Optimal anticoagulation strategy for atrial fibrillation ablation: are all direct oral anticoagulants and vitamin K antagonists the same? - a meta-analysis of embolic and bleeding complications in more than 31,500 patients

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Abstract

Introduction: The direct oral anticoagulants (DOACS) such as dabigatran (D), rivaroxaban (R), apixaban (A), and edoxaban (E) have become the leading anticoagulation strategy in atrial fibrillation (AF). Many studies have shown that the safety of DOACS is similar or better than warfarin (W) periprocedural pre- and post AF ablation. It is unclear if they fare the same compared to vitamin K antagonists (VKA) other than W, if individual DOACS have the same benefits, or if interrupted or uninterrupted regimens are better. Since complication rates of AF ablation are low, individual studies preclude an ability to answer this issue with certainty, and a meta-analysis would provide a better estimation.

Methods: We have evaluated all published manuscripts (n=53 enrolling 31,589 patients) that directly compare peri-AF ablation complication rates in patients receiving DOACS vs. VKA. Bleeding (vascular complications, pericardial effusion, or other bleeding) and embolic complications were the primary endpoints. Additionally, individual types of DOACS and VKA, interrupted and uninterrupted regimens, were compared. We used the Mantel-Haenszel random effect model to pool the study results, with a random effects model for heterogeneous samples/results.

Results: The 14270 patients on a DOACS (6943 D, 4269 R, 2457 A, 495 E) were similar to the 17319 patients on VKA. DOACS were either uninterrupted or minimally interrupted, and an uninterrupted VKA (UVKA) regimen was used in 13794 (80%) patients. Composite bleeding rates were significantly lower in patients treated with DOACS (6.6%) compared to VKA (8%) (OR 0.80, 95% CI 0.69-0.93; I^2 = 45%, p = 0.003), whereas the composite embolic rates were similar in both groups (0.38% in DOACS vs 0.38% in VKA, OR 0.76, 95% CI 0.53-1.1; I^2 = 0%, p = 0.15). The interrupted DOACS regimen had lower bleeding events than uninterrupted VKA (OR 0.71, CI 0.57-0.89, I^2 = 34%, p = 0.02), with no difference in thromboembolic complications. D was associated with lower bleeding complications than UVKA (OR 0.81, 95%, CI 0.66-0.98, I^2 = 32%, p = 0.03), while R and A were similar to UVKA.

Conclusions: This meta-analysis demonstrates that DOACS should be preferred to VKA for peri-AF ablation anticoagulation. Minimally interrupted DOACS demonstrate lower bleeding complications with similar risk for thromboembolism. Future studies should determine the optimal time to stop and restart of the DOACS relative to the ablation.

Keywords

atrial fibrillation, dabigatran, rivaroxaban, apixaban, edoxaban, DOACS, NOAC, warfarin, Coumadin, phenprocoumon, acenocoumarol, VKA, vitamin K antagonists, atrial fibrillation ablation, pulmonary vein isolation

Introduction

Catheter ablation has become one of the main strategies in the treatment of symptomatic atrial fibrillation (AF)[1], either as a first line or after failing an antiarrhythmic medication. Peri-procedural anticoagulation is critical, as the risk of stroke is heightened due to intracardiac catheter manipulation, endothelial inflammation, or damage[2] and restoration of sinus rhythm with atrial stunning [3–5]. Traditionally, vitamin K antagonists (VKA), as warfarin or other derivatives, such as phenprocoumon, acenocoumarol, marcoumar (with a longer half-life), have been used, either continuously or interrupted with heparin bridging, as the anticoagulation strategy. Although no standardized protocol exists, it has been suggested that an uninterrupted VKA protocol, with the procedure performed during therapeutic INR, might be superior[6,7] to a bridging strategy.

The direct oral anticoagulants (DOACS) including the direct thrombin inhibitor, dabigatran (D) approved by the FDA in 2010, and the factor Xa factor inhibitors, rivaroxaban (R) approved in 2011, apixaban (A) in 2013, and edoxaban (E) in 2015, have been shown in large studies to be at least as effective as VKA in reducing the risk of stroke in patients with non-valvular AF[8–11]. Currently, these agents are the preferred anticoagulation strategy for peri-procedural anticoagulation for AF ablation, avoiding the disadvantages of frequent INR checks, additional need for transesophageal echocardiograms, or postponing procedures due to nontherapeutic anticoagulation with VKA. Despite widespread adoption of the DOACS, a significant

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number of procedures are still performed while patients are on VKA. On the other hand, there is only a trifling experience with the approved reversal agents for DOACS [12] in the procedural settings due to the low incidence of life-threatening bleeding in general, high cost, and short shelf life. In addition, different responses to intra-procedural heparin administration [13,14] could lead to increased peri-procedural thromboembolic events.

Multiple small series have compared DOACS with various VKA agents as anticoagulation strategies for AF ablation, examining both interrupted and uninterrupted strategies, and concerns have been raised regarding a possible higher incidence of peri-procedural embolic and bleeding rates for DOACS compared with warfarin (W) [15–17]. However, given the low procedural complication rates, these studies may be too small to compare different anticoagulation regimens and agents accurately.

The objective of the current meta-analysis is to review all the available studies to date that compare the thromboembolic and bleeding complications of DOACS versus VKA regimens and to identify the safety of different peri-ablation anticoagulation strategies, including (1) uninterrupted and interrupted regimens, (2) individual DOACS (dabigatran, rivaroxaban, or apixaban) vs. uninterrupted VKA, and (3) DOACS vs. non-warfarin VKA.

Methods

1. Data sources

A comprehensive search was conducted in PubMed Central, EMBASE, and Ovid-Medline databases from October 2010 to October 2023, dating back to the FDA approval of dabigatran in the USA. The keywords used were “DOACS”, “dabigatran”, “rivaroxaban”, “apixaban” or “edoxaban” and “VKA”, “warfarin”, “phenprocoumon”, “acenocoumarol” and “atrial fibrillation”, “atrial fibrillation ablation”, “ablation”, “catheter ablation”, “pulmonary vein isolation”, “PVI”, “AFib ablation”, “AF ablation”. No language restriction was used.

2. Study selection

The studies were included in the analysis if they enrolled patients undergoing AF ablation, had two arms as peri-procedural anticoagulation strategies: DOACS (D, R, A or E), and VKA (either continuous or interrupted with heparin bridging), and compared peri-procedural bleeding and/or thromboembolic complications, up to 30 days, between the two anticoagulation strategies. Studies with the change of pre- vs post-procedure anticoagulation strategy were excluded.

The study selection strategy following PRISMA guidelines is presented in Figure 1. Of 2746 studies, after a thorough screening and evaluation process, 53 full-text[13–65] studies were included.

The strength of evidence of the studies was evaluated based on the type of study (randomized, observational, prospective, retrospective, etc.), study limitations, directness, consistency, precision, and risk for bias[66]. Using the GRADE suggested ratings, the studies were categorized into: High, Moderate, Low, or Insufficient, based on the confidence that the estimated effect is close to the true one for the outcome[66].

3. Data extraction

The studies were reviewed for design, inclusion criteria, total number of patients, number of patients in each group, baseline characteristics including age, gender, $CHADS_2$ and CHA_2DS_2VASc scores, prior stroke, use of antiplatelet medication, left ventricular function and left atrial dimensions, details regarding holding and restarting the anticoagulation in the D, R, A and E arms, the bridging strategy for VKA patients, and INRs for patients on uninterrupted VKA, the ablation strategy, and peri-procedural complications (up to 30 days post procedure) in each group. Complications were categorized into:

- Thromboembolic (TE) complications: stroke or transient ischemic attack [TIA], other systemic TE, and deep vein thrombosis (DVT) with or without pulmonary embolism)
- Major bleeding complications: any significant bleeding that required intervention (cardiac tamponade, access site bleeding, etc) or any significant bleeding (GI, hemoptysis, etc.) with hemoglobin fall > 2g/l or required blood product transfusion
- Minor bleeding complications: no intervention necessary, including pericardial effusions that were conservatively managed or small groin hematomas

4. Study outcomes

The primary outcomes for this study included total complications, thromboembolic and composite, major and minor bleeding complications in patients treated with the DOACS regimen vs patients on VKA.

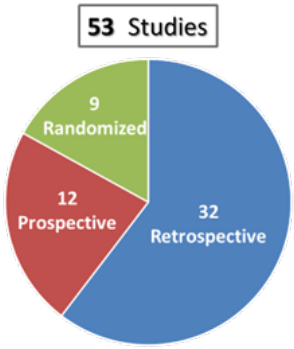
The secondary outcomes included:

1. Thromboembolic, major and minor bleeding of interrupted and uninterrupted DOACS versus uninterrupted VKA.
2. Thromboembolic, major, and minor bleeding of DOACS versus interrupted VKA.
3. Thromboembolic and bleeding of D, R, A compared to uninterrupted VKA (evaluation of E versus VKA could not be performed due to a low number of patients)
4. Thromboembolic, major, and minor bleeding comparison between DOACS and uninterrupted non warfarin VKA

5. Statistical analysis

Meta-analysis data were reported as odds ratio (OR) with the 95% confidence interval (CI). The Mantel-Haenszel random effect model was used to pool the study results, and a random effects model was used to pool heterogeneous samples/results. The RevMan 5.3 software [Review Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014] was used for the analysis. A $p < 0.05$ was considered statistically significant.

Statistical heterogeneity among included studies was assessed using chi^2 and I^2. The I^2 statistic describes the proportion of variation in the treatment estimate unrelated to sampling error. A zero value indicates no heterogeneity, 25–49% low, 50–74% moderate, and > 75% a high degree of heterogeneity. A funnel plot was used to assess the potential for publication bias in the dataset (Figure 2).[67]



14,270 DOACs

DOACs	Total	Uninterrupted	Interrupted
Dabigatran	6,943	1,274	4,043
Rivaroxaban	4,269	1,610	2,008
Apixaban	2,457	1,650	580
Edoxaban	495	429	66

17,319 VKA

VKA	Total	Uninterrupted	Interrupted
Warfarin	14,782	10,777	4,005
Non-Warfarin	2,537	2,469	68

Complication	DOACs	VKA	Events DOACs	Total DOACs	Events VKA	Total VKA	Odd Ratio, 95% CI	P-value
Thromboembolic	Entire Cohort	Entire Cohort	54	14270	66	17319	0.76 [0.53, 1.10]	0.15
	Uninterrupted	Uninterrupted	14	5027	16	5011	0.94 [0.47, 1.88]	0.87
	Interrupted	Uninterrupted	20	6739	22	8370	0.83 [0.44, 1.56]	0.56
	Entire Cohort	Interrupted	5	3958	10	4033	0.55 [0.21, 1.47]	0.23
	Entire Cohort	Non-Warfarin	21	3086	27	2537	0.59 [0.33, 1.05]	0.07
	Dabigatran	Uninterrupted	27	5536	44	8255	0.81 [0.50, 1.32]	0.40
	Rivaroxaban	Uninterrupted	4	3450	12	3923	0.62 [0.26, 1.50]	0.29
	Apixaban	Uninterrupted	5	1710	9	3219	1.32 [0.52, 3.38]	0.56
Major Bleeding	Entire Cohort	Entire Cohort	201	14270	346	17319	**0.71 [0.57, 0.89]**	**0.002**
	Uninterrupted	Uninterrupted	72	5027	92	5011	0.77 [0.56, 1.08]	0.13
	Interrupted	Uninterrupted	75	6739	182	8370	**0.64 [0.44, 0.94]**	**0.02**
	Entire Cohort	Interrupted	15	3958	50	4033	**0.36 [0.20, 0.66]**	**0.0008**
	Entire Cohort	Non-Warfarin	65	3086	94	2537	0.78 [0.55, 1.12]	0.18
Minor Bleeding	Entire Cohort	Entire Cohort	718	14270	999	17319	**0.84 [0.73, 0.98]**	**0.03**
	Uninterrupted	Uninterrupted	321	5027	322	5011	1.01 [0.85, 1.20]	0.90
	Interrupted	Uninterrupted	224	6739	365	8370	**0.76 [0.63, 0.91]**	**0.004**
	Entire Cohort	Interrupted	182	3958	322	4033	0.72 [0.49, 1.05]	0.09
	Entire Cohort	Non-Warfarin	171	3086	181	2537	0.76 [0.55, 1.05]	0.10
Total Bleeding	Dabigatran	Uninterrupted	388	5536	655	8255	**0.81 [0.67, 0.98]**	**0.03**
	Rivaroxaban	Uninterrupted	237	3450	419	3923	0.87 [0.72, 1.05]	0.14
	Apixaban	Uninterrupted	159	1710	406	3219	0.88 [0.71, 1.09]	0.25

Central Figure.

Results

1. Studies' characteristics

The 53 studies included 31589 patients of which 14270 patients were on DOACS [6943 (49%) on D, 4269 (30 %) on R, 2457 (17%) on A and 495 (3%) on E] and 17319 were on VKA [13246 (76 %) uninterrupted, 2469 (14%) non-warfarin VKA]. In some studies, lower doses of D (110 mg vs 150 mg) [26,35,51,60]and R (15 mg and 10 mg vs 20 mg)[37,60] were used as recommended by the health systems of specific countries. The characteristics of the studies are shown in Table 1. The majority of the studies (32 studies) were retrospective series, including 3 case-matched and one survey; the

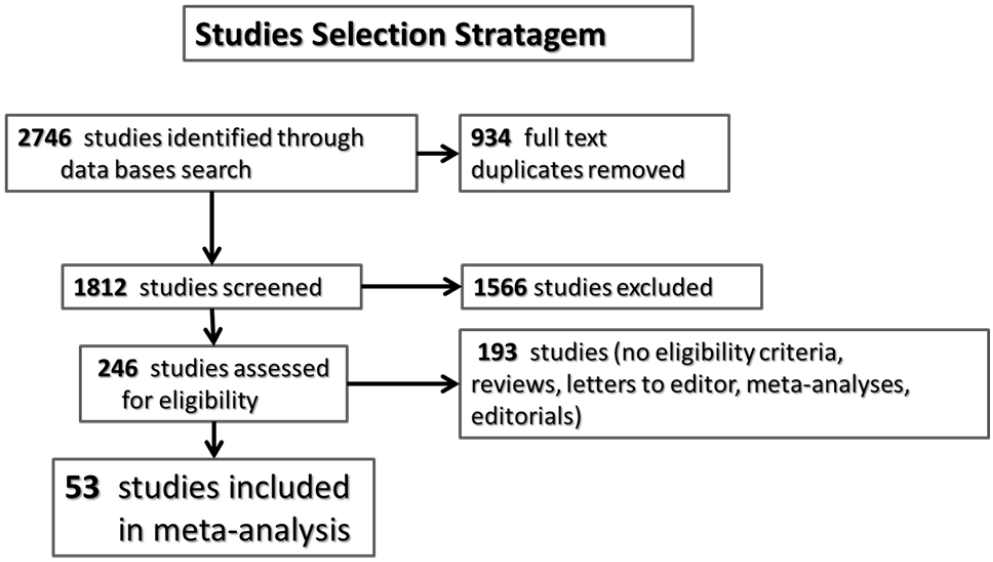


Figure 1 - Studies selection Stratagem.

other 21 were prospective studies, including 9 randomized trials and one case-matched. There were 13 multicenter studies with up to 104 participating centers and a survey with data from 179 sites. A funnel plot used to assess the potential for publication bias in the dataset showed no evidence of significant bias.[67] (Figure 2)

2. Patient characteristics

The clinical baseline characteristics of the studied patients are displayed in Table 2.

In general, the patients included in the studies were relatively young (DOACS 61 ± 10 years vs VKA 62 ± 10 years), with only 6 studies having older patients in the VKA group, and one study with older patients in the DOACS group. There was a male predominance (DOACS 72% vs VKA 70%), with the majority of the patients having a $CHADS_2$ and CHA_2DS_2VASc score less than 2, and only a few studies indicating that the VKA group had a slightly higher score. The majority of patients had paroxysmal atrial fibrillation, with 6 studies indicating that DOACS had a higher percentage of paroxysmal atrial fibrillation than VKA, with only three series enrolling mostly non-paroxysmal atrial fibrillation[24,28,30]. In the series that reported, the left ventricular function was normal with a mildly to moderately enlarged left atrium.

3. Peri-procedural anticoagulation protocols

The anticoagulation was usually started 3-4 weeks before the procedure, with the uninterrupted VKA group targeting an INR of 2-3 on the day of ablation. In the interrupted group, the VKA was usually stopped 3-5 days prior, and either unfractionated heparin or low molecular weight heparin was used for bridging, which was continued after the procedure until the INR was therapeutic. The period for which the DOACS were stopped before the procedure varied among the studies: 21 studies[14,17,21,22,24,25,27,33,37,38,41,42,44,46,48–50,54,62,64,65] included 5027 patients using an uninterrupted DOACS regimen, 31 studies[13,18–20,23,26,28,30,31,34–36,39,40,42,43,45–47,51–55,58–63,65] included 77691 patients for whom the DOACS were interrupted, including 15 studies[18,19,28,30,31,34–36,39,43,45,51,55,58,59] with 3071 patients for whom the DOACS were stopped > 24h before the procedure. The rest of the studies had variations in the time DOACS were held, but the majority were held 12-48 hours before the procedure. There was usually no heparin bridging when the DOACS were interrupted. In the majority of studies, DOACS were resumed a few hours after hemostasis or the night of the procedure, with a smaller number the next morning; in the vast majority of cases, DOACS were restarted within 24 hours post-procedure, with only a minority of studies reporting the use of short heparin bridging. (Table 3)

More than half of the centers reported using pre-procedural TEE or CT angio to exclude intracardiac thrombus, and there were no significant differences between the two groups.

4. Procedure characteristics

The primary ablation strategy for AF was pulmonary vein isolation using radiofrequency energy, with cryoballoon technology being used in 7 studies[21,40,45,53,57,60,61]. Additional linear and CFAE ablation was performed based on operator preference, mostly in patients with persistent atrial fibrillation. Additional atrial flutter ablation was performed in a significant minority of the patients.

In all the studies that reported intra-procedural anticoagulation, heparin bolus, fixed or weight-based, was used either before or after the trans-septal puncture. The majority of the studies also employed continuous heparin infusion. The target ACT was usually > 300 secs, generally achieved in both groups. Several studies reported lower levels of ACT despite higher requirements for heparin in the DOACS group. Intracardiac echo to guide the trans-septal puncture and ablation was not used routinely. Partial or full reversal of heparin with protamine was utilized for many patients. (Table 4)

Table 1 - Studies' Characteristics.

No.	Author *Journal, Year*	Year	No. of centers	Study period	Type of study	GRADE Quality Rating	Number of patients							
							Total	DOAC	D	R	A	E	UVKA	IVKA
1	**Armbruster HL et al.** *Annals of Pharm 2015*	2015	1	Jan 2012-Dec 2013	Retrospective analysis	Moderate	374	201	123	61	17		173	
2	**Arshad A et al.** *PACE 2014*	2014	4	Oct 2010-Oct 2012	Retrospective analysis	Moderate	882	374	374				276	232
3	**Bassiouny M et al.** *Circ Arrhythmia EP 2013*	2013	1	Dec 2010-Jul 2012	Prospective registry	Moderate	999	376	376				623	
4	**Calkins H et al.** *NEJM 2017*	2017	104	April 2015-July 2016	Prospective randomized	High	635	317	317				318	
5	**Cappato R et al.** *European Heart Journal 2015*	2015	37	Feb 2013-Sep 2014	Prospective randomized	High	248	124		124			124	
6	**De Heide J et al.** J Int Card Electrophys 2018	2018	1	Jan 2013-Apr 2017	Retrospective analysis	Low	637	117	68	14	30	5	520	
7	**DiBiase L et al.** *Heart Rhythm 2015*	2015	4	June 2013-July 2014	Prospective match cohort	High	400	200			200		200	
8	**Dillier R et al.** *Circ Arrhythmia EP 2014*	2014	1	Feb 2012-May 2013	Retrospective analysis - matched	Moderate	544	272		272			272	
9	**Efremidis M et al.** *J of Electrocardiology 2015*	2015	1	June 2013-Sep 2014	Prospective registry	Moderate	149	64	64				85	
10	**Enriquez AD et al.** *PACE 2017*	2017	1	Jan 2013-Nov 2014	Retrospective analysis	Low	471	258		258			213	
11	**Garcia LI et al.** *J Afib 2014*	2014	1	Jul 2011-Oct 2012	Retrospective analysis	Low	325	126	126				199	
12	**Gjermeni D et al.** European Heart Journal 2023	2023	1	Jan 2011-May 2017	Retrospective analysis	Moderate	2219	1290	697	399	194		929	
13	**Gunawardene et al.** *Clin Res Cardiol 2017*	2017	1	Jan 2011-Dec 2014	Retrospective analysis	Moderate	1440	441	147	253	41		488	511
14	**Haines DE et al.** *J Int Card Electrophys 2013*	2013	4	Nov 2010-Nov 2011	Retrospective analysis	Low	404	202	202				162	40
15	**Hohnloser SH et al.** European Heart Journal 2019	2019	58	March 2017-Sep 2018	Prospective randomized	High	553	375				375	178	
16	**Ichiki H et al.** *PACE 2013*	2013	1	Apr 2010-Jul 2012	Prospective registry	Low	237	36	36				201	
17	**Imamura K et al.** *J Int Card Electrophys 2013*	2013	1	Apr 2011-Nov 2012	Prospective analysis	Moderate	227	101	101					126
18	**Kaess BM at al.** *Am J Cardiol 2015*	2015	1	Mar 2014	Retrospective case matched	Moderate	315	105			105		210	
19	**Kaiser D et al.** *J Int Card Electrophys 2013*	2013	1	Jan 2011-Aug 2012	Retrospective analysis	Low	257	122	122				135	
20	**Kaseno K et al.** *Circ Journal Jap 2012*	2012	1	Apr 2011-Jan 2012	Retrospective analysis	Moderate	211	110	110				101	
21	**Kim JS et al.** *Heart Rhythm 2013*	2013	1	Jan 2011-Aug 2012	Case-control analysis	Moderate	763	191	191				572	
22	**Kimura T et al.** JACC 2018	2018	2	Jul 2014-Jan 2016	Prospective randomized	High	127	64		64			63	
23	**Kirchhof P et al.** European Heart Journal 2018	2018	49	Feb 2015-Apr 2017	Prospective randomized	High	633	318			318		315	
24	**Kochhauser S et al.** *Can J of Card 2014*	2014	1	Oct 2010-Oct 2013	Retrospective analysis	Moderate	680	361	220	141				319
25	**Koetkuerk B et al.** Cardiovasc Therap 2016	2016	1	Aug 2012-May 2015	Retrospective analysis	Moderate	409	259	48	193	18		150	
26	**Konduru SV et al.** *J Int Card Electrophys 2012*	2012	1	Jan 2011-Aug 2011	Retrospective analysis	Moderate	76	24	24				52	
27	**Kuwahara T et al.** *J of Card Electrophys 2016*	2016	3	NR	Prospective randomized	High	200	100			100		100	
28	**Lakkireddy D et al.** *JACC 2012*	2012	8	Jan 2010-Jul 2011	Prospective registry	Moderate	290	145	145				145	
29	**Lakkireddy D et al.** *JACC 2014*	2014	8	Jan 2012-Mar 2013	Prospective registry	Moderate	642	321		321			321	
30	**Lin J et al.** *J Afib 2014*	2014	1	Jan 2010-Dec 2012	Retrospective analysis	Low	324	181	181					143
31	**Maddox W et al.** *J Card Electrophysiol 2013*	2013	1	Nov 2010-Jan 2012	Retrospective analysis	Low	463	212	212				251	
32	**Mugnai G et al.** American J of Card 2017	2017	2	Jun 2013-Sep 2015	Retrospective analysis	Moderate	454	164	60	71	33			290
33	**Muller P et al.** J Interv Card Electro 2016	2016	1	NR	Prospective cohort	Moderate	192	106					43	43
34	**Murakawa Y et al.** *J of Arrhythmia 2015*	2015	179	Sep 2011-Sep2012	Retrospective survey	Low	2349	541	504	37			1808	
35	**Nagao T et al.** *Heart Rhythm 2015*	2015	1	April 2012 Aug 2014	Retrospective analysis	Moderate	869	499	239	102	158		370	
36	**Nagao T et al.** *PACE 2015*	2015	1	April 2013 Mar 2014	Retrospective analysis	Moderate	342	105			105		237	
37	**Nagao T et al.** *Internal Med 2015*	2015	1	April 2012 Nov 2013	Retrospective analysis	Moderate	363	173	173				190	
38	**Nin T et al.** *PACE 2013*	2013	1	Apr 2011-May 2012	Prospective randomized	High	90	44	44					46
39	**Nogami A et al.** JAMA 2019	2019	28	May 2014-Sep 2015	Prospective randomized	High	442	220	220				222	
40	**Okishige K et al.** *J of Card 2017*	2017	1	NR	Prospective registry	Moderate	257	238	66	81	30	61	19	
41	**Reynolds MR et al.** *JACC EP 2018*	2018	18	Dec 2015-Jan 2017	Retrospective analysis	Moderate	590	295			295		295	
42	**Rilling A et al.** *JCE 2016*	2016	1	Oct 2013-Oct 2014	Prospective registry	Moderate	444	324	51	193	80		120	
43	**Snipelisky D et al.** *J Int Card Electrophys 2012*	2012	1	Jan 2011-Dec 2011	Retrospective analysis	Low	156	31	31					125
44	**Snipelisky D et al.** *J Int Card Electrophys 2014*	2014	1	Jan 2011 - 2014	Retrospective analysis	Moderate	217	130	90	40				87
45	**Somani R et al.** *Cardiovasc Therap 2014*	2014	1	Nov 2010-Jan 2012	Retrospective analysis	Moderate	207	43	43				95	69
46	**Stepanyan G et al.** *J Int Card Electrophys 2014*	2014	1	Jan 2011-Sep 2013	Retrospective analysis	Moderate	301	187	89	98			114	
47	**Tang I et al.** *Frontiers in Med 2020*	2020	1	Jan 2010-Dec 2018	Retrospective analysis	Low	4520	1876	865	1011			796	1848
48	**Tao S et al.** *J Int Card Electroph 2017*	2017	1	Nov 2012-Mar 2014	Prospective cohort	Moderate	147	76		76			71	
49	**Tscholl V et al.** Clinical Cardio 2017	2017	1	NR	Retrospective analysis	Low	200	153	31	67	55		47	
50	**Vlachos K et al.** Clinical Cardio 2017	2017	1	June 2013-Dec 2016	Prospective cohort	Moderate	474	338	114	110	114		136	
51	**Yamaji H et al.** *Clin Drug Inv 2013*	2013	1	Mar 2009-Dec 2011	Retrospective analysis	Moderate	503	106	106				203	194
52	**Yanagisawa S et al.** *JACC Clin Electrpph 2018*	2018	1	Jan 2009-Jun 2017	Retrospective analysis	Moderate	2164	1129	333	228	514	54	1035	
53	**Yoshimura et al.** *Journal of Card 2017*	2017	1	Mar 2013-Dec 2014	Prospective randomized	High	174	105		55	50		69	

Table 2 - Patients Baseline Characteristics, *p value < 0.05; W – warfarin; BMI – body mass index; TIA - transient ischemic attack; LVEF – left ventricular ejection fraction; LA – left atrium; NR – not reported.

No.	Author	Age (yrs)		Male (%)		BMI		Prior stroke/TIA (%)		$CHADS_2$		CHA_2DS_2-VASc		Parox AF (%)		LVEF (%)		LA dimension	
		DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA
1	Armbruster HL et al.	60 ± 10	64 ± 10*	76	72	30 ± 6	29 ± 7	6	11	NR	NR	≥ 2 - 51 %	≥ 2 - 66 %	NR	NR	NR	NR	NR	NR
2	Arshad A et al.	61 ± 12	62 ± 11	71	67	29 ± 6	31 ± 6*	10	8	1.1 ± 1.1	1.3 ± 1.2*	NR	NR	56	60	56 ± 10	55 ± 10	45 ± 9 mm	44 ± 8 mm
3	Bassiouny M et al.	59 ± 11	63 ± 10*	75	73	30 ± 5	31 ± 6	6	8	≥ 2 - 20 %	≥ 2 - 29 %*	NR	NR	57	55	55	55	32 ml/m^2	34 ml/m^2
4	Calkins H et al	59 ± 10	59 ± 10	73	77	29	29	3	3	NR	NR	2	2.2	67	69	NR	NR	NR	NR
5	Cappato et al.	59 ± 10	60 ± 10	69	73	30 ± 6	29 ± 6	0	2	0.7+ 0.7	0.8 ± 0.9	1.5 ± 1.3	1.5 ± 1.3	77	70	NR	NR	NR	NR
6	DiBiasi L et al.	66 ± 10	66 ± 10	71,5	71.5	29 ± 6	30 ± 6	6	5	1.3 ± 0.9	1.3 ± 0.8	2.3 ± 1.4	2.3 ± 1.4	16.5	16.5	56 ± 9	57 ± 11	45 ± 8 mm	45 ± 9 mm
7	De Helde J et al.	60 ± 9	60 ± 10	72	68	27 ± 3	28 ± 4	NR	NR	NR	NR	≥ 2 - 34 %	≥ 2 - 47 %	74	76	NR	NR	43 ± 7	42 ± 6
8	Dillier R at al.	62 ± 11	64 ± 10	68	68	27 ± 4	27 ±4	6	7	0.9 ± 0.8	1.0 ± 0.9	1.8 ± 1.4	2.0 ± 1.5	49	46	60 ± 37	56 ± 7	44 ± 6	45 ± 7
9	Efremidis et al.	57 ± 12	58 ± 9	70	69	27 ± 3	27 ± 3	NR	NR	0.7 ± 0.8	0.8 ± 0.9	1.1 ± 1.1	1.2 ± 1.2	65	63	61 ± 6	59 ± 6	NR	NR
10	Enriquez AD et al	61 ± 10	60 ± 10	71	72	NR	NR	NR	NR	NR	NR	1.6 ± 1.4	1.9 ± 1.3	65	53	NR	NR	NR	NR
11	Garcia LI et al.	62 (55-69)	65 (58-72)*	72	66	31 ± 6	30 ± 7	9	19	0.98 ± 1.5	1.2 ± 1.4*	2.1 ± 0.3	2.7 ± 0.2*	28	29	57 ± 10	55 ± 10	NR	NR
12	Giermeni D. et al.	62 ± 10	65 ± 10	69	64	28 ± 5	29 ± 7	7	10	NR	NR	≥ 2 - 42 %	≥ 2 - 58 %	76	65	NR	NR	NR	NR
13	Gunawardene el al.	64 ± 10	64 ± 10	71	66	27 ± 4	27 ± 4	9	12	1 (1;2)	1 (1;2)	2 (1;3)	2 (1;3)	0	0	57 ± 8	58 ± 8	NR	NR
14	Haines DE et al.	60 ± 10	60 ± 11	74	69	NR	NR	7	9	NR	NR	1.6 ± 1.3	1.9 ± 1.4	58	52	56 ± 10	57 ± 9	44 ± 7 mm	44 ± 9 mm
15	Hohnloser SH et al.	60 (53-67)	61 (52-67)	71	73	28(25–31)	28(26–31)	5	5	NR	NR	≥ 2 - 50 %	≥ 2 - 50 %	68	69	NR	NR	NR	NR
16	Ichiki H et al.	57 ± 11	60 ± 10	83	78	NR	NR	NR	NR	1.1 ± 1.1	1.0 ± 1.0	NR	NR	70	50*	65 ± 8	64 ± 11	65 ± 24 ml/m^2	70 ± 24 ml/m^2
17	Imamura K et al.	61 ± 10	62 ± 8	75	71	NR	NR	6	8	0.9 ± 0.9	1.1 ± 1.0	1.6 ± 1.2	1.8 ± 1.2	56	49	63 ± 8	62 ± 9	41 ± 7 mm	42 ± 7 mm
18	Kaess BM et al.	63 ± 12	64 ± 10	67	67	27 ± 5	27 ± 4	8	7	1.2 ± 1.1	1.0 ± 0.9	2.1 ± 1.8	2.0 ± 1.5	54	54	58 ± 7	56 ± 6	44 (39,49)	44 (40,49)
19	Kaiser D et al.	58 ± 11	64 ± 10*	64	68	31 ± 6	31 ± 6	7	6	1.2 ± 1	1.6 ± 1*	1.8 ± 1.4	2.5 ± 1.4*	69*	47	62 ± 8*	59 ± 11	38 ± 9 mm	43 ± 8 mm
20	Kaseno K et al.	59 ± 10	62 ± 8	75	79	24 ± 3	24 ± 4	4	5	≥ 2 - 8%	≥ 2 - 14%	NR	NR	83*	55	64 ± 10	63 ± 10	39 ± 6 mm	43 ± 7 mm
21	Kim JS et al.	61 ± 10	61 ± 10	80	74	31 ± 6	32 ± 6	3	8	1.0 ± 0.9	1.1 ± 1.0	1.6 ± 1.3	1.7 ± 1.3	53	48	58 ± 9	57 ± 11	43 ± 7 mm	44 ± 7 mm
22	Kimura T et al.	59 (52-65)	62 (53-67)	53	53	24(22–25)	24(22–26)	NR	NR	NR	NR	NR	NR	63	67	56(51-58)	56(52-57)	39 (35-42.5)	37 (33-43) mm
23	Kirchhof P et al.	64 (57,70)	64 (58,70)	69	65	28(25,32)	28(26,32)	7.5	7.3	NR	NR	2.4(1.2)	2.4(1.2)	NR	NR	NR	NR	NR	NR
24	Kochhauser S et al.	60 ± 10	62 ± 11	76	73	NR	NR	NR	NR	0.9 ± 0.6	0.8 ± 0.5	1.5 ± 0.8	1.4 ± 0.8	74	69	NR	NR	41 ± 5 mm	42 ± 6 mm
25	Koetkuerk B et al.	61 ± 10	62 ± 10	62	53	NR	NR	NR	NR	NR	NR	1.5 ± 1.0	2.1 ± 1.5	62*	47	61 ± 10	58 ± 9	33 ± 11 mm	35 ± 13 mm
26	Konduru SV et al.	57 ± 10	61 ± 10	79	67	NR	NR	0	0	NR	NR	NR	NR	79	56	NR	NR	NR	NR
27	Kuwahara T et al.	65 ± 9	66 ± 8	75	72	NR	NR	NR	NR	NR	NR	2.1 ± 1.3	2.4 ± 1.4	59	60	64 ± 9	62 ± 9	41 ± 7 mm	42 ± 6 mm
28	Lakkireddy D at al.	60 ± 10	60 ± 10	79	79	NR	NR	3	6	≥ 2 - 23%	≥ 2 - 19%	1.6 ± 1.4	1.5 ± 1.3	57	57	56 ± 10	56 ± 10	45 ± 25 mm	44 ± 8 mm
29	Lakkireddy D et al.	63 ± 10	63 ± 10	69	69	30 ± 6	30 ± 6	11	8	1.2 ± 1	1.2 ± 1	2.2 ± 1.6	2.2 ± .2	51	51	58 ± 8	57 ± 8	44 ± 8 mm	43 ± 8 mm
30	Lin J et al.	60 ± 9	60 ± 10	80	75	NR	NR	5	8	≥ 2 - 13%	≥ 2 - 25%*	NR	NR	75	69	NR	NR	NR	NR
31	Maddox W et al.	62 ± 12	63 ± 10	76*	67	NR	NR	4	4	0.9 ± 0.9	0.9 ± 0.9	1.7 ± 1.5	1.7 ± 1.3	63	57	53 ± 4	54 ± 5	NR	NR
32	Muqnai G et al.	63 ± 10*	59 ± 11	72	71	27 ± 4	27 ± 5	NR	NR	NR	NR	1.8 ± 1.3	1.5 ± 1.3	NR	NR	57 ± 9	58 ± 7	44 ± 9 mm	44 ± 9 mm
33	Muller P et al.	63 ± 1	64 ± 2	64	58	NR	NR	5	10	NR	NR	2.3 ± .2	2.2 ± 1.3	44	58	58 ± 1	57 ± 1	44 ± 1 mm	44 ± 1 mm
34	Murakawa Y et al.	60 ± 11	63 ± 10*	76	76	NR	NR	NR	NR	NR	NR	1.5 ± 1.3	1.9 ± 1.5*	70*	61	65 ± 9*	63 ± 10	40 ± 6 mm	41 ± 6* mm
35	Nagao T et al.	60 ± 12	61 ± 11	74	74	24 ± 3	24 ± 3	5	5	0.8 ± 1	0.8 ± 0.9	1.5 ± 1.5	1.5 ± 1.5	75	73	62 ± 8	61 ± 9	39 ± 7 mm	40 ± 7 mm
36	Nagao T et al.	61 ± 13	62 ± 9	73	73	24 ± 4	24 ± 4	6	6	0.8 ± 1.1	0.8 ± 0.9	NR	NR	76	81	62 ± 9	62 ± 9	37 ± 6 mm	40 ± 2 mm
37	Nagao T et al.	59 ± 13	59 ± 9	77	77	24 ± 4	24 ± 3	4	5	0.6 ± 0.9	0.7 ± 0.9	1.2 ± 1.2	1.3 ± 1.4	72	64	62 ± 7	61 ± 7	38 ± 6 mm	39 ± 7 mm
38	Nin T et al.[36]	61 ± 11	61 ± 6	84	80	24 ± 4	24 ± 3	4	11	≥ 2 - 18%	≥ 2 - 20%	NR	NR	76	71	61 ± 7	62 ± 8	39 ± 7 mm	40 ± 8 mm
39	Nogami A et al.	65(59-71)	66(59-71)	78	72	24(22-26)	24(22-26)	7	5	NR	NR	2 (1-3)	2 (1-3)	63	62	66(60-71)	65(60-70)	NR	NR
40	Okishige K et al.	64 ± 12	65 ± 11	68	74	24	25	NR	NR	1 ± 1	1.9 ± 1*	NR	NR	NR	NR	64 ± 10	68 ± 8	40 ± 7 mm	42 ± 6 mm
41	Reynolds MR et al.	64 ± 10	64 ± 10	67	68	31 ± 6	32 ± 7*	3	5	NR	NR	2.3 ± 1.6	2.6 ± 1.5	65	64	57 ± 9	55 ± 10	NR	NR
42	Rilling A et al.	65 ± 10	67 ± 11	58	66	28 ± 14	28 ± 4	7	11	NR	NR	2 (1,3)	3 (2,4)*	40	43	NR	NR	NR	NR
43	Snipelisky D et al.	61	65	81	74	NR	NR	NR	NR	0.84	1.22	NR	NR	68	46	NR	NR	NR	NR
44	Snipelisky D et al.	66	66	69	62	29	30	8	5	1	1.4	NR	NR	NR	NR	NR	NR	NR	NR
45	Somani R et al.	60 ± 10	62 ± 8	84	77	NR	NR	2	7	0.6 ± 0.7	0.8 ± 0.9	NR	NR	70	66	NR	NR	34 ± 13 ml/m2	39 ± 12 ml/m2
46	Stepanyan G et al.	60 ± 11	63 ± 10	62	67	NR	NR	7	10	≥ 2 - 7%	≥ 2 - 7%	NR	NR	77*	63	NR	NR	NR	NR
47	Tang I et al.	59 ± 11	58 ± 11	66	66	NR	NR	7	6	NR	NR	≥ 2 - 44 %	≥ 2 - 43 %	80	79	NR	NR	NR	NR
48	Tao S et al.	66 ± 9	66 ± 11	74	66	24 ± 4	24 ± 4	11	7	1.3 ± 1	1.5 ± 1.1	2.2 ± 1.3	2.5 ± 1.5	72	77	67 ± 8	64 ± 11	40 ± 5 mm	41 ± 6 mm
49	Tscholl V et al.	63 ± 1	68 ± 9*	59	47	28 ± 6	30 ± 5	6	4	NR	NR	2.6 ± 1.7	3.1 ± 1.2	53	38	64 ± 8	64 ± 7	43 ± 3 mm	42 ± 7 mm
50	Vlanchos K et al.	58 ± 12	59 ± 10	68	70	28 ± 14	32 ± 40	NR	NR	NR	NR	1.3 ± 1.2	1.4 ± 1.1	65	58	60 ± 7	59 ± 7	NR	NR
51	Yamaji H et al.	60 ± 8	62 ± 8	75	76	NR	NR	5	4	NR	NR	1.8 ± 1.6	1.7 ± 1.5	65	62	60 ± 6	60 ± 8	43 ± 6 mm	41 ± 5 mm
52	Yanagisawa et al.	63 ± 8	63 ± 8	73	75	24 ± 5	24 ± 4	7	9	1.1 ± 1	1.1 ± 1	1.9 ± 1.3	1.9 ± 1.2	68	68	62 ± 8	60 ± 10	39 ± 7 mm	40 ± 7 mm
53	Yoshimura et al.	59 ± 11	61 ± 8	82	75	24 ± 4	25 ± 4	14	10	1.1 ± 1.1	1.0 ± 1.0	1.7 ± 1.4	1.5 ± 1.3	61	51	64 ± 9	64 ± 9	42 ± 6 mm	44 ± 6 mm

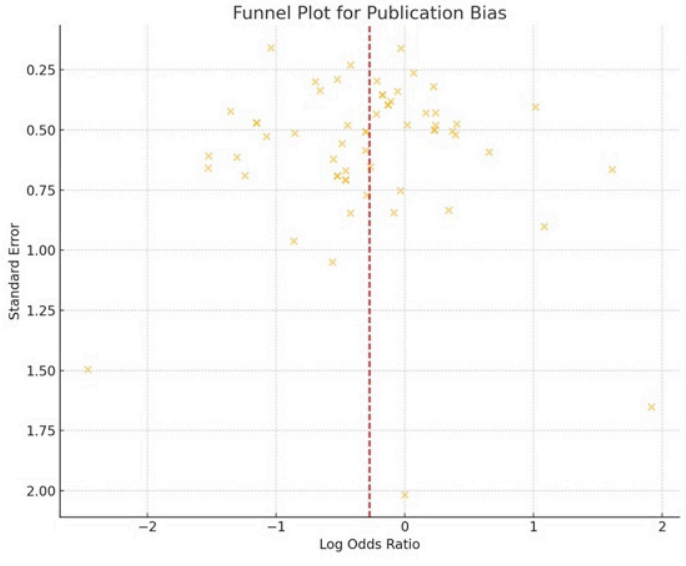


Figure 2 - Funnel Plot for publication bias.

5. Complications

In the 31589 patients, there were a total of 2384 (7.5%) complications, with 973 (6.8%) complications in the DOACS group representing a significantly lower rate than 1411 (8.1%) complications in the VKA group (OR = 0.80, CI 0.69-0.93, I^2 = 48%, p = 0.004) (Figure 3).

The thromboembolic complication rates were similar between the groups, 54 (0.38%) for patients on DOACS vs. 66 (0.38%) for patients on VKA (OR 0.76, 95% CI 0.53-1.10, I^2 = 0%, p = 0.15) (Figure 4), with significantly lower total bleeding complications in the DOACS group 919 (6.4%) patients vs. VKA group 1345 (7.8%) patients (OR 0.80, 95% CI 0.69-0.93, I^2 = 46%, p = 0.003) (Figure 5), driven by a lower incidence in both major bleeding [201 (1.4%) vs. 346 (2.0%)] and minor bleeding [718 (5%) vs. 999 (5.8%)] rates in DOACS group compared to VKA group(OR 0.71, CI 0.57-0.89, I^2 = 11%, p = 0.002 and OR 0.84, CI 0.73-0.98, I^2 = 31%, p = 0.03) (Figure 6).

6. Complications of interrupted and uninterrupted peri-procedural anticoagulation strategies

Interrupted and uninterrupted peri-procedural anticoagulation with either DOACS or VKA are used in the current practice. Continuous VKA has been suggested to be superior to interrupted VKA[1,6]; however, the optimal peri-procedural DOACS strategy still remains unclear[54,68,69]. In order to evaluate the safety of different strategies, we have evaluated the complications of (1) interrupted and (2) uninterrupted DOACS strategies compared to continuous VKA, as well as (3) DOACS (both interrupted and uninterrupted) with interrupted W subgroups separately. One study[31] did not report complications separately for each W group and was not included in this analysis.

(1) There were 21 studies[14,17,21,22,24,25,27,33,37,38,41,42,44,46,48–50,54,62,64,65] including 10038 patients on uninterrupted anticoagulation (5027 on uninterrupted DOACS and 5011 patients on continuous VKA). The overall complication numbers were similar between the 2 uninterrupted anticoagulation strategies 408 (8.1%) for patients on DOACS and 430 (8.6%) for patients on VKA with no differences in thromboembolic events 14 (0.3%) for DOACS vs. 16 (0.3%) for VKA

Table 3 - Anticoagulation Characteristics; D – dabigatran; R – rivaroxaban; W – warfarin; N/A -not applicable; NR – not reported; CW – continuous warfarin; TEE – transesophageal echocardiogram; UFH – unfractionated heparin; LMWH – low molecular weight heparin

No.	Author	Pre procedure anticoagulation		Antiplatelets (%)		DOAC		VKA Type	VKA bridging protocol		INR (CVKA)	Pre-procedureTEE	
		DOAC	VKA	DOAC	VKA	Stop pre	Start post		Pre	Post		DOAC	VKA
1	Armbruster HL et al. *Annals of Pharm 2015*	NR	NR	20	27	3 doses D 1-2 doses R	4h post procedure	Warfarin	Uninterrupted		2.6 ± 0.7	For persistent AF	For persistent AF
2	Arshad A et al. *PACE 2014*	≥ 4 weeks	≥ 4 weeks	28.6*	16.1	12-48 h	Evening of procedure	Warfarin	Uninterrupted or W stopped 5 days with LMWH	W night of procedure; LMWH 0.5-0.6 mg/kg	2.4 ± 0.4	TEE at 3/4 centers; as needed 1/4 centers	TEE at 3/4 centers;as needed 1/4 centers
3	Bassiouny M et al. *Circ Arrhythmia EP 2013*	≥ 4 weeks	≥ 4 weeks	33	39*	12-24 h	Immediate post-procedure	Warfarin	Uninterrupted		2.4	As needed 12%	As needed 25%*
4	Calkins H et al. *NEJM 2017*	≥ 4 weeks	≥ 4 weeks	19	23	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.3	100%	100%
5	Cappato R et al. *European Heart Journal 2015*	≥ 3 weeks or 1-7 days - TEE or ICE	≥ 3 weeks or 1-7 days - TEE or ICE	30	23	Uninterrupted		VKA	Uninterrupted		NR	If necessary	If necessary
6	De Heide J et al. J Int Card Electrophys 2018	≥ 3 weeks	≥ 3 weeks	NR	NR	>24h; 1-2 doses held	Evening of procedure	Marcoumar Acenocoumarol	Uninterrupted		NR	100%	100%
7	DiBiase L et al. *Heart Rhythm 2015*	≥ 3 weeks	≥ 3 weeks	30.5	38.5	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.5 ± 0.5	Not mandated	Patients in AF and INR < 2.0
8	Dillier R et al. *Circ Arrhythmia EP 2014*	≥ 4 weeks	≥ 4 weeks	16	15	Uninterrupted	12- 22 h	Phenprocoumon	Uninterrupted		2.1 ± 0.4	100% TEE or CT	100% TEE or CT
9	Efremidis M et al. *J of Electrocardiology 2015*	≥ 3 weeks	≥ 3 weeks	NR	NR	24h	Immediate post-procedure	Acenocoumarol	Uninterrupted		2.4 ± 0.2	100%	100%
10	Enriquez AD et al. *PACE 2017*	NR	NR	NR	NR	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.3 ± 0.4	NR	NR
11	Garcia LI et al. *J Afib 2014*	NR	NR	15	23	96 h	Next AM with LMWH 0.5 mg/kg x 3 doses; UFH IV 4-6h post	Warfarin	Uninterrupted		2.2 (1.8-2.5)	100%	100%
12	Gjermeni D et al. European Heart Journal 2023	NR	NR	NR	NR	<48h (prior to 2015) post 2015- uninterrupted	Evening of procedure	Phenprocoumon	Uninterrupted		NR	At physician discretion	At physician discretion
13	Gunawardene et al. *Clin Res Cardiol 2017*	NR	NR	NR	NR	48 h	Evening of procedure	VKA	Uninterrupted or LMWH	Uninterrupted or LMWH	NR	100%	100%
14	Haines DE et al. *J Int Card Electrophys 2013*	NR	NR	65	47	<12-48 h 22% bridge LMWH	12 ± 10 h	Warfarin	Uninterrupted in 80% LMWH bridge	LMWH	2.3 ± 0.7	Pts not on continuous AC	Pts not on continuous AC
15	Hohnloser SH et al. European Heart Journal 2019	≥ 3 weeks	≥ 3 weeks	NR	NR	Uninterrupted	Uninterrupted	VKA	Uninterrupted		NR	100% TEE or ICE	100% TEE or ICE
16	Ichiki H et al. *PACE 2013*	NR	NR	NR	NR	Morning of procedure	Evening of procedure	Warfarin	Uninterrupted		1.99 ± 0.6	100%	100%
17	Imamura K et al. *J Int Card Electrophys 2013*	≥ 4 weeks	≥ 4 weeks	8	7	24 h for CHADS 0-1; 12 h CHADS >1	3h post-procedure	Warfarin	W stopped 3 days; UFH bridge	UFH + W 3 h post procedure	N/A	100%	100%
18	Kaess BM at al. *Am J Cardiol 2015*	≥ 4 weeks	≥ 4 weeks	22	15	Uninterrupted	Uninterrupted	Phenprocoumon	Uninterrupted		2.1 ± 0.4	100% TEE or CT	100% TEE or CT
19	Kaiser D et al. *J Int Card Electrophys 2013*	NR	NR	58	51	24-30 h CrCl > 50 ml/min 3-5 days CrCl 15-30 ml/min	Immediate post-procedure	Warfarin	Uninterrupted	Uninterrupted; 24% UFH bridge	≥ 1.5	SR- TEE per operator; AF- TEE 100%	AF- TEE 100%
20	Kaseno K et al. *Circ Journal Jap 2012*	26 ± 43 days	≥ 4 weeks	NR	NR	Morning of procedure	Morning after procedure 10000 UFH first 24h	Warfarin	Uninterrupted	Uninterrupted + 10000 UFH first 24h	2.4 ± 0.4	100%	100%
21	Kim JS et al. *Heart Rhythm 2013*	≥ 4 weeks	≥ 4 weeks	36	43	24-30 h	Immediate post-procedure	Warfarin	Uninterrupted		2.4 ± 0.3	100%	100%
22	Kimura T et al. JACC 2018	≥ 4 weeks	≥ 4 weeks	NR	NR	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.2 (1.7-2.8)	100%	100%
23	Kirchhof P et al. European Heart Journal 2018	≥ 4 weeks	≥ 4 weeks	3.5	6	Uninterrupted	Uninterrupted	VKA	Uninterrupted		NR	87%	87%
24	Kochhauser S et al. *Can J of Card 2014*	≥ 4 weeks	≥ 4 weeks	NR	NR	> 24 h	8 h	Warfarin	W stopped 4 days, LMWH bridge 2 days	W night of procedure + LMWH bridging	NR	100%	100%
25	Koektuerk B et al. Cardiovasc Therap 2016	NR	NR	NR	NR	24 h	Evening of procedure	Phenprocoumon	Uninterrupted		NR	100%	100%
26	Konduru SV et al. *J Int Card Electrophys 2012*	NR	NR	54	29*	Uninterrupted or 24 h	Evening of procedure	Warfarin	Uninterrupted		2.2 ± 0.3	100%	100%
27	Kuwahara T et al. *J of Card Electrophys 2016*	≥ 30 days	≥ 30 days	NR	NR	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.2 ± 0.6	NR	NR
28	Lakkireddy D et al. *JACC 2012*	≥ 4 weeks	≥ 4 weeks	34	34	Morning of procedure	3 h post hemostasis	Warfarin	Uninterrupted		2.0-3.5	100%	none
29	Lakkireddy D et al. *JACC 2014*	≥ 4 weeks	≥ 3 weeks	31	26	Uninterrupted	≥ 3 h post hemostasis	Warfarin	Uninterrupted		2.3 ± 0.4	100%	Only for low INR
30	Lin J et al. *J Afib 2014*	NR	NR	NR	NR	36 h	Morning after procedure	Warfarin	W stopped 3-5 days; LMWH bridge	W night of, LMWH morning post procedure	N/A	Most of patients	Most of patients
31	Maddox W et al. *J Card Electrophysiol 2013*	≥ 4 weeks	≥ 4 weeks	NR	NR	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.3 ± 0.5	100%	100%
32	Mugnai G et al. American J of Card 2017	NR	NR	NR	NR	> 24-36 h	Evening of procedure	Warfarin Acenocoumarol	W stopped > 24 h, if INR<2, bridged w LMWH	LMWH same day of procedure	NR	100%	100%
33	Muller P et al. J Interv Card Electro 2016	NR	NR	NR	NR	Uninterrupted or 24 h	Evening of procedure	VKA	VKA stopped 5-7 days, bridged w LMWH	heparin infusion 4 h initial and LMWH day after procedure	NR	100%	100%
34	Murakawa Y et al. *J of Arrhythmia 2015*	NR	NR	NR	NR	0-24h	NR	Warfarin	Uninterrupted		NR	NR	NR
35	Nagao T et al. *Heart Rhythm 2015*	≥ 4 weeks	≥ 4 weeks	9	7	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		NR	100%	100%
36	Nagao T et al. *PACE 2015*	≥ 4 weeks	≥ 4 weeks	11	11	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.2 ± 0.5	100%	100%
37	Nagao T et al. *Internal Med 2015*	≥ 4 weeks	≥ 4 weeks	9	9	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.2 ± 0.5	100%	100%
38	Nin T et al. *PACE 2013*	≥ 3 weeks	≥ 3 weeks	NR	NR	> 24 h	Immediate post-procedure	Warfarin	W stopped > 24 h	≥ 4 h post procedure hemostasis	1.8 ± 0.4	100%	100%
39	Nogami A et al. JAMA 2019	≥ 4 weeks	≥ 4 weeks	NR	NR	1-2 doses withheld, UFH bridging if > 24 h	8 h post procedure	Warfarin	Uninterrupted		NR	86%	84%
40	Okishige K et al. *J of Card 2017*	≥ 4 weeks	≥ 4 weeks	NR	NR	12-24 h, one dose held	Evening of procedure	Warfarin	Uninterrupted		NR	NR	NR
41	Reynolds MR et al. *JACC EP 2018*	≥ 3 weeks	≥ 3 weeks	24	32	Uninterrupted Morning of procedure	Evening of procedure	Warfarin	Uninterrupted		2.3 ± 0.5	46%	69%
42	Rilling A et al. *JCE 2016*	NR	NR	3	2	> 36 h	Evening of procedure	Phenprocoumon	Uninterrupted		2.3 (2.1,2.5)	100%	100%
43	Snipelisky D et al. *J Int Card Electrophys 2012*	NR	≥ 30 days	NR	NR	Morning of procedure	Evening of procedure	Warfarin	W stopped > 24 h	Evening of procedure	2-3	NR	NR
44	Snipelisky D et al. *J Int Card Electrophys 2014*	NR	NR	4	10	R night prior D morning of procedure	Evening of procedure	Warfarin	W stopped > 24 h	Evening of procedure	NR	NR	NR
45	Somani R et al. *Cardiovasc Therap 2014*	≥ 4 weeks	≥ 4 weeks	NR	NR	> 24-30h	Immediate post-procedure	Warfarin	Uninterrupted; W stopped 1 week - LMWH until 24-30h prior procedure	Uninterrupted; LMWH 1/2 dose 4h post hemostasis; 12h full dose	NR	100%	100%
46	Stepanyan G et al. *J Int Card Electrophys 2014*	≥ 1 week	NR	NR	NR	> 24-36 h	Morning after procedure; UFH infusion 6 h post procedure	Warfarin	Uninterrupted		NR	PeAF and inconsistent AC last 30 days	PeAF and inconsistent AC last 30 days
47	Tang I et al. *Frontiers in Med 2020*	NR	NR	NR	NR	Morning of procedure	Evening of procedure	Warfarin	Uninterrupted; W stopped 3-5 days; LMWH bridge	Uninterrupted; W night of procedure, LMWH bridge	NR	100%	100%
48	Tao S et al. *J Int Card Electroph 2017*	≥ 4 weeks	≥ 4 weeks	8	14	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.2	100%	100%
49	Tscholl V et al. Clinical Cardio 2017	NR	NR	NR	NR	Morning of procedure	Uninterrupted	Phenprocoumon	Uninterrupted		1.8 ± 0.5	100%	100%
50	Vlachos K et al. Clinical Cardio 2017	≥ 2 months	NR	NR	NR	Uninterrupted R Morning of procedure D, A	Uninterrupted Evening of procedure	Acenocoumarol	Uninterrupted		NR	100%	100%
51	Yamaji H et al. *Clin Drug Inv 2013*	≥ 30 days	≥ 30 days	NR	NR	Morning of procedure	3 h post hemostasis	Warfarin	Uninterrupted; W stopped 48 h; UFH subcutaneous bid	Uninterrupted; ; UFH subcutaneous until INR ≥ 2.0	2-3	100%	100%
52	Yanagisawa S et al. *JACC Clin Electrpph 2018*	≥ 3 weeks	≥ 3 weeks	9	16	Uninterrupted	Uninterrupted	Warfarin	Uninterrupted		2.0 ± 0.6	100%	100%
53	Yoshimura et al. *Journal of Card 2017*	NR	NR	NR	NR	R uninterrupted A morning of procedure	Evening of procedure	Warfarin	Uninterrupted		2.0 ± 0.6	100%	100%

(OR 0.794, CI 0.47-1.88, I^2 = 0%, p = 0.87), major or minor bleedings 72 (1.4%) for DOACS vs. 92 (1.8%) for VKA (OR 0.77, CI 0.56-1.08, I^2 = 0%, p = 0.13) and 321 (6.4%) for DOACS vs. 322 (6.4%) for VKA (OR 1.01, CI 0.85-1.20, I^2 = 0%, p = 0.90), respectively. (Figure 7 A, B, C, D)

(2) Interrupted DOACS strategy (≥ 1 doses held) compared with uninterrupted VKA was evaluated in 27 studies[13,15,16,18–20,23,26,28,30,34–36,40,46,47,52–55,58–63,65] that included 15109 patients (6739 patients on interrupted DOACS and 8370 patients on uninterrupted VKA). The total number of complications was lower in the interrupted DOACS strategy with 318 (4.7%) events compared with uninterrupted VKA 569 (6.8%) events (OR 0.72, CI 0.57-0.89, I^2 = 38%, p = 0.003). The superiority of the interrupted DOACS regimen was driven by lower rates of both major and minor bleedings [75 (1.1%) DOACS vs. 182 (2.2%) VKA (OR 0.64, CI 0.44-0.94, I^2 = 28%, p = 0.02) and 224 (3.3%) DOACS vs 365 (4.4%) VKA (OR 0.76, CI 0.63-0.91, I^2 = 0%, p = 0.004), respectively], with no difference in thromboembolic complications 20 (0.3%) DOACS vs.

Table 4 - Procedural Characteristics; W – warfarin; TS –transseptal puncture; ACT – activated clotting time.

No.	Author	Ablation characteristics				Intra-procedural anticoagulation					
		ICE use	Type of ablation	Procedure time (min)		Heparin bolus	Before TS	Heparin drip	Target ACT (s)	Achieved ACT		Protamine
				DOACs	VKA					DOACs	VKA	
1	Armbruster HL et al. *Annals of Pharm 2015*	NR	NR	NR	NR	50 U/Kg for W; 75 U/Kg for NOAC	Yes	No	≥ 350	NR	NR	Yes
2	Arshad A et al. *PACE 2014*	Yes	PVI, CFAE, Linear ablations	225 ± 66	222 ± 60	70-100 U/kg	Yes	18 U/kg/h	300-400	358 ± 42	341 ± 45	Yes
3	Baseiouny M et al. *Circ Arrhythmia EP 2013*	Yes	PVI, Atrial Flutter	NR	NR	80-150 U/kg	Randomly	Yes	350-450	344 ± 5	392 ± 7*	Partial
4	Calkins H et al. *NEJM 2017*	NR	PVI, Linear lesions, CFAE, other regions as needed	NR	NR	Yes	Randomly	NR	> 300	NR	NR	NR
5	Cappato R et al. *European Heart Journal 2015*	NR	NR	NR	NR	NR	NR	NR	300-400	302 ± 49	358 ± 42*	27%of pts
6	De Heide J et al. *J Int Card Electrophys 2018*	Yes	PVI, Linear lesions, CFAE, other regions as needed	164 ± 69	160 ± 37	10000 U for W 13000 for Apixaban	Yes	No	> 300	NR	NR	NR
7	DiBlase L et al. *Heart Rhythm 2015*	No	PVI	184 ± 39	185 ± 58	100 U/kg	No	NR	350-400	360 ± 23	388 ± 18	NR
8	Dillier R et al. *Circ Arrhythmia EP 2014*	No	PVI	NR	NR	Yes	No	Yes	> 300	NR	NR	No
9	Efremidis M et al. *J of Electrocardiology 2015*	Yes	NR	166 ± 51	155 ± 54	NR	Yes	No	≥ 350	NR	NR	Yes
10	Enriquez AD et al. *PACE 2017*	No	PVI, CFAE	151 (116,200)	141 (98-185)	50-60 U/kg	No	Yes	270-300	278 ± 32	289 ± 35*	No
11	Garcia Li et al. *J Afib 2014*	NR	PVI, Linear ablations for persistent, Atrial Flutter	NR	NR	100 U/kg	No	No	350-400	NR	NR	Yes
12	Gjermeni D et al. *European Heart Journal 2023*	No	PVI, AF ablation, Atrial Flutter	NR	NR	10000 U	Yes	Yes	> 300	NR	NR	NR
13	Gunawardene et al. *Clin Res Cardiol 2017*	NR	PVI, Linear lesions, CFAE, Atrial Flutter	172 ± 63	175 ± 64	Yes	No	NR	> 300	293 ± 35	307 ± 35	NR
14	Haines DE et al. *J Int Card Electrophys 2013*	NR	PVI w or w/o substrate modification	242 ± 76	250 ± 87	NR	NR	NR	300-350	>300 (92.7%)	>300 (90.1%)	NR
15	Hohnloser S H et al. *European Heart Journal 2019*	Yes	AF ablation	NR	NR	NR	NR	Yes	300-400	303	338*	NR
16	Ichiki H et al. *PACE 2013*	NR	CFAE, PVI	225 ± 55	225 ± 49	NR	NR	NR	≥ 250	276 ± 15	286 ± 27	NR
17	Imamura K et al. *J Int Card Electrophys 2013*	Yes	PVI, Additional foci and CFAE, Atrial Flutter	253±54	267±57	NR	No	No	≥ 300	NR	NR	Partial
18	Kaess BM et al. *Am J Cardiol 2015*	No	PVI and CFAE, additional lesion set as needed	145 (105,208)	139 (93,183)	50-60 U/Kg	No	No	250-300	258 ± 26	288 ± 34	No
19	Kaiser D et al. *J Int Card Electrophys 2013*	Yes	PVI, Linear ablations, CFAE, Atrial Flutter	NR	NR	Yes	After First	Yes	300-350	NR	NR	Yes
20	Kaseno K et al. *Circ Journal Jap 2012*	NR	PVI, Linear ablations, CFAE, Atrial Flutter	163 ± 43	167 ± 45	NR	NR	NR	300-350	NR	NR	NR
21	Kim J S et al. *Heart Rhythm 2013*	NR	PVI (unless operator chose otherwise)	209 ± 81	207 ± 92	Yes	No	Yes	300-350	321 ± 23	339 ± 19*	NR
22	Kimura T et al. *JACC 2018*	No	Catheter Ablation	216(170–260.5)	190 (159–243	100 U/kg	Yes	Yes	300-350	99.2 (289.2–311.8 1.3 (324.4–368.		yes
23	Kirchhof P et al. *European Heart Journal 2018*	Yes	AF ablation	136 (110, 175)	135 (105, 172	100 U/kg	Randomly	No	>300	10.0 (273.0, 350.0 8.5 (304.0, 396.		NR
24	Kochhauser S et al. *Can J of Card 2014*	Yes	NR	NR	NR	NR	NR	NR	> 350	347 ± 32	352 ± 39	Yes if ACT > 300 s
25	Koektuerk B et al. *Cardiovasc Therap 2016*	No	PVI, cryo ablation	88 ± 25	102 ± 29	100 U/kg	No	No	300-350	NR	NR	Yes
26	Konduru SV et al. *J Int Card Electrophys 2012*	NR	AF ablation	257 ± 55	252 ± 46	70 U/kg	Yes	Yes	≥ 350	320 ± 20	363 ± 36*	NR
27	Kuwahara T et al. *J of Card Electrophys 2016*	NR	PVI, Linear lesions, CFAE for persistent AF	156 ± 48	160 ± 44	100 U/kg	Yes	No	> 300	322 ± 30	357 ± 35*	NR
28	Lakkireddy D et al. *JACC 2012*	Yes	PVI and CFAE, additional lesion set as needed	208 ± 73	203 ± 61	10,000 U	Yes	No	300-400	NR	NR	NR
29	Lakkireddy D et al. *JACC 2014*	Yes	PVI, Linear lesions, CFAE for persistent AF	195 ± 62	198 ± 66	10,000 U	Yes	No	300-400	NR	NR	NR
30	Lin J et al. *J Afib 2014*	NR	NR	NR	NR	100 U/kg	No	No	NR	NR	NR	NR
31	Maddox W et al. *J Card Electrophysiol 2013*	Randomly	PVI, CFAE, Linear ablations	87 ± 28	88 ± 31	200 U/kg	Randomly	No	≥ 350-400	387 ± 79	394 ± 124*	Yes 40-50 mg
32	Mugnai G et al. *American J of Card 2017*	No	PVI, cryo ablation	77 ± 25	81 ± 44	70 U/kg	NR	Yes	≥ 250	NR	NR	Yes
33	Muller P et al. *J Interv Card Electro 2016*	No	PVI	135 ± 7	124± 6	5000 IE	Yes	Yes	≥ 300	300 ± 5	313 ± 9	No
34	Murakawa Y et al. *J of Arrhythmia 2015*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
35	Nagao T et al. *Heart Rhythm 2015*	Yes	PVI, CFAE, Linear ablations, Atrial Flutter as needed	139 ± 50	142 ± 52	80-100 U/kg	Yes	No	300-350	NR	NR	Yes 30-40 mg
36	Nagao T et al. *PACE 2015*	Yes	PVI, CFAE, Linear ablations, Atrial Flutter	2.2 ± 0.8 (h)	2.7 ± 0.8 (h)	5000 U	Yes	No	300-350	326 ± 52	358 ± 55*	Yes 30-40 mg
37	Nagao T et al. *Internal Med 2015*	Yes	PVI, CFAE, Linear ablations, Atrial Flutter	153 ± 46	168 ± 40	5000 U	Yes	No	300-350	344 ± 54	358 ± 47*	Yes 30-40 mg
38	Nin T et al. *PACE 2013*	No	PVI, Atrial flutter	NR	NR	100 U/kg	No	No	300-400	NR	NR	Yes
39	Nogami A et al. *JAMA 2019*	Yes	AF ablation	NR	NR	Yes	Randomly	Yes	300-400	NR	NR	Yes
40	Okishige K et al. *J of Card 2017*	Yes	PVI, cryo ablation	NR	NR	NR	No	No	> 300	NR	NR	NR
41	Reynolds MR et al. *JACC EP 2016*	NR	NR	NR	NR	Yes	Yes	NR	> 300	381 ± 48	429 ± 118*	Yes
42	Rilling A et al. *JCE 2016*	NR	PVI	130 ± 51	128 ± 40	Yes	No	NR	> 250	388 ± 54*	334 ± 67	NR
43	Shipelisky D et al. *J Int Card Electrophys 2012*	Randomly	PVI, Other ablations	NR	NR	8,000-12,000 U	NR	No	≥ 350	413 ± 56	432 ± 33*	Yes for PAF
44	Shipelisky D et al. *J Int Card Electrophys 2014*	NR	PVI, cryo ablation	184	180	8,000-12,000 U	NR	No	≥ 350	402	425	Not routine
45	Somani R et al. *Cardiovasc Therap 2014*	Randomly	PVI for PAF; PeAF additional CFAE, lesion set	NR	NR	100 U/kg	No	No	250-350	NR	NR	No
46	Stepanyan G et al. *J Int Card Electrophys 2014*	Yes	PVI; Linear lesions, CFAE, Atrial Flutter as needed	NR	NR	Yes	After First	Yes	≥ 350	335 ± 78*	298 ± 40	Yes
47	Tang I et al. *Frontiers in Med 2020*	NR	Radiofrequency or cryo ablation	NR	NR	100 U/kg	No	NR	250-350	NR	NR	No
48	Tao S et al. *J Int Card Electroph 2017*	NR	PVI; Linear lesions, CFAE, Atrial Flutter as needed	215 ± 49	222 ± 58	3000 U	No	Yes	≥ 300	304 ± 29	324 ± 38*	Yes 40 mg
49	Techoll V et al. *Clinical Cardio 2017*	No	PVI, cryo ablation	131 ± 30	148 ± 38	NR	No	NR	≥ 300	314 ± 43	380 ± 68*	No
50	Vlachos K et al. *Clinical Cardio 2017*	No	AF ablation	NR	NR	100 U/kg	No	NR	300-400	NR	NR	No
51	Yamaji H et al. *Clin Drug Inv 2013*	No	PVI	100 ± 28	97 ± 26	100 U/kg	Yes	400 U/h	300-350	318 ± 34	318 ± 23	Yes 20-30 mg
52	Yanagisawa S et al. *JACC Clin Electroph 2018*	Yes	PVI; Linear lesions, CFAE, Atrial Flutter as needed	NR	NR	80-100 U/kg	Yes	NR	300-350	309 (267,352)	320 (278,360)	Yes 30-50 mg
53	Yoshimura et al. *Journal of Card 2017*	No	PVI and CFAE	NR	NR	NR	NR	NR	> 300	NR	NR	NR

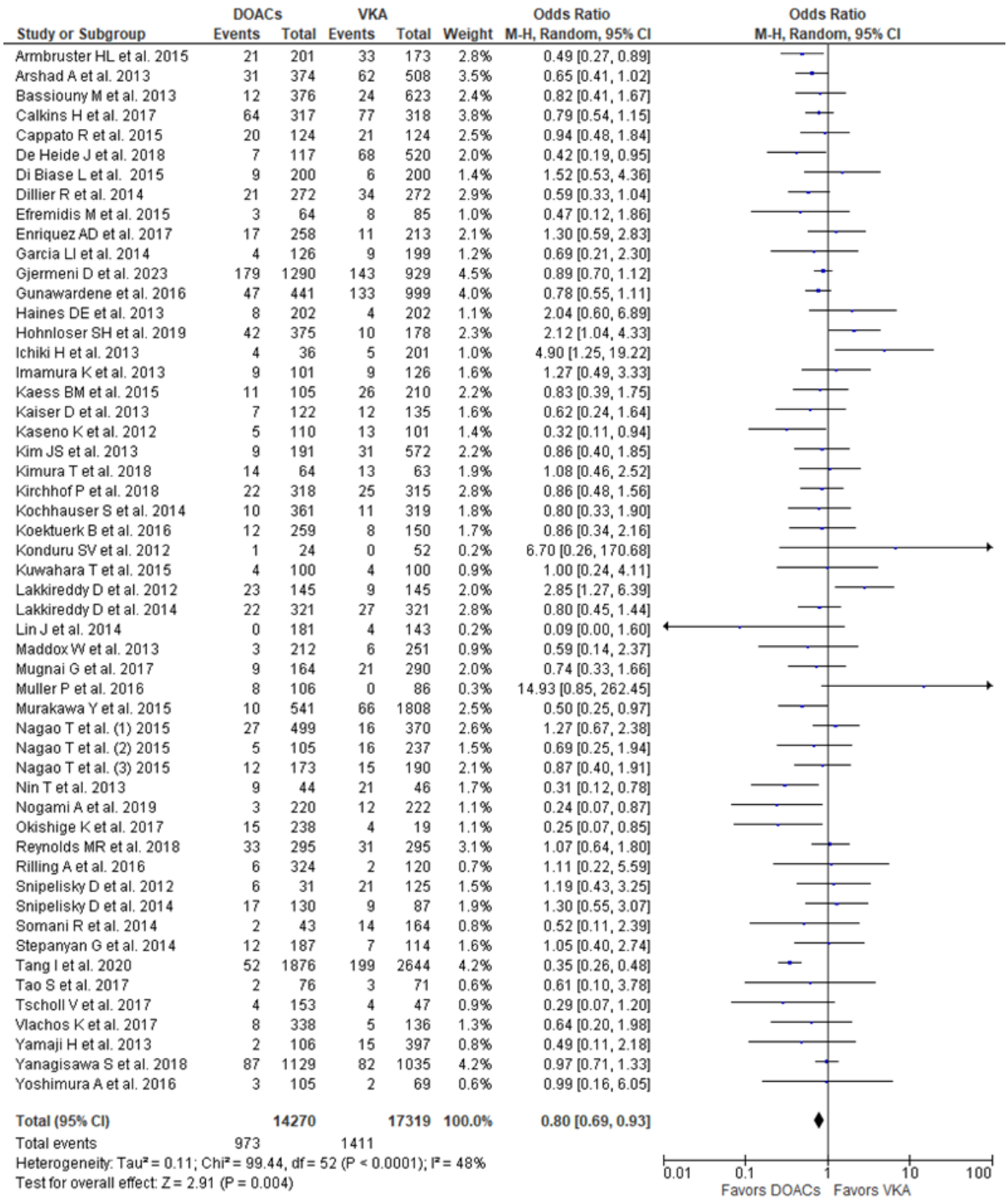


Figure 3 - Total Complications – Entire Cohort.

22 (0.3%) VKA (OR 0.83, CI 0.44-1.56, I^2 = 0%, p = 0.56). (Figure 8 A, B, C, D)

(3) There were 13 trials[19,30,32,39,43,45,46,51,56–58,60,63] that included an interrupted VKA group, 7 of them[32,39,43,45,51,56,57] had interrupted the VKA group only, with a total of 7991 patients. On comparing the 3958 patients on DOACS with 4033 patients on interrupted VKA, there was a lower total complication rate 202 (5%) DOACS vs. 382 (9.5%) VKA (OR 0.64, CI 0.44-0.92, I^2 = 62%, p = 0.02), driven by a decrease in major bleeding complications, 15 (0.4%) DOACS vs. 50 (1.2%) VKA (OR 0.36, CI 0.20-0.66, I^2 = 0%, p = 0.0008), with lower numerical but no difference in thromboembolic and minor bleeding events, 5 (0.1%) DOACS vs. 10 (0.2%) VKA (OR 0.55, CI 0.21-1.47, I^2 = 0%, p = 0.23) and 182 (4.6%) DOACS vs. 322 (8.0%) VKA (OR 0.72, CI 0.49-1.05, I^2 = 59%, p = 0.09). (Figure 9 A, B, C, D)

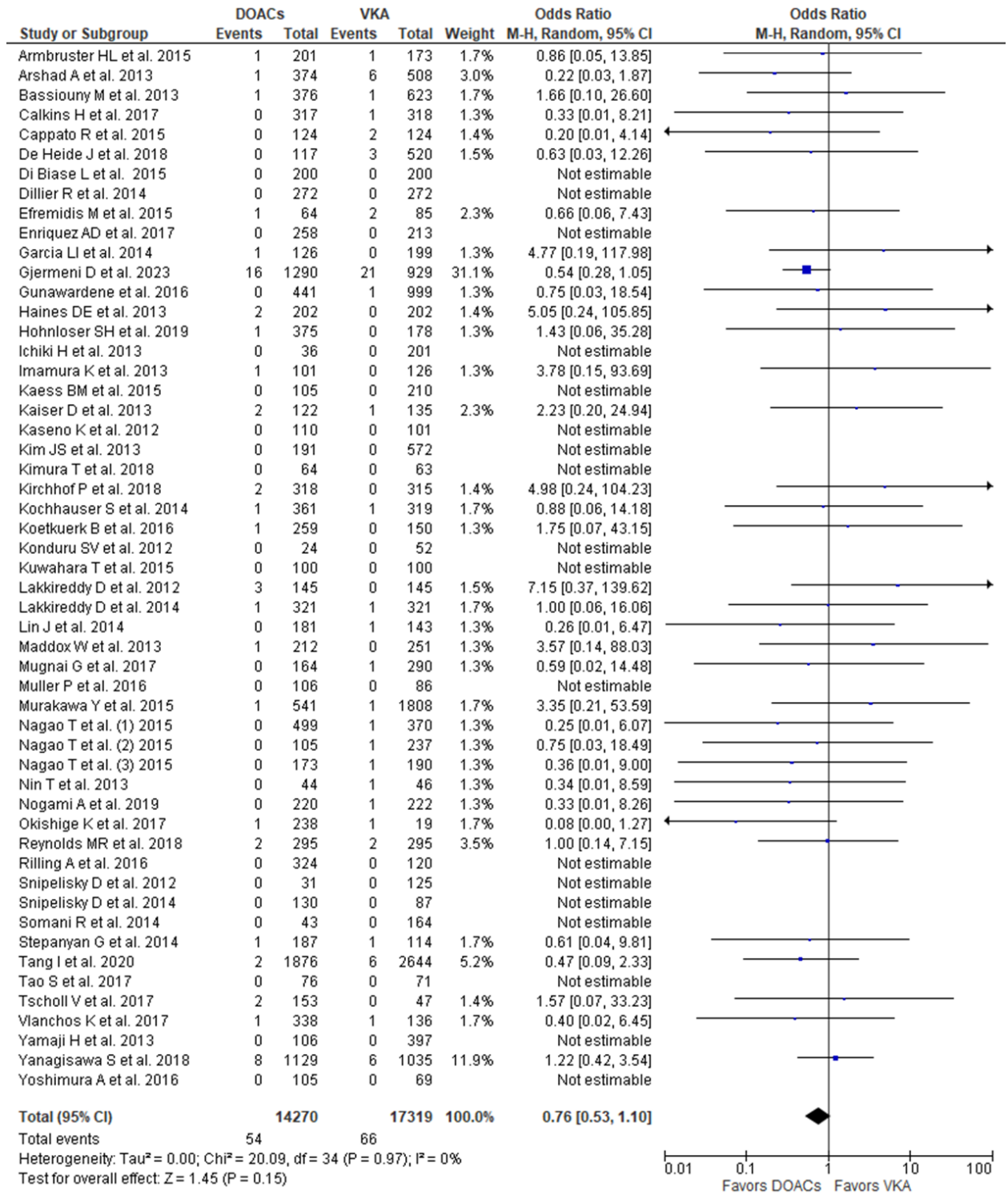


Figure 4 - Thromboembolic Complications – Entire Cohort.

7. Complications of DOACS versus VKA anticoagulants other than warfarin

There were 10 studies[23,25,26,29,33,40,45,55,61,62] that evaluated the bleeding and thromboembolic complications of non-warfarin (W) VKA (phenprocoumon, acenocoumarol) in comparison with DOACS and included a total of 5623 patients (3086 on DOACS and 2537 on nonWVKA). Total complications were lower in the DOACS group, 260 (8.4%), compared with the non-WVKA group, 285 (11.2%). The risk for thromboembolic, major, and minor bleeding complications was similar for both groups: 0.7% DOACS vs 1.1% nonWVKA, 2.2% DOACS vs 3.7% nonWVKA, and 5.6% DOACS vs 7.1% nonWVKA, respectively. (Figure 10 A, B, C, D)

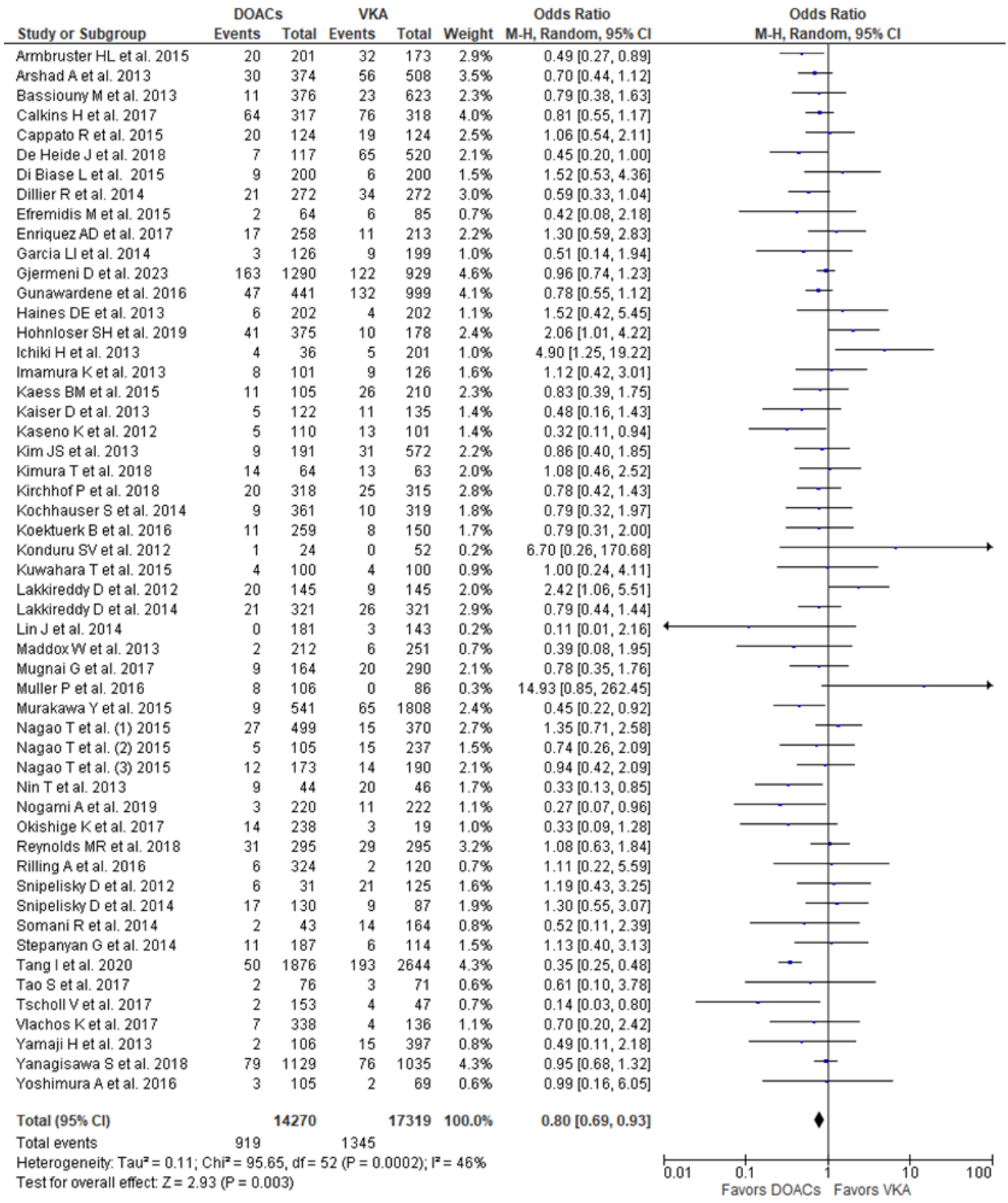


Figure 5 - Total Bleeding Complications – Entire Cohort.

8. Individual DOACS complications compared to VKA

The safety profile of each of the 3 main DOACS: D, R, and A, was evaluated compared to VKA. The subgroups included 5536 patients on D, which were compared with 8255 patients on VKA, 3849 patients on R, 4852 patients on VKA, and 1913 patients on A, compared with 4148 patients on VKA. There was a significant decrease in number of total complications in dabigatran group, with 414 (7.5%) vs 692 (8.4%) in VKA group (OR 0.81, CI 0.67-0.98, p = 0.03, I^2 = 35%) due to a decrease in bleeding complications, 5.3% D vs. 7.0% VKA (OR 0.81, CI 0.67-0.98, p = 0.03, I^2 = 32%), and no difference in thromboembolic events, 0.49% D vs. 0.53% VKA (OR 0.81, CI 0.50-1.32, p = 0.62, I^2 = 0%). (Figure 11 A) There were 211 complications (6.1%) in the R group and 312 complications (8.0%) in the VKA group, with no significant difference in the total, bleeding,

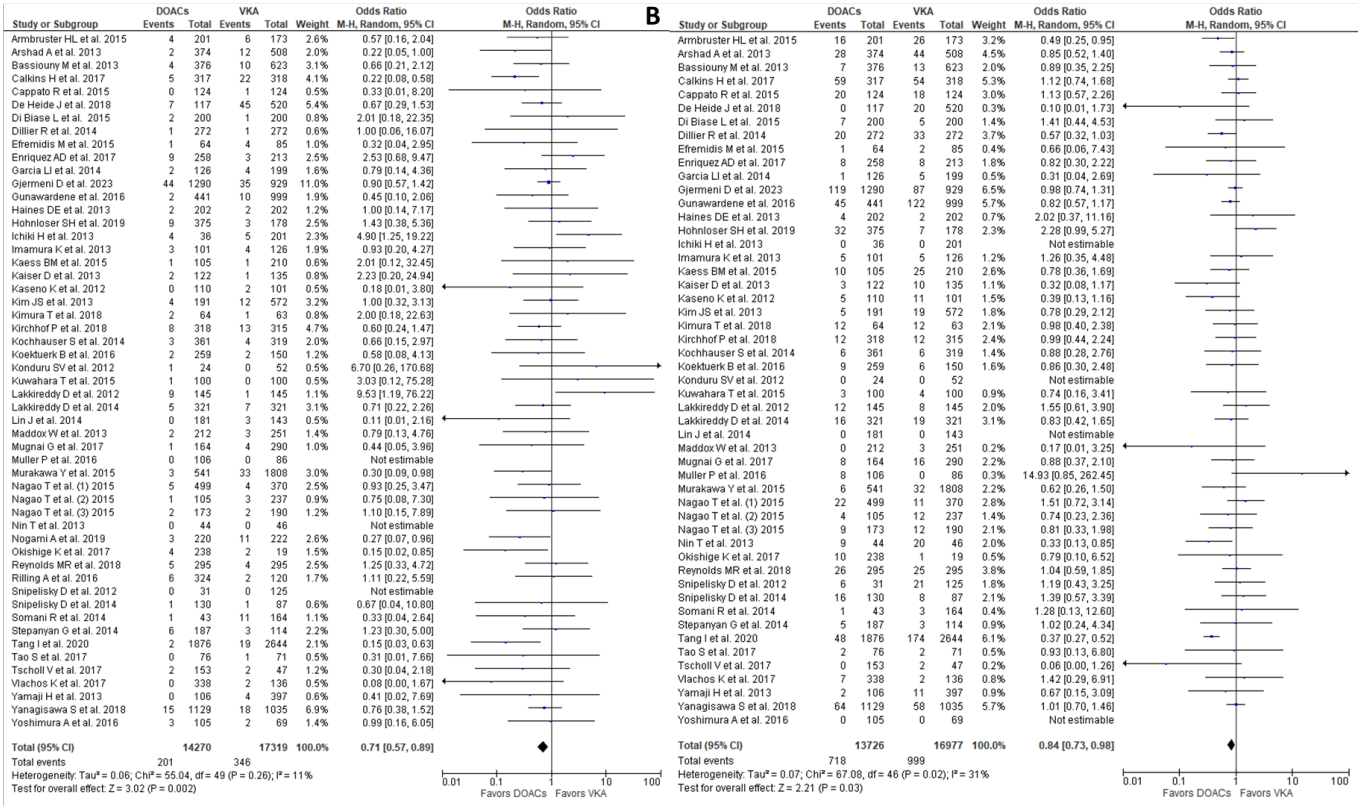


Figure 6 - Major (A) and Minor (B) Bleeding Complications – Entire Cohort.

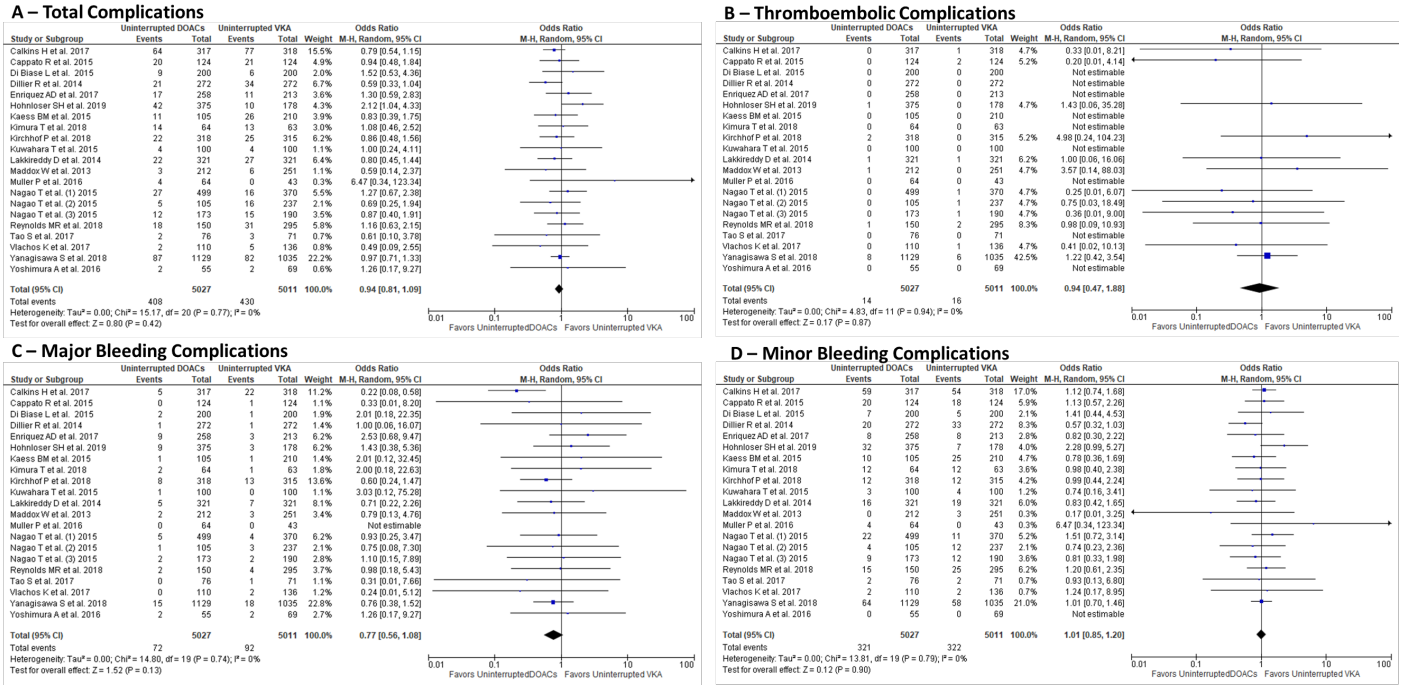


Figure 7 - Complications Uninterrupted DOACS vs. Uninterrupted VKA.

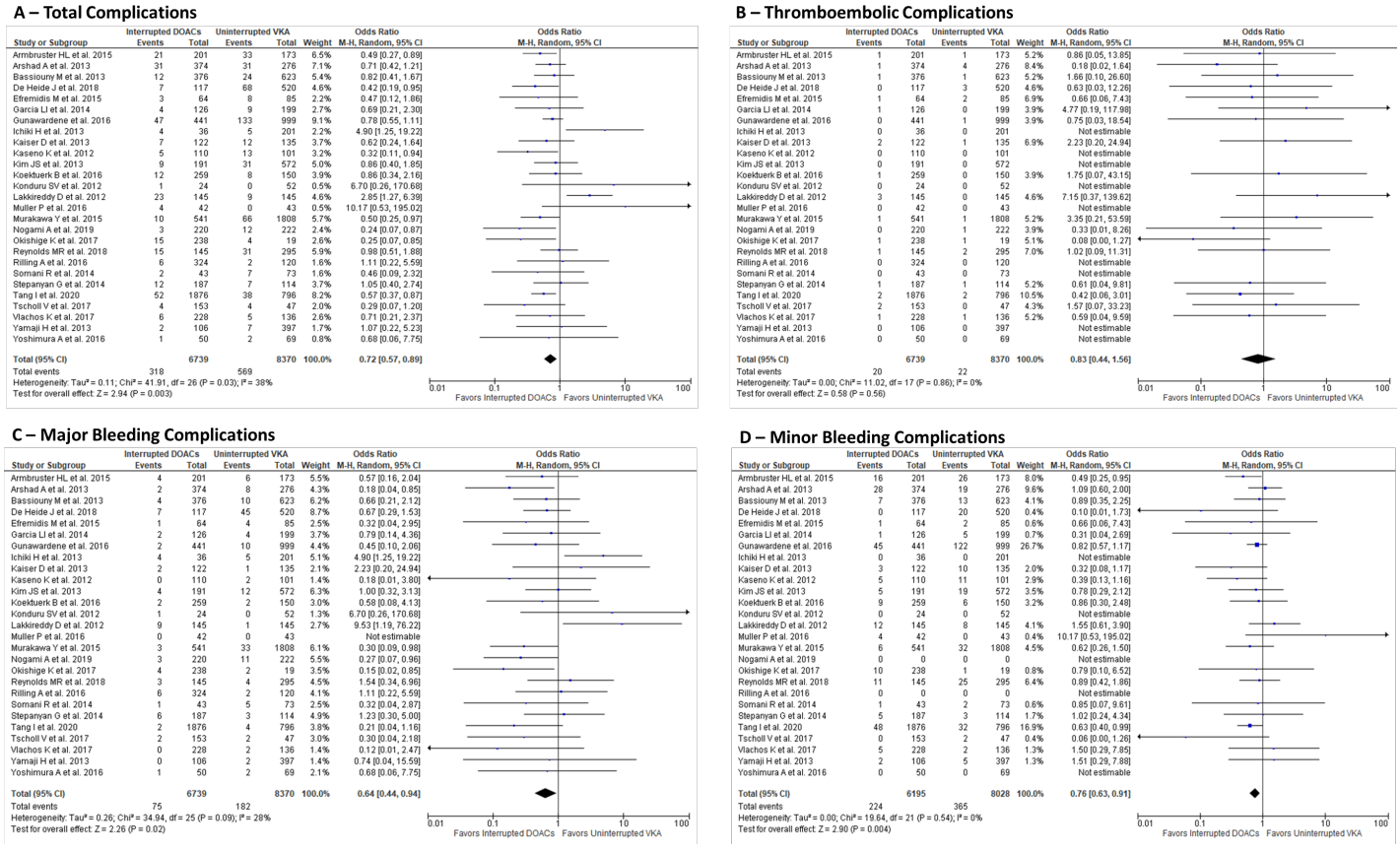


Figure 8 - Complications Interrupted DOACS vs. Uninterrupted VKA.

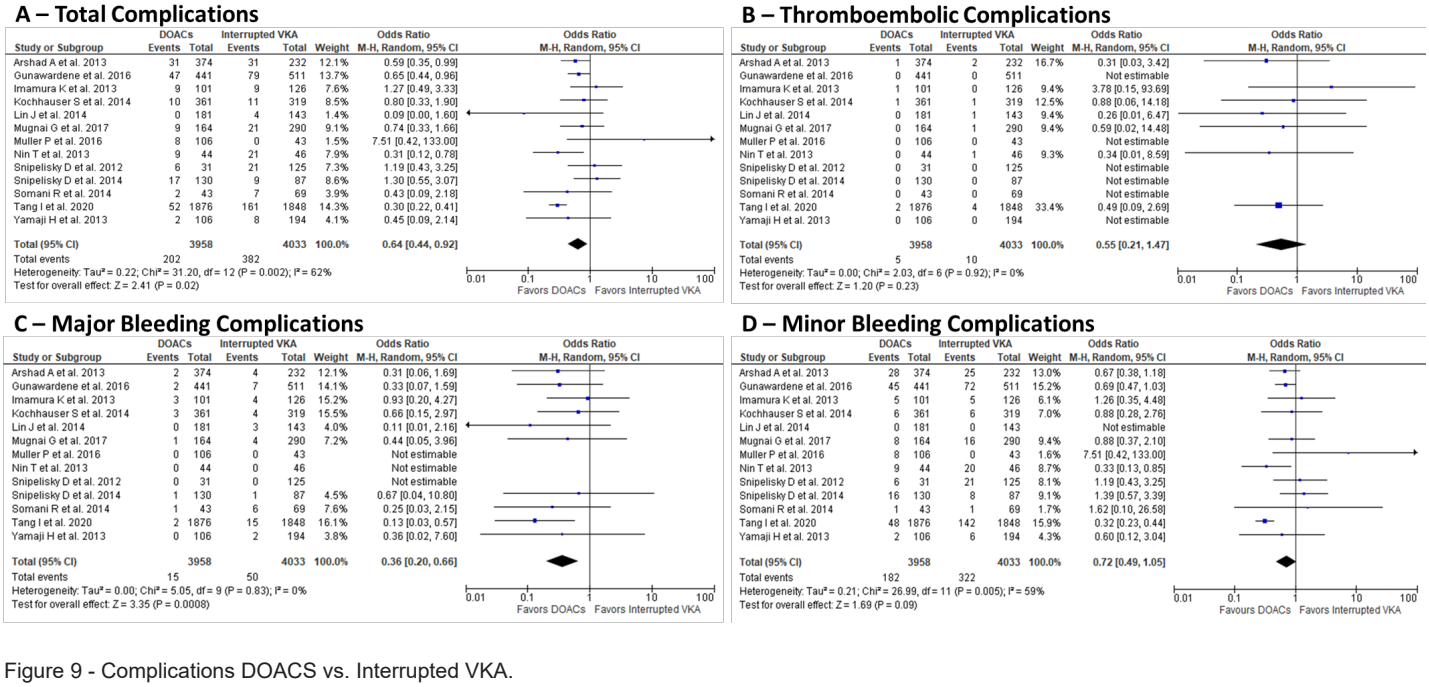


Figure 9 - Complications DOACS vs. Interrupted VKA.

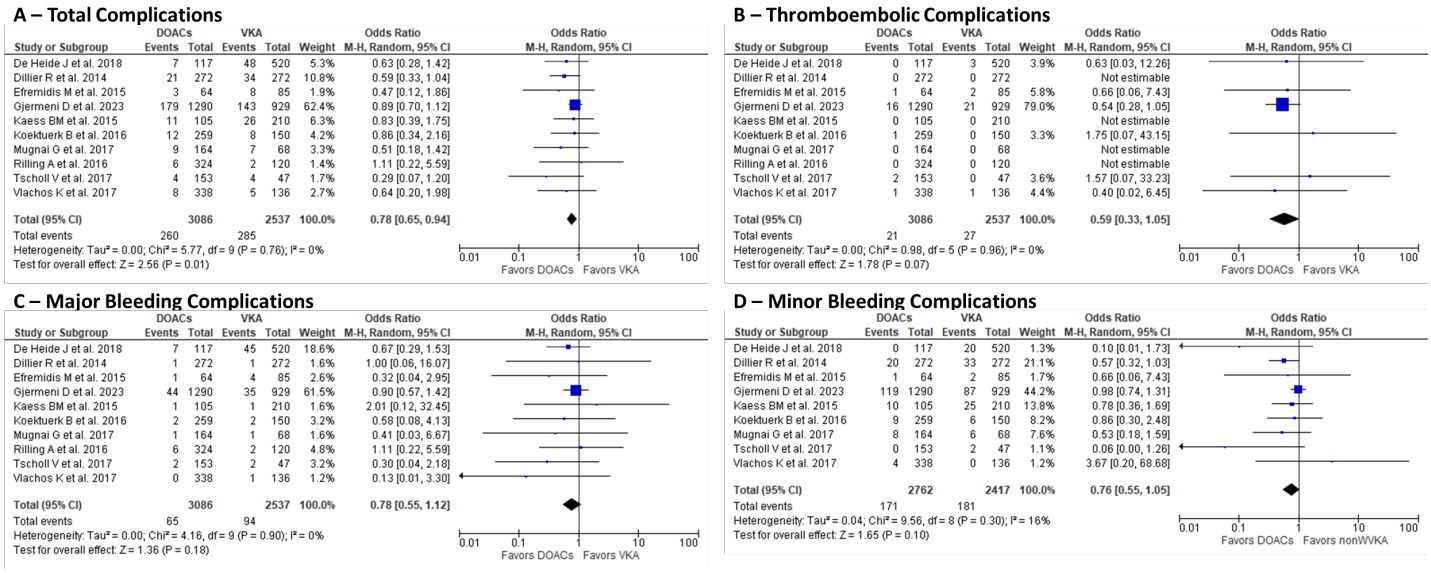


Figure 10 - Complications DOACS vs non-Warfarin VKA.

and thromboembolic complication rates between the groups. (Figure 11 B) There were 153 complications (8.9%) in the A group and 296 complications (9.2%) in the VKA group, with no significant difference in the rates of total, bleeding, and thromboembolic complications between the groups (Figure 11C).

Discussion

This meta-analysis demonstrates that interrupted DOACS regimens are superior to uninterrupted VKA regimens in reducing bleeding complications, with no increase in thromboembolic events. This is the largest, with 31,589 patients, most comprehensive, and the only meta-analysis of thromboembolic and bleeding complications comparing all the available DOACS (D, R, A, and E) with VKA as peri-ablation anticoagulation strategies. To our knowledge, it included all published full-text series through October 2023, which enrolled patients with consistent anticoagulation regimens pre- and post-ablation.

The major findings of our study included: 1) Overall, the DOACS peri-AF ablation anticoagulation strategy is superior to VKA with a significant decrease in bleeding complications and similar thromboembolic complications. 2) Uninterrupted regimes with DOACS and VKA yielded similar total, bleeding, and thromboembolic events. 3) Interrupted DOACS regimen was superior to uninterrupted VKA with lower bleeding complications, and no increase in thromboembolic complications. 4) DOACS strategy was superior to non-WVKA regimens for total complications. 5) DOACS regimen had lower bleeding complications compared to interrupted VKA. 6) D peri-AF ablation resulted in lower complications than VKA, driven by a decrease in post-procedural bleeding. The R and A had complications similar to those of VKA.

This is the first meta-analysis to show that an interrupted DOACS regimen is superior to an uninterrupted VKA (Central Figure).

Important for the interpretation and the reliability of the results, our analysis did not find any strong evidence in favor of publication bias in the dataset of trials included.

The initial concerns of increased total complications with D, raised by Lakkireddy et al[15] and Ichiki et al[16] studies, are not supported in the current meta-analysis. Those prior results were driven by an unusually high incidence of cardiac tamponade and pericardial effusions in the D group [15 in 145 patients (10%),[15] and 4 in 36 patients (11.1%)[16], respectively]. It is notable that patients in these series underwent extensive AF ablation, which may not be representative of the experiences of other centers. Interestingly enough, the strategy of interrupted DOACS yielded better results than uninterrupted regimens, likely due to the lower incidence of bleeding found in patients taking D compared with those on A and R. The vast majority of patients taking D had at least one dose of medication held before the procedure (> 80%), in contrast, the medication was uninterrupted in > 75% of patients taking the A and R.

9. Prior meta-analyses of DOACS vs VKA

Several other meta-analyses were published that compared DOACS with VKA, mainly W. The current meta-analysis included all the studies in these prior analyses if they conformed to the inclusion criteria of our study. No prior meta-analysis has compared specifically the continuous and interrupted DOACS and VKA regimens, which are still widely used in clinical practice. During the effort to acquire all relevant published data, we also found that some previous meta-analyses failed to include all the studies reported during their specified search periods or had restrictive searching criteria. Several of the prior meta-analyses included studies with inconsistent anticoagulation strategies pre vs. post ablation, with change from VKA to DOACS, or fully interrupted peri-procedural anticoagulation, thus introducing selection bias in their results.

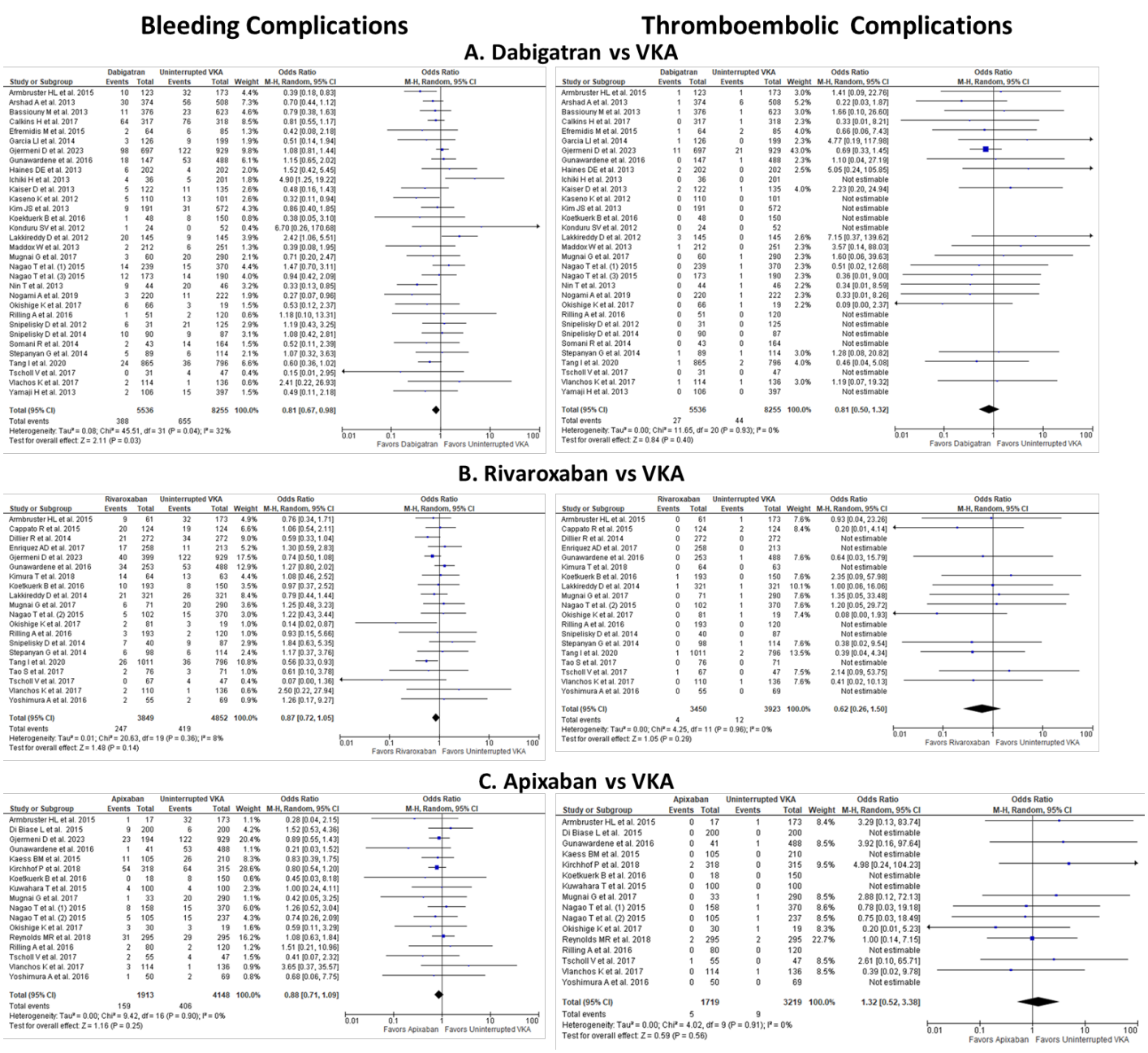


Figure 11 - Bleeding and Thromboembolic Complications of Dabigatran, Rivaroxaban, Apixaban Compared to VKA.

One of the first meta-analyses of D vs W published by Steinberg[70] reported similar composite total complications, but with the D group having a higher incidence of thromboembolic events, the only meta-analysis to reach this conclusion, most likely due to a small number of studies included. Rui Providencia[71] included studies using periprocedural D and W, which demonstrated no difference in thromboembolic events or major bleeding and a lower incidence of minor bleeding with D use. Several other early meta-analyses of D vs. W[72–74] showed no difference in the thromboembolic or bleeding complications.

Subsequent meta-analyses by Aryal[75] and Phan[76,77] that included R and D comparing with W strategies, showed comparable safety with all 3 strategies, but these analyses included either studies with significant changes amongst pre- and post-procedural anticoagulation strategies, or a post hoc analysis of the Rocket AF study that lumped together patients post-electrical or pharmacologic cardioversion with AF ablation patients[78]. Thus the results of these meta-analyses have to be interpreted with caution as might be skewed given such inhomogeneous groups.

More recent meta-analyses by Ukaigwe[79], Lu[80] and Bladino[81], comparing either interrupted or uninterrupted A to W demonstrated similar bleeding and thromboembolic events between the two groups.

Overall, the results of these meta-analyses are mixed, based on the series included, the majority of which show no benefit

of uninterrupted or interrupted DOACS over VKA, and one reported an increased thromboembolic event with DOACS. Thus, a more comprehensive meta-analysis, including more patients and consistent anticoagulation protocols, helps provide a better understanding of the benefits and risks of different anticoagulation protocols. In our meta-analysis, we have shown a significant benefit from DOACS over VKA.

10. Interrupted vs. uninterrupted VKA

The peri-procedural strategy at the beginnings of AF ablation was interrupted W with heparin bridging, however several studies, including a randomized trial, Di Biase[6], and 2 meta-analyses, by Santangeli[7] in 2012 and more recent one by Bawazeer[82] in 2021 suggested that uninterrupted VKA is safe and superior to bridged VKA strategy with less thromboembolic events without significant increase in bleeding complications. However, other studies, including one of the studies from the current meta-analysis, Arshad et al.[19], found a higher percentage of major complications with uninterrupted W arm (4.3%), driven by major bleeding, when compared with both bridged W (2.6%) or D (0.8%) arms. There are some proponents of interrupted peri-procedural anticoagulation, without bridging, or only post-procedural anticoagulation, especially in low stroke risk patients. Winkle et al.[83] evaluated interrupted peri-procedural anticoagulation in 2334 patients and found a low rate of total peri-procedural complications (1.5%) with a 0.3% TIA/stroke rate using this strategy.

The use of the interrupted VKA strategy has faded lately. However, there are still sites using interrupted anticoagulation to avoid cancellation of the procedure due to supra- or subtherapeutic INR and some operators' perception of safer management of intraprocedural major bleeding complications without the anticoagulation effect of VKA.

The studies included in this meta-analysis reflect real-world practice, with a large variance regarding the timing of holding the VKA strategy studies, which had different timing and bridging modalities. Our meta-analysis, which included more than 4000 patients with interrupted VKA, showed a significant increase in major bleeding events compared with DOACS.

Current guidelines[1] We recommend a continuous anticoagulation strategy peri-procedural for atrial fibrillation ablation with a class I indication. In our meta-analysis, we found no difference in complication rates between uninterrupted DOACS and uninterrupted VKA.

11. Interrupted vs. Uninterrupted DOACS

In the current practice, most patients are on DOACS, and it is unclear if continuous or minimally interrupted without a bridging strategy is better. There is a concern that uninterrupted anticoagulation may lead to a higher risk of access site bleeding or cardiac tamponade. The minimally interrupted DOACS approach, with no bridging may theoretically reduce these risks without significantly compromising thromboembolic protection. Proponents of the minimally interrupted strategy argue that a brief discontinuation of DOACS may reduce bleeding complications during catheter manipulation without significantly increasing the risk of thromboembolism. Although hard to rigorously prove in a trial, skipping 1 or 2 doses might decrease the severity of a complication such as cardiac tamponade, were it to happen, and possibly make managing such complications easier to handle.

A trial by Nakamura[84] randomized 846 patients to either uninterrupted or interrupted (the day of the procedure and restarted the next morning) DOACS and showed no differences in bleeding or thromboembolic events. In addition, a 2021 meta-analysis by van Vugt[69] including 2168 patients evaluating strategies of minimally interrupted versus uninterrupted DOACS administration found no difference in bleeding nor in embolic complications.

In our meta-analysis, there was a large variability in peri-procedural DOACS strategies, with 5027 patients on uninterrupted DOACS and 6739 patients using a minimally interrupted DOACS strategy. There was no difference in the thromboembolic or bleeding incidence when compared with uninterrupted DOACS and uninterrupted VKA regimen; however, the minimally interrupted DOACS had a significantly lower incidence of major bleeding events compared with uninterrupted VKA, with no increase in thromboembolic complications.

Despite the lack of guideline recommendations on the minimally interrupted use of DOACS, this strategy is increasingly adopted in clinical practice. Our data suggests that minimally interrupted DOACS use may be a reasonable strategy for reducing bleeding risk without increasing thromboembolic complications. Further large-scale studies are needed to precisely define the optimal periprocedural anticoagulation strategy, especially in high-risk patient populations.

12. Limitations

This study's limitations are those inherent to any meta-analysis. The data analyzed emanates mainly from observational studies, with only a minority of the trials being randomized, controlled, or prospective. One third of the trials were reported in abstract format, and despite best attempts to gather information, including direct contact with the author, some data remained incomplete. The lack of evidence for publication bias provides reassurance regarding the robustness of our broad inclusion strategy. There is a significant variability among individual studies, translating into heterogeneity in the reported data for total and bleeding complications (I^2 ~ 30). The meta-analysis could not control the variation of practices among different institutions or other factors that might alter the risk for complications, including operator experience, ablation strategies and duration, TEE and ICE usage, and patient risk factors. Nonetheless, the very large sample protects against some of these potential biases.

Conclusion

This meta-analysis demonstrates in over 31,500 patients that DOACS are a great alternative to VKA in patients undergoing ablation for AF with lower bleeding rates. There is no significant increase in thromboembolic events and a decrease in total complications.

Minimally interrupted DOACS proves to be a viable strategy, with lower bleeding complications than uninterrupted VKA and similar risk for thromboembolism. Future studies should determine the optimal time to stop and restart of the DOACS relative to the ablation.

Ethics approval and consent to participate

This study does not require institutional review board approval.

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Conflicts of Interest

The authors declare no conflict of interest.

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