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Incidence of intracardiac thrombus formation prior to electrical cardioversion in respect to the mode of oral anticoagulation

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Abstract

Aims: To evaluate the incidence of newly diagnosed intracardiac thrombi (ICT) in respect to the mode of OAC in patients undergoing cardioversion (CV).

Methods and results: We prospectively assessed transesophageal echocardiography (TEE) and OAC therapy prior to CV in AF patients with ≥48-hour duration scheduled for CV. A total of 60 first-time ICT (4.7%) were diagnosed in 1,286 TEE, with highest rate in patients without OAC (9.6% vs. OAC 4.1%, P = 0.009) and an apparently lower rate in nonvitamin K antagonist anticoagulants (NOAC) therapy compared to vitamin K antagonist (VKA) (2.5% vs. 5.3%, P = 0.02). VKA therapy control 4 weeks prior to CV was overall average (time in therapeutic range 60%) and patients showed more frequently clinical characteristics and TEE parameters associated with risk for ICT. Even among patients with effective OAC therapy (uninterrupted NOAC and VKA therapy with international normalized ratio (INR) ≥2.0 for 3 weeks), ICT occurred in 2.7%, but with no difference between both groups (P = 0.22). There was no difference between different types of NOAC. Independent predictors for ICT were history of embolism, hypertension, BMI, absence of OAC, renal function, reduced atrial appendage flow, and presence of spontaneous echo contrast.

Conclusion: NOAC therapy seems favorable in the overall prevention of ICT, although this is likely to be caused by suboptimal VKA therapy control and differences in the overall health status between VKA and NOAC patients. ICT occurred even with effective OAC therapy suggesting individual TEE-guided cardioversion in patients at risk.

KEYWORDS

atrial fibrillation, cardioversion, NOAC, oral anticoagulation, thrombus

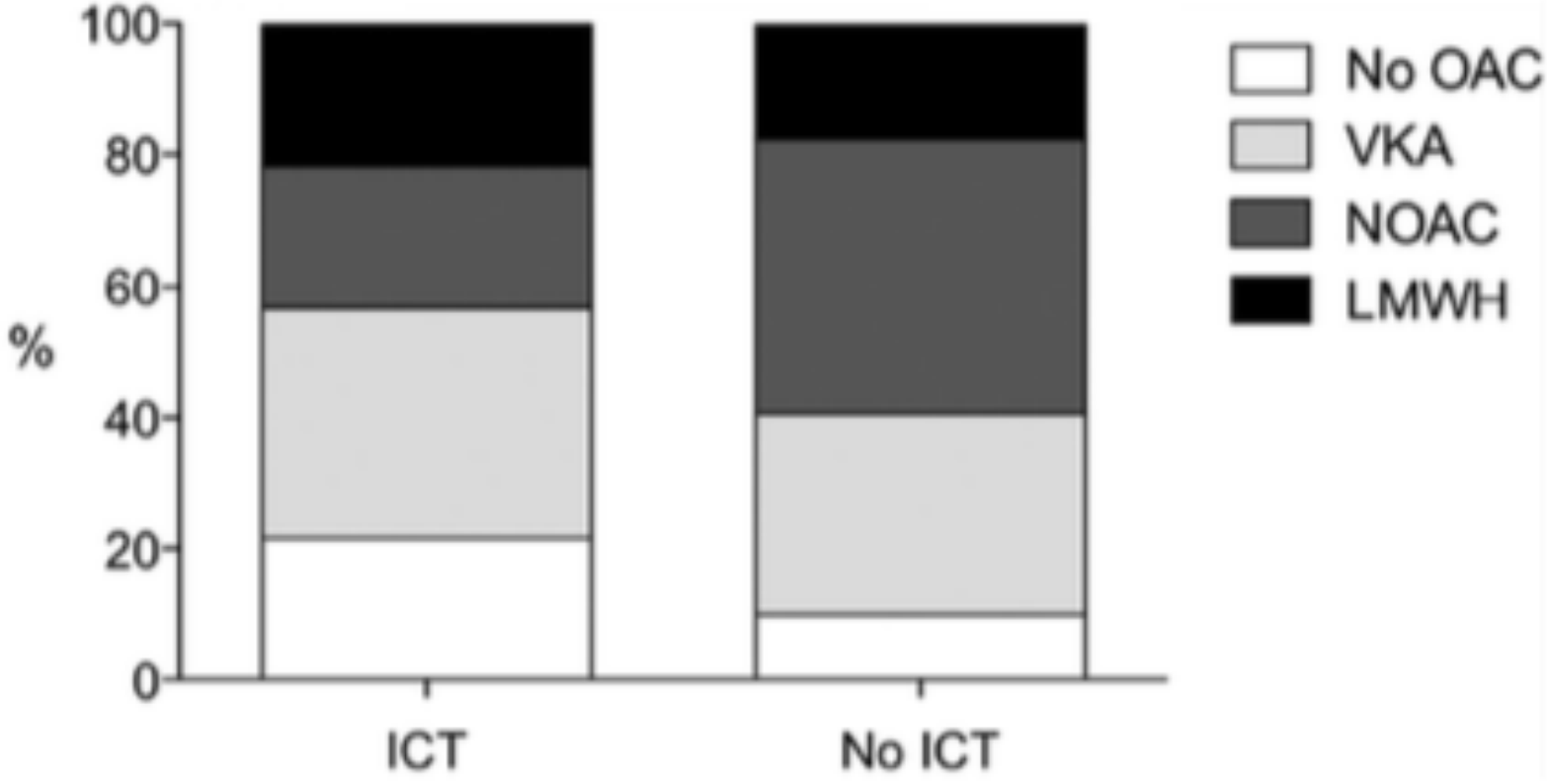

FIGURE 1 Oral anticoagulation regimen in patients with and without thrombus. OAC = oral anticoagulation; VKA = vitamin K antagonists; NOAC = nonvitamin K anticoagulants; LMWH = low molecular weight heparin; ICT = intracardiac thrombus

TABLE 1 Patient characteristics

	Total (n = 1,286)	Thrombus (n = 60, 4.7%)	No thrombus (n = 1,226, 95.3%)	P
Age, years	67.6 ± 11.2	68.3 ± 10.8	67.5 ± 11.2	0.673
Male sex, n (%)	896 (69.7)	46 (67.7)	863 (70.4)	0.157
Body mass index, kg/m^2	27.6 ± 5.3	29.2 ± 5.5	27.5 ± 5.2	0.240
CHA_2DS_2-VASc-Score (mean, range)	3 (0–9)	3.5 (1–8)	3 (0–9)	<0.001
0, n (%)	85 (6.7)	0	85 (6.9)	
1, n (%)	188 (14.6)	4 (6.7)	184 (15)	
2, n (%)	292 (22.7)	12 (20)	280 (22.8)	
3, n (%)	309 (24)	14 (23.3)	295 (24.1)	
≥4, n (%)	412 (32)	30 (50)	382 (31.2)	
EHRA-Score, n (%)				0.393
I	111 (8.6)	4 (6.7)	107 (8.7)	
II	633 (49.2)	24 (40)	609 (49.5)	
III	489 (38)	28 (46.7)	461 (37.6)	
IV	53 (4.1)	4 (6.7)	49 (4)	
Left atrial appendage velocity, m/s	0.37 ± 0.19	0.18 ± 0.13	0.38 ± 0.18	<0.001
Spontaneous echo contrast, n (%)	125 (9.7)	50 (83.3)	75 (6.1)	<0.001
LVEF, n (%)				
≥ 55%	871 (67.7)	24 (40)	847 (69.1)	<0.001
45–54%	135 (10.5)	3 (5)	132 (10.7)	0.196
30–44%	143 (11.1)	12 (20)	132 (10.7)	0.350
< 30%	138 (10.7)	21 (35)	117 (9.5)	<0.001
Serum creatinine, mg/dL	1.1 ± 0.6	1.3 ± 0.4	1.1 ± 0.6	0.004
Glomerular filtration rate, mL/min	70.3 ± 23.9	66.3 ± 34.6	70.5 ± 23.2	0.025
Potassium, mmol/L	4.2 ± 1.1	4.2 ± 0.6	4.2 ± 0.5	0.857

Type of arrhythmia, n (%)				0.142
Atrial fibrillation	924 (71.9)	50 (83.3)	874 (69.1)	
Atrial flutter	144 (11.2)	4 (6.7)	140 (11.4)	
Atypical flutter	218 (17)	6 (10)	212 (17.3)	
Coronary artery disease, n (%)	368 (28.6)	24 (40)	344 (28.1)	0.056
Cardiomyopathy, n (%)				
Ischemic CMP	110 (8.6)	10 (16.7)	100 (8.2)	0.031
Dilated CMP	89 (6.9)	9 (15)	80 (6.5)	0.019
Tachycardia related	48 (3.7)	8 (13.3)	40 (3.3)	0.001
HCM	26 (2)	3 (5)	23 (1.9)	0.117
Other type of CMP	16 (1.2)	4 (6.7)	12 (1)	0.005
CABG	104 (8.1)	11 (18.3)	93 (7.6)	0.007
Valve surgery	60 (4.7)	1 (1.7)	59 (4.8)	0.213
Diabetes mellitus type 2	208 (16.2)	15 (25)	193 (15.7)	0.071
Hypertension	909 (70.7)	51 (85)	858 (70)	0.013
History of embolism	151 (11.7)	17 (28.3)	134 (10.9)	<0.001
Beta blocker	828 (64.4)	47 (78.3)	781 (63.7)	0.081
Class I AAD	121 (9.4)	1 (1.7)	120 (9.8)	0.026
Class III AAD	267 (20.8)	15 (25)	252 (20.6)	0.412
Class IV AAD	8 (0.6)	0	8 (0.7)	1

EHRA = European Heart Rhythm Association; LVEF = left ventricular ejection fraction; CMP = cardiomyopathy; HCM = hypertrophic cardiomyopathy; CABG = coronary artery bypass graft; AAD = antiarrhythmic drug; continuous variables: means ± standard deviations, categorical variables: counts (percentages); P-values from Mann-Whitney-tests for continuous and from Fisher's exact tests for categorical variables.

TABLE 2 Oral anticoagulation therapy regimen

Oral anticoagulation	Total (n = 1,286)	Thrombus (n = 60)	No thrombus (n = 1,226)	P
Oral anticoagulation, n (%)	1,150 (89.4)	47 (78.3)	1,103 (90)	
No oral anticoagulation, n (%)	136 (10.6)	13 (21.7)	123 (10)	0.009
Group of oral anticoagulation, total, n (%):	922 (100)	34 (100)	888 (100)	
Vitamin-K antagonists	396 (43.0)	21 (61.8)	375 (42.2)	0.019
NOAC (total)	526 (57.0)	13 (38.2)	513 (57.8)	
Type of oral anticoagulation total, n (%):	1,150 (100)	47 (100)	1,103 (100)	0.055
Vitamin-K antagonists	396 (34.4)	21 (44.7)	375 (34.0)	
Rivaroxaban 20 mg qd	296 (25.7)	4 (8.5)	292 (26.5)	
Rivaroxaban 15 mg qd	51(4.4)	3 (6.4)	48 (4.4)	
Rivaroxaban interrupted	13 (1.2)	0 (0)	13 (1.1)	
Dabigatran 150 mg bid	71 (6.2)	2 (4.3)	69 (6.3)	
Dabigatran 110 mg bid	32 (2.8)	1 (2.1)	31 (2.8)	
Dabigatran interrupted	3 (0.3)	0 (0)	3 (0.3)	
Apixaban 5 mg bid	42 (3.7)	1 (2.1)	41 (3.7)	
Apixaban 2.5 mg bid	15 (1.3)	1 (2.1)	14 (1.3)	
Apixaban interrupted	3 (0.3)	1 (2.1)	2 (0.2)	
Low molecular weight heparin	228 (19.8)	13 (27.7)	215 (19.5)	

qd = quaque die (once a day); bid = bis in die (twice a day); NOAC = nonvitamin K antagonist oral anticoagulants.

TABLE 3 Subgroup analysis of patients with optimal oral anticoagulation therapy

Optimal oral anticoagulation	Total (n = 561)	Thrombus (n = 15)	No thrombus (n = 546)	P
Optimal VKA therapy	136 (24.2)	6 (40)	130 (23.8)	
Optimal NOAC therapy	425 (75.8)	9 (60)	416 (76.2)	0.216
Age, years	66.7 ± 10.3	71.3 ± 8.7	66.6 ± 10.4	0.042
Male sex, n (%)	374 (66,7)	10 (66.7)	364 (66.7)	1
Body mass index, kg/m^2	27.5 ± 5.1	27.9 ± 5.9	26.6 ± 5.1	0.967
CHA_2DS_2-VASc-Score (mean, range)	3 (0–9)	4 (2–7)	3 (0–9)	<0.001
0, n (%)	36 (6.4)	0	36 (6.6)	
1, n (%)	100 (17.8)	0	100 (18.3)	
2, n (%)	132 (23.5)	1 (6.7)	131 (24)	
3, n (%)	145 (25.8)	6 (40)	139 (25.5)	
≥4, n (%)	148 (27.1)	8 (53.3)	140 (24.9)	
EHRA-Score, n (%)				0.432
I	50 (8.9)	2 (13)	48 (8.8)	
II	280 (49.9)	5 (33.3)	275 (50.4)	
III	211 (37.6)	8 (53.3)	203 (37.2)	
IV	20 (3.6)	0	20 (3.7)	
Left atrial appendage velocity, m/s	0.4 ± 0.2	0.2 ± 0.1	0.4 ± 0.2	<0.001
Spontaneous echo contrast, n (%)	42 (7.5)	13 (86.7)	29 (5.3)	<0.001
LVEF, n (%)				
≥55%	421 (75)	10 (66.7)	411 (75.3)	0.549
45–54%	51 (9.1)	1 (6.7)	50 (9.2)	1
30–44%	42 (7.5)	0	42 (7.7)	0.618
<30%	47 (8.4)	4 (26.7)	43 (7.9)	0.03

Serum creatinine, mg/dL	1.1 ± 0.4	1.4 ± 0.5	1.1 ± 0.3	0.017
Glomerular filtration rate, mL/min	71.3 ± 21.6	57 ± 18.7	71.7 ± 21.5	0.013
Potassium, mmol/L	4.2 ± 0.5	3.9 ± 0.5	4.2 ± 0.5	0.071
Type of arrhythmia, n (%)				0.689
Atrial fibrillation	395 (70.4)	12 (80)	383 (70.1)	
Atrial flutter	49 (8.7)	0	49 (9)	
Atypical flutter	117 (20.9)	3 (20)	114 (20.9)	
Coronary artery disease, n (%)	127 (22.6)	5 (33.3)	122 (22.3)	0.348
Cardiomyopathy, n (%)				
Ischemic CMP	34 (6.1)	1 (6.7)	33 (6)	0.613
Dilated CMP	31 (5.5)	2 (13.3)	29 (5.3)	0.199
Tachycardia related	21 (3.7)	0	21 (3.8)	1
HCM	11 (2)	1 (6.7)	10 (1.8)	0.260
Other type of CMP	5 (0.9)	1 (6.7)	4 (0.7)	0.127
CABG	29 (5.2)	3 (20)	26 (4.8)	0.037
Diabetes mellitus type 2	65 (11.6)	4 (26.7)	61 (11.2)	0.084
Hypertension	389 (69.3)	12 (80)	377 (69)	0.571
History of embolism	63 (11.2)	7 (46.7)	56 (10.3)	0.001
Beta blocker	370 (66)	10 (66.7)	360 (65.9)	1
Class I AAD	56 (10)	1 (6.7)	55 (10.1)	1
Class III AAD	142 (25.3)	6 (40)	136 (24.9)	0.226
Class IV AAD	3 (0.5)	0	3 (0.5)	1

Optimal oral anticoagulation therapy is defined as INR ≥ 2 for 3 weeks prior to TEE in VKA treatment and uninterrupted and correct dose in NOAC therapy. VKA = vitamin K antagonists; NOAC = non-vitamin K antagonist oral anticoagulants. Abbreviations are the same as in Table 1.

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TABLE 4 Patients under VKA treatment

VKA therapy	Total (n = 396)	Thrombus (n = 21)	No thrombus (n = 375)	P
INR	2.41 ± 0.6	2.35 ± 0.6	2.41 ± 0.6	0.505
TTR available, n (%)	280 (70.7)	19 (90.5)	261 (69.6)	0.048
Time in therapeutic range, %INR ≥ 2	60 ± 29	50 ± 22	61 ± 30	0.075
Over last 3 weeks, n (%)	136 (34.3)	6 (28.6)	130 (34.7)	0.644
INR ≥ 2 over last 4 weeks, n (%)	121 (30.6)	6 (28.6)	115 (30.7)	1

VKA = vitamin K antagonists; TTR = time in therapeutic range; INR = international normalized ratio.

TABLE 5 Baseline characteristics in patients with different regimes of anticoagulation

	VKA (n = 396)	NOAC (n = 526)	P
Age, years	67.8 (10.1)	67.2 (11.1)	0.284
Male sex, n (%)	274 (69.2)	337 (64.1)	0.106
Body mass index, kg/m^2	28.1 (5.0)	27.3 (5.2)	0.009
CHA_2DS_2-VASc-score	2.95 (1.4)	2.62 (1.5)	0.001
EHRA-Score, n (%)			0.029
I	20 (5.0)	53 (10.0)	
II	212 (53.5)	261 (49.6)	
III	146 (36.9)	197 (37.5)	
IV	18 (4.5)	15 (2.9)	
Left atrial appendage flow, m/s	0.34 (0.17)	0.37 (0.19)	0.003
Spontaneous echo contrast, n (%)	49 (12.4)	36 (6.8)	0.006
Left ventricular ejection fraction, n (%):			
>55%	269 (67.9)	383 (72.8)	0.109
45–54%	35 (8.8)	52 (9.9)	0.649
30–44%	49 (12.4)	46 (8.7)	0.080
<30%	43 (10.9)	45 (8.6)	0.258
Serum creatinine, mg/dL	1.19 (0.57)	1.06 (0.37)	<0.001
Glomerular filtration rate, mL/min	68.3 (26.4)	71.9 (21.3)	0.001
Potassium, mmol/L	4.2 (0.46)	4.2 (0.44)	0.124
Type of arrhythmia, n (%)			0.229
Atrial fibrillation	292 (73.7)	377 (71.7)	
Atrial flutter	24 (6.1)	48 (9.1)	
Atypical flutter	80 (20.2)	101 (19.2)	

Coronary artery disease, n (%)	111 (28.0)	128 (24.3)	0.225
Cardiomyopathy, n (%)			
Ischemic CMP	30 (7.6)	36 (6.8)	0.700
Dilated CMP	39 (9.8)	29 (5.5)	0.015
Tachycardia related	15 (3.8)	19 (3.6)	1
HCM	14 (3.5)	6 (1.1)	0.02
Other type of CMP	6 (1.5)	5 (1.0)	0.544
CABG	30 (7.6)	29 (5.5)	0.223
Diabetes mellitus type	71 (17.9)	63 (12.0)	0.014
Hypertension	304 (76.8)	350 (66.5)	0.001
History of embolism	58 (14.7)	54 (10.3)	0.053
Class I AAD	32 (8.1)	54 (10.3)	0.303
Beta blocker	273 (68.9)	342 (65.0)	0.230
Class III AAD	108 (27.3)	123 (23.4)	0.192

Abbreviations are the same as in Table 1.

TABLE 6 Univariate analysis of predictors for thrombi

Univariate predictors	Odds ratio	95% Confidence interval	P
CHA_2DS_2-VASc-Score	1.41	1.20–1–66	≤0.001
Body mass index	1.05	1.01–1.10	0.023
History of embolism	3.24	1.79–5.84	≤0.001
>3 prior cardioversions	0.49	0.49–0.24	0.047
Oral anticoagulation therapy	0.40	0.21–0.77	0.006
Rivaroxaban therapy	0.13	0.04–0.04	≤0.001
Aspirin therapy	2.23	1.10–4.53	0.027
Beta-blocker therapy	2.07	1.11–3.86	0.023
Coronary artery disease	1.71	1.01–2.91	0.048
CABG	2.74	1.38–5.44	0.004
Hypertension	2.43	1.18–4.99	0.015
Dilated CMP	2.53	1.20–5.32	0.015
Ischemic CMP	2.25	1.11–4.58	0.025
Other CMPs	7.23	2.26–23.12	0.001
Tachycardia related CMP	4.56	2.03–10.24	≤0.001
Left ventricular ejection function			
>55%	0.31	0.18–0.52	≤0.001
30–44%	2.07	1.07–4.00	0.030
<30%	5.10	2.91–8.97	≤0.001
Spontaneous echo contrast	76.7	37.43–157.33	≤0.001
Left atrial appendage flow	0.09	0.05–0.15	≤0.001
Serum creatinine	1.97	1.18–3.31	0.010
Glomerular filtration rate	0.64	0.42–0.99	0.047
Mechanical valve	5.18	0.57–47.05	0.144

Variables tested as predictors of left atrial thrombus by univariate regression analyses ($P < 0.05$).

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TABLE 7 Multivariate analysis of predictors for thrombi

	Odds ratio	95% Confidence interval	P
History of embolism	2.79	1.19–6.57	0.019
Oral anticoagulation therapy	0.17	0.06–0.52	0.002
Body mass index	1.07	1.00–1.15	0.045
Hypertension	5.54	1.79–17.13	0.003
Tachycardia related CMP	8.70	2.63–28.77	≤0.001
Spontaneous echo contrast	71.34	29.36–173.36	≤0.001
Left atrial appendage flow	0.2	0.10–0.40	≤0.001
Serum creatinine	29.4	2.97–291.76	0.004
Glomerular filtration rate	17.94	2.91–110.53	0.002
Mechanical valve	3,42	0.06–182.81	0.544

Predictors for thrombus formation identified by stepwise backward multivariate logistic regression analysis adjusted for mechanical valve type and oral anticoagulation therapy.

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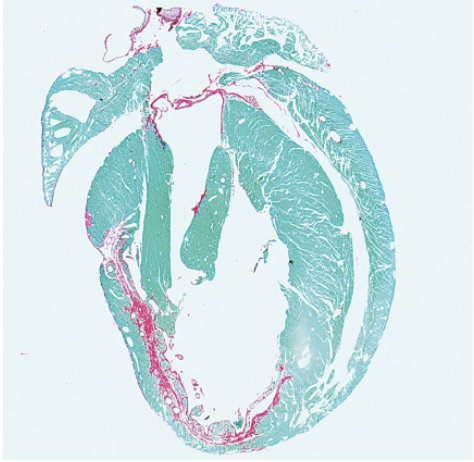
5 | STUDY LIMITATIONS

This study is a single-center prospective investigation with a nonrandomized protocol. Although randomized data are requested to clarify critical aspects on this issue, the present study provides a relevant assessment of real-world OAC therapy and thrombus incidence in the setting of cardioversion beyond the scope of large sponsored clinical trials.

No routine long-term follow-up was performed to reveal potential delayed events. Nevertheless, other studies report the majority of thromboembolic events immediately after cardioversion as pathophysiologically expected.[15] Further, the definition of thrombus preformation remains indistinctly to certain degree due to paucity of standardized grading systems of SEC and possible interoperator interpretation differences.

The duration of current AF episodes can influence thrombus formation within early phase of onset ≤48 hours.[4] We did not evaluate the AF duration beyond the assessment of longer or shorter than 48 hours due to difficulty in correct verification of AF duration in routine clinical setting. Yet, differences in AF duration beyond ≥48 hours could potentially influence thrombus formation, although data are sparse.

Data regarding NOAC adherence was based on the information provided verbally by patients during interrogation. Although patients were asked explicitly in this regard, inaccuracy cannot be ruled out completely. Edoxaban was not in routine clinical use at the time point of investigation and therefore no conclusions can be drawn for this substance. Another limitation was the low proportion of patients with optimal VKA therapy and that VKA treatment in our study population is almost exclusively performed with phenprocoumon. Results for VKA treatment therefore may not be automatically transferable to warfarin.



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6 | CONCLUSIONS

ICT formation remains a potential risk in patients with indication for cardioversion. The apparent favorable effect of NOAC therapy in prevention of thrombus formation compared to VKA therapy in this study is likely to be caused by the difficulty of achieving optimal VKA therapy control and due to differences in the overall health status between both the OAC groups. Yet, even optimal OAC, with either VKA or NOAC, could not prevent thrombi formation entirely, thus increasing the risk for possible thromboembolic events among these patients. Clinical risk factors such as CHA_2DS_2-VASc-Score and history of prior embolic events may help to identify some but not all patients at risk and to guide decision making on TEE-guided cardioversion. Further studies are needed to clarify these aspects and develop optimal strategies.