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CLINICAL RESEARCH
Ventricular arrhythmias

Non-invasive stereotactic arrhythmia radiotherapy for ventricular tachycardia: results of the prospective STARNL-1 trial

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Aims Stereotactic arrhythmia radiotherapy (STAR) is suggested as potentially effective and safe treatment for patients with therapy-refractory ventricular tachycardia (VT). However, the current prospective knowledge base and experience with STAR is limited. In this study we aimed to prospectively evaluate the efficacy and safety of STAR.

Methods and results The StereoTactic Arrhythmia Radiotherapy in the Netherlands no.1 was a pre-post intervention study to prospectively evaluate efficacy and safety of STAR. In patients with therapy-refractory VT, the pro-arrhythmic region was treated with a 25 Gy single radiotherapy fraction. The main efficacy measure was a reduction in the number of treated VT-episodes by ≥50%, comparing the 12 months before and after treatment (or end of follow-up, excluding a 6-week blanking period). The study was deemed positive when ≥50% of patients would meet this criterion. Safety evaluation included left ventricular ejection fraction, pulmonary function, and adverse events. Six male patients with an ischaemic cardiomyopathy were enrolled, and median age was 73 years (range 54–83). Median left ventricular ejection fraction was 38% (range 24–52). The median planning target volume was 187 mL (range 93–372). Four (67%) patients completed the 12-month follow-up, and two patients died (not STAR related) during follow-up. The main efficacy measure of ≥50% reduction in treated VT-episodes at the end of follow-up was achieved in four patients (67%). The median number of treated VT-episodes was reduced by 87%. No reduction in left ventricular ejection fraction or pulmonary function was observed. No treatment related serious adverse events occurred.

Conclusions STAR resulted in a ≥ 50% reduction in treated VT-episodes in 4/6 (67%) patients. No reduction in cardiac and pulmonary function nor treatment-related serious adverse events were observed during follow-up.

Clinical trial registration Netherlands Trial Register—NL7510.

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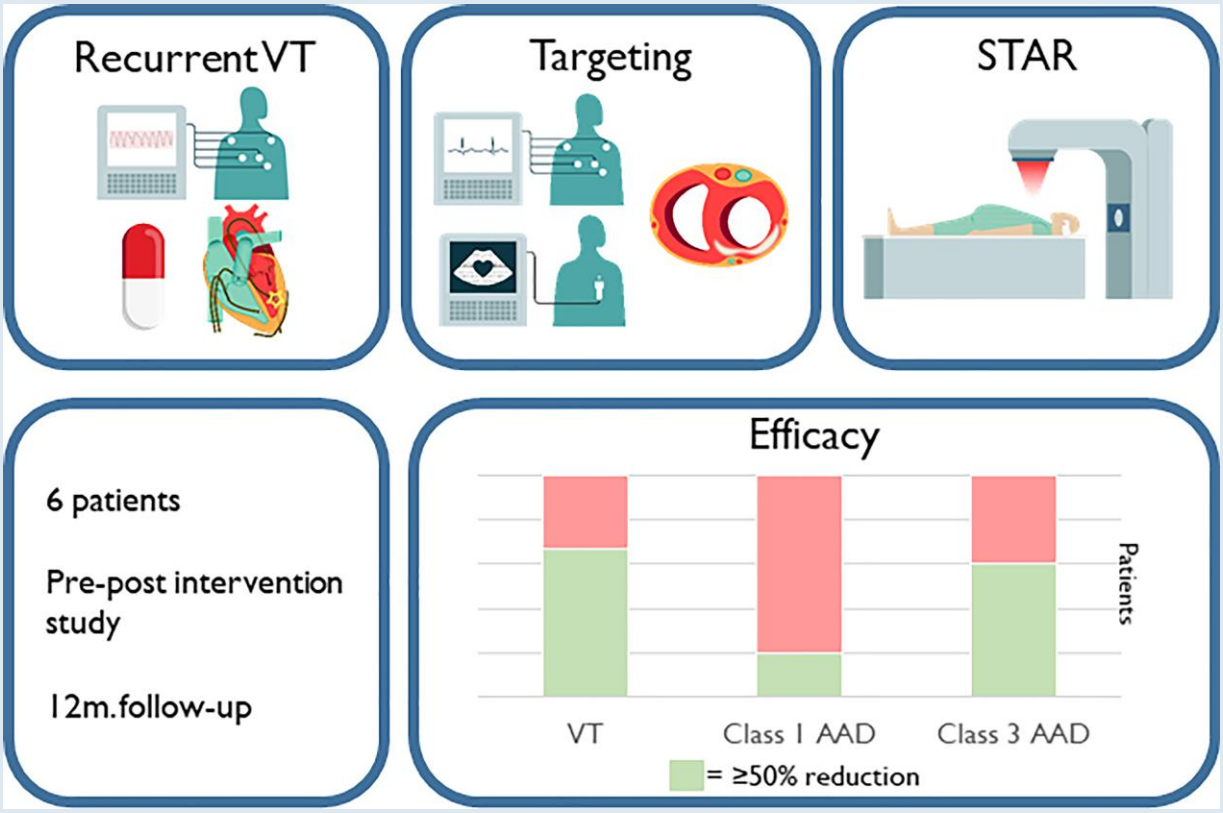
Graphical Abstract



Shown is the summary of the methodology and the primary and secondary efficacy measures. In green, the proportion of patients meeting the ≥50% cut-off criteria. AAD, antiarrhythmic drugs; STAR, stereotactic arrhythmia radiotherapy; VT, ventricular tachycardia.

Keywords Cardiac radioablation • Stereotactic arrhythmia radiotherapy • Ventricular tachycardia • Non-invasive • Stereotactic radiotherapy

What's new?

- The StereoTactic Arrhythmia Radiotherapy in the Netherlands no.1 (STARNL-1) trial is the first completed prospective trial in Europe.
- Results from the prospective STARNL-1 trial reproduces the efficacy and safety results from the Electrophysiology-Guided Non-invasive Cardiac Radioablation for Ventricular Tachycardia trial.
- Stereotactic arrhythmia radiotherapy did not result in a reduction in left ventricular ejection fraction or pulmonary function.

Introduction

Ventricular tachycardia (VT) and ventricular fibrillation (VF) pose a direct threat to patients and increases the risk of mortality and morbidity. Consequently, VT/VF is associated with both a reduction in quality of life and in a high and costly health care consumption.[1] In patients at risk for VT/VF, an implantable cardioverter defibrillator (ICD) is advised which is able to terminate this life-threatening arrhythmia.[2,3] Prevention of VT/VF recurrence consists of anti-arrhythmic drugs and/or invasive catheter ablation.[2–4] Anti-arrhythmic drugs may, however, lack sufficient efficacy and may lead to serious side effects and toxicity.[5,6] Multiple trials showed that invasive VT catheter ablation can be employed to disrupt the pro-arrhythmic ventricular substrate.[7] However, of all invasive arrhythmia ablation, VT ablation has the lowest success rate.[6,8,9] Patients who fail these conventional therapies are considered 'therapy-refractory' and the remaining treatment strategy for these patients is still undecided while their quality of life further diminishes and morbidity, health care consumption and risk of mortality further increases.[10]

Stereotactic arrhythmia radiotherapy (STAR) or cardiac radioablation has evolved as a new and promising treatment modality for patients with therapy-refractory VT.[11] STAR is a non-invasive treatment in which high doses of radiation are used to precisely 'ablate' the determined pro-arrhythmic ventricular substrate.[12] This pro-arrhythmic substrate is determined based on electro-anatomical information including VT ECGs, results of electrophysiological mapping, and cardiac imaging.[13] The delivered radiation dose appears to induce electrophysiological changes altering the pro-arrhythmic substrate.[11,14,15] Clinical experience of STAR is very limited but is steadily growing since the first reports in 2014–2015.[11,16,17] Evidence regarding efficacy and safety is mainly based on case reports and case series,[12,16,18–21] and evidence based on completed prospective trials is scarce ($n = 22$ patients).[22,23] More prospective trials evaluating STAR are thus needed to confirm the promising results.

Therefore, the StereoTactic Arrhythmia Radiotherapy in the Netherlands no.1 (STARNL-1) trial was designed in order to prospectively evaluate efficacy and safety of STAR. In this contribution, the main results of the STARNL-1 trial are presented.

Methods

Trial design

The STARNL-1 trial was a prospective monocentre single-arm pre-post intervention study (Netherlands Trial Register: NL7510). The local institutional ethical review board approved the study. An independent Data and Safety Monitoring Board semi-annually reviewed study efficacy and safety data, including stopping rules, and provided recommendations on study continuation. All patients provided signed informed consent for trial participation. The study data are available from the corresponding author on reasonable request.

Table 1 Patient demographics

Variable	$N = 6$
Male, *n* (%)	6 (100)
Median age, years (range)	73 (54–83)
Median body mass index, kg/m^2 (range)	28 (23–39)
Diabetes mellitus type 2, *n* (%)	1 (17)
Chronic kidney disease, stage ≥3, *n* (%)	3 (50)
Hypertension, *n* (%)	4 (67)
Peripheral arterial vascular disease, *n* (%)	3 (50)
Atrial fibrillation, *n* (%)	4 (67)
Prior cardiac surgery, *n* (%)	3 (50)
Prior amiodarone pulmonary toxicity, *n* (%)	1 (17)
Type of cardiomyopathy	
Ischaemic cardiomyopathy, *n* (%)	6 (100)
Median left ventricular ejection fraction, % (range)	38 (24–52)
NYHA class, *n* (%)	
II	3 (50)
III	3 (50)
Anti-arrhythmic drugs pre-treatment	
Amiodarone and mexiletine combination therapy, *n* (%)	4 (67)
Amiodarone, *n* (%)	5 (83)
Median daily dose, mg (range)[a]	400 (200–400)
High-dose amiodarone, ≥ 300 mg/day, *n* (%)[a]	4 (80)
Low-dose amiodarone, < 300 mg/day, *n* (%)[a]	1 (20)
Mexiletine, *n* (%)	5 (83)
Median daily dose, mg (range)[a]	600 (300–1000)
High-dose mexiletine, ≥ 600 mg/day, *n* (%)[a]	4 (80)
Low-dose mexiletine, < 600 mg/day, *n* (%)[a]	1 (20)
β-blocker, *n* (%)	6 (100)
Catheter ablation	
Previous catheter ablation, *n* (%)	6 (100)
Median number of catheter ablations, *n* (range)	2 (1–5)
Total number of prior catheter ablation approaches, *n*	12
Endocardial, *n*	10
Epicardial, *n*	2
Implantable cardioverter defibrillator, *n* (%)	6 (100)

[a]Of patients on this type of medication.

Patients

Patients were eligible if they were >18 years of age, had an ICD implanted, were capable of limited self-care according to the Eastern Cooperative Oncology Group performance status, and had therapy-refractory VT.[24] Therapy-refractory VT was defined as the occurrence of ≥3 treated VT-episodes {ICD-treated [antitachycardia pacing (ATP) or cardioversion/shocks], external cardioversion/defibrillation or i.v. administration of anti-arrhythmic drugs for VT conversion} within 3 months before enrolment, and recurrence of VT after failure of, or intolerance to, at least one class 1 or class 3 anti-arrhythmic drug and at least one catheter ablation [or considered unsuitable for a (repeat) procedure, e.g. epicardial substrate and previous thoracic surgery]. Patients were ineligible when they had a history of radiation treatment in the thorax or upper abdominal region, suffered from interstitial pulmonary disease, chronic kidney disease grade 4–5 or were pregnant. Patients who died during the study follow-up were not replaced.

Study procedures

At baseline, patients underwent 12-lead ECGs, ICD readouts, laboratory tests, echocardiography, pulmonary function tests and the Short Form-36 quality of life questionnaire. ICDs were reprogrammed with a low monitor-only and/or low ATP-only zone to document and treat the potential occurrence of slow VTs (see Supplemental material online). Radiation treatment was performed according to standard stereotactic oncological radiotherapy techniques with additional heart rhythm monitoring. After treatment, patients were admitted to the cardiac care unit for at least 24 h with telemetric observation. For safety evaluations, (repeated) 12-lead ECGs and laboratory tests, ICD readout and echocardiography were performed. Subsequent study visits occurred at 1, 3, 6, and 12 months after treatment. During each study visit, ICD readouts and 12-lead ECGs were performed. Additionally, at the 3- and 12-month study visit, the laboratory tests, echocardiography, pulmonary function tests, and Short Form-36 quality of life questionnaires were repeated. During every study visit, a reduction in the daily dose of antiarrhythmic drugs was considered; amiodarone was tapered off prior to mexiletine reduction due to its potential (long-term) toxicity. The occurrence of adverse events was continuously evaluated (see below).

Targeting and treatment

For targeting, all available electro-anatomical information was used. This included VT exit sites from 12-lead VT ECGs,[25] maps from previous invasive electrophysiology studies and cardiac imaging modalities such as echocardiograms (including deformation imaging), computed tomography (CT) scans, nuclear imaging, and magnetic resonance imaging (MRI). The optimal targeting strategy depended on patient characteristics (e.g. MRI incompatible ICD) and determined in our multidisciplinary STAR team including cardiologist-electrophysiologist(s), imaging cardiologist(s), radiologist(s), and radiation oncologist(s). Targeting was guided by the American Heart Association 17-segment model.[26,27] All patients underwent a 4D-CT for radiotherapy treatment planning purposes (slice thickness 2.5 mm, Revolution CT, GE Healthcare). To aid anatomic orientation on the radiotherapy planning system, semi-automatic angulation and segmentation was performed as previously described.[14] The clinical target volume (CTV) was delineated by a cardiologist-electrophysiologist in close collaboration with other members of the STAR team. Subsequently, an internal target volume (ITV) was created to correct for cardiorespiratory motion based on the 4D-CT. The ITV was then isotropically expanded with a 5 mm uncertainty margin creating the planning target volume (PTV) to which a radiation dose of 25 Gy was prescribed. For all patients a three-arc Volumetric-Modulated Arc Therapy stereotactic treatment plan was created in which 95% of the PTV received at least 100% of the prescribed dose and dose escalation in the ITV up to 140% of the prescribed dose was allowed (RayStation 9A, RaySearch, Sweden). If organ at risk dose constraints as described by Benedict *et al.*[28] could not be satisfied regional underdosage of the PTV was accepted. All patients were treated on the Agility™ linear accelerator

(Elekta, Sweden) and no intensive immobilization system to reduce motion during treatment was used.

Outcome measures

Efficacy

The main efficacy measure was a reduction in the number of treated VT-episodes by ≥50% at 1 year after treatment compared to the year before treatment or end of follow-up (excluding events in a 6-week blanking period). Additionally, the occurrence and change percentages were evaluated for treated VT-episodes, non-treated sustained VT-episodes, and electrical cardioversions/shocks. For patients who died within the study follow-up, the period from treatment until death was compared to a pre-treatment period of the same size (e.g. 7 months post-treatment vs. 7 months pre-treatment). Episodes of VT were annotated according to a predefined definition available in the Supplementary material online. The secondary efficacy measure was a ≥ 50% reduction in daily dose class 1 (mexiletine) and/or 3 (amiodarone) anti-arrhythmic drugs at the end of follow-up compared to pre-treatment. The study was deemed positive with ≥50% of patients meeting the abovementioned ≥50% cut-off criterion for treated VT-episodes.

Safety

The main safety measure for adverse cardiac effects was a > 25% relative decrease in left ventricular ejection fraction (LVEF) measured by echocardiography at 1 year after treatment compared to baseline. The main safety measure for adverse pulmonary effects was a > 25% relative decrease in forced expiratory volume in 1 s (FEV1) or diffusing capacity (DLCOc) measured by pulmonary function tests at 1 year after treatment compared to baseline. Main safety analyses included only patients who completed the study follow-up, yet all available data is presented. Safety analysis also included evaluation and synthesis of adverse events according to the Common Terminology Criteria for Adverse Events (s version 5.0), with treatment relatedness (not, unlikely, possibly, probable, or definite treatment-related) scored conservatively by the research team.

Table 2 Targeting and treatment characteristics

Variable	*n* = 6
Available targeting data	
Clinical VT	
Median number of ICD VT morphologies (range)	9 (3–14)
12-lead VT ECG, *n* (%)	6 (100)
Median number of VT exit site segments (range)	4 (1–6)
Invasive electrophysiological maps, *n* (%)	6 (100)
Cardiac CT scan, *n* (%)	6 (100)
Cardiac MRI, *n* (%)	4 (67)
Nuclear scan, *n* (%)	1 (17)
Treatment characteristics	
Median target volumes, ml (range)	
Clinical target volume	46 (15–87)
Internal target volume	77 (41–211)
Planning target volume	187 (93–372)
Median stereotactic body radiotherapy beam-on time, s (range)	277 (217–313)
Median number of left ventricle segments receiving a mean cut-off dose, *n* (range)	
≥15 Gy	8 (3–12)
≥20 Gy	8 (2–10)
≥25 Gy	5 (1–8)
≥30 Gy	1 (0–2)

CT, computed tomography; ECG, electrocardiogram; ICD, Implantable cardioverter defibrillator; MRI, magnetic resonance imaging; VT, ventricular tachycardia

Statistical analysis

Sample size calculations were based on the main efficacy measure and performed using a paired samples *t*-test. Based on previous data, a reduction of 80% for treated VT-episodes was expected. For this study, we considered the number of events at a mean of 25 episodes before treatment, and 5 episodes after treatment with a standard deviation of the difference of 13. To provide a high degree of confidence (power 80%) and a significance level of 5%, a sample size of 6 patients was consequently determined. Medians and ranges are used to present continuous variables. To compare paired data (i.e. VT-episodes), the Wilcoxon signed-rank test was used. The study was not powered to evaluate significant changes in daily doses of anti-arrhythmic drugs, LVEF, FEV1, DLCOc and mean results of the Short Form-36 quality of life questionnaires, therefore significance levels are not reported for these evaluations. Statistical analysis was performed with SPSS Statistics (version 26.0, IBM Corporation, Armonk, NY USA) and MedCalc (version 18.5, MedCalc Software, Ostend, Belgium).

Results

Patient population

Table 1 summarizes the patient demographics. From 2019 to 2022, six consecutive patients with a median age of 73 years (range 54–83) were included. All patients were male and suffered from ischaemic cardiomyopathy with a median left ventricle ejection fraction of 38% (range 24–52) resulting in New York Heart Association (NYHA) class II-III functional symptoms. All patients underwent a previous catheter ablation with a median number of 2 (range 1–5) ablations per patient. Amiodarone plus mexiletine combination therapy was used by four patients (67%). One patient (17%) did not use amiodarone due to prior severe amiodarone pulmonary toxicity.

Targeting and treatment

Table 2 describes the targeting and treatment characteristics. From all patients (*n* = 6, 100%), 12-lead VT electrocardiograms, prior invasive electrophysiological maps and cardiac CT scans were used for targeting. The median number of documented VT exit sites was 4 (range 1–6). The median clinical target volume was 46 mL (range 15–87) resulting in a median planning target volume of 187 mL (range 93–372). Beam-on time was in all patients below 6 min. Per patient, the median number of segments receiving mean doses of ≥25 Gy and ≥30 Gy were 5 (range 1–8) and 1 (range 0–2), respectively.

Follow-up

Follow-up was completed by 4 (67%) of the patients, two patients (33%, P1 and P3) died during the follow-up period of 12 months. Both patients died from non-cardiac causes unlikely related to treatment at 7 and 11 months after treatment respectively and are discussed in the survival section (see details below).

Efficacy

Ventricular tachycardia

The main efficacy measure of ≥50% reduction in treated VT-episodes was achieved in four patients (67%), as outlined in the *Graphical Abstract* and *Figure 1*. The median number of treated VT-episodes reduced from 31 (range 8–138) before treatment to 9 (range 0–109) after treatment, resulting in a median change of −87% (*Figure 1A*, *P* = 0.075). During the blanking period, 34 treated VT episodes occurred with a median of 1

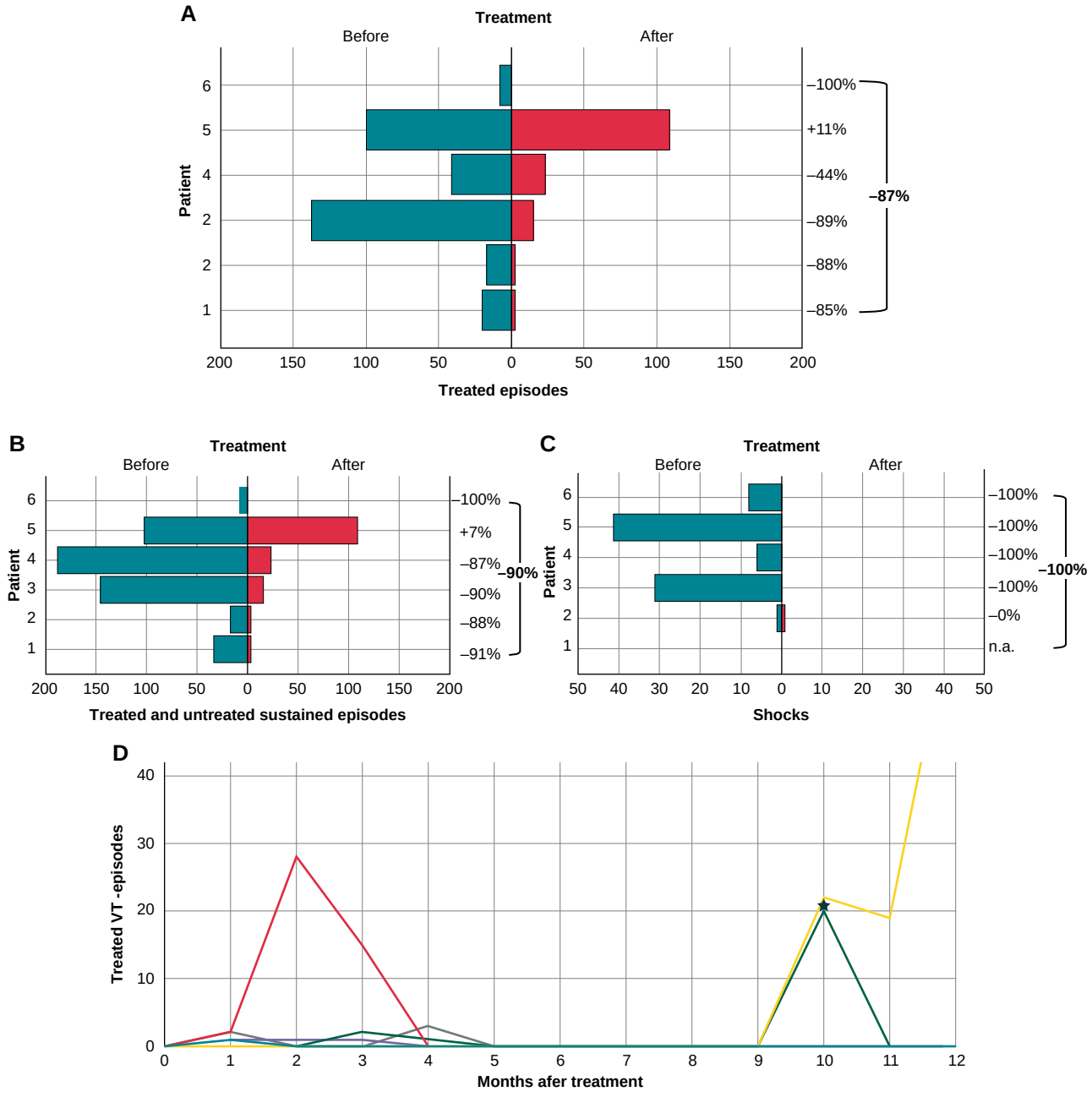


Figure 1 Overview of treatment efficacy. The number of episodes is outlined per patient before and after treatment including the individual and median change percentages for (*A*) treated VT episodes, (*B*) treated and untreated sustained VT-episodes, and (*C*) shocks. (*D*) Number of treated VT episodes in the months after treatment (including events in the blanking period). One patient (dark blue) received an additional invasive catheter ablation at 10 months after treatment as indicated by the star. Throughout *Figure 1D* and *2A–C*, the same colour coding is used for the individual patient. VT, ventricular tachycardia.

(range 0–30) per patient. Recurrences did occur in five (83%) patients. For the combination of treated plus sustained but non-treated VT-episodes, the median number of episodes reduced from 68 (range 8–188) to 9 (range 0–109) with a subsequent median significant change percentage of −88% (*Figure 1B*, $P = 0.046$). After treatment, only 1 ICD shock occurred resulting in a median change of 100% (*Figure 1C*). Recurrences occurred in 5 (83%) patients. From one patient (P1), a 12-lead electrocardiogram (ECG) of a VT occurring in the blanking period was available and showed VT exit side in a segment adjacent to the area targeted by STAR. Two other patients (P4 and 5) had 12-lead ECGs available from recurrences after the blanking period VT exit sites were located adjacent to, or in the targeted segments. In one of those patients (P5) an additional invasive catheter ablation was successfully performed at 10 months after treatment. *Figure 1D* shows the number of treated VTs per month (including events the blanking period) for every patient. The timing of VT recurrence varied

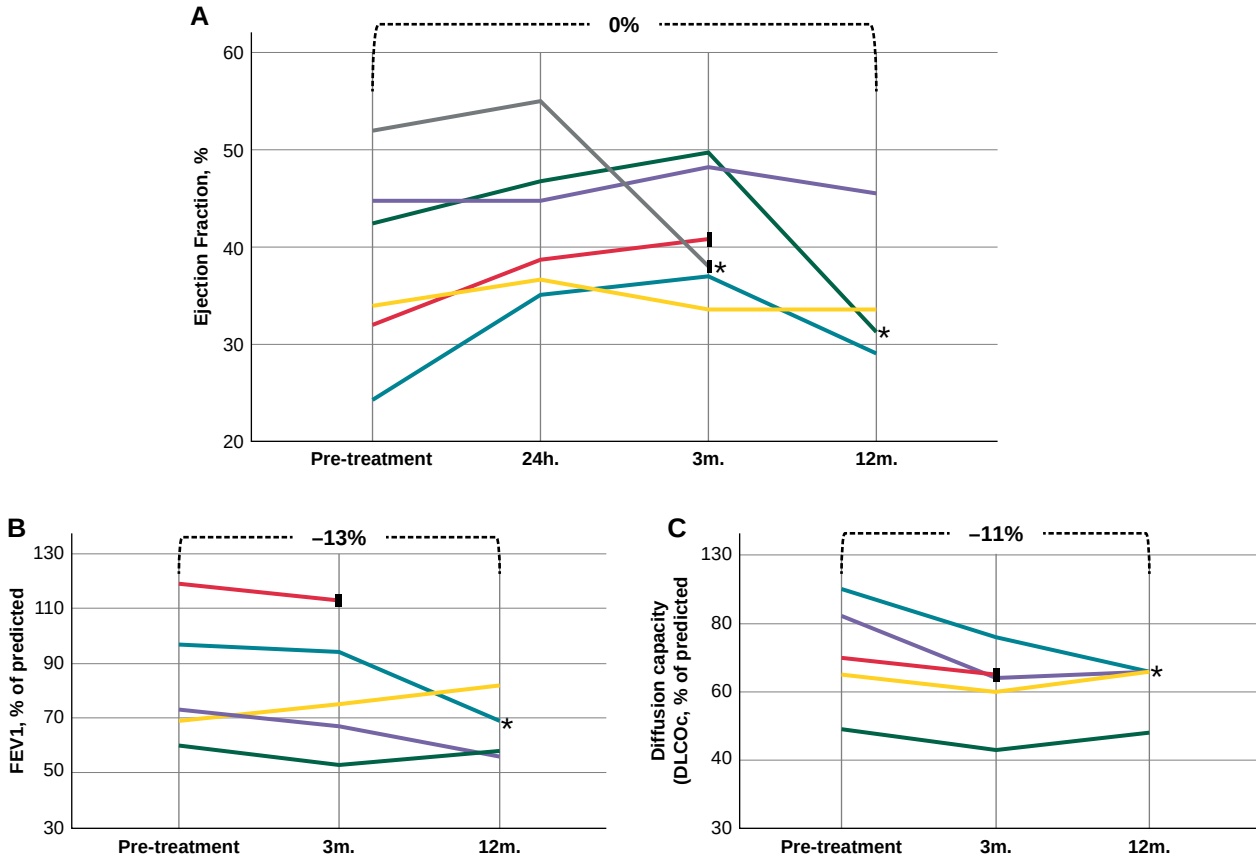


Figure 2 Overview of the main safety measure results. (*A*) The left ventricular ejection fraction, (*B*) FEV1, and (*C*) the DLCOc) over time. The '%' indicates the median percentage change comparing pre-treatment to 12-months for the patients completing the 12 month follow-up. The vertical black line indicates the death of a patient. *≥25% reduction. Throughout *Figure 1D* and *2A–C*, the same colour coding is used for the individual patient. DLCOc, diffusion capacity; FEV1, forced expiratory volume in 1 s.

per patient and was either early, mostly in the blanking period, or late in the follow-up when anti-arrhythmic drugs were tapered off.

Antiarrhythmic drugs

The secondary efficacy measure was a ≥ 50% reduction in daily dose class 1 (mexiletine) and/or 3 (amiodarone) anti-arrhythmic drug (*Graphical Abstract*). In three of the six (50%) patients, at least one of the anti-arrhythmic drugs was reduced by 50% at the end of follow-up. Five patients were on amiodarone pre-treatment, in three (60%) of those patients the daily dose was reduced by ≥50% at the end of follow-up [median change −93% (range −100 to 0)]. In one (20%) of five the patients on mexiletine pre-treatment, the daily dose was reduced ≥50% [median reduction: 0% (range −60 to +33)].

Safety

In *Figure 2*, the results of the main safety measures are presented.

Left ventricular ejection fraction

Left ventricular ejection fraction did not worsen. During the study [relative change +12% (−26 to +52)] and 12 months after treatment for patients completing the 12-month follow-up [relative change 0% (range −26 to +19), $n = 4$]. In two (33%) patients, a relative reduction percentage of ≥25% was observed (*Figure 2A*).

Pulmonary function tests

The parameters for pulmonary function tests, FEV1 and DLCOc, were slightly reduced (*Figure 2B* and *C*). In one patient a reduction of ≥25% was observed for both FEV1 and DLCOc, this patient was recovering from a COVID-19 infection 3 weeks prior to the test. For FEV1, the median change at 3 months was −5% (range −12 to +9, $n = 5$) and −12% (range −22 to −7, $n = 5$) for DLCOc. At 12 months, for the three patients completing the 12-month follow up, the change was −13% (range −29 to +19) for FEV1 and −11% (range −27 to 0) for DLCOc.

Adverse events

Table 3 shows an overview of the occurrence of possibly, probable and definite, STAR-related adverse events. Predefined safety stopping rules were not met. No possibly, probable or definite treatment-related serious adverse event occurred.

Adverse events ≤90 days

During treatment, the only adverse event that occurred was a radiation therapy-induced electrical reset of the ICD in one patient (P6) which was resolved by restoring previous settings. After treatment, three (50%) patients experienced fatigue. In most patients ($n = 5$, 83%), compared to pre-treatment, the NT-ProBNP was increased after 24 h. However, no symptoms or signs of (progression of) heart failure were observed. In one patient (P4), an episode of asymptomatic

Table 3 Possibly, probable and definite treatment-related adverse events

Adverse event	Number of occurrences				
	CTCAE grade				
	1 Mild	2 Moderate	3 Severe	4 Life-threatening	5 Death
≤90 days					
Alanine aminotransferase increased	1				
Alkaline phosphatase increased	1				
Aspartate aminotransferase increased	2				
Chest wall pain	2				
Fatigue	3				
ICD reset		1			
Malaise	1				
Myocardial injury		1			
NT-ProBNP increased	5				
Non-cardiac chest pain	1				
Pericardial effusion		1			
Pneumonitis		1			
Thrombocytopenia	1				
>90 days					
Chest wall pain	1		1		
Intracardiac thrombus		1			
Pericardial effusion		2			
Pneumonitis	1				

ICD, implantable cardioverter defibrillator.

transient myocardial damage was observed within hours after treatment with increased troponin levels and ST segment changes in the inferior leads corresponding to the irradiated area which resolved after two days. In another patient (P1), asymptomatic pericardial effusion was observed 24 h after treatment which was managed conservatively and resolved after 6 days. In this same patient (P1), 56 days after treatment, whilst the patient was on low-dose amiodarone, a pneumonitis occurred which resolved after steroid treatment.

Adverse events >90 days

During the follow-up, two patients (P1 and P6) showed pericardial effusion after 97– and 211-days respectively. In both patients no invasive measures were taken. In one patient (P1), pericardial effusion was resolved at a follow-up echocardiogram 1 month later. In the other patient (P6), it was still asymptomatically present at the end of follow-up whilst receiving colchicine. In one patient (P2) after 133 days left thoracic chest wall pain developed which corresponded to the irradiated field. The patient was treated with steroids and a cervical nerve root block with good results; however, mild symptoms were still present at the end of follow-up (CTCAE grade 3). Lastly, prior to death, in one patient (P3) an intracardiac thrombus, possibly radiation related, was observed. More details on this are presented in the survival section.

Survival

Two (33%) patients deceased during the study follow-up of non-cardiac causes. In both cases, no ventricular arrhythmias occurred in the period before death.

One patient (P1) died because of aspiration 7 months after treatment. This patient had a history of peripheral artery disease and a pre-existent ulcer at his foot prior to treatment, which eventually progressed to gangrene and requiring a lower leg amputation 6 months after treatment. After discharge, there was progressive cognitive decline and the patient died from aspiration. There were no signs of (post-operative) infection or heart failure.

The other patient (P3) died because of progressive respiratory failure unlikely related to radiotherapy at 11 months after treatment. This patient had initially mild but later progressive coughing and dyspnoea. Laboratory tests showed elevated infection parameters and blood cultures revealed a streptococcus parasanguinis. COVID-19 was ruled out. Thoracic CT scan showed pulmonary abnormalities suggestive for pneumonitis mainly in the right lung (which did not correspond with the dose distribution of the radiotherapy, mean right lung dose 0.8 Gy compared to mean left lung dose of 3.2 Gy). Pulmonary embolism was ruled out. Amiodarone-induced pulmonary toxicity with co-infection was suspected, and oxygen therapy, intravenous steroids, and antibiotics were started. Echocardiography revealed no signs of endocarditis, but an intracardiac thrombus as incidental finding wherefore anticoagulation was started and without clinical sequela (possibly radiation related, CTCAE grade 3, see above). Additional diagnostic imaging for endocarditis was not performed due to rapid progression of the respiratory failure. Despite extensive (supportive) treatment, dyspnoea and coughing progressed and the patient eventually opted for palliative sedation. Autopsy revealed diffuse alveolar pulmonary damage and the cardiac thrombus showed a small area of infiltration with lymphocytes and granulocytes, suggestive of

endocarditis, but no evidence of bacteria or yeast. In multi-disciplinary consultations, the respiratory failure was concluded to be probably related to amiodarone toxicity (albeit without classical foamy macrophages) in combination with infection, but radiation induced pneumonitis was deemed unlikely as the radiation dose to the affected areas of the lungs was very low. During the course of the disease, no VTs occurred.

Patient-reported quality of life

Patient reported quality of life questionnaires revealed improved quality of life in eight of nine domains (89%) at 12 months follow-up for patients completing the follow-up ($n = 4$) (see Supplementary material online, *Figure S1*). Both summary scale scores improved; a median improvement +68% (range: + 21 to +121) was observed for the mental component summary and +13% (range: −6 to +27) for the physical component summary

Discussion

Our prospective STARNL-1 trial shows the effectiveness and safety of STAR in six patients with therapy-refractory recurrent VT. The positive study result was achieved for the predefined efficacy measure: in most patients the number of treated VT-episodes reduced by ≥50%, whilst class three anti-arrhythmic drugs were simultaneously tapered-off (*Graphical Abstract*). Safety results were also promising, both the main cardiac and pulmonary safety measures were not exceeded, and no treatment related serious adverse events occurred, although several adverse events occurred. These results support the role of STAR in patients with therapy-refractory VT and are in line with the two previous prospective trials,[22,23] preliminary results of the prospective STereotactic RadioAblation by Multimodal Imaging for Ventricular Tachycardia trial,[29] as well as published case series.[12,18–20,30]

Efficacy

Our results show a marked reduction of ≥50% in treated VT-episodes in most patients. After treatment, only one VT-episode requiring electrical cardioversion was observed, resulting in a median reduction of 100%. Moreover, the effect of STAR may well be underestimated due to ICD reprogramming after treatment with (much) lower anti-arrhythmic therapy zones. High doses of anti-arrhythmic drugs may lead to slow VTs only detectable with (very) low ICD zones. Even though these slow VTs are usually haemodynamically tolerated, they are clinically relevant as they can lead to swiftly progressive heart failure. In all our patients, the ICDs were programmed with low monitor- and ATP-only zones to document and treat these slow VTs despite the risk of ATP-induced worsening of arrhythmias (VT acceleration or VF induction). Therefore, it is likely that in the period before treatment not all VTs have been documented whilst we are confident that we did not miss any VT after treatment. The effect of a low ATP-only zone is very notable when comparing the number of treated and non-treated VT-episodes before and after treatment. In none of the patients ATP induced worsening of arrhythmias. In previous trials a reduction in (treated plus untreated sustained) VT-episodes of ≥50% was achieved in 93% (13/14),[23] 75% (3/4)[29] and 0% (0/5, no blanking period applied)[22] compared to 83% (5/6) of patients in our trial. When comparing these results, it is important to acknowledge the differences in patient population (i.e. ischaemic vs. non-ischaemic cardiomyopathies who are usually more difficult to treat—albeit that our patients had complex VT-substrates with many VT-morphologies from different segments), the use of a blanking period, used definition of VT, the previously mentioned ICD (re)programming, and additional therapies such as invasive catheter ablation and (changes in) anti-arrhythmic drugs.

Recurrence of VT

Although markedly reduced, recurrence of VT was observed in most of the patients directly after treatment. These direct effects have also previously been observed.[12,31–35] Usually, VT recurred within the first 4 months after treatment whilst patients were on lower but still substantial doses of anti-arrhythmic drugs. Interestingly, no VT occurred in the subsequent 5 months until reaching a second peak of recurrences after 9 months. Potentially, radiation induces several changes with electrophysiological effects, e.g. acute inflammation (i.e. direct pericardial effusion in P1, myocardial damage in P4), electrical reprogramming (functional alterations in gap-junctions and ion-channels),[15] later inflammation (pericardial effusion), and fibrosis.[11] In three patients, the recurrences of VT were documented on 12-lead ECG from which the VT exit site was estimated.[25] Two (67%) patients showed VT exit sites from segments adjacent to the target receiving mean doses of 11 Gy (P1) and 21–22 (P4) Gy, respectively. One patient showed VT exit sites from segments within the target receiving mean doses of 22 and 25 Gy (P5); however, that segment was not fully covered by the CTV. There a several potential possibility to explain these recurrences. Firstly, the observed recurrences could be explained by incorrect targeting, physiologic resistance to STAR or a non-durable effect. Secondly, the observation that VT exit sites are also located within segments receiving doses >20 Gy could imply, as also previously reported, that high(er) doses may be needed to fully treat the VT-substrate in patients with ischaemic cardiomyopathy (although lower doses may already induce electrophysiological alterations).[15] Alternatively, radiation may also create pro-arrhythmic substrate allowing 'new' VTs to arise.

Safety

STAR treatment did not result in treatment related serious adverse events during the 1-year follow-up of our STARNL-1 prospective trial, although most patients experienced possibly, or likely, treatment related adverse events. Like other reports, we have observed pneumonitis and pericardial effusion to be important adverse events. Pericardial effusion was, however, asymptomatic (although reaching 1–2 cm) but did not compromise any of the affected patients. Still, with the risk of progression resulting in (pre-symptomatic) haemodynamic compromise, active screening should be considered for pericardial effusion. We also consider preventive colchicine treatment for upcoming patients to putatively lower the chance of reactive pericarditis. Chest-wall pain potentially related to STAR has not previously been reported but was frequent in our cohort. In addition, we are the first to evaluate functional pulmonary safety and despite the occurrence of pneumonitis, the relative reduction in FEV1 and DLCOc was mild and did not result in symptoms. LVEF remained relatively stable during follow-up. However, it would be relevant to study more detailed functional parameters (i.e. global longitudinal strain) and evaluate radiotherapy dose-dependency. Also, a potential pro-thrombotic effect of STAR in patients with already a low-flow status, as also previously suggested, cannot be excluded albeit that in our study this in itself had no clinical sequala.[10] Still, we treated our patients with 3 months of anticoagulation post-treatment, and in upcoming patients we now consider indefinite anticoagulation in patients without other indication. In addition, patients undergoing arrhythmia radiotherapy remain at significant risk for morbidity and mortality.

Limitations, clinical implications, and future perspective

The STARNL-1 study is limited by the non-randomized monocentre design with strict inclusion criteria, limited patient numbers and no long-term follow-up. However, prospective evidence is still sparse, and one could thus argue whether randomized multicentre studies with less strict inclusion criteria are appropriate at the current stage.

The STARNL-1 trial is the first completed prospective trial in Europe. Within the other prospective trials, only 30 therapy refractory patients reportedly have been treated with follow-up ranging from 6–12 months and the current trial increases the number of patients to 36 (+20%). The overall efficacy results are encouraging with reduction in VTs, enabling clear reduction in amiodarone dosage and improvements in quality of life, comparable to the other studies.[23,29] However, many aspects of the treatment are yet to be elucidated, e.g. optimum dose, timing of effect, long(er)-term safety, observer variation in in target delineation, before this therapy can be more progressively implemented as therapeutic option for patients with recurrent VT.[22,36,37] Therefore, in our centre STAR is still considered a last-resort therapy for patients with therapy refractory VT. Notably, we have experienced that VT-recurrence after STAR was amenable to repeat catheter VT-ablation as opposed to pre-treatment VTs in these patients. Furthermore, as expected, mortality is high in this therapy-refractory and fragile patient population, also evidenced by our reported mortality of 33%. In previous studies, mortality ranges from 20–50%, and it is unknown whether STAR improves survival.[12,18–23,29] Eventually, randomized trials comparing STAR vs. repeat catheter ablation in therapy refractory VT patients would be needed to confirm the true benefit of this new treatment. For now, we pledge for STAR-treatments within prospective clinical trials and registries in which ICD programming as well as VT definitions are predefined as this would allow for reproducibility and comparisons between studies.

Conclusion

The STARNL-1 trial shows that in patients with therapy-refractory VT, stereotactic arrhythmia radiotherapy resulted in a reduction in treated VT-episodes in the majority of patients, whilst anti-arrhythmic drugs were reduced. No reduction in cardiac and pulmonary function nor treatment-related serious adverse events were observed during follow-up. In addition, quality of life showed improvement in most domains. Still, patients amenable to arrhythmia radiotherapy remain at risk for morbidity and mortality.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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