 2016, Hobbs et al., 2005, Huang et al., 2018, Jaakkola et al., 2017, Kearly et al., 2014, Lau e al., 2012, Loehr et al., 2019, Morgan and Mant 2002, Orchard et al., 2016, Ostgren et al., 2004, Quinn et al., 2018 Rhys Azhar & foster 2013, Rodriguez-Captain et al., 2016, Scalvini et al., 2005, Scalvini et al., 2010, Schabel et al., 2012, Smyth et al., 2016, Solimon et al., 2010, Yan et al., 2018	35
7- lead ECG	Baber t al., 2010	1
3- lead ECG	Bury et al., 2015	1
1 lead ECG – smartphone based alive cor	Brunner et al., 2017, Chan et al., 2016, Chan et al., 2017, Godin et al., 2019, Grubb et al., 2019, Chan et al., 2018, Chan et al., 2017, Cunha et al., 2020, Halcox et al., 2017, Jaakkola et al., 2017, Lau et al., 2012, Lowres et al., 2014, Orchard et al., 2016, Soni et al., 2018	14
1 lead handheld portable ECG Zenicor	Berge et al., 2017, Chazal et al., 2018, Engdahk et al., 2013, Svennberg et al., 2015	4
1 lead CardioCard	Muthalay et al., 213	1
1 lead Cardio-A Palm ECG	Omboni and Verberk 2015	1
1 lead MyDiagnostick	Kassenbrood et al., 2016	1
1 lead Omron Monitor	Kearly et al., 2014	1
1 lead HeartCheck	Quinn et al., 2018	1
Pulse Palpation	Benito et al., 2015, Cunha et al., 2020, Fitzmaurice et al., 2007, Blanco et al., 2017, Hald et al., 2016, Hobbs et al., 2005, Jaakkola et al., 2017, Lowres et al., 2014, Morgan and Mant 2002, Quinn et al., 2018, Rhys, Azhar and Foster 2013, Smyth et al, 2016	12
Cardiac Examination	Berge et al., 2018	1
24-48 hour Holter Monitor	Salvatori et al., 2015, Loehr et al., 2019, Quinn et al., 2010	3
Medical Records	Clua-Espuny 2013	1
Cardio Rhythm Smartphone 3PG waveforms	Chan et al., 2016 Yan et al., 2018	2
MicrolifeAFIB (BP monitor used to detect AF)	Bacchini et al., 2019, Chan et al., 2017, Kearly et al., 2014, Omboni and Verberk 2015, Quinn et al., 2018, Wiesel, Abraham and Messineo 2013, Wiesel and Salomone 2017	7
Zio Patch XT (single channel ECG patch monitor)	Heckbert et al., 2018, Steinhubl et al., 2018, Turakhra et al., 2015	3
Applewatch Photoplethysmography	Perex et al., 2019	1
Heartrak 2 (ECG event monitor)	Wiesel, Abraham and Messineo 2013	1

*Some studies employed more than one methods of screening

young. The sample consisted of 320 (37.5%) men; the mean age was 42.3 ± 17.5 years. Only 127 (14.8%) participants were aged >65 years old [14]. AF prevalence is known to increase significantly with advancing age and therefore the reported 0% prevalence should be interpreted with caution.

Prevalence rates of AF varied across continents, which, could be due to genetic or environmental factors. The prevalence of primary AF risk factors, for instance hypertension and diabetes, are increased in racial and ethnic minorities [30]. However, it has been shown consistently in epidemiological studies and clinical trials, that there is a lower incidence and prevalence of AF in ethnic and racial minorities[30,31]. In this study, it was apparent that prevalence rates were generally lower in low and lower middle-income countries compared to upper middle income and high income countries. Ethnic and racial minorities are less likely to be insured and have primary care providers andthe limited participation of minorities in trials for AF management and stroke prevention has previously been recognised[30,31].

Only two community-screening studies took place in African countries (Tanzania and Uganda)[15,16]. In both studies,screening took place in rural villages. It is feasible that many older people with comorbidities and at high risk of AF might not have had the means to travel to the centres to partake in the screening programme hence the younger profile of the study participants [14].As AF is often asymptomatic, AF may be viewed as less of a public health concern therefore screening initiatives may not be a priority in lower income countries with limited health resources. Opportunistic screening is often reliant on patients attending paid appointments, or a government-funded appointment. People in lower income countries are more likely to have limited resources to access healthcare making opportunistic screening challenging in these populations[31].Clinicians have also argued that AF might be lower in ethnicity minority groups due to AFpresenting differently in these individuals. There is evidence to suggest that ethnic minority individuals may be more likely to have paroxysmal AF rather than persistent AF [63]. Paroxysmal AF screening lacks research across all ethnicities due to its more time constraining screening process. The U.N projects that the average life expectancy in Tanzania is 65.46 years and in Uganda is 63.41 years. Therefore, lower life expectancy and survivorship bias could be another factor that links ethnic minorities to lower AF prevalence levels[31].

Across all studies, it was evident that the prevalence of AF significantly increased with advancing age. Higher prevalence was observed when targeted screening of older adults occurred, as evidenced in the prevalence studies conducted in Sweden [28-30] which had the highest prevalence rates in Europe. They targeted individuals aged 70-76 years of age and therefore the higher prevalence rates are expected given the population under investigation.As the goal of medical screening is detection of cases with an elevated probability of having the disorder of interest then future studies should target individuals at greatest risk of AF including older adults >65 years of age which is consistent with European guidelines whereby screening is recommended in all patients >65 years of age [8].

Setting

The majority of researchers collected data in either community or urban/rural primary care settings. Primary care mainly consisted of GP practices. Community screening consisted mainly of screening centres, home visits and pharmacies. Only one study took place across multiple different settings. Using multiple different settings showed signs of inconsistencies and higher risk of bias because researchers employed different protocols, methods and data collection tools in each of the settings. Furthermore, participant recruitment varied in the multiple settings, with one site using cardiologists who already knew the patients' medical history prior to opportunistically screening for AF[32].

Type of Screening

Four studies used both opportunistic and systematic screening studies [29, 33-35]. Overall, no significant difference was evident in the outcomes of studies that used opportunistic versus systemic screening. Therefore, neither approach is considered superior. Both approaches have strengths and limitations but both forms are effective if executed in an appropriate manner. Systematic screening can be conducted over a shorter timeframe than opportunistic screening; however, opportunistic screening can be more cost effective than systematic screening [10]. Furthermore, primary care providers, including general practitioners, community health workers and pharmacists, are in a unique position to be proactive with their patients and actively seek patients with AF through opportunistic screening programmes [3, 11].

Data Collectors

The research team, cardiologists and general practitioners most frequently conducted data collection. Approximately half of study teams used at least one cardiologist to review ECG readings and confirm AF diagnoses. Most papers highlighted the importance of using the resources of a cardiologist to review new AF diagnoses. However, the use of a cardiologist was not feasible or attainable in some studies due to limited resources. In the absence of an expert cardiologist in the research team to confirm diagnoses, participants were told to contact a GP/cardiologist for review. In the majority of studies, the data collector(s) were either research personnel or a health professional, however, in four studies, layperson volunteers were trained to use portable ECG devices to screen for AF[15, 17, 20, 36]. Furthermore, in eight studies, participants were the data collectors, and one project a Clinical Events Adjudication Committee was employed.

Novel technologies

The emergence of various novel technologies has significantly widened the scope for ECG monitoring and detection within the community based setting. SMART technologiesfor AF detecting and monitoring include the Cardiio Rhythm Smartphone®[19, 26], Apple watch photothermography[37] and Alivecor® which was the most frequently utilised SMART technology in the literature(n=14)[17, 38, 39]. In a recent systematic review, the Alivecor® was found to be convenient, valid, and a feasible means of monitoring for AF that can be successfully implemented into both opportunistic and systematic screening strategies for AF[40]. The advent of SMART devices will undoubtedly increase the opportunities for AF screening across a range of settings but especially in the community and home setting. Additional advantages of these technologies over traditional methods include accessibility, low cost and ease of use. The latter is particularly encouraging as this means that a wider range of health and social care professionals and patients, can use these devices and proactively partake in AF screening. It is important however, that high quality research is conducted to establish accuracy and validity for these emerging devices. If being used independently, appropriate support is required to ensure patient safety.

Strengths

Scoping reviews have been described as a process of mapping the existing literature or evidence base [41]. We followed the methodology of the Preferred Reporting Items for Systematic Reviews and MetaAnalyses extension for Scoping reviews (PRISMAScR)[11] and systematically and comprehensively searched, analysed and synthesised the research literature on screening for AF in community settings and primary care settings.

Limitations

Scoping reviews differ from other types of systematic reviews in that they provide an overview of the existing literature without quality assessment or extensive data synthesis [41]. Due to high heterogeneity across studies in terms of prevalence of AF and the different population screened and the diversity of methodological approaches employed in AF screening research it is not possible to conduct a meta-analysis and pool data [42].Instead, we present a narrative synthesis of the findings and an overview of the existing literature without quality assessment.

Conclusion

Despite the significant range in the prevalence of newly diagnosed AF cases across the studies (0-34%), the prevalence of AF was consistently found to increase with advancing age across the studies thus demonstrating the association between higher prevalence of AF and advancing age. Future studies of opportunistic or systematic screening for AF should target individuals at greatest risk of the condition including older adults >65 years of age. In the main, studies took place in community settings primarily in primary care and GP practices. The 12-lead ECG was the most frequently employed clinical technique employed in screening for AF. This was followed by smartphone based AliverCor® (1 lead ECG) and pulse palpation. Emerging novel technologies will undoubtedly increase the opportunities for AF screening across a range of settings, including community and home settings, which will increase the accessibility of AF screening and allow for more health and social professionals to partake in opportunistic screening of high-risk populations. Furthermore, SMART technologies also have the potential for greater self-monitoring in home settings. There is a need for larger scale, high quality studies investigating AF screening, with robust methodologies across a wider demographic, to provide accurate prevalence data for AF and to establish the accuracy and validity of the various traditional approaches versus new and novel technologies for AF screening.

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Intraluminal Esophageal Temperature Monitoring Using the Circa S-Cath™ Temperature Probe to Guide Left Atrial Ablation in Patients with Atrial Fibrillation

Lisa WM Leung, Zaki Akhtar, Jamal Hayat, Mark M Gallagher

To The Editor

Bhuta S et al[1] have recently published an interesting study investigating the usefulness of esophageal temperature probe monitoring to guide left atrial ablations. Avoidance of esophageal injury during left atrial ablations remains an important area of study to prevent severe thermal injury that may manifest as esophageal-pericardial or atrio-oesophageal fistulas, both potentially life-threatening conditions.

There are a wide range of commercially available esophageal temperature monitoring probes;the one investigated by Bhuta et al was the S-Cath (Circa Scientific LLC, Englewood, CO, USA), a multi-sensor probe with 12 insulated sensors placed uniformly along the length of the device. The probe's physical profile differs from other devices: It is flexible and self-expands into an S profile, with the purpose of delivering data from the full length and width of the portion of the esophageal lumen that is exposed to thermal threat. The advantage with this design is that it may avoid the need to adjust the probe positionduring ablation.

The study methods involved reducing the power of the ablation by 10W if temperatures rose above 39 degrees or if the rate of temperature rise exceeded 0.2degrees per second. If temperature rise continued despite dialling down on the power, ablation would be halted and the same endoscope probe that was to be used post-procedure to evaluate for thermal lesions was used to mechanically deviate the esophagus. Temperature measurements were therefore used reactivelyto trigger multiple protection strategies: ablation power limitation, force limitation and mechanical deviation of the esophagus.

The timing of the endoscopy was split into 2 groups, either immediately post-ablation with the temperature probe still in situ (n=18) or to the following day (n=18). It was not clear as to why the timing of the endoscopy had to be split or how the patients were allocated to each time window.We note that in most contemporary studies ofablation-related thermal injury, endoscopy occurs at 12-72 hours post ablation. Immediate endoscopy post ablation may be less specific at identifying clinically important thermal lesions from ablation but instead identify more trivial lesions or mechanical trauma.

The study results were interesting:Lesions were observed in patients who had supposedly had the benefit of the protection of intensive temperature monitoring by the circa device, but many of these were interpreted as evidence of mechanical trauma. The manuscript did not include enough data or photographic evidence to verify this interpretation. A sceptical viewpoint would be that the study yielded 5/36 (13.9%) positive endoscopic findings, a rate of injury thatis similar to most non-protected series.

A recent randomized trial investigating the efficacy of the S-Cath esophageal temperature monitoring probe compared to controls with no esophageal temperature monitoring during AF ablation found no evidence that its use reduced thermal injury- the S-Cath group had more endoscopically detected thermal lesions compared to controls (6/44, 13.6% versus 2/42, 4.76%; p=0.27).[2] The study had a similar protocol to that of Bhuta et al, including the use of power titration after a significant temperature rises (>39°C). Apart from this study, only 1 other randomized trial addressed the value of esophageal temperature monitoring during AF ablation:The OPERA trial[3] also which investigated the SensithermTMdevice (FIAB, Firenze, Italy) found no evidence that these probes reduced thermal injury.

Key Words
Atrial Fibrillation, Calcification

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Other methodsfor avoiding thermal injury to the esophagusinclude mechanical deviation and active thermal protection. Mechanical deviation devicessuffer from the same lack of randomised trial evidence as the temperature monitoring devices. Active thermal protection, by contrast, has shown clear benefit in one substantialrandomised trial,[4] and supportive evidence from a meta-analysis of several earlier small studies.[5] All methods are worthy of further study in this important aspect of AF ablation,but the trial evidence to date indicates a clear leader: Thermal protection rather than temperature monitoring or mechanical deviation is the most promising alternative.

Yours sincerely,
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Zaki Akhtar
Jamal Hayat
Mark M Gallagher

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Response to a Letter to the Editor

We appreciate the concerns raised by Dr. Leung and colleagues in their letter to the editor regarding our original manuscript published in the Journal of Atrial Fibrillation1. In response to those concerns we can provide the following additional details regarding our study.

The first point raised by Leung LSW, et.al. was the "skeptical" viewpoint that the so-called mechanical traumatic lesions observed in 4 of 36 patients were actually thermal lesions, resulting in an event rate of 5 of 35 patients (13.9%). No figure is shown of these lesions as noted by Leung LSW, et.al. However, we would like to clarify that these lesions in question were described by the endoscopist as 3 mm superficial linear erosions, consistent with minor trauma likely during placement of the temperature probe itself and not likely thermal lesions. These lesions were also all reported to be ≤30 cm from the incisor teeth (in areas above the LA where no ablation was performed. The only lesion that was reported as possibly related to thermal injury (and described as a 3 mm edematous focus without erosion seen in the figure) was at 32 cm from the incisors near the LA.

The question raised by Leung LSW, et.al. as to why our study was divided into two groups (i.e. one with immediate endoscopy and one 24 hours after ablation) is due to the very fact pointed out by Leung LSW, et.al. with the statement "Immediate endoscopy post ablation may be less specific at identifying clinically important thermal lesions from ablation but instead identify more trivial lesions or mechanical trauma". We were indeed also concerned that immediate endoscopy might be insensitive to, and thus miss some thermal lesions if they took up to 24 hours do develop, thus the rationale for performing endoscopy in the second group at least 24 hours after ablation.

With regards to the comparison of our study with that of other randomized trials (including that referenced by Leung LSW, et.al. by Meininghaus DG, et.al.), due to our more aggressive protocol of power delivery reduction as LET approached 39 °C, the average maximum LET observed in all patients in our study was 37.8±1.42°C (range 36.90-39.50°C), whereas in the study by Meininghaus DG, et.al. for example the maximum LET observed was ≥40 °C in 79.5%, ≥41 °C in 63.6%, and ≥42 °C in 29.5% of patients, with their highest observed temperature 43.4°C. They also report that the likelihood of new endoscopically detected lesions was associated with these much higher temperatures. In addition up to 25% of patients in the study by Meininghaus DG, et.al. had a posterior box ablation lesion performed, which by its very nature may increase exposure of the esophagus to a greater risk of thermal injury. None of the patients in our study underwent box lesion ablation. Thus, these two studies are not really that comparable in our opinion, and maintaining lower LETs <40 °C does in fact appear to reduce risk of esophageal injury according to our data.

As noted by Leung LSW, et.al. esophageal protection by esophageal cooling may indeed be associated with fewer esophageal lesions by maintaining a lower LET, as even our data suggests.

However, we disagree with the following statements made that "All methods are worthy of further study in this important aspect

of AF ablation, but the trial evidence to date indicates a clear leader: Thermal protection rather than temperature monitoring or mechanical deviation is the most promising alternative." To our knowledge, there has in fact been no randomized study published using endoscopic documentation of esophageal thermal protection versus careful temperature monitoring associated with esophageal movement in the event of unacceptable LET rises observed during LA ablation. It is also possible that placement of a thermal protection device may cause esophageal injury, especially if not carefully done by trained users, and would also likely be more costly than existing LET monitoring and esophageal manipulation devices.

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Meta-Analysis of Catheter Ablation Compared with Drug Therapy as First Line Treatment Strategy of Paroxysmal Atrial-Fibrillation

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Letter To Editor

In the United States, the prevalence atrial fibrillation(AF) in 2010 was reported to be 2% among individuals less than 65 years old and 9% among individuals more than 65 years old.[1] The recent 2020 European society of cardiology (ESC) guidelines for the diagnosis and management of AF recommends "AF catheter ablation for pulmonary vein insolation (PVI) should/may be considered as first-line rhythm control therapy to improve symptoms in selected patients with symptomatic paroxysmal AF episodes (Class IIa, Level B)".While randomized controlled trials (RCTs) in the past have studied catheter ablation as a first line treatment compared with antiarrhythmic drugs among patients with paroxysmal AF, the results were inconsistent.[2,3] Recently published EARY AF and STOP AF trials reported favourable results supporting catheter ablation as a first line strategy in patients with paroxysmal AF.[4,5] We performed an updated study level meta-analysis of RCTs comparing catheter ablation as a first line treatment with antiarrhythmic drugs in patients with paroxysmal AF. Considering the small sample size of published RCTs a pooled analysis will provide a sturdy conclusion.

Embase, MEDLINE/PubMed, and Cochrane Library were systematically searched for relevant trials independently by two reviewers (AK and AAA) from the inception of the database through November, 2020. No language-based restrictions were imposed. Two reviewers (AK) and (AAA) extracted relevant data independently by using a predetermined data collection table. Any discrepancies between the reviewers were resolved by mutual consensus and after consultation with other authors. The endpoints of interest were recurrence of atrial tachycardia and recurrence of symptomatic atrial fibrillation/atrial tachycardia at 12-24 months. We used Mantel-Haenszel method with Paule-Mandel (PM) estimator of tau2 and Hartung-Knapp-Sidik-Jonkmanthe adjustment to calculate risk ratio (RR) with 95% confidence interval (CI). All analysis was carried out using R version 4.0.3 and using "meta" package.

Five RCTs consisting a total of 794 patients were included in the present analysis.[2–6] Three of the included studies used radiofrequency ablation while two studies used cryoablation. Catheter ablation as compared with antiarrhythmic drugs in patients with paroxysmal atrial fibrillation were associated with significantly lower risk of recurrence of any atrial tachycardia at follow-up [RR: 0.66; 95%CI: 0.56;0.77; I2:0%] [Figure, (A)]. However, catheter ablation as compared with antiarrhythmic drugs in patients with paroxysmal atrial fibrillation were associated with similar risk of recurrence of symptomatic atrial fibrillation/tachycardia at follow-up [RR: 0.49; 95%CI: 0.19;1.28; I2:69%] [Figure, (B)].

The present meta-analysis reported catheter ablation compared with antiarrhythmic drugs in paroxysmal AF to be superior in terms of recurrence of atrial tachycardia, while no difference was noted in the recurrence of symptomatic atrial fibrillation/tachycardia. The strengths of our study included use of Paule-Mandel (PM) estimator of tau[2] and Hartung-Knapp-Sidik-Jonkmanthe adjustment to account for small number of included studies and substantial heterogeneity. Further endpoints with similar range of follow up were analysed to avoid heterogeneity. With the recent RCTs and the results of the EAST trial, there is a likely push towards early restoration of sinus rhythm with the ever-increasing prevalence of AF.[7]

Key Words
Atrial Fibrillation; Catheter ablation; Drug Therapy; First line therapy

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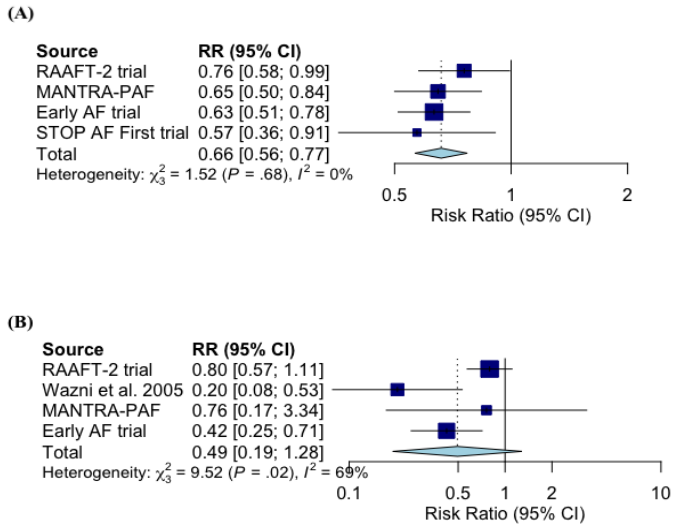

Figure 1: **(A) Forest plot for recurrence of all atrial tachycardia; catheter ablation was associated with significantly reduced risk of recurrence of atrial tachycardia compared with antiarrhythmic drug therapy;(B) Forest plot for recurrence of symptomatic atrial fibrillation/atrial tachycardia; there was no difference in the risk of symptomatic atrial fibrillation/tachycardia between the two treatment strategies; RR: Risk ratio; CI: Confidence Interval.**

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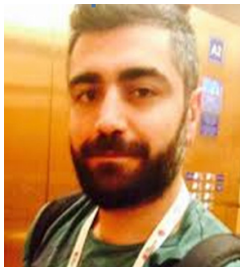

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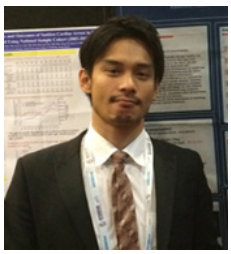

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