Ethanol Ablation for Ventricular Arrhythmias: A Systematic Review and Metanalysis

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Abstract

Introduction: Ethanol ablation (EA) has emerged as an alternative option for subjects with ventricular arrhythmias (VAs) refractory to conventional medical and ablative treatment. However, data on efficacy and safety of EA remain sparse.

Methods: A systematic literature search was conducted. The primary outcomes were 1) freedom from the targeted VA and 2) freedom from any VAs post EA. Additional safety outcomes were also analysed.

Results: Ten studies were selected, and a population of 174 patients (62.3±12.5 years, 94% male) undergoing 185 procedures were included. The overall acute success rate of EA was 72.4% ($CI_{95\%}$ 6.6-7.8). After a mean follow-up of 11.3±5.5 months, the incidence of relapse of the targeted VA was 24.1% ($CI_{95\%}$ 1.7-3.2), while any VAs post EA occurred in 41.2% ($CI_{95\%}$ 3.3-4.9). The overall incidence of procedural complications was 14.1% ($CI_{95\%}$ 0.98-2.0), with pericardial complications and complete atrioventricular block being the most frequent. An antegrade transarterial approach was associated with a higher rate of VA recurrences and complications compared to a retrograde transvenous route; however, differences in the baseline population characteristics and in the targeted ventricular areas should be accounted.

Conclusion: Data derived from observational non-controlled studies, with low-methodological quality, suggest that EA is a valuable option for VAs refractory to conventional treatment. EA can result in 1-year freedom from VA recurrence in 60 to 75% of the patients. However, anatomical or technical challenges preclude acute success in almost 30% of the candidates and the rate of complication is non-negligible, highlighting the importance of a careful patient selection.

Key words: ethanol ablation; alcohol ablation; ventricular tachycardia; ventricular ectopy; catheter ablation.

Introduction

Catheter ablation is an established treatment for both idiopathic and scar-related ventricular arrhythmias (VA), and now has a class I indication in selected patients [1]. Prospective and randomised studies have shown that catheter ablation is more effective, compared to antiarrhythmic drugs, for reduction of appropriate implantable cardioverter defibrillator (ICD) therapies, ventricular tachycardia (VT) storm and cardiac hospitalisation [2-3]. Ablation energy is traditionally delivered in the endocardial ventricular surface, however a combined epicardial-endocardial approach with a sub-xiphoid access has emerged as a valuable strategy for targeting epicardial circuits. Despite the growing experience and the technological improvement, acute failure of catheter ablation remains not negligible and as such VAs cannot be satisfactorily controlled in at least 10-20% of the patients undergoing this procedure [4].

First reported in the late 1980s [5], ethanol ablation (EA) has more recently re-emerged as an alternative option for subjects with drug-refractory VAs where conventional ablation has failed. Such a technique involves instillation of ethanol in the arterial or venous vessel supplying blood flow to the arrhythmogenic substrate. High concentrations of ethanol solubilize the cell membranes and alter the tertiary protein structures, leading to immediate cell death [6]. Despite the growing interest on this approach, data on efficacy and safety of ethanol ablation for VAs remain sparse [1]. In this report, we aim systematically to review the available evidence in the literature and assess the efficacy and safety of this procedure.

Methods

This study was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7] and was also in accordance with the recommendations from the Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [8]. The prespecified study protocol was

registered on PROSPERO (International Prospective Register of Systematic Reviews; unique identifier CRD42020223420).

Study Selection

A systematic electronic search was performed using the Cochrane Search Strategy [9] on PubMed, EMBASE and Cochrane database (from inception to December 2020) with no language limitations, using the following search string: "ventricular tachycardia" OR "ventricular arrhythmia" AND ("ethanol ablation" OR "alcohol ablation").

The population, intervention, comparison and outcome (PICO) approach was used [10]. The population of interest was patients with any VA, and the intervention was EA. Comparison was any other ablation strategy, if applicable. The primary outcomes were: 1) freedom from the targeted VA at the end of follow-up; 2) freedom from any VA at the end of follow-up. Additional outcomes included: 1) acute success, which was defined as non-inducibility of the targeted ventricular tachycardia (VT) or elimination of the targeted premature ventricular complex (PVC) at the end of the procedure, with no further VAs inducible; 2) periprocedural mortality; 3) periprocedural complications, which were assessed on a study-by-study basis.

Observational non-controlled case series required a minimum of 3 patients to be considered eligible. Review articles, editorials and case reports were not considered eligible for the purpose of this study.

Reference lists of all accessed full-text articles were further searched for sources of potentially relevant information.

Two independent reviewers (AC and RP) screened all abstracts and titles to identify potentially eligible studies, and the full text of was subsequently interrogated. Agreement of the two reviewers was required for studies to be considered eligible for analysis. Study quality was formally evaluated using the *National Heart, Lung, and Blood Institute Quality Assessment*

Tool for Case Series Studies [11] by two reviewers (AC, RP). An agreement between the two reviewers was mandatory for the final classification of studies. A third author (NP) intervened to resolve disputes whenever the two reviewers were in disagreement regarding the inclusion or classification of a study.

Where available the following data were extracted from the selected studies: study design, study population characteristics (age and sex), VT cycle length, follow-up duration, technique used, definition of success/relapse, post-procedural monitoring, and use of anti-arrhythmic agents. Patient-level data were obtained whenever these were available in the manuscripts.

Statistical analysis

Continuous variables were reported as mean±standard deviation or median, and categorical variables as n (%), weighted for the sample size of each study and according to standard error by logarithmic transformation. In order to pool results in a consistent format, in the absence of patient-level data the results reported as median, range and interquartile were converted into mean and deviation standard using the methods proposed by Luo et al [12]. Overall incidences and 95% confidence interval were estimated. Funnel plot analysis was used to evaluate potential publication bias, and statistical heterogeneity on each outcome of interest was quantified using the I^2 test. Comprehensive Meta-Analysis software (Trial Version) was used for the analyses.

Results

Study selection and patient characteristics

A total of 10 studies meeting the inclusion criteria were identified. The selection process is illustrated in Figure 2 (PRISMA) and a total population of 174 patients (62.3±12.5 years, 94% male) undergoing 185 procedures were included. As many as 43.8% had ischaemic

cardiomyopathy, 28.9% non-ischaemic cardiomyopathy, and 25.8% a structurally normal heart; 71.2% had an implantable-cardioverter defibrillator in situ. The mean left ventricular systolic function was 37.8±13.6%. The targeted arrhythmia was VT in 124 patients (71.3%), and PVC in the remaining. All the patients were refractory to at least one antiarrhythmic drug and all those from the most recent studies (2007 onward) underwent at least one previously failed endocardial and/or epicardial catheter ablation. There was a perfect agreement between investigators on the inclusion of the selected studies. Baseline data and the design of selected studies are summarised in Table 1.

The 10 studies included in the analysis were all case series, and all but 3 were retrospective [12-14]. All the studies were observational, with no control group and all but 3 [12-13, 15] were single-centre. According to the *National Heart, Lung, and Blood Institute Quality Assessment Tool for Case Series Studies* [11] a maximum of 9 criteria apply for case series as shown in Supplementary Table 2. One study fulfilled 9 criteria [12], 5 studies fulfilled 8 criteria [13, 15-18, 2 studies fulfilled 7 criteria [19-20], one study fulfilled 6 criteria [22] and another 5 criteria [5]. Both authors (AC and RP) were in agreement regarding study classification.

Procedural Data

A combination of activation mapping, pace-mapping and/or substrate mapping was adopted in all the studies, with additional use of unipolar mapping through an angioplasty guide-wire advanced into the targeted vessels in 4 series [12-13, 15-17]. Only 3 studies reported on the procedure duration [13, 16-17] and fluoroscopy time [12-13, 17] (Table 2). Concomitant radiofrequency catheter ablation was performed during the same session in 21 cases (11.3%). 3-D mapping was used in 6 studies [12-13, 14-16, 18]. An antegrade trans-arterial coronary approach was adopted in 7 studies [5, 14-16, 18-20] equating to 96 patients (55.2%), while a retrograde coronary venous approach was used in the remaining. The targeted areas were

reported in all but two studies [14, 20] and included: left ventricular (LV) summit in 56 patients, LV wall in 34 patients (inferior/posterior-lateral or lateral LV wall in 22 patients, anterior LV wall in 2 patients, unknown in the remaining), interventricular septum in 37 patients, aorto-mitral continuity in 3, right ventricular outflow tract in one, and LV apex in 3. Six studies reported the total amount of ethanol administered, which varied between 1.0 to 10.00 ml per patient. In 7 series, equating to a total of 108 procedures (58.4%), saline infusion was injected in order to confirm the adequate identification of the arrhythmogenic area before ethanol instillation. Detailed procedural data are presented in Table 2b. Figure 2 shows a summary of the key steps used in the different studies for the antegrade trans-arterial vs. retrograde coronary sinus approach technique.

Efficacy of Catheter Ablation

Among 185 attempted procedures, 32 (17.3%) were aborted (i.e., ethanol not injected) due absence of suitable vessel or impossibility to engage the targeted vessel. Of the 153 procedures where a suitable vessel was identified/accessed, 134 (87.6%; $CI_{95\%}$8.1-9.2) were acutely successful. Accounting for both the aborted and failed procedures, the overall acute success rate was 72.4% ($CI_{95\%}$ 6.6-7.8). The pooling of our data shows that after a mean follow-up of 11.3±5.5 months the incidence of relapse of the targeted VA was 24.1% ($CI_{95\%}$ 1.7-3.2), while any VA post EA occurred in 41.2% ($CI_{95\%}$ 3.3-4.9). These results are shown in Figure 3. The highest rate of relapse (100%) was reported by *Roqa-Luque et al* [16], although all the patients included in that study had a significant reduction of the VAs burden. *Segal et al* [15] reported the lowest rate of recurrence of the targeted VA (0%), however 2 patients (40%) during follow-up suffered from relapse of VTs with a different morphology compared to those treated with EA. Among the 32 patients (22.2%) undergoing a redo ablation following the index EA, the rate of any VA recurrence was 32.3% ($CI_{95\%}$2.5-4.1). Sixteen patients (9.2%; $CI_{95\%}$0.6-1.4)

died during follow-up, the most common cause was incessant VT causing refractory heart failure. These data are summarised in Table 3.

Procedural complications

The overall incidence of procedural complications was 14.1% ($CI_{95\%}$ 0.98-2.0). Four studies reported absence of any procedural complication [12, 14, 19-20]. In the remaining 6 studies, the rate of procedural complications varied between 7.9% to 43%. Overall, the most common complication was complete heart block which occurred in 12 patients (6.9%) undergoing EA with a trans-arterial coronary approach; this was persistent in 8 patients (4.6%) who required permanent pacemaker implantation. Complete heart block did not occur in any patient undergoing EA via a retrograde coronary venous route. Pericardial complications occurred in 6 patients (3.4%), including effusion requiring urgent pericardiocentesis in 3 (1.8%).

The overall periprocedural mortality rate was 1.1% (2 patients; $CI_{95\%}$ 0.0-0.4). One patient died due to cholesterol embolization with subsequent multi-organ failure; another patient died on day 3 post procedure following a vein graft thrombosis (not targeted during EA) causing acute inferior myocardial infarction and subsequent cardiogenic shock.

Antegrade coronary trans-arterial vs. retrograde coronary venous approach

The antegrade or retrograde approaches were attempted in 96 and 78 patients, respectively. There were some differences in the baseline population characteristics: in the retrograde group, 42% of the participants had a structurally normal heart and 43% a non-ischemic cardiomyopathy, while the large majority of those in the antegrade group had ischemic cardiomyopathy (88%). The most commonly targeted areas for the antegrade vs. retrograde group were the interventricular septum (60.0%) and the left ventricular summit (71.8%), respectively.

The rate of failure due to impossibility of identifying/accessing the selected branches was higher with an antegrade vs. retrograde approach (23.6%, $CI_{95\%}$ 1.6-3.2 vs. 8.9%, $CI_{95\%}$ 0.4-1.7). Whenever adequate vessels were identified and hence EA performed, complete acute success was achieved in 77.8% ($CI_{95\%}$ 6.7-8.5) vs. 98.6% ($CI_{95\%}$ 9.3-10-0) of the procedures with the antegrade and retrograde technique, respectively. The antegrade route was associated with a higher incidence of any VAs recurrences during follow-up (55.5%, $CI_{95\%}$ 4.5-6.6 vs. 25.0%, $CI_{95\%}$ 1.6-3.6), as well as a higher incidence of procedure complications (17.0%, $CI_{95\%}$ 1.1-2.5 vs. 10.1%, $CI_{95\%}$ 0.5-1.9).

Underlying heart disease

Outcomes in relation to the underlying heart disease were available for all but one study [19]. The rate of deferred procedures due to unsuitable vessel was 27.6% ($CI_{95\%}$ 1.8-4.0), 5.3% ($CI_{95\%}$ 0.1-1.7) and 16.1% ($CI_{95\%}$ 0.7-3.1) for patients with ischemic cardiomyopathy, non-ischemic cardiomyopathy and structurally normal heart, respectively; excluding the aborted cases, acute success was high in all the subgroups (95.2%, $CI_{95\%}$ 8.4-9.9; 97.1%, $CI_{95\%}$ 8.6-9.9; and 100%, $CI_{95\%}$ 0.9-1.0; respectively). The rate of recurrence of the targeted VA during follow-up was higher in subjects with non-ischemic cardiomyopathy (33.3%, $CI_{95\%}$ 2.0-5.0) vs. ischemic cardiomyopathy (21.4%, $CI_{95\%}$ 1.2-3.6) vs. structurally normal heart (19.2%, $CI_{95\%}$ 0.8-3.8). However, the overall incidence of any VA post EA was similar in the participants with ischemic cardiomyopathy (33.3%, $CI_{95\%}$ 2.1-4.8) vs. non-ischemic cardiomyopathy (33.3%, $CI_{95\%}$ 2.0-5.0), while it remained lower in those with structurally normal heart (19.2%, $CI_{95\%}$ 0.8-3.8). These results are shown in Supplementary Table 1.

Discussion

The main finding of the present systematic review is that the acute success rate of EA appears moderate, with only 72.4% of the procedures being acutely successful. Absence of a suitable vessel or impossibility to access the targeted branch were the most common reasons for procedure failure (17.3%). Whenever EA is technically feasible, mid-term success rate appears high, with 75.9% of the patients remaining free from the targeted VA and 58.8% remaining free from any VAs. However, the incidence of procedural complications is not negligible (14.1%), with a 1.1% rate of peri-procedure mortality.

A sub-analysis of the procedural techniques shows that, compared to an antegrade trans-arterial coronary approach, a retrograde coronary venous route is associated with numerically more favourable efficacy and safety outcomes, with 75% of the patients free from any VAs recurrences during the follow-up and no periprocedural mortality; however, differences in the targeted arrhythmogenic areas and in the baseline population characteristics should be accounted in the interpretation of these results. Finally, efficacy of EA is comparable among subjects with ischemic vs. non-ischemic cardiomyopathy.

The efficacy of EA appears similar to catheter ablation for VAs. In the Multicenter Thermocool VT Ablation Trial [22], 231 patients with ischemic cardiomyopathy and recurrent monomorphic VT were treated with catheter ablation. After a follow-up of 6 months, 53% of the participants were free from recurrent incessant or intermittent VT. In the HELP-VT study, which prospectively enrolled 227 patients undergoing VT ablation, VT-free survival at 1-year follow-up was 40.5% and 57% in subjects with non-ischemic or ischemic cardiomyopathy, respectively [23]. In respect of the EA outcomes according to the underlying heart disease, we have identified a numerically higher rate of recurrence of the targeted VA in patients with non-ischemic vs. ischemic cardiomyopathy (33.3% vs. 21.4%, respectively), however this difference was not confirmed when analysing the separate outcome of freedom from any VA

during follow-up. In line with previous literature on catheter ablation, success rate was higher in the subgroup of patients with a structurally normal heart [24-25].

With regards to safety, the incidence of complications with EA appears high (14.1%) and transient/persistent complete heart block represented the most common adverse event. Indeed, the risk of complications appears to be higher than what is reported for catheter ablation for VT, which is associated with an overall risk of 8-10% according to a previous metanalysis [26]. Although the overall net benefit of EA might remain acceptable in subjects with refractory VAs, these findings should be carefully considered during patient selection and consenting. Importantly, based on our data the risk of complications with a retrograde coronary venous approach is lower compared to an arterial trans-coronary strategy (10.1% vs. 17.0%), with none of the patients experiencing new onset of conduction system abnormalities and no periprocedural mortality. Nonetheless, the different myocardial areas targeted during EA using the retrograde vs. antegrade approach (mostly left ventricular summit vs. interventricular septum, respectively) should be accounted in the interpretation of these results, with septal targets being conceivably associated with an increased risk of damaging the conduction system following ethanol injection.

Another important limitation of EA, as emerged from the pooling of our data, is the impossibility of localising or selectively cannulating an adequate vessel supplying the arrhythmogenic myocardium in a significant proportion of patients, who are therefore precluded from this treatment option. Such a restriction can be secondary to an unfavourable coronary or venous anatomy, but also to the presence of extensive coronary artery disease especially in subjects with ischaemic VA [6]. A retrograde venous approach seems to at least partially overcome this issue, especially for VAs arising from the left ventricular summit. However, the experience with the retrograde technique for non-LV summit areas appears more limited, with overall less than 30 cases reported in the literature. The high degree of inter-

individual variability of the coronary venous anatomy and the necessity to identify suitable veins without vein-to-vein collaterals (in order to avoid ethanol bypassing the targeted myocardium), should also be accounted as possible pitfalls of this approach [27]. A controlled intramural perforation of the venule adjacent to the arrhythmogenic area, or a "double-balloon" technique where a second angioplasty balloon is placed downstream of the ethanol injection (in order to force the ethanol into any intramural branches between the balloons), have been described as possible strategies to overcome challenging coronary venous anatomies [13, 26]. The long-term outcomes of EA might also be affected by the new development of collaterals bypassing the vessel targeted during the procedure, however a repeated EA targeting the collaterals supplying the arrhythmogenic myocardium has been shown to be feasible in selected cases [5].

To summarise, our findings suggest that even though EA can be employed in patients with VAs refractory to conventional medical and ablative treatment, strong and high-quality data supporting its use and efficacy are absent. Given the technical challenges and the non-negligible risk of complications, EA should be adopted in a very selected population and preferably in highly specialised centres. A retrograde coronary venous approach appears to be safer and more effective compared to a trans-arterial coronary route, however further studies are required to confirm these findings especially in subjects with VAs arising from non-LV summit areas.

To the best of our knowledge, this is the first study to systematically review the available literature and pool together the data on this topic. However, several limitations should be acknowledged. Firstly, we could not analyse data from case-control design due to the absence of control groups in all the studies. However, given the intrinsic nature of EA which usually represents the last resort in patients with VAs refractory to conventional treatments, it is unlikely that comparison or randomised study evaluating EA vs. other treatments will ever be

performed. Secondly, many of the studies included were retrospective, single-centre and based on small cohorts. Thirdly, some of studies included were performed in the early 90', before the introduction of the modern catheter ablation technology; it is conceivable that many of the patients included in such series could have been treated nowadays with endocardial and/or epicardial catheter ablation. Fourthly, most of the studies were performed in high volume units and by highly experienced operators, as such our results might not be generalisable to less experienced centres.

Conclusions

Data derived from observational non-controlled case series, with low-methodological quality, suggest that EA is a valuable treatment option for VAs refractory to conventional medical and ablative treatment. However, anatomical or technical challenges preclude acute success in almost 30% of the candidates. Whenever feasible, EA can result in freedom from any VA recurrence in up to 58.8% of the patients, and freedom from the targeted VA in up to 74.9%. Importantly, the complication rate for this procedure is not negligible (14.1%) suggesting that careful patient selection may be of paramount importance.

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References

[1] Cronin EM, Bogun FM, Maury P, Peichl P, Chen M, Namboodiri N, Aguinaga L, Leite LR, Al-Khatib SM, Anter E, Berruezo A, Callans DJ, Chung MK, Cuculich P, d'Avila A, Deal BJ, Della Bella P, Deneke T, Dickfeld TM, Hadid C, Haqqani HM, Kay GN, Latchamsetty R, Marchlinski F, Miller JM, Nogami A, Patel AR, Pathak RK, Saenz Morales LC, Santangeli P, Sapp JL Jr, Sarkozy A, Soejima K, Stevenson WG, Tedrow UB, Tzou WS, Varma N, Zeppenfeld K. 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias: Executive summary. *Heart Rhythm*. 2020;17:e155-e205.

[2] Martinez BK, Baker WL, Konopka A, Giannelli D, Coleman CI, Kluger J, Cronin EM. Systematic review and meta-analysis of catheter ablation of ventricular tachycardia in ischemic heart disease. *Heart Rhythm*. 2020;17:e206-e219.

[3] Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, Gonzalez MD, Worley SJ, Daoud EG, Hwang C, Schuger C, Bump TE, Jazayeri M, Tomassoni GF, Kopelman HA, Soejima K, Nakagawa H; Multicenter Thermocool VT Ablation Trial Investigators. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. *Circulation*. 2008;118:2773-2782.

[4] Tokuda M, Kojodjojo P, Tung S, Tedrow UB, Nof E, Inada K, Koplan BA, Michaud GF, John RM, Epstein LM, Stevenson WG. Acute failure of catheter ablation for ventricular tachycardia due to structural heart disease: causes and significance. *J Am Heart Assoc*. 2013;2:e000072.

[5] Brugada P, de Swart H, Smeets JL, Wellens HJ. Transcoronary chemical ablation of ventricular tachycardia. *Circulation*. 1989;79:475-482.

[6] Schurmann P, Peñalver J, Valderrábano M. Ethanol for the treatment of cardiac arrhythmias. *Curr Opin Cardiol*. 2015;30:333-343.

[7] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of internal medicine.* 2015;162:777-784.

[8] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012.

[9] Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1 (updated September 2020). Cochrane, 2020

[10] Menzies D. Systematic reviews and meta-analyses. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease*. 2011;15:582-593.

[11] National Heart LaBI. Quality Assessment Tool for Case Series Studies.

[12] Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27:1785-1805.

[12] Tavares L, Lador A, Fuentes S, Da-Wariboko A, Blaszyk K, Malaczynska-Rajpold K, Papiashvili G, Korolev S, Peichl P, Kautzner J, Webber M, Hooks D, Rodríguez-Mañero M, Di Toro D, Labadet C, Sasaki T, Okishige K, Patel A, Schurmann PA, Dave AS, Rami TG, Valderrábano M. Intramural Venous Ethanol Infusion for Refractory Ventricular Arrhythmias: Outcomes of a Multicenter Experience. *JACC Clin Electrophysiol*. 2020;6:1420-1431.

[13] Da-Wariboko A, Lador A, Tavares L, Dave AS, Schurmann PA, Peichl P, Kautzner J, Papiashvili G, Valderrábano M. Double-balloon technique for retrograde venous ethanol ablation of ventricular arrhythmias in the absence of suitable intramural veins. *Heart Rhythm*. 2020:S1547-5271(20)30523-3.

[14] Kay GN, Epstein AE, Bubien RS, Anderson PG, Dailey SM, Plumb VJ. Intracoronary ethanol ablation for the treatment of recurrent sustained ventricular tachycardia. *J Am Coll Cardiol*. 1992;19:159-168.

[15] Segal OR, Wong T, Chow AW, Jarman JW, Schilling RJ, Markides V, Peters NS, Wyn Davies D. Intra-coronary guidewire mapping-a novel technique to guide ablation of human ventricular tachycardia. *J Interv Card Electrophysiol*. 2007;18:143-54.

[16] Roca-Luque I, Rivas-Gándara N, Francisco-Pascual J, Rodriguez-Sanchez J, Cuellar-Calabria H, Rodriguez-Palomares J, García-Del Blanco B, Pérez-Rodon J, Santos-Ortega A, Rosés-Noguer F, Marsal R, Rubio B, García DG, Moya Mitjans A. Preprocedural imaging to guide transcoronary ethanol ablation for refractory septal ventricular tachycardia. *J Cardiovasc Electrophysiol*. 2019;30:448-456.

[17] Kreidieh B, Rodríguez-Mañero M, Schurmann P, Ibarra-Cortez SH, Dave AS, Valderrábano M. Retrograde Coronary Venous Ethanol Infusion for Ablation of Refractory Ventricular Tachycardia. *Circ Arrhythm Electrophysiol*. 2016;9(7):10.1161.

[18] Kay GN, Epstein AE, Bubien RS, Anderson PG, Dailey SM, Plumb VJ. Intracoronary ethanol ablation for the treatment of recurrent sustained ventricular tachycardia. *J Am Coll Cardiol*. 1992;19:159-168.

[19] Kumar S, Barbhaiya CR, Sobieszczyk P, Eisenhauer AC, Couper GS, Nagashima K, Mahida S, Baldinger SH, Choi EK, Epstein LM, Koplan BA, John RM, Michaud GF, Stevenson WG, Tedrow UB. Role of alternative interventional procedures when endo- and

epicardial catheter ablation attempts for ventricular arrhythmias fail. *Circ Arrhythm Electrophysiol*. 2015;8:606-615.

[20] Nellens P, Gürsoy S, Andries E, Brugada P. Transcoronary chemical ablation of arrhythmias. *Pacing Clin Electrophysiol*. 1992;15:1368-1373.

[21] Gursoy S, Nellens P, Guiraudon G, Brugada J, Brugada P. Epicardial and subselective transcoronary chemical ablation of incessant ventricular tachycardia. *Cathet Cardiovasc Diagn*. 1993;28:323-327.

[22] Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, et al. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. *Circulation* 2008; 118: 2773-2782.

[23] Dinov B, Fiedler L, Schonbauer R, Bollmann A, Rolf S, Piorkowski C, et al. Outcomes in catheter ablation of ventricular tachycardia in dilated nonischemic cardiomyopathy compared with ischemic cardiomyopathy: results from the Prospective Heart Centre of Leipzig VT (HELP-VT) Study. *Circulation* 2014; 129: 728-736.

[24] Dukkipati SR, Choudry S, Koruth JS, Miller MA, Whang W, Reddy VY. Catheter Ablation of Ventricular Tachycardia in Structurally Normal Hearts: Indications, Strategies, and Outcomes-Part I. J Am Coll Cardiol. 2017 Dec 12;70(23):2909-2923.

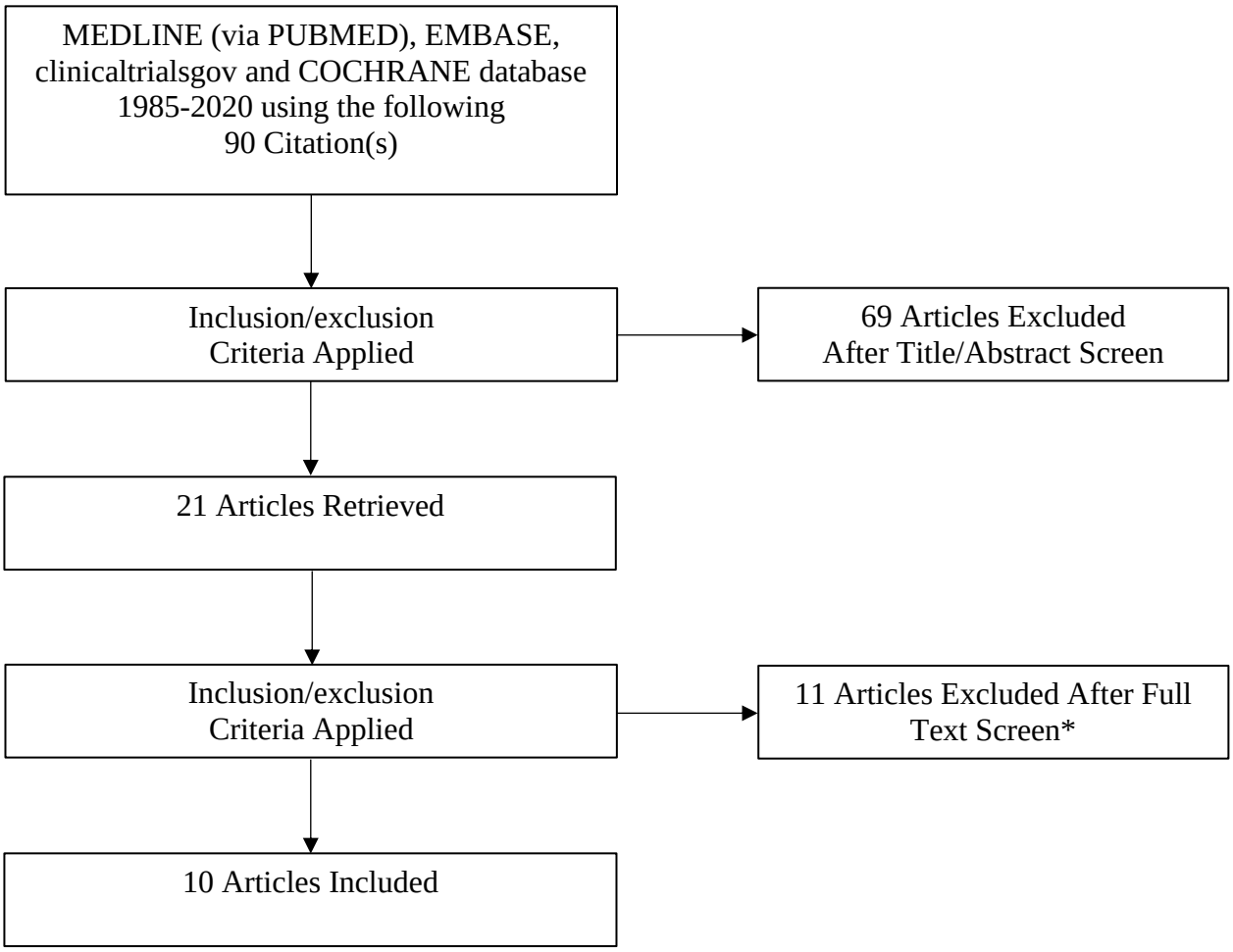
[25] Creta A, Chow AW, Sporton S, Finlay M, Papageorgiou N, Honarbakhsh S, Dhillon G, Graham A, Patel KHK, Dhinoja M, Earley MJ, Hunter RJ, Lowe M, Rowland E, Segal OR, Calabrese V, Ricciardi D, Lambiase PD, Schilling RJ, Providência R. Catheter ablation for fascicular ventricular tachycardia: A systematic review. Int J Cardiol. 2019 Feb 1;276:136-148.

[26] Pothineni NV, Deshmukh A, Padmanabhan D, Kovelamudi S, Patel NJ, Badheka AO, et al. Complication rates of ventricular tachycardia ablation: Comparison of safety outcomes

derived from administrative databases and clinical trials. *International journal of cardiology* 2015; 201: 529-531.

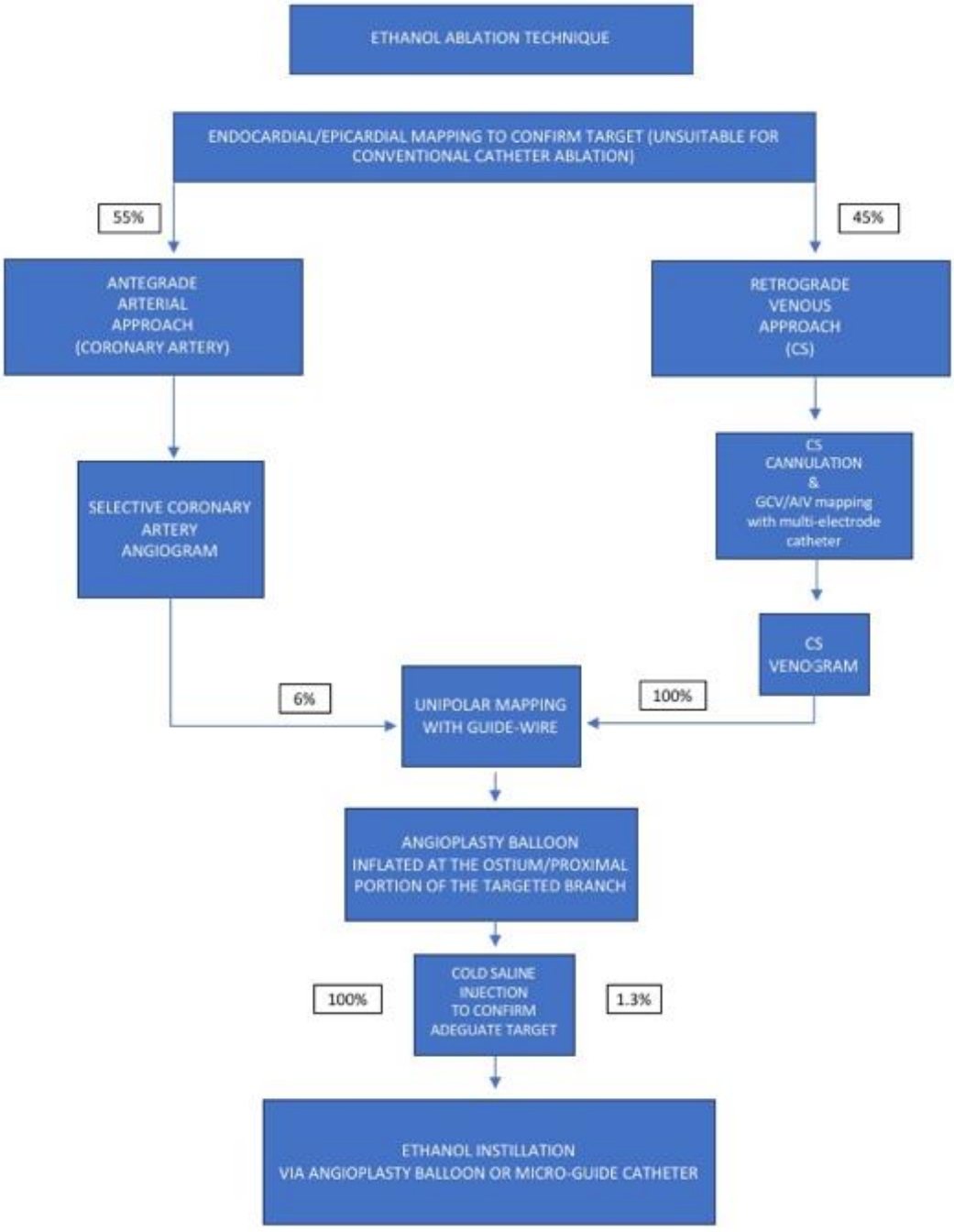
[27] Tavares L, Valderrábano M. Retrograde venous ethanol ablation for ventricular tachycardia. *Heart Rhythm*. 2019;16(3):478-483.

Figure 1. PRISMA



Note. *Two articles were excluded because their data had been reported in a more recent publication overlapping and expanding the population of the same centre, as stated by the authors [19].

Figure 2. Key steps for ethanol ablation using antegrade trans-arterial coronary and retrograde venous coronary sinus technique.



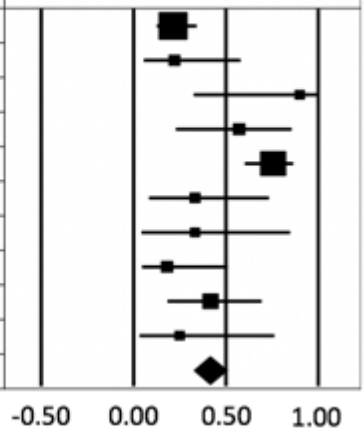
Notes. Percentages represent the proportion of the procedures for which each step was adopted in the studies included (percentage on the left refers to the antegrade approach, on the right to the retrograde approach).

Abbreviations. CS: coronary sinus. GCV: great cardiac vein. AIV: anterior interventricular vein.

Figure 3. Forest plot of the included studies for the endpoint of recurrence rate of any ventricular arrhythmia (A) and targeted ventricular arrhythmia (B) at the end of follow-up, highlighting the statistic relevance of the results from each single study. CI, confidence interval.

A

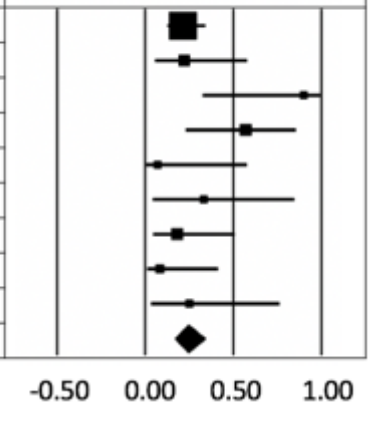
Author	*Event Rate*	*Lower Limit*	*Upper Limit*	*Z-value*	*p-Value*	*Event Rate (95% CI)*
Tavares	0.214	0.126	0.341	-3.990	0.000	
Da-wariboko	0.222	0.056	0.579	-1.562	0.118	
Roqa-Luque	0.900	0.326	0.994	1.474	0.140	
Kreidieh	0.571	0.230	0.856	0.377	0.706	
Kumar	0.756	0.603	0.863	3.111	0.002	
Segal	0.333	0.084	0.732	-0.800	0.423	
Gursoy	0.333	0.043	0.846	-0.566	0.571	
Nellens	0.182	0.046	0.507	-1.924	0.054	
Kay	0.417	0.185	0.692	0.575	0.566	
Brugada	0.250	0.034	0.762	-0.951	0.341	
Cumulative	0.413	0.327	0.505	-1.855	0.064	



I^2 73%

B*

Author	*Event Rate*	*Lower Limit*	*Upper Limit*	*Z-value*	*p-Value*	*Event Rate (95% CI)*
Tavares	0.214	0.126	0.341	-3.990	0.000	
Da-wariboko	0.222	0.056	0.579	-1.562	0.118	
Roqa-Luque	0.900	0.326	0.994	1.474	0.140	
Kreidieh	0.571	0.230	0.856	0.377	0.706	
Segal	0.071	0.004	0.577	-1.748	0.081	
Gursoy	0.333	0.043	0.846	-0.566	0.571	
Nellens	0.182	0.046	0.507	-1.924	0.054	
Kay	0.083	0.012	0.413	2.266	0.022	
Brugada	0.250	0.034	0.762	-0.951	0.341	
Cumulative	0.244	0.168	0.340	-4.735	0.000	



I^2 30%

Note. *Kumar's series [19] was excluded as no relevant data to this endpoint could be extrapolated from the article for the entire population included in that study.

Table 1. Baseline population characteristics

Study	Date of Procedures/ Country	Centres (N)	Design	Prospective/ Retrospective	Pts (N)[A]	Total number of EA procedures/ attempted procedures (N)	Age (years)	Female gender N (%)	Mean LVEF (%)	Background (N)	ICD N (%)	Previous failed AADs N (%)	Previous endocardial and/or epicardial catheter ablation (N patients) % N of procedures
Tavares 2020	N/A US/Argentina/ Czech Republic/ Georgia/Japan/ New Zealand/Poland/ Russia/Spain	10	Case Series	Prospective	63 (56)[A]	56 (63)	63.0±14.0	25 (40%)	45.2±15.0	ICM (7) SNH (29) NICM (27)	29 (46%)	1.3±0.7	62 (98%) 1 (median)
Da-wariboko 2020	N/A US/Czech Republic/ Georgia	3	Case Series	Prospective	8 (8)[A]	9/9[B]	62.3±22	None	31.5±13	ICM(5), SNH (2), NICM (1)	6 (75%)	2±0	8 (100%) 1.6±0.5
Roca-Luque 2019	2017-2018 Spain	1	Case Series	Retrospective	3 (3)[A]	4/4	76±11	None	45.3±12.6	Valvular cardiopathy (1) NICM (2)	3 (100%)	NA	3 (100%) 2.3±0.4
Kreidieh 2016	2011-2016 US	1	Case Series	Retrospective/ Prospective	7 (7)[A]	7/7	62.2±12.6	1 (14%)	41.1±20.6	ICM (2) NICM (5) SNH (2)	4 (57%)	NA	6 (86%) 1.8±1.0
Kumar 2015	N/A US	1	Case Series	Retrospective	46 (38)[A]	41/50[B]	62±11b	NA	32±14b	N/A[C]	N/A[C]	4±2b	46 (100%) 2±1[D]
Segal 2007	N/A UK	2	Case Series	Retrospective	6 (6)[A]	6/6	64±14	4 (67%)	43.2±12.9	ICM (4), NICM (1), unknown (1)	2 (33%)	1.8±0.4	6 (100%) N/A
Gursoy 1993	1991-92 Belgium	1	Case Series	Retrospective	3 (3)[A]	3/4[B]	66±4	None	22±3	ICM (3)	None	2±0	None
Nellens 1992	NA Belgium	1	Case Series	Retrospective	12 (10)[A]	11/13[B]	62±6	NA	NA	ICM (11), NICM (1)	NA	NA	None
Kay 1992	1989-1991 US	1	Case Series	Prospective	23 (10)[A]	12/25[B]	59.1±12.4	2 (8.7%)	33±10	ICM (23)	1 (4.3%)	100% NA	None
Brugada 1989	1988 Netherland	1	Case Series	Retrospective	3 (3)[A]	4/4[B]	56±10	None	16±6	ICM (3)	None	2±1	None
Total					174 (144)[A]	153 (185)	62.3±12.5	7 (6%)[E]	37.8±13.6[F]	ICM (43.8%)[G] NICM (28.9%)[G] SNH (25.8%)[G] Other (1.6%)[G]	45 (38.8%)[E]		131 (75.3%)

Abbreviations. US: United States of America; UK: United Kingdom; EA: ethanol ablation; ICM: ischaemic cardiomyopathy; NICM: non-ischaemic cardiomyopathy; SNH: structurally normal heart. **Notes**. A: number in bracket refers to patients whose EA was completed (excluding failed cases). B: one or more patients underwent multiple EA procedures. C: data provided for the whole population included in that study, however not all the participants underwent EA; 94% of the global population included in the study had an ICD. D: this refers to global population of the study, although only 46 out of 67 patients were in the EA group. E: this refers to a population of 116 patients, after excluding Kumar's and Nellens' study as no relevant data available. F: this refers to a population of 162 patients, after excluding Nellen's study as no relevant data available. G: this refers to a population of 128 patients, after excluding Kumar's study as relevant data not available.

Table 2-A. Procedural details

Study	Procedure duration (min)	Fluoroscopy time (min)	Mapping system	Clinical arrhythmia N (%)	Incessant VAs	Cycle length of VTs (mean)	Epi Mapping % (N)	RFA during the same procedure N (%)	Unipolar mapping through intra-vessel guidewire	Indication for EA
Tavares 2020	NA	32 (median)	CARTO-3 or NavX	VT 18 (28.6%) PVC 45 (71.4%)	NA	NA	NA	17 (29.7%)	Y	RFA failed
Da-wariboko 2020	272±32	21 (median)	NA	VT 6 (75%) PVC 2 (25%)	NA	NA	NA	None	Y	RFA failed
Roca-Luque 2019	147±27	NA	Ensite-Precision 100%	VT 3 (100%)	None	NA	None	None	N	RFA failed
Kreidieh 2016	273±56	47±26	CARTO-3 (4) NavX (3)	VT 4 (57.1%) PVC 3 (42.9%)	85.7% (6)	NA	43% (3)	3 (43%)	Y	RFA failed[A]
Kumar 2015	NA	NA	CARTO 100%	VT 46 (100%)	NA	NA	NA	None	N	RFA failed[B]
Segal 2007	NA	NA	CARTO or NavX	VT 6 (100%)	50% (3)	348±102.1	None	1 (17%)	Y	RFA failed
Gursoy 1993	NA	NA	Not-applicable	VT 3 (100%)	100% (3)	530±26	None	None	N	Not-applicable
Nellens 1992	NA	NA	Not-applicable	VT 12 (100%)	100% (12)	NA	None	None	N	Not-applicable
Kay 1992	NA	NA	Not-applicable	VT 23 (100%)	None	378±73	None	None	N	Not-applicable
Brugada 1989	NA	NA	Not-applicable	VT 3 (100%)	100% (3)	417±60	None	None	N	Not-applicable

Abbreviations. VA: ventricular arrhythmia; VT: ventricular tachycardia; RFA: radiofrequency ablation; EA: ethanol ablation; NA: not available; PVC; premature ventricular complex; Y: yes; N: no. **Notes**. A: RFA failed at endocardial and/or epicardial sites, or not attempted due to contiguity with coronary arteries, or presence of the earliest activation site at a broad area, or earliest activation obtained within a coronary vein. B: RFA failed at endocardial and/or epicardial, or epicardial access failed or felt to e prohibited given prior cardiac surgery or likely pericardial adhesions.

Table 2-B. Procedural details

Study	Target area (N)	Retrograde coronary venous or antegrade trans-arterial coronary EA	Targeted vessel (N)	Number of vessels targeted (N)	Ethanol injected (ml)	Use of saline/iced saline before EA	Tecnique	Definition of success
Tavares 2020	LV summit (48), LV wall (10), mitral annulus (2), LV apex (2), inferior septum (1)	Retrograde coronary venous	Proximal AIV-septal (36), LV annular vein (5), posterolateral vein (5), distal AIV (3), proximal AIV-diagonal vein (2), lateral vein (2), GCV-AIV junction diagonal vein (1), GCV-marginal vein (1), MCV septal (1)	1 (median)	4 (median)	N	Selective coronary sinus angiogram Unipolar activation mapping via angioplasty guide-wire Ethanol injected through angioplasty balloon or FineCross catheter (before ethanol instillation, contrast was injected to assess the size of the branch and the extent of the targeted tissue reached, i.e. myocardial staining)	Non inducibility of VT or elimination of PVC
Da-wariboko 2020	LV summit (3), lateral/postero-lateral LV wall (5)	Retrograde coronary venous	Posterolateral vein (2), lateral vein (1), MCV (1), AIV (3), LV annular vein (1)	1.0±0	7.1±15.6	N	Selective coronary sinus angiogram Unipolar activation mapping via angioplasty guide-wire Ethanol injected through inflated angioplasty balloon (occlusion verified with contrast), with second angioplasty balloon placed downstream of the ethanol injection in order to force the ethanol into any intramural branches between the balloons (double balloon technique) Contrast injection to assess amount of targeted tissue reached (myocardial staining)	Non inducibility of VT or elimination of PVC
Roca-Luque 2019	Intramural septum 3	Antegrade trans-arterial coronary	Septal branches of LAD (3)	2.0±1.0	NA	N	Selective coronary angiogram Ethanol injected through inflated angioplasty balloon (occlusion verified with contrast) Periprocedural cardiac CT/cMRI to guide identification of the targeted area	Non inducibility of any VT
Kreidieh 2016	LV summit 5	Retrograde coronary venous	Septal branches of AIV (5), postero-lateral vein (1), MCV (1)	NA	1.0-4.0	Y (for one case only)	Selective coronary sinus angiogram Unipolar mapping through angioplasty guide-wire (connected to alligator clip) Ethanol injected through angioplasty balloon, which was left inflated for 2-8min (occlusion and absence of collaterals verified with contrast)	Non inducibility of any VT or elimination of PVC (after 20 seconds of ethanol infusion)

Kumar 2015	Intramural (32) Epicardial (14) Interventricular septum (31), inferior wall (9), anterior wall (1), lateral LV wall (1), aorto-mitral continuity (3), RVOT (1)	Antegrade trans-arterial coronary	LMS branch (1), distal LAD (1), septal LAD branches (23), diagonal LAD branch (1), obtuse marginal LCx branches (7), left postero-lateral (1), right postero-lateral (2), posterior descendent (7), mid/distal RCA branches (2), conus RCA branch (3)	1.2±0.4	2.6±1.2	Y	Selective coronary angiogram Ethanol injected through angioplasty balloon, which was left inflated for 10min (occlusion verified with contrast) Further injections (up to 5) is perfusion still present	Complete success: non-inducibility of any VT Partial success: abolishment of at least one spontaneous VT
Segal 2007	Posterior (1), posteroseptal (1), posterobasal (1), inferior (1), anterobasal (1)	Antegrade trans-arterial coronary	LCx (3), first obtuse marginal artery via a saphenous vein graft (1), tight postero-lateral artery (1), first diagonal branch (1)	1.0±0 (2.66±1.21 mapped)	NA	Y	Selective coronary angiogram Unipolar intracoronary mapping through guidewire (with indifferent electrode in vena cava and uninflated angioplasty balloon advanced to expose 5 mm distal tip of the guidewire) Ethanol injected through inflated angioplasty balloon (occlusion verified with contrast)	Non inducibility of any VT
Nellens 1992	NA	Antegrade trans-arterial coronary	NA	NA	NA	Y	Selective coronary angiogram NA	Non inducibility of any VT
Gursoy 1993	Posterolateral wall (2), inferior wall (1)	Antegrade trans-arterial coronary	LCx (3)[A]	1.0±1.0	5.7±3.8	Y	Selective coronary angiogram Ethanol injected through guide catheter/ angioplasty balloon/18-G needle after epicardial surgical access	Non inducibility of any VT
Kay 1992	NA	Antegrade trans-arterial coronary	Branches of LAD (4), LCx (2) or RCA (5)	1.0±0	2.0[B]	Y	Selective coronary angiogram Ethanol injected through 2.7F polyethylene infusion catheter	Non inducibility of any VT
Brugada 1989	Interventricular septum (2), apex (1)	Antegrade trans-arterial coronary	Septal branches of LAD (2), conus branch of LAD (1), posterior descendent (1), right ventricular branch of RCA (1)	1.7±1.2	3.0±2.6	Y	Selective coronary angiogram Ethanol injected through guide catheter	Non inducibility of any VT

Abbreviations. EA: ethanol ablation; LV: left ventricle; AIV: anterior interventricular vein; MCV: middle cardiac vein; GCV: great cardiac vessel; LAD: left anterior descending artery; LMS: left main steam; LCx: circumflex artery; RCA: right coronary artery; VT: ventricular tachycardia; PVC: premature ventricular complex; CT: computerised tomography; cMRI: cardiac magnetic resonance imaging; NA: not available; Y: yes; N: no. **Notes**. A: selective incannulation was not possible in 1 patient, who subsequently underwent epicardial ethanol injection with thoracotomy approach. B: only one patient received 2ml, 4ml and 8ml of the ethanol with successive ablative procedures.

Table 3. Outcomes

Study	Procedural Complications % (N)	EA attempted but not feasible (no suitable vessel or impossibility to engage targeted vessel, or cold saline not effective)	Peri-Procedure Mortality % (N patients)	FUP duration (months)	Mortality during FUP % (N patients)	Acute success (excluding aborted cases)	Recurrence of targeted VT/PVC after index EA % (N procedures)	Recurrence of any ventricular arrhythmia after index EA % (N procedures)	VT burden decrease after index EA % (N patients)	Redo ablation (any technique) post index EA % (N patients)	Recurrence of targeted VT/PVC after redo ablation (any technique) post index EA % (N patients)
Tavares 2020	7.9% (5): pericardial effusions requiring pericardiocentesis (3)[A], post-operative atrial fibrillation (1), post-procedure pericarditis (1)	11.1% (7)	0%	9±4months 274.8±117.8[B] 354 days (median)	0%	98.2% (55)	21.4% (12)	21.4% (12)	98.2%	16.1% (9)	5.4% (3)
Da-wariboko 2020	None	0%	0%	11±9 347±285days (median 313.5)	0%	100% (9)	25% (2)	25% (2)	NA	12.5% (1)	NA
Roca-Luque 2019	33.3% (1): transient CHB	0%	0%	6±2 6.3±2.1 months (median 7 months)	0%	100% (4)	100% (4)	100% (3)	100% (3)	33.3% (1)	100% (4)
Kreidieh 2016	43% (3): pericardial effusion (1)[C,D] ethanol-induced myocardial injury (1)[B], coronary sinus dissection (1)	0%	0%	19±24 590±722 days (median 207 days)	0%	100% (7)	57% (4)	57% (4)	NA	43% (3)	14.3% (1)
Kumar 2015	32% (12): CHB (7), stroke (1), increased ventricular pacing requirement (1), contrast nephropathy (1), cholesterol embolization (1), hypotension requiring IABP (1), coronary vasospasm (1)	17.4% (8)	2.6% (1)[E]	12±0 12 months	27% (10)	66% (25)[F]	N/A[G]	81.6% (31)	100% (38)[H]	39.5% (15)	79% (30)
Segal 2007	None	17% (1)	0%	19±17 months (range 2-42months)	17% (1)	100% (5)	0%	40% (2)	100% (6)	0%	Not applicable
Gursoy 1993	None	33% (1)[I]	0%	7.7±4.2 months (median 9 months)	33% (1)	100% (3)	33% (1)[J]	33% (1)	100% (3)	0%	33% (1)[J]
Nellens 1992	None	17% (2)	0%	15±12.8 months[B] 2-44 (median 10 months)	25% (3)	100% (10)	20% (2)	20% (2)	N/A	10% (1)	10% (1)
Kay 1992	40% (4): transient CHB (2), persistent CHB (1), Dressler's syndrome (1)	56.5% (13)	10%[K]	12±7months 372±210 days (range 102-788 days)	10% (1)	80% (11)	10% (1)	50% (5)	N/A	10% (1)	40% (4)
Brugada 1989	33% (1): transient CHB requiring PPM	0%	0%	5.6±3.5 months (median 6 months)	0%	100% (5)	33% (1)[L]	33% (1)	66% (2)	33% (1)	0%
Total	**14.1%** (26) $CI_{95\%}$0.98-2.0	**17.3%** (32) $CI_{95\%}$1.2-2.3	**1.1%** (2) $CI_{95\%}$0.0-0.3	**11.3±5.5**	**9.2%** (16) $CI_{95\%}$0.6-1.4	**87.6%** (134) $CI_{95\%}$8.1-9.2	**24.1%** (27)[M] $CI_{95\%}$1.7-3.2	**41.2%** (63) $CI_{95\%}$3.3-4.9	-	**22.2%** (32) $CI_{95\%}$1.5-2.8	**32.3%** (44)[N] $CI_{95\%}$2.5-4.1

Abbreviations. EA: ethanol ablation; FUP: follow-up; VT: ventricular tachycardia; PVC: premature ventricle complex; NA: not available; CHB: complete heart block; IABP: intra-aortic balloon pump. **Notes**: A: these occurred in patients with only attempted EA. B: this was estimated using the methods proposed by Luo et al [12]. C: this occurred in a patient who had concomitant epicardial access; D: same patient; E: multi-organ failure due to cholesterol embolization; F: this includes partial success and does not include repeated EA procedures; G: of the 31 patients who had VT recurrences, 15 underwent redo electrophysiology study which revealed VT occurring from different origin compared to the target VT in all but 1 patient; H: significant reduction of number of defibrillator shocks and/or antiarrhythmic drugs used. I: one patient required thoracotomy approach for ethanol ablation; J: one patient had early recurrence on day one after procedure, but none afterward; K: one patient died for cardiogenic shock at day 5 post EA, after having suffered from a myocardial infarction at day 3 post EA due to occlusion of a by-pass graft which was not cannulated during the EA procedure; L: one patient had recurrence 5 weeks following first EA due to development of collateral circulation supplying the arrhythmogenic area. M: excluding Kumar's study as no relevant data available. N: excluding Da-wariboko's study as no relevant data available.