



Ablation strategies for arrhythmogenic right ventricular cardiomyopathy: a systematic review and meta-analysis

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Abstract

Background Catheter ablation for ventricular tachycardia (VT) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) has significantly evolved over the past decade. However, different ablation strategies showed inconsistency in acute and long-term outcomes. **Methods** We searched the databases of Medline, Embase and Cochrane Library through October 17, 2019 for studies describing the clinical outcomes of VT ablation in ARVC. Data including VT recurrence, all-cause mortality, acute procedural efficacy and major procedural complications were extracted. A meta-analysis with trial sequential analysis was further performed in comparative studies of endo-epicardial versus endocardial-only ablation. **Results** A total of 24 studies with 717 participants were enrolled. The literatures of epicardial ablation were mainly published after 2010 with total ICD implantation of 73.7%, acute efficacy of 89.8%, major complication of 5.2%, follow-up of 28.9 months, VT freedom of 75.3%, all-cause mortality of 1.1% and heart transplantation of 0.6%. Meta-analysis of 10 comparative studies revealed that compared with endocardial-only approach, epicardial ablation significantly decreased VT recurrence (OR: 0.50; 95% CI: 0.30–0.85; $P = 0.010$), but somehow increased major procedural complications (OR: 4.64; 95% CI: 1.28–16.92; $P = 0.02$), with not evident improvement of acute efficacy (OR: 2.74; 95% CI: 0.98–7.65; $P = 0.051$) or all-cause mortality (OR: 0.87; 95% CI: 0.09–8.31; $P = 0.90$). **Conclusion** Catheter ablation for VT in ARVC is feasible and effective. Epicardial ablation is associated with better long-term VT freedom, but with more major complications and unremarkable survival or acute efficacy benefit.

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Keywords: Arrhythmogenic right ventricular cardiomyopathy; Catheter ablation; Ventricular tachycardia

1 Background

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined cardiomyopathy characterized by progressive fibrofatty replacement and inflammatory infiltration from epicardium to endocardium.^[1] The altered histomorphology serves as the substrate for abnormal electric propagation which predisposes to the development of reentrant ventricular tachycardia (VT).^[2] Despite the therapeutic mainstay such as antiarrhythmic drugs or appropriate

implantable cardioverter-defibrillator (ICD) interventions to improve the prognosis of ARVC VT,^[3] adjunctive treatment with radiofrequency catheter ablation can further reduce VT burden and improve the quality of life.^[4,5]

In the past decade, epicardial ablation approach has gained wide acceptance in centers with high volume of VT ablation procedures, which demonstrated an increased acute success rate as compared with endocardial-only ablation in patients with ARVC VT.^[6,7] However, it should be noted that this complex approach seemed to possess much higher potential risks, and the short and long-term benefits remained inconsistent.^[8,9] Therefore, the optimal ablation strategy is still unclear. In order to provide a comprehensive assessment of different ablation strategies in ARVC population, we performed a systematic review with meta-analysis and trial sequential analysis. The results of this study may aid the decision-making process of the VT ablation strategy in ARVC.

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2 Methods

This systematic review was performed according to the protocol reported by PRISMA statement.^[10] We searched the Medline, Embase and Cochrane Library with the key-word strings (“arrhythmogenic right ventricular cardiomyopathy” OR “ARVC” OR “ARVD” OR “arrhythmogenic right ventricular dysplasia”) AND (“ablation”) to identify all pertinent studies published from January 1, 1990 to October 17, 2019. No language restriction was applied. Additionally, we reviewed reference lists of the eligible studies for further search.

We filtered these studies for inclusion in two steps. Firstly, the titles and abstracts were screened to exclude duplications, reviews, editorials, correspondences, case reports, conference abstracts, and irrelevant records. Secondly, the full text of these potentially relevant papers was systematically read for a final decision of inclusion. Discrepancies were resolved by consensus. Two independent investigators (LSS and LML) conducted the screening and full-text evaluation according to the prespecified inclusion criteria: (1) the diagnosis of ARVC was based on the original 1994 International Task Force criteria (TFC) or the revised 2010 TFC;^[11,12] (2) the study describing the clinical outcomes of catheter ablation for VT in patients with ARVC; and (3) the outcomes included at least one of the following items: acute procedural efficacy (defined as no inducibility of any VT at the end of the ablation); major procedural complications (defined as complications requiring intervention, such as pericardial tamponade, pericarditis, ventricle perforation, pneumothorax, pulmonary thromboembolism and other vascular complications); VT recurrence (defined as occurrence of any VT during follow-up) and all-cause mortality.

The quality assessments were given to all included studies using the Newcastle-Ottawa Scale (NOS).^[13] For each study, a score of more than five stars was regarded as moderate to high quality. Then, two independent reviewers (LSS and LML) undertook the data extraction using the standardized reporting forms including the following information: first author, publication year, study region, study design, patient demographics, baseline characteristics, procedural information, follow-up time and outcomes.

In meta-analysis, the dichotomous outcomes were summarized as odds ratios (OR) and 95% confidence intervals (CIs). Before pooling these data, Cochran’s Q test was used to assess heterogeneity with a *P* value < 0.1 representing significant heterogeneity. The *I*² index thresholds of 25%, 50% and 75% indicated low, moderate, and high degrees of heterogeneity, respectively. If low or no heterogeneity was present, a fixed effect model was applied, otherwise a ran-

dom effect model was used. Meanwhile, sensitivity analyses were performed by omitting one study in each turn to evaluate the influence on the overall effect size. The likelihood of publication bias was assessed by funnel plots and begg’s test.^[14]

To confirm whether the comparative studies had enough sample size to reach firm evidence, we conducted *post hoc* trial sequential analysis (TSA).^[15] The required information size (RIS) of each outcome was calculated based on type I error of 5% and type II error of 20% (power of 80%). The trial sequential monitoring boundaries were constructed based on O’Brien-Fleming alpha spending function. The cumulative Z-curve of each meta-analysis was plotted to assess its crossing of monitoring boundaries or RIS. If the Z-curve crosses any of these boundaries, it indicates the present level of evidence is sufficient and no further studies are required, otherwise additional studies are needed to reach firm conclusions.

The statistical analyses were performed using Review Manager Software Version 5.3 (Nordic Cochrane Center, Copenhagen, Denmark), Stata Statistical Software Version 14.0 (Stata Corporation, College Station, TX) and TSA Software Version 0.9.5.10 Beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark).

3 Results

As shown in Figure 1, the initial search identified 1070 records from the database, 1016 of which were excluded after screening titles and abstracts for the following reasons: (1) duplications (*n* = 314); (2) case reports (*n* = 122); (3) conference abstracts (*n* = 277); (4) reviews, correspondences, editorials (*n* = 118); and (5) irrelevant studies (*n* = 185). Among the remaining 54 studies, 30 were removed after full text review (25 for not meeting the inclusion criteria, 2 for overlapping population, 3 for absence of sufficient baseline or follow-up data for extraction). Finally, 24 studies were included for systematic review.^[4,6-9,16-34] Among them, 10 comparative studies of endo-epicardial ablation versus endocardial-only ablation were further selected for meta-analysis.^[6,8,9,17-21,23,24]

Table 1 summarized the general characteristics of included studies. The final review consisted of 24 studies (7 prospective design and 17 retrospective design, no randomized controlled trials) with 717 patients published between 2004 and 2019. Ablation strategies included epicardial with/without endocardial ablation (*n* = 289; 40.3%) and endocardial-only ablation (*n* = 428; 59.7%). Both ablation approaches shared the similar male proportion (73.6% vs. 71.7%),

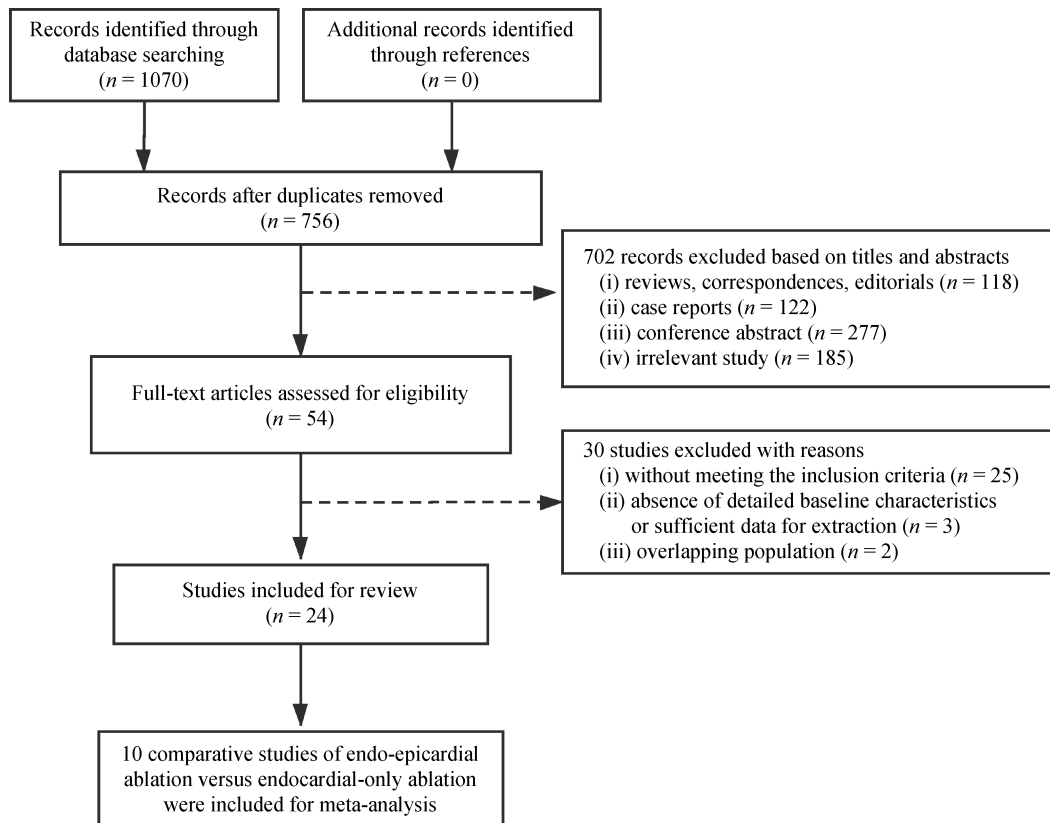


Figure 1. Flow diagram for selection of articles.

mean age (41.4 *vs.* 42.3 years), left ventricular ejective fraction (55.3% *vs.* 55.7%) and VT inducibility rate before ablation (96.8% *vs.* 98.9%) (Figure 2). In addition, the literatures of epicardial ablation were mainly published after 2010, and presented with higher rates of ICD implantation (73.7% *vs.* 44.0%), longer procedural time (4.5 *vs.* 3.3 h) and fluoroscopy time (50.8 *vs.* 40.7 min), as well as relatively shorter duration of follow-up (28.9 *vs.* 38.2 months).

Among the 10 comparative studies, a total of 426 patients including 184 with endo-epicardial ablation and 242 with endocardial ablation were enrolled for meta-analysis. No study had less than 7 stars based on NOS criteria, indicating acceptable quality. Funnel plot and Begg's test indicated no significant publication bias.

As presented in Table 2, the acute efficacy of VT non-inducibility post-ablation appeared to be higher with epicardial approach (89.8% *vs.* 73.5%). In endocardial-only ablation cohort, the publications after 2010 showed a higher acute efficacy than that before 2010 (79.5% *vs.* 67.6%). Furthermore, 6 studies with 204 patients that reported the effect of different ablation strategies on acute efficacy were included for meta-analysis. As shown in Figure 3, the epicardial approach indicated not significant improvement of acute procedural efficacy (OR: 2.74; 95% CI: 0.98–7.65;

$P = 0.051$) (Figure 3A). However, more studies are required to confirm this result according to the TSA analysis.

A total of 13 patients with epicardial ablation experienced major complication events, 10 of which were associated with intrapericardial access (six pericardial tamponade/RV laceration, one constrictive pericarditis, one intestinal perforation, one acute pericarditis, and one delayed myocardial infarction related to coronary involvement), two were deep venous thrombosis and the remaining one died from postoperative pulmonary complications. The incidence of major procedural complications in epicardial group was almost five folds of that in endocardial group (5.2% *vs.* 1.1%). Meta-analysis of 397 patients from eight studies by a fixed effect model also confirmed a higher incidence of major complication with epicardial approach (OR: 4.64; 95% CI: 1.28–16.92; $P = 0.02$; $I^2 = 0$) (Figure 3B). However, the TSA result indicated a possibility of false positivity due to no crossing of RIS or trial sequential monitoring boundary. Additional studies are needed to reach a consistent conclusion.

As described in Table 2, the approach referred to epicardial ablation reported lower VT recurrence (24.7% *vs.* 39.8%). The difference was meta-analyzed with 305 patients from 8 studies by a fixed effect model based on the

Table 1. Baseline characteristics of ARVC patients undergoing catheter ablation.

Study	Region	Design	Size, <i>n</i>	Age, yrs	Males, <i>n</i>	LVEF	With an ICD	AAD before ablation	VT inducibility
Epicardial ± endocardial ablation									
Aras 2019 ^[16]	Turkey	Prospective, single center	11	36.6 ± 6.8	6 (54.5%)	56.5 ± 5.3	11 (100%)	11 (100%)	11 (100%)
Laredo 2019* ^[17]	France	Retrospective, multicenter	4	51.5 ± 27.0	4 (100.0%)	49.5 ± 22.3	3 (75.0%)	4 (100%)	4 (100%)
Mathew 2019* ^[18]	Germany	Retrospective, single center	21	NR	NR	NR	NR	NR	NR
Santangeli 2019* ^[19]	USA et al.	Prospective, multicenter	23	46.5 ± 13.6	19 (82.6%)	60.3 ± 7.4	0	18 (78.3%)	22 (95.7%)
Souissi 2018* ^[20]	France	Retrospective, multicenter	9	NR	NR	NR	NR	9 (100%)	NR
Berrueto 2017 ^[7]	Spain	Prospective, multicenter	34	40.8 ± 13.1	29 (85.3%)	52.3 ± 12.1	34 (100%)	27 (65.8%)	NR
Müssigbrodt 2017* ^[9]	Germany	Retrospective, single center	22	51.7 ± 13.3	17 (77.3%)	58 ± 7	22 (100%)	22 (100%)	NR
Wei 2017* ^[6]	China	Retrospective, single center	17	40.5 ± 11.5	13 (76.5%)	NR	4 (23.5%)	NR	NR
Berte 2016* ^[21]	France et al.	Retrospective, multicenter	4	NR	NR	NR	4 (100%)	4 (100%)	4 (100%)
Philips 2015 ^[22]	USA	Retrospective, single center	30	33.1 ± 11.1	16 (53.3%)	NR	NR	NR	28 (93.3%)
Santangeli 2015* ^[8]	USA	Retrospective, single center	39	NR	NR	NR	NR	NR	NR
Philips 2012* ^[23]	USA	Retrospective, multicenter	23	NR	NR	NR	NR	NR	NR
Bai 2011* ^[24]	USA et al.	Prospective, multicenter	26	37 ± 11	18 (69.2%)	53 ± 10	26 (100%)	26 (100%)	26 (100%)
Schmidt 2010 ^[25]	Germany	Prospective, single center	13	43 ± 18	10 (76.9%)	55 ± 8	7 (53.9%)	NR	12 (92.3%)
Garcia 2009 ^[26]	Spain	Retrospective, single center	13	43 ± 15	10 (76.9%)	NR	12 (92.3%)	13 (100%)	13 (92.3%)
Summary	-	5 Prospective studies; 10 Retrospective studies	289	-	142/193 (73.6%)	-	123/167 (73.7%)	134/146 (91.8%)	120/124 (96.8%)
Endocardial-only ablation									
Laredo 2019* ^[17]	France	Retrospective, multicenter	19	41.9 ± 14.2	19 (100%)	56 ± 6.9	16 (84.2%)	18 (94.7%)	17 (89.5%)
Mathew 2019* ^[18]	Germany	Retrospective, single center	26	NR	NR	NR	NR	NR	NR
Santangeli 2019* ^[19]	USA et al.	Prospective, multicenter	9	39.8 ± 11.0	4 (44.4%)	61.9 ± 4.0	0	4 (44.4%)	9 (100%)
Souissi 2018* ^[20]	France	Retrospective, multicenter	40	NR	NR	NR	NR	40 (100%)	NR
Müssigbrodt 2017* ^[9]	Germany	Retrospective, single center	23	54.9 ± 15.1	13 (56.5%)	54 ± 10	23 (100%)	23 (100%)	NR
Wei 2017* ^[6]	China	Retrospective, single center	31	39.8 ± 13.9	20 (64.5%)	NR	7 (22.6%)	NR	NR
Berte 2016* ^[21]	France et al.	Retrospective, multicenter	3	NR	NR	NR	3 (100%)	3 (100%)	3 (100%)
Santangeli 2015* ^[8]	USA	Retrospective, single center	23	NR	NR	NR	NR	NR	NR
Hros̆ova' 2012 ^[27]	Czech	Retrospective, single center	9	40 ± 17	8 (88.9%)	56.7 ± 10.6	2 (22.2%)	3 (33.3%)	9 (100%)
Philips 2012* ^[23]	USA	Retrospective, multicenter	64	NR	NR	NR	NR	NR	NR
Bai 2011* ^[24]	USA et al.	Prospective, multicenter	23	34 ± 14	15 (65.2%)	57 ± 7	23 (100%)	23 (100%)	23 (100%)
Nair 2011 ^[28]	India	Prospective, single center	15	44 ± 15	12 (80.0%)	NR	2 (13.3%)	15 (100%)	15 (100%)
Nogami 2008 ^[29]	Japan	Retrospective, single center	18	48 ± 11	13 (72.2%)	NR	2 (11.1%)	12 (66.7%)	18 (100%)
Dalal 2007 ^[30]	USA	Retrospective, multicenter	24	36 ± 9	11 (45.8%)	NR	5 (20.8%)	15 (62.5%)	24 (100%)
Yao 2007 ^[4]	China	Retrospective, single center	32	37.2 ± 12.8	26 (81.3%)	55 ± 10	2 (6.3%)	32 (100%)	NR
Satomi 2006 ^[31]	Japan	Prospective, single center	17	47 ± 17	13 (76.5%)	NR	0	15 (88.2%)	17 (100%)
Miljoen 2005 ^[32]	France	Retrospective, single center	11	50 ± 17	8 (72.7%)	54 ± 9	4 (36.4%)	11 (100%)	11 (100%)
Verma 2005 ^[33]	USA	Retrospective, single center	22	41 ± 15	15 (68.2%)	55 ± 8	18 (81.8%)	22 (100%)	22 (100%)
Marchlinski 2004 ^[34]	USA	Retrospective, single center	19	47 ± 18	18 (94.7%)	NR	14 (73.7%)	NR	19 (100%)
Summary	-	4 Prospective studies; 15 Retrospective studies	428	-	195/272 (71.7%)	-	121/275 (44.0%)	236/265 (89.1%)	187/189 (98.9%)

Data are presented as mean ± SD or *n* (%). AAD: anti-arrhythmic drugs; ICD: implantable cardioverter-defibrillator; NR: not reported; VT: ventricular tachycardia; *study included both endocardial-only ablation and epicardial ± endocardial ablation patients.

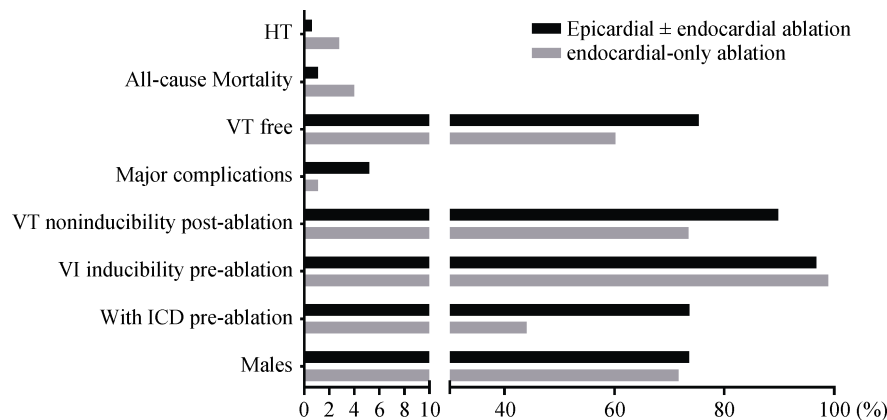


Figure 2. The amalgamated data of different ablation strategies. All data were presented as the percentage. HT: heart transplantation; ICD: implantable cardioverter-defibrillator; VT: ventricular tachycardia.

heterogeneity test among individual studies ($I^2 = 0$). The pooled data also indicated a significant decrease of VT recurrence with endo-epicardial ablation (OR: 0.50; 95% CI: 0.30–0.85; $P = 0.010$) (Figure 3C). The TSA analysis showed that the cumulative Z-curve crossed the trial sequential monitoring boundary which indicated a sufficient sample size to confirm our conclusion.

The data in Table 2 indicated lower all-cause mortality (1.1% vs. 4.0%) and heart transplantation (0.6% vs. 2.8%) with epicardial ablation. However, the meta-analysis of 246 patients from 6 studies by a random model based on the heterogeneity test ($I^2 = 67\%$) showed not significant difference in all-cause mortality (OR: 0.87; 95% CI: 0.09–8.31; $P = 0.90$) (Figure 3D). Although with moderate heterogeneity between 5 studies, the sensitivity analysis revealed no individual study excessively affected the pooled result. In TSA, the cumulative Z-curve did not exceed either RIS or trial sequential monitoring boundary, which suggested a possibility of false negativity in the current results, and more participants are required for further investigation.

4 Discussion

This study analyzed the clinical outcomes of different VT ablation strategies in ARVC. The main findings were that compared with the endocardial-only ablation, the epicardial ablation decreased the VT recurrence, increased the risk of major procedural complications and showed no extra benefits in acute procedural efficacy or all-cause mortality.

Ventricular tachycardia is a common feature in ARVC with an incidence rate of 28% to 35%.^[35,36] As a recommended treatment, catheter ablation can reduce the VT burden, while its acute and long-term efficacy remains controversial.^[37,38] Recently, the application of 3-D electroanatomic mapping technology enabled the accurate identification

of VT origins and unveiled the epicardial substrates in ARVC.^[26] The reported studies with epicardial ablation strategy seemed to increase the ablation efficacy. However, it's noteworthy that the epicardial access with dry pericardiocentesis also increased the procedural complications. In view of the limited evidence of efficacy and safety in a single study, this meta-analysis was performed to give a comprehensive comparison between the epicardial ablation and endocardial-only ablation.

The pooled data in this study further demonstrated the clinical superiority of epicardial approach in long-term VT control. Interestingly, these two ablation strategies showed no difference in acute ablation efficacy. One explanation was that the application of voltage mapping and new ablation catheters (e.g., irrigated tip ablation catheter with a contact force sensor) allowed to identify and eliminate the abnormal potentials and achieve a more completed transmural ablation from the endocardial side, which may partly diminish the difference in acute ablation success. However, the limited sample size may underestimate the difference and the P value of acute efficacy in this meta-result has already shown the tendency to support epicardial approach. In addition, considering the progressive nature of ARVC, the short follow-up periods with epicardial ablation due to the late promotion of this strategy may also underestimate the VT recurrence. Therefore, the difference of acute and long-term VT control between these two strategies remains to be verified by high-volume RCTs or cohorts with long-term follow-up durations.

Just as every coin has two sides, epicardial ablation also brings procedural complications. Sacher, *et al.*^[39] reported an incidence rate of acute or delayed complication to be 7%, which was in line with the findings by Philips, *et al.*^[23] In this study, the pooled data indicated more procedural complications with epicardial ablation, most of which were

Table 2. Procedural data and outcomes of ARVC patients undergoing catheter ablation.

Study	Size, n	PT, h	FT, min	VT noninducibility post-ablation	Major complications, n	FU, months	AAD after ablation	VT free, n	Death (n)	HT, n
Epicardial ± endocardial ablation										
Aras 2019 ^[16]	11	4.1	6.5	8 (72.7%)	0	14.8 ± 4.0	11 (100%)	9 (81.8%)	0	0
Laredo 2019* ^[17]	4	NR	NR	3 (75.0%)	0	37.2 ± 27.6	3 (75.0%)	4 (100%)	0	0
Mathew 2019* ^[18]	21	5.0	20.0	NR	1 (pericardial tamponade%)	50.8 [†]	NR	NR	NR	NR
Santangeli 2019* ^[19]	23	NR	NR	23 (100.0%)	1 (RV laceration%)	46.2 ± 17.9	NR	19 (82.6%)	0	0
Souissi 2018* ^[20]	9	NR	NR	NR	1 (intestinal perforation%)	64 ± 51 [†]	9 (100%)	NR	NR	0
Berruezo 2017 ^[7]	34	NR	NR	31 (91.2%)	2 (pericardial tamponade%)	32.2 ± 21.8	21 (51.2%)	28 (82.4%)	1	NR
Müssigbrodt 2017* ^[9]	22	3.4	41.8	19 (86.4%)	NR	31.1 ± 27.4 [†]	19 (86.4%)	13 (59.1%)	NR	NR
Wei 2017* ^[6]	17	NR	NR	17 (100%)	0	71.4 ± 45.7 [†]	NR	12 (70.6%)	0	0
Berte 2016* ^[21]	4	NR	NR	3 (75.0%)	NR	12.8 ± 8.7	NR	3 (75.0%)	0	0
Philips 2015 ^[22]	30	NR	82.2	29 (96.7%)	1 (acute pericarditis%)	19.7 ± 11.7	10 (33.3%)	22 (73.3%)	0	0
Santangeli 2015* ^[8]	39	NR	NR	NR	5 (2 DVT, 1 pericardial effusion, 1 RV puncture, 1 constrictive pericarditis%)	56 ± 44 [†]	NR	30 (76.9%)	NR	NR
Philips 2012* ^[23]	23	NR	NR	NR	2 (1 death, 1 delayed myocardial infarction%)	88.3 ± 66 [†]	9 (39.1%)	15 (65.2%)	1	0
Bai 2011* ^[24]	26	5.3	65.9	26 (100.0%)	0	40.8 ± 10.3	8 (30.8%)	22 (84.6%)	0	0
Schmidt 2010 ^[25]	13	NR	NR	7 (53.8%)	NR	12.1	NR	8 (61.5%)	NR	NR
Garcia 2009 ^[26]	13	NR	NR	11 (84.6%)	0	18.3 ± 12.7	11 (84.6%)	10 (76.9%)	0	1
Summary	289	–	–	177/197 (89.8%)	13/250 (5.2%)	–	101/172 (58.7%)	195/259 (75.3%)	2/185 (1.1%)	1/160 (0.6%)
Endocardial-only ablation										
Laredo 2019* ^[17]	19	NR	NR	8 (42.1%)	0	62.4 ± 39.6	17 (89.5%)	17 (89.5%)	3	3
Mathew 2019* ^[18]	26	4.2	13.5	NR	0	50.8 [†]	NR	NR	NR	NR
Santangeli 2019* ^[19]	9	NR	NR	9 (100.0%)	0	55.2 ± 18.7	NR	7 (77.8%)	0	0
Souissi 2018* ^[20]	40	NR	NR	NR	2 (1 tamponade and hemothorax, 1 femoral arterio-venous fistula%)	64 ± 51 [†]	39 (97.5%)	NR	NR	2
Müssigbrodt 2017* ^[9]	23	2.7	30.2	19 (82.6%)	NR	31.1 ± 27.4 [†]	19 (82.6%)	13 (56.5%)	NR	NR
Wei 2017* ^[6]	31	NR	NR	22 (71.0%)	0	71.4 ± 45.7 [†]	NR	11 (35.5%)	4	1
Berte 2016* ^[21]	3	NR	NR	3 (100.0%)	NR	24.7 ± 11.0	NR	3 (100.0%)	0	0
Santangeli 2015* ^[8]	23	1.3	NR	NR	0	56 ± 44 [†]	NR	14 (60.9%)	NR	NR
Hros'ova' 2012 ^[27]	9	3.3	32.0	8 (88.9%)	NR	52 ± 31	1 (11.1%)	8 (88.9%)	0	0
Philips 2012* ^[23]	64	NR	NR	NR	0	88.3 ± 66 [†]	39 (60.9%)	29 (45.3%)	0	0
Bai 2011* ^[24]	23	3.9	51.3	23 (100.0%)	0	39.2 ± 3.7	18 (78.3%)	12 (52.2%)	0	0
Nair 2011 ^[28]	15	NR	NR	13 (86.7%)	0	25 ± 16	15 (100%)	13 (86.7%)	0	0
Nogami 2008 ^[29]	18	3.6	NR	8 (44.4%)	NR	61 ± 38	13 (72.2%)	12 (66.7%)	3	NR
Dalal 2007 ^[30]	24	NR	NR	10 (41.7%)	1 (death%)	32 ± 36	20 (83.3%)	4 (16.7%)	1	2
Yao 2007 ^[4]	32	3.4	42.0	24 (75.0%)	0	28.6 ± 16	23 (71.9%)	26 (81.3%)	0	0
Satomi 2006 ^[31]	17	NR	NR	15 (88.2%)	0	26 ± 15	9 (52.9%)	13 (76.5%)	0	0
Miljoen 2005 ^[32]	11	3.5	23.0	8 (72.7%)	0	36	7 (63.6%)	5 (45.5%)	1	NR
Verma 2005 ^[33]	22	NR	83.0	18 (81.8%)	1 (pericardial tamponade%)	37	22 (100%)	14 (63.6%)	0	0
Marchlinski 2004 ^[34]	19	4.2	NR	14 (73.7%)	0	27 ± 22	NR	17 (89.5%)	NR	1
Summary	428	–	–	202/275 (73.5%)	4/375 (1.1%)	–	242/317 (76.3%)	218/362 (60.2%)	12/297 (4.0%)	9/327 (2.8%)

Data are presented as mean ± SD or n (%). ARVC: arrhythmogenic right ventricular cardiomyopathy; DVT: deep venous thrombosis; FT: fluoroscopy time; FU: follow-up; NR: not reported; PT: procedural time; RV: right ventricular; VT: ventricular tachycardia; HT: heart transplantation. *Indicating the comparative studies of combined endo-epicardial ablation versus endocardial-only ablation; †indicating the follow-up time in whole population.

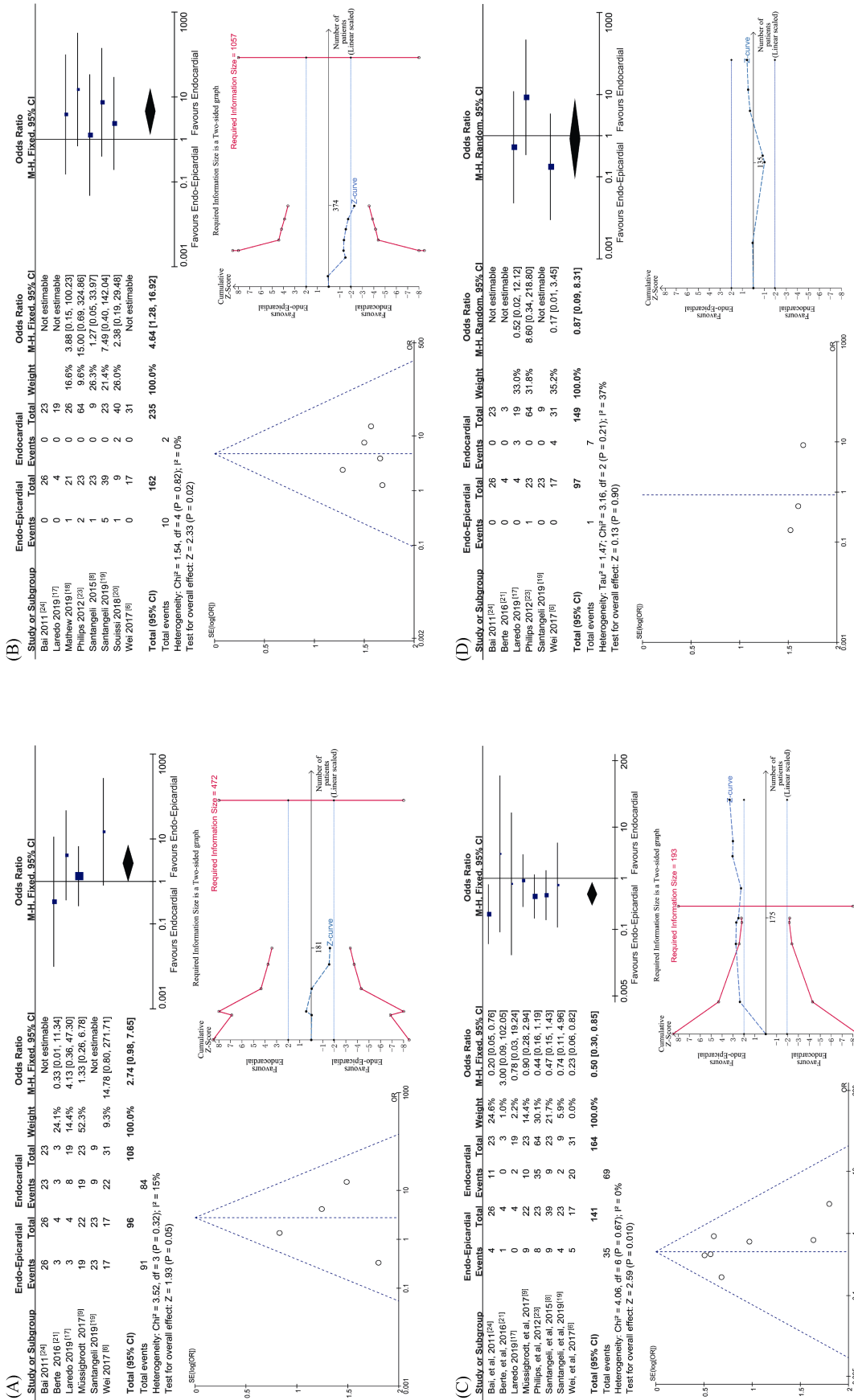


Figure 3. Meta-analysis and trial sequential analysis of the clinical outcomes with two ablation strategies. (A): Forest plot, funnel plot and trial sequential analysis of acute procedural efficacy; (B): forest plot, funnel plot and trial sequential analysis of the major procedural complications; (C): forest plot, funnel plot and trial sequential analysis of the VT recurrence; and (D): forest plot, funnel plot and trial sequential analysis of the all-cause mortality.

associated with subxiphoid intrapericardial access and ablation. The increased complications may prolong the hospitalization period and increase the health-care costs. Consequently, these findings did not provide compelling evidence for the overall superiority of epicardial approach as a preferred ablation strategy of VT in patients with ARVC, and the epicardial ablation needs to be prudently performed in experienced centers after carefully weighing the benefits and the risks.

Several previous studies with endocardial-only ablation described relatively high all-cause mortalities. Notably, less than 30% of patients had an ICD and most of the death events attributed to sudden cardiac death, whereas the recent studies with epicardial ablation always had more ICD implantation. In this meta-analysis, these two ablation strategies showed a similar ICD occupation, therefore avoiding the indirect survival benefit from a higher ICD implantation rate. The pooled data indicated no additional survival benefit with epicardial ablation. In fact, the causes of death in ARVC are varied, whatever the endocardial or epicardial approach, catheter ablation could not improve the mortality caused by heart failure or other reasons. Certainly, due to the relatively short follow-up durations and insufficient sample sizes according to TSA analysis, this result also had the risk of failing to present the difference.

There are several limitations to note. Firstly, these ablation studies mostly focused on the population with approximately normal LVEF, which may limit the generalization of the conclusion to the patients with cardiac dysfunction. Furthermore, the included studies were published with a long time period, therefore the evolution of therapeutic strategy may also affect the ablation outcomes. Thirdly, most studies were retrospective, single-center studies with relatively small sample sizes, which reduced the level of clinical evidence. To compensate this weak point, we did trial sequential analysis to confirm the reliability of results. Nevertheless, the large-scale, prospective, multicenter trials shall further contribute to our conclusion. Finally, due to the limitation of data availability in some publications, we could not give a comprehensive analysis of part clinical outcomes. Therefore, a completed collection of these parameters by contacting principal investigator for pertinent information should be considered in future work.

In summary, Catheter ablation for VT in ARVC is feasible and effective. Although epicardial ablation indicates better long-term VT freedom, it is also related to higher incidence of major procedural complications with not evident survival or acute efficacy benefit.

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