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ORIGINAL ARTICLE

Impact of gender in patients with device-related thrombosis after left atrial appendage closure – A sub-analysis from the multicenter EUROC-DRT-registry

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Abstract

Background: Device-related thrombosis (DRT) is a common finding after left atrial appendage closure (LAAC) and is associated with worse outcomes. As women are underrepresented in clinical studies, further understanding of sex differences in DRT patients is warranted.

ABBREVIATIONS: AF, atrial fibrillation; CI, confidence interval; DAPT, dual antiplatelet therapy; DRT, device-related thrombosis; FU, follow-up; HR, hazard ratio; LAA, left atrial appendage; LAAC, left atrial appendage closure; LUPV, left upper pulmonary vein; NOAC, novel oral anticoagulant; OAC, oral anticoagulation; SEC, spontaneous echocardiographic contrast; TEE, transesophageal echocardiography; TIA, transient ischemic attack; TTE, transthoracic echocardiography; VKA, vitamin K antagonist.

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Methods and Results: This sub-analysis from the EUROC-DRT-registry compromises 176 patients with diagnosis of DRT after LAAC. Women, who accounted for 34.7% (61/176) of patients, were older (78.0 ± 6.7 vs. 74.9 ± 9.1 years, $p = .06$) with lower rates of comorbidities. While DRT was detected significantly later in women (173 ± 267 vs. 127 ± 192 days, $p = .01$), anticoagulation therapy was escalated similarly, mainly with initiation of novel oral anticoagulant (NOAC), vitamin K antagonist (VKA) or heparin. DRT resolution was achieved in 67.5% (27/40) of women and in 75.0% (54/72) of men ($p = .40$). In the remaining cases, an intensification/switch of anticoagulation was conducted in 50.% (9/18) of men and in 41.7% (5/12) of women. Final resolution was achieved in 72.5% (29/40) cases in women, and in 81.9% (59/72) cases in men ($p = .24$). Women were followed-up for a similar time as men (779 ± 520 vs. 908 ± 687 days, $p = .51$). Kaplan–Meier analysis revealed no difference in mortality rates in women (Hazard Ratio [HR]: 1.73, 95%-Confidence interval [95%-CI]: .68–4.37, $p = .25$) and no differences in stroke (HR: .83, 95%-CI: .30–2.32, $p = .72$) within 2 years after LAAC.

Conclusion: Evaluation of risk factors and outcome revealed no differences between men and women, with DRT in women being diagnosed significantly later. Women should be monitored closely to assess for DRT formation/resolution. Treatment strategies appear to be equally effective.

KEYWORDS
atrial fibrillation, device-related Thrombus, left atrial appendage closure, sex differences

1 | BACKGROUND

Left atrial appendage (LAA) closure (LAAC) is considered an alternative to oral anticoagulation (OAC) in patients with atrial fibrillation (AF) and contraindications for OAC.[1–3] Device-related thrombosis or thrombus (DRT) (Figure 1) can be a major complication after LAAC with detrimental effects, such as increased rates of stroke,[4–6] the need for resumed or intensified OAC or even interventional/surgical extraction.[7,8] While risk factors and treatment regimens have been previously evaluated, little is known about how risk factors, treatment, and outcome of DRT differ with regards to the sex of the respective patients. Generally, women have consistently been underrepresented in clinical studies.[9] A recent study found no difference in the incidence of DRT after LAAC between men and women.[10] Given that women have a greater burden of AF[11] and an increased risk for fatal stroke with impaired outcome compared to men,[12] further understanding of gender differences in patients with DRT is warranted. Also, women's cardiac dimensions differ significantly including left atrial size and function,[13] the latter of which seems to play a role in the occurrence of DRT.[4] This sub-analysis from the multicenter EUROC-DRT registry focuses on differences between men and women regarding risk factors, timing of DRT diagnosis, management of DRT, and outcomes.

2 | METHODS

2.1 | Study population

This sub-analysis of the multicenter EUROC-DRT registry included patients who underwent LAAC at 22 European and Canadian centers, and in whom a DRT was diagnosed post-procedurally during clinical follow-up (FU).[4,6,14] For further analysis, eight of the participating centers contributed a set of patients without diagnosis of DRT after LAAC, who also underwent LAAC in the same study period. All patients that underwent LAAC at the respective sites gave informed consent to be included in the respective LAAC registry, which were approved by local ethical committees. After discharge, all patients underwent routine clinical and imaging FUs, and if found to have DRT, were included in the EUROC-DRT registry. Information on patients included clinical and echocardiographic baseline characteristics, procedural data, and device types. Device position was assessed post-procedurally by transesophageal echocardiography (TEE). Complete LAA occlusion and implantation depth were rated, as previously described.[4,14] After DRT diagnosis, information on medical treatment strategies and adjustment were documented. Also, long-term outcome was assessed by clinical and telephone FUs.

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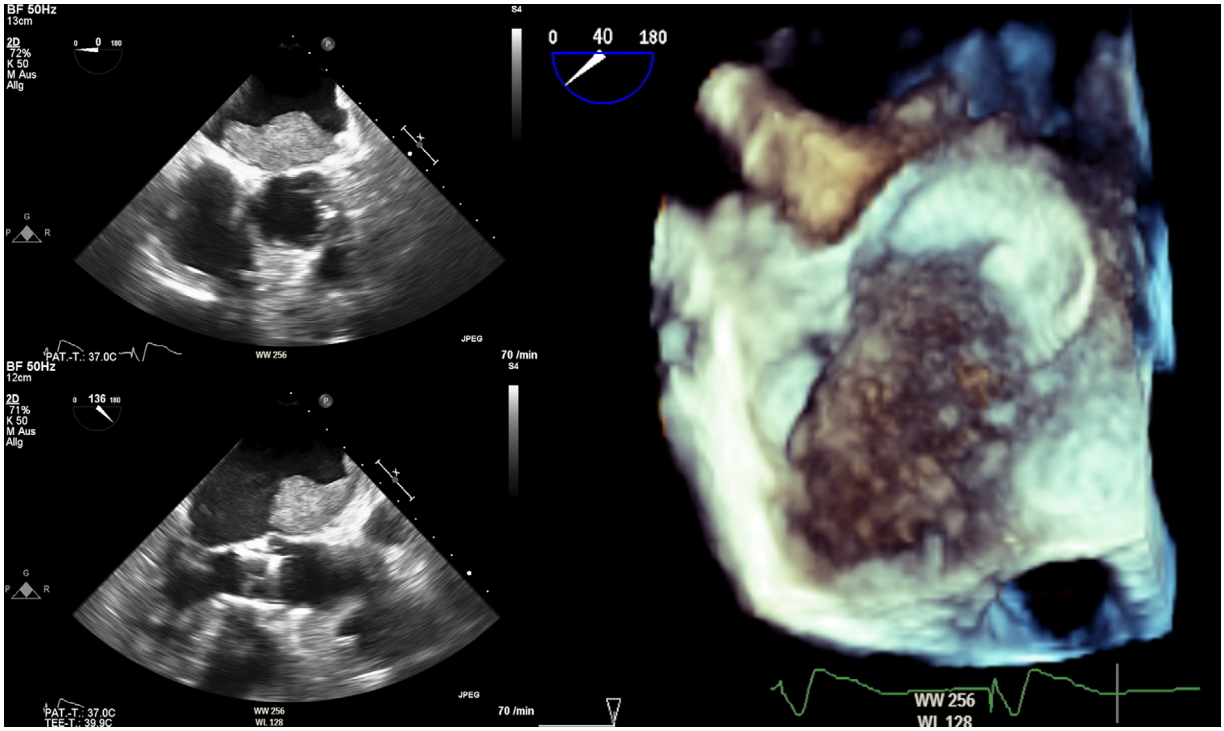

FIGURE 1 Echocardiographic images obtained in 2-dimensional and 3-dimensional transesophageal echocardiography of an 87-year-old female patient with diagnosis of a large DRT after implantation of a 20 mm Amulet Amplatzer device. DRT, device-related thrombosis.

2.2 | Statistical analysis

Categorical variables were displayed as frequencies and percentages, further descriptive analysis was conducted by using Chi-square analysis. Continuous variables were presented as mean ± standard deviation. Mann–Whitney U analysis was used for comparison of the central tendencies. For analysis of the long-term outcome, that is occurrence of DRT, stroke as well as assessment of mortality, Kaplan–Meier estimates were performed. All statistical analyses were performed with SPSS software version 25.0.0.1 (IBM Corporation, Somers, NY). Statistical significance was assumed when the null hypothesis could be rejected at $p < .05$.

3 | RESULTS

3.1 | Baseline characteristics

This study comprised 176 patients with established diagnosis of DRT after LAAC. Hereof, 61 (34.7%) patients were women and 115 (65.3%) were men (Table 1). There was a trend for women with DRT to be older than men (78.0 ± 6.7 vs. 74.9 ± 9.1 years, $p = .06$). Furthermore, there was a numerically greater proportion of paroxysmal AF (39.3% vs. 28.7%) in women, without reaching statistical significance ($p = .15$). Baseline cardiovascular comorbidities were higher in men, with higher rates of coronary artery disease ($p = .02$) and a trend towards higher rates of previous strokes or transient ischemic attacks (TIA) ($p = .19$). Given the nature of its calculation, the CHA_2DS_2-VASC score was higher in women (4.9 ± 1.8 vs. 4.1 ± 1.7, $p < .01$). There was a trend to better left ventricular ejection fraction in women compared to men (55.6 ± 11.3% vs. 52.5 ± 10.5%, $p = .08$), while spontaneous echo contrast (SEC) was reported in 52.0% of women and 40.7% of men ($p = .34$). Worse left ventricular diastolic dysfunction was found in women than in men (E/e' ratio: 16.5 ± 9.1 vs. 11.7 ± 7.8, $p = .05$).

3.2 | Procedural characteristics and postprocedural anticoagulation

Pacifier and non-pacifier occluders were equally implanted in men and women, with 63.1% (111/176) of patients receiving pacifier and 36.9% (65/176) receiving non-pacifier occluders. Of note, implanted occluders were numerically smaller in women compared to men but not statistically different (24.7 ± 4.1 vs. 25.7 ± 3.6 mm, $p = .12$). Complete occlusion of the LAA (i.e., peri-device flow < 3 mm) was achieved in more than 90% of cases in both groups ($p = .31$). Occluders were implanted slightly more ostial with an average implantation depth along the left upper pulmonary vein (LUPV) ridge of 10.7 ± 8.7 mm in women and 12.6 ± 8.4 mm in men ($p = .23$), resulting in a similar rate of ostial and thus optimal position (44.8% in women and 38.5% in men; $p = .41$). Anticoagulation at discharge did not differ between both groups: 60.6% (103/170) of overall cases received dual antiplatelet therapy, 22.9% (39/170) were treated with antiplatelet monotherapy, while 7.1% (12/170) and 4.2% (7/170) received a vitamin K antagonist (VKA) or a novel oral anticoagulant (NOAC), respectively.

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TABLE 1 Patient and echocardiographic baseline characteristics, procedural characteristics, and postprocedural anticoagulation, distinguished by gender with diagnosis of DRT.

	DRT $N = 176$	Male with DRT $N = 115$	Female with DRT $N = 61$	p-value
Baseline characteristics				
Age (years)	76.0 ± 8.4	74.9 ± 9.1	78.0 ± 6.7	.06
Paroxysmal AF	57 (32.4%)	33 (28.7%)	24 (39.3%)	.15
Non-paroxysmal AF	119 (67.6%)	82 (71.3%)	37 (60.7%)	.15
Coronary artery disease	59 (36.9%)	45 (43.3%)	14 (25.0%)	.02
Prior myocardial infarction	33 (20.4%)	23 (21.9%)	10 (17.5%)	.51
Diabetes mellitus	42 (23.9%)	25 (21.7%)	17 (27.9%)	.36
Prior stroke/TIA	87 (49.4%)	61 (53.0%)	26 (42.6%)	.19
HAS-BLED-score	3.3 ± 1.2	3.3 ± 1.2	3.3 ± 1.2	.91
CHA_2DS_2-VASC-score	4.4 ± 1.8	4.1 ± 1.7	4.9 ± 1.8	<.01
Echocardiographic parameters				
LVEF (%)	53.6 ± 10.8%	52.5 ± 10.5%	55.6 ± 11.3%	.08
E/e' ratio	13.5 ± 7.1	11.7 ± 7.8	16.5 ± 9.1	.05
SEC (I–III°)	37 (44.0%)	24 (40.7%)	13 (52.0%)	.34
LAA peak velocity (cm/s)	34.6 ± 18.3	34.2 ± 17.5	35.1 ± 19.8	.98
Procedural characteristics				
Occluder size (mm)	25.3 ± 3.8	25.7 ± 3.6	24.7 ± 4.1	.12
Pacifier occluder	111 (63.1%)	73 (63.5%)	38 (62.3%)	.88
Non-pacifier occluder	65 (36.9%)	42 (36.5%)	23 (37.7%)	.88
Complete occlusion	155 (93.9%)	102 (95.3%)	53 (91.4%)	.31
LUPV ridge length (mm)	12.1 ± 8.5	12.6 ± 8.4	10.7 ± 8.7	.23
Valvular side length (mm)	4.2 ± 10.0	3.5 ± 4.1	5.6 ± 16.9	.38
Ostial position	37 (38.5%)	24 (38.5%)	13 (44.8%)	.41
Anticoagulation at discharge				
VKA	12 (7.1%)	7 (6.3%)	5 (8.6%)	.57
NOAC	7 (4.2%)	4 (3.6%)	3 (5.2%)	.84
ASS/other antiplatelet	39 (22.9%)	28 (25.0%)	11 (19.0%)	.38
DAPT	103 (60.6%)	66 (58.9%)	37 (63.8%)	.54
Triple	1 (.6%)	1 (.9%)	0 (0%)	.47
Heparin	5 (3.0%)	3 (2.7%)	2 (3.4%)	.37
No therapy	3 (1.8%)	3 (2.7%)	0 (0%)	.21

Abbreviations: AF, atrial fibrillation; ASS, acetylsalicylic acid; DAPT, dual antiplatelet therapy; DRT, device-related thrombosis; LA, left atrium; LAA, left atrial appendage; LUPV, left upper pulmonary vein; LV, left ventricle; LVEF, left ventricular ejection fraction; NOAC, novel oral anticoagulant; SEC, spontaneous echocardiographic contrast; TIA, transient ischemic attack; VKA, vitamin K antagonist.

3.3 | Comparison of baseline characteristics in patients without DRT

For further analysis, differences in baseline characteristics between men and women without DRT were assessed (Table SI). Women without DRT were also older, had higher rates of paroxysmal AF, slightly higher rates of prior stroke/TIA and also had a slightly better ejection fraction than men without DRT. In line with the results regarding women and men with DRT, procedural characteristics did not significantly differ between women and men without DRT. Also, no difference in post-procedural anticoagulation between women and men without DRT were noticed.

Moreover, women with DRT were compared against women without DRT (Table SII). Women with DRT were slightly older (78.0 ± 6.7 vs. 76.2 ± 8.4 years, $p = .24$), while the CHA_2DS_2-VASC- and HAS-BLED-score did not differ between both groups ($p = .71$ and $p = .26$, respectively). Women with DRT showed an insignificantly lower left ventricular ejection fraction (55.2 ± 11.8% vs. 57.7 ± 10.2%, $p = .16$) and higher rates of SEC (52.9% vs. 29.5%, $p < .01$). Procedural characteristics did not differ between women with and without DRT, with

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TABLE 2 Characteristics of DRT and data on DRT treatment regimen, distinguished by gender.

	DRT $N = 176$	Male with DRT $N = 115$	Female with DRT $N = 61$	p-value
DRT characteristics				
Days to DRT detection	143 ± 221	127 ± 192	173 ± 267	.01
DRT size vertically (mm)	11.2 ± 6.8	10.7 ± 6.2	12.2 ± 7.9	.41
DRT size horizontally (mm)	13.2 ± 12.1	12.8 ± 13.0	13.8 ± 9.8	.17
Full DRT resolution with initial therapy attempt	81 (72.3%)	54 (75.0%)	27 (67.5%)	.40
Switch of therapy made after residual DRT	14 (46.7%)	9 (50.0%)	5 (41.7%)	.65
NOAC/VKA at any point	82 (59.4%)	53 (59.6%)	29 (59.2%)	.97
Full resolution achieved	88 (78.6%)	59 (81.9%)	29 (72.5%)	.24
Any bleeding under DRT therapy	11 (7.7%)	6 (6.6%)	5 (9.8%)	.49
Last FU after LAAC (days)	866 ± 638	908 ± 687	779 ± 520	.51
Last FU after DRT detection (days)	646 ± 536	668 ± 553	604 ± 505	.58

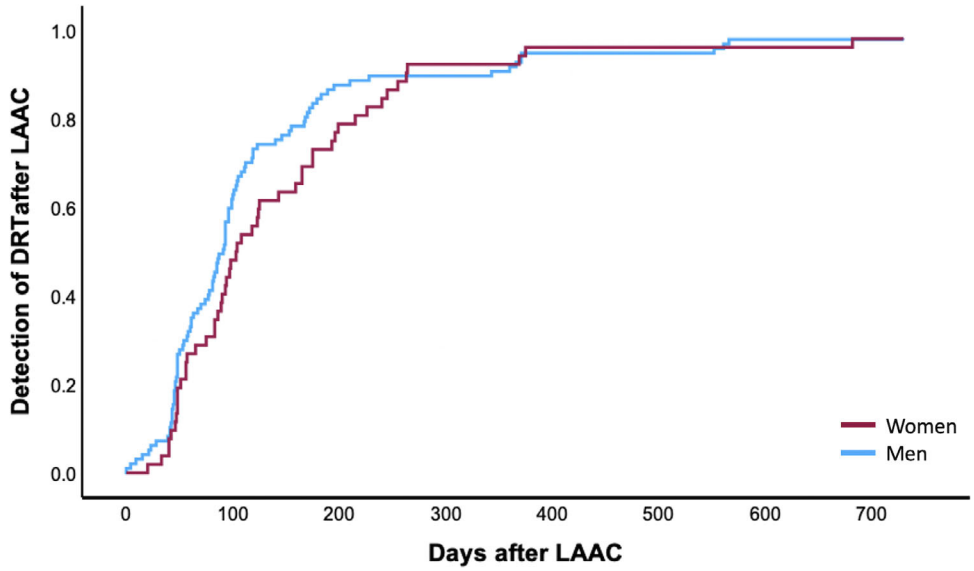

FIGURE 2 Kaplan–Meier analysis for timing of DRT detection after LAAC in men and women. DRT, device-related thrombosis; LAAC, left atrial appendage closure.

complete occlusion achieved in > 80% in both groups ($p = .39$). There was also no difference in anticoagulation regimen at discharge.

3.4 | DRT characteristics

DRT was detected after a mean of 143 ± 222 days after LAAC in the overall group. In this matter, timing of DRT detection was significantly later in women at mean 173 ± 267 days, compared to men at 127 ± 192 days after LAAC ($p < .01$) (Table 2, Figure 2). DRT size was non-significantly larger in women than in men (vertical size: 12.2 ± 7.9 vs. 10.7 ± 6.2 mm, $p = .41$; horizontal size: 13.8 ± 9.8 vs. 12.8 ± 13.0 mm, $p = .17$). After detection, treatment was mainly switched to NOAC (women: 30.0%, men: 30.5%) and VKA (women: 22.0%, men: 24.4%) (Table SIII). A third treatment regimen with heparin was administered in 32.0% of women and in 24.4% of men. Under the initial treatment attempt, DRT resolution was achieved in 72.3% (81/112) of patients, with a numerically lower, yet statistically insignificant, resolution rate of 67.5% (27/40) in women than with 75.0% (54/72) in men ($p = .40$). In the remaining 30/31 cases with residual DRT (no information in one case), an intensification of anticoagulation or switch of treatment was conducted in 41.7% (5/12) of women and in 50.0% (9/18) of men. As a result, final resolution of DRT was documented in 72.5% (29/40) of women, and in 81.9% (59/72) of men ($p = .24$). Of note, after LAAC, women were followed-up for 779 ± 520 days, while men were followed up for 908 ± 687 days ($p = .51$). Bleeding under any established DRT treatment regimen occurred in 7.7% (11/143) of cases, without significant differences between both genders ($p = .49$).

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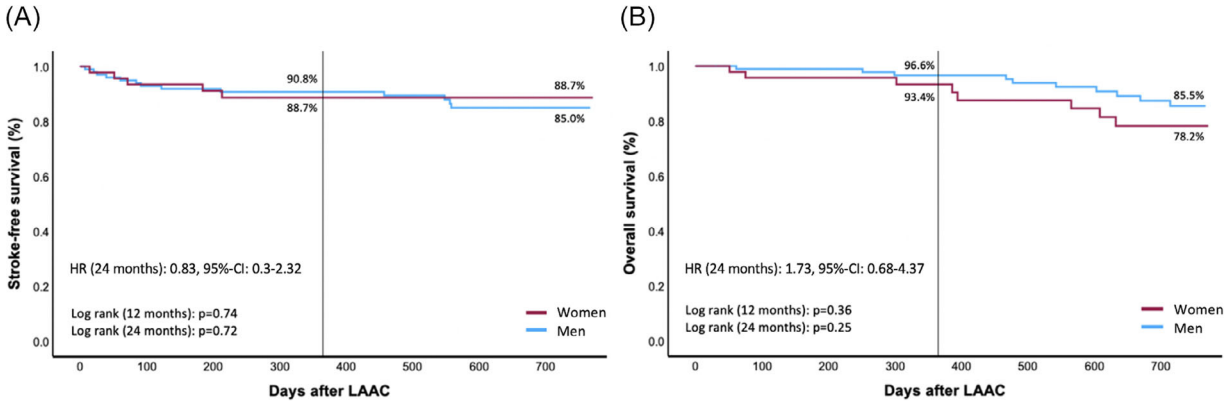

FIGURE 3 Kaplan–Meier analysis of 2-year outcome after LAAC in men and women. (A) Incidence of stroke/TIA displayed as stroke-free survival after LAAC. (B) Overall mortality displayed as overall survival after LAAC. LAAC, left atrial appendage closure; TIA, transient ischemic attack.

3.5 | Outcome

Long-term outcomes in terms of stroke-free survival and mortality are displayed in Figure 3. Stroke or TIA occurred mainly within the first year after LAAC, both, in men and women, without any significant differences after 1 and 2 years. Overall mortality revealed no significant difference after 1 year (overall survival: 93.4% vs. 96.6%, log rank: $p = .36$) and after 2 years (overall survival: 78.2% vs. 85.5%, log rank: $p = .25$) in women compared to men.

4 | DISCUSSION

This sub-analysis from the multicenter EUROC-DRT registry focused on sex-differences in patients with DRT. Generally, women with AF are more likely to suffer from stroke with worse clinical outcome.[15] At the same time, women also appear to benefit more from LAAC in terms of stroke risk reduction.[10] As DRT after LAAC is associated with an increased risk of stroke,[6] further understanding of sex differences is warranted.

As the registry does not include consecutive patients from all centers, conclusions about the incidence of DRT in women cannot be drawn. Recent representative studies on the use of LAAC[1,16–18] found that 30%–40% of all patients undergoing LAAC were women. This corresponds well to the observed prevalence of the female gender in the present analysis (34.7%). Of note, prior studies on DRT, our own EUROC-DRT registry[4] and a study by Simard et al.[5] revealed similar fractions of women with and without DRT after LAAC. Another recent study by Paitazoglou et al.[18] found a rate of 4.2% of men developing DRT, compared to only 2.7% of women, while De Caterina et al. found similar rates of DRT between men and women.[10]

As one of the major findings of this study, DRT was diagnosed significantly later in women than in men. As most patients undergo routine imaging FU after LAAC (usually after approximately 3 months) a significant portion of DRT is diagnosed at this point. In our study, DRT in women were diagnosed on average after approximately 6 months. Of note, a prior analysis found that approximately 20% of all DRT are diagnosed beyond 6 months after LAAC,[14] so called late DRT.

As a possible explanation, formation of DRT could have occurred much earlier, with delayed detection being a circumstance due to unstandardized FU protocols. As men were also followed-up numerically longer than women in this study, it appears as if women were less likely to undergo routinely conducted echocardiographic follow-ups within our registry.

Risk factors for the formation of DRT have been analyzed before, in this matter, older age, non-paroxysmal AF, history of prior stroke/TIA, spontaneous echo contrast, subostial occluder implantation and hypercoagulability disorders have been identified as independent factors.[4,5] Also, echocardiographic parameters regarding left atrial dimension and function have been mentioned to differ between patients with and without DRT formation.[4,5] In the present analysis, many baseline characteristics did not significantly differ between men and women. This was also observed in the overall cohort from the EUROC-DRT registry, which also included cases without DRT. In line with data on sex differences in patients undergoing LAAC,[18] women with DRT were numerically older, while men with DRT featured higher rates of non-paroxysmal atrial AF and coronary artery disease. Also, a history of prior stroke/TIA was more often present in men than in women in this analysis. While suboptimal occluder position and its impact on DRT formation have been intensively discussed,[4,5,19,20] device position appeared to be more ostial in women than in men. This however may be explained by definition of ostial position[14] and the fact that left atrial appendages trend to be smaller in women.[13,21] Hence, it is our opinion that no sex-related increased DRT risk can be attributed to device positioning. As a crucial finding, diastolic function, quantified as E/e' ratio, was worse in women compared to men with DRT. The impact of diastolic function has already been described in patients with late DRT, detected beyond 6 month after LAAC.[14] Hereby, increased E/e' ratios are likely representative of increased filling pressures and possibly left atrial sizes.

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As described above, DRT was diagnosed significantly later in women than in men. The combination of impaired diastolic function and female gender emphasized the need for further long-term echocardiographic examinations to rule out formation of late DRT. In this context, the impact of diastolic and left atrial function and their respective influence on DRT formation require further investigation. As previously discussed, atrial parameters, such as indexed minimal left atrial volume (LAVImin) appear to be predictive in heart failure[22] and could also reduce left atrial function, a condition, which may promote DRT formation.

As another finding, post-detection treatment regimens did not differ between men and women, with most patients receiving VKA, NOAC or heparin. This is of special interest, as gender differences have been revealed concerning the prescription of anticoagulation between men and women. In this context, women were less likely to receive anticoagulation compared to men for atrial fibrillation.[23] Treatment regimen appeared to be effective in both sexes, with final documentation of DRT resolution in 72% of women and 82% of men. Also, no difference between women with and without DRT were observed. Of note, as no consensus on optimal medical treatment exists, larger studies attributed effectiveness of anticoagulation therapy for AF in both sexes, albeit women being underrepresented.[18,24,25] A recent study found women on VKA to be less likely in therapeutic range than men,[26] while another study showed greater beneficial effects of NOAC in women compared to men.[27] Therefore, it remains for future, prospective trials to evaluate the optimal treatment regimen for patients with DRT, in this matter, focus on sex-differences are warranted. Clinical outcome within 2 years after LAAC revealed increased rates of stroke/TIA in DRT patients, however no differences were found between men and women. As women were approximately 3 years older than men on average, overall mortality was insignificantly increased in women.

In summary, this analysis provides a deeper understanding of DRT and its gender related differences. While women have been underrepresented in clinical trials and feature an increased risk of stroke, especially when AF is diagnosed, this study provides positive and negative aspects for women with DRT. On the one hand, it appears that women were equally prone to DRT formation without increased risk and had an equal risk for DRT-related stroke. On the other hand, it appears as if DRT were underdiagnosed in women, which may be due to unstandardized follow-up protocols. Therefore, this study emphasizes the need for intensified routine FUs after LAAC, in order to detect DRT until further understanding of DRT and optimized treatment regimen become available. In this matter, we encourage to conduct prospective, randomized trials with equal emphasis on men and women with proof of DRT.

5 | CONCLUSION

Device-related thrombosis remains a relevant finding after left atrial appendage closure and therefore, remains of crucial interest for further investigation. This analysis, which addresses the impact of gender on DRT, found a similar risk for DRT formation as well as DRT-associated stroke. Implementation of routine follow-up protocols is desperately needed to systematically screen for DRT, especially in women.

6 | LIMITATIONS

This study has several limitations: First, all patients included in the registry were collected retrospectively at several participating sites, therefore standardized protocols and follow-ups were not employed, which could have impacted the presented results. All participating centers performed echocardiographic examination independently without adjudication by an independent core laboratory. Also, data sets were incomplete in a significant portion of patients, especially data on post-procedural echocardiographic assessment of occluder position and data on DRT treatment regimen were incomplete, limiting the quality of the study. Also, no information is given on dates of follow ups at the individual sites, therefore it is unclear whether DRT was simply detected belated at first echocardiographic FU or developed in-between two FUs. Information on patients with residual DRT also needs to be interpreted with caution, as information on further FU is simply lacking and fate of these patients and DRT regression remains unclear.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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