A comparable efficacy and safety between intracardiac echocardiography and transesophageal echocardiography for percutaneous left atrial appendage occlusion

Ru-xing Wang[1], Zhi-Yuan Zhang[1], Feng Li[1], Jie Zhang[1], Lei Zhang[1], Huan-Huan Liu[1], Ning Zhao[1], Fan Yang[1], Qi Kong[1], Yi-Ting Zhou[1], and Ling-Ling Qian[1]

[1]Wuxi People's Hospital

January 31, 2023

Abstract

Background: Accumulated clinical studies utilize intracardiac echocardiography (ICE) to guide percutaneous left atrial appendage closure (LAAO), but its procedural success and safety compared to traditional transesophageal echocardiography (TEE) remain elusive. We performed a meta-analysis to compare efficacy and safety between ICE and TEE for LAAO. **Methods:** Studies were screened with four online databases (including the Cochrane Library, Embase, PubMed, and Web of Science) from their inception to 1 December 2022. We utilized random or fixed-effect model to synthesize the clinical outcomes. Subgroup analysis was performed to screen the potential confounding factors. **Results:** A total of twenty eligible studies with 3,610 atrial fibrillation patients (1,564 patients for ICE and 2,046 patients for TEE) were enrolled. Compared with TEE group, there was no significant difference in procedural success rate (RR=1.01; 95% CI: 1.00,1.02; P=0.171; I^2=0.00%), total procedural time [weighted mean difference (WMD) = -5.58; 95%CI: -15.97, 4.81; P=0.292; I^2=96.40%], contrast volume (WMD=-2.61; 95%CI: -12.25, 7.02; P=0.595; I^2=84.80%), and fluoroscopic time (WMD=-0.34; 95%CI: -2.09, 1.41; P=0.705; I2=82.80%) in the ICE group. Subgroup analysis revealed ICE showed less contrast use than TEE in the lower proportion paroxysmal atrial fibrillation group and lower proportion hypertension. **Conclusion:** Our study suggests that ICE may have comparable efficacy and safety compared to TEE for LAAO.

Title Page

Title: A comparable efficacy and safety between intracardiac echocardiography and transesophageal echocardiography for percutaneous left atrial appendage occlusion

Running title : LAAO outcomes of ICE versus TEE

Authors: Zhi-Yuan Zhang, MD#, Feng Li, MD#, Jie Zhang, MD#, Lei Zhang, MD, Huan-Huan Liu, MD, Ning Zhao, MD, Fan Yang, MD, Qi Kong, MD, Yi-Ting Zhou, MD, Ling-Ling Qian, PhD, Ru-Xing Wang, MD, PhD

#The first three authors contributed equally to this work.

Author Affiliations:

Department of Cardiology, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi 214023, China.

***Correspondence author:**

Dr. Ru-Xing Wang, Department of Cardiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, No. 299, Qingyang Road, Wuxi 214023, China. Tel: 0086-510-85351593; Email: *ruxingw@aliyun.com.*

Founding

None.

Authors contribution: Ru-Xing Wang developed the concept of the study; Zhi-Yuan Zhang, Feng Li, Jie Zhang designed this study and carried out the data analysis; Feng Li, and Zhi-Yuan Zhang conducted meta-analysis registration in PROSPERO platform with the help from Ru-Xing Wang; Zhi-Yuan Zhang wrote the manuscript with help from Feng Li, Jie Zhang, Lei Zhang, Huan-Huan Liu, Ning Zhao, Fan Yang, Qi Kong; Yi-Ting Zhou, Ling-Ling Qian, and Ru-Xing Wang provided critical reviews of the paper. All authors have read and approved the final manuscript.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

Not applicable

Ethics approval

Not applicable.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract

Background:

Accumulated clinical studies utilize intracardiac echocardiography (ICE) to guide percutaneous left atrial appendage closure (LAAO), but its procedural success and safety compared to traditional transesophageal echocardiography (TEE) remain elusive. We performed a meta-analysis to compare efficacy and safety between ICE and TEE for LAAO.

Methods:

Studies were screened with four online databases (including the Cochrane Library, Embase, PubMed, and Web of Science) from their inception to 1 December 2022. We utilized random or fixed-effect model to synthesize the clinical outcomes. Subgroup analysis was performed to screen the potential confounding factors.

Results:

A total of twenty eligible studies with 3,610 atrial fibrillation patients (1,564 patients for ICE and 2,046 patients for TEE) were enrolled. Compared with TEE group, there was no significant difference in procedural success rate (RR=1.01; 95% CI: 1.00,1.02; P =0.171; I^2=0.00%), total procedural time [weighted mean difference (WMD) = -5.58; 95%CI: -15.97, 4.81; P =0.292; I^2=96.40%], contrast volume (WMD=-2.61; 95%CI: -12.25, 7.02; P =0.595; I^2=84.80%), and fluoroscopic time (WMD=-0.34; 95%CI: -2.09, 1.41; P =0.705; I2=82.80%) in the ICE group. Subgroup analysis revealed ICE showed less contrast use than TEE in the lower proportion paroxysmal atrial fibrillation group and lower proportion hypertension.

Conclusion:

Our study suggests that ICE may have comparable efficacy and safety compared to TEE for LAAO.

1. Introduction

Atrial fibrillation (AF) is the most common persistent atrial arrhythmia worldwide. The prevalence of AF in adults is currently estimated to be between 2% and 4%, with a 2.3-fold increase expected due to extended life expectancy in the general population and increased search for undiagnosed AF[1]. Cardioembolic stroke is

the most concerning complication of AF. Due to abnormal blood flow in the left atrium, the thrombus from the left atrial appendage (LAA) is more likely to rupture, subsequently leading to thromboembolisms in the peripheral and cerebral arteries[2]. The primary prevention strategy of thromboembolism for AF is the use of oral anticoagulants (OACs). However, challenge remains due to the limitation of adherence and bleeding risk for safety and efficacy of OACs. Since most thrombus in nonvalvular AF originates from the LAA, left atrial appendage occlusion was emerging as an alternative for OACs. TEE is the standard imaging modality to guide LAAO and is the most widely used imaging modality. However, it has some significant limitations, such as the need for general anesthesia and a dedicated anesthetist, as well as a significant logistical burden.

Recently, an expert consensus suggested that ICE might be severed as an alternative imaging modality to guide LAAO[3]. However, studies comparing TEE with ICE for LAAC are limited, leading to the related outcomes (e.g., efficacy and safety outcomes) remaining elusive. Therefore, we evaluated the clinical outcomes of TEE and ICE guidance for LAAO to further assess the safety and efficacy outcomes between two imaging modalities.

2. Methods

2.1. Study Design

This systematic review was conducted according to the PRISMA guidelines. The registered protocol displayed in the PROSPERO database (CRD42022368692).

2.2. Search Strategy

Two independent reviewers (Z.Y.Z and F.L) conducted comprehensive searches of four online databases (Cochrane Library, Embase, PubMed and Web of Science) from inception to 1 December 2022. Search keywords were "ICE","Intracardiac echocardiography","TEE ","transesophageal echocardiography" ,"atrial fibrillation", "LAAC", "left atrial appendage closure", "LAAO", and "left atrial appendage occlusion" Clinical studies related to the outcomes of ICE or outcomes comparing TEE vs. ICE for endocardial LAAO were included. Reference lists of review articles were hand searched, and eligible articles were searched for potential publications not previously identified.

2.3. Search Design

Two reviewers (Z.Y.Z and J.Z) independently searched the literature and screen the titles, abstracts and full texts to select all relevant studies that met the inclusion criteria. A study would be included if the following criteria were met: (1) randomized controlled trials and cohort, observational studies, and single-arm studies; (2)studies comparing clinical outcomes comparing TEE vs. ICE for endocardial LAAO, including efficacy outcome (e.g., procedural success) and safety outcomes (e.g. short-term complications and long-term complications); (3) studies with full text published in peer-reviewed journals; and studies containing the most data for multiple publications of the same study . Case reports, editorial, review articles, studies without original data letters and studies reporting clinical outcomes with hybrid LAAO procedures were excluded. Meanwhile, a third reviewer (R.X.W) resolved any disagreements about eligibility

2.4. Data Extraction and Quality Assessment

Data from eligible studies included in the analysis were extracted by two independent researchers (Z.Y.Z and F.L), and any potential disagreements were resolved by a third researcher (R.X.W). The extracted data mainly includes: title, first author, publication year, study design, sample size, follow-up time, LAAO device, Pre-procedure imaging and ICE Location. Meanwhile we also extracted relevant clinical outcomes, including: acute procedural success, total procedural time, Fluoroscopic time, Contrast volume, short-term complications and long-term complications.

Two independent researchers (Z.Y.Z and J.Z) evaluated study quality by two appraisal tools. The Newcastle-Ottawa Quality Assessment Scale was used to evaluated the two-arm observation [4]. The Institute of Health Economics checklist was used for the single-arm study[5]. Any disagreements were discussed and resolved by consulting a third researcher (R.X.W).

2.5. Statistical Analysis

Stata version 16.0 was used for statistical analyses. Continuous variables are displayed as means +- SD, and categorical variables are presented as frequencies and percentages. For observational studies with two arms, we calculated the relative risk (RR) and corresponding 95% confidence intervals (CI) for each outcome, whereas for single-arm analysis, we calculated the incidence of events (number of events divided by number of patients) and 95% confidence intervals. $P< 0.05$ was considered statistically significant.

Meanwhile, chi-square tests and I-squared (I^2) are used to quantify and assess statistical heterogeneity among studies. If the I^2 value was more than 50% and/or $P< 0.05$ for the chi-squared test, we considered the between-study heterogeneity to be significant, and we would adopt a random-effect model. Otherwise, we would adopt fixed-effect model. Sensitivity analysis was performed by sequentially omitting one study at a time to assess the effect of a single study on the overall risk, and potential publication bias was also evaluated via Egger's test.

In addition, subgroup analysis was conducted to screen potential determinants of LAAO outcomes between ICE and TEE groups. According to the characteristics of eligible studies, a total of eight subgroup factors were identified, including study design, elderly age cutoff, ICE group sample size, AF type, male proportion, hypertension proportion, device types and duration of follow up. If the study design included more than one center, it was defined as a multicenter subgroup; otherwise, it was defined as a single-center subgroup. According to age cut-off values of 75, it was divided into [?] 75 years subgroup and <75 years subgroups. If more than 50% of patients have paroxysmal AF, they are classified as [?]50% PAF group, otherwise they are classified as <50% PAF group. According to the proportion of the male, they were divided into subgroups with [?] 70% and subgroups with < 70%. Similarly, the proportion of hypertension with "[?] 90%" and "< 90%" subgroup also was defined. According to the sealing position, the existing sealers can be roughly divided into plug type and disc type. Plug type sealers, also known as single sealers, including Watchman, Plaato, and Lefort. Disc sealer is also called dual sealer, including ACP, Lambre, Lacbes, and Leftear. If the LAAO devices included only dual-seal mechanism devices, it was assigned to dual-seal mechanism subgroup, and if the LAAO devices included only single-seal mechanism devices, it was assigned to the single-seal mechanism subgroup. In addition, studies using both dual-seal mechanism devices and single-seal mechanism devices are divided into muti-seal mechanism subgroup. Follow-up time was divided into two subgroups ([?]12 months and <12 months).

3. Results

3.1. Study selection and quality assessment

This meta-analysis includes 20 studies with a total of 3,610 AF patients (1,564 patients for ICE and 2,046 patients for TEE) consisting of 10 observational two-arm studies (965 ICE patients and 2,046 TEE patients)[6-15]and 10 single-arm studies (599 ICE patients)[16-25]. The selection flowchart was displayed in **Figure 1** . The average age of the patients included in the studies ranged from 71.3 to 80.3 years. Among the included clinical studies, the mean CHA2DS2-VASc score and HAS-BLED score ranged from 3.9 to 5.3 and 2.4 to 4.4. Eleven studies included Watchman or Watchman FLX[6, 8, 9, 13, 16, 17, 19-23], six included the ACP or Amulet device[10, 11, 14, 18, 24, 25] and three studies included both[7, 12, 14]. The baseline characteristics and procedure-related indexes of the eligible studies were presented in **Table 1** . In this meta-analysis, all two-arm studies had a moderate-to-high quality (**Supplementary Table 1**). Ten single-arm studies all had a score higher than fifteen (**Supplementary Table 1**).

3.2 Primary outcome

3.2.1 Procedural success rate

All eligible two-arms studies reported the acute procedural success data and there was no significant difference in procedural success rate (RR=1.01; 95% CI: 1.00,1.02; P =0.171; I2=0.00%) between two groups (**Figure 2**)[6-15]. Our result was similar to those of several other meta-analyses[26-28]. Subgroup analysis was performed with a total of eight subgroup factors for the acute procedural success of LAAO, and the

results are displayed in**Figure 3** . There was no significant difference between TEE group and ICE group in the study design subgroup, follow-up subgroup, ICE sample size subgroup, male proportion subgroup, age cutoff subgroup, hypertension proportion subgroup, paroxysmal AF proportion subgroup, and device types subgroup, suggesting that all subgroup results were consistent with the pooled result.

We also performed a sensitivity analysis and the results showed no significant change, ranging from 1.00 (95% CI: 0.99,1.02) to 1.01 (95% CI:1.00,1.03), in the overall combined proportion, suggesting that there was no single study in the domination of the combined proportion and heterogeneity. Moreover, no publication bias was presented in Egger's test (P =0.208).

3.2.2 Pooled rate of procedural success in ICE group

A total of 20 eligible studies (1,564 patients undergoing LAAO with ICE procedural guidance) reported the rate of procedural success in ICE Group[6-15] . The pooled rate of procedural success was 0.99 (95% CI: 0.98–1.0; P = 0.02; I2 = 43.69%) with the random-effect model (**Figure 4**). Meanwhile we performed a subgroup analysis with eight subgroup factors for procedural success in ICE group, and the results are shown in **Table 2** . Overall, the pooled rate of procedural success in ICE Group does not differ significantly between subgroups.

Also, sensitivity analysis showed that no significant change was detected in the overall combined proportion, ranging from 0.98 (95% CI: 0.97, 0.99) to 0.99 (95% CI: 0.98,1.00), indicating that no single study dominated the combined proportion and heterogeneity. Moreover, Egger's test was performed and result showed no publication bias (P =0.068). which indicated that the results were considered to be robust.

3.3 Secondary outcome

3.3.1 Total procedure time

A total of ten clinical studies provided the total procedural time, and the data on the total procedural time was similar between groups [WMD = -5.58;95%CI: -15.97,4.81; P =0.29][6-15]. Significant heterogeneity was observed (I2 =96.4%) (**Figure 5**). Subgroup analysis was performed with a total of eight subgroup factors for total procedure time, and the results are displayed in **Supplementary Table 2** . Interestingly, in the paroxysmal AF proportion [?] 50% subgroup, the procedural time in the TEE group was shorten than in the ICE group (WMD: -12.08; 95% CI: 7.6–20.8; P = 0.000; I2 = 98.2%). Sensitivity analysis showed that no significant change, ranging from-7.80 (95% CI: -18.72,3.11) to -1.35 (95% CI: -10.13,7.44), was detected in the overall combined proportion. Moreover, no publication bias was shown in Egger's test(P =0.535).

3.3.2 Contrast volume

All studies selected involving a total of six eligible studies reporting the contrast volume[6-8, 10, 13, 14]. The pooled results indicated that compared with the TEE procedure, the ICE procedure showed no significant difference (WMD -2.61; 95%CI: -12.25, 7.02; P =0.595; I2=84.80%) **(Figure 6).** The subgroup analysis showed that in the paroxysmal AF <50% subgroup, the ICE group's contrast volume was significantly decreased compared with the TEE group [WMD -15.02; 95%CI: -27.08, -3.07; P = 0.015; I2 = 78.60%]. Moreover, in the hypertension proportion < 90% subgroup, the contrast volume in the ICE group was much lower than that in the TEE group [WMD-12.95; 95%CI: -22.83, -3.07; P = 0.010; I2=62.90%] **(Supplementary Table 3)** .

Meanwhile, sensitivity analysis showed that no single study dominated the combined proportion and heterogeneity, ranging from -4.81 (95% CI: -15.29, 5.66) to 1.26 (95% CI: -8.55, 11.06). Moreover, Egger's test was performed and result showed no publication bias (P=0.371). which indicated that the results were considered to be robust.

3.3.3Fluoroscopic time

A total of ten eligible studies reported the fluoroscopic time and the pooled result showed that the fluoroscopic time guided by ICE was significantly equivalent to that guided by TEE (WMD -0.34; 95%CI: -2.09, 1.41; P

=0.705; I2=82.80%) (**Figure 7**)[6-15]. Subgroup analysis was performed with a total of 8 subgroup factors for the fluoroscopic time, and the results are displayed in**Supplementary Table 4** . No significant change was detected in the overall combined proportion by sensitivity analysis, ranging from-0.72 (95% CI: -2.48, 1.03) to 0.07 (95% CI: -1.74, 1.87). Moreover, no publication bias was shown in Egger's test (P =0.941).

3.3.4 Pooled safety outcomes

Common perioperative complications include cardiac effusion, cardiac tamponade, Device migration, Device thrombus, Stroke/TIA, bleeding, hematoma, renal complications, cardiac arrest, death, et al. The data on procedural complications was available in nine clinical studies[6-8, 10-15].Complications from each study are listed independently in **Supplementary Table 5** and**Supplementary Table 6** . The rate of procedural complications in ICE group is similar to that of TEE group (RR:0.82; 95%CI: 0.58,1.16;P =0.261; I2=23.50%) (**Figure 8**). Sensitivity analysis was performed and the results showed no significant change in the overall combined proportion, ranging from 0.70 (95%CI:0.45,1.10) to 0.87 (95%CI:0.61,1.25). Egger's test also showed no publication bias (P =0.696). Meanwhile, seven clinical studies were followed up and reported long-term adverse events [6-11, 14]. In terms of long-term adverse events, the ICE group showed a similar result to TEE group (RR=0.86; 95%CI: 0.64,1.16; P =0.329; I2=41.10%) (**Figure9**).

4. Discussion

Among 20 enrolled published original articles, a total of 3,610 patients (1,564 patients for ICE and 2,046 patients for TEE) were evaluated. Compared to several other meta-articles, we enrolled recent publications and single-arm studies. Meanwhile we performed a subgroup analysis for each endpoint event. Our main findings are as follows: 1) Compared with TEE group, ICE group showed comparable efficacy and safety outcomes for LAAO, including the acute procedural success rate, total procedure time, contrast volume, the fluoroscopic time and safety outcomes. 2) ICE-guided LAAO might reduce the use of contrast agent than TEE-guided LAAO in the lower proportion PAF, as well as lower proportion hypertension.

AF is an important pathogenesis of ischemic stroke, and approximately 5% of stroke patients are associated with AF per year, which leads to a high mortality and morbidity[3]. Left atrial appendage closure has been demonstrated to be an alternative to prevent stroke in patients with AF, particularly those who are intolerant to oral anticoagulants. Intraoperative imaging is a crucial factor for LAAC, and although TEE is currently the mainstream method, ICE is increasingly being used as an alternative to TEE.

In this meta-analysis, we compared the acute procedural success between the TEE and ICE groups, and similar to other studies, there was no noteworthy difference between the two groups[26-28]. Then we conducted a subgroup analysis to further compare the advantages and disadvantages of the two groups. The result shows that regardless of the subgroup, there was no significant difference in acute procedural success rate. TEE which is the gold standard imaging method for LAAO can providing clear images of the right atrium, left atrium, atrial septum and left atrial appendage anatomy for left atrial appendage occlusion, but it has some disadvantages: 1. it requires general anesthesia 2. it can damage the esophagus 3. it produces aerosols with a risk of virus transmission, etc. To explore the safety of ICE and TEE,we counted both the preprocedural complications and the long-term complications. For the short-term adverse events, the results show that ICE seems to be not-inferior to TEE for guiding LAA occlusion procedures in terms of peri-procedural complications. The results of the long-term adverse events were likely between groups, indicating ICE had a reliable performance on safety.

Meanwhile, for procedural time and the fluoroscopic time, we recognized that the pooled rates were similar between ICE group and TEE group. TEE-guided LAAC typically requires general anesthesia, endotracheal intubation, and post-anesthesia care, thus it requires longer periods of the total in-room time and the turnaround time. But it doesn't influence the procedural time which indicate the time from puncture to closure. Interestingly, there was no remarkable difference in the total contrast volume required between the ICE and TEE groups, but in subgroup analysis it was found that in paroxysmal AF <50% subgroup and blood pressure < 90 subgroup, the contrast volume in the ICE group was much lower than that in the TEE group.

In addition, two studies compared the cost of hospitalization between ICE group and TEE group[8, 9]. The drug and personnel cost savings associated with routine use of ICE guidance and local anesthesia may outweigh the cost of ICE catheters. Thus, the global charges (hospital charges and professional fees) were similar in the ICE and TEE groups.

5. Limitations

There are several limitations in our study. First, studies enrolled in this meta-analysis are nonrandomized, observational design, thus selection bias is impossible to avoid. Second, the sample size included in the study is small which may affect the stability of the result indicators, reduce the efficiency of the test, and may bias the research results. Third, different studies were followed with different tests, which led to biased follow-up. In addition, clinical studies did not have uniform definitions of procedural success and procedure-related complications.

6. Conclusions

Our results demonstrate that ICE may have comparable efficacy and safety compared to TEE.

Reference

[1] Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC [J]. Eur Heart J, 2021, 42(5): 373-498. DOI: 10.1093/eurheartj/ehaa612.

[2] Jame S, Barnes G. Stroke and thromboembolism prevention in atrial fibrillation [J]. Heart, 2020, 106(1): 10-7. DOI: 10.1136/heartjnl-2019-314898.

[3] Berti S, Pastormerlo L E, Korsholm K, et al. Intracardiac echocardiography for guidance of transcatheter left atrial appendage occlusion:an expert consensus document [J]. Catheter Cardiovasc Interv, 2021, 98(4): 815-25. DOI: 10.1002/ccd.29791. Epub 2021 Jun 4.

[4] Furlan A D, Pennick V, Bombardier C, et al. 2009 updated method guidelines for systematic reviews in the cochrane back review group [J]. Spine (Phila Pa 1976), 2009, 34(18): 1929-41. DOI: 10.1097/BRS.0b013e3181b1c99f.

[5] Guo B, Moga C, Harstall C, et al. A principal component analysis is conducted for a case series quality appraisal checklist [J]. J Clin Epidemiol, 2016, 69. DOI: 10.1016/j.jclinepi. 2015.07.010.

[6] Gianni C, Horton R P, Della Rocca D G, et al. Intracardiac echocardiography- versus transesophageal echocardiography-guided left atrial appendage occlusion with Watchman FLX [J]. J Cardiovasc Electrophysiol, 2021, 32(10): 2781-4. DOI: 10.1111/jce.15220. Epub 2021 Sep 5.

[7] Pommier T, Guenancia C, Richard C, et al. Safety and efficacy of left atrial appendage occlusion with the ACP or Watchman device guided by intracardiac echocardiography from the left atrium [J]. Clin Cardiol, 2021, 44(10): 1402-8. DOI: 10.1002/clc.23696. Epub 2021 Sep 8.

[8] Alkhouli M, Chaker Z, Alqahtani F, et al. Outcomes of routine intracardiac echocardiography to guide left atrial appendage occlusion [J]. JACC Clin Electrophysiol, 2020, 6(4): 393-400. DOI: 10.1016/j.jacep. 2019.11.014.

[9] Hemam M E, Kuroki K, Schurmann P A, et al. Left atrial appendage closure with the Watchman device using intracardiac vs transesophageal echocardiography: procedural and cost considerations [J]. Heart Rhythm, 2019, 16(3): 334-42. DOI: 10.1016/j.hrthm. 2018.12.013.

[10] Nielsen-kudsk J E, Berti S, De backer O, et al. Use of intracardiac compared with transesophageal echocardiography for left atrial appendage occlusion in the amulet observational study [J]. JACC Cardiovasc Interv, 2019, 12(11): 1030-9. DOI: 10.1016/j.jcin. 2019.04.035.

[11] Berti S, Pastormerlo L E, Santoro G, et al. Intracardiac versus transesophageal echocardiographic guidance for left atrial appendage occlusion: the LAAO Italian multicenter registry [J]. JACC Cardiovasc Interv, 2018, 11(11): 1086-92. DOI: 10.1016/j.jcin. 2018.05.008.

[12] Kim D Y, Shin S Y, Kim J-S, et al. Feasibility of intracardiac echocardiography imaging from the left superior pulmonary vein for left atrial appendage occlusion [J]. Int J Cardiovasc Imaging, 2018, 34(10): 1571-9. DOI: 10.1007/s10554-018-1374-5. Epub 2018 May 22.

[13] Frangieh A H, Alibegovic J, Templin C, et al. Intracardiac versus transesophageal echocardiography for left atrial appendage occlusion with watchman [J]. Catheter Cardiovasc Interv, 2017, 90(2): 331-8. DOI: 10.1002/ccd.26805. Epub 2016 Sep 21.

[14] Korsholm K, Jensen J M, Nielsen-kudsk J E. Intracardiac echocardiography from the left atrium for procedural guidance of transcatheter left atrial appendage occlusion [J]. JACC Cardiovasc Interv, 2017, 10(21): 2198-206. DOI: 10.1016/j.jcin.2017.06.057.

[15] Reis L, Paiva L, Costa M, et al. Registry of left atrial appendage closure and initial experience with intracardiac echocardiography [J]. Rev Port Cardiol (Engl Ed), 2018, 37(9): 763-72. DOI: 10.1016/j.repc.2018.03.009.

[16] Dallan L A P, Arruda M, Yoon S-H, et al. Novel computed tomography angiography-based sizing methodology for Watchman FLX device in left atrial appendage closure [J]. J Cardiovasc Electrophysiol, 2022, 33(8): 1781-7. DOI: 10.1111/jce.15548. Epub 2022 May 26.

[17] Turagam M K, Neuzil P, Hala P, et al. Intracardiac echocardiography-guided left atrial appendage closure with a novel foam-based conformable device: safety and 1-Year outcomes [J]. JACC Clin Electrophysiol, 2022, 8(2): 197-207.DOI: 10.1016/j.jacep.2021.10.001. Epub 2021 Nov 24.

[18] Chen Y-H, Wang L-G, Zhou X-D, et al. Outcome and safety of intracardiac echocardiography guided left atrial appendage closure within zero-fluoroscopy atrial fibrillation ablation procedures [J]. J Cardiovasc Electrophysiol, 2022, 33(4): 667-76. DOI: 10.1111/jce.15370. Epub 2022 Jan 25.

[19] Turagam M K, Neuzil P, Petru J, et al. Intracardiac echocardiography-guided implantation of the Watchman FLX left atrial appendage closure device [J]. J Cardiovasc Electrophysiol, 2021, 32(3): 717-25. DOI: 10.1111/jce.14927. Epub 2021 Feb 10.

[20] Filby S J, Dallan L A P, Cochet A, et al. Left atrial appendage occlusion using cardiac CT angiography and Intracardiac echocardiography: A prospective, single-center study [J]. J Invasive Cardiol, 2021, 33(11): E851-E6.

[21] Korsholm K, Samaras A, Andersen A, et al. The Watchman FLX device: first european experience and feasibility of intracardiac echocardiography to guide implantation [J]. JACC Clin Electrophysiol, 2020, 6(13): 1633-42. DOI: 10.1016/j.jacep.2020.06.028.

[22] Khalili H, Patton M, Taii H A, et al. 4D volume intracardiac echocardiography for Intraprocedural guidance of transcatheter left atrial appendage closure [J]. J Atr Fibrillation, 2019, 12(4): 2200. DOI: 10.4022/jafib.2200.

[23] Matsuo Y, Neuzil P, Petru J, et al. Left atrial appendage closure under intracardiac echocardiographic guidance: feasibility and comparison with transesophageal echocardiography [J]. J Am Heart Assoc, 2016, 5(10). DOI: 10.1161/JAHA.116.003695.

[24] Masson J-B, Kouz R, Riahi M, et al. Transcatheter left atrial appendage closure using Intracardiac echocardiographic guidance from the left atrium [J]. Can J Cardiol, 2015, 31(12). DOI: 10.1016/j.cjca.2015.04.031.

[25] Berti S, Paradossi U, Meucci F, et al. Periprocedural intracardiac echocardiography for left atrial appendage closure: a dual-center experience [J]. JACC Cardiovasc Interv, 2014, 7(9): 1036-44. DOI:

10.1016/j.jcin.2014.04.014.

[26] Ribeiro J M, Teixeira R, Puga L, et al. Comparison of intracardiac and transoesophageal echocardiography for guidance of percutaneous left atrial appendage occlusion: a meta-analysis [J]. Echocardiography, 2019, 36(7): 1330-7. DOI: 10.1111/echo.14415. Epub 2019 Jun 19.

[27] Liang G, Xu B, Wang S, et al. Imaging with intracardiac echocardiography compared to transesophageal echocardiography during left atrial appendage occlusion [J]. Rev Cardiovasc Med, 2020, 21(1). DOI: 10.31083/j.rcm.2020.01.569.

[28] Akella K, Murtaza G, Turagam M, et al. Evaluating the role of transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) in left atrial appendage occlusion: a meta-analysis [J]. J Interv Card Electrophysiol, 2021, 60(1): 41-8. DOI: 10.1007/s10840-019-00677-x. Epub 2020 Jan 17.

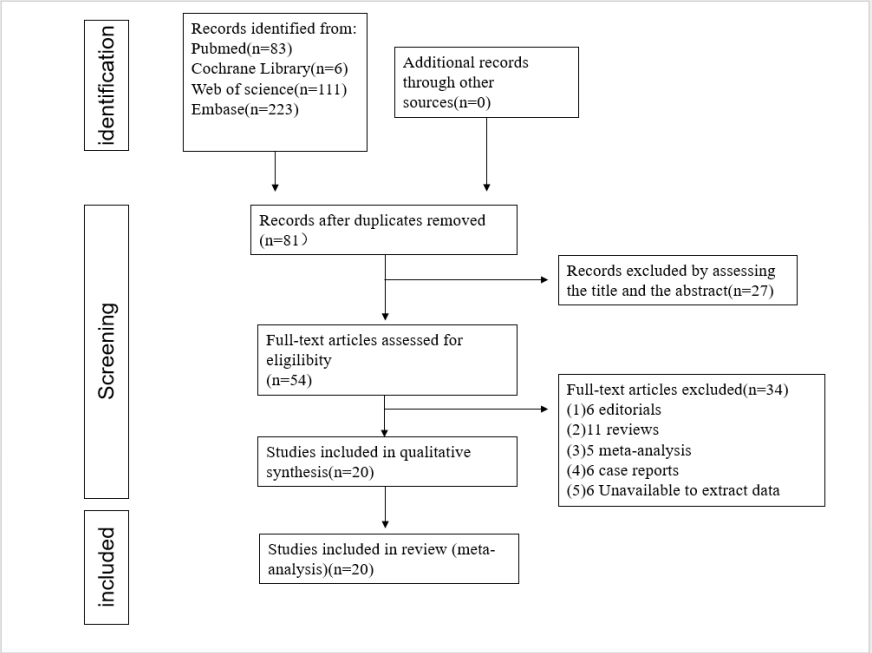

Figure 1. The flowchart of the study selection

Table 1. Baseline characteristics and procedure-related indices of eligible studies

First author	Year	Study design	Follow-up (Months)	ICE Sample size	ICE Sample size	Gender (m
				ICE Group	TEE Group	ICE Group
Gianni	2021	Single-center	2	122	68	66
Pommier	2021	Single-center	1	175	49	70
Alkhouli	2020	Single-center	1.5	90	196	62.2
Hemam	2019	Multi-center	4	53	51	62.3
Nielsen-Kudsk	2019	Multi-center	12	130	955	60
Berti	2018	Multi-center	15	187	417	66
Kim	2018	Multi-center	25.6	41	103	58.5
Frangieh	2017	Single-center	0	32	44	81
Korsholm[1]	2017	Single-center	1.7	109	107	62
Reis	2018	Single-center	23	26	56	53
Dallan	2022	Single-center	1.5	136		55.1

First author	Year	Study design	Follow-up (Months)	ICE Sample size	ICE Sample size	Gender (m
Turagam[1]	2022	Single-center	12	15		33
Chen	2022	Single-center	12	56		57.1
Turagam[2]	2021	Single-center	1.5	30		53
Filby	2021	Single-center	1.5	71		54.9
Korsholm[2]	2020	Single-center	1.7	92		25
Khalili	2019	Single-center	0	15		73
Matsuo	2016	Single-center	1.5	27		40.7
Masson	2015	Single-center	2	37		67.6
Berti	2014	Multi-center	0	121		57

First author	Pre-procedure imaging	Pre-procedure imaging	Mean CHADS-VASc	Mean CHADS-VAS
	ICE Group	TEE Group	ICE Group	TEE Group
Gianni	CT/TEE	CT/TEE	4.1±1.4	4.3±1.3
Pommier	CT	CT	4.2±1.38	4.5±1.49
Alkhouli	CT/TEE	CT/TEE	4.7 ± 1.4	4.8 ± 1.6
Hemam	NA	NA	4.5±1.8	4.5±1.6
Nielsen-Kudsk	CT and TEE	CT and TEE	4.1 ± 1.6	4.2 ± 1.6
Berti	TEE	TEE	4.27±1.40	4.25±1.40
Kim	TEE	TEE	4.3 ± 1.4	4.3 ± 1.4
Frangieh	NA	NA	4.3±5.2	4±1.5
Korsholm[1]	CT	CT	4.1 ± 1.6	4.4 ± 1.6
Reis	TEE	TEE	4.7±1.4	4.7±1.4
Dallan	CT		4.4 ± 1.3	
Turagam[1]	TEE		4.1 ± 1.7	
Chen	NA		4.0±1.5	
Turagam[2]	NA		4.6 ± 1.6	
Filby	CT		4.2±1.4	
Korsholm[2]	CT		3.9 ± 1.7	
Khalili	TEE		4.6±1	
Matsuo	TEE		5.3±1.6	
Masson	NA		4.5±1.3	
Berti	TEE		4.4 ± 1.3	

Note: AF: Atrial fibrillation; LAAO: Left atrial appendage closure; CAD: Coronary artery disease; ICE: Intracardiac echocardiography; TEE: Transesophageal echocardiography.

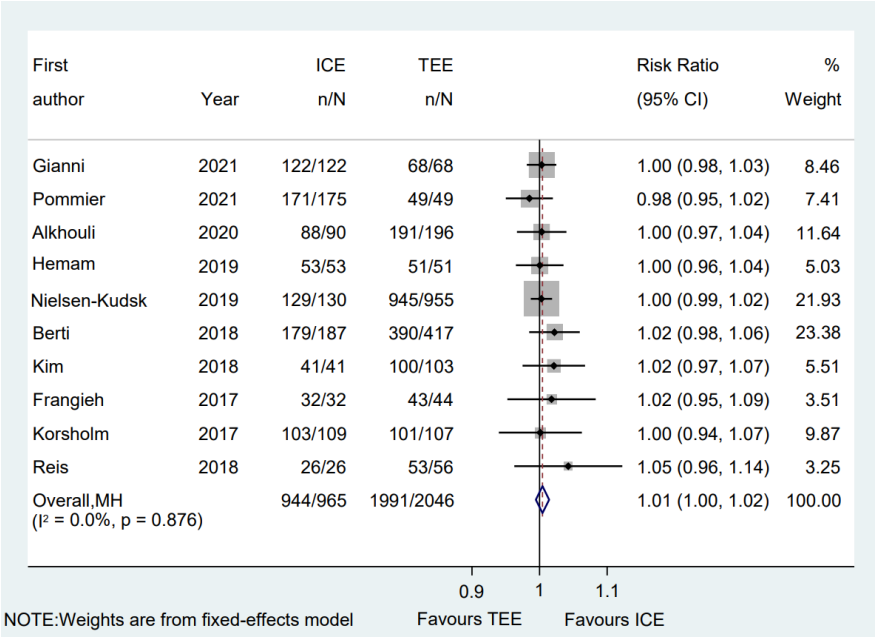

Figure 2. Forest plot of the procedural success between ICE and TEE groups. Comparison of the rates of the procedural success between ICE and TEE groups. ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; RR: risk ratio; CI: confidence interval.

Figure 3. Forest plot of subgroup analysis of the procedural success between ICE and TEE groups. Subgroup analysis of the rates of the procedural success between ICE and TEE groups. ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; RR: risk ratio; CI: confidence interval.

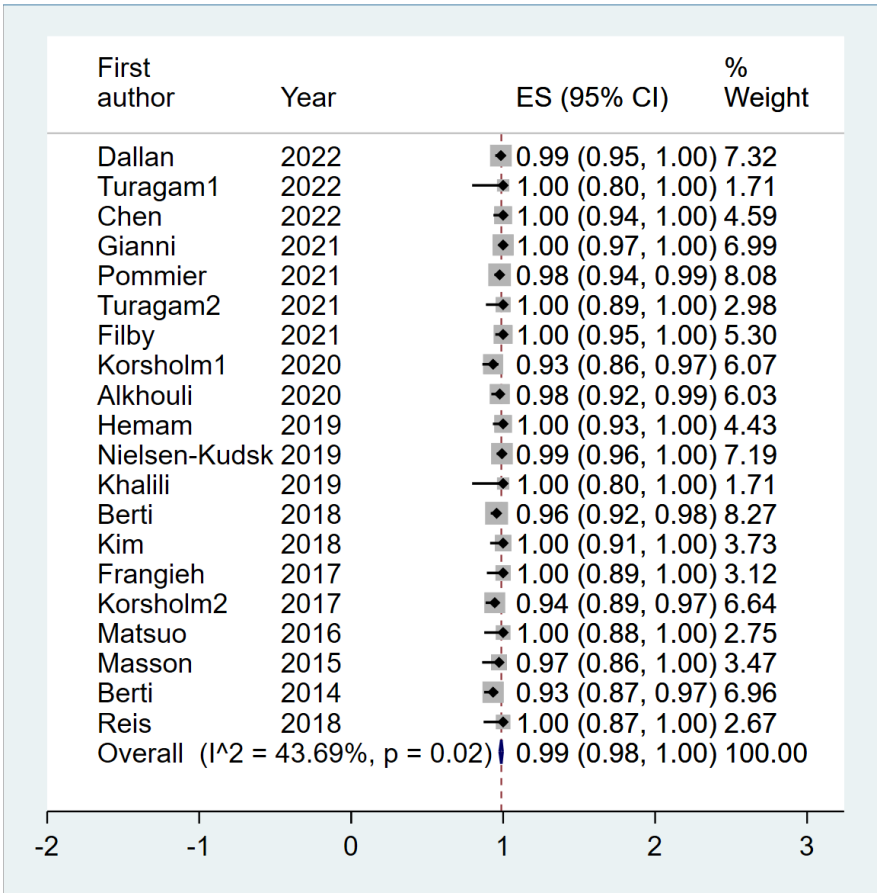

Figure 4. Forest plot of the pooled rate of the procedural success in ICE groups. The line of equity refers to the pooled result of eligible studies in the forest plots. ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; ES: effect size; CI: confidence interval.

Table 2. Subgroup analysis of the rate of procedural success in ICE group

Subgroup Factors	Numbers of Study	Pooled incidence	95% CI	I^2 (%)	*P* for interaction
Study design					0.670
Multi-centered	5	0.99	(0.98,1.0)	31.86	
Single-centered	15	0.98	(0.95,1.0)	66.08	
Follow up					0.580
<12	14	0.97	(0.97,1.0)	51.19	?¿?
12	6	0.98	(0.98,1.0)	26.56	
ICE Sample size					0.280
>100	7	0.98	(0.95,0.99)	68.51	?¿?
100	13	0.99	(0.98,1.0)	4.01	
Male proportion					0.990
<70	16	0.99	(0.97,1.0)	54.17	?¿?
70	3	0.99	(0.97,1.0)	-	
Age cutoff					0.890?¿?
75	11	0.99	(0.97,1.0)	35.33	
<75	8	0.99	(0.96,1.0)	60.83	

Subgroup Factors	Numbers of Study	Pooled incidence	95% CI	I^2 (%)	*P* for interaction
HT proportion					0.720
<90	10	0.98	(0.96,1.0)	57.21	?¿?
90	4	0.99	(0.97,1.0)	0	
PAF proportion					0.580
>50	5	0.98	(0.96,1.0)	52.71	?¿?
50	8	0.98	(0.96,0.99)	42.03	
Devices type					0.230
Dual-seal mechanism	6	0.94	(0.94,0.99)	57.64	
Single-seal mechanism	11	0.98	(0.98,1.0)	26.89	
Muti-seal mechanism	2	0.96	(0.96,1.0)	-	

Note: ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; CI: confidence interval

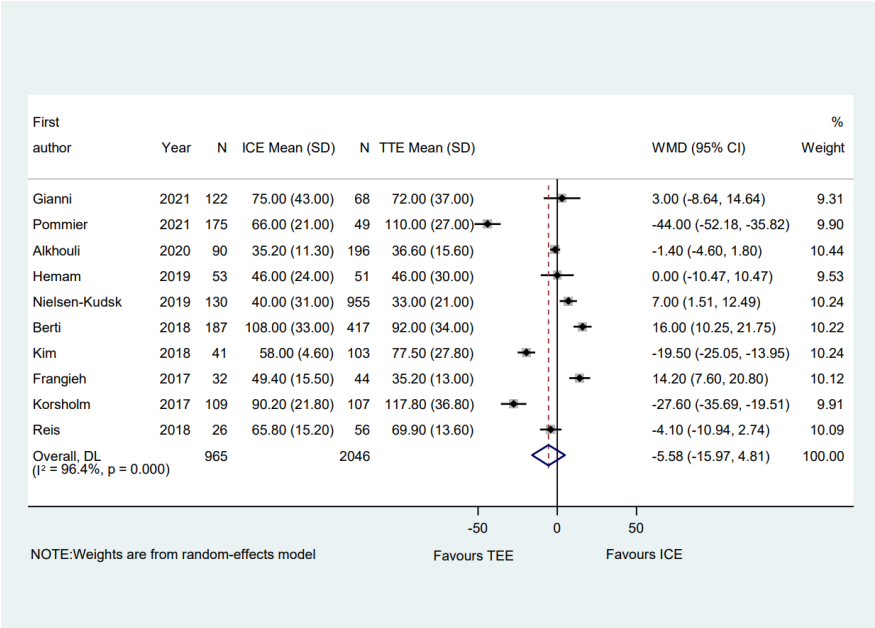

Figure 5. Forest plot of the total procedural time between ICE and TEE groups. Comparison of the rates of the total procedural time between ICE and TEE groups. ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; WMD: weighted mean difference; CI: confidence interval.

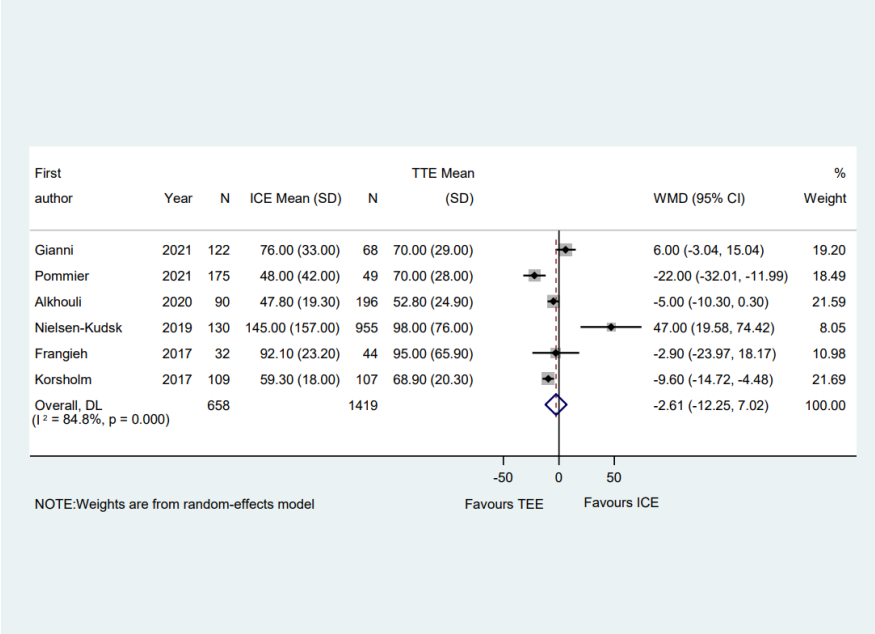

Figure 6. Forest plot of the contrast volume between ICE and TEE groups. Comparison of the rates of the contrast volume between ICE and TEE groups. ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; WMD: weighted mean difference; CI: confidence interval.

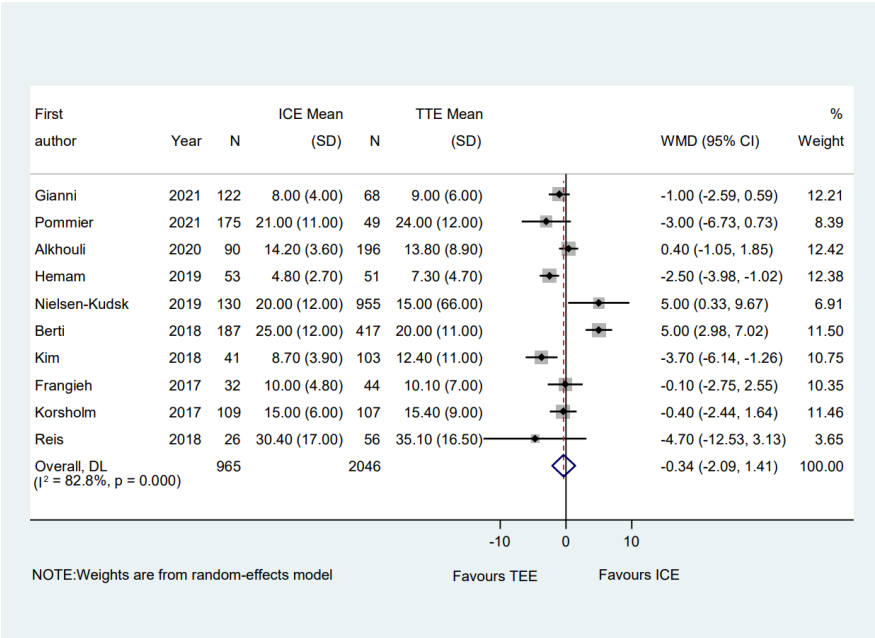

Figure 7. Forest plot of the fluoroscopic time between ICE and TEE groups. Comparison of the rates of the fluoroscopic time between ICE and TEE groups. ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; WMD: weighted mean difference; CI: confidence interval.

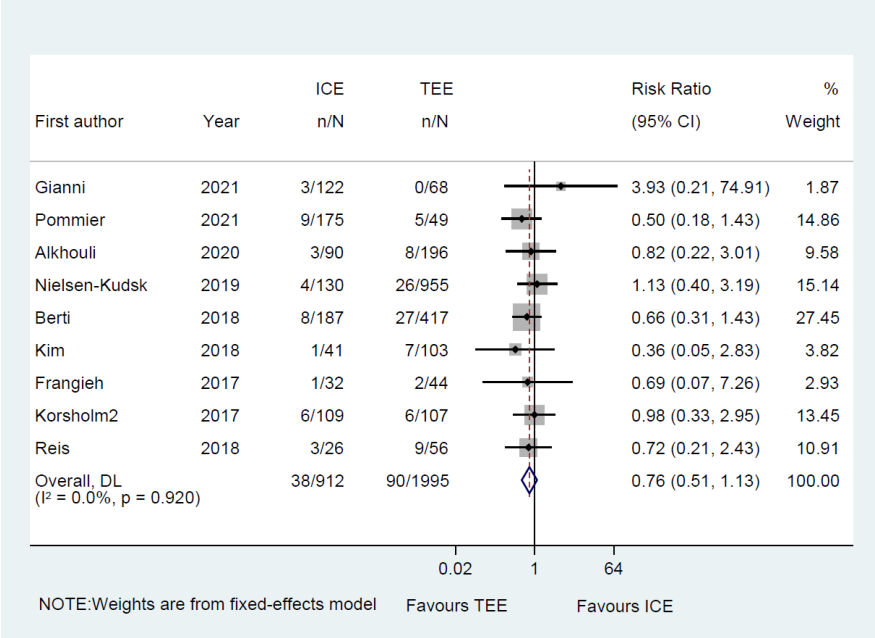

Figure 8. Forest plot of the preprocedural complications between ICE and TEE groups. Comparison of the rates of the preprocedural complications between ICE and TEE groups. ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; RR: risk ratio; CI: confidence interval.

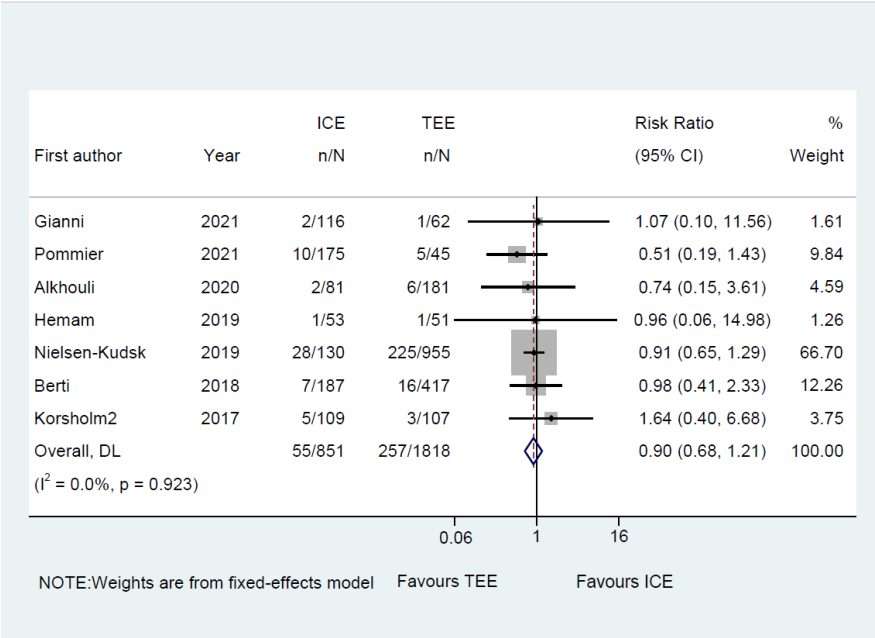

Figure 9. Forest plot of the long-term adverse events between ICE and TEE groups. Comparison of the rates of the long-term adverse events between ICE and TEE groups. ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; RR: risk ratio; CI: confidence interval.

Supplementary Table1 Quality assessment of eligible studies according to the Newcastle-Ottawa Quality

Assessment Scale

First author	Year	Selection	Selection	Selection	Selection	Comparability	Outcome	Outcome	Outcome
		Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
Gianni	2021								
Pommier	2021								
Alkhouli	2020								
Hemam	2019								
Nielsen-Kudsk	2019								
Berti	2018								
Kim	2018								
Frangieh	2017								
Korsholm[1]	2017								
Reis	2018								

Quality assessment of the single-arm studies according to the Institute of Health Economics checklist

First author	Year	Study objective	Study design	Study population	Intervention and cointervention	Outcome mea
Dallan	2022	1	2	3	2	3
Turagam[1]	2022	1	2	3	2	3
Chen	2022	1	2	3	2	3
Turagam[2]	2021	1	2	3	2	3
Filby	2021	1	2	3	2	3
Korsholm[2]	2020	1	2	3	2	3
Khalili	2019	1	2	3	2	3
Matsuo	2016	1	2	3	2	3
Masson	2015	1	2	3	2	3
Berti	2014	1	3	3	2	3

Supplementary Table 2. Subgroup analysis of total procedure time between ICE group and TEE group

Subgroup factors	Numbers of study	WMD (95%CI)	I^2 (%)	*P* value	*P* for interaction
Study design					0.344
Multi-center	4	0.88 (-15.84, 17.61)	96.4	0.918	
Single-center	6	-9.94 (-24.90, 5.02)	96.8	0.193	
Follow up					0.421
<12	6	-9.32 (-15.35, 6.70)	96.8	0.254	?¿?
12	4	-0.14 (-15.74, 15.46)	96.5	0.913	

Subgroup factors	Numbers of study	WMD (95%CI)	I^2 (%)	*P* value	*P* for interaction
ICE Sample size					0.588
>100	5	-9.07 (-31,36, 13.22)	97.9	0.425	?¿?
100	5	-2.28 (-12.52, 7.95)	93.5	0.786	
Male proportion					0.694
<70	7	-3.21 (-13.70, 7.28)	95.2	0.548	?¿?
70	2	-5.75 (-71.88, 42.19)	99.2	0.610	
Age cutoff					0.800?¿?
75	5	-4.30 (-20.3, 11.43)	97.3	0.592	
<75	4	-7.58 (-27.53, 12.38)	96.5	0.457	
HT proportion					0.810
<90	4	-14.35 (-42.06, 13.37)	97.8	0.310	?¿?
90	2	-10.30 (-28.04, 7.43)	96.7	0.255	
PAF proportion					0.014
>50	1	14.20 (7.60, 20.80)	-	0.000	?¿?
50	4	-18.66 (-43.95, 6.63)	98.2	0.148	
Devices type					0.024
Dual-seal mechanism	3	-1.35 (-23.92, 21.23)	97.4	0.907	
Single-seal mechanism	4	4.02 (-4.61, 12.65)	82.9	0.361	
Muti-seal mechanism	2	-31.56 (-55.57, -7.55)	95.8	0.010	

Note: ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; WMD: weighted mean difference;

CI: confidence interval.

Supplementary Table 3. Subgroup analysis of Contrast volume between ICE group and TEE group

Subgroup Factors	Numbers of Study	WMD (95%CI)	I^2 (%)	*P* value	*P* for interaction
Study design		47.00(19.58, 74.42) -7.01(-14.76, 0.75) -7.01(-14.76, 0.75) 47.00(19.58, 74.42) 0.48(-15.67, 16.64) -4.88(-10.01, 0.26) 2.17(-8.78,13.12) -14.79(-32.94,3.36) 1.60(-20.59, 23.79) -2.50(-14.51, 9.51) -12.95(-22.83, -3.07) -5.00(-10.30, 0.30) -2.90(-23.97, 18.17) -15.02(-27.08, -2.97) 17.03(-38.34, 72.40) -0.74(-8.49, 7.46) -22.00(-32.01, -11.99)			0.000
Multi-centered	1		-	0.001	
Single-centered	5		78.1	0.076	
Follow up					0.000
<12	5		78.1	0.076	
[?]12	1		-	0.001	
ICE Sample size					0.536
>100	4		90.8	0.953	
[?]100	2		0.00	0.063	
Male proportion					0.117
<70	4		86.7	0.697	
[?]70	2		61.2	0.110	
Age cutoff					0.750
[?]75	3		91.7	0.887	
<75	3		77.1	0.683	

Subgroup Factors	Numbers of Study	WMD (95%CI)	I^2 (%)	*P* value	*P* for interaction
HT proportion					0.164
<90	3		62.9	0.010	
[?]90	1		-	0.064	
PAF proportion					0.328
>50	1		-	0.787	
[?]50	2		78.6	0.015	
Devices type					0.004
Dual-seal mechanism	2		93.7	0.860	
single-seal mechanism	3		52.8	0.547	
Muti-seal mechanism	1		-	0.000	

Note: ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; WMD: weighted mean difference;

CI: confidence interval.

Supplementary table 4. Subgroup analysis of fluoroscopic time between ICE group and TEE group

Subgroup Factors	**Numbers of Study**	**WMD (95% CI)**	**WMD (95% CI)**	**I^2 (%)**	***P* value**	***P* for inte**
Study design						0.608
Multi-center	4	0.763(-3.80,5.32)	0.763(-3.80,5.32)	93.7	0.036	
Single-center	6	-0.453(-1.32,0.41)	-0.453(-1.32,0.41)	0.0	0.305	
Follow up						0.823
<12	6	-0.95(-2.04,0.13)	-0.95(-2.04,0.13)	46.6	0.085	?¿?
12	4	0.73(-4.90,6.37)	0.73(-4.90,6.37)	91.1	0.799	
ICE Sample size						0.145
>100	5	1.02(-1.96,4.0)	1.02(-1.96,4.0)	86.6	0.503	?¿?
100	5	-1.59(-3.44,0.26)	-1.59(-3.44,0.26)	69.3	0.092	
Male proportion						0.437
<70	7	0.14(-1.96,2.25)	0.14(-1.96,2.25)	87.8	0.894	?¿?
70	2	-1.24(-4.02,1.54)	-1.24(-4.02,1.54)	35.0	0.381	
Age cutoff						0.232?¿?
75	5	0.85(-2.28,3.98)	0.85(-2.28,3.98)	90.4	0.594	
<75	4	-1.25(-2.67,0.17)	-1.25(-2.67,0.17)	43.9	0.086	
HT proportion						0.292
<90	4	-1.49(-2.87,-0.10)	-1.49(-2.87,-0.10)	33.5	0.035	?¿?
90	2	-1.39(-5.54,2.84)	-1.39(-5.54,2.84)	87.5	0.455	
PAF proportion						0.899
>50	1	-0.10(-2.75,2.55)	-0.10(-2.75,2.55)	-	0.941	?¿?
50	4	-0.42(-4.54,3.71)	-0.42(-4.54,3.71)	91.3	0.843	
Devices type						0.259
Dual-seal mechanism	3	3.02(-1.08,7.12)	3.02(-1.08,7.12)	76.8	0.482	
Single-seal mechanism	4	-0.87(-2.27,0.52)	-0.87(-2.27,0.52)	0.00	0.670	
Muti-seal mechanism	2	-3.49(-5.53,1.45)	-3.49(-5.53,1.45)	-	0.115	

Note: ICE: intracardiac echocardiography; TEE: transesophageal echocardiography; WMD: weighted mean difference;

CI: confidence interval.

Supplementary Table5 . Preprocedural complications between ICE group and TEE group.

Study	Year	ICE
Gianni	2021	Major bleeding (3)
Pommier	2021	Major bleeding (4), Vascular complications (1), Device-related outcomes (3), Cerebrovascular diseas
Alkhouli	2020	Major bleeding (1), Vascular complications (1), Cerebrovascular diseases (1)
Hemam	2019	-
Nielsen-Kudsk	2019	Vascular complications (1), Major bleeding (3)
Berti	2018	Device-related outcomes (1), Cerebrovascular diseases (1), Major bleeding (6)
Kim	2018	Major bleeding (1)
Frangieh	2017	Major bleeding (1)
Korsholm[1]	2017	Major bleeding (2), Vascular complication (4)
Reis	2018	Major bleeding (3)
Dallan	2022	Cardiac arrest (1), Major bleeding (7), vascular complication (1)
Turagam[1]	2022	-
Chen	2022	Major bleeding (2)
Turagam[2]	2021	-
Filby	2021	Cardiac arrest (1), Major bleeding (1)
Korsholm[2]	2020	Major bleeding (5)
Khalili	2019	-
Matsuo	2016	Cerebrovascular diseases (1), Vascular complications (3)
Masson	2015	Cardiac arrest (1), Major bleeding (2)
Berti	2014	Device-related outcomes (1), Cerebrovascular diseases (1), Major bleeding (2), Vascular complicatio

Note: Cerebrovascular diseases: Ischemic stroke, TIA, cerebral hemorrhage; Device-related outcomes: Device thrombus, Device migration, [?]5mm peri-device flow; Major bleeding: Cardiac effusion, Cardiac tamponade, Major bleeding event.

Supplementary Table6 . Follow up complications between ICE group and TEE group.

Study	Year	Follow up(months)	ICE
Gianni	2021	2	Device-related outcomes (2)
Pommier	2021	1	Device-related outcomes (10)
Alkhouli	2020	1.5	Device-related outcomes (2)
Hemam	2019	4	Device-related outcomes (1)
Nielsen-Kudsk	2019	12	Death (8), Cerebrovascular disease (6), Major bleeding (13), Renal complicati
Berti	2018	15	Cerebrovascular diseases (7)
Kim	2018	25.6	-
Frangieh	2017	0	-
Korsholm	2017	1.7	Cerebrovascular diseases (1), Device-related outcomes (1), Major bleeding (3)
Reis	2018	23	Device-related outcomes (1), Major bleeding (3), Cerebrovascular diseases (1)
Dallan	2022	1.5	Device-related outcomes (1)
Turagam[1]	2022	12	Death (2)
Chen	2022	12	Death (1), Device-related outcomes (2), Major bleeding (1)

Study	Year	Follow up(months)	ICE
Turagam[2]	2021	1.5	Death (1), Major bleeding (2)
Filby	2021	1.5	-
Korsholm	2020	1.7	Death (1), Cerebrovascular diseases (1)
Khalili	2019	0	-
Matsuo	2016	1.5	Device-related outcomes (3)
Masson	2015	2	Death (2)
Berti	2014	0	-

NOTE: Cerebrovascular Diseases: Ischemic stroke, TIA and Cerebral hemorrhage; Device-related outcomes: Device thrombus, Device migration and [?]5mm peri-device flow; Major bleeding: Cardiac effusion, Cardiac tamponade and Major bleeding event; Renal complications: Acute renal failure, Chronic renal failure, Renal insufficiency, Acute kidney injury and Cardiorenal syndrome.

Supplementary Table 7 . Publication bias and sensitivity analysis of primary outcomes.

Primary outcomes	**Sensitivity analysis**	**Sensitivity analysis**	***P* for egger's**
	Lower range	Upper range	
Procedural success	1.00 (95% CI, 0.99-1.02)	1.01 (95% CI:1.00,1.03)	0.208
Pooled rate of procedural success in ICE group	0.98 (95% CI: 0.97,0.99)	0.99 (95% CI: 0.98,1.00)	0.959
Total procedure time	-7.80 (95% CI: -18.72,3.11)	-1.35 (95% CI: -10.13,7.44)	0.535
Contrast volume	-4.81 (95% CI: -15.29,5.66)	1.26 (95% CI: -8.55,11.06)	0.371
Fluoroscopic time	-0.72 (95% CI: -2.48,1.03)	0.07 (95% CI: -1.74,1.87)	0.941
procedural complications	0.70(95%CI:0.45,1.10)	0.87(95%CI:0.61,1.25)	0.696
long-term adverse events	0.84(95%CI:0.62,1.13)	0.93(95%CI:0.54,1.60)	0.094

Note: CI: confidence interval.