To date, multiple modes of research have been leveraged to study the optimal cryoballoon ablation parameters to safely, effectively, and efficiently isolate the pulmonary veins for the treatment of atrial fibrillation. Basic scientific investigation, preclinical studies, clinical observations, trials, and, more recently, computational modeling have helped to generate and test new hypotheses for the advancement of cryoballoon treatment in patients with atrial fibrillation. In this review, we examine the data and evidence that have contributed to the development of patient-tailored dosing strategies that are currently used for pulmonary vein isolation by using the Arctic Front series of cryoballoon ablation catheters.

**KEYWORDS** Ablation; Atrial fibrillation; Cryoballoon; Dosing; Safety; Time-to-pulmonary vein isolation

(Heart Rhythm 2020;17:1185–1192) © 2020 The Authors. Published by Elsevier Inc. on behalf of Heart Rhythm Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

**A. Introduction**

Pulmonary vein (PV) isolation (PVI) remains the cornerstone of catheter ablation of atrial fibrillation (AF). The goal of catheter ablation for the treatment of AF is permanent ablation of targeted atrial tissue with preservation of collateral or nontargeted structures in the path of energy delivery. Specifically, energy delivered via an ablation catheter is titrated to mitigate the risk of undesired energy transfer beyond the atrial tissue. To optimize this balance of energy transfer, the Arctic Front series of cryoballoon ablation catheters (Medtronic, Inc, Minneapolis, MN) has been investigated in vitro and in vivo animal models and clinical studies. Recently, a computational model was developed to predict cardiac tissue responses during cryoballoon ablation. Modeling may explain how biophysical characteristics of cryoballoon lesions underlie clinical findings and help define future avenues for investigation. Here, we review the outcomes from bench and bedside studies that have advanced current understanding and knowledge of tailored cryoballoon dosing. Furthermore, we explore how ongoing research continues to shape cryoblation dosing algorithms in order to maximize the safety and efficacy of PVI for the treatment of patients with AF.

Dr Aryana has received consulting fees, speaker honoraria, and research grants from Medtronic. Dr Ellenbogen has received consulting fees from Medtronic. Drs Braegelmann and Lim are employees of Medtronic. 

**Address reprint requests and correspondence:** Dr Arash Aryana, Dignity Health Heart and Vascular Institute and Mercy General Hospital, 3941 J St, Suite #350, Sacramento, CA 95819. E-mail address: a_aryana@outlook.com.

---

1547-5271/© 2020 The Authors. Published by Elsevier Inc. on behalf of Heart Rhythm Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
C. Clinically investigated dosing paradigms

C.1. Conventional dosing strategies

To achieve PVI using the first-generation Arctic Front cryoballoon (Medtronic, Inc), applications were typically performed using 240–360 seconds with multiple freeze-thaw-refreeze cycles per PV.5 The technologically improved Arctic Front Advance balloon contains 8 injection ports placed distally (as compared with the 4 equatorial ports on the Arctic Front) to improve cooling across the distal hemisphere of the cryoballoon.6 This improved cooling mechanism enhances the efficiency with which energy is transferred during cryoablation. Early experiences with the Arctic Front Advance balloon while using conventional (Arctic Front–type) dosing schemes exposed an increased risk of complications, indicative of a higher likelihood of cryothermal energy propagation beyond the PVs.7–9 Meanwhile, preclinical research using this balloon demonstrated that acute and durable transmural PVI at 30 days postablation was not different between balloon demonstrated that acute and durable transmural PVI at 30 days postablation was not different between 2-minute and 4-minute applications with Arctic Front Advance in an animal model.6 Therefore, in place of longer cryoapplications, two 180- or 240-second cryoapplications were adopted with the goal of rebalancing safety and efficacy.6,10–12 While shorter freezes were widely adopted, research on empirically shortened cryoapplications and patient-tailored dosing strategies continued (Figure 1).13–19

C.2. Empiric single-freeze dosing paradigms

Fixed-duration, single-freeze dosing schemes using Arctic Front Advance have been investigated in several studies (Table 1). An early study examined outcomes in a small cohort of patients with AF (n = 45) treated with Arctic Front Advance and reported 82% freedom from arrhythmia recurrence at 1 year.15 Later studies corroborated no difference in safety or efficacy 1–2 years after ablation in cohorts treated with a single 240-second application compared with those treated with two 240-second applications per PV.14,15 Both Ciconte et al16 and Miyazaki et al17 evaluated the outcomes of a single 180-second freeze in larger cohorts and reported freedom from AF of 80.4% and 71.6% at 1 year, respectively. In a cohort of 301 patients treated with a single 180-second application, Coutiño et al15 found that 68.8% of patients remained free from recurrent AF after a single procedure 3 years postablation and concluded that a single 3-minute freeze strategy may be effective for long-term freedom from AF. A prospective, multicenter, randomized trial found no difference in freedom from AF in patients treated with two 180-second applications vs those treated with a single 200- to 260-second freeze (87.3% vs 89.1%, respectively; P = .78).19 Moreover, these authors found no difference in the frequency of gaps in PVI lesions on delayed-enhancement magnetic resonance imaging (46% vs 36%; P = .38).19 Together, these data suggest that a fixed-duration, single-freeze, 180-second application per PV did not impact the observed outcome of freedom from AF.

C.3. Time-to-isolation–guided dosing

Introduction of the inner lumen circular mapping catheter (Achieve, Medtronic, Inc) allowed for real-time PV potential monitoring during cryoballoon ablation. The disappearance of PV potentials during a freeze corresponds to cardiomyocytes in the muscular sleeves reaching temperatures that renders the cells electrically dormant (≤23°C).2 The time to disappearance of PV potentials during a cryoballoon application has been termed time to isolation (TTI). It is important to point out that at TTI, the cells have not necessarily reached a lethal freeze temperature, but the disappearance of PV potentials is indicative of circumferential cold propagation through the tissue, which has been studied as an indicator of lesion durability. A variety of parameters (eg, balloon-to-PV occlusion scores, balloon temperatures at various points during the freeze, freeze duration, and TTI) have been evaluated as intraprocedural predictors of durable PVI.20,21 In an analysis of PV reconnection in patients who underwent a repeat procedure after index cryoballoon PVI, neither the number nor the duration of freezes predicted PV reconnection. The only independent predictors of durable PVI at the time of the repeat procedure were TTI and the balloon interval thaw time to 0°C (iTT0).21 Specifically, if TTI was <60 seconds and iTT0 >10 seconds, then there was a <0.9% risk of PV reconnection at repeat ablation. Since iTT0 cannot be determined until the completion of the cryoapplication, it is not possible to use this parameter to prospectively guide the freeze duration. Hence, TTI has emerged as the quintessential variable that is most commonly used to guide cryoballoon dosing and duration.

Studies designed to evaluate TTI-guided dosing include prospective, randomized, multicenter trials that characterized differences in outcomes between patients treated with TTI.
dosing algorithms and those treated with conventional, fixed, freeze-thaw-refreeze cycles (Table 2). Collectively, these data indicate a reduction in procedural duration, with no significant difference in freedom from AF in patients treated with a TTI-guided approach vs conventional nonstandardized dosing strategies.22–24 An initial report by Reissmann et al25 evaluated the outcomes in patients treated with TTI + 120 seconds irrespective of TTI (mean application duration of 190 seconds). The ICE-T trial reported no differences in outcomes between patients treated with a single 240-second application (if TTI <75 seconds) and a second group treated with 2 sequential 240-second applications.21 In the Cryo-DOSING study,22 the authors used more stringent TTI cutoffs with defined alternatives.22 In this study, the authors prospectively used a TTI of <60 seconds as the threshold for a single TTI + 120-second freeze as well as the need for a second “bonus” freeze if a TTI of <60 seconds was not observed. We observed a reduction in procedural duration in the TTI-guided arm as compared with the conventional nonstandardized application group.22 Ferrero-de-Loma-Osorio et al23 further pushed the bounds of the minimum first application duration through a prospective, randomized, multicenter noninferiority study in which a conventional freeze cohort treated with two 180-second applications was compared with a cohort treated with a TTI + 60-second first freeze followed by a 120-second bonus freeze. Once again, the authors reported a reduction in procedural duration, with no difference in 1-year freedom from AF recurrence.24

With TTI emerging as the most significant indicator of lesion durability capable of facilitating a reduction in application and procedure times, the cryoballoon design has been modified accordingly to improve the ability to assess and record PV potentials during cryoballoon ablation. The most notable design change in the third-generation cryoballoon (Arctic Front Advance ST, Medtronic, Inc) was a shortened catheter tip, which was reduced by 40%. This catheter was reported to increase the frequency with which PV potentials could be visualized by as much as 30%.26–28 An improved ability to observe PV potentials has also been reported using the fourth-generation short-tip cryoballoon (Arctic Front Advance Pro, Medtronic, Inc).29–31 This improved TTI assessment and monitoring can enhance the ability to individually tailor cryoballoon applications.

### D. Impact of cryoballoon ablation dosing on procedural safety

Preclinical and clinical studies have evaluated the risk of collateral injury to nontargeted tissues such as the phrenic nerve (PN), esophagus, and lungs during cryoballoon ablation. The presence and extent of pulmonary and bronchial injuries after PV ablation with Arctic Front Advance using ultracold (<−65°C), prolonged (360 seconds), and conventional (180 seconds) cryoapplications have been evaluated in a porcine model.32 This study found that cryoballoon PVI could elicit acute bronchial inflammation, bleeding, and mucosal injury. The mechanism appeared to be direct collateral injury. While these unfavorable outcomes were significantly augmented by ultracold cryoapplications, they were also evident with prolonged cryoapplications. In humans, when the esophagus lies adjacent to the left PVs, it tends to be closer in proximity to the left atrium/the PVs (particularly, the left inferior PV). Clinically, longer applications at this site have been associated with a higher incidence of atrioesophageal fistula.33

Most clinical studies comparing shortened applications to conventional dosing have reported no difference in overall safety outcomes between cohorts.30,32,34 Low rates of adverse events after cryoballoon ablation may limit the ability to detect an effect22,34; therefore, several recent studies35–38 have specifically examined the outcomes of cryoballoon dosing on collateral injury (Table 3). Chun et al35 prospectively evaluated the outcomes between patients treated with a single 240-second application and those ablated with 2 sequential 240-second applications per PV and found a trend toward higher PN and esophageal complications (6% vs 18%, respectively; P = .06).33 Molenaar et al35 evaluated the rate of PN palsy in a cohort of 222 patients randomized to either short (mean of 105 seconds), medium (mean of 164 seconds), or long (mean of 224 seconds) cryoapplications with a freeze-thaw-refreeze cycle in all patients. The authors reported an overall PN palsy rate of 18% (39 of 222). Not surprisingly, this rate was significantly lower in the short cryoapplication group than in those treated with medium and long durations (1.7%, 6.5%, and 6.8%, respectively; P < .001).35 Additionally, 2 published reports36,37 specifically investigated esophageal injury as a result of cryoballoon PVI. In both studies, the authors sought

### Table 1 Studies evaluating single-procedure outcomes of fixed-duration, single-freeze cryoballoon ablation dosing strategies

<table>
<thead>
<tr>
<th>Study</th>
<th>Single-freeze arm (no. of patients)</th>
<th>Application duration (s)</th>
<th>Bonus-freeze arm (no. of patients)</th>
<th>Mean follow-up (y)</th>
<th>Freedom from recurrent AF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wissner et al13</td>
<td>45</td>
<td>240</td>
<td>–</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>Heeger et al14</td>
<td>60</td>
<td>240</td>
<td>60</td>
<td>2</td>
<td>69 vs 67 (P = .69)</td>
</tr>
<tr>
<td>Mortser et al15</td>
<td>70</td>
<td>240</td>
<td>70</td>
<td>1</td>
<td>74 vs 71 (P = .74)</td>
</tr>
<tr>
<td>Ciconte et al16</td>
<td>143</td>
<td>180</td>
<td>–</td>
<td>1</td>
<td>80.4</td>
</tr>
<tr>
<td>Miyazaki et al17</td>
<td>108</td>
<td>180</td>
<td>–</td>
<td>1</td>
<td>71.6</td>
</tr>
<tr>
<td>Coutino et al18</td>
<td>301</td>
<td>180</td>
<td>–</td>
<td>3</td>
<td>68.8</td>
</tr>
<tr>
<td>Miyamoto et al19</td>
<td>55</td>
<td>180–240</td>
<td>55</td>
<td>1</td>
<td>89 vs 87 (P = .78)</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation.
### Table 2  Studies evaluating TTI-guided cryoballoon ablation dosing paradigms

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (no. of patients)</th>
<th>Cryoballoon ablation dosing scheme</th>
<th>Mean no. of freezes</th>
<th>Comparative (control) arm scheme</th>
<th>Mean freeze duration (s)</th>
<th>Freedom from recurrent AF at 1 y (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aryana et al(^{22})</td>
<td>355</td>
<td>TTI + 120 s (no bonus freeze)</td>
<td>1.7 ± 0.8 per PV</td>
<td>240 s × 2</td>
<td>249 ± 34 vs 226 ± 46</td>
<td>82 vs 78 (P = .14)</td>
</tr>
<tr>
<td>Chun et al(^{23})</td>
<td>100</td>
<td>240 s (no bonus freeze)</td>
<td>5 ± 1 per patient (1.2 per PV)</td>
<td>240 s × 2</td>
<td>230 vs 397 (P &lt; .001)</td>
<td>88 vs 82 (P = .80)</td>
</tr>
<tr>
<td>Ferrero-de-Loma-Osorio et al(^{24})</td>
<td>140</td>
<td>TTI + 60 s, and a 120-s bonus freeze</td>
<td>9.6 ± 2 per patient (2.4 per PV)</td>
<td>180 s × 2</td>
<td>113 vs 175 (P &lt; .001)</td>
<td>78 vs 79 (P = .87)</td>
</tr>
<tr>
<td>Reissmann et al(^{25})</td>
<td>60</td>
<td>TTI + 120 s (no bonus freeze)</td>
<td>1.2 ± 0.5 per PV</td>
<td></td>
<td>192 ± 41</td>
<td>72</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; PV = pulmonary vein; TTI = time-to-pulmonary vein isolation.

### Table 3  Studies evaluating the outcomes of cryoapplication duration on collateral injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (total no. of patients)</th>
<th>Experimental arm dosing scheme</th>
<th>Control arm dosing scheme</th>
<th>Procedural success</th>
<th>Procedural adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molenaar et al(^{26})</td>
<td>222</td>
<td>Two short (105 s) applications</td>
<td>Two medium (164 s) or 2 long (224 s) applications</td>
<td>↓ PV isolation with short (62%) vs medium (75%) or long (78%) applications (P &lt; .001)</td>
<td>↓ PN palsy with short (1.7%) vs medium (6.5%) or long (6.8%) applications (P = .006)</td>
</tr>
<tr>
<td>Yoshiga et al(^{27})</td>
<td>100</td>
<td>180 s (no bonus freeze)</td>
<td>A 180-s and a 120-s bonus freeze</td>
<td>Freedom from AF at 1 y: 77.6% vs 78.8% (P = .75)</td>
<td>ETI: 9% (experimental) vs 27.3% (control) (P = .033)</td>
</tr>
<tr>
<td>Cordes et al(^{17})</td>
<td>70</td>
<td>TTI + 120 or 180 s (if TTI not available)</td>
<td>Two 180-s applications</td>
<td>AF recurrence at 6 mo: 3.5% vs 16% (P = .17)</td>
<td>EE incidence: 6% (experimental) vs 26% (control) (P = .003); EE diameter: 11 mm (experimental) vs 17 mm (control) (P &lt; .001)</td>
</tr>
<tr>
<td>Valles et al(^{18})</td>
<td>157</td>
<td>TTI + 60 s (90–180 s; no bonus freeze)</td>
<td>Two 180-s applications</td>
<td>Freedom from AF at 18 mo: 79.7% vs 78.4% (P = .50)</td>
<td>Major and minor complications: 6.8% (experimental) vs 18.8% (control) (P = .02)</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; EE = esophageal edema; ETI = asymptomatic excessive gastroesophageal transmural injury by endoscopy; PN = phrenic nerve; PV = pulmonary vein; TTI = time-to-pulmonary vein isolation.
to evaluate asymptomatic esophageal lesions by evaluating for erythema, edema, erosion, ulceration, or gastroparesis as a consequence of periesophageal nerve injury. In the first study, Yoshiga et al\(^{36}\) compared patients who received an initial 180-second cryoapplication followed by a 120-
second cryoapplication with those treated with a single 180-second freeze. The authors reported that although cryoballoon and luminal esophageal temperatures did not differ between those treated with and without a second freeze, 27.3\% of patients who received a second application (9 of 33) exhibited evidence of thermal esophageal injury 1–2 days postablation as compared with 9\% of those who received a single freeze (6 of 67) (\(P = .033\)). Furthermore, the authors identified a “bonus” freeze as the only independent predictor of esophageal injury after cryoballoon ablation.\(^{36}\) Likewise, Cordes et al\(^{37}\) found that patients treated with a conventional dosing approach (2 sequential 180-second applications) vs those treated with a tailored strategy (TTI + 120 seconds or a single 180-second application when TTI could not be recorded) had larger areas of esophageal edema (17 mm vs 11 mm; \(P < .001\)) and more frequent areas classified as “large” edema (26\% vs 6\%; \(P = .003\)). In this study, there were no observed differences in the anatomical proximity of the esophagus and the left atrium between the cohorts, nor were there any differences in cryoballoon nadir temperature. Once again, a conventional nonstandardized cryoablation approach was identified as a significant predictor for esophageal edema (\(P < .001\)).\(^{37}\) Valles et al\(^{38}\) reported an overall reduction in combined major and minor complications in patients treated with a “single-shot” ablation approach with variable duration (a minimum of 90 seconds with a bonus freeze if deemed necessary on the basis of TTI and nadir temperature) vs a conventional cohort who received at least 2 applications per PV (180 seconds each). While major complications including atroesophageal fistula, transient ischemic attack and stroke, pericardial effusion, and tamponade were not significantly different between the cohorts, events related to cryoenergy delivery (ie, PN palsy, atroesophageal fistula, and PV stenosis) were significantly reduced in patients with tailored vs conventional dosing (3 patients vs 8 patients; \(P = .047\)).\(^{38}\) Collectively, these data suggest that shortened cryoballoon application times may reduce the risk of undesired energy transfer to collateral tissue.

E. Future considerations and limitations of cryoballoon dosing

E.1. Translating preclinical observations to clinical practice

Preclinical models have been leveraged to investigate lower bounds for cryoballoon application durations. In a study by Su et al\(^{39}\) 30 canine PVs were isolated using 5 cryoballoon dosing methods with the goal of defining the minimum application duration required to complete a circumferential transmural lesion. The ablation doses were predefined as TTI plus an incremental addition to the cryoapplication (60, 90, 120, or 150 seconds) as compared with a conventional treatment arm of two 180-second applications. The mean TTI was 27 seconds across the applications that resulted in a mean ablation time of 90 seconds in the shortest duration cohort. There were no differences observed among the 5 treatment arms with respect to ablation lesion durability as assessed by entrance and exit block, gross lesion morphology, and histopathological examinations of lesion circumferentially and transmurally, 1 month postablation.\(^{39}\) While a minimum ablation duration required to achieve transmural lesions using the 23-mm cryoballoon was not observed since an ineffective freeze duration cohort was not established, overall, the data suggested that TTI + 60 seconds (90 seconds in total) was adequate in creating transmural lesions in a canine model.\(^{39}\) Independently, this observation was corroborated by a preclinical study that monitored impedance rise as a surrogate measure of circumferential ice formation on the cryoballoon surface using an experimental catheter.\(^{40}\) The authors reported that an impedance of 500 \(\Omega\) reached within 90 seconds (2 applications per PV) yielded 100% PVI durability, 1 month postablation.\(^{40}\) Although different methods were used to determine ablation duration, both these studies suggest that a 90-second freeze duration is adequate for durable PVI in a canine model. This preclinical evidence may suggest that minimum duration thresholds also exist in patients, but there are many limitations to the applicability of these data to clinical practice. Importantly, the myocardial tissue is relatively thin in the canine model as compared with the human model, perhaps allowing for shorter applications to achieve transmural lesions. While preclinical evidence may provide a proof of concept, the minimum required freeze duration may depend on a variety of individual patient characteristics and clinical thresholds have yet to be defined.

Computational modeling may help bridge the gaps between basic science, preclinical research, and clinical observations while generating hypotheses that can be tested in clinical trials. In a recent publication, Getman et al\(^{41}\) leveraged fundamental understandings of cellular responses to cryothermal energy in order to determine the required duration of cryoablation using Arctic Front Advance and Arctic Front Advance Pro catheters. The model calculated the predicted TTI and the total freeze duration required to achieve circumferential, transmural PVI at varying PV tissue depths. It identified that for a PV tissue thickness of 3 mm, a TTI of \(~60\) seconds required a total ablation time of \(~160\) seconds for full, circumferential, and transmural penetration of lethal temperature \((-20^\circ\text{C})\) into the cardiac tissue.\(^{41}\) These computational data closely mirror the clinical paradigms that have reported successful outcomes of TTI-guided dosing described in the previous sections. Having said that, this computational model was premised on a circular PV morphology with homogeneous tissue composition and depth. However, since such homogeneity is rarely observed clinically, it is uncertain how closely this model can predict clinical behavior. Future iterations of this model should account for heterogeneity in tissue morphology, structure, and thickness as well as cryoballoon alignment and
E.2. Anatomical considerations for cryoballoon dosing

Most cryoballoon ablation dosing studies have reported reduced application durations and fewer total applications without compromising lesion durability or clinical outcomes.19,22,34 However, recent insights counter universal reductions in freeze duration. An evaluation of cryoballoon lesion durability in patients undergoing a repeat procedure initially treated with a single 180- or 240-second application when TTI < 75 seconds was recently reported.42 While the mean TTI was not different between patients treated with a single 180-second freeze and those treated with a single 240-second freeze (35 seconds vs 42 seconds, respectively; \( P = .12 \)), the authors reported that patients treated with 240-second applications were more likely to exhibit durable PVI at the time of the repeat procedure than did those treated with a 180-second application (61% vs 35% of patients; \( P = .02 \) and 88% vs 69% of PVs; \( P < .001 \), respectively).42

More specifically, the authors found that the left-sided PVs were more durably isolated in the single 240-second freeze cohort than in the single 180-second freeze cohort. The authors surmised that the thicker myocardial tissue around the left PVs may require additional time for transmural, durable isolation of the left PVs. The left PV ostia tend to be smaller in diameter (for instance, as compared with the right superior PV); the myocardial ridge separating the left PVs and the left atrial appendage tends to be thicker than the surrounding PV tissue; and there is a need to manage risk posed to the nearby esophagus. These reports suggest a need to consider PV anatomical influences on cryoballoon dosing.

Prior studies have illustrated the benefits associated with wide antral PVI.53 Recently, several authors have used the cryoballoon to perform the same.34–47 Such an approach sometimes requires utilization of non-PV occlusive cryoapplications, particularly in those with large-sized atria. Not only can non-PV occlusive applications help create antral cryoablation lesions, but they are also often required for isolation of large-sized PVs (ie, left common PVs). Additionally, they may aid in effectively avoiding certain types of procedural complications such as PV stenosis and PN injury. While there is no consensus on the appropriate dosing for nonocclusive cryoballoon applications, most authors have successfully used a series of overlapping 120-second applications for this purpose. While there are limited data on long-term durability of these lesion sets, the authors have previously reported an 88% durability at 9 months of follow-up in patients who subsequently required a repeat procedure.48

Additional research is clearly needed to examine the safety, efficacy, and optimal dosing approach for nonocclusive PV applications using the cryoballoon.

E.3. Limitations of cryoballoon dosing

While patient-tailored approaches have been the focus of many studies, the optimal approach to cryoballoon ablation has not been defined. There is considerable heterogeneity in both the patient-tailored strategies tested (eg, empiric single-freeze duration and TTI algorithms) and the conventional paradigms to which they are compared (Tables 1 and 2). This makes meaningful comparison among trials and identification of a single optimal approach rather difficult. Furthermore, many trials have not identified a difference in safety or efficacy between the dosing paradigms tested. For example, the CIRCA-DOSE randomized trial reported that there was no difference in freedom from recurrence between 346 randomized patients treated with 2 cryoapplications of 2- or 4-minute duration and those treated with contact force-sensing radiofrequency ablation (\( P = .87 \)).34 In addition, no differences in serious adverse events were reported (\( P = .24 \)).34 These findings suggest that clinical outcomes of cryoballoon PVI may be consistent regardless of the technical approach used in large randomized clinical trials.22,54

Efforts to determine whether there are truly no differences in patient outcomes among techniques or whether clinical trials have not yet been designed to detect differences between these varied approaches are needed. Finally, it is important to acknowledge that dosing algorithms do not guarantee a safe harbor; patient-tailored approaches need to be vetted to ensure a safe and effective therapy.

Conclusion

Research on ablation dosing using the Arctic Front cryoballoon series of catheters underscores the value of a well-investigated dosing algorithm to optimize the treatment of patients with AF. The combined insight from fundamental scientific experiments, preclinical studies, and clinical investigations have transformed cryoballoon dosing paradigms from multiple, long, fixed applications to tailored-dosing strategies guided by biophysical feedback. Optimization of cryoablation dosing has proven critical to enhancing procedural efficiency, preserving efficacy, and improving the procedural safety margin. Moreover, translating basic research and preclinical findings into clinical practice is quintessential for advancement of our understanding in this clinical space, which is further facilitated by tools such as computational modeling. Further research is also needed to elucidate the appropriate cryoballoon dosing approach for nonocclusive PV applications. Lastly, it will remain to be determined whether the reported biophysical metrics and findings will hold true for other non–Arctic Front series of cryoballoon ablation catheters. Given the differences in balloon and catheter designs, there is a definite need for additional research and investigation on acute and long-term efficacy and safety as well as dosing pertaining to these alternate ablation tools.
References


