

ORIGINAL RESEARCH

VENTRICULAR ARRHYTHMIAS - RADIOTHERAPY

Efficacy and Safety of Stereotactic Radiotherapy in Patients With Recurrent Ventricular Tachycardias The Czech Experience



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ABSTRACT

BACKGROUND Stereotactic arrhythmia radiotherapy (STAR) has been proposed recently in patients with refractory ventricular tachycardia (VT).

OBJECTIVES The purpose of this study was to describe the efficacy and safety of STAR in the Czech Republic.

METHODS VT patients were recruited in 2 expert centers after at least 1 previously failed catheter ablation (CA). A precise strategy of target volume determination and CA was used in 17 patients treated from December 2018 until June 2022 (EFFICACY cohort). This group, together with an earlier series of 19 patients with less-defined treatment strategies, composed the SAFETY cohort (n = 36). A dose of 25 Gy was delivered.

RESULTS In the EFFICACY cohort, the burden of implantable cardioverter-defibrillator therapies decreased, and this drop reached significance for direct current shocks (1.9 ± 3.2 vs 0.1 ± 0.2 per month; $P = 0.03$). Eight patients (47%) underwent repeated CA for recurrences of VT during 13.7 ± 11.6 months. In the SAFETY cohort (32 procedures, follow-up >6 months), 8 patients (25%) presented with a progression of mitral valve regurgitation, and 3 (9%) required intervention (median follow-up of 33.5 months). Two cases of esophagitis (6%) were seen with 1 death caused by the esophago-pericardial fistula (3%). A total of 18 patients (50%) died during the median follow-up of 26.9 months.

CONCLUSIONS Although STAR may not be very effective in preventing VT recurrences after failed CA in an expert center, it can still modify the arrhythmogenic substrate, and when used with additional CA, reduce the number of implantable cardioverter-defibrillator shocks. Potentially serious side effects require close follow-up.
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Manuscript received May 3, 2023; revised manuscript received November 27, 2023, accepted December 4, 2023.

Catheter ablation (CA) has become a strategy of choice for the management of electrical storm and/or recurrent ventricular tachycardias (VTs) in patients with structural heart disease of different etiology.¹⁻³ However, the efficacy of CA could be limited by the large size of the substrate and/or by the inability to reach its critical region for various reasons, such as deep intramyocardial location, the presence of old thrombus, or adhesions within the pericardial sac. Among alternative strategies, stereotactic body radiotherapy (SBRT) or more specifically, stereotactic arrhythmia radiotherapy (STAR), has been employed. The first case reports on the therapeutic use of STAR in cases of failed CA were published <10 years ago.^{4,5} Since then, several groups published their initial experience with this strategy in relatively small clinical studies or case series.⁶⁻¹⁰ Since our first case report,⁴ the number of STAR procedures performed by our consortium increased. In the meantime, we have unified CA strategies and indicated to STAR only the patients who had VT recurrences despite repeated ablations in 1 of the 2 expert centers. We also developed a reproducible strategy of accurate image integration, ie, merging data on substrate extent and location from an electroanatomic mapping system with computed tomography (CT) scans.¹¹ This approach appeared important for precise targeting of the critical region of the substrate.¹²

The primary goal of this report is to describe the efficacy of STAR in a subgroup of patients with failed repeated CA in an expert center in whom the above-sophisticated planning strategy was used (EFFICACY cohort). The secondary goal is to evaluate the safety of STAR in the entire Czech patient population (SAFETY cohort).

METHODS

PATIENT POPULATION. In the EFFICACY cohort, before STAR, patients underwent 2 or more CAs for recurrent, scar-related VT in the 2 Czech expert centers, using the endocardial and/or epicardial approach, and had subsequent VT recurrences. In addition, the most accurate strategy of target volume determination was used. This cohort consisted of 17 patients treated from December 2018 until June 2022. The SAFETY cohort consisted of all cases from the EFFICACY cohort and the early series of 19 patients with a less stringent CA strategy and less exact method of STAR target determination from January 2014 through December 2018. With the 3 patients who had 2 STAR procedures, the total number of STAR

procedures in the SAFETY cohort reached 39. Subjects with mechanical assist devices were excluded. All subjects were provided information about the potential benefits and risks of the treatment by a team of electrophysiologists who performed CA and radiation oncologists responsible for radiation therapy. The patients gave their written informed consent, and the Ethics Committees of all involved institutions approved the study protocol.

ARRHYTHMOGENIC SUBSTRATE DETERMINATION.

In the EFFICACY cohort, regions of the substrate responsible for inducible or spontaneously occurring VTs were defined based on an integrated approach. An electroanatomic mapping system (CARTO 3, Biosense Webster, Inc) was used. In brief, 3-dimensional (3D) electroanatomic bipolar voltage maps of the left and/or right ventricles were constructed in sinus rhythm or during right ventricular pacing. The scar was defined by bipolar voltage <0.5 mV (normal tissue >1.5 mV). The dense scar was defined as areas of noncapture at an output of 10 mA and labeled in gray. Intracardiac echocardiography was used as a part of the ablation protocol to define the extent and location of the scar. All late and abnormal potentials were tagged in the maps. In addition, pace mapping during sinus rhythm was used to assess slow conduction channels and their exits. In tolerated VTs, entrainment mapping was also used to further specify the re-entrant circuit. Epicardial mapping was employed when a critical part of the substrate was suspected to be distant from the endocardium or when electrocardiography suggested epicardial origin. All the above information was used to identify critical components of re-entry VTs. In addition, the aortic arch was mapped with precise tagging of the orifice of the left main coronary artery as an anatomical landmark for CT image registration. The right ventricular implantable cardioverter-defibrillator (ICD) lead tip was annotated on the 3D map for the same reason. Patients from the earlier period had less uniform mapping and CA strategy and fewer ablations before STAR.

CATHETER ABLATION. CA was performed with an irrigated tip catheter (Thermocool or Thermocool SmartTouch, Biosense Webster, Inc) using a SmartAblate generator (Biosense Webster, Inc) and power-controlled mode (30-45 W and irrigation flow of 30 mL/min). The goal of CA was a complete modification of the substrate and non-inducibility of VTs. Eliminating late or fragmented potentials and

ABBREVIATIONS AND ACRONYMS

CA	= catheter ablation
CT	= computed tomography
CTV	= clinical target volume
ICD	= implantable cardioverter-defibrillator
LV	= left ventricular
PTV	= planning target volume
STAR	= stereotactic arrhythmia radiotherapy
VT	= ventricular tachycardia

achieving local noncapture and/or core isolation of the scar area were the main strategies of substrate modification.

CLINICAL TARGET VOLUME DETERMINATION. Since 2014, 3 different strategies of clinical target volume (CTV) determination have been used. In the initial series of 15 patients, CTV was marked by a side-by-side visual comparison of 3D electroanatomic maps of the arrhythmogenic substrate with CT scans. In the subsequent series of 6 patients, positron emission tomography/CT and body surface mapping (CardioInsight, Medtronic) during induced VTs were used to approximate the CTV. Finally, a novel strategy of co-registration of electroanatomic maps with preprocedural CT scans was used in 17 patients.^{11,12}

STAR PLANNING. All patients underwent inspiratory breath-hold CT scanning with intravenous contrast enhancement before STAR. The internal target volume was calculated to account for heart contractions. The existing ICD lead was used as a fiducial marker to compensate for respiratory movements. No additional margin for planning target volume (PTV) delineation was added to reduce radiation toxicity in the initial series of 10 patients.⁸ Later, we added an isometric margin of 3 mm in all patients. Since 2020 (last 10 patients), an additional 2 mm margin into the left ventricular (LV) cavity or patient-specific motion margin was employed.¹³ We used the MultiPlan treatment planning system with sequential dose optimization and the CyberKnife radiosurgery system (both from Accuray, Inc). The metal deletion technique was used to evaluate how artifacts from leads influenced dose distribution. Monte Carlo dose calculation was applied to determine how proximity to lung tissues affected the dose distribution.

STAR PROCEDURE. Radiotherapy was performed in a single session without general anesthesia or sedation, as previously described.⁸ The patient was placed on a robotic couch and monitored for respiratory activity. A correlation model was created between the spontaneous respiratory excursions and the movement of the lead. This enabled tracking the target volume without requiring the invasive placement of additional fiducial markers. During treatment, the manipulator synchronized its movement with the movement of the ICD lead and compensated for any deviation of the electrode position from the reference CT-scan position. In addition, x-rays were used at least once every 60 seconds to adapt to possible changes in respiratory movements. A dose of 25 Gy was optimized to cover at least 95% of the PTV. In case of conflict with dose-volume constraints for

Organs at Risk, the dose and/or coverage were decreased. Irradiated ventricular segments were classified according to the recommendation of the American Heart Association.¹⁴ The cardiologist supervised the entire procedure.

ASSESSMENT OF EFFICACY AND SAFETY. All patients were followed in the institutional outpatient clinics. The patients were evaluated every 6 months unless the clinical status changed. The follow-up visits included ICD interrogation and echocardiography. Chest x-ray was performed when clinically indicated.

Study endpoints included the first ICD therapy after STAR, assessed separately for episodes of anti-tachycardia pacing (ATP) and direct current (DC) shocks, repeated CA or STAR, and all-cause death. No blanking period was used. Arrhythmia burden (assessed as the average number of ATP and DC shocks per month) was investigated in 6-month periods starting 6 months before the index STAR. Acute and late radiation-induced events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 scale.

STATISTICAL ANALYSIS. Continuous variables were expressed as a mean \pm SD or median (IQR) for non-normally distributed data, and compared by Wilcoxon signed rank test for dependent samples and Mann-Whitney *U* test for independent samples. Categorical variables were expressed as percentages and compared by Fisher exact test. In the EFFICACY cohort, Kaplan-Meier graphs were used to plot the event-free survival for individual endpoints. Arrhythmia burden was assessed in 6-month intervals before and after STAR. In a considerable proportion of patients, the duration of these periods was not exactly 6 months because of variations in the scheduling of outpatient visits (with device memory check-ups) in the COVID-19 period and caused by other logistic or clinical reasons. Therefore, the rate of ICD therapies was always related to the true duration of a particular follow-up period. Analysis was performed “per patient” in the EFFICACY cohort and “per procedure” in the SAFETY cohort. The assessment of the risk for the progression of mitral valve disease associated with irradiation of basal compared with the remaining LV segments was logically the predefined analysis. It appeared subsequently that irradiation of basal inferior (and specifically basal inferolateral) segments is associated with even higher risk. Therefore, post hoc analysis was performed for the segments comprising the corresponding half and one-third of the perimitral area. A *P* value ≤ 0.05 was

considered significant. All analyses were performed using the STATISTICA Version 12 software (Statsoft Inc).

RESULTS

PATIENT POPULATION. The clinical characteristics of both patient cohorts are listed in [Table 1](#). In the EFFICACY cohort, dilated cardiomyopathy was the underlying heart disease in 10 cases, followed by ischemic cardiomyopathy in 5. One patient had large cardiac fibroma, and another had burned-out hypertrophic cardiomyopathy. Before the STAR, patients underwent a median of 2 (Q1, Q3: 2, 3) endocardial ablations, and 10 of 17 had an epicardial approach. Two of them already had 1 prior STAR session and had VT recurrences. The SAFETY cohort consisted of 36 subjects with 3 repeated STAR procedures. The proportion of ischemic cardiomyopathy was higher in this group caused by their higher recruitment in the early phase of our experience. All patients with heart failure had optimized medical therapy before and after STAR.

STAR PROCEDURE. As assessed in the SAFETY cohort, the median procedure duration was 58 minutes (Q1, Q3: 50, 69 minutes; range 42-82 minutes). The median of PTV was 39.4 mL (Q1, Q3: 22.2, 62.1 mL, range 12.6-90.5 mL). The median of the isodose line with the prescribed radiation dose was 78% (Q1, Q3: 76%, 82%; range 66% to 84%), the median of the conformity index was 1.23 (Q1, Q3: 1.17, 1.31; range 1.11 to 1.78), and the median of homogeneity index was 1.28 (Q1, Q3: 1.22, 1.32; range 1.19 to 1.52).

EFFICACY OF STAR. [Figure 1](#) provides an overview of all ablation procedures before or after the index STAR for the EFFICACY cohort and also indicates the follow-up duration until the last clinical visit or death. All patients had at least 1 CA before STAR ([Figure 2](#)). The mean follow-up period after STAR was 13.7 ± 11.6 months. During this period, 8 patients (47%) underwent at least 1 repeated CA for clinically relevant recurrences of VT (including repeated STAR in one) ([Figure 3](#)). At 1 year of follow-up, mortality reached 47%, with the rate of redo ablations 67% in surviving patients, and 50% when analyzing all subjects. Two patients (#3 and #7) died very early after STAR (within 3 months) without the indication for redo CA and 3 others died (#1, #2, and #5) without subsequent CA within 20 months ([Figure 1](#)). The lack of ICD data between the last outpatient visit and death in most deceased patients does not exclude VT recurrences treated by ICD. Virtually all surviving patients experienced some ICD therapies during the

	EFFICACY Cohort (n = 17)	SAFETY Cohort (n = 36)
Men	88	92
Age, y	65 ± 11	66 ± 10
Ischemic cardiomyopathy	29	56
Coronary artery bypass grafting	24	38
Left ventricular ejection fraction, %	30 ± 10	31 ± 9
NYHA functional class	2.2 ± 0.5	2.4 ± 0.6
Brain natriuretic peptide, pg/mL	434 (204-820)	820 (390-2,540)
Diabetes mellitus	29	28
Chronic renal disease	47	28
Betablocker	94	97
Amiodarone	76	74
Sotalol	18	8
Number of prior endocardial ablations	2.2 ± 0.8	1.8 ± 0.9
Number of prior epicardial ablations	0.6 ± 0.5	0.4 ± 0.5

Values are %, mean ± SD, or median (IQR). Characteristics are calculated "per patient" in the EFFICACY cohort and "per procedure" in the SAFETY cohort.

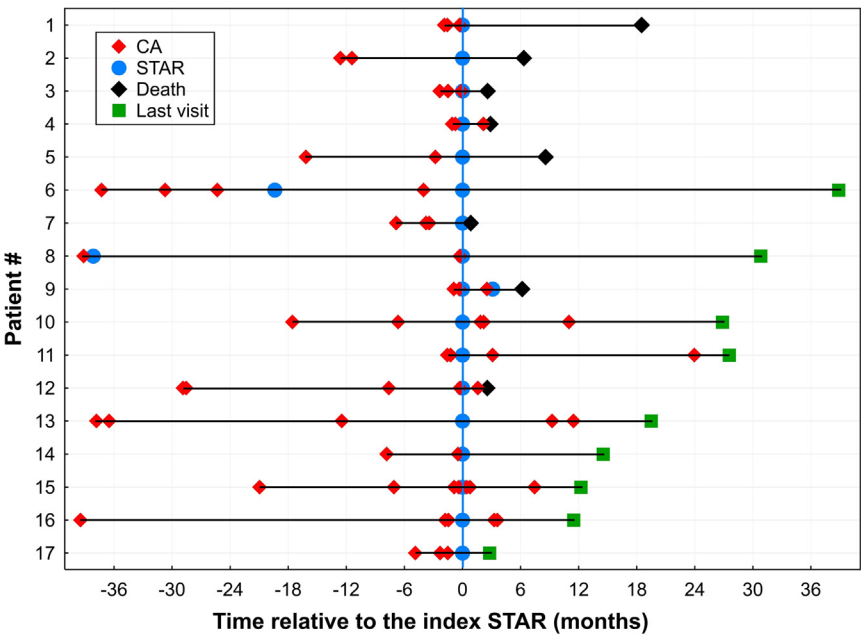
follow-up ([Figure 4](#)). The rates of DC shock and ATP at 1 year were 80% and 100%, respectively. Notably, the burden of ICD therapies decreased, and this drop reached statistical significance for ICD shocks during the follow-up ([Figure 5](#), [Table 2](#)). However, only 10 patients survived beyond the onset of the efficacy evaluation period (6-18 months after STAR), 9 of them had analyzable data from ICD, and only 5 of them were free from re-do CA by the time of the last visit or death.

Substrate remapping and reablation were performed at a mean interval of 8 months (Q1, Q3: 2, 10 months) after STAR in 8 subjects. A total of 23 and 27 distinct VT morphologies were inducible before and after STAR, respectively. In total, 12 pairs of VTs (44%) were identified that had identical morphology before and after radiotherapy. The mean cycle length of these VT pairs decreased from 392 ± 98 ms to 456 ± 73 ms ($P = 0.03$) after STAR. The detailed analysis goes beyond the scope of this paper.

SAFETY OF STAR. Acute adverse effects (CTCAE version 5.0) were observed after 4 of 39 procedures (10%) and consisted of nausea (Grade 2 radiation-related toxicity). All of these patients responded well to setron-based antiemetic drugs administered for 3 days.

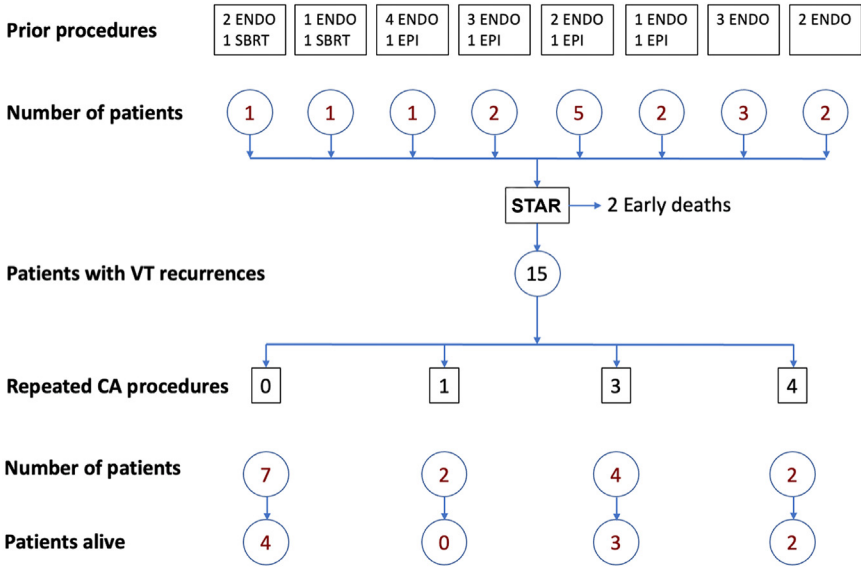
Long-term radiation-related side effects (CTCAE version 5.0) were evaluated after 32 of 39 procedures with a follow-up duration of at least 6 months. In this subgroup, the median duration of follow-up was

FIGURE 1 Time-Axis Plot With Historical and Follow-Up Ablation Procedures for 17 Consecutive Patients in the EFFICACY Cohort



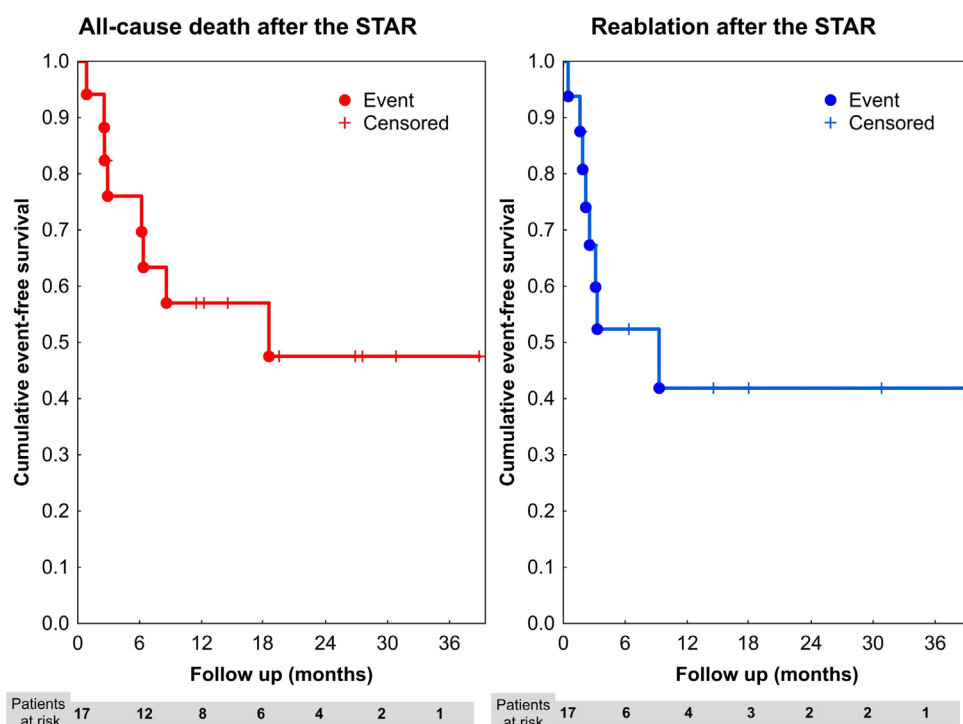
Individual axes are centered according to the index stereotactic arrhythmia radiotherapy (STAR) (time = 0). Red diamonds = catheter ablations (CAs); blue circles = STAR; black diamonds = death; green squares = last outpatient visit.

FIGURE 2 Flowchart of the EFFICACY Cohort



The diagram depicts the distribution of ablation procedures before and after the index stereotactic arrhythmia radiotherapy (STAR).

FIGURE 3 Kaplan-Meier Survival Curves After the Index STAR in the EFFICACY Cohort



The left panel is for all-cause death; the right panel is for reablation caused by recurrent ventricular tachycardia (VT). Actuarial overall survival was 57% and 48% at 12 and 24 months, respectively. STAR = stereotactic arrhythmia radiotherapy.

33.5 months (Q1, Q3: 18.0, 44.6 months; range 6.2-71.9 months). No significant change was observed in LV ejection fraction within 6 months after STAR ($31\% \pm 10\%$ vs $31\% \pm 10\%$; $P = 0.75$).

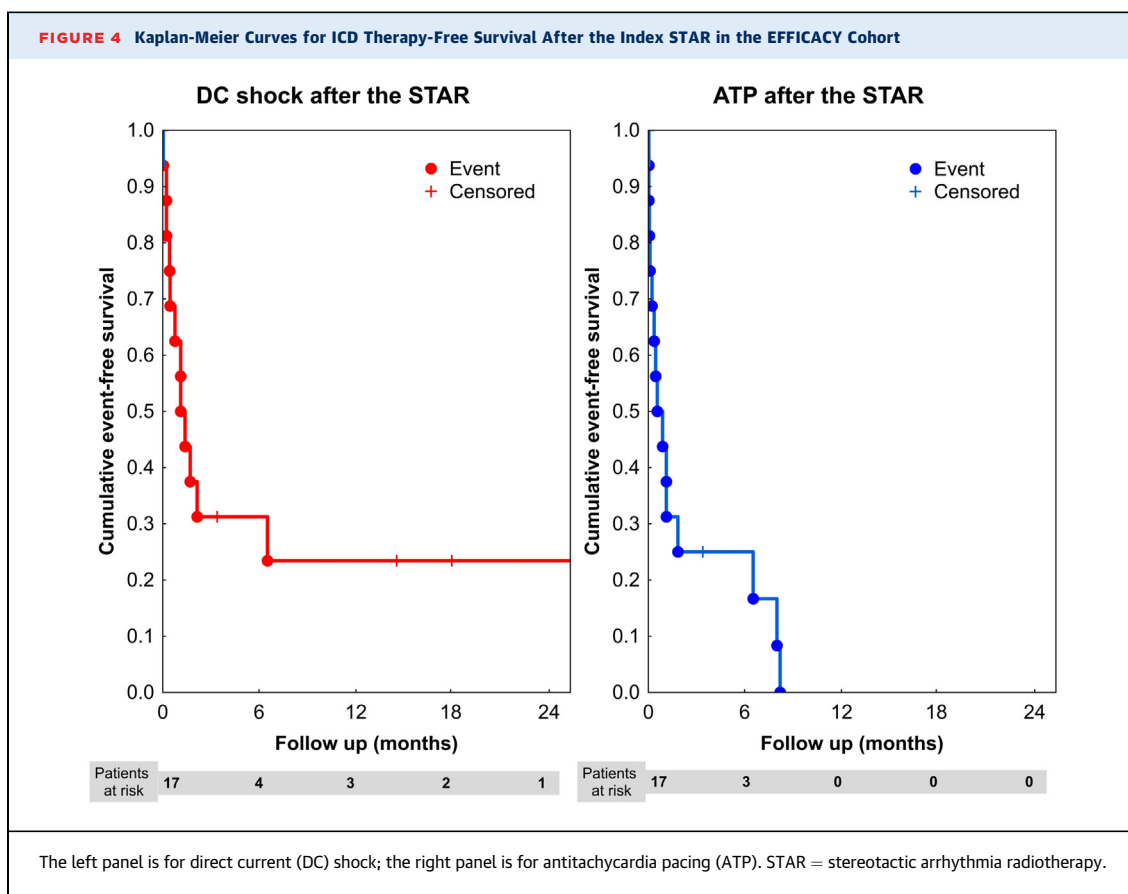
Two patients had 2 STAR procedures and no long-term side effects. Four patients (12%) presented with radiological signs of lung fibrosis in a small area at a close distance from the PTV. Importantly, adverse effects potentially related to STAR occurred in 12% of cases. Eight patients (25%) gradually developed progression of known mitral valve regurgitation after STAR, and 3 (9%) of them had to undergo mitral valve intervention (Grade 4 toxicity). Two patients had transvenous edge-to-edge repair (22 and 49 months after STAR), and 1 subject had mitral valve replacement (33 months after STAR). Altogether, 7 patients had a progression of restrictive changes on the posterior leaflet; 1 had a progression of mitral annulus dilatation. The grade of mitral regurgitation changed from a pre-SBRT value of 1.6 ± 0.5 to 3.4 ± 0.5 at the last assessment. The risk of mitral valve disease progression significantly increased when 1 of 3 basal inferior LV segments was irradiated, and this risk was

even higher when either the basal inferior or inferolateral LV segment was targeted (Table 3). Papillary muscles were part of the PTV in 14 of 32 patients with follow-up longer than 6 months and did not play a role in the progression of mitral regurgitation. Mitral valve disease progressed in 4 of 14 (29%) with papillary muscle in PTV which was comparable to 4 cases of mitral valve disease in 18 (22%) patients with papillary muscles outside the PTV ($P = 0.50$).

One significant tricuspid regurgitation (Grade 3 toxicity) was most probably unrelated to STAR. Two cases of esophagitis (6%) were seen with 1 (3%) radiation toxicity-related death (Grade 5 toxicity) caused by the unresectable esophago-pericardial fistula at 9 months after STAR.¹⁵ This patient had previous bypass surgery using a gastroepiploic artery, which could increase the vulnerability of the esophagus.

Importantly, no ICD generator or lead malfunction was observed in our series of patients.

OVERALL MORTALITY. Of 36 patients who underwent STAR for recurrent VTs, 18 (50%) died during the median follow-up of 26.9 months (Q1, Q3: 8.6,



43.1 months; range 0.9-71.9 months). The causes of death were as follows: progression of heart failure in 12 patients, and sudden death during recurrence of myocardial infarction, sudden unwitnessed death, COVID-19 pneumonia, pneumonia after stroke, carcinoma, and bleeding caused by esophago-pericardial fistula, each in 1 patient.

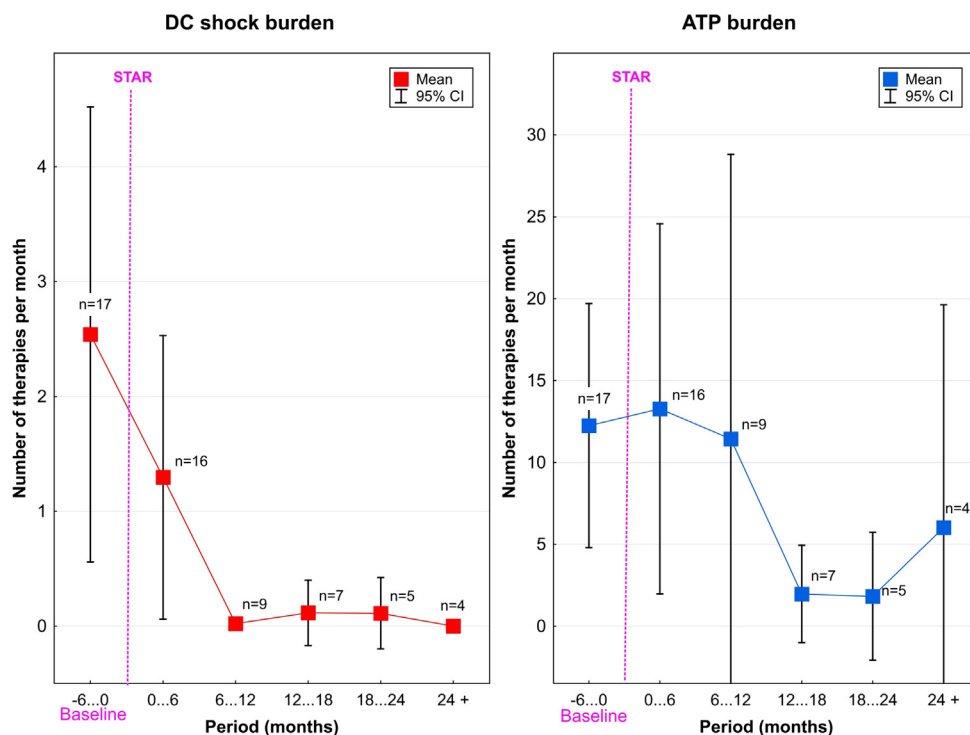
DISCUSSION

This observational study represents the third-largest published series on the efficacy of STAR in managing VT and the largest cohort on the long-term safety of the procedure. The results can be summarized as follows: 1) STAR by itself has uncertain efficacy in the prevention of VT recurrences when indicated as a bail-out procedure after previous CA procedures in an expert center despite the use of a high-accuracy method of CTV determination; 2) the net treatment effect of STAR together with subsequent CA consisted of a significant decrease of ICD shocks during the follow-up; 3) several adverse effects potentially linked to STAR were noted, including 3 mitral valve interventions for progression

of mitral regurgitation and 1 STAR-related death caused by esophago-pericardial fistula; and 4) the mortality in the study population was relatively high and reflected mainly the severity of the underlying advanced heart disease ([Central Illustration](#)).

EFFICACY OF STAR. Several rather small clinical studies reported on the early experience with STAR in patients with VT who failed previous CA or who were considered high-risk for CA. Our early experience with 10 patients showed a significant reduction of VT burden after STAR by 88%.⁸ However, during a median follow-up of 28 months, VT recurred in 8 of 10 patients. Patients in this early series had predominantly ischemic cardiomyopathy with less complex substrates. In addition, the strategy of CA before STAR was less comprehensive, and endpoints were variably defined. In contrast, the EFFICACY cohort in the current study had a higher proportion of patients with nonischemic cardiomyopathy, and the CA strategy was standardized in both centers, including the procedural endpoints. These factors may explain more optimistic results reported by our group earlier.⁸

FIGURE 5 Reduction in ICD Therapies Burden After the Index STAR in the EFFICACY Cohort



The dotted magenta line indicates the time of the STAR. The left panel is for direct current (DC) shock; the right panel is for antitachycardia pacing (ATP). Abbreviation as in [Figures 1 and 2](#).

The largest prospective study on 19 patients with refractory VT and/or ventricular ectopy causing cardiomyopathy (ENCORE VT [Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia] study) was published by Robinson et al.⁷ Importantly, patients with more than 3 distinct clinical VT morphologies or more than 5 induced VT morphologies were not included in the study. Three patients did not have previous CA for various reasons. The majority of patients were on more than 1 antiarrhythmic drug. High-dose amiodarone (>300 mg daily) was used in 8 patients. Imaging strategies combined with body surface mapping were used to define the STAR treatment volume. The aim was to target all areas of ventricular scar, approximating the VT exit site and harboring related circuits using the TrueBeam or Edge (Varian) delivery system. A significant reduction of VT episodes or ectopic burden was observed in 17 of 18 patients (94%) during the median follow-up of 13 months. In 16 VT patients, a 94% reduction of VT episodes was observed outside of the 6-week blanking period. This allowed a decrease in antiarrhythmic medication.

Despite the significant decrease in VT burden, many patients (11 of 16, 69%) had recurrences of VT between the end of the 6-week blanking period and the 6-month visit. In contrast, all of our patients had at least 1 previous CA performed in 2 expert centers, and the antiarrhythmic medication consisted of amiodarone in a dose of 200 mg daily. Patients with multiple morphologies of clinical or inducible VTs were not excluded. We used a different delivery system: CyberKnife. No blanking period was employed in our study. All of these factors might contribute to the differences in efficacy and the need for additional CA. The threshold for redo CA in our centers is lower than elsewhere, and CA as an established therapy is preferred to the escalation of antiarrhythmic treatment or redo STAR. Remapping data suggested slowing of clinical VT after SBRT, which may explain better efficacy of ATP and subsequent CA.

Other authors also reported their early experience with STAR with variable results and usually short-term follow-up. Although most of them observed a significant reduction of VTs, the overall efficacy is not very high. Lloyd et al⁹ found a significant reduction of

TABLE 2 Comparison of ICD Therapies in EFFICACY Cohort at Baseline and During the Follow-Up

	Baseline		Months 6-18		P Value
	N	Mean ± SD	N	Mean ± SD	
Unpaired comparison					
ATP/month	17	12.2 ± 14.5	9	10.2 ± 22.4	0.13
DC shock/month	17	2.5 ± 3.9	9	0.1 ± 0.2	0.005
ATP + DC shock/month	17	14.8 ± 16.2	9	10.3 ± 22.4	0.07
Paired comparison					
ATP/month	9	19.9 ± 16.6	9	10.2 ± 22.4	0.17
DC shock/month	9	1.9 ± 3.2	9	0.1 ± 0.2	0.03
ATP + DC shock/month	9	21.9 ± 19.2	9	10.3 ± 22.4	0.11
Analysis was performed for all available data (unpaired comparison) and in a pairwise fashion that included only patients who survived >6 months. P-values are either Mann-Whitney U test, or Wilcoxon signed rank test, as appropriate. ATP = antitachycardia pacing; DC = direct current.					

VT episodes in a cohort of 10 patients with advanced heart failure and VT over the mean follow-up of 176 days. However, 2 patients were placed in a hospice, and 3 other subjects underwent a heart transplant. Carbucicchio et al¹⁰ reported a significant reduction of VT therapies after STAR in a group of 7 patients at 6 months of follow-up, although only 2 were free from recurrent VTs. Chin et al¹⁶ described an apparent benefit of STAR (decrease of VT episodes or their absence) in 33% of their 8-patient series. However, even in patients who benefited from STAR, there was a variable temporal pattern in response, and most patients had recurrences of VT. Gianni et al¹⁷ demonstrated VT recurrences in all 5 patients who underwent STAR after failed CA. The first Asian experience with 7 patients was published by Ho et al.¹⁸ Again, 4 of 5 subjects with structural heart disease had recurrences of VT after STAR. Another report from Asia described STAR in 3 patients.¹⁹ During 13.5 ± 2.8 months, patients had a significantly lower burden, but they all had recurrences of VT and died within this period. A study by Qian et al²⁰ described the results of STAR in treating 6 patients

with VT and postinfarction cardiomyopathy. Besides a reduction in device shocks, device-treated or sustained VT episodes were not significantly decreased, and 50% of subjects died within a follow-up period of 231 days. A recent study by Ninni et al²¹ reported on clinical outcomes associated with STAR using the CyberKnife system in 17 patients with refractory electrical storm. In 5 patients with incessant VT, the time to effectiveness ranged from 1 to 7 weeks after STAR. Among the 12 remaining patients, early VT recurrences occurred in 7. After a median of 12.5 months (Q1, Q3: 10.5, 17.8 months) of follow-up, a significant reduction of the VT burden was observed beyond 6 weeks. However, many patients had CA shortly before STAR or were sedated and treated by antiarrhythmic drugs.

Our data from the EFFICACY cohort with reasonably long follow-up correspond to the previously mentioned experience and suggest that the efficacy of STAR per se is rather low. Practically all studies showed that STAR does not suppress all VTs and that VT recurrences are common. However, reducing device shocks appears to be the most reproducible result

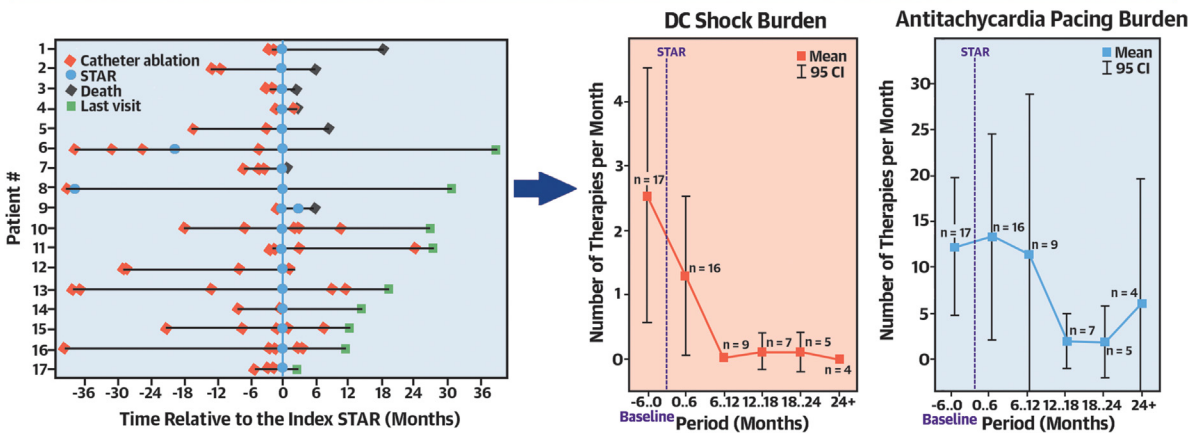
TABLE 3 Relationship Between Irradiated Myocardial Segments and the Progression of Mitral Valve Disease

Relationship Between the Number of Irradiated Segments and the Regression of Mitral Valve Disease					
	Segments	Risk (%)	Irradiated Region		
Irradiated Region	Risk of Significant Mitral Valve Regurgitation (n = 32)			Risk (%)	P Value
Basal segments	# 1-6	7/19 (37)	Rest of segments	1/13 (8)	0.07
Basal inferior segments	# 3-5	6/12 (50)	Rest of segments	2/20 (10)	0.02
Basal inferolateral segments	# 4-5	6/10 (60)	Rest of segments	2/22 (10)	0.005
Risk of Significant Mitral Valve Regurgitation Requiring Valve Intervention (n = 32)					
Basal segments	# 1-6	3/19 (16)	Rest of segments	0/13 (0)	0.20
Basal inferior segments	# 3-5	3/12 (25)	Rest of segments	0/20 (0)	0.04
Basal inferolateral segments	# 4-5	3/10 (30)	Rest of segments	0/22 (0)	0.02
Left ventricular segments are numbered according to the recommendation of the American Heart Association expert document. ¹⁴ P values are single-sided Fisher exact test.					

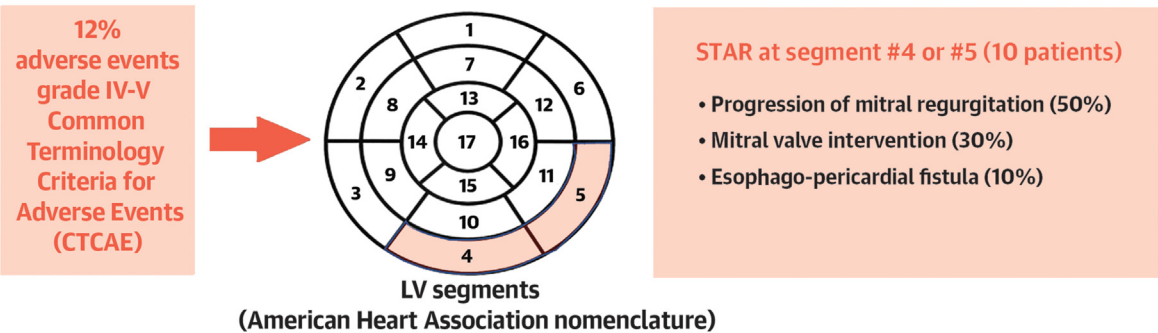
CENTRAL ILLUSTRATION The Main Results of the Study in the EFFICACY and SAFETY Cohorts

Summary of Results on Efficacy (upper panel) and Safety of Stereotactic Arrhythmia Radiotherapy (STAR) for VT (lower panel)

Efficacy Cohort (n = 17)



Safety Cohort (n = 39; 32 with follow-up >6 months)



Hašková J, et al. J Am Coll Cardiol EP. 2024;10(4):654-666.

The upper panel shows a time-axis plot with historical and follow-up ablation procedures in the EFFICACY cohort and reduction in ICD therapies burden after the index STAR. The lower panel summarizes the rate of adverse events grade IV-V (Common Terminology Criteria for Adverse Events) and the relationship of STAR segments #4 and #5 to adverse events. ICD = implantable cardioverter-defibrillator; STAR = stereotactic arrhythmia radiotherapy; VT = ventricular tachycardia.

of STAR for recurrent VT after previous CA. In this context, it is important to emphasize that such an effect was obtained in almost all patients on top of previous CA procedures. Not only that, at the time when we observed a significant reduction of ICD shocks, a large proportion of patients had already received subsequent CA for clinically significant recurrences of VT, which precluded any meaningful

statistical analysis of the effect of standalone STAR. This observation supports the view that STAR may rather have an adjuvant role to CA than become the first-line therapy managing VT in structural heart disease. Failure of repeated CA in an expert center appears to select patients who probably have more diffuse substrates or more advanced heart disease. Without a head-to-head randomized comparison of

both strategies, ideally in a less diseased population, it would be impossible to evaluate the true efficacy of standalone STAR.

SAFETY OF STAR. The main strength of our study is the analysis of the long-term side effects of STAR. The most frequently observed side effect in our series was a significant progression of mitral valve regurgitation. A detailed analysis of the relationship between the irradiated regions and the risk of mitral valve disease progression showed that STAR targeting the basal inferior and inferolateral segment of the LV significantly increased this risk. We revealed that further restriction of the posterior leaflet was primarily responsible for the progression of mitral regurgitation (Supplemental Table 1). The most serious complication in our series was death caused by esophago-pericardial fistula.¹⁵ The patient had irradiation of the basal LV segments, and previous coronary artery bypass grafting using a gastroepiploic artery could increase tissue vulnerability in this region. Interestingly, another case of gastro-pericardial fistula requiring surgical repair was reported (in abstract form only) 2.4 years after STAR.²² Other groups reported rather less-severe cases of toxicity, such as pericardial effusions. However, the follow-up was relatively short.

Our observations open the question of the risks and benefits of STAR. Considering that none of the previously published series reports on a median follow-up longer than 12 months, we feel that the risk of late adverse effects could be significantly under-reported. Longer vigilant follow-up is necessary to describe the actual safety profile of STAR for VT. Due to this uncertainty about safety, STAR should not be performed outside of clinical studies on the management of intractable VTs.

MORTALITY AFTER STAR. Because STAR is often indicated in a population of patients in the terminal phase of heart failure, long-term survival is limited. Robinson et al²² presented preliminary follow-up data from the ENCORE study. The 1- and 2-year overall survival rates were 72% and 58%, with 8 deaths being recorded. Regarding their relation to STAR, 4 had a possible relationship (2 heart failure, 2 VT recurrences). Chin et al¹⁶ reported 3 deaths out of 8 patients, and Gianni et al¹⁷ reported 2 deaths from heart failure out of 5 patients. Carbuicchio et al¹⁰ observed 3 deaths in a series of 7 patients; 1 of them was unexplained. In the Taiwanese experience with 3 cases of STAR, all patients died (within 14 months).¹⁸ Another center from Taiwan reported on 3 patients, and all died during 13.5 ± 2.8 months.¹⁹ Similarly, in a study by Qian et al,²⁰ 3 of 6 patients died.

Our data from the SAFETY cohort with a median follow-up of 26.9 months align with these reports. We report 50% mortality, mainly from nonarrhythmic causes. The fact that there was no significant difference in LV ejection fraction after STAR does not indicate the worsening of heart failure caused by radiotherapy. Rather, this implies that STAR could be employed as adjuvant therapy for patients with VTs and comorbidities when CA fails, is impossible because of access issues, or is considered technically demanding and associated with a substantial risk of failure or complications. In patients with less advanced heart failure or with fewer comorbidities, other treatment modalities such as LV assist device implant or heart transplant should be considered after failed repeated CA instead of STAR.

STUDY LIMITATIONS. The evaluation of STAR efficacy was limited not only by a relatively small sample size but also by a high mortality rate and shorter follow-up compared with the SAFETY cohort. The lack of a control group does not allow assessment of the causal effect of STAR (plus CA) on the decrease of ICD therapies. Because a substantial proportion of patients had another CA for VT recurrences after STAR, we can only speculate that the therapeutic effect is caused by the synergism of both modalities. The absence of data on ICD therapies between the last outpatient visit and death in most deceased patients might partly contribute to lower arrhythmic burden after STAR. Other bias-introducing factors that favor a decrease in arrhythmia burden may include selection bias caused by patient enrollment in the period of frequent ventricular arrhythmias, changes in anti-tachycardia function programming during the follow-up, and relatively high mortality of the sicker patient cohort. Furthermore, it is important to emphasize that the strategy of CA, as well as the technique of CTV determination, developed significantly between 2014 and 2020. A higher number of previous CA procedures and more nonischemic patients compared with the historical cohort of our first 10 cases suggest that our EFFICACY cohort consists of patients who are truly resistant to CA in the expert center with access to all contemporary technologies for CA. This was the reason why we separately analyzed efficacy in the most homogeneous cohort and safety in the entire patient population.

It is also important to mention that STAR in our cohort was not delivered by the C-arm technology, which differs from robotic linear accelerators. However, there is no data that either technology has different clinical efficacy or is more prone to toxicity.²³ We are also aware of some targeting inaccuracies when using the ICD lead to track respiratory

movements. Therefore, we use safety margins as published recently.¹³

CONCLUSIONS

STAR per se has limited efficacy in highly selected patients with structural heart disease and recurrent VT after previous CA in an expert center. Because many patients required another CA early during the follow-up after STAR to treat the VT recurrences, our study suggests that the decreased number of ICD shocks was caused by the synergistic effect of STAR and follow-up CA. The long-term safety of STAR is still unknown, and observed delayed side effects may limit its use. At present, STAR should be offered only as a bail-out strategy for patients with VTs and comorbidities when CA fails or is not feasible.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by grant project AZV NU20-02-00244 from the Ministry of Health of the Czech Republic. This work was also supported by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, Project No. LX22NPO5104), funded by the European Union-Next Generation EU. Dr Cvek has received personal fees from Accuray, and Roche for

lectures. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: Patients with structural heart disease and VT recurrent after CA in an expert center may benefit from targeted STAR of the myocardial substrate and better quality of life because of fewer device shocks. However, the risk of adverse effects has to be considered.

TRANSLATIONAL OUTLOOK: More information is needed about the effects of STAR on the myocardial substrate and the optimal dose to improve efficacy and minimize the risk of serious side effects.

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KEY WORDS catheter ablation, complications, stereotactic arrhythmia radiotherapy (STAR), ventricular tachycardia

APPENDIX For a supplemental table, please see the online version of this paper.