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Stereotactic arrhythmia radioablation (STAR)—A systematic review and meta-analysis of prospective trials on behalf of the STOPSTORM.eu consortium

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ABSTRACT

Stereotactic arrhythmia radioablation (STAR) is a noninvasive treatment of refractory ventricular tachycardia (VT). In this study, we aimed to systematically review prospective trials on STAR and pool harmonized outcome measures in a meta-analysis. After registration in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023439666), we searched OVID Medline, OVID Embase, Web of Science Core Collection, the Cochrane Central Register of Controlled Trials, and Google Scholar on November 9, 2023, to identify reports describing results of prospective trials evaluating STAR for VT. Risk of bias was assessed using the Risk Of Bias In Non-randomized Studies of Interventions tool. Meta-analysis was performed using generalized linear mixed models. We identified 10 prospective trials in which 82 patients were treated with STAR between 2016 and 2022. The 90-day rate of treatment-related grade $\geq$3 adverse events was 0.10 (95% confidence interval [CI] 0.04–0.2). The proportions of patients achieving given VT burden reductions were 0.61 (95% CI 0.45–0.74) for $\geq$95%, 0.80 (95% CI 0.62–0.91) for $\geq$75%, and 0.9 (95% CI 0.77–0.96) for $\geq$50% in 63 evaluable patients. The 1-year overall survival rate was 0.73 (95% CI 0.61–0.83) in 81 patients, 1-year freedom from recurrence was 0.30 (95% CI 0.16–0.49) in 61 patients, and 1-year recurrence-free survival was 0.21 in 60 patients (95% CI 0.08–0.46). Limitations include methodological heterogeneity across studies and moderate to significant risk of bias. In conclusion, STAR is a promising treatment method, characterized by moderate toxicity. We observed 1-year mortality of $\approx$27% in this population of critically ill patients suffering from refractory VT. Most patients experience a significant reduction in VT burden; however, 1-year recurrence rates are high. STAR should still be considered an investigational approach and recommended to patients primarily within the context of prospective trials.

KEYWORDS Cardiac SBRT; Cardiac radioablation; Arrhythmia; Refractory VT; STOPSTORM; Ventricular tachycardia; Stereotactic arrhythmia radioablation; Stereotactic body radiotherapy

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A. Introduction

Data from prospective trials on stereotactic arrhythmia radioablation (STAR) for ventricular tachycardia (VT), also known as cardiac stereotactic body radiotherapy or cardiac radioablation, are continuously emerging. Through a multidisciplinary approach, STAR leverages precise delivery of high-dose radiotherapy to treat the proarrhythmic substrate, offering an alternative for patients who are ineligible for or who have failed ≥1 conventional catheter ablation procedures. Since the landmark Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia (ENCORE-VT) study,[1] STAR has been increasingly used for compassionate treatments and in early-phase prospective trials. However, the strategy of relying on noninvasive electrocardiographic imaging (ECGI) for localizing the radiotherapy target has not been widely accepted,[2] as few as 13% of European investigators self-report using ECGI for clinical purposes,[3] and the variability in treatment protocols and patient selection criteria highlights the need for harmonization.

Both the mechanism and the process of STAR treatment are complex. Initially, STAR was believed to create a conduction block by inducing transmural fibrosis and causing loss of myocyte architecture.[4] However, more recent research indicates that in its currently prescribed dose, STAR leads to functional cardiomyocyte reprogramming.[5] Intraprocedural compensation for the combination of cardiac and respiratory motion proved challenging as oncology-grade linear accelerators were not designed for simultaneous gating.[6,7] Then, the utilization of invasive electroanatomic mapping (EAM) necessitated adjustments of previously described ECGI workflow to ensure a proper coregistration of surface maps with radiotherapy planning computed tomography,[8] which led to the development of automated solutions.[9,10] Integrating several systems necessitated quality control to reduce the detrimental effect of data transfers on reproducibility.[11] STAR requires the establishment of new multidisciplinary teams and challenges the precision of both electrophysiological mapping and focused radiotherapy. Yet, in the 5 years after the ENCORE-VT trial,[1] many institutions contributed their own experience and solutions to the existing body of knowledge.

While multiple prospective studies on STAR have been published over the last year, there is a large heterogeneity in terms of treatment indications, workflows, and study methodologies, and a systematic synthesis of the available data has not been performed. Therefore, to give readers a better understanding of the clinical data from prospective trials on STAR, we conducted a systematic review and summarized the available evidence. Moreover, a meta-analysis was performed to quantify predefined efficacy and safety outcomes, including previously unpublished data retrieved specifically for this study.

B. Methods

The study complied with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, incorporating the PRISMA 2020 checklist (Online Supplemental File 1) and the PRISMA for Abstracts checklist (Online Supplemental File 2).[12] The PICOS framework was used to formulate the research question (Online Supplemental File 3). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023439666) before initiating the study.

B.1. Search strategy

We conducted searches in OVID Medline, OVID Embase, Web of Science Core Collection, the Cochrane Central Register of Controlled Trials, and Google Scholar search engine (top 200 hits) on November 9, 2023, for articles published until August 2023. No language or other restrictions were imposed. The search strategy was adapted from a previously published systematic review,[13] and a detailed description can be found in Online Supplemental File 4.

B.2. Study selection

We included original publications that describe the results of prospective trials investigating the use of STAR in treating VT. We excluded case reports, letters to the editor, commentaries, reviews, and preclinical or technical papers. Abstracts from major conferences were retrieved to screen for corresponding full-text publications. After deduplication was performed using the Rayyan platform (Qatar Computing Research Institute, Doha, Qatar),[14] abstract screening was independently conducted by 2 authors, followed by independent full-text screening by 2 authors. In both instances, any conflicts were resolved through mediation by a third author. A backward citation search was conducted to identify additional relevant studies.

B.3. Data extraction

Two authors independently extracted the data from studies using Google Sheets and Microsoft Excel software. Extracted data included details on the clinical characteristics of the patients, prior and current cardiological treatment, STAR planning, and radiotherapy delivery. The extracted end points included reduction of VT burden (overall and stratified by reaching 50%, 75%, and 95% reduction thresholds), 1-year overall survival, 1-year freedom from recurrence (FFR), 1-year recurrence-free survival (RFS), and rates of treatment-related grade ≥3 adverse events (AEs) in the first 90 days after STAR. AEs were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE)[15] or equivalent grade representing severe or medically significant AEs if another classification was used. Possibly, probably, or definitely related attribution was regarded as "treatment related" for the purpose of this review. If timing and attribution were not specified, but relevance could not be ruled out, the AE was conservatively designated as treatment related and as having occurred within 90 days of treatment. In the case of multiple records describing results of a single trial, the most recent data for a given end point were retrieved. WebPlotDigitizer software (v.4.6, Automeris LLC, Pacifica, CA) was used to retrieve data from figures.[16] If necessary, the corresponding authors were contacted to retrieve additional information. Any conflicts were resolved through mediation by a third author.

B.4. Quality assessment

The risk of bias was assessed independently by 2 authors using the Risk Of Bias In Non-randomized Studies of Interventions tool.[17] Conflicts were resolved through mediation by a third author.

B.5. Statistical analysis

For the purpose of meta-analysis, the rates of VT burden reduction, treatment-related grade ≥3 AEs in the 90 days after STAR, and probabilities of overall survival, RFS, and FFR were analyzed as proportions. For VT reduction and toxicity, the numerator was the number of patients experiencing a given end point. The overall survival, RFS, and FFR numerator were obtained by multiplying 1-year probability estimated using the Kaplan-Meier method by the total number of analyzed patients, rounding to the nearest integer. The denominator was the total number of patients in a given analysis. If the input values were not directly provided in the manuscript, individual patient data retrieved from the manuscript or through correspondence with the authors were used to calculate rates, or probabilities estimated using the Kaplan-Meier method.

Meta-analyses were performed using the generalized linear mixed model (GLMM) with the logit transformation as the measure of effect size, using the metaprop function in the metafor package with the method set to "GLMM" and summary measure set to "PLOGIT." Confidence intervals (CIs) for individual study results were calculated as exact binomial (Clopper-Pearson) intervals and with Hartung-Knapp adjustment. The logit-transformed rates were back-transformed to probabilities to facilitate interpretation of forest plots, which were used to present outcomes with 95% CIs for individual studies and meta-analytic averages. The forest plots presenting reductions in VT burden were further stratified into 2 groups to reflect different time periods used for VT burden reduction calculation. For toxicity and overall survival, sensitivity analysis was performed by excluding studies at high risk of bias.

Heterogeneity between studies was assessed using the Cochran Q test. Publication bias was assessed using funnel plots, and in cases where ≥10 studies were included in an analysis, the Peters linear regression test was used to assess plot asymmetry formally.

Statistical analyses were performed using R software v4.3.2 (R Foundation for Statistical Computing, Vienna, Austria), including "survival," "meta," and "metafor" packages. *P* values <.05 were considered significant. All tests were 2-sided.

C. Results

Out of the 1861 records initially retrieved, we identified 10 full-text manuscripts published between 2019 and 2023, describing the results of 10 prospective trials in which 84 patients were enrolled and 82 underwent treatment with STAR between 2016 and 2022. The PRISMA flowchart describing the search process is presented in Online Supplemental File 5, and basic study characteristics can be found in Table 1. Three trials were performed in the United States (39 patients),[1,18,19] 5 in Europe (n = 36),[20–24] and 2 in Asia (n = 9).[25,26] The majority of the trials were either single center (n = 63)[1,19–21,24–26] or bicentric (n = 16),[18,23] and only 1 trial was multicenter (n = 5).[22] Four publications reported on the final trial outcomes (n = 41),[1,18,23,24] 3 reported interim results (n = 16),[20,22,25] and 3 reported outcomes from prospective registries (n = 27).[19,21,26] Safety was included among primary study end points in all trials except for 1 prospective registry.[21] No controlled trials were identified. Additional data on efficacy outcomes were retrieved for 5 trials through correspondence with the authors.[1,21–24]

Most patients were male (n = 73 [87%]), with the median age of patients included in the studies ranging from 65 to 80 years. Two patients did not receive STAR because of declining health status after enrollment. A significant number of patients suffered from nonischemic cardiomyopathy (n = 32 [38%]), and 20 patients (24%) did not have catheter ablation before STAR. The median left ventricular ejection fraction (LVEF) ranged from 21% to 38% between studies, and in the majority of cases, the New York Heart Association functional class was II or III. A detailed description of clinical characteristics, including the use of antiarrhythmic drugs, can be found in Online Supplemental File 6.

All treated patients received a single dose of 25 Gy, in most cases delivered using a C-arm linear accelerator platform (n = 76 [93%]). There were noticeable differences in median irradiated volumes, which ranged from 52.2 to 198.3 cm^3 at the study level and from 17.5 to 372 cm^3 in individual patients. Similarly, modalities used to define target volumes significantly differed between studies; however, most authors used cardiac computed tomography and 12-lead cardiac electrocardiography. In each study, either EAM or ECGI was included in the process of defining the target volume. The procedural details of STAR are summarized in Online Supplemental File 7. In several cases, the authors refer to a separate article for treatment protocol[2,27–30] or quality assurance tools description.[9,10]

C.1. Risk of bias analysis

The results of the risk of bias analysis are presented in Online Supplemental File 8. One study was assessed as having a low risk of bias (n = 19),[1] and 7 studies had a moderate risk of bias (n = 52).[18–20,22–25] The majority of concerns regarded the domains of measurement bias and missing data and, less frequently, selection of participants or confounding. Two studies were assessed as having a serious risk of bias (n = 12).[21,26] In both cases, the concerns regarded the domain of quality of reporting (ie, efficacy outcomes), and in 1 case, also a domain of measurement bias.[21]

C.2. Toxicity

The data on treatment-related grade ≥3 AEs in the first 90 days after treatment were retrieved for every trial (Figure 1).

Table 1 Basic characteristics of studies included in the systematic review of prospective trials on cardiac stereotactic body radiation therapy

Study	Study registration	Study name abbreviation	Years of accrual	Study type	Study group (treated)	Median FU (mo)	Primary end point
Robinson et al[1]	NCT02919618	ENCORE-VT	2016–2018	Prospective trial; final results; single center	19	13	1. Safety: defined as the rate of treatment-related SAEs (CTCAE v4.0) in the first 90 d after STAR 2. Efficacy: defined as any reduction in the number of ICD treatments for VT or 24-h PVC burden comparing the 6-mo period before and after STAR, with a 6-wk blanking period
Gianni et al[18]	NCT02661048	CyberHeart Inc. -001	2018	Prospective trial; final results; bicentric	5	12*	1. Safety: defined as the rate of treatment-related SAEs (RTOG) in the first 12 mo after STAR
Carbucicchio et al[20]	NCT04066517	STRA-MI-VT	2019–2020	Prospective trial; interim analysis; single center	7	8	1. Safety: defined as the rate of treatment-related AEs during acute and long-term FU 2. Efficacy: defined as the reduction in VT episodes and ICD shocks at 3 and 6 mo after STAR
Molon et al[21]	n/a	n/a	2020–2021	Prospective registry; single center	6	9	1. Efficacy: defined as the reduction in arrhythmic burden after STAR on the basis of ICD readouts
Chang et al[26]	KCT0004302	HeartSABR	2019–2020	Prospective registry; single center	6	12.3	1. Efficacy: defined as the reduction in VT episodes and ICD therapies at 1 and 12 mo after STAR 2. Safety: defined as the assessment of any acute and late treatment-related AEs
Krug et al[22]	NCT03867747	RAVENTA	2019–2021	Prospective trial; interim analysis; multicenter	5	6	1. Feasibility of full-dose application 2. Safety: defined as the rate of treatment-related grade $\geq$3 SAEs in the first 30 d after STAR

Miszczyk et al[23]	NCT04642963	SMART-VT	2020–2022	Prospective trial; final results; bicentric	11	22.2	1. Safety: defined as the rate of treatment-related grade ≥3 AEs (CTCAE v5.0) in the first 90 d after STAR
van der Ree et al[24]	NL7510	STARNL-1	2019–2022	Prospective trial; final results; single center	6	12	1. Efficacy: defined as the reduction in treated VT episodes at 1 y after STAR or at the end of FU (excluding 6-wk blanking period) 2. Safety: defined as a decrease in LVEF, FEV1, or DLCO at 1 y after STAR
Amino et al[25]	jRCTs032190041	SRAT	2019–2021	Prospective trial; interim analysis; single center	3	6	1. Safety: defined as acute to late myocardial impairment, including systolic and/or diastolic cardiac dysfunction, pericarditis, pericardial effusion, myocardial ischemia, and heart failure 2. Efficacy: undefined
Arkles et al[19]	n/a	n/a	n/a	Prospective registry; single center	14	n/a	1. Efficacy: defined as the reduction in VT burden, ATP, and ICD shocks 2. Safety: undefined

AE = adverse event; ATP = antitachycardia pacing; CTCAE = Common Terminology Criteria for Adverse Events; DLCO = diffusing capacity of the lungs for carbon monoxide; FEV1 = forced expiratory volume in the first second; FU = follow-up; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; n/a = not applicable/available; PVC = premature ventricular contraction; RTOG = Radiation Therapy Oncology Group; SAE = serious adverse event; STAR = stereotactic arrhythmia radioablation; VT = ventricular tachycardia.
*Mean.

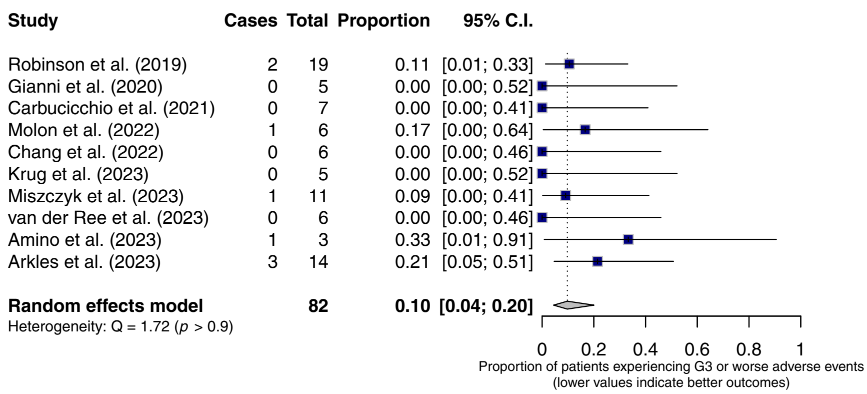

Figure 1
Rates of grade 3 (G3) or worse treatment-related adverse events in the first 90 days after stereotactic arrhythmia radioablation. CI = confidence interval.

The estimated rate was 0.1 (95% CI 0.04–0.2), and there was no significant heterogeneity. In total, 9 treatment-related grade ≥3 AEs were reported, including 4 grade 5 events, and the most common was heart failure (n = 6). Four studies (n = 23) reported no AEs of interest.[18,20,22,24] The individual descriptions of all possibly treatment-related AEs are presented in Online Supplemental File 9. There was no evidence of significant heterogeneity or publication bias (Online Supplemental File 10A).

C.3. Reduction in VT burden

The data on patients with a reduction in treated VT episodes equal to or greater than a threshold of 95%, 75%, or 50%, respectively, were retrieved for a total of 61 evaluable patients in 8 trials. Initially, the time frames and definitions used for VT burden reduction calculation varied significantly between studies; however, after harmonization, we could adjust the definitions (Table 2) and time frames for VT burden reduction calculation in most cases (Online Supplemental File 11A). The majority of patients experienced ≥95% VT burden reduction (Table 2). On the basis of the results of the meta-analysis, we estimated that the proportions of patients achieving a given VT burden reduction were 0.61 (95% CI 0.45–0.74), 0.80 (95% CI 0.62–0.91), and 0.9 (0.77–0.96) for ≥95%, ≥75%, and ≥50% thresholds, respectively, as presented in Online Supplemental Files 11B–D. Considering residual differences in methods of VT burden reduction calculation, the meta-analytic averages should be interpreted with caution. There was no evidence of significant heterogeneity.

C.4. Overall survival

The data on 1-year survival were retrieved for every trial, and the meta-analytic average of the 1-year overall survival rate was 0.73 (95% CI 0.61–0.83) (Figure 2). There was no evidence of significant heterogeneity or publication bias (Online Supplemental File 10B).

C.5. FFR

The data on FFR were available for 61 patients treated in 9 trials. The FFR was calculated from STAR until the first treated VT episode in 7 studies[1,20–25] and until the first treated or detected VT episode in the remaining 2 studies.[18,26] At 1 year, the rate of patients without recurrence was 0.30 (95% CI 0.16–0.49) (Online Supplemental File 12). There was no evidence of significant heterogeneity.

C.6. RFS

The data on the combined RFS end point were available for 60 patients treated in 8 trials (Figure 3). The RFS combined overall survival and FFR end points, which resulted in a 1-year rate of 0.21 (95% CI 0.08–0.46). There was no evidence of significant heterogeneity.

C.7. Reporting bias and sensitivity analyses

The funnel plots for all relevant analyses are presented in Supplementary File 10. In general, there was no significant evidence of reporting bias. To address the 2 studies assessed as having a serious risk of bias,[21,26] a sensitivity analysis was performed for the rate of grade ≥3 AEs and 1-year survival. In both cases, the estimations were comparable with the primary analyses; the rate of treatment-related grade ≥3 AEs remained at 0.1 (Online Supplemental File 13A), and the 1-year survival decreased by 0.01 to 0.72 (Online Supplemental File 13B). In addition, a table with input data for time-to-event analyses, including 1-year survival, FFR, and RFS probabilities as calculated in individual studies using the Kaplan-Meier method, is provided in Online Supplemental File 14.

D. Discussion

In this study, we present a synthesis of the available evidence on STAR for VT from prospective clinical trials, including an analysis of partially unpublished efficacy outcome data harmonized across studies. The present study showed the following primary findings. First, the data stem from small trials presenting a large methodological heterogeneity, in terms of both procedural characteristics and outcome reporting. Although the nominal prescribed dose was equal in all included studies, the details of target volume definition, integration with electrophysiological data, radiation therapy planning, and STAR delivery differ significantly. Second,

Table 2 Summary of the VT burden reduction in evaluable patients treated in prospective studies investigating STAR for the treatment of therapy-refractory VT

Study	N (evaluable)	VT burden definition used for this analysis	Adjusted time frame for VT burden reduction calculation	≥95% VT burden reduction, % (n)	≥75% VT burden reduction, % (n)	≥50% VT burden reduction, % (n)
Robinson et al[1]	18	ICD-treated VT episodes or 24-h PVC burden	6 mo before STAR compared with 6 mo after, excluding events in the first 6 wk	61% (11)	89% (16)	94% (17)
Molon et al[21,*]	5	ICD-treated VT episodes	6 mo before STAR compared with 6 mo after, excluding events in the first 4 wk	60% (3)	60% (3)	100% (5)
Amino et al[25]	3	Treated VT episodes	6 mo before STAR compared with 6 mo after, excluding events in the first 6 wk	67% (2)	67% (2)	67% (2)
Arkles et al[19]	12	Treated VT episodes	6 mo before STAR compared with 6 mo after, excluding events in the first 6 wk	75% (9)	83% (10)	83% (10)
van der Ree et al[24,*]	6	Treated VT episodes	6 mo before STAR compared with 6 mo after, excluding events in the first 6 wk	33% (2)	100% (6)	100% (6)
Gianni et al[18]	4[†]	ICD-treated VT episodes	3 mo before STAR compared with 6 mo after, excluding events in the first 3 mo	25% (1)	25% (1)	75% (3)
Carbucicchio et al[20]	4	ICD-treated VT/VF episodes	3 mo before STAR compared with 6 mo after, excluding events in the first 3 mo	50% (2)	100% (4)	100% (4)
Miszczyk et al[23,*]	9[†]	ICD-treated VT episodes	3 mo before STAR compared with 6 mo after, excluding events in the first 3 mo.	80% (8)	80% (8)	90% (9)
Chang et al[26]	0	n/a	n/a	n/a	n/a	n/a
Krug et al[22]	0	n/a	n/a	n/a	n/a	n/a

ICD = implantable cardioverter-defibrillator; n/a = not applicable/available; PVC = premature ventricular contraction; STAR = stereotactic arrhythmia radioablation; VF = ventricular fibrillation; VT = ventricular tachycardia.
*Additional data retrieved for this analysis through correspondence with the authors.
†One patient was excluded because of the lack of treated VT episodes during the pre-STAR period within the adjusted time frame.

periprocedural and short-term treatment-related AEs are rare in most studies, but data on long-term AEs are still scarce. Third, while mortality can be expected in this population of patients with advanced heart failure, the available data do not rule out a possible contribution of STAR. Fourth, although VT burden decreases significantly in most cases, recurrences are common, indicating that the efficacy of STAR cannot be well-described by either of these measures alone. STAR assumes the role of a temporary solution in the continuum of care for critically ill patients with advanced heart failure and recurrent VT refractory to other antiarrhythmic therapeutic options. Therefore, durable VT burden reduction could be sufficient to justify the treatment even in the case of residual arrhythmic events. Finally, to date, the efficacy and durability of the effect of STAR in the setting of patients with less complicated VT as a competitive treatment option to catheter ablation have not been assessed, and no data from controlled trials are available to date.

Notably, since the publication of the ENCORE-VT trial in 2019,[1] only 3 prospective trials (n = 22) were completed

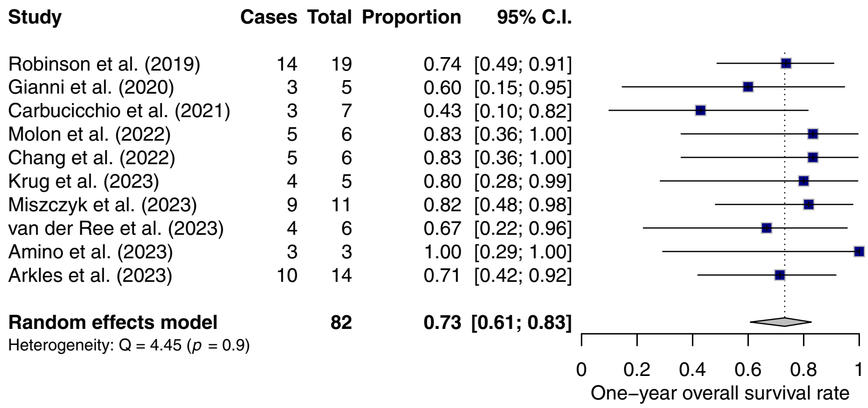

Figure 2
One-year overall survival after stereotactic arrhythmia radioablation. CI = confidence interval.

and published the primary outcome results.[18,23,24] The slow accrual might be associated with the strict inclusion criteria, limiting the application of STAR to critically ill patients suffering from refractory VT. Initially, STAR was proposed as an ECGI-guided noninvasive solution, performable even without a prior catheter ablation map.[2] However, few studies implemented ECGI in their clinical workflow,[20,21] and most authors relied on data from invasive EAM. In addition, out of a wide range of additional medical imaging techniques used, it remains unclear which are useful for target determination and for which patients.

Although all studies used both efficacy and safety end points, there is a large variability in outcome definitions, rendering comparisons difficult. First, the observation time frames, including the incorporated blanking periods, differ between studies. Second, implantable cardioverter-defibrillator (ICD) programming and arrhythmia annotation after STAR vary largely, and in some cases, were not reported. In particular, the programmed rates of the ICD monitor-only and antitachycardia pacing zones are of interest, because these patients often have slow VTs. We therefore encourage using predefined standardized ICD programming protocols after STAR in the setting of a clinical trial, preferably with a low detection zone to prevent missing VT recurrences.

The mortality of patients undergoing STAR was explored in a recently published pooled analysis of mostly retrospective studies.[31] Benali et al[31] estimated the 1-year mortality rate to be 32% (95% CI 23%–41%), which is statistically not different from the 27% (95% CI 17%–39%) estimate presented in our meta-analysis. The majority of deaths were attributable to worsening of heart failure (52%), followed by noncardiac mortality (41%). Very few patients died directly of VT recurrences.[31] In patients undergoing catheter ablation, baseline factors significantly influence short-term mortality, and there is a significant negative selection bias for STAR associated with the inclusion of patients who are either unfit for or refractory to catheter ablation. For instance, the 1-year mortality rate for patients with nonhemodynamically tolerated VT undergoing catheter ablation can be as high as 33% as compared with 11% in patients with hemodynamically tolerated VT.[32] Similarly, patients with a high PAINESD risk score exhibit a 1-year mortality of 28% as compared with 9% in patients with lower scores.[33] Nonetheless, heart failure remains the leading cause of death and should be reported carefully. For example, Robinson et al[1] reported that 8 of the 9 grade ≥3 heart failure events (89%) that occurred during a median follow-up of 13 months in 19 patients in the ENCORE-VT trial were treatment related. On the contrary, Miszczyk et al[23] reported that only 1 of the 8 grade ≥3 heart failure events (12%) that occurred during a median follow-up of 22 months in 11 patients were treatment related, and van der Ree et al[24] reported no such events during a median follow-up

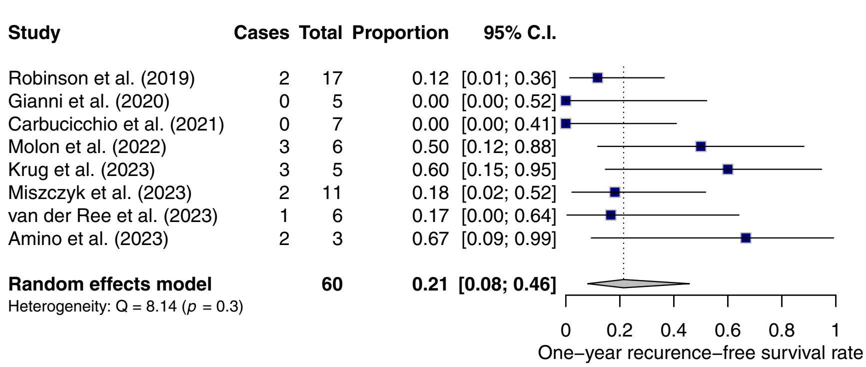

Figure 3
One-year recurrence-free survival after stereotactic arrhythmia radioablation. CI = confidence interval.

of 12 months in 6 patients. Such heterogeneity is possible but could also indicate different patterns of reporting AE attribution. It is known that recurrent VT can lead to rapid worsening of heart failure. Considering that recurrence rates are high in patients undergoing STAR, a valid argument can be made to classify such events as efficacy failure rather than possibly treatment-related AEs. Interestingly, an improvement in ventricular function after a low-dose whole-heart radiation therapy was recently reported in murine heart failure models[34] and in a subgroup of patients (n = 9) treated in the ENCORE-VT trial, who underwent repeated cardiac magnetic resonance imaging. Possible explanations for the latter include a reduction in VT burden and/or antiarrhythmic drugs. Irrespective of the interpretation, robust and transparent reporting and a conservative approach toward AE scoring are encouraged to avoid overlooking a possible contribution of STAR to mortality through cardiac toxicity (disguised as a natural course of advanced heart failure).

The efficacy of STAR is consistently reported as high, albeit not durable. This could be explained by the hypothesis that STAR's mechanism of action involves functional remodeling, leading to improved conduction velocity, rather than permanent morphological changes.[5,35] This theory is supported by reports of rapid onset of the antiarrhythmic effect and case reports of post-STAR explanted hearts in which, despite clinical efficacy, a transmural scar could not be identified.[5,36,37] However, a complementary function of $\geq$2 mechanisms leading to a durable ablative effect cannot be excluded,[38] and a recent report suggested another layer of complexity.[39] The authors claimed that while most of the 14 analyzed recurrences were located near the irradiated region, none appeared within the planning target volume. The limited intraobserver agreement in defining target volumes has been shown in preclinical studies, and it is possible that the persistence of the effect could be improved through improving quality control.[11] Moreover, while the subset of patients with extensive or closely located recurrences is unlikely to benefit from salvage STAR, remote substrates could be a target for retreatment.[40] As the risk of cumulative late toxicity is unknown, re-STAR should be considered experimental and performed accordingly. While short-term treatment-related cardiac toxicity in the included studies was moderate, there is significant confounding associated with the progressive concomitant heart disease to which many AEs are attributed. Several authors elaborated on this subject; for example, van der Ree et al[41] analyzed a single institutional database to assess LVEF and valve function. In long-term follow-up, the authors found no significant LVEF alteration but a pattern of worsening of valve function. On the contrary, despite many initial concerns, STAR does not seem to lead to clinically relevant ICD malfunctions.[23,42] Nonetheless, data on long-term toxicity remain scarce, as most studies reported only short-term toxicity. Reporting of long-term results is necessary.

There are several limitations to our study. First, the relatively homogeneous study population limits the generalizability of our results, particularly for young patients, females, and individuals without heart failure. There is also little evidence of the efficacy and safety of STAR in patients with premature ventricular contractions, and the efficacy and safety of STAR in patients with primary arrhythmia syndromes remains largely unaddressed. Second, the follow-up period is moderately short. The increasing popularity of STAR might lead to inclusion of patients with longer life expectancy. In such cases, inconsistent AE reporting and lack of data on long-term events could lead to underestimation of treatment toxicity. Third, pooling data from low-volume, single-arm trials limits our capacity to compare efficacy with standard-of-care treatments, and introduces significant procedural heterogeneity, as well as risk of bias due to selective reporting. It is important to acknowledge that the effect of STAR may be overestimated because of regression toward the mean. Accordingly, as patients are often qualified for STAR at peak VT burden, it is likely that some degree of reduction would be observed regardless of intervention. Despite including prospective studies performed under predefined local protocols and standardized institutional workflows, the present analysis summarizes the best evidence, pending data from randomized clinical trials. Lastly, despite contacting the corresponding authors, we were not able to obtain data for the primary outcomes for all included studies. Most of the limitations of these data are currently being addressed by the ongoing Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary consortium (ie, the lack of standardization) and the Cardiac RADIoablation Versus Repeat Catheter Ablation: a Pivotal Randomized Clinical Trial Evaluating Safety and Efficacy for Patients With High-risk Refractory Ventricular Tachycardia randomized controlled trial (ClinicalTrials.gov identifier NCT05765175; ie, the lack of controlled trials).

Conclusion

STAR is a promising treatment modality aimed to help patients suffering from VT refractory to standard-of-care treatment. The treatment is associated with moderate toxicity, with approximately 10% rate of early ($\leq$90 days) treatment-related grade $\geq$3 AEs. We observed 1-year mortality of $\approx$27% in this critically ill patient population suffering from refractory VT. Despite high 1-year recurrence rates, most patients experienced a marked reduction in VT burden. This highlights the necessity for comprehensive metrics to accurately represent the clinical outcomes of STAR.

Given the largely unexplored late toxicity and the absence of comparative data, STAR should still be regarded as an investigational treatment method and offered to patients primarily within the context of well-designed prospective trials.

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