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ORIGINAL ARTICLE
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Comparison of phenprocoumon with direct oral anticoagulants in catheter ablation of atrial fibrillation

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Aims

In patients undergoing catheter ablation for atrial fibrillation (AF), direct oral anticoagulants (DOACs) are as effective and safe as the vitamin K antagonist (VKA) warfarin. Phenprocoumon has a different pharmacokinetic profile compared with warfarin and is the most used VKA in Germany. The aim of the study was to compare DOAC with phenprocoumon.

Methods and results

In this retrospective single-centre cohort study, 1735 patients who underwent 2219 consecutive catheter ablations for AF between January 2011 and May 2017 were included. All patients were in-hospital for at least 48 h after catheter ablation. The primary outcome was defined as peri-procedural thrombo-embolic events. The secondary outcome was any bleeding according to the International Society on Thrombosis and Haemostasis (ISTH). The mean age of the patients was 63.3 years. Phenprocoumon was prescribed in 929 (42%) of the cases, and in 697 (31%) dabigatran, 399 (18%) rivaroxaban, and 194 (9%) apixaban. During hospitalization, 37 (1.6%) thrombo-embolic events occurred, including 23 transient ischaemic attacks (TIAs). Compared with the use of phenoprocoumon, the use of DOAC was significantly associated with a lower thrombo-embolic risk [16 (1.2%) vs. 21 (2.2%), odds ratio (OR)], 0.5 [95% confidence interval (CI) 0.2–0.9], $P = 0.04$. No statistically significant association with bleeding risk was observed [phenprocomoun: 122 (13%); DOAC: 163 (12.6%); OR 0.9 (95% CI 0.7–1.2); $P = 0.70$]. Interruption of oral anticoagulation (OAC) was associated with an increased risk for thrombo-embolic complications [OR 2.2 (1.1–4.3); $P = 0.031$], and bleeding [OR 2.5 (95% CI 1.8–3.2), $P = 0.001$].

Conclusion

In patients undergoing catheter ablation for AF, the use of DOAC was associated with a reduced risk of thrombo-embolic events compared with phenprocoumon. Non-interrupted oral anticoagulation (OAC) therapy was associated with a reduced risk of peri-procedural thrombo-embolic and any bleeding complications.

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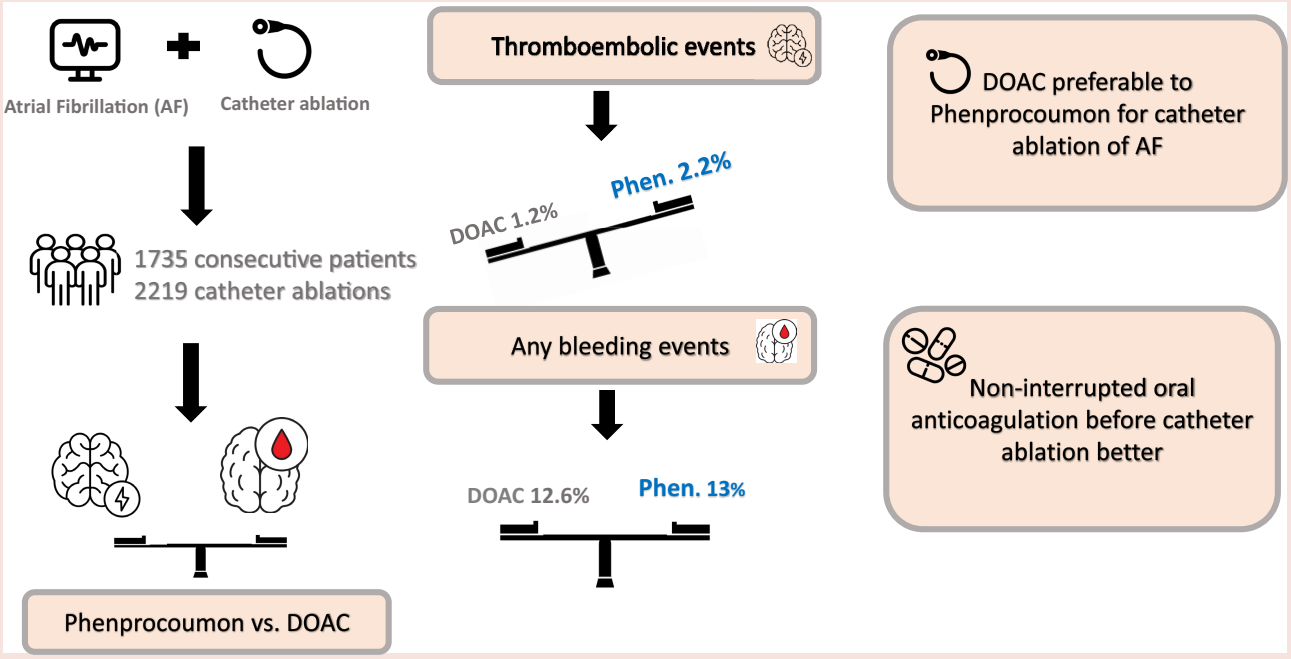
Graphical Abstract



Keywords Oral anticoagulation • Atrial fibrillation • Catheter ablation • Phenprocoumon

Introduction

Atrial fibrillation (AF) is associated with high risk of all-cause mortality and morbidity which is mainly attributed to stroke.[1,2] Guidelines recommend catheter ablation for the management of AF. Complications of catheter ablation include peri-procedural thrombo-embolic events which occur in 1–6% of the patients.[3] Anticoagulation reduces thrombo-embolic risk in patients with AF.[4] The most frequently used vitamin K antagonist (VKA) in Europe is phenprocoumon (phen.). In other countries, warfarin is the first choice. The longer elimination half-life of phenprocoumon (110–130 h) compared with warfarin (24–33 h)[5] suggests more consistent plasma levels for phenprocoumon potentially reducing the risk for thrombo-embolic events. Despite the different pharmacokinetics of VKA,[5] recent major trials that led to drug approval for AF treatment compared direct oral anticoagulants (DOACs) with warfarin.[6–12] With the development of DOACs different trials among non-valvular AF patients, showed similar efficacy and safety of DOAC to warfarin.[13–15] During catheter ablation, uninterrupted rivaroxaban,[6,7] apixaban,[8] edoxaban,[9] and dabigatran can be used with similar efficacy and similar or improved[10,11] safety compared with warfarin in catheter ablation for AF. Bridging therapy with low-weight molecular heparin (LWMH) was not safe for VKA and DOAC.[16,17] The impact of DOAC interruption on the day of catheter ablation is unknown. The European Society of Cardiology suggests that oral anticoagulation (OAC) should not be interrupted for catheter ablation.[18]

This study aimed to assess the association of DOAC compared with phenprocoumon with peri-procedural thrombo-embolic events and any bleeding complications among patients undergoing catheter ablation of AF.

Methods

Study design and population

This is an observational retrospective cohort study. A total of 1735 consecutive patients underwent 2219 catheter ablation procedures for AF from January 2011 to May 2017 at Herz-Zentrum Bodensee, Konstanz, Germany, and were included in the study after approval from the ethics committee (Stuttgart, approval number: F-2019-047). Only patients who received a left atrial ablation procedure (AF or left atrial flutter) were included in this analysis. Patients taking edoxaban at the time of catheter ablation were excluded due to the small number of cases (only 21). Patients with a VKA other than phenprocoumon were also excluded from the study. Patients were grouped according to the type of OAC received prior to catheter ablation. Patients were observed during the in-hospital stay (minimum of 48 h after catheter ablation).

Catheter ablation procedure and hospitalization

Patients were hospitalized on the day prior to the planned procedure. No changes were made to the current OAC therapy. Prior OAC therapy was continued as selected from the referring physician and no further pre-ablation selection to receive either DOAC or phenprocoumon occurred. Oral anticoagulation was started on the day of the procedure or 1 day before the procedure in patients without prior OAC prescription according to the treating electrophysiologist. For patients with prescribed VKA, the dose on the night prior to the ablation was adjusted according to the INR on admission day. During the years 2011–15, DOACs were interrupted for ≤48 h prior to the ablation and bridged with LMWH. For catheter ablations occurring in 2015 or later, anticoagulation was not interrupted according to the treating physician and the in-hospital protocol.

A pre-procedural transoesophageal echocardiography (TEE) to exclude left atrial or left atrial appendage thrombi was performed at the discretion

of the physician. Although some patients had clear spontaneous echo-contrast (SEC) Grade 3, catheter ablation was performed in these patients because of significant symptoms and/or severe heart failure. Procedural strategies were performed per standard of care and were consistent irrespectively of the operator performing the catheter ablation. Two trans-septal sheaths were introduced via the femoral vein, using the modified Seldinger technique. Prior to trans-septal puncture, patients received 10 000 IE unfractionated heparin. Activated clotting time (ACT) was measured every 30 min to achieve ACT >300 s. The trans-septal sheath was continuously flushed with heparinized saline. Removal of all sheaths followed without previous antagonizing heparin and irrespectively of ACT time at the end of intervention.

Clinical examination after the procedure was performed by a board-certified neurologist in all cases if neurological deficits were noted during the in-hospital stay. If a neurological deficit or delayed awakening was detected in the structured post-ablation neurological exam, immediate cerebral imaging was performed. Oral anticoagulation was interrupted in cases of intracerebral or other clinically relevant non-major or major bleedings, otherwise OAC was continued without interruption. Since only the in-hospital peri-procedural complications were observed, alterations on therapy do not impact the outcomes and are not shown.

Patients were followed on an in-hospital basis for at least 48 h after catheter ablation as per standard practice.

Study outcomes

The primary outcome was defined as in-hospital peri-procedural thrombo-embolic event during or after catheter ablation. A thrombo-embolic event was suspected with the occurrence of persistent neurologic deficits (stroke), transient and sudden neurologic deficits (transient ischaemic attack, TIA), or clinical and imaging evidence of sudden interruption of arterial or venous blood flow to an organ or body part by a clot. A TIA based on the typical clinical course was considered the primary outcome, even in the presence of unremarkable cerebral imaging.[19] The secondary outcome was defined as any bleeding according to the international society on thrombosis and haemostasis (ISTH).[20]

Statistical considerations

For statistical analysis, SPSS, Statistics[21] was used. Descriptive statistics were reported as mean values and standard deviations for continuous data and frequencies with percentages for nominal variables (dichotomic data). The χ^2 test of independence and Pearson correlation tests were used to analyse normally distributed data. To compare means for the continuous variables, one-way analysis of variance (ANOVA) test was used. A *P*-value of ≤ 0.05 was considered statistically significant.

In order to assess the association of other exploratory variables with outcomes, logistic regression (logit) for possible explanatory variables, such as age, sex, comorbidities, and procedural characteristics was performed. The odds ratio (OR) with a 95% confidence level (CI) was calculated from the values of log-odds. Two separate models of multivariable analysis were created for both dependent variables: thrombo-embolic events and any bleedings. The association of similar exploratory independent variables with the two outcomes was assessed through these two models. For each exploratory independent variable included in the multivariable regression, another separate logistic regression with interaction term was performed. The interactions between each exploratory independent variable (e.g. age, sex, comorbidities and procedural characteristics) with DOAC treatment vs. treatment with phenprocoumon and its association with outcomes, thrombo-embolic and any bleeding, were assessed.

Results

Patient population

A total of 1735 consecutive patients underwent 2219 catheter ablation for AF from January 2011 until May 2017 at the Herz-Zentrum Bodensee, Konstanz, Germany, and were included for this analysis. The mean age of the patients undergoing catheter ablation was 63.3 years and 1488 (67%) were of male sex (*Table 1*). Nearly half of the cases were anticoagulated with the VKA, phenprocoumon (929, 42%), and the other half with one of the DOAC rivaroxaban 399 (18%), dabigatran 697 (31%), and apixaban 194 (9%) (*Table 1*).

The main comorbidities were hypertension (1294, 58%) coronary artery disease (301, 13%), renal impairment (215, 10%), and of the cases had a prior stroke or TIA (190, 5%). Seventeen cases (0.8%) had a mitral valve stenosis and as a consequence valvular AF.

CHA2DS2-VASC score >2 at the time of catheter ablation was present in 1079, 49% of the cases (*Table 1*). Patients with phenprocoumon had a higher thrombo-embolic risk (CHA_2DS_2 -VASC > 2: phen 58% vs. DOAC 42%; $P < 0.001$).

Sixty per cent of the cases undergoing catheter ablation of AF received TEE prior to the procedure (*Table 2*). Spontaneous echo-contrast Grade 3 (severe or moderate) was detected in 6% of the cases. The mean duration of catheter ablation was 149 ± 56 min. Heparin doses required to reach the target ACT observed in cases with phenprocoumon therapy (9370 ± 5526 international units, IU) were lower than the ones taking a DOAC (13.000 ± 6734 IU). Intraoperative cardioversion was indicated in 710 (32%) cases (*Table 2*). Oral anticoagulation was interrupted in 679 (30%) of the cases on the ablation day. Direct oral anticoagulants were interrupted more often than phenprocoumon (DOAC 34% vs. phenprocoumon 26%, $P < 0.001$). During this time, bridging therapy with LWMH such as enoxaparin or certoparin-natrium followed.

Primary and secondary outcomes

Thirty-seven (1.6%) peri-procedural thrombo-embolic events occurred. Twenty-three (1%) of the thrombo-embolic events were a TIA and 14 patients had a stroke. Peripheral thrombo-embolic events did not occur. Direct oral anticoagulant was associated with fewer peri-procedural thrombo-embolic events than phenprocoumon (16, 1.2% vs. 22, 2.2% respectively). Anticoagulation with DOAC vs. phenprocoumon associated with lower thrombo-embolic risk with an OR 0.5 (95% CI 0.2–0.9, $P = 0.04$). There was a higher incidence of stroke in the phenprocoumon group compared with DOAC (1 vs. 0.3%, $P = 0.02$). The incidence of transient neurological attacks was not different between the two groups ($P = 0.30$) (*Table 3*).

A total of 285 (12.8%) bleeding complications occurred. The majority of bleedings were minor bleedings, 206 (9.2%). No significant difference regarding the occurrence of any bleeding complications after catheter ablation was observed (phenprocoumon 122, 13% vs. DOAC 163, 12.6%, $P = 0.70$) with an OR 0.9 (95%CI 0.7–1.2), when treated with a DOAC.

Minor bleedings occurred more frequently in patients treated with phenprocoumon, whereas there was no statistically significant difference among both groups for non-major but clinically relevant (NMCR) and major bleedings (*Table 3*).

After the occurrence of an outcome, OAC was paused in *n* 71 (3.2%) of the cases. Stroke occurred in eight cases and a TIA in seven cases. None of these cases had a concomitant bleeding. In all other cases, OAC was paused because of the occurrence of a relevant bleeding.

Patients treated with dabigtran had the lowest rate of major bleedings, 6 (0.08%) (*Figure 1*).

The rates of peri-procedural any bleeding complications were comparable among the different anticoagulation agents (phenprocoumon 13%, rivaroxaban 10%, dabigatran 14%, apixaban 12%, $P = 0.09$), but the rates of NMCR and major bleedings differed significantly ($P < 0.05$) (*Figure 1*).

Other characteristics associated with outcomes

Intraoperative cardioversion was associated with an increased thrombo-embolic risk [OR 2.5 (95% CI 1.2–5.1), $P = 0.011$] (*Table 4*). The interruption of anticoagulation associated with increased risk of thrombo-embolic complications when compared with uninterrupted anticoagulation therapy before ablation [OR 2.2 (95% CI 1.1–4.3), $P = 0.031$] (*Table 4*). In

Table1 Demographic characteristics of the patients undergoing catheter ablation for cases anticoagulated with phenprocoumon (vitamin K antagonist) and rivaroxaban, dabigatran, apixaban (direct oral anticoagulant)

Demographic characteristics, mean value, n (%)	*Phen. n 929 (42%)*	*Rivaroxaban n 399 (18%)*	*Dabigatran n 697 (31%)*	*Apixaban n 194 (9%)*	*Total cases n 2219*	*P-value*
Age on Ablation	64.8 ± 9.7	64.3 ± 9.1	60.2 ± 11	65.7 ± 9.7	63.3 ± 10	0.001
Male sex	600 (64)	273 (68)	507 (73)	108 (56)	1488 (67)	0.001
BMI	28.5 ± 7.3	28.6 ± 5.5	27.4 ± 5	27.5 ± 4.9	28.1 ± 6.2	0.001
Atrial fibrillation						0.001
Paroxysmal atrial fibrillation	607 (65)	284 (71)	554 (79)	144 (74)	1589 (72)	
Persistent atrial fibrillation	322 (35)	115 (29)	143 (20)	50 (26)	630 (28)	
NYHA >2	538 (58)	174 (44)	344 (49)	83 (43)	1139 (51)	0.001
Hypertension	592 (64)	239 (60)	347 (50)	116 (60)	1294 (58)	0.001
Diabetes mellitus						0.012
Oral therapy	81 (9)	44 (11)	45 (6)	19 (1)	189 (8)	
Insulin therapy	33 (3)	7 (2)	10 (1)	4 (0.2)	54 (2)	
Coronary artery disease	157 (17)	42 (10)	76 (19)	26 (16)	301 (13)	0.002
Hyperlipidaemia	137 (15)	60 (15)	93 (13)	25 (13)	315 (14)	0.872
Prior stroke	51 (5)	24 (6)	22 (3)	12 (6)	109 (5)	0.073
Prior TIA	46 (5)	7 (2)	23 (3)	5 (2)	81 (4)	0.024
CHADS VASC score						0.001
CHADS VASC ≤ 2	390 (42)	206 (52)	449 (64)	95(49)	1140 (51)	
CHADS VASC >2	539 (58)	193 (48)	248 (36)	99 (51)	1079 (49)	
Chronic/acute renal impairment						0.001
GFR < 60	104 (11)	29 (7)	42 (6)	16 (8)	191 (9)	
GFR < 30	7 (0.7)	1 (0.3)	3 (0.4)	8 (4)	19 (1)	
Dialysis	5 (0.5)	0 (0)	0 (0)	0 (0)	5 (0)	
Hepatic impairment	3 (0.3)	0 (0)	3 (0.4)	5 (2)	11 (0.5)	0.001
Any prior bleeding	13 (1)	8 (2)	12 (2)	12 (6)	45 (2)	0.001
HAS BLED score						0.001
HAS BLED ≤2	630 (68)	274 (69)	424 (61)	133 (68)	1461 (66)	
HAS BLED >2	299 (32)	125 (31)	273 (39)	61 (32)	758 (34)	

Values are in number and percentage for categorical variables and in mean value for continuous variables. The *P*-value is calculated with χ^2 of independence for dichotomic variables and one-way ANOVA test for continuous variables.
BMI, body mass index; NYHA, New York Heart Association Functional Classification; TIA, transitory ischaemic attack; GFR, glomerular filtration rate.

the regression analysis with interaction terms, the interruption of DOAC therapy was significantly associated with a higher risk of thrombo-embolic events, compared with the interruption of phenprocoumon [OR 3.7 (95% CI 1.0–4.3), $P = 0.016$] (see Supplementary material online, *Table S1*). Increased CHA2DS2-VASC Score was a risk factor for thrombo-embolic events [OR 1.6 (95% CI 1.0–2.7), $P = 0.48$] (*Table 4*). Male sex compared with the female sex was a favourable predictor, associating with reduced risk of bleeding with an OR 0.6 (95% CI 0.5–0.89), $P = 0.005$. An increase in age related to slightly increased bleeding risk [OR 1.03 (95% CI 1.0–1.1), $P = 0.007$] (*Table 5*).

Interruption of OAC before catheter ablation was a strong predictor for an increased risk of bleeding [OR 2.5 (95% CI 1.9–3.2), $P = 0.001$] (*Table 5*). The 2.3% thrombo-embolic events occurred when anticoagulation was interrupted and 1% thrombo-embolic events occurred when anticoagulation was not interrupted prior to ablation, $P = 0.06$. The interruption of DOAC before catheter ablation related to increased peri-procedural bleeding risk when compared with the interruption of phenprocoumon [OR 2.3 (95% CI 1.8–3.2), $P = 0.001$] (see Supplementary material online, *Table S2*).

Since the peri-procedural management of OAC changed after 2015 to address for prescription bias, the rates of peri-procedural thrombo-embolic and any bleeding events for DOAC and phenprocoumon procedures performed during 2011–15 with 2015–17 were compared (see Supplementary material online, *Figure S1*). No statistically significant difference was observed (see Supplementary material online, *Figure S1*).

Discussion

The main findings of this observational study are: (i) rates of thrombo-embolic events were lower in patients treated with DOAC compared with patients treated with phenprocoumon in patients undergoing catheter ablation for AF without an increased bleeding risk; (ii) uninterrupted anticoagulation therapy prior to catheter ablation associated with lower peri-procedural thrombo-embolic and/or bleeding risk; and (iii) uninterrupted DOAC compared with uninterrupted phenprocoumon was associated with less peri-procedural complications.

Association of direct oral anticoagulant and phenprocoumon with thrombo-embolic risk

The pharmacokinetics of phenprocoumon warfarin differs. The elimination half-life of phen. is three times longer than warfarin and might

Table 2 Procedural characteristics of cases undergoing catheter ablation of atrial fibrillation under phenprocoumon (vitamin K antagonist) and rivaroxaban, dabigatran, apixaban (direct oral anticoagulant) in numbers and percentages for categorical variables and mean values with standard deviation for continuous variables

Procedural characteristics, mean value, *n* (%)	Phen. *n* 929 (42%)	Rivaroxaban *n* 399 (18%)	Dabigatran *n* 697 (31%)	Apixaban *n* 194 (9%)	Total cases *n* 2219	*P*-value
Cryo-balloon ablation	167 (18)	119(30)	214(31)	71 (37)	571 (26)	0.001
RF-ablation	762 (82)	280(70)	483(69)	123 (63)	1648 (74)	
Pulmonary vein isolation						0.002
First PVI	561 (60)	275 (70)	488 (70)	134 (69)	1458 (66)	
Re-PVI	271 (29)	95 (24)	153 (22)	44 (23)	563 (25)	
>2 PVI	97 (11)	29 (6)	56 (8)	16 (8)	198 (9)	
Transoesophageal echocardiography	621 (67)	194 (24)	409 (59)	110 (57)	1334 (60)	0.001
Spontaneous echo contrast (SEC3)	81 (9)	18 (5)	23 (3)	13 (7)	135 (6)	0.001
Total heparindosis during ablation (IU)	9370 ± 5526	14 041 ± 5531	13 356 ± 7434	13 992 ± 4223	11 847 ± 6600	0.001
Duration of catheter ablation (min)	169 ± 57	131 ± 53	133 ± 74	121 ± 49	149 ± 56	0.001
ACT > 300s	749 (80)	297 (74)	489 (70)	130 (67)	1665 (75)	0.001
Intraoperative cardioversion	339 (36)	114 (29)	206 (30)	51 (26)	710 (32)	0.001
Interruption of anticoagulation	226 (26)	14 (4)	437 (63)	2 (1)	679 (30)	0.001

The *P*-value is calculated with $\chi 2$ of independence for dichotomic variables and one-way ANOVA test for continuous variables.
RF, radiofrequency; SEC 3, spontaneous echo-contrast Grade 3; ACT, activated clotting time.

Table 3 Outcomes in number and percentage for phenprocoumon (vitamin K antagonist) and direct oral anticoagulant

Outcome	Phen. *n* 929 (42%)	DOAC *n* 1290 (58%)	Total cases *n* 2219 and (%)	*P*-value
Thrombo-embolic events	**21 (2.2)**	**16 (1.2)**	**37 (1.6)**	***P* = 0.04**
TIA	12 (1.3)	11 (0.8)	23 (1)	*P* = 0.3
Stroke	**10 (1)**	**4 (0.3)**	**14 (0.6)**	***P* = 0.02**
Bleeding events in total	122 (13)	163 (12.6)	285 (12.8)	*P* = 0.7
Minor bleeding	**87 (9.3)**	**119 (9.2)**	**206 (9.2)**	***P* = 0.01**
NMCR bleeding	30 (3.3)	32 (2.5)	62 (2.7)	*P* = 0.4
Major bleeding	5 (0.5)	12 (0.9)	17 (0.8)	*P* = 0.4

P-value is calculated with χ^2 test. Statistically siginificant differences are represented in bold.
TIA, transitory ischaemic attack; NMCR, non-major but clinically relevant.

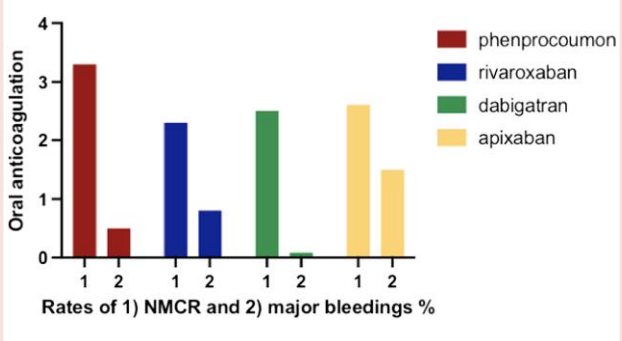


Figure 1 Rates of non-major but clinically relevant and major bleedings (%) for phenprocoumon (vitamin K antagonist), rivaroxaban, dabigatran, and apixaban. Figure 1 was made with Prism 9.2.0 (GraphPad software, La Jolla, CA, USA).

provide more stable anticoagulation.[5] Randomized clinical trials compared the efficacy and safety of DOAC with warfarin. It is unclear if similar results regarding efficacy and safety are also given when comparing DOAC with phenprocoumon.

In patients undergoing catheter ablation of AF, treatment with DOAC was associated with lower rates of peri-procedural thrombo-embolic complications compared with phenprocoumon, 1.2 vs. 2.2%, respectively. When compared with the literature,[12–15] the rate of thrombo-embolic events for patients treated with DOAC undergoing catheter ablation in this study seems high. The VENTURA study compared rivaroxaban with VKA (warfarin) after catheter ablation.[6] The rates of thrombo-embolic events were 0% for rivaroxaban compared with 3% for patients taking warfarin. RE-CIRCUIT, compared dabigatran 150 mg with uninterrupted warfarin showing 0% systemic thrombo-embolies for patients treated with dabigatran and one TIA event in the warfarin group.[10] The higher thrombo-embolic rates for patients treated with DOAC in this study compared to RE-CIRCUIT

Table 4 Logistic regression analysis for each possible explanatory variable (logit) regarding thrombo-embolic events for all patients

Independent variables	ß	Standard error	OR	CI	*P*-value
Age on ablation	0.011	0.029	1.011	0.956–1.070	0.693
Male sex	−0.557	0.411	0.573	0.256–1.282	0.175
Persistent atrial fibrillation	−0.199	0.157	0.820	0.603–1.114	0.204
NYHA	−0.364	0.335	0.695	0.360–1.341	0.278
Hypertension	−0.208	0.559	0.813	0.272–2.431	0.710
Diabetes mellitus	0.040	0.440	1.040	0.439–2.466	0.928
Coronary artery disease	-0.424	0.369	0.654	0.317–1.349	0.251
Prior stroke	0.173	0.827	1.189	0.235–6.012	0.834
Prior transitory ischaemic attack	−0.979	1.192	0.376	0.036–3.891	0.412
CHA_2DS_2-VASC score	**0.490**	**0.248**	**1.633**	**1.004–2.655**	**0.048**
HAS BLED score	−0.534	0.413	0.586	0.261–1.317	0.196
Chronic/acute renal impairment	−0.010	0.573	0.990	0.322–3.043	0.986
Cryo-balloon ablation	−0.798	0.587	0.450	0.143–1.423	0.174
Re-PVI	−0.358	0.326	0.681	0.359–1.288	0.237
Transoesophageal echocardiography	−0.017	0.386	0.983	0.461–2.097	0.965
Duration of catheter ablation (min)	**0.007**	**0.003**	**1.007**	**1.001–1013**	**0.027**
ACT > 300s	0.613	0.505	1.847	0.687–4.964	0.224
Intraoperative cardioversion	**0.920**	**0.362**	**2.509**	**1.233–5.105**	**0.011**
Interruption of anticoagulation	**0.770**	**0.357**	**2.159**	**1.073–4.347**	**0.031**

OR was calculated from the values of log-odds. The CI was defined as 95%. Statistically significant values are represented in bold.
NYHA, New York Heart Association Functional Classification; ACT, activated clotting time; PVI, pulmonary vein isolation; OR, odds ratio; CI, confidence interval.

Table 5 Logistic regression analysis for each possible explanatory variable (logit) regarding any bleeding events for all patients

Independent variables	ß	Standard error	OR	CI	*P*-value
Age on Ablation	**0.029**	**0.011**	**1.030**	**1.008–1.052**	**0.007**
Male sex	**−0.460**	**0.163**	**0.631**	**0.459–0.868**	**0.005**
Persistent atrial fibrillation	0.020	0.049	1.020	0.927–1.123	0.684
NYHA	0.084	0.131	1.088	0.841–1.406	0.522
Hypertension	−0.232	0.204	0.793	0.531–1.184	0.256
Diabetes mellitus	0.047	0.181	1.048	0.735–1.495	0.795
Coronary artery disease	−0.165	0.132	0.847	0.654–1.098	0.211
Prior stroke	−0.776	0.429	0.460	0.198–1.068	0.071
Prior transitory ischaemic attack	0.098	0.387	1.103	0.517–2.353	0.801
CHA_2DS_2-VASC score	−0.027	0.102	0.937	0.796–1.189	0.790
HAS BLED score	0.101	0.136	1.106	0.847–1445	0.457
Chronic/acute renal impairment	0.126	0.190	1.134	0.781–1.647	0.509
Cryo-balloon ablation	−0.101	0.160	0.904	0.660–1.238	0.530
Re-PVI	−0.017	0.112	0.983	0.789–1.225	0.881
Transoesophageal echocardiography	0.256	0.140	1.291	0.981–1.700	0.068
Duration of catheter ablation (min)	0.001	0.001	1.001	0.998–1.003	0.656
ACT > 300 s	−0.072	0.154	0.930	0.688–1.258	0.640
Intraoperative cardioversion	−0.216	0.149	0.805	0.602–1.078	0.145
Interruption of anticoagulation	**0.896**	**0.137**	**2.449**	**1.871–3.205**	**<0.001**

The OR was calculated from the values of log-odds. The CI was defined as 95%. Statistically significant values are in represented in bold.
NYHA, New York Heart Association Functional Classification; ACT, activated clotting time; PVI, pulmonary vein isolation; OR, odds ratio, CI, confidence interval.

may be explained by the lower CHA_2DS_2-VASC Score (specifically 1.5) in patients included in the VENTURA study.[6] This might be explained by the higher co-morbidity and higher thrombo-embolic risk in patients in this observational study compared with other randomized controlled trials.[6] In fact, also the increase in CHA_2DS_2-VASC score with 1 point increased thrombo-embolic risk in this patient cohort.

RE-CIRCUIT was designed with the aim of showing non-inferiority for ischaemic events of dabigatran compared with warfarin. Systemic thrombo-embolies were part of the composite endpoint.[10] For dabigatran, most of the thrombo-embolic events in this patient cohort were TIAs (*n* 9) when compared with Strokes (*n* 2). In the majority of thrombo-embolic events, a TIA was diagnosed, although often without a clear correlate on imaging. The analysis of thrombo-embolic events in this study was based exclusively on clinical findings and sequences that made the diagnosis of TIA most likely. The reason for this approach was the timing of cerebral imaging, which was not systematic but clinic-oriented. All patients underwent computed tomography to exclude intracerebral haemorrhage, but only a small proportion underwent magnetic resonance imaging if the clinical course was unremarkable.

Despite the different pharmacokinetics of phenprocoumon and warfarin, the finding of reduced risk of thrombo-embolic events (stroke and TIA) for DOAC compared with VKA (phenprocoumon) is consistent with the results of other randomized trials comparing DOAC with VKA (warfarin), suggesting that DOAC should be preferred over VKA for catheter ablation of non-valvular AF.[6–10]

Association of direct oral anticoagulant and phenprocoumon with bleeding

The long elimination half-life of phenprocoumon could increase the risk of bleeding, as high plasma levels would persist for longer periods of time.[5] A total of 285 (12.8%) peri-procedural bleeding complications occurred, which were predominantly minor bleeding rather than NMCR or major bleedings. The rates of total bleedings in VENTURA were similar to the ones in this study with 17% bleedings for rivaroxaban and 15% for the warfarin group.[6]

When considering all DOAC compared with phenprocoumon, there was a trend to higher minor bleeding and NMCR bleeding complications for phenprocoumon. Despite the long elimination half-life of phenprocoumon compared with warfarin and the DOACs, and thus the more difficult adjustment of the dose to the INR value, peri-procedural bleeding complications were not more frequent with phenprocoumon compared with the DOACs.

The DOAC with the lowest major bleeding rate in our study was dabigatran with 0.08% major bleedings (*Figure 1*). There was a significantly lower major bleeding risk for dabigatran in this study compared with the major bleeding rates for patients treated with dabigatran in RE-CIRCUIT (1.6% major bleedings).[10]

Higher plasma concentration of dabigatran was observed after a delayed intake.[19] This is a plausible explanation for the higher bleeding risk after interruption of dabigatran in RE-CIRCUIT when compared with this study in which anticoagulation was not interrupted for ablations after 2015. Nevertheless, even in RE-CIRCUIT, dabigatran was more favourable than VKA with fewer major bleeding at 7 days after the ablation procedure.[10]

Interruption of anticoagulation before catheter ablation and association with outcomes

The thrombo-embolic risk was two-fold increased when anticoagulation was interrupted before catheter ablation compared with uninterrupted anticoagulation therapy. Therefore, it also does not seem plausible that the possible reaching of a stable plasma level of phenprocoumon[5] could allow somehow to leave the doses before catheter ablation out.

The interruption of DOAC therapy was associated with an increased thrombo-embolic risk significantly compared with the interruption of phenprocoumon (see Supplementary material online, *Table S1*). This could be due to the shorter half-life of DOAC and the importance of achieving a steady state depending on the single DOAC intake.[22]

No standardized definition of uninterrupted anticoagulation exists. This might explain different rates of peri-procedural events from former studies comparing uninterrupted anticoagulation therapy (DOAC vs. warfarin). In most of the studies, the dose before catheter ablation was actually withheld.[6–10,12–15] In the here presented study, 'uninterrupted' was defined as continued anticoagulation intake including the day of ablation. The guidelines of the European Society of Cardiology recommend performing catheter ablation with uninterrupted anticoagulation.[18] One study suggested that uninterrupted apixaban therapy is similar to uninterrupted phenprocoumon in patients undergoing catheter ablation in terms of outcomes.[23] Further randomized studies need to investigate the best practical use of DOAC in catheter ablation.

Limitations of the study

Since this is an observational retrospective analysis, these results do not imply causality and should be considered hypothesis-generating. One of the most important limitations is the non-randomized nature of the study. To adjust for confounding factors, we used a multivariable regression model.[24] The single-centre character of this study limits the generalizability of the results. A time bias may have been introduced during the course of the study given differential prescription patterns while the operator's experience increased. A longer follow-up in time could be of importance to better understand the risk factors for complications and to optimize the anticoagulation therapy.

Conclusions

Anticoagulation with DOAC is associated with lower thrombo-embolic risk compared with phenprocoumon in patients undergoing catheter ablation of AF. Bleeding events related to catheter ablation were similar among the groups. Uninterrupted OAC before catheter ablation was associated with a reduced risk of thrombo-embolic events. Non-interrupted DOAC therapy was associated with reduced peri-procedural bleeding and thrombo-embolic complications compared with non-interrupted phenprocoumon therapy.

Lead author biography

Diona Gjermeni is a medical doctor at the University Heart center Freiburg - Bad Krozingen. She does clinical research mainly focusing on atithrombotic and anticoagulation therapy.

Data availability

Data not available due to privacy/ethical restrictions.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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