Medtronic

ARCTIC FRONT®
2AF232, 2AF282

Cardiac CryoAblation Catheter

Technical Manual

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

The following are trademarks or registered trademarks of Medtronic in the United States and possibly in other countries: Arctic Front, FlexCath, Medtronic

Explanation of symbols

Refer to the package labels to see which of the following symbols apply to this product

LOT	Lot number
REF	Reorder number
	Use by
STERILE EO	Sterilized using ethylene oxide
	Do not reuse
	Do not resterilize
	Do not use if package is damaged
	Package contents
	Consult instructions for use
	Fragile: handle with care
	Keep dry
	Product documentation
	Temperature limitation
	Do not freeze
	Cardiac cryoablation catheter
	Open here
! USA	For US audiences only

1 Description

The Arctic Front Cardiac CryoAblation Catheter (Arctic Front Cryoballoon) is a flexible, over-the-wire balloon catheter used to ablate cardiac tissue. It is used together with the FlexCath Steerable Sheath, the CryoConsole, and related components. The balloon reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the balloon segment. A thermocouple positioned inside the balloon provides temperature reading capability. The catheter is introduced into the vasculature by traditional minimally invasive techniques. The Arctic Front Cryoballoon is available in 2 models, as described in the following table:

Model	Inflated balloon diameter
2AF232	23 mm
2AF282	28 mm

For details about the CryoConsole and how to use it with the catheter to perform cryoablation procedures, see the *CryoConsole Operator' Manual*.

1.1 Contents of package

The catheter is supplied sterile. The package contains the following items:

- 1 Arctic Front Cardiac CryoAblation Catheter
- product documentation

2 Indications for use

The Arctic Front Cardiac CryoAblation Catheter is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

3 Contraindications

Use of the Arctic Front Cardiac CryoAblation Catheter is contraindicated as follows:

- in the ventricle because of the danger of catheter entrapment in the chordae tendineae
- in patients with active systemic infections
- in conditions where the manipulation of the catheter within the heart would be unsafe (for example, intracardiac mural thrombus)
- in patients with cryoglobulinemia
- in patients with one or more pulmonary vein stents

4 Warnings and precautions

Anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures. Administer anticoagulation therapy during and post-procedure according to the institutions standards. The Arctic Front Cardiac CryoAblation Catheter was not studied for the safety of changes in anticoagulation therapy in patients with paroxysmal atrial fibrillation.

Balloon inflation/deflation – Use the Manual Retraction Kit in the event inflating or deflating the balloon is unsuccessful. (Refer to the operators manual for more detailed instructions on the Manual Retraction Kit).

- Do not inflate the balloon inside the sheath. Always verify with fluoroscopy that the balloon is fully outside the sheath before inflation to avoid catheter damage.
- Do not inflate the balloon while the catheter is positioned inside a pulmonary vein. Always inflate the balloon in the atrium and then position it at the pulmonary vein ostium. Inflating the balloon in the pulmonary vein may result in vascular injury.

Biohazard disposal – Discard all used catheters and sterile components in accordance with hospital procedures.

Cardioversion/defibrillation during ablation procedure – Disconnect the catheters electrical connection prior to cardioversion/defibrillation. Failure to do so may trigger system messages indicating a need for catheter exchange.

Catheter handling –

- Use extreme care when manipulating the catheter. Lack of careful attention can result in injury such as perforation or tamponade.
- Do not use excessive force to advance or withdraw the catheter, especially if resistance is encountered.
- Do not use the catheter if it is kinked, damaged, or cannot be straightened.
- Straighten the cooling segment before inserting or withdrawing the catheter.
- Do not at any time preshape or bend the catheter shaft or cooling segment. Bending or kinking the catheter shaft may damage internal structures and increase the risk of catheter failure. Prebending of the distal curve can damage the catheter.
- Catheter advancement should be performed under fluoroscopic guidance.
- The catheter should be replaced if a System Notice (message on the CryoConsole user interface) recommends it.
- Do not position the cryoballoon catheter within the tubular portion of the pulmonary vein to minimize phrenic nerve injury and pulmonary vein stenosis.

Catheter integrity – Do not use the catheter if it is kinked or damaged. If the catheter becomes kinked or damaged while in the patient, remove it and use a new catheter. Prior to injecting, the physician should ensure that there is no kink in the catheter.

Correct guide wire insertion and positioning – Do not advance the balloon beyond the guide wire to reduce the risk of tissue damage.

- Ensure the guide wire is inserted into the catheter and through the balloon portion for adequate support during vascular access insertion. Failure to do so may result in catheter damage.

Cryoablation near prosthetic heart valves – Do not pass the catheter through a prosthetic heart valve (mechanical or tissue). The catheter may become trapped in the valve, damaging the valve and causing valvular insufficiency or premature failure of the prosthetic valve.

Cryoadhesion – Do not pull on the catheter, sheath, umbilical cables, or console while the catheter is frozen to the tissue, as this may lead to tissue injury.

Do not resterilize – Do not resterilize this device for purpose of reuse. Resterilization may compromise the structural integrity of the device or create a risk of contamination from the device that could result in patient injury, illness, or death.

Embolism risk – Introducing any catheter into the circulatory system entails the risk of air or gas embolism, which can occlude vessels and lead to tissue infarction with serious consequences. Always advance and withdraw components slowly to minimize the vacuum created and therefore minimize the risk of air embolism.

Environmental limits – Perform cryoablation procedures only within the environmental parameters. Operating outside these parameters may prevent the start or completion of a cryoablation procedure. Refer to the Specifications Table on page page 12 for environmental parameters.

Fluid incursion – Do not expose the catheter handle or coaxial and electrical connectors to fluids or solvents. If these components get wet, the Arctic Front Cryoballoon may not function properly, and connector integrity may be compromised.

Fluoroscopy required for catheter placement – The use of fluoroscopy during catheter ablation procedures presents the potential for significant x-ray exposure to both patients and laboratory staff. Extensive exposure can result in acute radiation injury and increased risk for somatic and genetic effects. Only perform catheter ablation after giving adequate attention to the potential radiation exposure associated with the procedure, and taking steps to minimize this exposure. Give careful consideration before using the device in pregnant women.

For single use only – This device is intended only to be used once for a single patient. Do not reuse, reprocess, or resterilize this device for purpose of reuse. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device or create a risk of contamination of the device that could result in patient injury, illness, or death.

Frequent flushing of the guide wire lumen – Flush the guide wire lumen initially and then to prevent coagulation of blood in the lumen. Flush the guide wire lumen with saline after each contrast injection.

Improper connection – Do not connect the cryoablation catheter to a radiofrequency (RF) generator or use it to deliver RF energy. Doing this may cause catheter malfunction or patient harm.

Induced arrhythmias – Catheter procedures may mechanically induce arrhythmias.

Leakage current from connected devices – Use only isolated equipment (IEC 60601-1 Type CF equipment, or equivalent) with the CryoConsole and catheters or patient injury or death may occur.

Other catheters, devices, or wires – Avoid catheter entanglement with other catheters, devices, or wires. Such entanglement may necessitate surgical intervention.

Phrenic nerve impairment – Stop ablation immediately if phrenic nerve impairment is observed. Use continuous phrenic nerve pacing throughout each cryoablation application in the right pulmonary veins. To avoid nerve injury, place a hand on the abdomen, in the location of the diaphragm to assess for changes in the strength of the diaphragmatic contraction or loss of capture. In case of no phrenic nerve capture, frequently monitor diaphragmatic movement using fluoroscopy. Position the balloon as antral as possible and not in the tubular portion of the pulmonary vein. New onset hemi-diaphragmatic movement disorder, detected by radiologic assessment, was observed in 11.2% (29/259) of all cryoablation procedures (See Section 5.8.4 for study results).

Post-ablation period – Closely monitor patients undergoing cardiac ablation procedures during the post-ablation period for clinical adverse events.

Pressurized refrigerant – The catheter contains pressurized refrigerant during operation. Release of this gas into the circulatory system due to equipment failure or misuse could result in gas embolism.

Pulmonary vein narrowing or stenosis – Catheter ablation procedures inside or near pulmonary veins may induce pulmonary vein narrowing and/or stenosis. Do not ablate in the tubular portion of the pulmonary vein. The occurrence of this complication may necessitate percutaneous angioplasty or surgical intervention. Seven of 228 (3.1%) cryoablated study subjects had one or more stenosed pulmonary veins (PV's) detected during study imaging (See Section 5.8.3 for study results.)

Required use environment – Cryoablation procedures should be performed only in a fully equipped facility.

RF ablation – Before powering up an RF generator or applying RF energy, disconnect the cryoablation catheter from the CryoConsole to avoid a System Notice message and unnecessary catheter replacement.

Septal damage – Always deflate the balloon and withdraw it into the transseptal sheath before removing it from the left atrium. Crossing the septum while the balloon is unsheathed, inflated, or inflating in the septal puncture site may cause serious septal damage.

Steerable sheath compatibility – Use only the 12 Fr FlexCath Steerable Sheath with the Arctic Front Cardiac CryoAblation Catheter. Using another sheath may damage the catheter or balloon segment.

Sterile package inspection – Inspect the sterile packaging and catheter prior to use. If the sterile packaging or catheter is damaged, do not use the catheter. Contact your Medtronic representative.

System compatibility – Use only Medtronic cryoablation catheters, refrigerant tanks, and components with the CryoConsole. The safety and use of other catheters or components has not been tested.

Qualified users – This equipment should be used only by or under the supervision of physicians trained in left atrial cryoablation procedures.

5 Clinical summary

Study title:	STOP-AF: A Randomized, Controlled Clinical Trial of Catheter Cryoablation in the Treatment of Paroxysmal Atrial Fibrillation
Number of centers:	26 centers in the United States and Canada
Number of subjects:	245 randomized subjects

5.1 Study purpose

To evaluate the safety and effectiveness of the Arctic Front Cardiac Cryoablation Catheter System, including the FlexCath Steerable Sheath, Freezor MAX Cardiac Cryoablation Catheter, and CryoConsole (Gen V) in adult patients with paroxysmal atrial fibrillation who have failed one or more Atrial Fibrillation drugs.

5.2 Study scope, design and methods

The study was a prospective, randomized, controlled, multicenter, pivotal clinical investigation conducted at 26 investigational sites (23 in the United States and 3 in Canada). Subjects with paroxysmal atrial fibrillation (PAF) referred for ablative intervention after efficacy failure of one or more Study Atrial Fibrillation (AF) Drugs (flecainide, propafenone, or sotalol) (Amiodarone was not considered a study AF Drug) were randomized 2:1 to cryoablation intervention (Experimental Subjects, ES) or to a Study AF Drug (Control Subjects, CS). Subjects were followed for 12 months with scheduled and symptom-driven assessments to detect recurrent atrial fibrillation by means of periodic electrocardiograms, weekly scheduled trans-telephonic monitoring, patient-initiated trans-telephonic monitoring, and 24-hour Holter monitoring at 6 and 12 months. The first 90 days after study therapy was initiated was considered a blanked period for all subjects.

5.3 Study endpoints

The primary effectiveness outcome was Treatment Success, defined on the basis of Chronic Treatment Failure events and the occurrence of Acute Procedural Success.

- **Treatment Success:** (TS), defined for CS as freedom from any Chronic Treatment Failure events, and for ES as both Acute Procedural Success and freedom from Chronic Treatment Failure from Day 0 through the 12 month follow-up visit. This comparison of proportions was to be performed using a 2-sided Fisher's Exact Test of binomial proportions with $a = 0.05$ and $b = 0.20$, with an estimate of TS in the groups of 40% Control and 60% Experimental and a 2:1 randomization, giving a sample size calculation of 240 evaluable subjects.
  - **Acute Procedural Success:** (APS), defined as the electrical isolation of ≥ 3 pulmonary veins from the left atrium (as reported after the first procedure) was an additional primary effectiveness outcome measure, for ES only.
  - **Chronic Treatment Failure:** (CTF), defined as Detectable AF (during the Non Blanked Follow-up Period), the use of Non Study AF Drugs, or an AF Intervention (Day 0 through the 12 month follow-up).

The initial cryoablation treatment date or the first day of AF Drug therapy was considered the Start Date for all subjects. Subjects were then followed for 12 months from their Start Date with scheduled and symptom-driven assessments to detect recurrent AF (Detectable AF) by means of periodic electrocardiograms (ECG), weekly scheduled transtelephonic monitoring (TTM), subject-initiated TTMs, and 24-hour Holter monitoring at 6- and 12- months. The 90 day interval following the Start Date was considered a Blanked Follow-up Period for all subjects. It was during this time period that the Control Subjects underwent AF Drug optimization and that Experimental Subjects were allowed one repeat cryoablation as needed. Occurrences of AF during the Blanked Follow-up Period were not considered as Chronic Treatment Failure (CTF) and did not count as an event against the primary objective. Control Subjects were allowed one crossover cryoablation treatment only after they demonstrated CTF. All repeat and crossover cryoablations required review and approval by the Medical Monitor or Principal Investigator.

The primary safety outcomes were Cryoablation Procedure Events and Major Atrial Fibrillation Events.

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- **Cryoablation Procedure Events:** (CPE) defined for ES only as specifically categorized device- or procedure-related serious adverse events (SAE) with onset within 7 days of cryoablation (access site complications, cardiac damage, embolic complications, arrhythmias, persistent phrenic nerve palsy, or death) or with onset at any time through 12 months of follow-up (pulmonary vein stenosis or atrio-esophageal fistula). (Table 1)

Table 1. Cryoablation Procedure Event Categories

Cryoablation Procedure Events (CPE)	With onset between Day 0 and:
Access site complications requiring • Transfusion of 3 or more units; or • Surgical intervention; or • Permanent loss of functional impairment	Day 7
Cardiac damage (including MI)	Day 7
• Pulmonary vein stenosis	12-month follow-up visit*
• Atrio-esophageal fistula	12-month follow-up visit*
Embolic complications (including stroke)	Day 7
Arrhythmias	Day 7
Persistent phrenic nerve palsy	Day 7
Death	Day 7

*This CPE will be assessed through the completion of within window study follow-up.

- **Major Atrial Fibrillation Events:** (MAFE) defined for CS and ES as serious adverse events in the categories of cardiovascular death, myocardial infarction, stroke, or any hospitalization primarily related to AF recurrence/ablation, atrial flutter ablation (excluding Type I), systemic embolization, congestive heart failure, hemorrhagic event or anti-arrhythmic drug initiation, adjustment or complication. (Table 2)

Table 2. Major Atrial Fibrillation Events Categories

Major Atrial Fibrillation Events (MAFE)
Cardiovascular death
Myocardial infarction (MI)
Stroke
Associated with or leading to a hospitalization for (primary reason): • AF recurrence or ablation • Atrial flutter ablation (excluding Type I) • Systemic embolization (not stroke) • Congestive heart failure • Hemorrhagic event (not stroke) • Anti-arrhythmic drug initiation, adjustment, or complication

5.4 Subject accountability

Enrollment and accountability are summarized in the following table.

Table 3. Subjects accountability and disposition

Subject disposition	Control subjects	Experimental subjects	All subjects
Subjects provisionally enrolled and randomized	87	171	258
Screen failures	1	5	6
Withdrawal of consent	4	3	7
Subjects enrolled	82	163	245
Death	0	1	1
Lost to follow-up	0	0	0
Withdrawal of consent	3	0	3
Subjects completing 12 month follow-up	79	162	241
Control subjects crossing over to cryoablation	65	—	—
Experimental subjects undergoing reablation	—	31	—

Study populations for analysis were:

- **Safety Population** (n = 245): pre-specified, included all subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
- Effectiveness Populations
  - Modified intent-to-treat (n = 245): pre-specified included all subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
  - Per protocol Population (n = 181): pre-specified, included those subjects that received treatment in their randomized group and completed the Blanked Follow-up Period, having complete assessments for detection of AF through 12 months of follow-up including at least 80% compliance with rhythm monitoring, and having the absence of any major protocol violations.
- **Cryoablated Control Population** (n = 65): pre-specified, included those CS who underwent crossover cryoablation. Control subjects were allowed to undergo one cryoablation procedure under the protocol. All control subject crossovers were required to be approved by the Principal Investigator or Medical Monitor. Cryoablated control subjects were followed for 12 months from the date of the cryoablation procedure.
- **Reablated Experimental Population** (n = 31): pre-specified, included ES who underwent repeat cryoablation during the Blanked Follow-up Period. Experimental subjects were allowed to undergo an additional cryoablation procedure during the 90 day blanking period. Reablated experimental subjects maintained the same follow-up schedule as determined by initial study cryoablation procedure.

5.5 Subject demographics

The STOP AF study population consisted of mostly white ethnic background (94.3%), had a mean age of 56.6 years with 77.1% being male. The baseline characteristics were comparable between the randomized groups, as summarized in Table 4 and Table 5.

Table 4. Baseline demographics - age, echocardiography, AF symptoms, SF-36 score

	All subjects mean (SE) N median (min, max) N = 245	Control subjects mean (SE) N median (min, max) N = 82	Experimental subjects mean (SE) N median (min, max) N = 163	Difference [95% 95%C][a]	p value
Age (years)	56.6 (0.60) 245 57.0 (26, 75)	56.4 (1.04) 82 56.5 (26, 72)	56.7 (0.73) 163 58.0 (33, 75)	0.3 [-2.2, 2.8]	0.797
Left atrial AP diameter (mm)	40.5 (5.4) 245 40 (24, 54)	40.9 (6.0) 82 40.5 (28, 54)	40.3 (5.1) 163 40 (24, 50)	-0.7 [-2.1, -0.8]	0.353
Left ventricular EF (%)	60.2 (5.6) 244 60 (40, 76)	60.7 (6.4) 82 60 (45, 76)	60.0 (5.7) 162 60 (40, 75)	-0.7 [-2.3, -0.9]	0.407
Symptomatic AF in the 2 months prior to enrollment	23.2 (2.54) 239 10.0 (2, 300)	21.2 (3.63) 80 10.0 (2, 250)	24.3 (3.36) 159 10.0 (2, 300)	3.0 [-7.6, 13.7]	0.540
Overall SF-36 score	70.63 (1.115) 231 74.0 (15.0, 98.0)	70.37 (1.716) 78 74.50 (29.0, 98.0)	70.76 (1.442) 153 74.00 (15.0, 98.0)	0.4% [-4.3, 5.0%]	0.870

[a] AP = Antero-posterior; EF = Ejection Fraction

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Table 5. Baseline demographics - gender, ethnicity and NYHA Class

		All subjects % (n) N = 245	Control subjects % (n) N = 82	Experimental subjects % (n) N = 163	p value
Gender	Male	77.1% (189)	78.0% (64)	76.7% (125)	0.873
	Female	22.9% (56)	22.0% (18)	23.3% (38)	
Ethnicity	White	94.3% (231)	92.7% (76)	95.1% (155)	0.696
	Black	1.2% (3)	2.4% (2)	0.6% (1)	
	Hispanic	0.8% (2)	1.2% (1)	0.6% (1)	
	Asian	1.6% (4)	1.2% (1)	1.8% (3)	
	Other	2.0% (5)	2.4% (2)	1.8% (3)	
NYHA[a] Class	None / Class I	93.5% (229)	93.9% (77)	93.3% (152)	1.000
	Class II	6.5% (16)	6.1% (5)	6.7% (11)	
Cardio-vascular risk factors	Diabetes	7.3% (18)	8.5% (7)	6.7% (11)	0.612
	Hypertension	42.4% (104)	45.1% (37)	41.1% (67)	0.585
	Dyslipidemia	48.2% (118)	48.8% (40)	47.9% (78)	0.893

[a] NYHA = New York Heart Association

Previously failed AF Drugs for efficacy were comparable between study groups with 36% of all study subjects having failed flecainide, 47% having failed propafenone, and 29% having failed sotalol.

5.6 Results

5.6.1 Procedural data

The Arctic Front Cryocatheter parameters for first procedures in ES (n = 163) included approximately 3 cryoapplications for each of the 4 major pulmonary veins at a mean intra-catheter temperature between -48.6 and -54.1 °C, with a median duration of 240 seconds per cryoapplication (Table 6).

Table 6. Arctic Front Cryocatheter Cryoapplication Parameters by Pulmonary Vein Location, First Experimental Procedures (N = 163)

Cryoapplication parameters	RSPV[a] mean (SE) N median (min, max)	RIPV[a] mean (SE) N median (min, max)	LSPV[a] mean (SE) N median (min, max)	LIPV[a] mean (SE) N median (min, max)
# of cryo appe	2.9 (0.12) 161 3.0 (1, 11)	2.8 (0.14) 154 2.0 (0, 11)	3.6 (0.14) 150 3.0 (1, 12)	3.2 (0.11) 152 3.0 (1, 9)
Measured temp (°C)	-50.70 (0.73) 460 -51.0 (-80.0, 33.0)	-48.63 (1.00) 405 -48.0 (-81.0, 35.0)	-54.12 (0.79) 508 -55.0 (-81.0, 36.0)	-50.78 (0.78) 484 -49.0 (-81.0, 33.0)
Duration (secs)	196.9 (3.54) 473 240.0 (3, 240)	205.4 (3.69) 428 240.0 (3, 240)	219.3 (2.80) 534 240.0 (1, 240)	230.1 (2.07) 488 240.0 (4, 360)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The Freezor MAX Cryocatheter was used for gap cryoablations in a small proportion of major pulmonary veins during first experimental procedures (initial study cryoablation procedure). (Table 7)

Table 7. Freezor MAX Cryocatheter Use by Pulmonary Vein Location, First experimental procedures (N = 163)

Freezor MAX Cryocatheter Use	RSPV[a] % (n)	RIPV[a] % (n)	LSPV[a] % (n)	LIPV[a] % (n)
Experimental first procedures	4.9% (8)	9.2% (15)	4.3% (7)	4.3% (7)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The first experimental procedure lasted a mean of 371 minutes, with investigational devices inserted in the subject vasculature for a mean of 181 minutes. Cryoablation time averaged 65.7 minutes, and total fluoroscopy time averaged 62.8 minutes (Table 8).

Table 8. Cryoablation procedural durations, First experimental procedures (N = 163)

Procedure, Cryocatheter & fluoroscopy times	Total procedure duration mean (SE) N median (min, max)	Cryocatheter insertion time mean (SE) N median (min, max)	Total ablation time mean (SE) N median (min, max)	Total fluoroscopy time mean (SE) N median (min, max)
Experimental first procedures (min)	371.4 (7.89) 163 349.0 (200.0, 650.0)	181.2 (5.86) 162 169.0 (72.0, 427.0)	65.7 (2.70) 162 56.8 (17.0, 179.8)	62.8 (2.55) 162 54.0 (8.0, 229.0)

5.6.2 Compliance with follow-up and rhythm monitoring requirements

Follow-up compliance with key assessments was high, exceeding 90% in all cases except for Holter compliance which was as low as 72% at the 6 month follow-up visit in the Control group. The Holter monitoring assessment protocol requirements for cryoablated control subjects was reduced because cryoablated control subjects were considered chronic treatment failures. This meant further Holter monitoring was not required.

Pulmonary vein CT/MRI imaging was performed prior to a subjects first cryoablation procedure (Experimental and Cryoablated Control) as well as at 6 and 12 months post-cryoablation procedure for pulmonary vein stenosis surveillance (Table 9).

Table 9. Compliance with follow-up and monitoring requirements

Parameter		Control subjects%[a]	Experimental subjects%[b]	All subjects%[c]
Office visits	3 months	98.8%	100.0%	99.6%
	6 months	97.6%	100.0%	99.2%
	12 months	96.3%	99.4%	98.4%
Weekly TTMs		91.5%	91.5%	91.5%
Scheduled TTMs[d]		3,841	7,983	11,824
Unscheduled TTMs[d]		3,016	2,084	5,100
24[e] h Holter monitors	6 months[e]	72.8%	85.9%	81.6%
	12 months[f]	74.7%	88.9%	84.2%
Imaging of pulmonary veins	Baseline	100%	100%	100%
	6 months	95.4%	96.9%	96.5%
	12 months	93.8%	97.5%	96.4%

[a] Denominator = 82 except for imaging of pulmonary veins for which denominator = 65 cryoablated Control Subjects eligible for 6 month study and 47 eligible for 12 month study at time of report.
[b] Denominator = 163 Experimental Subjects.
[c] Denominator = 245 except for imaging of pulmonary veins for which denominator = 228 cryoablated subjects eligible for 6 month study and 205 eligible for 12 month study at time of report.
[d] Number of TTM recordings
[e] Has a holter recording between 150 and 210 days
[f] Has a holter recording between 335 and 395 days

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5.6.3 Effectiveness outcomes and measures

The STOP AF trial defined three (3) Primary Effectiveness Outcome Measures:

- **Acute Procedural Success (APS)**, the electrical isolation of ≥ 3 pulmonary veins from the left atrium as reported after the first procedure (ES).
- **Chronic Treatment Failure (CTF)**, defined as Detectable AF during the Non Blanked Follow-up Period, or use of Non Study AF Drugs, or an AF Intervention through the 12 month follow-up visit. The protocol stipulated that subjects could not be counted as a CTF for Detectable AF during the 90 day blanking period. However, subjects could have a CTF for use of Non Study AF Drugs or AF Intervention during the 90 day blanking period.
- **Treatment Success (TS)**, defined as:
  - **Experimental Subjects:** Acute Procedural Success and Freedom from Chronic Treatment Failure.
  - **Control Subjects:** Freedom from Chronic Treatment Failure.

Acute Procedural Success: Acute Procedural Success was achieved in 98.2% of ES. Electrical isolation was achieved in >95% of each of the 4 main pulmonary veins attempted. Electrical isolation was assessed by pacing to determine electrical conduction between the pulmonary vein and left atrium had been interrupted, by evidence of entrance and, where assessable, exit block (Table 10).

Table 10. Experimental First Procedures: Acute Pulmonary Vein Isolation rates

Vein(s)	Proportion isolated % (n / N)
≥ 3 PVs (APS[a])	98.2% (160 / 163)
RSPV[b]	98.1% (159 / 163)
RIPV[b]	97.4% (152 / 156)
LSPV[b]	96.7% (146 / 151)
LIPV[b]	97.4% (149 / 153)

[a] APS = Acute Procedural Success
[b] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior

Treatment Success: The Primary Effectiveness Outcome, Treatment Success, was observed in 69.9% of ES and 7.3% of CS (difference 62.6%, p < 0.001). (See Figure 1 and Table 11).

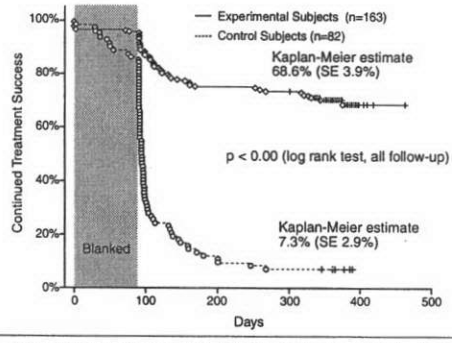

Figure 1. Kaplan Meier Display of Continued Treatment Success by Group Through 12 months, Modified Intent to Treat Population

Table 11. Primary effectiveness outcome: Treatment success (mITT Population)

Primary effectiveness outcome	Control subjects % (n / N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	p value
Treatment success	7.3% (6 / 82) [2.7, 15.2%]	69.9% (114 / 163) [62.3, 76.9%]	62.6% [53.6, 71.6%]	<0.001

Additional Measures of Effectiveness: Other relevant measures confirmed treatment effectiveness for PAF:

- **AF Drug Free Treatment Success:** Of the 114 ES with Treatment Success, 101 (62.0%) were Treatment Successes without the use of any AF Drugs at any time during the Non Blanked Follow-up Period.
  - 62.0% (101/163) of experimental subjects were off AF drugs during the entire non-blanked follow-up period, while 8% (13/163) of the experimental subjects that were considered treatment successes were treated with a previously failed AF drug during the non-blanked follow-up period (Table 11).

Table 12. Treatment Success and Atrial Fibrillation Drug Therapy

AF Drug Status during Non-Blanked Follow-up Period	Control Subjects % (n / N) [95% CI] N = 82	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment Success	7.3% (6 / 82) [2.7, 15.3%]	69.9% (114 / 163) [62.3, 76.9%]
Treatment Success Without Any AF Drugs[2]	0.0% (0 / 82) [0.0, 4.4%]	62.0% (101 / 163) [54.0, 69.4%]
Treatment Success With Any AF Drugs[3]	7.3% (6 / 82) [2.7, 15.3%]	8.0% (13 / 163) [4.3, 13.3%]

- **Reduced Use of AF Drugs:** 74% of all ES were off AF Drugs during the last 3 months of follow-up, and 87% of ES with Treatment Success were free from any AF Drug use during the last 3 months of follow-up.
- **Improved Quality of Life:** ES showed significantly improved SF-36 quality of life score through 12 months of follow-up in every subscale.
- **Reduced Symptoms:** ES had a significant reduction in AF symptomatic burden after cryoablation. At baseline 100% of patients had symptoms, at 12 months only 20% had symptoms from PAF.
- **Effectiveness by Balloon Size:** Treatment success was 70% among cryoablations with balloon size 23mm, 63.3% among cryoablations with balloon size 28mm, and 76.2% among subjects with both balloon sizes utilized (Table 13).

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Table 13. Primary Effectiveness Outcome: Proportion of ES with Treatment Success at the 12 Month Follow-up Visit

Cohort	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment success	69.9% (114 / 163) [62.3, 76.9%]
By balloon size:	
Balloon size 23 only	70% (35 / 50) [55.4, 82.1%]
Balloon size 28 only	63.3% (31 / 49) [48.3, 76.6%]
Both balloon sizes	76.2% (48 / 63) [63.8, 86.0%]

- **Effectiveness by number of procedures performed:** A post-hoc analysis revealed that procedure sequence had an impact on treatment success in the STOP AF trial. Figure 2 illustrates that treatment success improved as the number of procedures performed increased at a given site (see Table 13 and Figure 2).

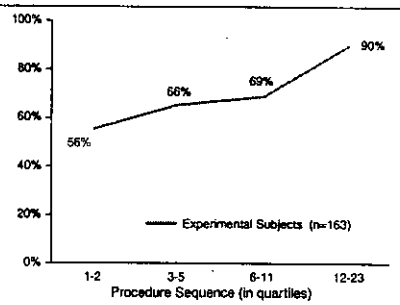

Figure 2. Procedure Frequency and Treatment Success

Atrial Flutter: Adjunctive cryoablation of the cavo-tricuspid isthmus (CTI) was performed in 66 ES. Bi-directional block was achieved in 97.0% of these subjects at the first attempt. Freedom from Flutter Chronic Treatment Failure (Flutter CTF) was observed in 70.7% (29 / 41) of those subjects with a history of atrial flutter at baseline and 84.0% (21 / 25) of those subjects with no history of atrial flutter at baseline.

5.7 Safety outcomes and measures

Serious Adverse Events were defined as any undesirable clinical occurrence in a study subject that included any of the following events:

- Any adverse event resulting in death
- Any adverse event, which is life-threatening
- Any adverse event resulting in inpatient hospitalization > 48 hours or prolongation of existing hospitalization by two or more days
- Any adverse event resulting in a persistent, significant disability or incapacity
- Any adverse event resulting in a congenital anomaly or birth defect

Primary Safety Outcome Measures were defined as:

- **Cryoablation Procedure Events** (CPEs), assessed only for ES for procedural safety, which were device or procedure-related serious adverse events (SAE) categorized as access site complications, cardiac damage, PV stenosis, embolic complications, arrhythmias, unresolved phrenic nerve palsy, and death; and
- **Major Atrial Fibrillation Events** (MAFEs), which were serious adverse events categorized as cardiovascular death, myocardial infarction, stroke, or hospitalization for AF. Overall disease and treatment morbidity, exclusive of the experimental cryoablation procedure, was assessed for both the control and experimental treatment subjects by this measure.

Primary Safety Outcomes (two were defined by the STOP AF Study Protocol):

- The proportion of experimental group safety subjects with one or more CPEs.
- The proportion of safety subjects in either group free of MAFEs at the 12 month follow-up visit.

Both safety outcomes met pre-specified criteria and success was achieved for the safety evaluation.

Cryoablation Procedure Events: Data for subjects who were randomized to the experimental therapy and received treatment are included in the analysis of CPE shown in the following table. ES had a 3.1% (6.3% UCB) rate of CPE compared to a pre-specified UCB of 14.8% ($p < 0.001$). Observed CPEs included 2 instances of cardiac damage (one peri-procedural MI, one perforation with tamponade), one arrhythmia, and two cases of pulmonary vein stenosis (Table 14).

Table 14. Primary safety outcome: Cryoablation procedure events

Primary safety outcome: CPE	Experimental subjects % (n / N)	95% upper confidence bound	p value
Experimental subjects with one or more CPE	3.1% (5 / 163)	6.3%	<0.001

Table 15 lists the individual CPEs that were reported during the STOP AF trial.

Table 15. Experimental Subjects; Cryoablation Procedure Event Categories

CPE Categories	Experimental Subjects % (n) N = 163	95% One-Sided Upper Confidence Bound[a]
Access site complications	0.0% (0)	1.8%
Cardiac damage (including myocardial infarction)	1.2% (2)	3.8%
Embolic phenomena (including stroke)	0.0% (0)	1.8%
Arrhythmias	0.6% (1)	2.9%
Persistent phrenic nerve injury[b]	0.0% (0)	1.8%
Death	0.0% (0)	1.8%
Pulmonary vein stenosis[c]	1.2% (2)	3.8%

[a] Based on Clopper-Pearson confidence intervals

[b] Four (4) Experimental subjects had phrenic nerve injury persisting at 12-months of follow-up; none were adjudicated as SAE. They were not included as a CPE because they were not adjudicated as an SAE.

[c] Five (5) Experimental Subjects had one or more pulmonary veins with stenosis during study follow-up; 2 of these adverse events were adjudicated as SAE.

Pulmonary Vein Stenosis: The PV stenosis rate was 3.1% (5/163) in ES and 3.1% (7/228) for all subjects having undergone cryoablation (Table 16). Stenosis was defined in the protocol as a reduction in the calculated pulmonary vein cross sectional area to <25% of the

baseline pulmonary vein cross sectional area. Five (5) subjects had radiologic findings only, without symptoms of any kind. Two (2) subjects experienced significant symptoms and disability (i.e. Serious Adverse Event) and therefore these two pulmonary vein stenosis events were adjudicated as a CPE.

Table 16. Occurrence of Pulmonary Vein Stenosis in Cryoablated Subjects

Proportion of Subjects	Experimental			Control	All Subjects
	One Cryoablation[a] % (n) [95% CI] [b] N = 132	Two Cryoablations (n) [95% CI][b] N = 31	Any Cryoablation % (n) [95% CI][b] N = 163	One Cryoablation (n) [95% CI][b] N = 65	Any Cryoablation (n) [95% CI][b] N = 228
Stenosis in ≥1 PV at 6 or 12 Months[c]	2.3% (3) [0.5, 6.5%]	6.5% (2) [0.8, 21.4%]	3.1% (5) [1.0, 7.0%]	3.1% (2) [0.4, 10.7%]	3.1% (7) [1.2, 6.2%]

[a] One ES also had RF ablation for atrial fibrillation 72 days after the initial cryoablation.
[b] Clopper-Person confidence intervals.
[c] Each subject is counted only once within each time point.
CI = confidence interval, PV = pulmonary vein.

Phrenic Nerve Palsy: Twenty-nine (29) occurrences of Phrenic Nerve Palsy (PNP) in 28 subjects were reported (Table 17). Overall, 11.2% (29 / 259) of all cryoablation procedures were associated with PNP. Twenty-five (25) (11%) were associated with PNP, which resolved within 12 months of follow-up, and 4 (1.8%) were associated with persistent PNP (Table 18). Fifteen (15) subjects were asymptomatic, 13 had one or more associated symptoms including dyspnea on exertion (6), dyspnea (5), shortness of breath (2), orthopnea (2) and cough (1) during the period in which hemi-diaphragmatic abnormalities were noted. One occurrence of PNP was adjudicated as an SAE.

Table 17. Phrenic Nerve Palsy; Procedures

Phrenic Nerve Palsy	First Experimental Ablation Subjects % (n) [95% CI] N = 163 [a]	Experimental Reablation Subjects % (n) [95% CI] N = 31 [a]	Crossover Control Ablation Subjects % (n) [95% CI] N = 65 [a]	All Ablated Subjects % (n) [95% CI] N = 228 [a]
Procedures free of PNP[b]	87.7% (143) [81.7, 92.3%]	90.3% (28) [74.2, 98.0%]	90.8% (59) [81.0, 96.5%]	88.8% (230) [84.3, 92.4%]
Procedures associated with PNP[b]	12.3% (20) [7.7, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.2% (29) [7.6, 15.7%]

[a] N = the total number of subjects undergoing cryoablation procedures of this type.
[b] One subject had 2 events of PNP, one with the first experimental cryoablation and one with the second, reablation procedure (both of which resolved).

Table 18. Phrenic Nerve Palsy; Subjects

Phrenic Nerve Palsy	First Experimental Ablation Procedures % (n) [95% CI] N = 163 [a]	Experimental Reablation Procedures % (n) [95% CI] N = 31 [a]	Crossover Control Ablation Procedures % (n) [95% CI] N = 65 [a]	All Ablation Procedures % (n) [95% CI] N = 259[a]
All Subjects with PNP	12.3% (20) [7.6, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	12.3% (28) [8.3, 17.3%]
Persistent PNP (radiographic)	2.5% (4) [0.7, 6.2%]	0.0% (0) [0.0, 11.2%]	0.0% (0) [0.0, 5.5%]	1.8% (4) [0.5, 4.4%]
Resolved PNP (radiographic)	9.8% (16) [5.7, 15.5%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.0% (25) [7.2, 15.8%]

[a] N = the total number of cryoablation procedures of this type.

Major Atrial Fibrillation Events: Data for subjects who were randomized to either experimental or drug treatment, received such treatment and were followed through 12 months post treatment start are included in the analysis for MAFE shown in the following table. The analysis was an evaluation of non-inferiority of MAFE rates in ES compared to Control. The clinically significant difference (δ) for establishing noninferiority for the MAFE free rate was set at 10% ES had a 96.9% Freedom from MAFE rate, compared to CS who had a 91.5% rate ($p < 0.0001$, non-inferiority for difference ≤10%) (see Table 19).

Table 19. Primary safety outcome: Freedom from MAFE

Primary safety outcome: Freedom from MAFE	Control subjects % (n /N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	Test for non-inferiority δ = 0.10 p value
Freedom from MAFE (through 12 month follow-up)	91.5% (75 / 82) [83.2, 96.5%]	96.9% (158 / 163) [93.0, 99.0%]	5.4% [-1.1, 12.1%]	<0.001

The observed categories of MAFEs are displayed for both treatment groups below (Table 20).

Table 20. Subjects with one or more MAFEs by category, safety population

MAFE Categories	Control subjects % (n / N) [95% CI]	Experimental subjects % (n / N) [95% 95% CI]	Difference [95% CI]	p value
Any MAFE	8.5% (7 / 82) [3.5, 16.8%]	3.1% (5 / 163) [1.0, 7.0%]	-5.4% [-12.1, 1.1%]	0.112
Cardiovascular death	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000
Hospitalization for:	7.3% (6 / 82) [2.7, 15.2%]	1.8% (3 / 163) [0.4, 5.3%]	-6.5% [11.5, 0.5%]	0.064
AF recurrence or ablation	6.1% (5 / 82) [2.0, 13.7%]	0.6% (1 / 163) [0.0, 3.4%]	-5.5% [-10.8, -0.2%]	0.017
Atrial flutter ablation (excluding Type I)	1.2% (1 / 82) [0.0, 6.6%]	0.0% (0 / 163) [0.0, 2.2%]	-1.2% [-3.6, 1.2%]	0.335
Systemic embolization (not stroke)	0.0% (0 / 82) [0.0, 4.4%]	0.0% (0 / 163) [0.0, 2.2%]	NA	NA
Congestive heart failure	0.0% (0 / 82) [0.0, 4.4%]	1.2% (2 / 163) [0.1, 3.4%]	-1.2% [-5.0, 2.5%]	1.000
Hemorrhagic event (not stroke)	2.4% (2 / 82) [0.3, 8.5%]	1.2% (2 / 163) [0.1, 4.4%]	-1.2% [-5.0, 2.5%]	0.603
Anti-arrhythmic drug: initiation, adjustment, or complication[a]	4.9% (4 / 82) [1.3, 12.0%]	0.6% (1 / 163) [0.0, 3.4%]	-4.3% [-9.1, 0.5%]	0.044
Myocardial infarction	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000
Stroke	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000

[a] Excludes control subject treatment initiation

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As described in Table 21, only 1 ES had a MAFE categorized as stroke. There was an additional 4 (3 ES and 1 CS) strokes reported during the 12 month follow-up. All 4 subjects had recovered completely at the time of the 12 month follow-up. Table 21 provides additional detail for the 5 strokes that were reported during the 12 month follow-up (1 MAFE stroke, 4 non-MAFE stroke).

Table 21. Subjects with Stroke During Study Follow-up

Group	Diagnosis (verbatim)	Onset	Ablation Related[a]	Clinical Outcome	Event Severity	SAE
Exp	Small hemorrhagic stroke	Day 183	No	Recovered completely	Mild	No
Exp	Lacunar infarct	Day 51	Unknown[b]	Recovered completely	Mild	No
Cont	Stroke	Same day as X-over ablation	Yes	Recovered completely	Severe	No
Exp	"Sees white spots in both eyes"	~1 month after cryoablation	No	Recovered completely	Mild	No
Exp	Subarachnoid hemorrhage	Day 260	No	Recovered completely	Severe	Yes

[a] Ablation-related = procedure-related or device-related adverse event.
[b] Age of infarct indeterminate when discovered and could not be temporally linked to procedure or device. Adjudicated as of unknown relatedness
Exp = Experimental, Cont = Control, X-over = crossover

5.8 Additional safety information from the STOP AF Pivotal Trial

5.8.1 Serious adverse events (SAE)
A total of 55 serious adverse events (SAE) in 32 study subjects were reported by investigators during the first 12 months of study follow-up (See Table 22). Twenty-two (22) SAE occurred in 12 CS (12 MAFE and 10 other SAE) (See Table 23) and 33 SAE occurred in 20 ES (5 CPE, 8 MAFE and 20 other SAE) (See Table 22). The overall proportion of CS with one or more SAE was 14.6% and for ES was 12.3%, a slightly lower rate of SAE occurrence that was not significantly different (p = 0.688).

Table 22. Subjects with one or more serious adverse events, safety population

Serious adverse events	Control subjects % (n /N)	Experimental subjects % (n / N)	Difference [95% CI]	p value
Serious adverse events	14.6% (12 / 82)	12.3% (20 / 163)	-2.3% [-11.5, 6.8%]	0.688

The SAE occurring in CS and ES are listed in the following tables (Table 23 and Table 22).

Table 23. Serious adverse events occurring in control subjects, safety population

Serious Adverse Events	Control Subjects % (n / n) N=82
Atrial Fibrillation	4.9% (4/82)
Atrial Flutter	2.4% (2/82)
Appendicitis	1.2% (1/82)
Atrial Thrombosis	1.2% (1/82)
Cardiac Tamponade	1.2% (1/82)
Cardio Respiratory Arrest	1.2% (1/82)
Gastrointestinal Hemorrhage	1.2% (1/82)
Injection Site Infection	1.2% (1/82)
Meningitis	1.2% (1/82)
Mental Status Changes	1.2% (1/82)
Pericardial Effusion	1.2% (1/82)
Phrenic Nerve Paralysis	1.2% (1/82)
Renal Failure Acute	1.2% (1/82)
Subdural Hematoma	1.2% (1/82)

Table 24. Serious adverse events occurring in experimental subjects, safety population

Serious Adverse Events	Experimental Subjects % (n / n) N=163
Pneumonia	2.5% (4/163)
Atrial Fibrillation	1.2% (2/163)
Deep Vein Thrombosis	1.2% (2/163)
Myocardial Infarction	1.2% (2/163)
Pulmonary Vein Stenosis	1.2% (2/163)
Asthenia	0.6% (1/163)
Asthma	0.6% (1/163)
Atrial Flutter	0.6% (1/163)
Cardiac Tamponade	0.6% (1/163)
Cardiopulmonary Failure	0.6% (1/163)
Escherichia Bacteremia	0.6% (1/163)
Gastrointestinal Hemorrhage	0.6% (1/163)
Ileitis	0.6% (1/163)
Multi Organ Failure	0.6% (1/163)
Pneumonitis	0.6% (1/163)
Pneumothorax	0.6% (1/163)
Pulmonary Embolism	0.6% (1/163)
Pyelonephritis Acute	0.6% (1/163)
Sepsis	0.6% (1/163)
Soft Tissue Hemorrhage	0.6% (1/163)
Subarachnoid Hemorrhage	0.6% (1/163)
Vessel Puncture Site Hematoma	0.6% (1/163)
Wegener S Granulomatosis	0.6% (1/163)

5.8.2 Death summary
No study subject died within 30 days of a cryoablation procedure. There was one death during the 12 month follow-up period. A 68 year old male Experimental Subject died shortly after a witnessed cardiac arrest occurring 10 months after cryoablation. The event was determined to be unrelated to the study devices, ablation procedure or approved anti-arrhythmic drug therapy.

5.8.3 Pulmonary vein stenosis

PV stenosis was defined by the study protocol as a 75% reduction in area which is roughly a 50% decrease in diameter. Assessment for PV dimensions was done at baseline of 6 and 12 months via CT/MRI scans. Seven of 228 (3.1%) cryoablated study subjects (5 ES and 2 Crossover CS) had one or more stenosed pulmonary veins (PVs) detected during study imaging. Two subjects were symptomatic and their pulmonary vein stenosis adverse events were adjudicated as SAEs and CPEs. Intervention was recommended for both subjects; one declined and the other had angioplasty and stenting with symptomatic improvement. Based on a multivariate analysis there are no known contributing factors to the incidence of PV stenosis.

5.8.4 Phrenic nerve injury

Cryoablation was associated with a high incidence of Transient Phrenic Nerve Dysfunction (TPND) occurring during procedures, which resolved by the end of the procedure and were almost always unassociated with subsequent phrenic nerve dysfunction. Phrenic nerve palsy (PNP), new onset hemi-diaphragmatic movement disorder detected by radiologic assessment, was found after 11.2% (29 / 259) of all cryoablation procedures of which 15 (51.7%) were asymptomatic. All but 4 cases resolved by the end of study follow-up, taking a mean of 158.2 days (range 1 to 407). Three of 4 persistent PNP cases were symptomatic during follow-up, but none were disabling and only 1 persistent PNP subject had symptoms at the 12 Month visit. Based on a multivariate analysis there are no known contributing factors to the incidence of Phrenic Nerve Palsy.

5.8.5 Strokes and TIAs

Strokes occurred in 5 study subjects (4 ES and 1 CS); only one of these was related to a cryoablation procedure or the devices in a Crossover Control Subject. Of these 5 strokes, one was a subarachnoid hemorrhage from an anterior cerebral artery aneurysm, another was characterized as "whites spots in both eyes" and stroke could not be excluded, and one was a small lacunar stroke found incidentally during a work-up of dizziness. All 5 strokes recovered completely by the conclusion of study follow-up.

5.8.6 Esophageal injury

Esophageal ulcerations have been observed in some subjects who undergo cryoablation with the Arctic Front Cryoablation Catheter. As with other forms of left atrial ablation, the physician should consider appropriate medical strategies to minimize the risk of esophageal injury.

One (1) investigational center performed esophagogastroduodenoscopy post-cryoablation procedure on 12 STOP AF subjects. Of the 12 subjects, 3 were discovered to have esophageal ulcerations. All 3 subjects had follow-up esophagogastroduodenoscopy and demonstrated resolution of esophageal ulceration.

5.8.7 Vascular access complications

Other than routine cases of bruise, hematoma and discharge, there were 4 procedures (4 / 259, 1.5%) associated with significant vascular access site adverse events requiring surgical intervention or transfusion: 1 new AV fistula, 1 worsened pre-existing AV fistula, 2 pseudoaneurysms, and one hemorrhage requiring transfusion. One subject had both an AV fistula and a pseudoaneurysm.

5.9 Summary of STOP AF Pivotal Trial adverse events as categorized using MedDRA

There were a total of 1,406 adverse events (AEs) reported in 235 study subjects during the 12 month period of study follow-up. Seventy-six (76) CS experienced 485 AEs and 159 ES experienced 921 AEs. Ten (10) study subjects had no AEs reported, 6-CS and 4-ES.

In total, 69.2% (45/65) of Crossover CS and 75.5% (123/163) of ES experienced at least one **procedure-related AE**. Overall, the most frequently reported procedure-related AEs (higher than 10%) were back pain (35 subjects, 15.4%) and vessel puncture site hematoma (26 subjects, 11.4%). Other fairly common (higher than 5%) procedure-related AEs included pharyngolaryngeal pain (22 subjects,9.6%), cough (21 subjects, 9.2%), nausea (19 subjects, 8.3%), and procedural pain (15 subjects, 6.6%).

A greater proportion of ES (46.0%) experienced at least one device-related AE compared to Crossover CS (23.1%). The most frequently reported device-related AEs (higher than 10%) were in the following System Organ Class (SOC): Injury, Poisoning and Procedural Complications (Control:12.3%; Experimental: 18.4%), Nervous System Disorders (Control:13.8%; Experimental: 16.6%), Respiratory, Thoracic and Mediastinal Disorders (Control: 6.2%; Experimental: 12.3%), and General Disorders and Administration Site conditions (Control: 4.6%; Experimental: 11.0%). Overall, the only device-related AE occurring in greater than 10% of all cryoablated subjects was phrenic nerve paralysis (28subjects, 12.3%). Other common (higher than 5%) device-related AEs included nerve injury (22 subjects, 9.6%), cough (15 subjects, 6.6%) and venous injury (14 subjects, 6.1%). The majority of the device-related AEs that were observed occurred in less than 2% of subjects.

5.10 Study conclusion

The STOP AF Pivotal Trial demonstrated that there is a reasonable assurance of safety and effectiveness to support the use of the Arctic Front Cardiac CryoAblation Catheter, the Freezor MAX Cryocatheter, FlexCath Steerable Sheath and the CryoConsole (Gen V) in the treatment of patients with drug resistant paroxysmal atrial fibrillation.

6 Adverse events

Potential adverse events associated with cardiac catheter cryoablation procedures include, but are not limited to, the following conditions:

- Anemia
- Anxiety
- Atrial flutter
- Back pain
- Bleeding from puncture sites
- Blurred vision
- Bradycardia
- Bronchitis
- Bruising
- Cardiac tamponade
- Cardiopulmonary arrest
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Cough
- Death
- Diarrhea
- Dizziness
- Esophageal damage
- Fatigue
- Fever
- Headache
- Hemoptysis
- Hypotension/hypertension
- Lightheadedness
- Myocardial infarction
- Nausea/vomiting
- Nerve injury
- Pericardial effusion
- Pulmonary vein stenosis
- Shivering
- Shortness of breath
- Sore throat
- Tachycardia
- Transient ischemic attack
- Urinary infection
- Vasovagal reaction
- Visual changes

7 Instructions for use

7.1 Connecting the catheter

To connect the catheter, follow these steps. (For more detailed instructions, see the *CryoConsole Operator's Manual*.)

1. Connect the non-sterile auto connection box to the CryoConsole.
2. Connect the Arctic Front cryoballoon to a sterile coaxial umbilical cable and a sterile electrical umbilical cable in a dry environment.
3. Connect the coaxial umbilical cable to the CryoConsole and connect the electrical umbilical cable to the auto connection box.

Note: The ECG cable is not required for an Arctic Front procedure, and should not be connected to the non-sterile auto connection box.

Note: If the balloon cannot be inflated or deflated using the CryoConsole, have a Manual Retraction Kit on hand during the procedure.

7.2 CryoAblation

To use the catheter for a cryoablation procedure, follow these steps. (For more detailed instructions, see the *CryoConsole Operator's Manual*.)

Note: Prior to introducing the Arctic Front into the patient, test the deflection mechanism by pulling on the lever on the handle to ensure it is operational.

Note: Always use the lever on the handle to straighten the distal segment before insertion or withdrawal of the catheter.

1. Using an aseptic technique, create a vascular access with an appropriate introducer. Obtain left atrial, transseptal access using a transseptal sheath and needle.
   - Place standard diagnostic pacing catheters.
   - Visualize left atrial anatomy to help select a balloon size, select balloon size.
   - Selection of balloon size should be based on PV diameter and shape, the surrounding anatomy, and desired position of the balloon outside the tubular portion of the PV. PV diameter ranges are recommended as follows:
     a) 23 mm balloon: 10-21 mm
     b) 28 mm balloon: 16-30 mm
2. Soak the balloon and sleeve then pull back the sleeve making sure the sleeve is still submerged.
3. Exchange the transseptal sheath over the guide wire for the FlexCath Sheath.
4. Insert the Arctic Front Cryocatheter over the guide wire into the FlexCath Sheath.
5. Under fluoroscopic guidance, track a 0.032" to 0.035" guide wire to the target pulmonary vein. Advance the Arctic Front cyrocatheter over the guide wire into the left atrium.
6. Set the treatment time on the CryoConsole screen, the preset ablation duration is 240 seconds.
7. Inflate the balloon in the left atrium.
8. To occlude blood flow, position the catheter at the ostium of the target pulmonary and not inside the tubular portion of the PV.
9. Verify the balloon position for complete occlusion.
   Note: If using a mixture of 50/50 contrast/saline be sure to flush the guide wire lumen with saline after each contrast injection.
10. Perform the cryoablation.
11. Wait for the cryoablation phase to complete (at the end of the preset time). The balloon remains inflated and the Thawing phase begins.
12. During the Thawing phase, watch the temperature indicator on the screen. When it reaches 10 °C, advance the blue push button on the catheter handle. Maintain pressure on the push button until the balloon deflates. The balloon deflates automatically when the temperature reaches 20 °C.
    Note: Advancing the push button on the catheter handle during balloon deflation stretches the balloon to maximum length allowing the folds in the balloon material to wrap tightly, reducing the profile of the balloon segment for ease of re-entry into the sheath.
13. As needed, perform additional treatments by positioning the balloon differently in the same pulmonary vein.
14. Position the catheter at the ostium of the next target pulmonary vein using the guide wire and/or deflection capabilities. Return to Step 7 and continue ablation.
15. Determine effective ablation of the cardiac tissue by assessing electrical isolation of the pulmonary vein from the left atrium after the cryoablation treatments have been completed.
16. After all treatments are completed, and after the balloon is deflated retract the catheter into the sheath.
17. Remove the catheter from the patient.

8 Specifications

Catheter shaft size	3.5 mm (10.5 Fr)
Tip outer diameter	3 mm (9 Fr)
Recommended introducer sheath	12 Fr FlexCath Steerable Sheath
Inner diameter of guide wire lumen	1.3 mm (0.049 in)
Inflated balloon diameter	Model 2AF232 - 23 mm Model 2AF282 - 28 mm
Shaft length (inflated)	100 cm
Number of thermocouples	1
Environmental parameters	
Storage	Greater than 0 °C (32 °F)
Operation	15 °C to 30 °C (60 °F to 86 °F) at altitudes less than 2400 meters (8000 feet) above sea level

9 Medtronic limited warranty

For complete warranty information, see the accompanying limited warranty document.

10 Service

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Medtronic

FREEZOR® MAX 239F3, 239F5

Cardiac CryoAblation Catheter

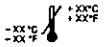
Technical Manual

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

The following are trademarks or registered trademarks of Medtronic in the United States and possibly in other countries: Arctic Front, Freezor, Medtronic

Explanation of symbols

Refer to the package labels to see which of the following symbols apply to this product

LOT	Lot number
REF	Reorder number
	Use by
STERILE EO	Sterilized using ethylene oxide
	Do not reuse
	Do not resterilize
	Do not use if package is damaged
	Package contents
	Consult instructions for use
	Fragile: handle with care
	Keep dry
	Product documentation
	Temperature limitation
	Do not freeze
	Cardiac cryoablation catheter
	Open here

1 Description

The Freezor MAX Cardiac CryoAblation Catheter is a flexible, steerable catheter used to ablate cardiac tissue. It is used together with the CryoConsole and related components. The tip of the Freezor MAX Cryocatheter reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the tip of the catheter. The catheter tip has an integrated thermocouple for temperature reading capability. The catheter is introduced into the vasculature by traditional minimally invasive techniques. The Freezor MAX Cryocatheter is available in 2 models, as described in the following table:

Model	Curves available
239F3 (medium)	blue curve 55 mm
239F5 (long)	orange curve 66 mm

For details about the CryoConsole and how to use it with the catheter to perform cryoablation procedures, see the *CryoConsole Operator Manual*.

1.1 Contents of package

The Freezor MAX Cardiac CryoAblation Catheter is supplied sterile. The package contains the following items:

- 1 Freezor MAX Cardiac CryoAblation Catheter
- product documentation

2 Indications for use

The Freezor MAX Cardiac CryoAblation Catheter is used as an adjunctive device in the endocardial treatment of paroxysmal atrial fibrillation in conjunction with the Arctic Front Cryocatheter for the following uses:

- gap cryoablation to complete electrical isolation of the pulmonary veins
- cryoablation of focal trigger sites
- creation of ablation line between the inferior vena cava and the tricuspid valve

3 Contraindications

Use of the Freezor MAX Cardiac CryoAblation Catheter is contraindicated in patients with the following conditions:

- active systemic infections
- cryoglobulinemia
- other conditions where the manipulation of the catheter would be unsafe (for example, intracardiac mural thrombus)

4 Warnings and precautions

Anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures. Administer anticoagulation therapy, during and post procedure according to the institutions standards. The Freezor MAX Cardiac CryoAblation catheter was not studied for the safety of changes in anticoagulation therapy in patients with paroxysmal atrial fibrillation.

Biohazard disposal – Discard all used catheters and sterile components in accordance with hospital procedures.

Cardioversion/defibrillation during ablation procedure – Disconnect the catheter's electrical connection prior to cardioversion/defibrillation. Failure to do so may trigger system messages indicating a need for catheter exchange.

Catheter handling –

- Use extreme care when manipulating the catheter. Lack of careful attention can result in injury such as perforation or tamponade.
- Do not use excessive force to advance or withdraw the catheter, especially if resistance is encountered.
- Do not use the catheter if it is kinked, damaged, or cannot be straightened.
- Straighten the cooling segment before inserting or withdrawing the catheter.
- Do not at any time preshape or bend the catheter shaft or cooling segment. Bending or kinking the catheter shaft may damage internal structures and increase the risk of catheter failure. Prebending of the distal curve can damage the catheter.
- Catheter advancement should be performed under fluoroscopic guidance.
- The catheter should be replaced if System Notice (a message on the CryoConsole user interface) recommends it.

Catheter integrity – Do not use the catheter if it is kinked or damaged. If the catheter becomes kinked or damaged while in the patient, remove it and use a new catheter. Prior to injecting, the physician should ensure that there is no kink in the catheter.

Catheter positioning around the chordae tendineae – Avoid positioning the catheter around the chordae tendineae, as this increases the likelihood of catheter entrapment within the heart, which may necessitate surgical intervention or repair of injured tissues.

Cryoablation near prosthetic heart valves – Do not pass the catheter through a prosthetic heart valve (mechanical or tissue). The catheter may become trapped in the valve, damaging the valve and causing valvular insufficiency or premature failure of the prosthetic valve.

Cryoadhesion – Do not pull on the catheter, sheath, umbilical cables, or console while the catheter is frozen to the tissue, as this may lead to tissue injury.

Do not resterilize – Do not resterilize this device for purpose of reuse. Resterilization may compromise the structural integrity of the device or create a risk of contamination from the device that could result in patient injury, illness, or death.

Embolism risk – Introducing any catheter into the circulatory system entails the risk of air or gas embolism, which can occlude vessels and lead to tissue infarction with serious consequences. Always advance and withdraw components slowly to minimize the vacuum created and therefore minimize the risk of air embolism.

Environmental limits – Perform cryoablation procedures only within the environmental parameters. Operating outside these parameters may prevent the start or completion of a cryoablation procedure. Refer to Specifications on page 12 for environmental parameters.

Fluid incursion – Do not expose the catheter handle or coaxial and electrical connectors to fluids or solvents. If these components get wet, the cryoablation system may not function properly, and connector integrity may be compromised.

Fluoroscopy required for device placement – The use of fluoroscopy during device ablation procedures presents the potential for significant x-ray exposure to both patients and laboratory staff. Extensive exposure can result in acute radiation injury and increased risk for somatic and genetic effects. Only perform device ablation after giving adequate attention to the potential radiation exposure associated with the procedure, and taking steps to minimize this exposure. Give careful consideration before using the device in pregnant women.

For single use only – This catheter is intended only to be used once for a single patient. Do not reuse or reprocess this device for purpose of reuse. Reuse or reprocessing may compromise the structural integrity of the device or create a risk of contamination from the device that could result in patient injury, illness, or death.

Improper connection – Do not connect the cryoablation catheter to a radiofrequency (RF) generator or use it to deliver RF energy. Doing this may cause catheter malfunction or patient harm.

Induced arrhythmias – Catheter procedures may mechanically induce arrhythmias.

Leakage current from connected devices – Use only isolated equipment (IEC 60601-1 Type CF equipment, or equivalent) with the CryoConsole and catheters or patient injury or death may occur.

Other catheters, devices, or wires – Avoid catheter entanglement with other catheters, devices, or wires. Such entanglement may necessitate surgical intervention.

Post-ablation period – Closely monitor patients undergoing cardiac ablation procedures during the post-ablation period for clinical adverse events.

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Pressurized refrigerant–The device contains pressurized refrigerant during operation. Release of this gas into the body into the circulatory system due to equipment failure or misuse could result in gas embolism.

Required use environment – Cryoablation procedures should be performed only in a fully equipped facility.

RF ablation – Before powering up an RF generator or applying RF energy, disconnect the cryoablation catheter from the CryoConsole to avoid an error message and unnecessary catheter replacement.

Sterile package inspection – Inspect the sterile packaging and catheter prior to use. If the sterile packaging or catheter is damaged, do not use the catheter. Contact your Medtronic representative.

System compatibility – Use only Medtronic cryoablation catheters, refrigerant tanks, and components with the CryoConsole. The safety and use of other catheters or components has not been tested.

Transaortic approach – Use adequate fluoroscopic visualization during a transaortic approach to avoid placing the ablation catheter within the coronary vasculature. Catheter placement within the coronary vasculature may cause vascular injury.

Qualified users – This equipment should be used only by or under the supervision of physicians trained in cryoablation procedures.

5 Clinical summary

Study title:	STOP-AF: A Randomized, Controlled Clinical Trial of Catheter Cryoablation in the Treatment of Paroxysmal Atrial Fibrillation
Number of centers:	26 centers in the United States and Canada
Number of subjects:	245 randomized subjects

5.1 Study purpose

To evaluate the safety and effectiveness of the Arctic Front Cardiac Cryoablation Catheter System, including the FlexCath Steerable Sheath, Freezor MAX Cardiac Cryoablation Catheter, and CryoConsole (Gen V) in adult patients with paroxysmal atrial fibrillation who have failed one or more Atrial Fibrillation drugs.

5.2 Study scope, design and methods

The study was a prospective, randomized, controlled, multicenter, pivotal clinical investigation conducted at 26 investigational sites (23 in the United States and 3 in Canada). Subjects with paroxysmal atrial fibrillation (PAF) referred for ablative intervention after efficacy failure of one or more Study Atrial Fibrillation (AF) Drugs (flecainide, propafenone, or sotalol) (Amiodarone was not considered a study AF Drug) were randomized 2:1 to cryoablation intervention (Experimental Subjects, ES) or to a Study AF Drug (Control Subjects, CS). Subjects were followed for 12 months with scheduled and symptom-driven assessments to detect recurrent atrial fibrillation by means of periodic electrocardiograms, weekly scheduled trans-telephonic monitoring, patient-initiated trans-telephonic monitoring, and 24-hour Holter monitoring at 6 and 12 months. The first 90 days after study therapy was initiated was considered a blanked period for all subjects.

5.3 Study endpoints

The primary effectiveness outcome was Treatment Success, defined on the basis of Chronic Treatment Failure events and the occurrence of Acute Procedural Success.

- **Treatment Success:** (TS), defined for CS as freedom from any Chronic Treatment Failure events, and for ES as both Acute Procedural Success and freedom from Chronic Treatment Failure from Day 0 through the 12 month follow-up visit. This comparison of proportions was to be performed using a 2-sided Fisher's Exact Test of binomial proportions with $\alpha = 0.05$ and $\beta = 0.20$, with an estimate of TS in the groups of 40% Control and 60% Experimental and a 2:1 randomization, giving a sample size calculation of 240 evaluable subjects.
  - **Acute Procedural Success:** (APS), defined as the electrical isolation of ≥ 3 pulmonary veins from the left atrium (as reported after the first procedure) was an additional primary effectiveness outcome measure, for ES only.
  - **Chronic Treatment Failure:** (CTF), defined as Detectable AF (during the Non Blanked Follow-up Period), the use of Non Study AF Drugs, or an AF Intervention (Day 0 through the 12 month follow-up).

The initial cryoablation treatment date or the first day of AF Drug therapy was considered the Start Date for all subjects. Subjects were then followed for 12 months from their Start Date with scheduled and symptom-driven assessments to detect recurrent AF (Detectable AF) by means of periodic electrocardiograms (ECG), weekly scheduled transtelephonic monitoring (TTM), subject-initiated TTMs, and 24-hour Holter monitoring at 6- and 12- months. The 90 day interval following the Start Date was considered a Blanked Follow-up Period for all subjects. It was during this time period that the Control Subjects underwent AF Drug optimization and that Experimental Subjects were allowed one repeat cryoablation as needed. Occurrences of AF during the Blanked Follow-up Period were not considered as Chronic Treatment Failure (CTF) and did not count as an event against the primary objective. Control Subjects were allowed one crossover cryoablation treatment only after they demonstrated CTF. All repeat and crossover cryoablations required review and approval by the Medical Monitor or Principal Investigator.

The primary safety outcomes were Cryoablation Procedure Events and Major Atrial Fibrillation Events.

- **Cryoablation Procedure Events:** (CPE) defined for ES only as specifically categorized device- or procedure-related serious adverse events (SAE) with onset within 7 days of cryoablation (access site complications, cardiac damage, embolic complications, arrhythmias, persistent phrenic nerve palsy, or death) or with onset at any time through 12 months of follow-up (pulmonary vein stenosis or atrio-esophageal fistula). (Table 1)

Table 1. Cryoablation Procedure Event Categories

Cryoablation Procedure Events (CPE)	With onset between Day 0 and:
Access site complications requiring • Transfusion of 3 or more units; or • Surgical intervention; or • Permanent loss of functional impairment	Day 7
Cardiac damage (including MI)	Day 7
• Pulmonary vein stenosis	12-month follow-up visit*
• Atrio-esophageal fistula	12-month follow-up visit*
Embolic complications (including stroke)	Day 7
Arrhythmias	Day 7
Persistent phrenic nerve palsy	Day 7
Death	Day 7

*This CPE will be assessed through the completion of within window study follow-up.

- **Major Atrial Fibrillation Events:** (MAFE) defined for CS and ES as serious adverse events in the categories of cardiovascular death, myocardial infarction, stroke, or any hospitalization primarily related to AF recurrence/ablation, atrial flutter ablation (excluding Type I), systemic embolization, congestive heart failure, hemorrhagic event or anti-arrhythmic drug initiation, adjustment or complication. (Table 2)

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Table 2. Major Atrial Fibrillation Events Categories

Major Atrial Fibrillation Events (MAFE)
Cardiovascular death
Myocardial infarction (MI)
Stroke
Associated with or leading to a hospitalization for (primary reason): • AF recurrence or ablation • Atrial flutter ablation (excluding Type I) • Systemic embolization (not stroke) • Congestive heart failure • Hemorrhagic event (not stroke) • Anti-arrhythmic drug initiation, adjustment, or complication

5.4 Subject accountability

Enrollment and accountability are summarized in the following table.

Table 3. Subjects accountability and disposition

Subject disposition	Control subjects	Experimental subjects	All subjects
Subjects provisionally enrolled and randomized	87	171	258
Screen failures	1	5	6
Withdrawal of consent	4	3	7
Subjects enrolled	82	163	245
Death	0	1	1
Lost to follow-up	0	0	0
Withdrawal of consent	3	0	3
Subjects completing 12 month follow-up	79	162	241
Control subjects crossing over to cryoablation	65	----	----
Experimental subjects undergoing reablation	----	31	----

Study populations for analysis were:

- Safety Population (n = 245): pre-specified, included all subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
- Effectiveness Populations
  - Modified intent-to-treat (n = 245): pre-specified included all subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
  - Per protocol Population (n = 181): pre-specified, included those subjects that received treatment in their randomized group and completed the Blanked Follow-up Period, having complete assessments for detection of AF through 12 months of follow-up including at least 80% compliance with rhythm monitoring, and having the absence of any major protocol violations.
- Cryoablated Control Population (n = 65): pre-specified, included those CS who underwent crossover cryoablation. Control subjects were allowed to undergo one cryoablation procedure under the protocol. All control subject crossovers were required to be approved by the Principal Investigator or Medical Monitor. Cryoablated control subjects were followed for 12 months from the date of the cryoablation procedure.
- Reablated Experimental Population (n = 31): pre-specified, included ES who underwent repeat cryoablation during the Blanked Follow-up Period. Experimental subjects were allowed to undergo an additional cryoablation procedure during the 90 day blanking period. Reablated experimental subjects maintained the same follow-up schedule as determined by initial study cryoablation procedure.

5.5 Subject demographics

The STOP AF study population consisted of mostly white ethnic background (94.3%), had a mean age of 56.6 years with 77.1% being male. The baseline characteristics were comparable between the randomized groups, as summarized in Table 4 and Table 5.

Table 4. Baseline demographics - age, echocardiography, AF symptoms, SF-36 score

	All subjects mean (SE) N median (min, max) N = 245	Control subjects mean (SE) N median (min, max) N = 82	Experimental subjects mean (SE) N median (min, max) N = 163	Difference [95% 95%CI]*	p value
Age (years)	56.6 (0.60) 245 57.0 (26, 75)	56.4 (1.04) 82 56.5 (26, 72)	56.7 (0.73) 163 58.0 (33, 75)	0.3 [-2.2, 2.8]	0.797
Left atrial AP diameter (mm)	40.5 (5.4) 245 40 (24, 54)	40.9 (6.0) 82 40.5 (26, 54)	40.3 (5.1) 163 40 (24, 50)	-0.7 [-2.1, -0.8]	0.353
Left ventricular EF (%)	60.2 (5.6) 244 60 (40, 76)	60.7 (6.4) 82 60 (45, 76)	60.0 (5.7) 162 60 (40, 75)	-0.7 [-2.3, -0.9]	0.407
Symptomatic AF in the 2 months prior to enrollment	23.2 (2.54) 239 10.0 (2, 300)	21.2 (3.63) 80 10.0 (2, 250)	24.3 (3.36) 159 10.0 (2, 300)	3.0 [-7.6, 13.7]	0.540
Overall SF-36 score	70.63 (1.115) 231 74.0 (15.0, 98.0)	70.37 (1.716) 78 74.50 (29.0, 98.0)	70.76 (1.442) 153 74.00 (15.0, 98.0)	0.4% [-4.3, 5.0%]	0.870

* AP = Antero-posterior; EF = Ejection Fraction

Table 5. Baseline demographics - gender, ethnicity and NYHA Class

		All subjects % (n) N = 245	Control subjects % (n) N = 82	Experimental subjects % (n) N = 163	p value
Gender	Male	77.1% (189)	78.0% (64)	76.7% (125)	0.873
	Female	22.9% (56)	22.0% (18)	23.3% (38)	
Ethnicity	White	94.3% (231)	92.7% (76)	95.1% (155)	0.696
	Black	1.2% (3)	2.4% (2)	0.6% (1)	
	Hispanic	0.8% (2)	1.2% (1)	0.6% (1)	
	Asian	1.6% (4)	1.2% (1)	1.8% (3)	
	Other	2.0% (5)	2.4% (2)	1.8% (3)	
NYHA* Class	None / Class I	93.5% (229)	93.9% (77)	93.3% (152)	1.000
	Class II	6.5% (16)	6.1% (5)	6.7% (11)	
Cardio-vascular risk factors	Diabetes	7.3% (18)	8.5% (7)	6.7% (11)	0.612
	Hypertension	42.4% (104)	45.1% (37)	41.1% (67)	0.585
	Dyslipidemia	48.2% (118)	48.8% (40)	47.9% (78)	0.893

* NYHA = New York Heart Association

Previously failed AF Drugs for efficacy were comparable between study groups with 36% of all study subjects having failed flecainide, 47% having failed propafenone, and 29% having failed sotalol.

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5.6 Results

5.6.1 Procedural data

The Arctic Front Cryocatheter parameters for first procedures in ES (n = 163) included approximately 3 cryoapplications for each of the 4 major pulmonary veins at a mean intra-catheter temperature between -48.6 and -54.1 °C, with a median duration of 240 seconds per cryoapplication (Table 6).

Table 6. Arctic Front Cryocatheter Cryoapplication Parameters by Pulmonary Vein Location, First Experimental Procedures (N = 163)

Cryoapplication parameters	RSPV[a] mean (SE) N median (min, max)	RIPV[a] mean (SE) N median (min, max)	LSPV[a] mean (SE) N median (min, max)	LIPV[a] mean (SE) N median (min, max)
# of cryo apps	2.9 (0.12) 151 3.0 (1, 11)	2.8 (0.14) 154 2.0 (0, 11)	3.6 (0.14) 150 3.0 (1, 12)	3.2 (0.11) 152 3.0 (1, 9)
Measured temp (°C)	-50.70 (0.73) 460 -51.0 (-80.0, 33.0)	-48.63 (1.00) 405 -48.0 (-81.0, 35.0)	-54.12 (0.79) 508 -55.0 (-81.0, 36.0)	-50.78 (0.78) 484 -49.0 (-81.0, 33.0)
Duration (secs)	196.9 (3.54) 473 240.0 (3, 240)	205.4 (3.69) 428 240.0 (3, 240)	219.3 (2.80) 534 240.0 (1, 240)	230.1 (2.07) 488 240.0 (4, 360)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The Freezor MAX Cryocatheter was used for gap cryoablations in a small proportion of major pulmonary veins during first experimental procedures (initial study cryoablation procedure). (Table 7)

Table 7. Freezor MAX Cryocatheter Use by Pulmonary Vein Location, First experimental procedures (N = 163)

Freezor MAX Cryocatheter Use	RSPV[a] % (n)	RIPV[a] % (n)	LSPV[a] % (n)	LIPV[a] % (n)
Experimental first procedures	4.9% (8)	9.2% (15)	4.3% (7)	4.3% (7)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The first experimental procedure lasted a mean of 371 minutes, with investigational devices inserted in the subject vasculature for a mean of 181 minutes. Cryoablation time averaged 65.7 minutes, and total fluoroscopy time averaged 62.8 minutes (Table 8).

Table 8. Cryoablation procedural durations, First experimental procedures (N = 163)

Procedure, Cryocatheter & fluoroscopy times	Total procedure duration mean (SE) N median (min, max)	Cryocatheter insertion time mean (SE) N median (min, max)	Total ablation time mean (SE) N median (min, max)	Total fluoroscopy time mean (SE) N median (min, max)
Experimental first procedures (min)	371.4 (7.89) 163 349.0 (200.0, 650.0)	181.2 (5.86) 162 169.0 (72.0, 427.0)	65.7 (2.70) 162 56.8 (17.0, 179.8)	62.8 (2.55) 162 54.0 (8.0, 229.0)

5.6.2 Compliance with follow-up and rhythm monitoring requirements

Follow-up compliance with key assessments was high, exceeding 90% in all cases except for Holter compliance which was as low as 72% at the 6 month follow-up visit in the Control group. The Holter monitoring assessment protocol requirements for cryoablated control subjects was reduced because cryoablated control subjects were considered chronic treatment failures. This meant further Holter monitoring was not required.

Pulmonary vein CT/MRI imaging was performed prior to a subjects first cryoablation procedure (Experimental and Cryoablated Control) as well as at 6 and 12 months post-cryoablation procedure for pulmonary vein stenosis surveillance (Table 9).

Table 9. Compliance with follow-up and monitoring requirements

Parameter		Control subjects%[a]	Experimental subjects%[b]	All subjects%[c]
Office visits	3 months	98.8%	100.0%	99.6%
	6 months	97.6%	100.0%	99.2%
	12 months	96.3%	99.4%	98.4%
Weekly TTMs		91.5%	91.5%	91.5%
Scheduled TTMs[d]		3,841	7,983	11,824
Unscheduled TTMs[d]		3,016	2,084	5,100
24[e] h Holter monitors	6 months[e]	72.8%	85.9%	81.6%
	12 months[f]	74.7%	88.9%	84.2%
Imaging of pulmonary veins	Baseline	100%	100%	100%
	6 months	95.4%	96.9%	96.5%
	12 months	93.8%	97.5%	96.4%

[a] Denominator = 82 except for imaging of pulmonary veins for which denominator = 65 cryoablated Control Subjects eligible for 6 month study and 47 eligible for 12 month study at time of report.
[b] Denominator = 163 Experimental Subjects.
[c] Denominator = 245 except for imaging of pulmonary veins for which denominator = 228 cryoablated subjects eligible for 6 month study and 205 eligible for 12 month study at time of report.
[d] Number of TTM recordings
[e] Has a holter recording between 150 and 210 days
[f] Has a holter recording between 335 and 395 days

5.6.3 Effectiveness outcomes and measures

The STOP AF trial defined three (3) Primary Effectiveness Outcome Measures:

- **Acute Procedural Success (APS)**, the electrical isolation of ≥ 3 pulmonary veins from the left atrium as reported after the first procedure (ES).
- **Chronic Treatment Failure (CTF)**, defined as Detectable AF during the Non Blanked Follow-up Period, or use of Non Study AF Drugs, or an AF Intervention through the 12 month follow-up visit. The protocol stipulated that subjects could not be counted as a CTF for Detectable AF during the 90 day blanking period. However, subjects could have a CTF for use of Non Study AF Drugs or AF Intervention during the 90 day blanking period.
- **Treatment Success (TS)**, defined as:
  - **Experimental Subjects:** Acute Procedural Success and Freedom from Chronic Treatment Failure.
  - **Control Subjects:** Freedom from Chronic Treatment Failure.

Acute Procedural Success: Acute Procedural Success was achieved in 98.2% of ES. Electrical isolation was achieved in >95% of each of the 4 main pulmonary veins attempted. Electrical isolation was assessed by pacing to determine electrical conduction between the pulmonary vein and left atrium had been interrupted, by evidence of entrance and, where assessable, exit block (Table 10).

Table 10. Experimental First Procedures: Acute Pulmonary Vein Isolation rates

Vein(s)	Proportion Isolated % (n / N)
≥ 3 PVs (APS[a])	98.2% (160 / 163)
RSPV[b]	98.1% (159 / 163)
RIPV[b]	97.4% (152 / 156)
LSPV[b]	96.7% (146 / 151)
LIPV[b]	97.4% (149 / 153)

[a] APS = Acute Procedural Success
[b] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior

Treatment Success: The Primary Effectiveness Outcome, Treatment Success, was observed in 69.9% of ES and 7.3% of CS (difference 62.6%, p < 0.001). (See Figure and Table 11).

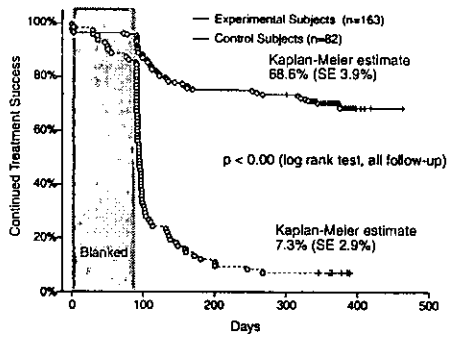

Figure 1. Kaplan Meier Display of Continued Treatment Success by Group Through 12 months, Modified Intent to Treat Population

Table 11. Primary effectiveness outcome: Treatment success (mITT Population)

Primary effectiveness outcome	Control subjects % (n / N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	p value
Treatment success	7.3% (6 / 82) [2.7, 15.2%]	69.9% (114 / 163) [62.3, 76.9%]	62.6% [53.6, 71.6%]	<0.001

Additional Measures of Effectiveness: Other relevant measures confirmed treatment effectiveness for PAF:

- **AF Drug Free Treatment Success:** Of the 114 ES with Treatment Success, 101 (62.0%) were Treatment Successes without the use of any AF Drugs at any time during the Non Blanked Follow-up Period.
  - 62.0% (101/163) of experimental subjects were off AF drugs during the entire non-blanked follow-up period, while 8% (13/163) of the experimental subjects that were considered treatment successes were treated with a previously failed AF drug during the non-blanked follow-up period (Table 11).

Table 12. Treatment Success and Atrial Fibrillation Drug Therapy

AF Drug Status during Non-Blanked Follow-up Period	Control Subjects % (n / N) [95% CI] N = 82	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment Success	7.3% (6 / 82) [2.7, 15.3%]	69.9% (114 / 163) [62.3, 76.9%]
Treatment Success Without Any AF Drugs[a]	0.0% (0 / 82) [0.0, 4.4%]	62.0% (101 / 163) [54.0, 69.4%]
Treatment Success With Any AF Drugs[a]	7.3% (6 / 82) [2.7, 15.3%]	8.0% (13 / 163) [4.3, 13.3%]

- **Reduced Use of AF Drugs:** 74% of all ES were off AF Drugs during the last 3 months of follow-up, and 87% of ES with Treatment Success were free from any AF Drug use during the last 3 months of follow-up.
- **Improved Quality of Life:** ES showed significantly improved SF-36 quality of life score through 12 months of follow-up in every subscale.
- **Reduced Symptoms:** ES had a significant reduction in AF symptomatic burden after cryoablation. At baseline 100% of patients had symptoms, at 12 months only 20% had symptoms from PAF.
- **Effectiveness by Balloon Size:** Treatment success was 70% among cryoablations with balloon size 23mm, 63.3% among cryoablations with balloon size 28mm, and 76.2% among subjects with both balloon sizes utilized (Table 13).

Table 13. Primary Effectiveness Outcome; Proportion of ES with Treatment Success at the 12 Month Follow-up Visit

Cohort	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment success	69.9% (114 / 163) [62.3, 76.9%]
By balloon size:	
Balloon size 23 only	70% (35 / 50) [55.4, 82.1%]
Balloon size 28 only	63.3% (31 / 49) [48.3, 76.6%]
Both balloon sizes	76.2% (48 / 63) [63.8, 86.0%]

- **Effectiveness by number of procedures performed:** A post-hoc analysis revealed that procedure sequence had an impact on treatment success in the STOP AF trial. Figure 2 illustrates that treatment success improved as the number of procedures performed increased at a given site (see Table 13 and Figure 2).

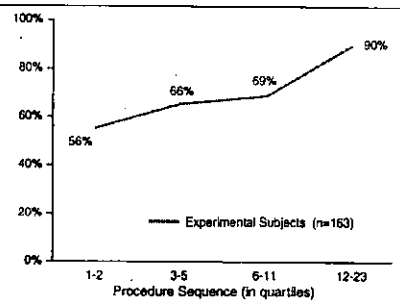

Figure 2. Procedure Frequency and Treatment Success
Atrial Flutter: Adjunctive cryoablation of the cavo-tricuspid isthmus (CTI) was performed in 66 ES. Bi-directional block was achieved in 97.0% of these subjects at the first attempt. Freedom from Flutter Chronic Treatment Failure (Flutter CTF) was observed in 70.7% (29 / 41) of those subjects with a history of atrial flutter at baseline and 84.0% (21 / 25) of those subjects with no history of atrial flutter at baseline.

5.7 Safety outcomes and measures
Serious Adverse Events were defined as any undesirable clinical occurrence in a study subject that included any of the following events:

- Any adverse event resulting in death
- Any adverse event, which is life-threatening
- Any adverse event resulting in inpatient hospitalization > 48 hours or prolongation of existing hospitalization by two or more days
- Any adverse event resulting in a persistent, significant disability or incapacity
- Any adverse event resulting in a congenital anomaly or birth defect

Primary Safety Outcome Measures were defined as:

- **Cryoablation Procedure Events** (CPEs), assessed only for ES for procedural safety, which were device or procedure-related serious adverse events (SAE) categorized as access site complications, cardiac damage, PV stenosis, embolic complications, arrhythmias, unresolved phrenic nerve palsy, and death; and
- **Major Atrial Fibrillation Events** (MAFEs), which were serious adverse events categorized as cardiovascular death, myocardial infarction, stroke, or hospitalization for AF. Overall disease and treatment morbidity, exclusive of the experimental cryoablation procedure, was assessed for both the control and experimental treatment subjects by this measure.

Primary Safety Outcomes (two were defined by the STOP AF Study Protocol):

- The proportion of experimental group safety subjects with one or more CPEs.
- The proportion of safety subjects in either group free of MAFEs at the 12 month follow-up visit.

Both safety outcomes met pre-specified criteria and success was achieved for the safety evaluation.

Cryoablation Procedure Events: Data for subjects who were randomized to the experimental therapy and received treatment are included in the analysis of CPE shown in the following table. ES had a 3.1% (6.3% UCB) rate of CPE compared to a pre-specified UCB of 14.8% ($p < 0.001$). Observed CPEs included 2 instances of cardiac damage (one peri-procedural MI, one perforation with tamponade), one arrhythmia, and two cases of pulmonary vein stenosis (Table 14).

Table 14. Primary safety outcome: Cryoablation procedure events

Primary safety outcome: CPE	Experimental subjects % (n / N)	95% upper confidence bound	p value
Experimental subjects with one or more CPE	3.1% (5 / 163)	6.3%	<0.001

Table 15 lists the individual CPEs that were reported during the STOP AF trial.

Table 15. Experimental Subjects; Cryoablation Procedure Event Categories

CPE Categories	Experimental Subjects % (n) N = 163	95% One-Sided Upper Confidence Bound[a]
Access site complications	0.0% (0)	1.8%
Cardiac damage (including myocardial infarction)	1.2% (2)	3.8%
Embolic phenomena (including stroke)	0.0% (0)	1.8%
Arrhythmias	0.6% (1)	2.9%
Persistent phrenic nerve injury[b]	0.0% (0)	1.8%
Death	0.0% (0)	1.8%
Pulmonary vein stenosis[c]	1.2% (2)	3.8%

[a] Based on Clopper-Pearson confidence intervals
[b] Four (4) Experimental subjects had phrenic nerve injury persisting at 12-months of follow-up; none were adjudicated as SAE. They were not included as a CPE because they were not adjudicated as an SAE.
[c] Five (5) Experimental Subjects had one or more pulmonary veins with stenosis during study follow-up; 2 of these adverse events were adjudicated as SAE.

Pulmonary Vein Stenosis: The PV stenosis rate was 3.1% (5/163) in ES and 3.1% (7/228) for all subjects having undergone cryoablation (Table 16). Stenosis was defined in the protocol as a reduction in the calculated pulmonary vein cross sectional area to <25% of the baseline pulmonary vein cross sectional area. Five (5) subjects had radiologic findings only, without symptoms of any kind. Two (2) subjects experienced significant symptoms and disability (i.e. Serious Adverse Event) and therefore these two pulmonary vein stenosis events were adjudicated as a CPE.

Table 16. Occurrence of Pulmonary Vein Stenosis in Cryoablated Subjects

Proportion of Subjects	Experimental			Control	All Subjects
	One Cryoablation[a] % (n) [95% CI][b] N = 132	Two Cryoablations (n) [95% CI][b] N = 31	Any Cryoablation % (n) [95% CI][b] N = 163	One Cryoablation (n) [95% CI][b] N = 65	Any Cryoablation (n) [95% CI][b] N = 228
Stenosis in ≥1 PV at 6 or 12 Months[c]	2.3% (3) [0.5, 6.5%]	6.5% (2) [0.8, 21.4%]	3.1% (5) [1.0, 7.0%]	3.1% (2) [0.4, 10.7%]	3.1% (7) [1.2, 6.2%]

[a] One ES also had RF ablation for atrial fibrillation 72 days after the initial cryoablation.
[b] Clopper-Person confidence intervals.
[c] Each subject is counted only once within each time point.
CI = confidence interval, PV = pulmonary vein.

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Phrenic Nerve Palsy: Twenty-nine (29) occurrences of Phrenic Nerve Palsy (PNP) in 28 subjects were reported (Table 17). Overall, 11.2% (29 / 259) of all cryoablation procedures were associated with PNP. Twenty-five (25) (11%) were associated with PNP, which resolved within 12 months of follow-up, and 4 (1.8%) were associated with persistent PNP (Table 18). Fifteen (15) subjects were asymptomatic, 13 had one or more associated symptoms including dyspnea on exertion (6), dyspnea (5), shortness of breath (2), orthopnea (2) and cough (1) during the period in which hemi-diaphragmatic abnormalities were noted. One occurrence of PNP was adjudicated as an SAE.

Table 17. Phrenic Nerve Palsy; Procedures

Phrenic Nerve Palsy	First Experimental Ablation Subjects % (n) [95% CI] N = 163 [a]	Experimental Reablation Subjects % (n) [95% CI] N = 31 [a]	Crossover Control Ablation Subjects % (n) [95% CI] N = 65 [a]	All Ablated Subjects % (n) [95% CI] N = 228 [b]
Procedures free of PNP[b]	87.7% (143) [81.7, 92.3%]	90.3% (28) [74.2, 98.0%]	90.8% (59) [81.0, 96.5%]	88.8% (230) [84.3, 92.4%]
Procedures associated with PNP[b]	12.3% (20) [7.7, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.2% (29) [7.6, 15.7%]

[a] N = the total number of subjects undergoing cryoablation procedures of this type.

[b] One subject had 2 events of PNP, one with the first experimental cryoablation and one with the second, reablation procedure (both of which resolved).

Table 18. Phrenic Nerve Palsy; Subjects

Phrenic Nerve Palsy	First Experimental Ablation Procedures % (n) [95% CI] N = 163 [a]	Experimental Reablation Procedures % (n) [95% CI] N = 31 [a]	Crossover Control Ablation Procedures % (n) [95% CI] N = 65 [a]	All Ablation Procedures % (n) [95% CI] N = 259[a]
All Subjects with PNP	12.3% (20) [7.6, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	12.3% (28) [8.3, 17.3%]
Persistent PNP (radiographic)	2.5% (4) [0.7, 6.2%]	0.0% (0) [0.0, 11.2%]	0.0% (0) [0.0, 5.5%]	1.8% (4) [0.5, 4.4%]
Resolved PNP (radiographic)	9.8% (16) [5.7, 15.5%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.0% (25) [7.2, 15.8%]

[a] N = the total number of cryoablation procedures of this type.

Major Atrial Fibrillation Events: Data for subjects who were randomized to either experimental or drug treatment, received such treatment and were followed through 12 months post treatment start are included in the analysis for MAFE shown in the following table. The analysis was an evaluation of non-inferiority of MAFE rates in ES compared to Control. The clinically significant difference (δ) for establishing noninferiority for the MAFE free rate was set at 10% ES had a 96.9% Freedom from MAFE rate, compared to CS who had a 91.5% rate ($p < 0.0001$, non-inferiority for difference ≤10%) (see Table 19).

Table 19. Primary safety outcome: Freedom from MAFE

Primary safety outcome: Freedom from MAFE	Control subjects % (n /N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	Test for non-inferiority δ = 0.10 p value
Freedom from MAFE (through 12 month follow-up)	91.5% (75 / 82) [83.2, 96.5%]	96.9% (158 / 163) [93.0, 99.0%]	5.4% [-1.1, 12.1%]	<0.001

The observed categories of MAFEs are displayed for both treatment groups below (Table 20).

Table 20. Subjects with one or more MAFEs by category, safety population

MAFE Categories	Control subjects % (n / N) [95% CI]	Experimental subjects % (n / N) [95% 95% CI]	Difference [95% CI]	p value
Any MAFE	8.5% (7 / 82) [3.5, 16.8%]	3.1% (5 / 163) [1.0, 7.0%]	-5.4% [-12.1, 1.1%]	0.112
Cardiovascular death	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000
Hospitalization for:	7.3% (6 / 82) [2.7, 15.2%]	1.8% (3 / 163) [0.4, 5.3%]	-6.5% [11.5, 0.5%]	0.064
AF recurrence or ablation	6.1% (5 / 82) [2.0, 13.7%]	0.6% (1 / 163) [0.0, 3.4%]	-5.5% [-10.8, -0.2%]	0.017
Atrial flutter ablation (excluding Type I)	1.2% (1 / 82) [0.0, 6.6%]	0.0% (0 / 163) [0.0, 2.2%]	-1.2% [-3.6, 1.2%]	0.335
Systemic embolization (not stroke)	0.0% (0 / 82) [0.0, 4.4%]	0.0% (0 / 163) [0.0, 2.2%]	NA	NA
Congestive heart failure	0.0% (0 / 82) [0.0, 4.4%]	1.2% (2 / 163) [0.1, 3.4%]	-1.2% [-5.0, 2.5%]	1.000
Hemorrhagic event (not stroke)	2.4% (2 / 82) [0.3, 8.5%]	1.2% (2 / 163) [0.1, 4.4%]	-1.2% [-5.0, 2.5%]	0.603
Anti-arrhythmic drug: Initiation, adjustment, or complication[a]	4.9% (4 / 82) [1.3, 12.0%]	0.6% (1 / 163) [0.0, 3.4%]	-4.3% [-9.1, 0.5%]	0.044
Myocardial infarction	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000
Stroke	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [-0.6, 1.8%]	1.000

[a] Excludes control subject treatment initiation

As described in Table 21, only 1 ES had a MAFE categorized as stroke. There was an additional 4 (3 ES and 1 CS) strokes reported during the 12 month follow-up. All 4 subjects had recovered completely at the time of the 12 month follow-up. Table 21 provides additional detail for the 5 strokes that were reported during the 12 month follow-up (1 MAFE stroke, 4 non-MAFE stroke).

Table 21. Subjects with Stroke During Study Follow-up

Group	Diagnosis (verbatim)	Onset	Ablation Related[a]	Clinical Outcome	Event Severity	SAE
Exp	Small hemorrhagic stroke	Day 183	No	Recovered completely	Mild	No
Exp	Lacunar infarct	Day 51	Unknown[b]	Recovered completely	Mild	No
Cont	Stroke	Same day as X-over ablation	Yes	Recovered completely	Severe	No
Exp	"Sees white spots in both eyes"	~1 month after cryoablation	No	Recovered completely	Mild	No
Exp	Subarachnoid hemorrhage	Day 260	No	Recovered completely	Severe	Yes

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[a] Ablation-related = procedure-related or device-related adverse event.

[b] Age of infarct indeterminate when discovered and could not be temporally linked to procedure or device. Adjudicated as of unknown relatedness

Exp = Experimental, Cont = Control, X-over = crossover

5.8 Additional safety information from the STOP AF Pivotal Trial

5.8.1 Serious adverse events (SAE)

A total of 55 serious adverse events (SAE) in 32 study subjects were reported by Investigators during the first 12 months of study follow-up (See Table 22). Twenty-two (22) SAE occurred in 12 CS (12 MAFE and 10 other SAE) (See Table 23) and 33 SAE occurred in 20 ES (5 CPE, 8 MAFE and 20 other SAE) (See Table 24). The overall proportion of CS with one or more SAE was 14.6% and for ES was 12.3%, a slightly lower rate of SAE occurrence that was not significantly different (p = 0.688).

Table 22. Subjects with one or more serious adverse events, safety population

Serious adverse events	Control subjects % (n /N)	Experimental subjects % (n / N)	Difference [95% CI]	p value
Serious adverse events	14.6% (12 / 82)	12.3% (20 / 163)	-2.3% [-11.5, 6.8%]	0.688

The SAE occurring in CS and ES are listed in the following tables (Table 23 and Table 24).

Table 23. Serious adverse events occurring in control subjects, safety population

Serious Adverse Events	Control Subjects % (n / n) N=82
Atrial Fibrillation	4.9% (4/82)
Atrial Flutter	2.4% (2/82)
Appendicitis	1.2% (1/82)
Atrial Thrombosis	1.2% (1/82)
Cardiac Tamponade	1.2% (1/82)
Cardio Respiratory Arrest	1.2% (1/82)
Gastrointestinal Hemorrhage	1.2% (1/82)
Injection Site Infection	1.2% (1/82)
Meningitis	1.2% (1/82)
Mental Status Changes	1.2% (1/82)
Pericardial Effusion	1.2% (1/82)
Phrenic Nerve Paralysis	1.2% (1/82)
Renal Failure Acute	1.2% (1/82)
Subdural Hematoma	1.2% (1/82)

Table 24. Serious adverse events occurring in experimental subjects, safety population

Serious Adverse Events	Experimental Subjects % (n / n) N=163
Pneumonia	2.5% (4/163)
Atrial Fibrillation	1.2% (2/163)
Deep Vein Thrombosis	1.2% (2/163)
Myocardial Infarction	1.2% (2/163)
Pulmonary Vein Stenosis	1.2% (2/163)
Asthenia	0.6% (1/163)
Asthma	0.6% (1/163)
Atrial Flutter	0.6% (1/163)
Cardiac Tamponade	0.6% (1/163)
Cardiopulmonary Failure	0.6% (1/163)
Escherichia Bacteremia	0.6% (1/163)
Gastrointestinal Hemorrhage	0.6% (1/163)
Ileitis	0.6% (1/163)
Multi Organ Failure	0.6% (1/163)
Pneumonitis	0.6% (1/163)
Pneumothorax	0.6% (1/163)
Pulmonary Embolism	0.6% (1/163)
Pyelonephritis Acute	0.6% (1/163)
Sepsis	0.6% (1/163)
Soft Tissue Hemorrhage	0.6% (1/163)
Subarachnoid Hemorrhage	0.6% (1/163)
Vessel Puncture Site Hematoma	0.6% (1/163)
Wegener S Granulomatosis	0.6% (1/163)

5.8.2 Death summary

No study subject died within 30 days of a cryoablation procedure. There was one death during the 12 month follow-up period. A 68 year old male Experimental Subject died shortly after a witnessed cardiac arrest occurring 10 months after cryoablation. The event was determined to be unrelated to the study devices, ablation procedure or approved anti-arrhythmic drug therapy.

5.8.3 Pulmonary vein stenosis

PV stenosis was defined by the study protocol as a 75% reduction in area which is roughly a 50% decrease in diameter. Assessment for PV dimensions was done at baseline of 6 and 12 months via CT/MRI scans. Seven of 228 (3.1%) cryoablated study subjects (5 ES and 2 Crossover CS) had one or more stenosed pulmonary veins (PVs) detected during study imaging. Two subjects were symptomatic and their pulmonary vein stenosis adverse events were adjudicated as SAEs and CPEs. Intervention was recommended for both subjects; one declined and the other had angioplasty and stenting with symptomatic improvement. Based on a multivariate analysis there are no known contributing factors to the incidence of PV stenosis.

5.8.4 Phrenic nerve injury

Cryoablation was associated with a high incidence of Transient Phrenic Nerve Dysfunction (TPND) occurring during procedures, which resolved by the end of the procedure and were almost always unassociated with subsequent phrenic nerve dysfunction. Phrenic nerve palsy (PNP), new onset hemi-diaphragmatic movement disorder detected by radiologic assessment, was found after 11.2% (29 / 259) of all cryoablation procedures of which 15 (51.7%) were asymptomatic. All but 4 cases resolved by the end of study follow-up, taking a mean of 158.2 days (range 1 to 407). Three of 4 persistent PNP cases were symptomatic during follow-up, but none were disabling and only 1 persistent PNP subject had symptoms at the 12 Month visit. Based on a multivariate analysis there are no known contributing factors to the incidence of Phrenic Nerve Palsy.

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5.8.5 Strokes and TIAs

Strokes occurred in 5 study subjects (4 ES and 1 CS); only one of these was related to a cryoablation procedure or the devices in a Crossover Control Subject. Of these 5 strokes, one was a subarachnoid hemorrhage from an anterior cerebral artery aneurysm, another was characterized as "whites spots in both eyes" and stroke could not be excluded, and one was a small lacunar stroke found incidentally during a work-up of dizziness. All 5 strokes recovered completely by the conclusion of study follow-up.

5.8.6 Esophageal Injury

Esophageal ulcerations have been observed in some subjects who undergo cryoablation with the Arctic Front Cryoablation Catheter. As with other forms of left atrial ablation, the physician should consider appropriate medical strategies to minimize the risk of esophageal injury.

One (1) investigational center performed esophagogastroduodenoscopy post-cryoablation procedure on 12 STOP AF subjects. Of the 12 subjects, 3 were discovered to have esophageal ulcerations. All 3 subjects had follow-up esophagogastroduodenoscopy and demonstrated resolution of esophageal ulceration.

5.8.7 Vascular access complications

Other than routine cases of bruise, hematoma and discharge, there were 4 procedures (4 / 259, 1.5%) associated with significant vascular access site adverse events requiring surgical intervention or transfusion: 1 new AV fistula, 1 worsened pre-existing AV fistula, 2 pseudoaneurysms, and one hemorrhage requiring transfusion. One subject had both an AV fistula and a pseudoaneurysm.

5.9 Summary of STOP AF Pivotal Trial adverse events as categorized using MedDRA

There were a total of 1,406 adverse events (AEs) reported in 235 study subjects during the 12 month period of study follow-up. Seventy-six (76) CS experienced 485 AEs and 159 ES experienced 921 AEs. Ten (10) study subjects had no AEs reported, 6-CS and 4-ES.

In total, 69.2% (45/65) of Crossover CS and 75.5% (123/163) of ES experienced at least one procedure-related AE. Overall, the most frequently reported procedure-related AEs (higher than 10%) were back pain (35 subjects, 15.4%) and vessel puncture site hematoma (26 subjects, 11.4%). Other fairly common (higher than 5%) procedure-related AEs included pharyngolaryngeal pain (22 subjects,9.6%), cough (21 subjects, 9.2%), nausea (19 subjects, 8.3%), and procedural pain (15 subjects, 6.6%).

A greater proportion of ES (46.0%) experienced at least one device-related AE compared to Crossover CS (23.1%). The most frequently reported device-related AEs (higher than 10%) were in the following System Organ Class (SOC): Injury, Poisoning and Procedural Complications (Control:12.3%; Experimental: 18.4%), Nervous System Disorders (Control:13.8%; Experimental: 16.6%), Respiratory, Thoracic and Mediastinal Disorders (Control: 6.2%; Experimental: 12.3%), and General Disorders and Administration Site conditions (Control: 4.6%; Experimental: 11.0%). Overall, the only device-related AE occurring in greater than 10% of all cryoablated subjects was phrenic nerve paralysis (28subjects, 12.3%). Other common (higher than 5%) device-related AEs included nerve injury (22 subjects, 9.6%), cough (15 subjects, 6.6%) and venous injury (14 subjects, 6.1%). The majority of the device-related AEs that were observed occurred in less than 2% of subjects.

5.10 Study conclusion

The STOP AF Pivotal Trial demonstrated that there is a reasonable assurance of safety and effectiveness to support the use of the Arctic Front Cardiac CryoAblation Catheter, the Freezor MAX Cryocatheter, FlexCath Steerable Sheath and the CryoConsole (Gen V) in the treatment of patients with drug resistant paroxysmal atrial fibrillation.

6 Adverse events

Potential adverse events associated with cardiac catheter cryoablation procedures include, but are not limited to, the following conditions:

- Anemia
- Anxiety
- Atrial flutter
- Back pain
- Bleeding from puncture sites
- Blurred vision
- Bradycardia
- Bronchitis
- Bruising
- Cardiac tamponade
- Cardiopulmonary arrest
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Cough
- Death
- Diarrhea
- Dizziness
- Esophageal damage
- Fatigue
- Fever
- Headache
- Hemoptysis
- Hypotension/hypertension
- Lightheadedness
- Myocardial infarction
- Nausea/vomiting
- Nerve injury
- Pericardial effusion
- Pulmonary vein stenosis
- Shivering
- Shortness of breath
- Sore throat
- Tachycardia
- Transient ischemic attack
- Urinary infection
- Vasovagal reaction
- Visual changes

7 Instructions for use

7.1 Connecting the device

To connect the catheter, follow these steps. (For more detailed instructions, see the *CryoConsole Operators Manual*.)

1. Connect the non-sterile auto connection box to the CryoConsole.
2. Connect the Freezor MAX cryocatheter to a sterile coaxial umbilical cable and a sterile electrical umbilical cable in a dry environment.
3. Connect the coaxial umbilical cable to the CryoConsole and connect the electrical umbilical cable to the connection box.

7.2 CryoAblation

To use the catheter for a cryoablation procedure, follow these steps. (For more detailed instructions, see the *CryoConsole Operators Manual*.)

Note: Use adequate filtering on the recording system to allow continuous monitoring of the surface electrocardiogram (ECG) during cryoapplications.

Note: Prior to introducing the Freezor MAX Cryocatheter into the patient, test the deflection mechanism by pulling back the lever on the handle to ensure that it is operational.

1. Using an aseptic technique, create a vascular access with a 10 Fr (minimum) introducer or sheath, and insert the Freezor MAX Cryocatheter.
2. Under fluoroscopic guidance, position the tip of the Freezor MAX Cryocatheter at the endocardial site for the cryoablation, ensuring good tip contact. As needed, deflect the catheter tip to facilitate positioning by using the lever on the handle to vary tip curvature. Pulling the thumb knob back causes the catheter tip to bend; pushing the knob forward causes the tip to straighten.
3. Set the treatment time on the CryoConsole screen, the preset ablation duration is 240 seconds.
4. Perform the cryoablation.
5. Wait for the cryoablation phase to complete (at the end of the preset time).
6. Remove the catheter from the point of cryoablation, making sure that the catheter is no longer adhered to the tissue.
7. If needed, perform additional cryoablation treatments.
8. Determine effective ablation of the cardiac tissue by assessing the inducibility of the target arrhythmia after the cryoablation treatments have been completed.

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9. Remove the catheter from the patient.

8 Specifications

Catheter shaft size	3 mm (9 Fr)
Recommended introducer sheath	3.3 mm (10 Fr) minimum
Tip outside diameter	8 mm
Shaft length	90 cm
Number of electrodes on tip	4
Spacing between electrodes	3 mm, 5 mm, 2 mm
Number of thermocouples	1
Curves available	Freezor MAX 239F3 - medium (blue curve 55 mm) Freezor MAX 239F5 - long (orange curve 66 mm)
Environmental parameters:	
Storage	Greater than 0 °C (32 °F)
Operation	15 °C to 30 °C (60 °F to 86 °F) at altitudes less than 2400 meters (8000 feet) above sea level

9 Medtronic limited warranty

For complete warranty information, see the accompanying limited warranty document.

10 Service

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. Medtronic also maintains a professional staff to provide technical consultation to product users. For more information, contact your local Medtronic representative, or call or write Medtronic at the appropriate telephone number or address listed on the back cover.

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