Summary of Safety and Clinical Performance (SSCP)

AtriCure cryoICE® system (CRYO2, CRYO3) and cryoFORM® (CRYOF) probes

24 September 2024

Rev G

OVERVIEW

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions for Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

INFORMATION INTENDED FOR USERS/ HEALTHCARE PROFESSIONALS:

1. Device Identification and General Information

Product Name:	**AtriCure cryoICE probes (CRYO2, CRYO3, CRYOF)**
Product Group/Family Basic UDI-DI	CRYO2/3/F: 08401439000000000000007ZP
Manufacturer Legal Name and Address: Single Registration Number (SRN)	AtriCure, Inc. 7555 Innovation Way Mason, OH 45040 USA SRN: US-MF-000002974
EU Auth Representative: Single Registration Number (SRN)	AtriCure Europe B.V. De entree 260 1101 EE Amsterdam NL SRN: NL-AR-000000165
Medical Device Scope Expression and Code:	Z120102, Cryosurgical units
Product Classification and Rule (per MDR):	CRYO2, CRYO3: CRYOF: Class III, Rule 6
Year when the first certificate (CE) was issued covering the device:	CRYO2: 2011 CRYOF: 2015 CRYO3: 2016
Notified Body Name, Address & Number:	BSI Say Building John M. Keynesplein 9 1066 EP Amsterdam NL CE 2797

2. Intended Use of the Device

2.1. Intended Purpose

- *cryoICE® system (CRYO2/CRYO3)*: The cryoICE system cryoablation probe was designed for treatment of cardiac arrhythmias by achieving controlled temperatures ranging from -50°C (-58°F) to -70°C (-94°F). The PROBE is a sterile, single-use cryosurgical instrument designed for use with the AtriCure Cryo Module (ACM).
- *cryoICE cryoFORM® (CRYOF)*: The cryoICE cryoFORM probe was designed for the treatment of cardiac arrhythmias by achieving controlled temperatures ranging from -50°C to -70°C. The PROBE is a sterile, single-use cryosurgical instrument designed for use with the AtriCure Cryo Module (ACM).

2.2. Indication(s) and target populations

- The cryoICE system cryoablation probe is indicated for use in the cryosurgical treatment of cardiac arrhythmias by freezing target tissues, creating an inflammatory response (cryonecrosis) that blocks the electrical conduction pathway. The target population is adult patients with cardiac arrhythmias.
- The cryoICE cryoFORM cryoablation probe is indicated for use in the cryosurgical treatment of cardiac arrhythmias by freezing target tissues, creating an inflammatory response (cryonecrosis) that blocks the electrical conduction pathway. The target population is adult patients with cardiac arrhythmias.

2.3. Contraindications and/or limitations

- There are no known contraindications.

3. Device Description

3.1. Description of the device

The AtriCure cryoICE system (CRYO2, CRYO3) and cryoFORM (CRYOF) probes create cryoablation lesions in tissue by delivering a cryogenic nitrous oxide (N_2O) energy source from the console (AtriCure Cryo Module, ACM) to the tip of the connected probe (CRYO2, CRYO3, or CRYOF). The probes (CRYO2, CRYO3, CRYOF) use a high-pressure cryogen (N_2O) to freeze target tissues, creating an inflammatory response, and ultimately, cryonecrosis. The cryogen is contained within the probe and does not contact the tissue.

The cryoprobes provide probe temperatures below -40°C, a temperature below where intra-cellular ice formation occurs (-20°C) and is considered lethal to cells. When high-pressure nitrous oxide is supplied to the cryoprobe via the ACM, rapid cooling is achieved via the Joule-Thompson effect, where pressurized gas expands through a fine orifice producing a rapid drop in temperature. The end effector, or cryotip, of the probes are malleable to allow access to varying anatomy.

The cryoprobes are comprised of a cryotip end effector, shaft, handle, thermocouple, inlet tube, and exhaust tube. The cryotip consists of an aluminum boiler and three internal inlet orifices distributed throughout the cryotip internally to provide uniform cooling. The 4 mm diameter cryotip is malleable throughout its 10 cm length, having a

minimum bend radius of 0.5 inches (CRYO2 and CRYO3); CRYOF with its corrugated stainless-steel tip has a minimum bend radius of 0.25 inches. A supplied forming tool can be used to bend the cryotip into the desired form. The cryotip is attached to an insulated rigid shaft that allows the surgeon to adjust the length of the exposed cryotip up to 10 cm in therapeutic length. A thermocouple is affixed to the proximal external surface of the shaft 5 mm from the cryotip tissue contacting surface to display real-time temperatures on the console. The handle is attached to the shaft. Inlet and exhaust tubes and thermocouple wire pass through the handle and connect to the ACM.

The cryoprobes are available as single-use disposable probes.

3.2. A reference to previous generation(s) or variants if such exist, and a description of the differences

- The CRYO1 Cryoablation Probe was originally approved by BSI in June 2009. The AtriCure CRYO2 was developed as an alternative to CRYO1.
    - Instead of being provided with probe protectors to protect the malleable tip during shipment, CRYO2 is shipped with a retractable rigid shaft covering the malleable tip.
    - Other minor changes included a more flexible tube set and changes within the handle to improve the manufacturing process.
- CryoFORM (CRYOF) is an extension of the CRYO2 cryoablation probe. Changes from CRYO2 include:
    - The cryotip is stainless steel making it easier to bend.
    - Construction is corrugated versus smooth.
    - The outside diameter varies along the length of the cryotip (3-4 mm) whereas the diameter of CRYO2 is static (4 mm).
    - The internal support spring of the probe was eliminated due to the corrugated stainless-steel design.
    - The tubeset was updated to improve flexibility; this update was also made to CRYO2 and CRYO3 in February 2020.
    - The rigid shaft colourant was changed from black to grey with addition of pad print.
- CRYO3 probe was a product line extension to CRYO2 and CRYOF. Changes include:
    - The cryotip malleable probe material (aluminum alloy) was changed to increase malleability. Bench testing demonstrated all acceptance criteria were met. The CRYO3 aluminum alloy was deemed biocompatible.
    - The rigid shaft colourant was changed from black to blue to visually differentiate CRYO2 and CRYO3. The base polycarbonate material is unchanged. Testing confirmed biocompatibility.
    - The probe internal spring (not visible or tissue contacting) was lengthened to provide additional shaping support.
- In February 2020, the following changes were approved by BSI:
    - CRYO2 and CRYO3 were modified to utilize the same long tube set material and same gas inlet/outlet connector as CRYOF to improve device manufacturability.
    - Packaging was changed from a cardboard insert in a Tyvek pouch to utilize a PETG thermoformed tray with Tyvek lid.
- In April 2020, the following non-substantial changes were made and approved by BSI:
    - Update to material of the short exhaust. The current Short Exhaust Hose covered by a Corrugated Outer Tube, was changed to a better insulated, more compliant tube, that was further covered by a Shrinkable Fabric material and an outer Woven Sheath. The inner and outer materials are the same as used on

the long tube set of the device. To accommodate the new Short Exhaust Hose, dimensional changes were made to mating components. The outer Woven Sheath is retained by Shrink Tube over the probe adapter. The retaining Shrink Tube at this distal end is a new material addition. The Shrink Tube on the proximal end is the same as used in the long tube set.

- An elastomeric washer was added internally within the handle to meet handle retention requirement.
- The thermocouple soldering process between the Probe Thermocouple and the Tubeset Thermocouple was updated from a manual to a semi-automated process.

3.3. Description of any accessories which are intended to be used in combination with the device

The cryoprobes are intended to be used with the ACM and its components (08401439000000000000004ZH). The ACM has two accessories: the exhaust hose connector (08401439000000000000005ZK) and the foot switch (08401439000000000000006ZM).

3.4. Description of any other devices and products which are intended to be used in combination with the device

See Section 3.3.

4. Risks and warnings

4.1. Residual risks and undesirable effects

Residual risks associated with use of the cryosurgical probes are described in the Warnings and Cautions in the Instructions for Use and in Section 4.2 of this SSCP and are listed in the following table.

Risk (harm)	Residual risk estimated occurrence[a]
Infection	<0.5%, between 1 in 200 and 1 in 1,000
Inconvenience and/or confusion	<0.5%, between 1 in 200 and 1 in 1,000
Failure to complete cryo portion of concomitant procedure	<0.5%, between 1 in 200 and 1 in 1,000
Failure to complete standalone CRYO procedure	<0.1%, less than 1 in 1,000
Bleeding requiring intervention	<0.5%, between 1 in 200 and 1 in 1,000
Injury requiring first aid	<0.1%, less than 1 in 1,000
Bleeding requiring a gauze cover/sponge	<0.5%, between 1 in 200 and 1 in 1,000

stick/pressure/intraoperative drainage	
Bleeding requiring stitches	<0.5%, between 1 in 200 and 1 in 1,000
Superficial frostbite	<0.1%, less than 1 in 1,000
Fourth degree burn	<0.1%, less than 1 in 1,000
Frostnip	<0.1%, less than 1 in 1,000
Deep frostbite	<0.1%, less than 1 in 1,000
Occlusion of major blood vessel	<0.1%, less than 1 in 1,000
Sinus arrest/bradycardia	<0.1%, less than 1 in 1,000
Atrioventricular block	<0.1%, less than 1 in 1,000
Stenosis of a vessel	<0.1%, less than 1 in 1,000
Stroke	<0.1%, less than 1 in 1,000
Minor injury requiring first aid	<0.1%, less than 1 in 1,000
Skin injury requiring first aid	<0.1%, less than 1 in 1,000
Discomfort	<0.1%, less than 1 in 1,000
Ventricular arrhythmia	<0.1%, less than 1 in 1,000
Systemic adverse reaction	<0.1%, less than 1 in 1,000
Nitrous oxide exposure to patient	<0.1%, less than 1 in 1,000
[a]Data generated from complaints.	

For each risk identified for the CRYO2, CRYO3, and CRYOF probes, the overall risk has been mitigated and reduced as far as possible.

4.2. Warnings and precautions

Warnings – CRYO2/3

- Carefully read ALL instructions PRIOR to use. Failure to follow these instructions, warnings, and cautions may lead to device damage and/or patient injury.
- Carefully read ALL instructions PRIOR to use. Failure to follow CryoICE Box (ACM) Console Warnings, Cautions, product description, flow rates, and features may lead to device damage and/or patient injury.
- Use of the PROBE should be limited to properly trained and qualified medical personnel. Failure to provide intended therapy and/or serious injury could occur with improper use of the device.

- The ACM Components are not suitable for use in the presence of a flammable anesthetic mixture which can cause a fire or explosion, resulting in user and patient injury death.
- If the sterile package is dropped and/or damaged or the sterile barrier is breached, discard device and DO NOT USE. Breach of sterile barrier can lead to infection.
- Forming the Malleable Section of the PROBE in any way other than indicated in the following instructions can damage the PROBE and potentially cause tissue damage.
- Do not bend Malleable Section of the PROBE during FREEZE or DEFROST mode. It can cause a high pressurized gas leak that can potentially lead to tissue perforation, unintended damage, or injury to user.
- Ensure the CONSOLE is in READY Mode and the PROBE temperature is above 0°C (32°F) before contacting tissue, to avoid unintended cryoadhesion
- Do not use excessive force when using the PROBE in order to prevent tissue damage.
- Do not use the PROBE to freeze tissue inside the beating heart. Use of the PROBE to freeze tissue inside the beating heart may result in severe injury to the patient.
- Cardiac surgical procedures may mechanically induce arrhythmias.
- Cryo–ablation involving coronary vessels has been associated with subsequent clinically significant arterial stenosis. It is unknown whether cryo–ablation with the PROBE will have such an effect, but as in all such procedures, care should be taken to minimize unnecessary contact with coronary vessels during cryo–ablation
- Before entering Freeze Mode, always confirm the placement of the Malleable Section of PROBE is as desired and there is no undesired tissue contact with the Malleable Section of PROBE or Rigid PROBE Shaft to prevent unintended cryoadhesion or cryoablation.
- Use care to avoid PROBE movement while cryoadhesion is present, to prevent inadvertent tissue damage.
- FOR SINGLE USE ONLY. DO NOT reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure, which in turn may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

Cautions – CRYO2/3

- The PROBE is only compatible with the ACM cryoICE Box. Do not use the PROBE with any other system to prevent injury and/or equipment damage.
- Do not restrict, kink, clamp, or otherwise damage the Malleable Section of PROBE or Tubing, as this may interrupt the gas supply path, preventing the PROBE from properly freezing and/or defrosting.
- Follow standard guidelines for the safe handling and storage of high-pressure gas tanks.
- Nitrous Oxide gas must be safely exhausted. Follow standard hospital guidelines for allowable concentration levels.
- Ensure the CONSOLE is in Ready Mode before attempting to connect the PROBE. The sudden release of pressurized gas may cause the PROBE to recoil, which may injure the operator or patient.
- Repetitive bends in the same location could damage the Malleable Section of PROBE causing device malfunction.
- The PROBE malleable tip should not be bent into a radius of less than 13mm (0.5 inches).
- Discontinue use immediately if a breach in the PROBE is suspected, to avoid the

release of pressurized N_2O gas and injury to the patient or user.

- The Malleable Section of the PROBE has a limited functional life; if greater than 8 bend cycles are intended, it is recommended to use a second probe.
- The distal end of the Rigid PROBE Shaft should not be bent more than 5 cm (2.0 inches) from straight
- Do not use the PROBE if damaged as it may result in device malfunction. Repetitive bends in the same location could cause damage to the Rigid PROBE Shaft. The Rigid PROBE Shaft has a limited functional life; if greater than 7 bend cycles are intended, it is recommended to use a second probe.
- Do not use the PROBE if damaged as it may result in device malfunction. The PROBE has a limited functional life; if greater than 14 Freeze/Defrost cycles are intended, it is recommended to use a second probe
- Use care while the CONSOLE is in Defrost Mode, as during N_2O gas venting, the PROBE may cool sufficiently to cause cryoadhesion.
- Ensure the CONSOLE is in Ready Mode before attempting to disconnect the PROBE. The sudden release of pressurized gas may cause the PROBE to recoil, which may injure the operator or patient.

Warnings – CRYOF

- Carefully read ALL instructions PRIOR to use. Failure to follow these instructions, warnings, and cautions may lead to device damage and/or patient injury.
- Carefully read ALL instructions PRIOR to use. Failure to follow CryoICE Box (ACM) Console Warnings, Cautions, product description, flow rates, and features may lead to device damage and/or patient injury.
- Use of the PROBE should be limited to properly trained and qualified medical personnel. Failure to provide intended therapy and/or serious injury could occur with improper use of the device.
- The ACM components are not suitable for use in the presence of a flammable anesthetic mixture which can cause a fire or explosion, resulting in user and patient injury death.
- Care should be exercised in patients with suspected or known allergies or hypersensitivity to nickel, which is present in small quantities in the cryoICE cryoFORM probe.
- The cryoICE cryoFORM probe contains a small fraction of cobalt which is considered a substance of concern.
- If the sterile package is dropped and/or damaged or the sterile barrier is breached, discard device and DO NOT USE. Breach of sterile barrier can lead to infection.
- Do not bend Malleable Section of the PROBE during FREEZE or DEFROST mode. It can cause a high pressurized gas leak that can potentially lead to tissue perforation, unintended damage, or injury to user.
- Ensure the CONSOLE is in READY Mode and the PROBE temperature is above 0°C before contacting tissue, to avoid unintended cryoadhesion.
- Do not use excessive force when using the PROBE in order to prevent tissue damage.
- Do not use the PROBE to freeze tissue inside the beating heart. Use of the PROBE to freeze tissue inside the beating heart may result in severe injury to the patient.
- Cardiac surgical procedures may mechanically induce arrhythmias.
- Cryo–ablation involving coronary vessels has been associated with subsequent clinically significant arterial stenosis. It is unknown whether cryo–ablation with the PROBE will have such an effect, but as in all such procedures, care should be taken to minimize unnecessary contact with coronary vessels during cryo–ablation.
- Before entering Freeze Mode, always confirm the placement of the Malleable Section of PROBE is as desired and there is no undesired tissue contact with the Malleable

Section of PROBE or Rigid PROBE Shaft to prevent unintended cryoadhesion or cryoablation.
- Use care to avoid PROBE movement while cryoadhesion is present, to prevent inadvertent tissue damage.
- FOR SINGLE USE ONLY. DO NOT reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure, which in turn may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

Cautions - CRYOF

- The PROBE is only compatible with the AtriCure cryoICE BOX. Do not use the PROBE with any other system, to prevent injury and/or equipment damage.
- Do not restrict, kink, clamp, or otherwise damage the Malleable Section of PROBE or Tubing, as this may interrupt the gas supply path, preventing the PROBE from properly freezing and/or defrosting.
- Follow standard guidelines for the safe handling and storage of high-pressure gas tanks.
- Nitrous Oxide gas must be safely exhausted. Follow standard hospital guidelines for allowable concentration levels.
- Ensure the CONSOLE is in Ready Mode before attempting to connect the PROBE. The sudden release of pressurized gas may cause the PROBE to recoil, which may injure the operator or patient.
- Discontinue use immediately if a breach in the PROBE is suspected, to avoid the release of pressurized N_2O gas and injury to the patient or user.
- The Malleable Section of the PROBE has a limited functional life; if greater than 4 bend cycles are intended, it is recommended to use a second probe.
- The distal end of the Rigid PROBE Shaft should not be bent more than 5 cm (2.0 inches) from straight
- Do not use the PROBE if damaged as it may result in device malfunction. Repetitive bends in the same location could cause damage to the Rigid PROBE Shaft. The Rigid PROBE Shaft has a limited functional life; if greater than 7 bend cycles are intended, it is recommended to use a second probe.
- Do not use the PROBE if damaged as it may result in device malfunction. The PROBE has a limited functional life; if greater than 7 Freeze/Defrost cycles are intended, it is recommended to use a second probe.
- Use care while the CONSOLE is in Defrost Mode, as during N_2O gas venting, the PROBE may cool sufficiently to cause cryoadhesion.
- Ensure the CONSOLE is in Ready Mode before attempting to disconnect the PROBE. The sudden release of pressurized gas may cause the PROBE to recoil, which may injure the operator or patient.

4.3. Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN) if applicable

AtriCure issued a recall notification for the CRYO2 probe on 21 November 2014 for a packaging defect with a potential for breach of sterility. Through 30 June 2024, there have been no other product recalls or FSCAs for CRYO2, CRYO3, or CRYOF.

5. Summary of clinical evaluation and post-market clinical follow-up (PMCF)

Through the clinical evaluation for CRYO2, CRYO3, and CRYOF, it is concluded that all clinical risks have been reduced as far as possible by device design, labeling, and training of intended users, in accordance with AtriCure Risk Management Program. The benefits of the CRYO2, CRYO3, and CRYOF probes continue to outweigh the risks. No new harms nor hazards have been identified and there are no unacceptable residual risks, and therefore no actions are required. The results of the data reveal positive performance results, low complication rates, and acceptance of the subject device within the medical community as safe and effective for ablation of cardiac tissue.

5.1. Summary of clinical data related to equivalent device, if applicable

In the Clinical Evaluation, AtriCure cryoprobes CRYO3 and CRYOF are considered equivalent to AtriCure cryoprobe CRYO2. Clinical Data from published literature are summarised in Section 5.3.

5.2. Summary of clinical data from conducted investigations of the device before the CE-Marking, if applicable

No clinical investigations were performed prior to original CE marking of CRYO2, CRYO3, and CRYOF. Ongoing clinical studies are summarised in Section 5.5.

5.3. Summary of clinical data from other sources, if applicable

Four published studies identified in the Clinical Evaluation literature search reported safety and performance associated with the cryoICE CRYO2 probe. Additional literature search results related to cryoablation with cryoICE and other cryoablation probes are summarised in Section 5.4.

Identity of the investigation/study	Chinese Clinical Trial Register number, ChiCTR-IOR-16008112 Han et al. Comparison of cryomaze with cut-and sew maze concomitant with mitral valve surgery: a randomized noninferiority trial[1]
Identity of the device	AtriCure cryoICE CRYO2 probe
Intended use of the device in the investigation	Cryosurgical ablation of cardiac arrhythmias
Objectives of the study	To determine whether cryomaze was noninferior to cut-and-sew-Maze (CSM) procedure in patients with persistent or longstanding persistent atrial fibrillation (AF), with a 15% margin to establish non-inferiority
Study design and duration of follow-up	Randomized, non-inferiority
Primary and secondary endpoint(s)	**Primary**: freedom from AF off anti-arrhythmic drugs (AADs) at 12 months after surgical ablation

	Secondary: freedom from AF/atrial flutter (AFL) at 3 and 6 months after surgery; a composite of serious adverse events	
Inclusion/exclusion criteria for subject selection	**Inclusion:** patients with persistent or longstanding persistent AF associated with mitral valve disease; undergoing mitral valve operations including combined aortic valve replacement, coronary artery bypass graft, and tricuspid valve operations. **Exclusion:** paroxysmal AF, not of age over 18 and less than 75; left atrium >80 mm, atrial calcification, left ventricular ejection fraction <0.30; contraindication to amiodarone or anticoagulation with warfarin, enrolled in other concurrent trials, prior cardiac surgery or other cardiac ablation, and 6-second pauses demonstrated on 24-h Holter.	
Number of enrolled subjects	N=100 subjects who received cryomaze N=100 subjects who received CSM	
Study population	<u>Cryomaze</u> Age: 59.39±7.52 Female: 64 (64%) Persistent AF: 56 (56%) Longstanding persistent AF: 44 (44%) Hypertension: 11 (11%) Prior stroke: 9 (9%) Diabetes: 5(5%) Left atrial diameter: 54.8±7.56 mm Left ventricular ejection fraction: 0.55±0.03	<u>CSM</u> Age: 58.15±7.49 54 (54%) Persistent AF: 43 (43%) Longstanding persistent AF: 57 (57%) Hypertension: 21 (21%) Prior stroke: 15 (15%) Diabetes: 4(4%) Left atrial diameter: 56.91±7.79 Left ventricular ejection fraction: 0.56±0.03
Summary of study methods	Patients were randomized to either cryomaze or CSM. After 3 months, AADs were withdrawn if patient was in sinus rhythm (SR). Patients were prospectively followed up at 1, 3, 6, and 12 months.	
Summary of results	**Clinical Benefit:** Freedom from AF was achieved in 85% (95% CI, 0.76–0.91) in the cryomaze group and 88% (95% CI, 0.80–0.94) in the CSM group, showing that cryomaze was noninferior to CSM at 12 months (P-value for noninferiority= 0.0065). There was no significant difference in serious adverse effects (n=12 in	

	cryomaze; n=17 in CSM; P=0.315). Perioperative bleeding and the length of surgery, intensive care unit stay, postoperative hospital stay; and the need for temporary pacing decreased significantly in the CryoMaze group.
Study Limitations	Primary endpoint determined by 24-h Holter rather than long-term monitoring; Margins based on absolute measures can potentially introduce bias towards non-inferiority; cut-and-sew maze is a complex procedure performed by a limited group of physicians
Any device deficiency or device replacements related to safety or performance during the study	None reported

Identity of the investigation/study	Clinicaltrials.gov: NCT01812356 Jeong et al. Randomized trial of concomitant maze procedure using nitrous-oxide versus argon-based cryoablation[2]	
Identity of the device	AtriCure cryoICE CRYO2 probe	
Intended use of the device in the investigation	Cryosurgical ablation of cardiac arrhythmias	
Objectives of the study	To compare the 1-year outcome of a concomitant maze procedure using N_2O-based cryoablation versus argon gas-based cryoablation	
Study design and duration of follow-up	Single center, prospective, randomized	
Primary and secondary endpoint(s)	**Primary:** AF recurrence at 12 months post-operatively **Secondary**: cardiac-related death, composite of major adverse cardiac-or-cerebrovascular related events	
Inclusion/exclusion criteria for subject selection	**Inclusion:** 18 years or older who underwent valve operation and concomitant cryomaze procedure for heart valve disease with persistent AF. **Exclusion**: previous cardiac surgery; infective endocarditis, congenital heart disease; old age >75 years; left atrial size >80 mm, connective tissue disease such as Behcet's disease; moderate or greater tricuspid regurgitation	
Number of enrolled subjects	N=30 who received cryoablation with cryoICE probe N=30 who received cryoablation with CryoFlex probe	
Study population	<u>Nitrous oxide</u> Age: 60±9	<u>Argon</u> Age: 55±9

	Female: 14 (46%) AF duration: 46±60 months Hypertension: 6 (20%) Diabetes: 5 (17%) Prior stroke: 4 (13%) EuroSCORE: 4.3±1.8 Left ventricular ejection fraction: 57±7.5% Left atrial dimension: 56±10 mm	Female: 20 (67%) AF duration: 47±59 months Hypertension: 4 (13%) Diabetes: 6 (20%) Prior stroke: 4 (13%) EuroSCORE: 3.9±1.6 Left ventricular ejection fraction: 56±13.5% Left atrial dimension: 59±9 mm
Summary of study methods	Patients enrolled from March 2013 through November 2015. Patients were randomized 1:1 to either cryomaze with a nitrous-oxide based probe (cryoICE, AtriCure) or argon-based probe (CryoFlex, Medtronic). Lesions created included pulmonary vein isolation, mitral isthmus, lower part of left atrium extended to left atrial appendage (LAA) to complete box lesion, cavo-tricuspid-isthmus, and superior vena cava to inferior vena cava line. Cryo application was 120 seconds using CryoFlex and 160 seconds using cryoICE. The primary cardiac surgery was performed after ablation; LAA was closed internally with a suture prior to mitral valve surgery.	
Summary of results	**Primary endpoint (Clinical Benefit):** Sinus rhythm was maintained at 12 months in 86.7% (26/30) of the cryoICE group and 86.7% of the CryoFlex group (p=1.00). 63% (19/30) of patients in both groups were in SR and off AADs. **Secondary endpoints:** Recurrence of atrial arrhythmias occurred in 10 [33%] in the N_2O group (cryoICE) versus 6 [20%] in the argon group (CryoFlex), p = 0.243). No early or late deaths occurred. Early and late complications were similar between groups. **cryoICE (nitrous oxide):** early: 1 bleeding, 2 low cardiac output, 1 effusion, 9 postoperative AF episodes; late: 1 pacemaker, 1 reoperation, 1 intracranial hemorrhage	

	Cryoflex (argon): early: 1 bleeding, 1 low cardiac output, 2 effusions, 10 post-operative AF episodes; late: 2 pacemakers, 2 reoperations, 2 intracranial hemorrhages; 1 stroke
Study Limitations	Single center study; small size; did not use 7-day Holter or loop recorders; short-term results
Any device deficiency or device replacements related to safety or performance during the study	None reported

Identity of the investigation/study	Li et al. Application of cryoablation in minimally invasive mitral valve surgery[3]
Identity of the device	AtriCure cryoICE (CRYO2)
Intended use of the device in the investigation	Cryoablation of cardiac arrhythmia
Objectives of the study	To summarise the clinical data of patients who experienced cryoablation in minimally invasive mitral valve surgery and to explore safety and effectiveness of the surgery
Study design and duration of follow-up	Single center, retrospective study
Primary and secondary endpoint(s)	Safety and efficacy of surgical procedure (cryoablation with minimally invasive mitral valve surgery)
Inclusion/exclusion criteria for subject selection	**Inclusion**: patients who received cryoablation and minimally invasive mitral valve surgery between August 2013 and July 2015
Number of enrolled subjects	N=35
Study population	Male/Female: 8/24 Rheumatic heart disease mitral valve lesions combining AF Simple mitral stenosis: 6 Simple mitral incompetence: 7 Mitral stenosis combining incompetence: 22 Left atrial thrombosis: 6 Tricuspid incompetence: 26 Persistent AF, 1-12 years: 34 Paroxysmal AF: 1 Left atrium diameter, mm (mean ± standard deviation): 30-87 (59.42±12.20)
Summary of study methods	All surgeries were performed under general anesthesia with cardiopulmonary bypass (CPB) established. Double lumen tracheal intubation was used in all cases; micro-incision was made at anterior lateral of right chest. CryoICE shapeable

	cryoablation metal probe was used in AF ablation, which was rapidly cooled down to -60°C with chilled and nitrous oxide gas (N_2O), then with a complete and secure contact with endocardial tissue to create damage curve (performing cryoablation for 90-120 seconds).
Summary of results	**Performance (Clinical Benefit)**: During the 18 months follow-up, no recurrence and death occurred. Sinus rhythm restoration rate at 3, 6, 12 and 18 months were 94.3%, 93.5%, 90.5% and 93.3% respectively. **Safety:** No death was observed in this group. Reexploration for bleeding was conducted for one case. Neurological symptoms, such as cerebral infarction or cerebral hemorrhage were not observed after surgery. Complications related to AF, such as pulmonary vein stenosis, damage of coronary artery, gullet, and phrenic nerve did not occur.
Study Limitations	Single-center, retrospective design
Any device deficiency or device replacements related to safety or performance during the study	None reported

Identity of the investigation/study	Clinicaltrials.gov: NCT05089877 Rodriguez et al. Long-term Performance and Safety of Cryoablation in Cardiac Surgery Patients with Atrial Fibrillation: Results of the FREEZE-AFIB Study[4]
Identity of the device	AtriCure cryoFORM (CRYOF)
Intended use of the device in the investigation	Cryosurgical treatment of cardiac arrhythmias
Objectives of the study	To evaluate the safety and performance of cryoFORM (CRYOF) device.
Study design and duration of follow-up	Post-market, single arm, multi-center, retrospective-prospective study with 12-month follow-up
Primary and secondary endpoint(s)	Primary Effectiveness: Freedom from documented AF, AFL, or AT lasting >30 seconds in duration at the last follow-up visit in the absence of Class I/III AADs (except AADs at doses not exceeding those previously failed). Rhythm status was assessed via 24-hour Holter at the 12-month visit. Holter data was reviewed by an independent core lab using a standardized evaluation protocol.

	Primary Safety Endpoint: The incidence of four MAEs within 30-days, if related to the device and/or ablation procedure per adjudication by an independent medical monitor (cardiac surgeon): Death; Stroke; Major Bleeding; and Myocardial Infarction.
Inclusion/exclusion criteria for subject selection	Inclusion Criteria: • Subject was greater than or equal to 18 years of age. • Subject had documented history of atrial fibrillation. • Subjects received surgical ablation for their atrial fibrillation using CRYOF and on whom at least the following lesions were performed: left and right pulmonary vein isolation, roof and floor lines, mitral annulus line, a connecting lesion from left atrial appendage to left pulmonary vein, coronary sinus lesion, and left atrial appendage (LAA) exclusion, with a lesion duration of at least 2 minutes. • Stable subject that underwent non-emergent cardiac surgical procedure(s) on cardiopulmonary bypass including open-heart surgery for one or more of the following: mitral valve repair or replacement, aortic valve repair or replacement, tricuspid valve repair or replacement, and coronary artery bypass procedures, or atrial septal defect (ASD) repair. • Left Ventricular Ejection Fraction >30% (determined by echocardiography or cardiac catheterization performed within 90 days of enrollment as documented in subject medical history). • Subject was willing and able to provide written informed consent.

	• Subject was willing and able to return for scheduled follow-up visits. Exclusion Criteria: • Stand-alone AF without indication(s) for concomitant coronary artery bypass graft (CABG) and/or valve surgery. • Previous left sided ablation procedures prior to surgical ablation. • Untreated atrial flutter and symptomatic ventricular arrythmia. • Known carotid artery stenosis greater than 80% prior to index ablation procedure. • Prior history of ischemic stroke or hemorrhagic stroke. • History of MI with ST elevation within 6 weeks prior to the index ablation • Documented AF duration of greater than 10 years. • Large left atrial size i.e., LA diameter >7 cm prior to the index ablation procedure. • Subjects with active systemic infection prior to index ablation procedure. • Subjects who had documented severe peripheral arterial occlusive disease defined as claudication with minimal exertion prior to the ablation procedure. • Subjects with history of renal failure requiring dialysis or hepatic failure prior to the ablation procedure. • A known drug and/or alcohol addiction. • Mental impairment or other conditions which may not allow the subject to understand the nature, significance, and scope of the study. • Subjects who were pregnant.

	• Subjects who had preoperative need for mechanical circulatory support or intravenous inotropes. • Subjects who were on anti-arrhythmic drug therapy for the treatment of another arrhythmia. • Subjects in currently undergoing chemotherapy. • Subjects on long term treatment with oral or injected steroids (not including intermittent use of inhaled steroids for respiratory diseases). • Subjects who had known connective tissue disorders at the time of index ablation procedure. • Subjects who had known hypertrophic obstructive cardiomyopathy at the time of index ablation procedure. • Subjects with known cold agglutinin. • Subjects who had or tested positive for COVID-19. • Subjects with bleeding disorders and/or inability to receive anticoagulation. • Subjects undergoing aortic dissection surgery as index procedure. • Cardiac surgical re-intervention since the index cardiac surgery with concomitant AF ablation procedure.
Number of enrolled subjects	N=39
Study population	N=33 Age: 68.7 years Male: 75.8% BMI: 27.5 kg/m^2
Summary of study methods	Treated subjects were assessed for primary safety through 30-days post-procedure. Primary performance was assessed at least through the 12-months post-procedure visit.

Summary of results	Primary safety was achieved, with 100% (33/33) of patients free from death, stroke, myocardial infarction, and major bleeding within 30-days post-procedure (95% CI 89.42%, 100%; p<0.0001). Ninety-seven percent of patients (32/33) were free from serious adverse events (SAEs) and permanent pacemaker (PPM) implantation through 12-months (95% CI 84.24%, 99.92%; p<0.0001). One patient (3%) experienced a SAE related to the surgical ablation procedure requiring PPM implant within 30-days. Twenty-four-hour Holter monitoring at 12-months post-procedure showed 89% (25/28) of patients with evaluable data were free from AA off AADs (95% CI 71.77%, 97.73%; p=0.0001), meeting primary performance.
Study Limitations	Retrospective component of study design
Any device deficiency or device replacements related to safety or performance during the study	Four non-serious events were submitted for adjudication of which none were assessed as an unanticipated device effect.

5.4. An overall summary of the clinical performance and safety

In addition to the studies summarised in Section 5.3, additional literature identified in the Clinical Evaluation reported favorable safety and performance outcomes in cohorts of patients who were treated with CRYOF, CRYO1 and CRYO2, unspecified cryoICE probe type, and/or cryoICE probes and cryoprobes by another manufacturer[5-18]. The clinical performance objective was demonstration of ≥55% freedom from AF, AFL or atrial tachycardia (AT) lasting >30 seconds in duration at 12-months following the ablation procedure in the absence of Class I or III AADs. This was derived from a meta-analysis of studies published between 2010 to 2018 that reported 12-month effectiveness outcomes of concomitant Cox-Maze procedures using radiofrequency (RF) and cryoablation in patients with persistent and longstanding persistent AF. The 55% clinical performance objective was based on the lower 95% confidence interval of the synthesized random effects estimate (48%) plus a 7% margin. For each study in the Clinical Evaluation, where reported, freedom from AF, freedom from AF/AFL/AT, or proportion in SR off AADs met this performance objective. In some studies, this endpoint was only reported with or without AAD use. The Clinical Evaluation supports the following Clinical Benefits statement: The clinical benefit of the cryoICE probes with the ACM is the restoration of normal sinus rhythm and freedom from atrial arrhythmia (atrial fibrillation, atrial flutter, and atrial tachycardia).

The clinical safety objective was Major Adverse Event (MAE) rate through 30-days post-procedure of ≤15%, which was derived from the previously described meta-analysis. The clinical safety objective of 15% was based on 1.5 times the 95% upper confidence interval (10%) of the synthesized random effects model. MAEs include death, stroke (regardless of level of disability), myocardial infarction, and major bleeding events within 30-days of the index procedure. The studies identified in the Clinical Evaluation met this safety endpoint. A study by Lapenna et al., which used AtriCure cryoprobes between 2007 and 2014, reported a

15% incidence of red blood cell transfusions during standalone ablation Cox-Maze IV procedures with radiofrequency and cryoablation, however the details of the transfusions were not specified.

Clinical data from relevant literature related to the described device, as well as market experience, demonstrates the benefit of the subject devices when used for their intended purpose. There is sufficient data to establish the continued safety and efficacy profile of the subject device(s) when used as intended. Risk reduction measures, as well as monitoring by AtriCure of post-market data, will continue in an effort to mitigate some of the harms or complications presented in this report, and to improve the overall safety of the subject device. Ongoing PMCF studies will provide relevant information to further analyze and monitor verification of safety and performance of the device when exposed to a larger and more varied population of clinical users and verification of performance of the cryosurgical system devices. Post-market surveillance will continue to be performed and reported in an annual Periodic Safety Update Report to evaluate any new risks (including hazards or hazardous situations) and changes to benefit-risk determination that require action.

5.5. Ongoing or planned post-market clinical follow-up

The ICE-AFIB clinical trial (NCT03732794 at clinicaltrials.gov) is an ongoing, AtriCure-sponsored clinical trial that is evaluating the safety and efficacy of CRYO2/3 to ablate cardiac tissue during open concomitant cardiac surgery for the treatment of persistent and long-standing persistent AF.

6. Possible diagnostic or therapeutic alternatives

A rhythm control strategy involves initial pharmacologic or electronic cardioversion, followed by pharmacologic treatment to maintain normal SR. However, antiarrhythmic medications are often not effective in maintaining SR. As a result, episodes of recurrent AF are typical, and patients with persistent AF may require multiple episodes of cardioversion. Implantable atrial defibrillators, which are designed to detect and terminate an episode of AF, may be an alternative in patients otherwise requiring serial cardioversions, but these have not yet achieved widespread use.
Patients with paroxysmal AF, by definition, do not require cardioversion, but may be treated pharmacologically to prevent further arrhythmic episodes.

The cited treatment options are not considered curative. A variety of ablative procedures have been investigated as potentially curative approaches, or perhaps modifying the arrhythmia such that drug therapy becomes more effective. Ablative approaches focus on interruption of the electrical pathways that contribute to AF, through modifying the triggers of AF and/or the myocardial substrate that maintains the aberrant rhythm.

Ablation of cardiac tissue with the less-intrusive method uses energy that destroys the tissue providing the errant signals by either burning or freezing it.

- Burning: The most common types of energy for ablation include RF, high-intensity ultrasound, laser, and microwave. These energy sources ablate the cardiac tissue by scarring or destroying the tissue in order to disrupt the electrical signals.
- Freezing: Cryoablation uses a pressurized refrigerant in the catheter or probe tip to ablate the source of the arrhythmia by freezing the tissue, thereby preventing the electrical signals from firing.

Radiofrequency energy is designed to apply a rapidly oscillating voltage differential between the electrodes that are in contact with cardiac tissue. As the RF energy is delivered to the

electrodes, the tissue captured between the electrodes is ablated creating the formation of a lesion. Limitations on the efficacy of this technology include the thickness of the tissue being ablated.

In addition to concomitant surgical ablation during open cardiac surgery, less invasive, transthoracic, endoscopic, off-pump procedures to treat drug-resistant AF are being developed and evaluated. The evolution of these procedures involves both different surgical approaches and different lesion sets. Alternative surgical approaches include mini-thoracotomy and total thoracoscopy with video assistance. Open thoracotomy and mini-thoracotomy employ CPB and open-heart surgery, while thoracoscopic approaches are performed on the beating heart. Thoracoscopic approaches do not enter the heart and use epicardial ablation lesion sets, whereas the open approaches use either the classic “cut and sew” approach or endocardial ablation.

Percutaneous catheter-based ablation is a well-established interventional approach for treating a variety of arrhythmias, in which intracardiac mapping identifies a discrete arrhythmogenic focus that is the target of ablation.

There are several options for treating patients with AF. These treatment options include:

- Pharmacologic intervention (i.e., anti-arrhythmic drugs) to maintain normal SR.
- Surgical intervention for ablation of the cardiac tissue (e.g., Cox Maze procedure, ablation using energy of RF and/or cryoenergy)
- Percutaneous catheter-based ablation (RF or cryoballoon)

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7. Suggested profile and training for users

Cardiothoracic surgeons are qualified by training and education to use the AtriCure cryoICE probes. AtriCure offers additional comprehensive education and training on the use of the AtriCure cryoICE probes per the device instructions for use. This training will be available to the clinicians using the AtriCure CRYO2, CRYO3, and CRYOF probes.

8. Reference to any harmonized standards and common specifications (CS) applied

Standard Number*	Standard Title	Compliance – Full, Partial, or No	Rationale if Partial/No
BS EN ISO 13485:2016+A11: 2021	Medical Devices – Quality management systems – Requirements for regulatory purposes	Full	Not Applicable (N/A)
BS EN ISO 14971:2019+A11: 2021	Medical Devices – Application of risk management to medical devices	Full	N/A

Standard Number*	Standard Title	Compliance – Full, Partial, or No	Rationale if Partial/No
BS EN ISO 14155:2020	Clinical investigation of medical devices for human subjects - Good clinical practice	Full	N/A
EN ISO 15223-1: 2021	Medical devices. Symbols to be used with medical device labels, labelling and information to be supplied: General requirements	Full	N/A
BS EN ISO 20417:2021	Medical devices — Information to be supplied by the manufacturer	Full	N/A
BS EN 62366-1:2015+A1:2020	Medical devices — Part 1: Application of usability engineering to medical devices	Full	N/A
ISTA 3A: 2018	International Safe Transit Association (ISTA) is the author of test procedures that define how packages should perform to ensure protection of their contents.	Full	N/A
EN IEC 63000 (RoHS) 2018	Technical documentation for the assessment of electrical and electronic products with respect to the restriction of hazardous substances	Full	N/A
BS EN ISO 14644-1: 2015	Cleanrooms and Associated Controlled Environments - Classification	Full	N/A
BS EN ISO 14644-2: 2015	Cleanrooms and Associated Controlled Environments – Monitoring	Full	N/A
BS EN 60601-1:2006+A2:2021	Medical electrical equipment. Part 1: General requirements for basic safety and essential performance– 3.1 edition	Full	N/A
BS EN 60601-1-2: 2015+A1:2021	Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests	Full	N/A

Standard Number*	Standard Title	Compliance – Full, Partial, or No	Rationale if Partial/No
BS EN ISO 11607-1: 2020	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems	Full	N/A
BS EN ISO 11607-2: 2020+A11: 2022	Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes	Full	N/A
BS EN ISO 10993-1:2020	Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process	Full	N/A
BS EN ISO 10993-4: 2017	Biological evaluation of medical devices – Part 4: Interactions with Blood	Full	N/A
BS EN ISO 10993-5: 2009	Biological evaluation of medical devices – Part 5: Cytotoxicity	Full	N/A
BS EN ISO 10993-10: 2023	Biological evaluation of medical devices – Part 10: Skin irritation/sensitization	Full	N/A
BS EN ISO 10993-11: 2018	Biological evaluation of medical devices – Part 11: Test for systemic toxicity	Full	N/A
BS EN ISO 10993-18: 2020+A1: 2023	Biological evaluation of medical devices – Chemical characterization	Full	N/A
BS EN ISO 11137-1 2015+A2 2019	Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices)	Full	N/A
BS EN ISO 11137-2 2015	Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose	Full	N/A
ASTM F1980-21: 2021	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices	Full	N/A
*The standards listed above include both recognised and harmonised standards.			

9. Revision history

SSCP Revision Number	Date Issued	Change Description	Validated by Notified Body (Yes or No)	Validation Language
1	See CEM-226.A in AtriCure Document Control for official date issued.	Initial Release	No	English
2	See CEM-226.B in AtriCure Document Control for official date issued.	• Updated wording of Target Patient Population in Section 2.2. • Updated Summary of Results fields of Section 5.3 to delineate primary endpoints or performance outcomes that support the Clinical Benefit. • Updated Section 5.4 to include Clinical Benefit statement. • Minor formatting and typographical edits throughout.	No	English
3	See CEM-226.C in AtriCure Document Control for official date issued.	• Validated by BSI with CEM-226.B changes and revised to CEM-226.C for translations only. No content changes from Rev B. Cover page date reflects Rev B approval date.	Yes	English
4	See CEM-226.D in AtriCure Document Control for official date issued.	• Defined acronyms at first mention and consistently used throughout document • Added Compliance columns to table in Section 8.	Yes	English
5	See CEM-226.E in AtriCure Document Control for official date issued.	• Validated by BSI with CEM-226.D changes and revised to CEM-226.E for attachment of translated files and certificate. No content changes from Rev D. Translated files remain at Rev D. Cover page date reflects Rev D approval date.	Yes	English

6	See CEM-226.F in AtriCure Document Control for official date issued.	• Revised Section 4: updated risk level of failure to “complete cryo portion of concomitant procedure”; added “nitrous oxide exposure to patient”. • Updated Section 5.3 to include FREEZE-AFIB Study publication. • Removed FREEZE-AFIB from section 5.5. • Updated Recalls section 4.3. • Update literature references in Section 5.4 and References. • Updated EN ISO 14971, BS EN ISO 11607-2, BS EN ISO 10993-10, BS EN ISO 10993-18, and ASTM F1980-21 standards in Section 8. • Added warning for CRYOF to align with IFU: “The distal end of the Rigid PROBE Shaft should not be bent more than 5 cm (2.0 inches) from straight”.	No	English
7	See CEM-226.G in AtriCure Document Control for official date issued.	• Revised to CEM-226.G for attachment of translated files and to note validation status.	Yes	English