Stereotactic Radioablation for Ventricular Tachycardia in Patients Untreatable by Catheter Ablation: Evidence of Efficacy, Safety, and Impact on Coronary Arteries

Short Title: Results from the STRA-MI-VT Trial

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ABSTRACT

Introduction

Ventricular tachycardia (VT) in patients with structural heart disease can be life-threatening and

may persist despite antiarrhythmic therapy and catheter ablation. When standard treatments are ineffective or contraindicated, stereotactic arrhythmia radioablation (STAR) has emerged as a non-invasive salvage option.

Methods

This prospective, single-center study included 19 patients with structural heart disease and recurrent VT unresponsive to conventional therapy and who were ineligible for ablation. Patients were selected by a multidisciplinary team and underwent cardiac CT and electroanatomic mapping for substrate characterization. STAR was delivered in a single 25Gy fraction using volumetric modulated arc therapy. Primary endpoints included safety (adverse events within 12 months) and efficacy (reduction in VT burden, assessed by ICD-recorded anti-tachycardia pacing [ATP] and shocks).

Results

During a median follow-up of 14 months [IQR 9–15], STAR was associated with a significant reduction in ICD therapies, with an average decrease of 81%. Mean ATP interventions/month dropped from 4.5±6.5 to 0.8±2.3 (p=0.029), and total ICD therapies/month decreased from 4.8±7.0 to 0.9±2.5 (p=0.032). Mild pulmonary injury and pericardial effusion occurred in 22.2% of patients. Most cases were asymptomatic; one patient (5.5%) required non-urgent pericardiocentesis. No significant changes in left ventricular function, valvular status, or coronary artery disease progression (assessed by CAD-RADS and PCAT analysis) were observed. One-year mortality was 33.3%; no deaths were directly attributable to STAR.

Conclusion

STAR shows promise as a safe, noninvasive option for patients with refractory VT and advanced

cardiomyopathy. Larger multicenter studies are needed to confirm long-term outcomes and better define its clinical role.

Keywords: ventricular tachycardia; stereotactic arrhythmia radioablation; electrical storm; catheter ablation; arrhythmogenic substrate; computed tomography.

WHAT'S NEW

- STAR significantly reduced the burden of ICD therapies, with a >80% decline in both antitachycardia pacing (ATP) and shocks compared with baseline. Safety was favorable: only mild, mostly asymptomatic pulmonary and pericardial findings were observed, without deterioration of left ventricular function, valve status, or progression of coronary artery disease.
- For the first time, coronary CT with CAD-RADS classification and PCAT attenuation analysis was systematically applied to assess coronary effects after STAR, revealing no signs of disease progression or increased vascular inflammation, thereby supporting the cardiac safety of the procedure.

INTRODUCTION

Ventricular tachycardia (VT) is a potentially life-threatening arrhythmia often associated with structural heart disease, myocardial infarction, or cardiomyopathy. Radiofrequency (RF) catheter ablation remains the first-line therapy for managing scar-related ventricular arrhythmias (VAs), demonstrating efficacy in reducing VT recurrence and decreasing implantable cardioverter-defibrillator (ICD) interventions[1]. However, in some cases, neither antiarrhythmic drugs nor

catheter ablation are adequately effective in preventing VT recurrence[2]. This can lead to multiple ICD interventions or electrical storm (ES), significantly increasing the risk of cardiac death[3]. Additionally, the presence of comorbidities, such as advanced cardiomyopathy, and anatomical challenges, including mechanical valve prostheses or scarring from prior cardiac surgery, can render catheter ablation technically complex or even unfeasible. Cardiac stereotactic body radiation therapy (STAR) has emerged as a promising noninvasive therapeutic option for patients with structural heart disease and refractory VT[4,5] and appeared to gain acceptance within the cardiology community in the last years[6]. This approach is particularly valuable in scenarios where standard therapies fail or where anatomical or procedural risks preclude invasive interventions[7,8]. A recent meta-analysis showed that among patients with refractory VT in context of structural heart disease, VT burden and ICD shocks are dramatically reduced following cardiac STAR, although the overall mortality in this population with heart failure and refractory VT receiving palliative cardiac STAR remains high[9]. Advanced imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), and electroanatomic mapping, enable precise identification of the arrhythmogenic substrate, ensuring accurate treatment delivery[10]. The mechanism by which STAR induces myocardial damage remains under investigation. Current evidence suggests a dynamic, multistep process involving radiation-induced fibrosis mediated by chemokines and cytokines[8]. Furthermore, experimental studies indicate that STAR may exert antiarrhythmic effects through electrical remodeling in the target area[11]. Recent years have seen increasing adoption of STAR, with multiple centers reporting experiences using standardized protocols and a consistent radiation dose of 25 Gy[4,12]. In this context, we report the results of a prospective phase Ib/II open-label study to validate the efficacy and safety of STAR in a well-defined cohort of patients with recurrent VT who were ineligible for conventional catheter ablation

and in whom a dedicated workflow was employed for treatment preparation, with specific attention given to STAR effects in the long term.

METHODS

STRA-MI-VT is a prospective, single-arm, single-center study. The study design has been previously detailed[13]. Preliminary results have been already reported[14]. This manuscript has been drafted in accordance with the tenets of the Helsinki Declaration. The study has been approved by the local institutional review board. The protocol has been registered on ClinicalTrials.gov (NCT04066517). The data underlying this article will be shared on reasonable request to the corresponding author. The protocol prescribes STAR for patients with VT that is refractory to or who are unsuitable candidates for standard medical or ablation therapy. Mapping and/or imaging integration data are used for target identification, to ensure accurate substrate characterization. Electroanatomic mapping (EAM) may be omitted in patients with contraindications to interventional procedures, with STAR guided exclusively by imaging techniques.

Patient population

Patients were prospectively enrolled among those admitted to the Centro Cardiologico Monzino IRCCS in Milan, Italy, a national referral center for VT ablation. A flowchart illustrating the screening, eligibility, and inclusion process is shown in Supplementary Figure 1. STAR procedures were performed at the Istituto Europeo di Oncologia IRCCS, Milan. A multidisciplinary expert panel—including electrophysiologists, a clinical cardiologist, a cardio-radiologist, radiation oncologists, an anesthesiologist, and a cardiac surgeon—

evaluated each case to rule out alternative treatments and confirm eligibility. A sample of 20 patients was estimated to provide 90% power to detect as statistically significant ($p < 0.05$) a 45% reduction in ventricular arrhythmic episodes, assuming a mean of 16 episodes in the 3 months prior to the procedure. As specified in the study protocol approved by the Ethics Committee, the planned follow-up duration for all patients was one year after the STAR procedure.

Enrollment criteria

Patients were eligible for inclusion if they:

- Had structural heart disease and recurrent VT, defined as three or more episodes requiring ICD intervention, unresponsive to pharmacological and non-pharmacological treatments.
- Had contraindications to conventional radiofrequency catheter ablation (RFCA) due to high procedural risk or were unsuitable for interventional or surgical approaches.
- Met additional criteria: LVEF ≥ 20%, age ≥ 50 years, presence of an ICD or subcutaneous ICD, and signed informed consent.

Exclusion criteria included: prior thoracic radiotherapy, active myocardial ischemia, cardiac revascularization within the last 120 days, NYHA class IV heart failure, life expectancy < 1 year.

Safety and study endpoints

The primary safety endpoint was the evaluation of STAR safety during the first month post-treatment, with follow-ups at 3, 6, and 12 months. During these visits, patients underwent chest CT scans, transthoracic echocardiograms, and consultations with radiation oncologists. Adverse events (AEs) and serious adverse events (SAEs) were classified according to CTCAE version 5.0 (with serious events including death, cardiac arrest, myocardial infarction, cardiogenic shock, pericarditis, radiation-induced oncogenesis, and others[15]) and further categorized by their relationship to STAR as unrelated, unlikely, possible, or definitive, as assessed by a multidisciplinary team during each follow-up visit. AEs and SAEs were reported according to current literature[16].

The primary efficacy endpoint was the monthly rate of treated VT or VF episodes recorded by ICDs at 3-, 6-, and 12-months post-STAR, compared to the 6 months before treatment. Specific metrics included: VT/VF episodes requiring antitachycardia pacing (ATP), VT/VF episodes triggering ICD shocks, and total ICD shocks administered. A 6-week "blanking period" was considered post-STAR to account for inflammation-related arrhythmias[17]. Antiarrhythmic treatments were maintained unless clinical conditions required adjustments. Secondary endpoints included VT episodes recorded in the monitor zone, all-cause mortality at 12 months, quality of life assessed using the SF-36 Health Questionnaire, and changes in cardiac function as evaluated by echocardiographic LVEF.

Interventional Workflow

The entire workflow consists in the following steps:

Step 1 - Cardiac CT. All per-protocol CCTs were performed using a Revolution CT (GE Healthcare) with the following parameters: slice configuration 256x0.625 mm, gantry rotation time 280 ms and prospective electrocardiogram triggering, covering the entire cardiac cycle (R-R phases from 0% to 100%), as previously described. Patients received a 1.5 mL/kg bolus of contrast medium (Iomeron 400 mg/mL), divided into 2 boluses: 80 mL contrast medium through an antecubital vein at an infusion rate of 5 mL/s, followed by 50 mL saline solution and a second bolus of contrast medium to reach the predetermined total dose of contrast medium. Imaging was performed using the bolus tracking technique. Timing for the scan was targeted to obtain good contrast enhancement of the left and right ventricles. A second set of breath-hold and electrocardiogram gated images was acquired eight minutes after injection of contrast agent (100 Kvp; 400 mA) for the detection of myocardial delayed enhancement (DE). For coronary artery evaluation, data sets of cardiac CT images were analyzed using a vessel analysis software (VesselAnalysis, CardioQ3 Package-GE Healthcare). Reconstructed images were evaluated independently by EACVI Level III certified readers with >10 years of clinical experience in CCT performance and analysis. Coronary segments were evaluated for the presence of stenoses according to CAD-RADS 2.0 system. More specifically, coronary artery stenosis was minimal (<25%), mild (25%-49%), moderate (50–69% diameter stenosis), severe (70–90% diameter stenosis), or subtotal/occluded (≥90% diameter stenosis). Obstructive CAD was defined as any coronary plaque ≥50% luminal diameter stenosis

In addition, in order to evaluate the coronary inflammation, the pericoronary adipose tissue (PCAT) was measured. The PCAT was defined as tissue with an attenuation on CCT between −190 and −30 HU and within a radial distance from the vessel wall equal to the vessel diameter. PCAT analysis was automatically performed by the software following quantitative plaque analysis (QAngio CT Research Edition version 3.2.0.13, Medis Medical Imaging Systems, Leiden, The Netherlands).

Step 2 - Electroanatomic mapping (EAM). High-density EAM was performed using the CARTO system (Biosense Webster). When possible, both endocardial and epicardial LV mapping were completed for accurate 3D scar characterization. Imaging data were integrated with pre-acquired DICOM files to validate VT substrate characterization.

Step 3 – CT and EAM merging: EAM dicom and CT dicom images were merged for precise STAR target delineation. Figure 1 provides an example of cardiac CT integration using In-HEART software in a patient with non-ischemic cardiomyopathy.

Step 4 – Treatment plan: The treatment plan was developed by a multidisciplinary expert panel comprising two electrophysiologists, a clinical cardiologist, a cardio-radiologist, a biomedical engineer, two radiation oncologists, and two medical physicists. The panel reached a consensus on the target area, identified using cardiac CT and additional data from ECG and electrocardiographic imaging (ECGI). CCT provided both the anatomical reference for organs at risk (OARs) and the imaging substrate for arrhythmogenic scar delineation. Specifically, the arterial-phase CCT served as the anatomical reference for cardiac chambers, valve planes, great vessels, coronary ostia/proximal segments, and adjacent organs at risks (OARs), while the delayed-enhancement (late iodine enhancement, LIE) CCT

(acquired at 8 minutes) was used to delineate the arrhythmogenic substrate, which defined the cardiac target volume (CTV). Fibrosis localization and scar characterization were instead performed on the CCT datasets, specifically on the LIE series. The analysis was conducted using dedicated cardiac software (GE Healthcare), by comparing regions of hyper-attenuation within the scar to remote healthy myocardium. OARs were defined on the cardiac CT co-registered with the planning CT. This approach allowed precise contouring of cardiac substructures while maintaining geometric consistency with the treatment planning dataset. Accordingly, CTV (IMG) was derived from LIE characteristics and lesion topology within the myocardium, in consensus with electrophysiologists, cardio-radiologists, and radiation oncologists. The CTV was contoured directly on the planning CT within the treatment planning system (TPS), after fusion of the arterial- and LIE-phase series. In accordance with ICRU Report 91, the 4D-CT was not used to refine the CTV, but rather to characterize target motion and generate the internal target volume (ITV). The 4D-CT was acquired under free-breathing conditions using a respiratory gating system, synchronized with the treatment planning CT, to capture the full range of cardiac and respiratory motion throughout the cycle. The CTV, defined on the cardiac CT (arterial and LIE phases), was propagated across all respiratory phases of the 4D-CT to assess displacement of the target region. The ITV was then created by encompassing the CTV positions across the respiratory phases—representing the composite volume of the target during the breathing cycle. Subsequently, a PTV was generated by adding a setup margin to the ITV to account for residual geometric uncertainties and daily positioning variations. In our workflow, it was not possible to directly evaluate CTV(IMG) motion during free breathing because this structure

is not visible on non-contrast 4D-CT. Therefore, as a surrogate, we assessed whole-heart motion across the ten respiratory phases of the 4D-CT and generated the ITV by expanding the CTV(IMG) to encompass the observed respiratory-induced displacement. We assumed that the CTV(IMG) moves synchronously with the overall heart motion. Cardiac beating was not considered in margin definition, in line with the protocol adopted in our previous STRA-MI-VT study[14]. InHEART was not used to generate or edit the CTV; its use was strictly limited to quality assurance (QA)—that is, visual cross-checking of scar localization and anatomic concordance—without any transfer of contours from InHEART to the TPS and without the use of non-CE-marked SBRT transfer tools. After CTV definition, the ITV and PTV were derived within the TPS using 4D-CT motion data and standard setup margins, with OAR cropping and refinements performed directly on the planning CT dataset. When available, EAM and/or ECGI information was used as input to corroborate the imaging-based target location; no EAM meshes were converted to DICOM for target transfer, and no EAM-derived structures were imported into the TPS. All final contours (CTV, ITV, PTV, and OARs) were defined and stored within the TPS and, when needed, exported or imported as DICOM RT-STRUCT. Treatment plans (VMAT, single 25 Gy fraction) were created and delivered from these TPS-native structures. InHEART served solely as a QA viewer and did not participate in any fusion, contour generation, editing, or transfer.

Dose constraints. Planning objectives and constraints were prospectively specified. For extracardiac OARs, single-fraction stereotactic body radiotherapy (SABR) limits routinely used in oncologic practice at our institution were applied[18]. For intracardiac substructures, in the absence of validated single-fraction limits, we adopted a conservative ALARA strategy

guided by prior STAR reports and feasibility trials[19,20]. Achieved dosimetry for CTV(EP/IMG), ITV, PTV (D98/95/50/2) and cardiac/serial OAR D2% are summarized in **Table 3**. In case of competing objectives, critical OAR sparing was prioritized while preserving target coverage when feasible.

Step 5 – Radiotherapy: Using the free-breathing CT, a volumetric modulated arc therapy (VMAT) treatment plan was processed with the Eclipse RapidArc Planning System (Varian Medical Systems) to deliver a total dose of 25 Gy in a single fraction. The treatment was administered with a Varian Trilogy linear accelerator while the patient remained immobilized in a custom cast. Patient setup positioning was verified and corrected, if necessary, using two cone-beam CT scans (image-guided radiotherapy, IGRT).

Step 6- Pre-Discharge Evaluation and Management: Patients were monitored continuously for five days post-STAR, with routine lab tests and echocardiographic assessments. A 20-day dexamethasone regimen (initiated at 8 mg/day with tapering) combined with gastroprotective agents was administered prophylactically to all patients, irrespective of target location, to minimize potential post-radiation inflammatory reactions involving the pericardium or adjacent pulmonary tissue. This approach reflects our institutional practice, consistent with the prophylactic use of corticosteroids in high-dose single-fraction stereotactic radiosurgery for oncologic indications (e.g., brain or lung treatments). The regimen was well tolerated, and no corticosteroid-related adverse effects were observed. The rationale for corticosteroid prophylaxis is supported by recent survey data showing similar use among stereotactic radiosurgery centers[21]. ICD functionality was evaluated prior to discharge. After STAR, ICD programming was modified to allow recording of

clinical non-sustained VTs (NIVTs) in the monitor zone. No changes were made to the VT therapeutic zone.

Follow-up

Patients attended weekly follow-ups during the first month, followed by in-hospital visits at 3, 6, and 12 months post-STAR. After the 12-month follow-up period, patients continued to be clinically monitored at the enrolling institution as part of standard care. Evaluations included 12-lead ECGs, ICD interrogations, echocardiograms, SF-36 questionnaires, and cardiac CT scans (3 and 12 months post-STAR). Thoracic CT scans during follow-up were also used to assess late adverse events related to STAR, including CAD progression (using **CAD-RADS classification**) and attenuation of pericoronary adipose tissue (PCAT) CAD severity was graded according to the CAD-RADS 2.0 classification system, and PCAT attenuation was quantified as a CT-based imaging biomarker of coronary inflammation. PCAT analysis was performed automatically using QAngio CT Research Edition v3.2.0.13 (Medis Medical Imaging Systems, Leiden, The Netherlands), following validated protocols. In detail, PCAT was defined as all voxels with attenuation between –190 HU and –30 HU within a radial distance from the outer vessel wall equal to the vessel diameter, as recommended by Antonopoulos AS et al.[22] and Oikonomou EK et al.[23]. Measurements were obtained for the proximal 40 mm segment of the RCA, as the most reproducible and least motion-affected vessel, and were averaged from three adjacent axial reconstructions (0.625-mm slice thickness).

CAD burden and PCAT attenuation were assessed on CCT performed at baseline and at 12-month follow-up after STAR. Coronary stenoses were graded according to the CAD-RADS 2.0 system. More specifically, coronary artery stenosis was minimal (<25%), mild (25%-49%),

moderate (50–69% diameter stenosis), severe (70–90% diameter stenosis), or subtotal/occluded (≥90% diameter stenosis). Obstructive CAD was defined as any coronary plaque ≥50% luminal diameter stenosis. PCAT attenuation was quantified as a CT-based imaging biomarker of coronary inflammation using a validated semi-automated algorithm implemented in QAngio CT Research Edition v3.2.0.13 (Medis Medical Imaging Systems, Leiden, The Netherlands). In accordance with previously published methodology[22,23]. PCAT was defined as all voxels with attenuation values between –190 HU and –30 HU within a radial distance from the outer vessel wall equal to the vessel diameter. Measurements were performed along the proximal 40 mm segment of the right coronary artery (RCA) reconstructed with 1-mm slice thickness to minimize motion artefacts. Two independent EACVI Level III readers manually adjusted vessel contours when required and repeated measurements in consensus. For each patient, mean and maximum PCAT attenuation values were recorded at baseline and 12 months.

Statistical analysis

All analyses were performed using STATA 14.0 (StataCorp LLC, College Station, TX). Continuous variables were reported as mean ± standard deviation (s.d.) or as median [interquartile range (1st–3rd quartile) (IQR)], if normally or non-normally distributed, respectively. Categorical variables were reported as counts (%). Comparisons were performed using the Chi-square or Fisher's exact test for categorical variables, and a Student's t-test or a Mann–Whitney U test for numerical variables, as appropriate according to their distribution. Incidence rates of events were presented as rate per month, inclusive of the corresponding confidence interval. For all time-dependent analyses, the time of censoring was defined either as the time of the outcome or the

time of last follow-up, whichever came first. A two-sided p value < 0.05 was considered significant throughout the manuscript.

RESULTS

Baseline characteristics of the study cohort

Baseline characteristics of the study cohort were summarized in **Table 1**. The study cohort consisted of 19 patients with a mean age of 69.7 ± 6.75 years, the majority of whom were male (89.5%). Structural heart disease was present in all patients, with non-ischemic cardiomyopathy observed in 57.9% and ischemic cardiomyopathy in 42.1%. The mean left ventricular ejection fraction (LVEF) was 31.7 ± 9.8%. Most patients had a cardiac resynchronization therapy defibrillator (CRT-D, 63.15%), while 21% had a single-chamber ICD and 15.8% had a dual-chamber ICD. Beta-blockers were used by 94.7% of patients. Failed attempts with antiarrhythmic drugs were common, including **amiodarone and mexiletine,** each used in **78.9%** of patients. Nearly half of the patients (42.1%) had experienced an electrical storm, and prior catheter ablation attempts had a median of 1 (IQR 1–2), with epicardial approaches used in 21%. In six patients, iterative VT below the tachycardia detection interval was observed. Factors precluding catheter ablation included endocavitary thrombus (31.6%), pericardial inaccessibility (26.3%), high procedural risks due to comorbidities (26.3%) and contraindications to LV access (26.3%). Note that some patients may presented more than one contraindication for conventional VT ablation.

STAR procedure

Treatment characteristics for each patient are shown in **Table 2**. The median CTV/IMG was 41.1 [11.1-94.3] cm^3, the median ITV was 104.9 [28.0-204.5] cm^3, and the median PTV was 187.6 [83.3-275.6] cm^3.

Efficacy of STAR

Figure 2 presents a summary of all ablation procedures performed before or after the index STAR, along with the follow-up duration until the final clinical visit or death. One patient was excluded before treatment as he did not complete the diagnostic phase because of severe worsening of heart failure. During a median follow-up time of 14 [9-15] months, two patients (10.5%) underwent at least one repeat CA for clinically significant VT recurrences. Specifically, patient #14 experienced an arrhythmic storm after eight months of follow-up, requiring urgent repeat ablation with an endo-epicardial approach. Patient #16, after 11 months of follow-up, received three shocks from the ICD, leading to severe cardiac function deterioration and recurrent heart failure. Consequently, the patient underwent a new ablation procedure with ECMO support using pulsed-field ablation.

Study endpoint analyses are summarized in **Table 3**. The full-cohort comparison included all 18 treated patients and evaluated the mean frequency of ICD therapies at baseline and post-STAR intervention. The mean number of ATP interventions per month after the blanking period significantly decreased from 4.5 ± 6.5 at baseline to 0.8 ± 2.3 post-STAR ($p = 0.029$); mean reduction 3.7 events/month, 95% CI 0.3–7.0). Similarly, the mean number of DC shocks per month after the blanking period decreased from 0.5 ± 0.8 to 0.1 ± 0.3 after STAR ($p = 0.055$); mean reduction 0.4 events/month, 95% CI 0.0–0.8). The combined number of ATP and DC shocks per month after the blanking period decreased from 4.8 (SD = 7.0) to 0.9 (SD = 2.5) post-STAR ($p = 0.032$); mean reduction 3.9 events/month (95% CI 0.3–7.5). **Figure 3** summarizes the event

rate (events per month) for ICD therapies (DC shocks + ATP) before and after the STAR intervention for individual patients. Regarding the primary outcome analysis, no significant differences in SBRT efficacy were observed when stratifying patients by ischemic versus non-ischemic cardiomyopathy (combined number of ATP and DC shocks per month: ischemic cardiomyopathy pre-STAR 4.6 ± 6.8 → post-STAR 0.7 ± 2.1 vs non-ischemic cardiomyopathy pre-STAR 4.9 ± 7.2 → post-STAR 1.0 ± 2.8; p = 0.78 for difference in STAR efficacy between groups).

Five patients presented with recurrent slow VTs, detected in the monitor zone after ICD programming was modified post-STAR. ATP therapy was subsequently modified according to VT cycle length, but only in cases of clinically significant VT recurrences detected in the monitor zone. Those episodes were included in the primary outcome (ATP therapy). A more detailed analysis is beyond the scope of this paper, as a subanalysis of slow VTs has been reported elsewhere[24].

Safety of STAR

At one year of follow-up, mortality reached 33.3% (n=6/18 patients treated), corresponding to an estimated survival of 67% (95% CI 47–91%). Patient #1 died 11 months after STAR due to worsening heart failure. Patient #4 died after 20 months due to a new myocardial infarction caused by restenosis of a previously treated coronary artery. Patient #6 died during post-STAR hospitalization from multiorgan failure following bacterial pneumonia and sepsis, with no recurrence of arrhythmia. Patient #7 was found dead at home three months after STAR, with no identified cause of death. The patient had been closely followed for symptomatic VT episodes below the TDI, which had resolved two months post-STAR. While an arrhythmic event was not

confirmed, a cardiac non-arrhythmic death cannot be excluded, as no autopsy was performed. Patient #8 died six months into follow-up due to bladder cancer, and patient #13 died four months post-treatment from worsening heart failure complicated by bronchopneumonia.

Acute symptoms related to STAR (**Table 4**), such as nausea and gastrointestinal disorders (grade 2), were observed only in patient #1. Among the adverse events definitively related to STAR, the most frequent were mild pulmonary injury and pericardial effusion, each observed in four patients (22.2%). Pulmonary damage typically appeared at the first follow-up as an area of inflammatory consolidation or interstitial reticulation, consistent with radiation-induced injury. In patients #4 and #18, the consolidation was located in the lower lobe of the left lung, while in patients #12 and #14, it was found in the pulmonary lingula. Clinically, none of the four patients reported symptoms or functional limitations related to pulmonary damage, except for patient #18, who experienced a persistent mild dry cough. Regarding pericardial effusion, it was mild in three cases and moderate in patient #14. This patient was under full anticoagulation therapy due to an unstable ventricular thrombus, and a non-urgent pericardiocentesis of a serous-hematic effusion was performed during the previously described redo catheter ablation. In all other cases, anti-inflammatory therapy was initiated, and patients remained asymptomatic throughout follow-up. No significant changes in left ventricular ejection fraction were observed over the 12-month follow-up period. Additionally, no signs of valvular deterioration were detected, either in terms of insufficiency or stenosis, for either the mitral or aortic valves. During follow-up, coronary CT was used to assess the potential impact of radiotherapy on plaque progression or deterioration. CAD was classified using the CAD-RADS system, and no progression of coronary stenosis was observed on CT scans performed at 3 and 12 months. No significant change was observed following STAR (baseline mean PCAT –93 ± 7 HU vs. follow-up –89 ± 8 HU; Δ = +4 ± 3 HU; p

= 0.27). CAD-RADS scores remained unchanged between baseline and follow-up (median 3, range 1–5), confirming the absence of coronary progression. A summary of baseline and post-STAR CAD-RADS scores and PCAT attenuation values for each patient has been added in **Supplementary Table 1**.

DISCUSSION

This study provides one of the longest follow-up data on the safety and efficacy of STAR in VT management. It is also the only cohort specifically analyzing radiological features potentially related to STAR-associated effects, including CAD-RADS assessment per single coronary artery and epicardial fat modifications as a marker of inflammation. Our findings can be summarized in three major observations:

1. A potential benefit in preventing VT recurrence was observed, with a significant reduction in appropriate ICD therapies after the blanking period when STAR was used as a bailout strategy in highly compromised patients.
2. Adverse events potentially related to STAR included pulmonary damage and pericardial effusion, each occurring in four patients (22.2%), but the rate of severe complication was extremely low. No significant changes in left ventricular ejection fraction were observed within 12 months, and no valvular deterioration or coronary artery disease progression was detected on follow-up imaging, as per CAD-RADS classification.

3. Mortality in the study population was relatively high, primarily reflecting the severity of the underlying advanced heart disease. However, no deaths were directly attributable to STAR.[25]

Patients Selection

The population included in the STRAMI-VT study consisted of highly fragile and clinically complex patients, most of whom were not candidates for conventional invasive ablation. At enrollment, 9 of 18 patients (50%) had not undergone prior catheter ablation owing to specific contraindications or excessive procedural risk. Among them, three had contraindications to left ventricular access due to double mitral/aortic valve surgical replacement, three had persistent endocavitary thrombi documented in their clinical history, and three were deemed at excessively high procedural risk because of severe comorbidities such as prior cardiac tamponade, recurrent pericarditis, previous atrial septal defect closure, severe COPD, or advanced peripheral arteriopathy. In addition, two patients presented with a deeply intramural substrate, further limiting the feasibility of a transcatheter approach. Collectively, these factors underline that this cohort represents a particularly vulnerable population in whom STAR was considered a bail-out, noninvasive therapeutic option when standard ablation was contraindicated or judged unsafe.

Efficacy of STAR

The efficacy of STAR in our study aligns with prior reports, suggesting a meaningful reduction in ventricular arrhythmia burden and ICD therapies[26]. Our findings show a **statistically significant decrease in ATP and ICD shocks,** reinforcing STAR's potential as a **noninvasive**

strategy to mitigate VT recurrence in patients with limited treatment options. This outcome is consistent with prior trials, such as the **ENCORE-VT trial**[27], which reported a **94% reduction in VT episodes outside the blanking period**. Similarly, multiple smaller studies, including those by **Lloyd et al.**[28]**, and Ho et al.**[29]**,** have documented **VT burden reductions ranging from 80% to 99%.** However, despite the observed short-term efficacy, VT recurrences remain common. This outcome is consistent with the ENCORE-VT phase I/II trial[27], which demonstrated a 94% reduction in VT episodes outside the blanking period and 72% 1-year survival. Similarly, the STOPSTORM meta-analysis[30], pooling 82 patients across 10 prospective studies, reported a 1-year survival of 73% (95% CI 61–83) and VT burden reduction ≥75% in 80% of patients. Our results—showing a 67% (95% CI 47–91) survival and significant ICD therapy reduction—are therefore comparable, considering our cohort's higher baseline risk and longer follow-up.

In our cohort, the reduction in ICD shocks and ATP therapies persisted through **12 months of follow-up** (even longer for some patients), highlighting a **sustained antiarrhythmic effect**, but the presence of post-STAR VT episodes suggests that **substrate modification remains incomplete.** This observation is in line with prior reports emphasizing that **STAR does not eliminate arrhythmogenic circuits**, but rather modifies conduction properties, potentially facilitating anti-tachycardia pacing (ATP) effectiveness. Notably, **remapping studies (i.e. Qian et al.**[31]**)** suggest that **VT recurrence often arises near but outside the primary treatment volume**, highlighting the importance of precise arrhythmic substrate delineation[32]. Our study supports these findings, as ATP efficacy appeared enhanced in post-STAR VT episodes, suggesting that while STAR may not

completely eradicate VT circuits, it can slow conduction within the scar, thereby increasing susceptibility to pacing-based therapies. Similar patterns were reported in the STOPSTORM meta-analysis[30], which found 1-year recurrence-free survival rates around 20%–30%, underscoring that arrhythmia suppression, not elimination, is the realistic therapeutic goal in this population. Similar effects were reported in the **Australian STAR experience by Das et al.**[33], where **post-STAR VT episodes often maintained identical morphologies to pre-STAR episodes,** implying **incomplete substrate homogenization rather than complete VT elimination**. Given these findings, STAR should be considered an adjunct rather than a standalone therapy for VT. The variable responses to STAR observed across studies suggest that patient selection, optimal radiation dosing, and improved targeting strategies remain critical areas for refinement[34]. Recent evidence by Rademaker et al[35]. confirms that STAR target delineation can be performed with excellent interobserver agreement using commercially available software, with a remarkably steep learning curve, underscoring the feasibility of standardized imaging-based workflows in clinical practice.

Beyond late fibrotic remodeling, emerging data suggest that RT can exert early, non-fibrotic electrophysiologic effects that plausibly account for VT suppression within days to weeks. Experimental and translational work has shown that 25 Gy RT does not produce transmural fibrosis in the timeframe of clinical benefit, yet is associated with upregulation of NaV1.5 and Cx43, increased ventricular conduction velocity, and shortening of the QRS in a subset of treated patients, consistent with radiation-induced conduction reprogramming[36]. Mechanistically, transient activation of cardiomyocyte Notch signaling appears sufficient to increase conduction and necessary for the full conduction response to RT, offering a

biologically plausible pathway for rapid antiarrhythmic effects that precede scar formation. These effects localize to viable border-zone myocardium rather than inert scar, supporting a model in which enhanced excitability and coupling rescue regions of conduction delay that sustain reentry. Dose–response data further indicate that conduction reprogramming can occur at 15–25 Gy, which may have implications for future dose-optimization studies balancing efficacy and safety. While autonomic modulation (e.g., transient changes in sympathetic/parasympathetic tone) is also discussed as a potential contributor in the field, the attached work primarily supports a myocardial conduction–mediated mechanism rather than an autonomic one.

In recent years, a paradigm shift toward imaging-guided ventricular arrhythmia management has emerged, particularly in high-risk populations where traditional EAM may be limited or contraindicated. Patients with ICD often exhibit suboptimal MRI quality due to device-related artifacts, and hemodynamically unstable individuals may not tolerate prolonged mapping procedures. In this context, CT-based approaches—central to the STAR workflow—offer a noninvasive, fast, and reproducible alternative for scar characterization and target definition. This aligns with findings by Penela et al. [37], who demonstrated in a large multi-center registry that pre-procedural scar characterization using cardiac CT or CMR, and even fully image-guided strategies, result in comparable or superior procedural and clinical outcomes compared to conventional mapping approaches. Additional support for CT-based imaging strategies comes from our previous work[38], which prospectively evaluated a CCT-only approach in patients undergoing endo-epicardial VT ablation. Our study reported a very high concordance (Cohen's k=0.933) between CCT and EAM in detecting myocardial fibrosis,

especially in ischemic cardiomyopathy. Importantly, CCT proved effective even in patients with absolute contraindications to CMR, such as unstable arrhythmias or nonconditional ICDs. Moreover, CCT provided excellent resolution for visualizing epicardial fat, myocardial scar, and surrounding thoracic structures, facilitating safer access planning. Interestingly, over time, operator preference shifted increasingly toward CCT, even in CMR-eligible patients, highlighting a growing trust in CT as a primary imaging modality.

Safety of STAR

The safety profile of STAR in our cohort was largely favorable, with no severe acute adverse events and only a limited number of radiation-related effects. Similar to prior studies, such as those by **Robinson et al.**[27], the most frequently observed complications were **pulmonary inflammation and pericardial effusion,** each occurring in **22.2% of our patients**. Pulmonary involvement manifested as localized inflammatory consolidation on imaging, aligning with previously described patterns of **radiation-induced lung injury**. However, in our cohort, **only one patient (5.5%) developed persistent symptoms (dry cough), while all others remained asymptomatic**, reinforcing findings from **Lloyd et al.**[28] **and Ninni et al.**[5] where **pulmonary fibrosis was observed without significant clinical impairment**. Pericardial effusion, which was reported in multiple STAR studies as a **radiation-related inflammatory response**, was mild in most cases, with **only one patient requiring pericardiocentesis, staged during a redo ablation**. This contrasts with previous reports of **late-stage pericarditis and progressive pericardial thickening**, suggesting that while pericardial involvement is common, **clinically significant effusions requiring intervention**

may be less frequent when appropriate follow-up and anti-inflammatory treatment are administered. In comparison, the ENCORE-VT trial[27] reported two grade ≥3 adverse events (10%) and no treatment-related deaths, while the STOPSTORM pooled analysis[30] found grade ≥3 events in 10% of patients and grade 4–5 events in only 2%. Our findings are therefore consistent with these large prospective datasets, supporting the overall safety of STAR when appropriate motion management, image guidance, and prophylactic anti-inflammatory regimens are applied.

Notably, **no significant deterioration in LVEF was observed in our cohort**, consistent with findings from **the Czech STAR experience[39] and** the **ENCORE-VT trial**[27], where **global cardiac function remained stable post-STAR**. Additionally, concerns regarding **radiation-induced valvular damage, particularly mitral regurgitation, have been raised in prior studies al.**[31,39]**,** yet our data showed **no progression of valvular dysfunction** over 12 months.

Differently from previous studies, the present work provides the first evaluation of potential radiotherapy-induced coronary artery damage following STAR. CAD represents the most frequent manifestation of radiation-induced cardiovascular disease, with reported incidences as high as 85% among patients receiving conventional thoracic radiotherapy[40], and it may remain clinically silent for years, typically manifesting after a latency period of approximately 15 years[41]. Acute vascular effects of radiotherapy include endothelial dysfunction and inflammatory-cell infiltration, which trigger oxidative stress, reactive oxygen species generation, and cytokine-mediated DNA injury. These processes promote persistent inflammation and progressive microvascular remodeling, ultimately leading to arterial wall

thickening, luminal stenosis, and atherosclerotic plaque development[42]. Advancements in contemporary radiation techniques have enabled highly precise dose calculations for cardiac structures and organs at risk, allowing for the definition of dose constraints associated with a low risk of complications. Modern planning strategies are specifically designed to minimize cardiac and coronary exposure, and emerging data suggest that the relationship between radiation dose and vascular injury may be more complex than previously assumed. In a study of breast cancer patients undergoing cardiac-exposed radiotherapy, Kotanidis et al.[43] reported no correlation between radiation dose and coronary inflammation progression, and, surprisingly, observed a significant reduction in perivascular inflammation and estimated cardiovascular risk at two years post-treatment. Similarly, Trabattoni et al. found normal coronary artery calcium (CAC) scores (Agatston = 0) in 63% of 91 women with early-stage breast cancer at least five years after radiotherapy, while CAC >300 was observed in only four patients (4.3%), all of whom had three to five cardiovascular risk factors at the time of treatment[44]. No differences were observed according to the irradiated breast side, suggesting a negative synergistic interaction between modifiable cardiovascular risk factors and radiation exposure, which may predict future coronary calcifications and cardiovascular events.

STAR delivers a high and highly conformal radiation dose focused on a three-dimensional cardiac target. By its nature, this approach involves irradiation of a target volume located in close proximity to the coronary arteries, as these structures are anatomically contiguous with the ventricular myocardium. Therefore, we systematically assessed CAD progression using cardiac CT and the CAD-RADS classification, detecting no significant worsening of

coronary stenosis at 3- and 12-month follow-up after STAR. These findings contrast with those of Das et al., who reported cases of subclinical CAD progression, thereby underscoring the importance of long-term coronary surveillance in future STAR-treated patients[33]. In recent years, it has emerged that vascular inflammation is a key driver of atherogenesis and a typical feature of vulnerable plaque rupture, leading to acute coronary syndromes even in the absence of obstructive CAD[23]. PCAT is defined as the adipose tissue layer located within a radial distance from the outer vessel wall equal to the vessel diameter, with attenuation values between –190 and –30 Hounsfield units[22]. Phenotypic changes in PCAT induced by vascular inflammation can be quantified with CCT. Inflammatory signals originating from the vascular wall modify the tissue composition of the surrounding perivascular fat, increasing its attenuation toward less negative values and thereby rendering PCAT a functional sensor of vascular inflammation. The fat attenuation index (FAI), and its standardized metric, the FAI Score, quantify these variations and provide a non-invasive estimate of coronary artery inflammation. In the ORFAN study, a longitudinal cohort including 40,091 consecutive patients undergoing clinically indicated CCTA with a median follow-up of 2.7 years, Chan et al. demonstrated that the FAI Score in any coronary artery independently predicted cardiac mortality and major adverse cardiovascular events (MACE), regardless of traditional cardiovascular risk factors and the presence or extent of CAD[45]. The novelty of our study lies in being the first to evaluate coronary plaque progression and inflammatory imaging biomarkers (PCAT attenuation) in patients undergoing STAR. At 12-month follow-up, no evidence of new or progressive coronary artery stenosis was observed, and mean and maximum PCAT attenuation values remained stable compared with baseline.

These findings suggest the absence of early coronary inflammation or accelerated atherosclerosis, supporting the short-term vascular safety of STAR. Nevertheless, we acknowledge that radiation-induced coronary artery stenosis may develop as a late complication of cardiac or thoracic radiotherapy. Our current observations therefore reflect only the short-term vascular profile of STAR and should not be interpreted as excluding potential long-term effects. These results are reassuring and highlight the importance of integrating dedicated longitudinal coronary imaging endpoints into future STAR trials to identify subclinical cardiac toxicity before clinical events occur. Collectively, the stability of PCAT attenuation in our series provides preliminary evidence of short-term vascular safety and reinforces the rationale for continued imaging surveillance to confirm the long-term coronary safety of STAR.

Limitations

This study has several limitations that should be acknowledged. First, it was conducted in a single center with a relatively small sample size of 19 patients, which may limit the generalizability of the findings. The single-center design also restricts external validation and introduces potential center-specific biases. Second, post-STAR electroanatomic mapping (EAM) was not performed, precluding a direct evaluation of substrate modification. However, this was due to the clinical condition of the enrolled patients, many of whom were critically ill or had contraindications to invasive procedures— reflecting the real-world clinical complexity of patients eligible for STAR. Lastly, although the present study includes one of the longest follow-up durations reported

to date in STAR cohorts, with several patients monitored for over one year (IQR: 15 months), the observation period remains relatively short to capture potential **late-onset radiation-induced effects,** which in oncologic settings may manifest after two or more years. Therefore, **continued long-term surveillance** of this population is warranted to confirm the durable safety profile of STAR. **Despite these limitations, the study provides valuable long-term data on STAR efficacy and safety, supported by multimodal imaging and structured clinical follow-up.**

CONCLUSION

STAR appears to be a promising adjunctive option for patients with refractory VT and severe cardiomyopathy, particularly those who are ineligible for catheter ablation. Larger prospective multicenter studies with longer follow-up and broader patient inclusion are needed to better define its clinical benefit, durability of response, and long-term safety in the management of ventricular arrhythmias.

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Table 1: Baseline characteristics of the study cohort (n=19)	
Age, mean ± s.d.	69.7±6.75
Gender, % (n)	
Male sex, n (%).	17 (89.5)
Structural heart disease	
Non-ischemic cardiomyopathy, n (%)	11 (57.9)
Ischemic cardiomyopathy, n (%)	8 (42.1)
LVEF mean±s.d.	31.7±9.8
Device, n (%)	
Single chamber ICD, n (%)	4 (21)
Dual chamber ICD, n (%)	3 (15.8)
CRT-D, n (%)	12 (63.15)
Drug therapy, n (%)	
BB, n (%)	18 (94.7)
ACEi or ARB, n (%)	11 (57.9)
Failed AAD, n (%)	
Amiodarone, n (%)	16 (84.2)
Sotalol	1 (5.2)
Mexiletine	15 (78.9)
History of electrical storm, n (%)	8 (42.1)
Electrical storm directly prior to STAR, n(%)	3 (15.8)
Failed catheter ablation, median [IQR]	1 [1-2]
Previous failed epicardial procedure, n (%)	4 (21.1)
Factors precluding catheter ablation, n(%)*	
Endocavitary ventricular/atrial thrombus, n(%)	6 (31.6)
Pericardial inaccessibility, n(%)	5 (26.3)
Contraindication to LV access, n(%)	5 (26.3)
High procedural risks for comorbidities,n(%)	5 (26.3)
Deep septal substrate	3 (15.8)

Abbreviations: LVEF: left ventricular ejection fraction, BB: beta-blockers, ICD: implantable cardioverter defibrillator; CRT-D: cardiac resynchronization therapy, STAR (stereotactic arrhythmia radioablation).

* It should be noted that some patients presented with more than one contraindication for conventional VT ablation.

1

Table 2: Treatment Characteristics				Treated cohort (n=18)
Median target volume, cm^3 (range)				
Cardiac Target Volume (CTV/IMG)				41.1 [11.1-94.3]
Internal Target Volume (ITV)				104.9 [28-204.5]
Planning Target Volume (PTV)				187.6 [83.3-275.6]
Dosimetry of the Target Coverage (percentage of prescription dose)				
	$D_{95\%}$	**D_{mean}**	**$D_{2\%}$**	
CTV/IMG	98.2 [96-100.2]	101.3 [100.3-103.4]	105.3 [102.7-109]	
ITV	98.1 [68.3-99.5]	101.7 [100.3-102.8]	105.6 [102.9-109.5]	
PTV	95 [72.7-97.4]	100.9 [99.6-102]	105.5 [103-109.1]	
Heart substructure median dose, Gy (range) 1				
Left main artery (LMA)				7.35 [0.6-25]
Circumflex arteria **(**CFX)				9 [0.3-24.6]
Right coronary artery (RCA)				4.2 (1.2-16.2]
Left anterior descending artery (LAD)				21.2 [0.97-25.5]
Aorta				2.6 [0.5-6.7]
Left Atrium				5.5 [1.95-11]
Right Atrium				3.2 [1.1-8.5]
Left ventricle				10.2 [1.9-21]
Right ventricle				9 [1.5-15.4]
Heart-PTV				5.5 [4-9.4]
Serial Organ -At-Risk $D_{2\%}$, Gy (range) 1				
Spinal cord				5.5 [2.5-8.7]

Esophagus	10.7	[4.8-20.5]
Stomach	11.1	[0.3-16]

Values are expressed as median [IQR]

Abbreviations: Gy: gray.

Table 3. Analysis was performed for all available data (full-cohort analysis) and in a pairwise fashion that included only patients who survived >6 months post-STAR. P-values are either Mann-Whitney U test, or Wilcoxon signed rank test, as appropriate.

ATP=antitachycardia pacing; DC=direct current.

Comparison of ICD Therapies after STAR Baseline and During the Follow-Up							
	Baseline			Post-STAR (after BP)			p
	N	Mean	S.D.	N	Mean	S.D.	
Full-Cohort Analysis							
ATP/month	18	4.5	6.5	18	0.8	2.3	**0.029**
DC shock/month	18	0.5	0.8	18	0.1	0.3	0.055
ATP + DC shock/month	18	4.8	7.0	18	0.9	2.5	**0.032**
Paired Follow-up Cohort Analysis							
ATP/month	15	4.3	7.1	15	1.1	2.7	0.114
DC shock/month	15	0.5	0.8	15	0.1	0.1	0.065
ATP + DC shock/month	15	4.8	7.0	15	1.2	2.8	0.075

Comparison of ICD Therapies after STAR Baseline and During the Follow-Up (including the blanking period)

	Baseline			Post-STAR (after BP)			p
	N	Mean	S.D.	N	Mean	S.D.	
Full-Cohort Analysis							
ATP/month	18	4.5	6.5	18	1.2	2.3	0.050
DC shock/month	18	0.5	0.8	18	0.1	0.3	0.051
ATP + DC shock/month	18	4.8	7.0	18	1.3	2.6	0.055
Paired Follow-up Cohort Analysis							
ATP/month	15	4.3	7.1	15	1.6	2.8	0.181
DC shock/month	15	0.5	0.8	15	0.1	0.2	0.070
ATP + DC shock/month	15	4.8	7.0	15	1.7	2.9	0.124

Table 4. Adverse events

Event	Patient	Grade (1-5)	Correlation with STAR	Time of apperance (months)
Nausea	1 patient (P01)	2	definite	1
Gastrointestinal disorders	1 patient (P01)	2	definite	1
Sars Cov 2	2 patients			
	(P03)	3	unrelated	1
	(P10)	2	unrelated	8
Vertebral Fracture	1 patient (P03)	3	unrelated	5
Pulmonary damage (transient* or permanent)	1 patient (P04*)	1	definite	4
	3 patients			
	(P12)	1	definite	4
	(P14)	1	definite	4
	(P18)	1	definite	3
Pericardial Effusion	4 patients			
	(P10)	2	definite	7
	(P12)	2	definite	4
	(P14)	3	definite	4
	(P17)	2	definite	6

Heart Failure	1 patient (P16)	3	unrelated	5
Cardiac death (heart failure)	1 patient (P01)	5	unrelated	11
Non-cardiac death (sepsis)	1 patient (P06)	5	unrelated	1
Non-cardiac death (acute viral pneumonitis)	1 patient (P13)	5	unrelated	4
Non-cardiac death (neoplasia)	1 patient (P08)	5	unrelated	6
Unexplained death	1 patient (P07)	5	not evaluable	3

Figure 1. Example of cardiac CT integration using In-HEART software in a patient with non-ischemic cardiomyopathy (NICM) and a scar located in the mid-basal and lateral-basal segments of the interventricular septum (IVS).

Panel 1: Post-processed scar localization showing myocardial layer involvement.

Panel 2: Scar density mapping.

Panel 3: Scar thickness visualization.

Panel 4: Anatomical reconstruction of the left ventricle with delineated scar zones.

Figure 2. Time-Axis Plot With Historical and Follow-Up Ablation Procedures.

Each horizontal line represents an individual patient undergoing STAR (stereotactic arrhythmia radioablation) therapy. The vertical blue dashed line denotes the timing of the STAR procedure (time zero). Red diamonds indicate ablation procedures performed prior to STAR ("Pre-STAR Ablation"). Blue circles mark the STAR treatment. Orange squares denote ablations performed after STAR ("Post-STAR Ablation"). Black Xs represent the date of death. Green Xs represent the most recent follow-up for patients still alive as of July 2025. Time on

the x-axis is expressed in months relative to STAR. Negative values represent months before STAR; positive values represent months after STAR.

Figure 3. Event rates (events per month) for ICD therapies (DC shocks + ATP) before and after the STAR intervention for individual patients. Red dots represent Pre-STAR event rates. Blue dots represent Post-STAR event rates. Dashed lines connect the paired values for each patient, indicating the change. Circled Patient IDs (1, 5, 6, 11, 13, 14) represent patients with an ischemic substrate.

Abbreviations: CT = computed tomography; NICM = non-ischemic cardiomyopathy; IVS = interventricular septum.

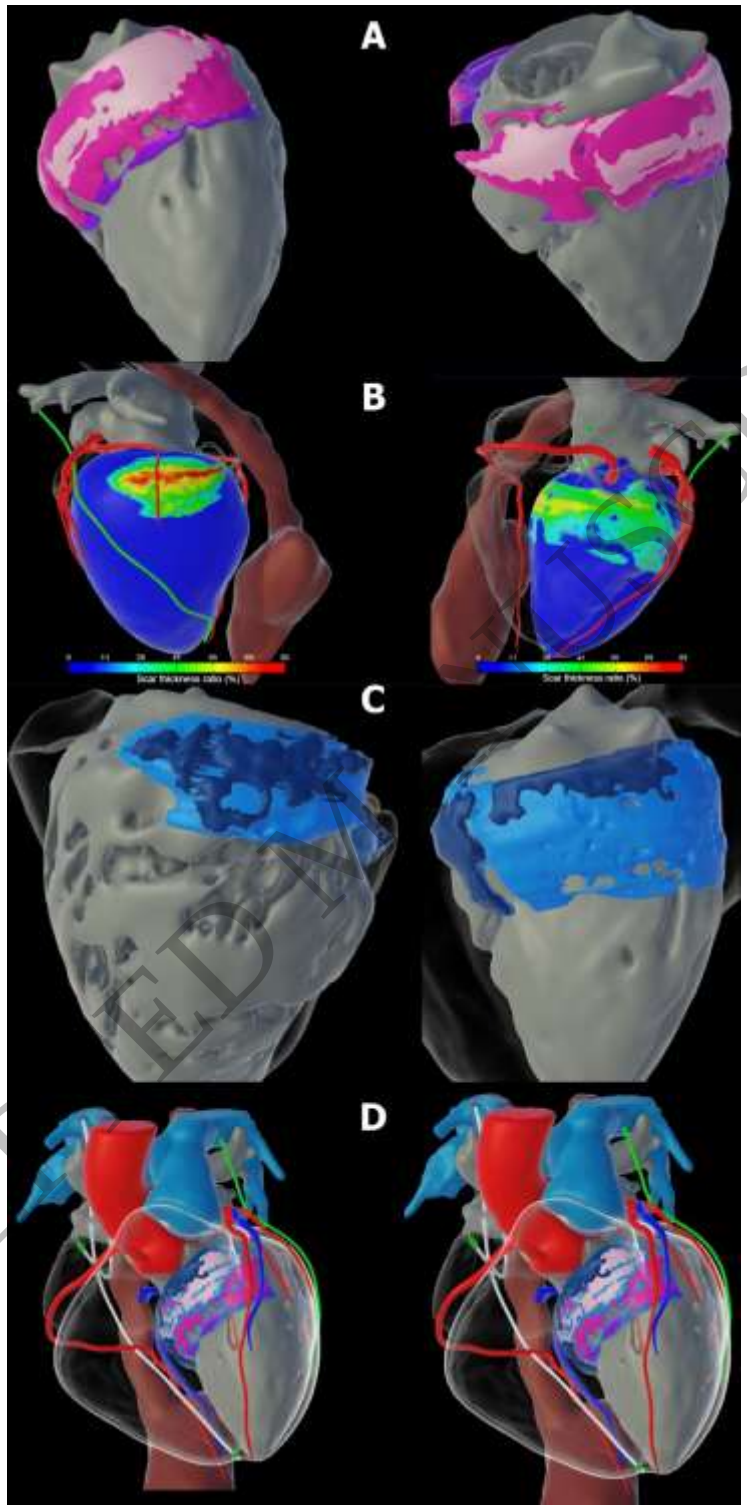

Figure 1
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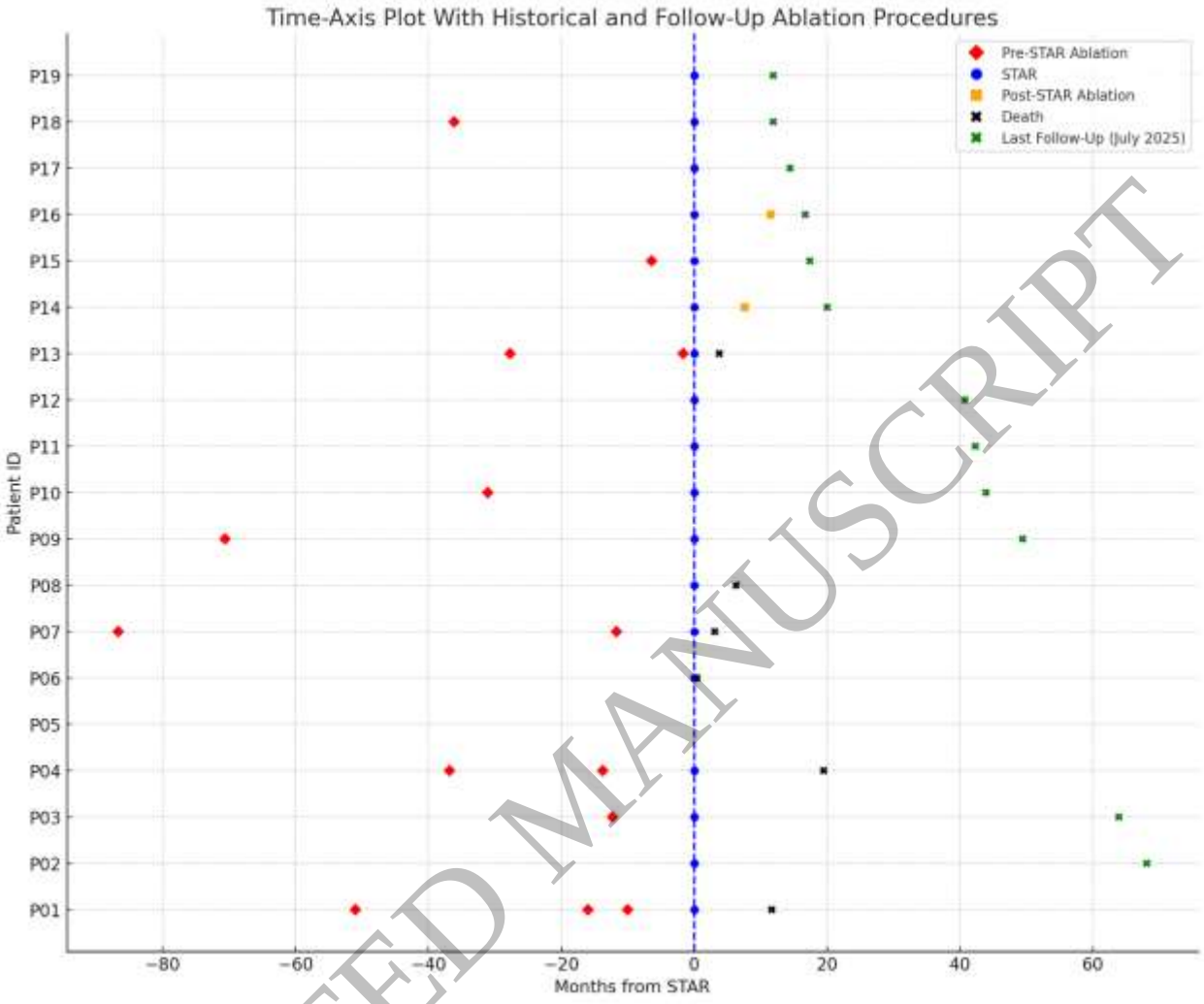

Figure 2
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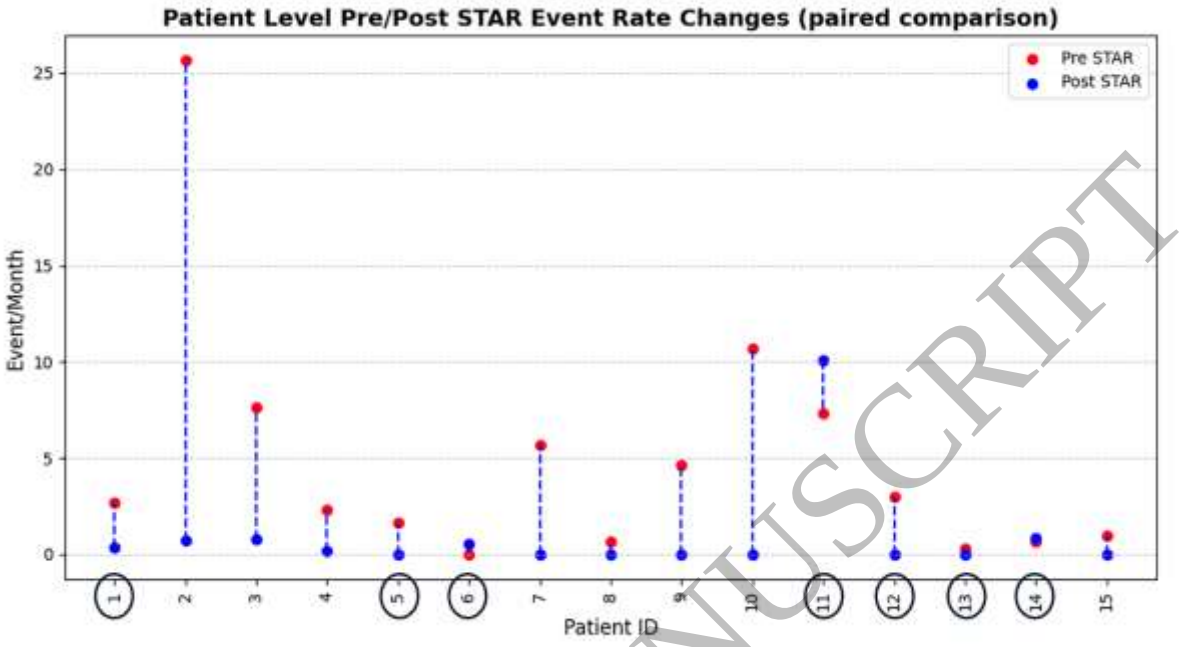

Figure 3
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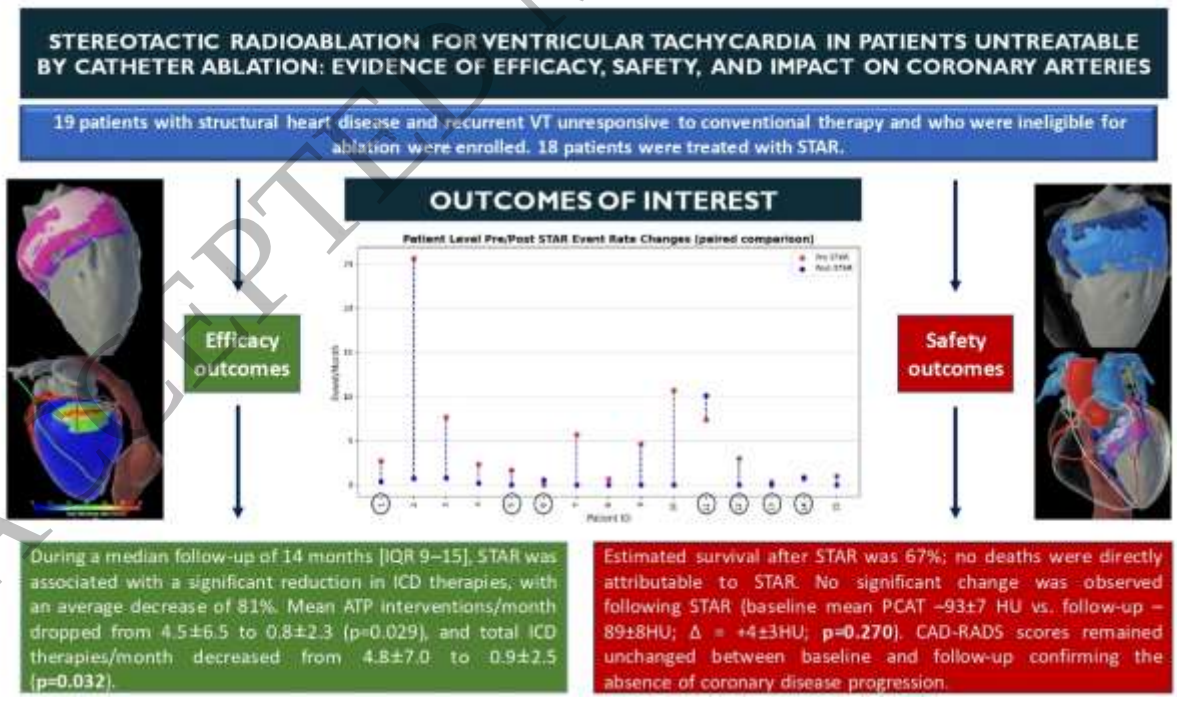

Graphical Abstract
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