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Adverse events in cryoballoon ablation for pulmonary vein isolation: Insight from the Food and Drug Administration Manufacturer and User Facility Device Experience

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Abstract

Background: Real-world clinical data on the adverse events related to the use of cryoballoon catheter for pulmonary vein isolation remains limited.

Objective: To report and describe the adverse events related to the use of Artic Front cryoballoon catheters (Arctic Front, Arctic Front Advance, and Arctic Front Advance Pro) reported in the Food and Drug Administration's (FDA) Manufacturers and User Defined Experience (MAUDE) database.

Methods: We reviewed all the adverse events reported to the FDA MAUDE database over a 10.7-year study period from January 01, 2011 to September 31, 2021. All events were independently reviewed by two physicians.

Results: During the study period, a total of 320 procedural-related adverse events reported in the MAUDE database were identified. The most common adverse event was transient or persistent phrenic nerve palsy (PNP), accounting for 48% of all events. This was followed by cardiac perforation (15%), pulmonary vein stenosis (8%), transient ischemic attack or stroke (6%), vascular injury (4%), transient or persistent ST-elevation myocardial infarction (3%), hemoptysis (2%), pericarditis (2%), and esophageal ulcer or fistula (1%). There were six reported intra-procedural death events as a result of cardiac perforation.

Conclusion: The two most common procedural adverse events associated with cryoballoon ablation were PNP and cardiac perforation. All cases of procedural mortality were due to cardiac perforation.

KEYWORDS
adverse events, atrial fibrillation, cryoballoon ablation, outcome assessment, pulmonary vein isolation

1 | INTRODUCTION

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in the United States. It affects approximately 1%–2% of the general population.[1] The estimated number of patients with AF in the United States will be between 12.1 and 15.9 million by 2050.[2] Early rhythm control strategy for AF with catheter ablation was associated with lower recurrence rate of AF and better quality of life than antiarrhythmic drug therapy alone.[3–7] The Arctic Front Cardiac CryoAblation Catheter system was first approved by the Food and Drug Administration (FDA) for the treatment of drug refractory paroxysmal AF in December 2010.[8] Several studies have shown that the cryoballoon-based technology is an effective and a feasible tool for isolating the pulmonary veins in patients with drug-refractory AF.[8–11]

The use of cryoballoon-based technology in catheter ablation for AF has gained significant traction since the post-market approval. This has necessitated close surveillance on the use of the cryoballoon for any procedure-related major adverse events. The rate of major complications (phrenic nerve palsy [PNP], pericardial effusion, pulmonary vein stenosis, hemoptysis, or stroke) associated with the use of this balloon-based technology was reported between 0.3% and 13.5% in the clinical trials and the expert centres.[8,11–17] However, real-world clinical data on the adverse events related to the use of cryoballoon in catheter ablation for AF remain limited. In this study, we aim to describe and analyse any adverse events related to the use of cryoballoon in catheter ablation for AF reported to the FDA's Manufacturers and User Defined Experience (MAUDE) database.

2 | METHODS

The MAUDE database includes report of any adverse events related to the medical devices. Reporting is mandatory by the manufacturers, the device user facilities, and the importers while voluntary by the healthcare professionals, the patients, and the consumers. This databank is publicly available and is updated monthly with medical reports containing information on the device, the event date, and the severity and the narratives of the reported events. Although this database cannot determine the standard event rates, it offers an important insight into frequently encountered procedure-related complications in a real-world setting. As the MAUDE database is de-identified, neither informed consent nor institutional board review was required to access the data.

We queried the database for any adverse events related to the use of Artic Front cryoballoon catheter (Arctic Front, Arctic Front Advance, and Arctic Front Advance Pro; Medtronic) from January 1, 2011 to August 31, 2021. We searched for all available adverse events reported in the category of "injury" and "death." All the reported events were independently reviewed by two physicians (M.C.T, J.L.T). In the event of disagreement, a third physician (J.Z.L) would cast the deciding vote. All the adverse events reported during or after the use of cryoballoon ablation for AF were included for data analysis. Duplicate reports were excluded from the data analysis. The data was analyzed and reported as percentages in this MAUDE reports.

3 | RESULTS

After screening all the reports available in the MAUDE database, we included 320 adverse events related to the use of cryoballoon ablation between January 2011 and August 2021. The overall adverse events are as depicted in Figure 1. Cryoballoon AF Registry reported a total of 3276 adult patients who underwent cryoballoon AF ablation over a period of 3.8 years from May 2016 to January 2020.[10]

3.1 | Adverse events

In this report, the first-generation Artic Front cryoballoon catheter was used in 33% of the total reported adverse events, the second-generation Artic Front Advance cryoballoon catheter was used in 55% of the total reported adverse events, and the next-generation Artic Front Advance Pro cryoballoon catheter was used in 5% of the total reported adverse events. Transient or persistent PNP was the most commonly reported adverse event during the study period, and it represented 48% ($n=153/320$) of the total adverse events. Among all PNP with site of ablation reported, 82% ($n=18/22$) occurred during ablation of right superior pulmonary vein, and 18% ($n=4/22$) occurred during ablation of right inferior pulmonary vein. The second most common adverse event was cardiac perforation, accounting for 15% ($n=49/320$) of all adverse events. Among the

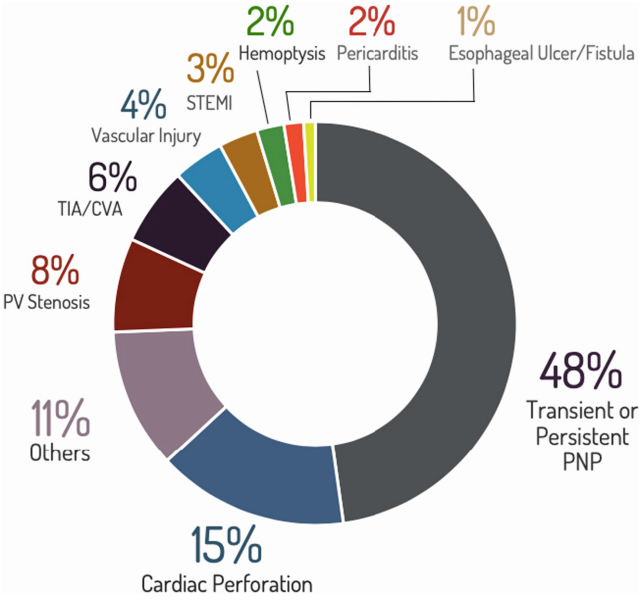

FIGURE 1 Overall adverse events related to the use of cryoballoon catheter.

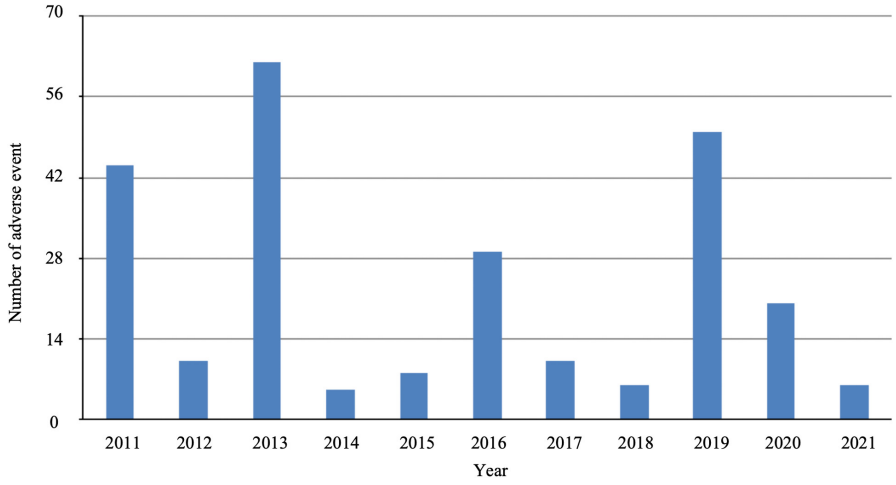

FIGURE 2 Annual adverse events reported between 2011 and 2021.

reported cardiac perforations, 42 of the events were complicated by cardiac tamponade. Among cases of cardiac perforation with reported interventions, 70% required pericardiocentesis alone ($n=21/30$) and 30% ($n=9/30$) required surgical repair. Other adverse events include pulmonary vein stenosis (8%, $n=24/320$), transient ischemic attack or stroke (6%, $n=20/320$), vascular injury (groin hematoma, femoral pseudoaneurysm, and femoral arteriovenous fistula) (4%, $n=13/320$), transient or persistent ST-elevation myocardial infarction (3%, $n=10/320$), hemoptysis (2%, $n=7/320$), pericarditis (2%, $n=5/320$), and esophageal ulcer or fistula (1%, $n=3/320$). Other nonspecific adverse events such as bleeding, deep vein thrombosis, and neck hematoma were reported in 11% ($n=36/320$) of the total adverse events. The yearly number of events reported is depicted on Figure 2.

Among all the reported adverse events, 57% of the events occurred peri-procedure, 19% of the events occurred immediately post-procedure, and 13% of the events occurred post-discharge or during follow-up. Six intra-procedural deaths (2%, $n=6/320$) were reported to MAUDE during the study period. All the death events occurred as a result of cardiac perforation. Left atrial tear was reported in one death, left superior pulmonary vein tear was reported in one death, while detailed procedural data was not available in the remaining deaths.

4 | DISCUSSION

In this study, our MAUDE database analysis revealed that (1) the most common adverse event related to the use of cryoballoon catheter for pulmonary vein isolation was transient or persistent PNP (48%); (2) cardiac perforation was the second most commonly reported adverse event, with 86% ($n=42/46$) of all instances of cardiac perforation being complicated by cardiac tamponade; and (3) intra-procedural death occurred in 1.9% of all the reported adverse events as a sequela of cardiac perforation.

Our findings are in line with the result of Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) trial. The most common adverse event reported after the cryoballoon ablation was PNP, followed by cardiac perforation, and pulmonary vein stenosis.[8] As reported in the literature, PNP is the most common adverse event related to the use of cryoballoon catheter and this occurred in 2.8%–13.5% of the patients.[7,8,11–16] While PNP in most cases may resolve within a year, 0.6% of them may have persistent PNP.[15,17] PNP occurred as a result of the close anatomical proximity of the right phrenic nerve and the right superior pulmonary vein during the balloon-based ablation approach.[18–20] In our analysis, 82% of PNP occurred during the ablation of the right superior pulmonary vein. Intra-procedural monitoring such as continuous abdominal palpation during phrenic nerve stimulation,[8,21–23] electromyographic monitoring of diaphragmatic compound motor action potential,[8,20,21,24,25] and femoral venous pressure waveform monitoring[26] may potentially be helpful for prevention of PNP. Other ablation techniques such as the "proximal seal technique" with time-to-isolation dosing,[20] and total freezing time reduction[14,27] have also been shown to reduce the risk of PNP.

Cardiac perforation was the second most common adverse event in our data analysis. In a recent meta-analysis of 14 randomized controlled studies and 34 observational studies comparing the safety of cryoballoon versus radiofrequency ablation procedure, the cryoballoon ablation group had a lower incidence of pericardial effusion and cardiac tamponade (relative risk, 0.58) compared with radiofrequency ablation group.[28] It was postulated that the extreme manipulation of catheter or probe devices within the cardiac chambers[13] and poor trans-septal puncture technique[13,29–32] are the major contributing factors to cardiac perforation. While most cases are mild and asymptomatic,[33] the development of hemodynamic instability should warrant a strong suspicion of a possible cardiac tamponade. The use of fluoroscopy to visualize a decrease in the excursion of cardiac silhouette[34] is one technique for early detection of cardiac perforation during the procedure. The use of intracardiac echocardiography has also been reported to improve procedural safety, efficacy,[35] and patient outcomes.[36]

The third-most common adverse event in our report was pulmonary vein stenosis. As reported by Knight et al. pulmonary vein stenosis occurs in 0.6% of the patients post-cryoballoon ablation.[8] The clinical diagnosis of pulmonary vein stenosis remains

challenging due to the non-specific clinical presentations and lack of symptoms in most patients.[37,38] Multiple predictors have been associated with the risk of pulmonary vein stenosis post-cryoballoon ablation procedural. These include the noncoaxial placement of cryoballoon into the pulmonary vein, a larger contact surface area of the cryoballoon to the pulmonary vein wall, and a horizontally connecting pulmonary vein.[39,40] The treatment options of symptomatic and/or severe pulmonary vein stenosis mainly consist of balloon venoplasty alone and/or balloon venoplasty with stenting.[37] However, pulmonary vein restenosis can still occur in 57% of pulmonary vein stenosis patients after initial balloon venoplasty treatment.[41]

The fourth most common adverse event reported in the MAUDE database was transient ischemic attack or stroke. The incidence of transient ischemic attack or stroke was 0.3% after the cryoballoon procedure in the STOP AF trial.[8] It was suggested that minimal interruption or uninterrupted anticoagulation is crucial role in minimizing the risk of transient ischemic attack or stroke post-cryoballoon ablation procedure.[42,43]

While the majority of adverse events in our data analysis were reported peri-procedurally or immediately post-procedure, 13% of them were noted post-discharge or during follow-up. This emphasizes the need for a close follow-up after the procedure to monitor for any potential post-procedure complications.[44] Some of the most serious potential complications of AF ablation such as atrioesophageal fistula may manifest after 2–6 weeks post-procedure.[45]

Several other studies have shown that there is no significant difference in the overall safety profile of the first-generation cryoballoon catheter as compared with the second-generation of cryoballoon despite an improvement in procedural efficacy.[46–48] Pandya et al. reported second-generation cryoballoon is associated with a higher risk of transient or persistent PNP after the procedure (OR: 1.64).[49] No significant difference has been found in the acute procedural safety profile between the second-generation cryoballoon catheter and the next-generation cryoballoon catheter.[50,51]

4.1 | Limitations

First, the MAUDE database is a collection of voluntarily (albeit mandatory) reported data on procedures performed with specific devices, therefore the data collected are likely to be incomplete, and the actual "denominator" is unknown, which limits our exploration in the incidence of complications reported. Second, reporting bias is likely to be present, with life-threatening adverse events being reported more frequently as compared to minor adverse events, which might be underreported to the FDA MAUDE database. Third, the adverse events might be underreported to a certain degree due to inactivation. In addition, the device data was not available in 7% of the cases due to incomplete information reported. Lastly, there is a risk of over-reporting adverse events because exclusion of duplicates cannot always be reliable due to the lack of identifier such as personal health information and serial number.

5 | CONCLUSION

The two most common adverse events associated with cryoballoon ablation were PNP and cardiac perforation. All cases of procedural mortality were due to cardiac perforation. Therefore, early recognition and management of cardiac perforation are important. Cryoballoon ablation should only be performed in hospitals with access to emergency surgical support when required.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to disclose.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

As the MAUDE database is de-identified, neither informed consent nor institutional board review was required to access the data.

PATIENT CONSENT STATEMENT

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

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