

**Device-related thrombus formation in patients received one-stop intervention for nonvalvular atrial fibrillation: A systemic review and meta-analysis**

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**Abstract**

**Introduction:** Combing CA and LAAO into one procedure has become a prospective measurement for patients with nonvalvular atrial fibrillation. Data on the incidence of DRT in one-stop intervention, treatment strategy and its clinical implications are limited.

**Methods:** A meta-analysis of observational studies evaluating the incidence, treatment strategy, and clinical implications of DRT was conducted.

**Results:** Overall 21 studies describing DRT events and one case were included in the study. The pooled incidence of DRT in one-stop intervention was 1.2% (range from 0% to 7.3%, 95%CI 0.7%-1.8%,  $I^2=0$ ). 56.25% of events were diagnosed in the first three months after the procedure. All cases were diagnosed with a trans-esophagus echocardiogram (TEE). All patients diagnosed with DRT were prescribed anticoagulant. And 63% (12/19) events

were reported with complete thrombus resolution. Anticoagulation duration varied greatly from 30d to 6m.

Unknown clinical events were reported relating to DRT.

**Conclusions:** DRT is an uncommon complication of the one-stop intervention. It occurs mainly in the first three months after the procedure. Anticoagulation seems to be an appropriate method for dissolving thrombus.

**Keywords:** Atrial Fibrillation, left atrial appendage occlusion, catheter ablation, one-stop intervention, device-related thrombosis

## **Introduction**

Globally, atrial Fibrillation has been a big burden for society. The incidence ranges from 1.5% to 2% . The management of atrial fibrillation includes relieving symptoms and reducing the rate of complications, especially stroke. Catheter ablation (CA) is being increasingly used as an effective rhythm control of atrial fibrillation. The left atrial appendage is reported as the major source of thrombus formation in nonvalvular atrial fibrillation patients <sup>1</sup>. Percutaneous left atrial appendage occlusion (LAAO) has been applied as an effective alternative to oral anticoagulant (OAC) particularly in those patients with high bleeding risk to decrease the risk of stroke. Recently Jiang Y had conducted a meta-analysis on the efficacy and safety of CA combined with LAAO and concluded that a single procedure with CA and LAAO is a feasible strategy with significant efficacy and safety <sup>2</sup>. So one-stop intervention may be increasingly used in clinical practice in the future.

As the endothelialization of LAAO, patients are still needed to get antithrombotic treatment in the short-term. While the type and duration are still controversial. Furthermore, the complications of this procedure,

such as DRT is uncommon but known in patients undergoing LAAO. Data from a recent meta-analysis suggested that DRT may be associated with a 4- to 5-fold increase in ischemic events<sup>3</sup>. However, there is no analysis focusing on the DRT in the one-stop intervention.

Therefore, in this study, we sought to perform a systemic review and meta-analysis to assess the incidence, treatment strategies, and clinical implications of DRT in patients accepting a one-stop intervention.

## **Methods**

### **Search strategy**

To identify related studies, two authors searched Pubmed, Cochrane Library, EMBASE, Web of science as well as the references of articles from the inception of each database to August 2020 independently. Keywords used were “atrial fibrillation” “left atrial appendage occlusion” “left atrial appendage closure” “device-related thrombus” “device-associated thrombus” “thrombus” “thrombosis” “thrombi”. Any disagreements were resolved through consensus and arbitration by mutual agreement.

### **Inclusion and Exclusion criteria**

The inclusion criteria were as follows: 1) studies on patients with nonvalvular atrial fibrillation receiving CA and LAAO in one procedure; 2) studies reporting the events of DRT. The exclusion criteria were as follows: 1) studies involving editorial, reviews, and duplicate reports; 2) studies with epicardial left atrial closure.

### **Data extraction**

Two authors (LX.H and JT.Z) independently reviewed the included studies carefully. Any disagreements between the two authors were resolved with a consultation with the senior investigator (M.T). And the following

study characteristics were extracted: first author, year of publication, study design, number of patients, clinical characteristics as well as data related to DRT (incidence, time of diagnosis, treatment at discharge, treatment at the time of diagnosis, associated events, resolution rate of DRT, and type of occlusion device).

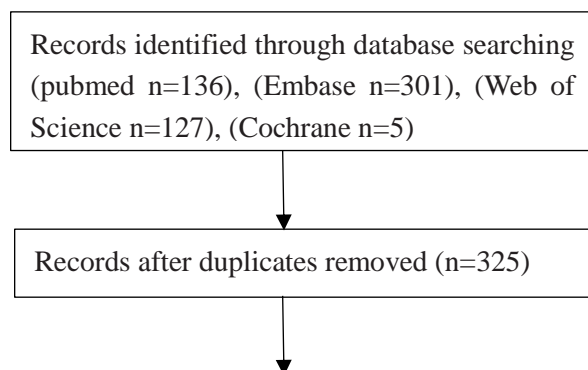
### Statistical analysis

Statistical analyses were performed using Stata 16.0 (Stata Corp., College Station, TX, USA). Higgins I-squared ( $I^2$ ) statistic was used to quantify the degree of heterogeneity<sup>4</sup>. Freeman-Tukey Double arcsine transformation was used to get the pooled incidence of DRT, to improve the reliability of the pooled result. Publication bias was formally assessed using Begg's funnel plot. Forest plots were generated to show the relative effect size of the individual studies on each clinical outcome.

### Results

#### Search and Synthesis of the Literature

A total of 569 articles were initially identified and screened from the literature search. After removing duplicate articles and screening the title and abstract of these studies, 40 studies were retrieved for full-text review. Of these, 18 excluded because of no reporting of DRT, duplicate report, or no one-stop intervention. The 21 included studies comprising 3 multicenter registries and 18 single-center registries. We also included one case report in analyzing the characteristics of DRT. Figure 1 shows the literature selection flowchart.



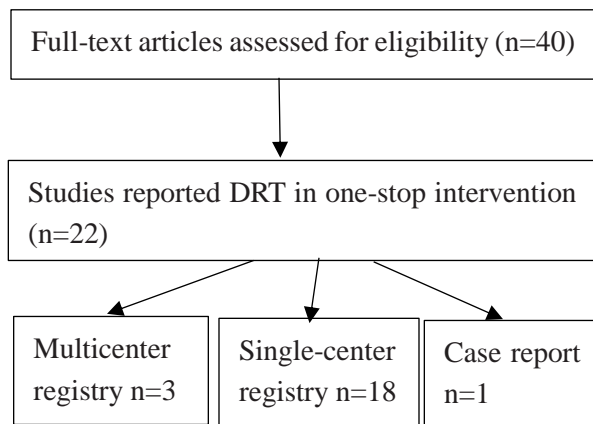


Figure 1 Flow of chart of literature selection

### **Incidence of DRT after the one-stop intervention**

The 21 included studies enrolled in 1708 patients with sample sizes ranging from 20 to 349 (Table 1). The Watchman was the mostly used device (at least 74.5%). Radiofrequency catheter ablation (RA) was the mostly used ablation method (at least 76%). The reported incidence of DRT varied from 0 to 7.3% in various studies. In larger series ( $n \geq 100$ ), the incidence varied from 0 to 2.11%. In total, there were 18 cases of DRT identified out of 1708 (case reports were excluded when calculating the overall incidence of DRT). In our pooled analysis, the mean incidence of DRT was 1.2% (0.7%-1.8%) (Figure 2). The MINORS score ranges from 9 to 12. Publication bias was analyzed by Begg's test (Figure 3).

Table1 Studies with Reported Events of DRT

Study	Country	Study type	Device/ablation	Number of cases/ implanted devices	TEE Follow-up (month)	MINORS score
Alipour 2015 <sup>5</sup>	Netherlands	Single-center registry	WM/RA	0/62	12	12

Calvo 2015 <sup>6</sup>	Spain	Single-center registry	29WM, 6ACP /RA	0/35	12	12
Chen 2020 <sup>7</sup>	China	Single-center registry	WM/RA	0/178	12	12
Du XF 2019 <sup>8</sup>	China	Single-center registry	83WM, 39ACP /RA	2/122	11.2±7.3	10
Fassini 2019 <sup>9</sup>	Italy	Single-center registry	WM ACP/CrA	1/49	≥24	10
Fassini 2015 <sup>10</sup>	Italy	Single-center registry	6WM 28ACP 12 RA 22CrA	0/34	6	9
Hu H 2018 <sup>11</sup>	China	Single-center registry	29WM 5ACP /RA	0/34	3	10
Huang W 2019 <sup>12</sup>	China	Single-center registry	Unknown	3/238	12	10
Kita K 2020 <sup>13</sup>	USA	Single-center registry	WM/RA	3/41	18.6 ± 8.6	12
Li X 2018 <sup>14</sup>	China	Single-center registry	WM/RA	0/25	6	10
Liu FZ 2019 <sup>15</sup>	China	Multicenter registry	48WM 2ACP; 40RA 10CrA	0/50	20.2 ± 11.5	12
Liu J 2020 <sup>16</sup>	China	Single-center registry	WM ACP Lambre/CrA	0/27	18 (range,9–23)	12
Mo BF 2020 <sup>17</sup>	China	Single-center registry	WM/RA	0/76	24	12
Panikker 2016 <sup>18</sup>	England	Single-center registry	WM/RA	1/20	12	12
Pelissero 2017 <sup>19</sup>	Mexico	Single-center registry	14WM,7ACP/RA &CrA	0/21	14.93 ± 10.05	10
Phillips 2020 <sup>20</sup>	Europe/Asia/Australia	Multicenter registry	WM/RA	3/142	24	10
Phillips 2016 <sup>21</sup>	Australia	Single-center registry	WM/ RA	2/98	12	10
Ren ZY 2020 <sup>22</sup>	China	Single-center registry	23Lefort 11Lacbes	0/42	22±11(3-35)	10

			8WM/CrA			
Romanov 2015 <sup>23</sup>	USA	Single-center registry	WM/RA	0/39	12	12
Walker 2012 <sup>24</sup>	Australia	Single-center registry	WM/RA	0/26	12	10
Wintgens 2018 <sup>25</sup>	Netherlands/Australia/Russia/Spain	Multicenter registry	WM/RA	3/349	3	10

WM : Watchman; RA : Radio frequency catheter ablation; CrA: Cryoballoon catheter ablation; TEE:

Transesophagus echocardiogram.

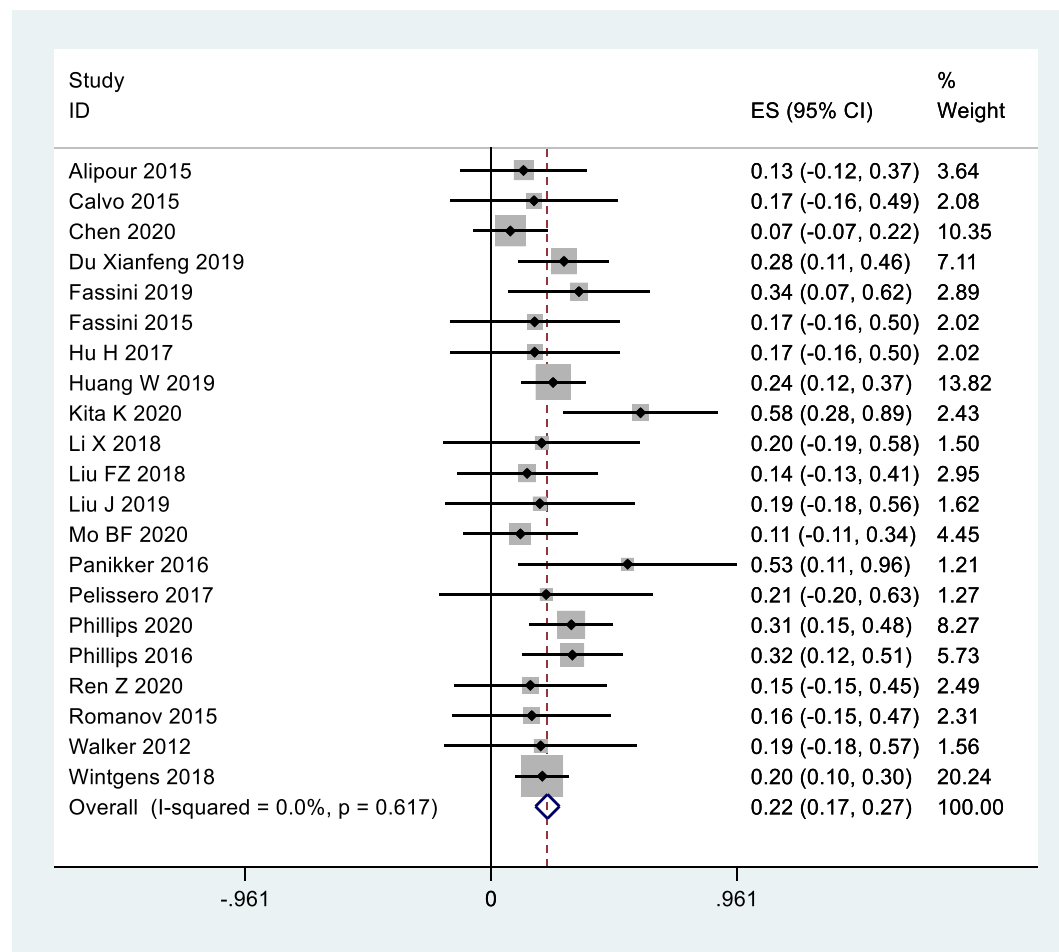


Figure2 Pooled incidence of DRT in the one-stop intervention using Freeman-Tukey Double arcsine

transformation, fixed-effect model.

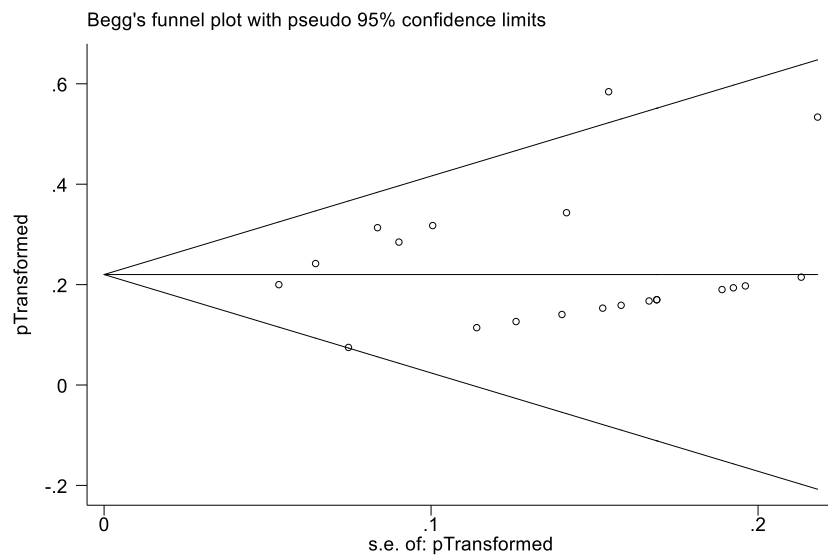


Figure3 Assessment of publication bias using Begg's test.





Table 2 Details of the reported cases

Case in Study	Age	Sex	Type of AF/ Catheter ablation	Peri-device leak	Timing and diagnosis modality	Treatment at discharge and duration	Treatment when diagnosis of DRT	Treatment type and duration	Compli cations	Thrombus resolution after antithrombotic treatment	Device/thrombus feature
Du XF 2019	63	M	PAF/RA	None	5m/TEE	NOAC*3m+  DAPT*2m	DAPT	Warfarin*6m	None	Dissolved	33mm WM/  Thrombus 10*4mm
Du XF 2019	70	F	CAF/RA	None	6m/TEE	OAC*3m+D  APT*3m	DAPT	OAC*2m	None	Dissolved	21mm WM/  Thrombus 15*8mm
Fassini 2019	Un	Un	U/CrA	<3mm	8w/TEE	NOAC*2m	NOAC	NOAC*1m	None	Dissolved	Un
Huang W 2019	Un	Un	Un/Un	Un	TEE	Un	Un	Un	Un	Un	Un
Huang W 2019	Un	Un	Un/Un	Un	TEE	Un	Un	Un	Un	Un	Un
Huang W 2019	Un	Un	Un/Un	Un	TEE	Un	Un	Un	Un	Un	Un

Kita K 2020	Un	Un	Un/RA	Un	3m or 6m/TEE	OAC*3m	DAPT	OAC	None	Un	WM
Kita K 2020	Un	Un	Un/RA	Un	3m or 6m/TEE	OAC*2m	None	OAC	None	Un	WM
Kita K 2020	Un	Un	Un/RA	Un	3m or 6m/TEE	OAC*2m	None	OAC	None	Un	WM
Panikker 2016	Un	Un	Un/RA	none	9m/TEE	Warfarin*5 m	SAPT	OAC	Un	Un	WM/  Thrombus 1*2mm
Phillips 2020	Un	Un	Un/RA	None	38d/TEE	NOAC*45d	NOAC	NOAC	None	Dissolved	WM/sessile
Phillips 2020	Un	Un	Un/RA	None	45d/TEE	NOAC*45d	NOAC	NOAC	None	Dissolved	WM/mobile
Phillips 2020	Un	Un	Un/RA	None	45d/TEE	NOAC*45d	NOAC	NOAC	None	Dissolved	WM
Phillips 2016	Un	Un	Un/RA	None	6w/TEE	NOAC*3m	NOAC	NOAC*4m	None	Dissolved	WM
Phillips 2016	Un	Un	Un/RA	None	1w/TEE	NOAC*3m	NOAC	NAC*5w	None	Dissolved	WM
Wintgens 2018	Un	Un	Un/RA	Un	<3m/TEE	Un	Un	OAC or LMWH	None	Dissolved	WM
Wintgens 2018	Un	Un	Un/RA	Un	<3m/TEE	Un	Un	OAC or LMWH	None	Dissolved	WM
Wintgens 2018	Un	Un	Un/RA	Un	<3m/TEE	Un	Un	OAC or LMWH	None	Dissolved	WM

Carlson 2017	75	F	Un/RA	None	11.5w/TEE	Warfin+AS  A*45d	DAPT	Warfrin+ASA*2m	Stroke  then  died	Un	WM/mobile
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WM: Watchman; RA: Radio frequency catheter ablation; CrA: Cryballoon catheter ablation; TEE: Transesophagus echocardiogram; Un: Unknown; ASA: Aspirin;

OAC: Oral anticoagulant; NOAC: Non-vitamin K antagonist oral anticoagulant; PAF: Paroxysmal atrial fibrillation; CAF: Persistent atrial fibrillation; DAPT: Dual antiplatelet therapy; SAPT: Single antiplatelet therapy

### Timing and Modality of Diagnosis

Of the 16 cases reported on the diagnosis time of DRT, most occurred during the first 3 months (9/16), 6 occurred at 3-6 months, and one case occurred during 6-12 months, no case was reported after 12 months (Figure 4). The diagnosis was made in all reported cases by TEE imaging.

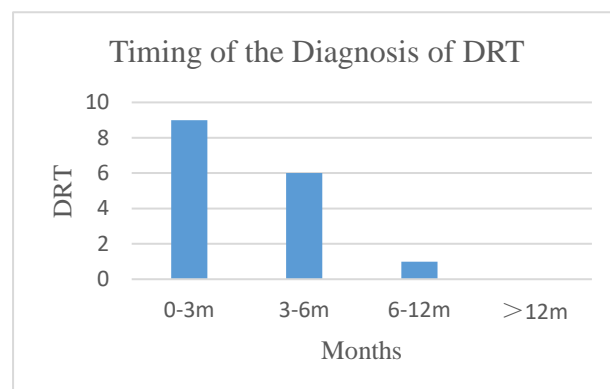


Figure4. Time of diagnosing DRT after the one-stop intervention. DRT: Device-related thrombus.

### Clinical implications, treatment strategies and predisposing factors of DRT

Most DRT were asymptomatic and discovered by TEE follow up, however, one case was reported with severe ischemic stroke and then died <sup>26</sup>. Overall, only 0.09% of one-stop intervention patients presented with ischemic stroke assumed related to DRT (1/1079). All cases were implanted with the watchman occlusion device. Only one case was ablated with cryoballoon ablation (6.25%, 1/16).

All patients receiving the one-stop intervention with reported treatment strategy were anticoagulated with different duration ranging from 45 days to 3 months. After the diagnosis of DRT, they were continued or restarted anticoagulation. One case received warfarin together with aspirin. The data on the duration of antithrombotic duration were missing in most cases. From the reported data, the duration of treatment ranges from 1 month to 6 months. Ultimately, complete thrombus

resolution under antithrombotic treatment was achieved. The recurrence rate was unknown because the follow-up time was too short.

Predisposing factors were scarcely mentioned in the reports. Carlson reported a case with anticoagulation discontinued at 45 days <sup>26</sup>. Kita K recognized two patients with DRT had self-discontinued OAC prematurely at the second month <sup>13</sup>.

## **Discussions**

Our study is the first meta-analysis focusing on the DRT in nonvalvular atrial fibrillation patients treated with concomitant CA and LAAO.

Compared with patients with sinus rhythm, the nonvalvular AF patients have a 5-fold increase in stroke risk. LAAO has gradually become an alternative to long-term anticoagulation especially in patients with high bleeding risk. CA is an effective method for symptomatic AF patients. Recently Ying Jiang had conducted a meta-analysis and concluded that the one-stop intervention had significant efficacy and could be safely and successfully performed in AF patients <sup>2</sup>. Because the one-stop intervention could merge a lot of operations into one procedure, it may have a better cost-effectiveness ratio. So this procedure could be prospective in the future. However, the long-term outcomes of this new therapeutic strategy have not been well established. DRT is a potential complication of LAAO. Therefore, we performed this meta-analysis to study DRT post CA and LAAO therapy.

In our study, the pooled incidence of DRT was approximately 1.2% and this was consistent with a recent meta-analysis conducted by Ying Jiang <sup>2</sup>. While Alkhouli reported the pooled incidence of DRT post only LAAO was 4% <sup>3</sup>, which was a little higher than our result. This could partially be explained by the enrollment of patients, for example, patients who are suitable for CA are more

likely to maintain sinus rhythm. Meanwhile, the true incidence might be difficult to evaluate because of the variations in surveillance protocols among the studies as well as the low sample size. In our study, a majority of DRT was found in the first three months after the procedure. This is probably related to the delayed endothelialization <sup>27</sup>. But cases of delaying thrombosis could not be neglected. This could be secondary to mechanical factors or systemic patient factors such as a low ejection fraction (EF), spontaneous echo contrast et al <sup>27</sup>. The formation of DRT is still obscure, as to the one-stop intervention, the evidence is fewer. Multiple studies have declared the proinflammatory effects of ablation within the left atrium and LAA, which may contribute to the formation of DRT <sup>28</sup>.

A case was reported with severe stroke after the diagnosis of DRT in our study. This patient had a history of bioprosthetic valve replacement and was anticoagulated 45 days. TEE performed after deployment revealed a large layered thrombus across the entirety of the WATCHMAN device along with a large mobile portion extending into the left atrium. The patient was given heparin drip along with warfarin. On the morning of postoperative day 2, the patient was noted to have right-sided weakness with subsequent unresponsiveness. Computed tomography of the head revealed a large left parietal hemorrhagic stroke<sup>26</sup>. Dukkupati et al. reported a relationship between DRT and ischemic events <sup>29</sup>. In the PROTECT AF study, the device thrombus-associated annualized stroke rate was 0.3% per 100 patient-years <sup>30</sup>. In the multicenter ACP registry, no embolic complications were reported in more than 1,000 patients and no relationship between DRT and stroke was identified <sup>31</sup>. Although it seems to be reasonable to regard DRT contributing to ischemic stroke, depending on the available data, we still could not draw a substantial conclusion.

The occurrence of DRT appears to be multifactorial and very complicated. Identifying predictors

of DRT is very important to recognize patients with a high risk of DRT formation and then take effective preventive measures. In the literature of researching one-stop interventions, scarcely data could be achieved until now, so conclusive evidence regarding these predictors could not be accumulated. According to evidence in only LAAO procedures, several clinical (stroke history, permanent AF, advanced age, large LAA, low EF, vascular disease history, higher CHA2DS2-VASc score, etc.), and procedural (deep implantation, lack of discharge antithrombotic treatment, etc.) factors are independent predisposing factors of DRT in individual studies<sup>29,32-34 31</sup>. Carlson reported a case with anticoagulation discontinued at 45 days<sup>26</sup>. In our meta-analysis, Kita K recognized two patients with DRT had self-discontinued OAC prematurely<sup>13</sup>. However, a clear association between the post-LAAO antithrombotic regimen and DRT was not demonstrated in Pracon's study<sup>34</sup>.

Besides, although TEE was used to follow up in all of our included studies, computed tomography imaging was also used in others<sup>35</sup>. TEE had some limitations, such as in patients with chronic hepatitis TEE was a contraindication, which may increase the loss of follow up. So computed tomography can be taken into consideration to follow up in the future.

There is no consensus on the treatment of DRT post-one-stop intervention up to now. Depending on our study, an overwhelming majority of DRT cases were completely dissolved after anticoagulation. But some reports did not describe if the patients were anticoagulated, and the duration was unknown either. Meanwhile, antithrombotic therapy to dissolve the thrombus may add the risk of a bleeding complication. So the treatment of DRT still needed to be evaluated carefully.

### **Limitations**

All studies were observational studies with DRT reported as an adverse event. Most studies did not describe the characteristics of thrombus. The demographics, treatment strategy, and prognosis of



patients with DRT was unrevealed. The size of DRT cases post-one-stop intervention was really small, so substantial conclusion on predisposing factors and clinical implications of DRT was difficult to be achieved. Besides, the definition of DRT was not unified, so the diagnosis can be operator dependent. Meanwhile, the follow-up duration maybe not long enough to observe the occurrence of DRT.

### **Conclusions**

Our meta-analysis suggests that DRT is infrequent in the one-stop intervention. Most of the DRTs occur early after the procedure. Anticoagulation seems to be an appropriate method for dissolving thrombus. Furthermore, more large prospective studies are needed to identify the real prevalence of DRT in the one-stop procedure, meanwhile to assess predisposing factors, treatment strategy, and clinical implications.

### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

### **Acknowledgements**

None.

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