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Benefits and Risks Associated with Long-term Oral Anticoagulation after Successful Atrial Fibrillation Catheter Ablation: Systematic Review and Meta-analysis

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Abstract

Oral anticoagulation (OAC) prevents thromboembolism yet greatly increases the risk of bleeding, inciting concern among clinicians. Current guidelines lack sufficient evidence supporting long-term OAC following successful atrial fibrillation catheter ablation (CA). A literature search was performed in PubMed, Google Scholar, Medline, and Scopus to seek out studies that compare continued and discontinued anticoagulation in post-ablation Atrial fibrillation (AF) patients. Funnel plots and Egger's test examined potential bias. Via the random-effects model, summary odds ratios (OR) with 95% confidence intervals (CI) were calculated using RevMan (5.4) and STATA (17.0). Twenty studies, including 22 429 patients (13 505 off-OAC) were analyzed. Stratified CHA_2DS_2-VASc score ≥ 2 examining thromboembolic events (TE) favored OAC continuation (OR 1.86; 95% CI: 1.02-3.40; $P = .04$). Sensitivity analysis demonstrated this association was attenuated. The on-OAC arm had greater incidence of major bleeding (MB) (OR 0.16; 95% CI: 0.08-0.95; $P < .00001$), particularly intracranial hemorrhage (ICH) and gastrointestinal bleeding (GI); (OR 0.17; 95% CI: 0.08-0.36; $P < .00001$) and (OR 0.12; 95% CI: 0.04-0.32; $P < .0001$), respectively. Our findings support sustained anticoagulation in patients with a CHA_2DS_2-VASc score of ≥ 2. Due to reduced outcome robustness, physician discretion is still advised.

Keywords

atrial fibrillation, Catheter ablation, oral anticoagulants, thromboembolism, major bleeding

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Introduction

Atrial fibrillation (AF), the most common cardiac arrhythmia worldwide, is associated with increased mortality and morbidity.[1–3] Its 3-5-fold increased mortality rate is primarily attributed to the increased risk of thromboembolic events (TE).[4] Catheter ablation (CA) has proven to be an effective rhythm control treatment by reducing TE risk in patients who have failed class I or III antiarrhythmic drug therapy.[1–3,5,6] CA is considered a safe intervention when performed by competent operators. However, periprocedural thromboembolic and hemorrhagic events may occur within weeks to months following the procedure.[1–3]

The current clinical practice guidelines (CPG) recommend oral anticoagulation (OAC) therapy for a minimum of 2 months post-CA regardless of stroke risk factors to prevent

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TE complications.[3] The decision to discontinue OACs is solely based on the patient's comorbidity status, stroke risk (CHA_2DS_2-VASc score; Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, prior Stroke or transient ischemic attack (TIA) or thromboembolism (2 points), Vascular disease, Age 65 to 74 years, Sex category), and bleeding risk (HAS-BLED score; Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile INR, Elderly (>65), Drugs/alcohol). Patients deemed with a high risk of stroke (ie, CHA_2DS_2-VASc score ≥2 in males or ≥3 in females/prior history of stroke) are recommended to remain on OACs. Despite the increased risk of major bleeding (MB), long-term OAC therapy is likewise recommended for intermediate stroke risk patients (CHA_2DS_2-VASc score 1 in males or 2 in females). Thus, raising the question of whether the benefits of OACs outweigh the risks in these risk groups.

Previous systematic reviews were primarily based on research conducted during the warfarin era, thereby underrepresents the current clinical setting in which direct oral anticoagulants are widely used.[7,8] This review further analyzes the types of TE and MB, namely intracranial hemorrhage (ICH), gastrointestinal bleeding (GI), intramuscular bleeding (IM) and other bleeding events following ablation in both comparison groups. Sensitivity analysis was used to test the robustness of the results. By pooling the latest data pertaining to TE and MB in patients on-OACs and off-OACs, this study examines the real-world risks and benefits of long-term OAC therapy post-CA.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines.[9] A review protocol was not registered for this review.

Data Sources and Search Strategy

A literature search was performed from PubMed, Google Scholar, Medline (via Ovid), and Scopus (from inception till April 20, 2022) for articles comparing continuation versus discontinuation of OACs post-ablation. The PICO (Population, Intervention, Comparison, and Outcomes) method was used to formulate the search strategy.[10] AF patients following a successful CA reflected population, discontinuation of OAC as intervention, continuation of OAC as a comparison, and thromboembolism and bleeding events as the outcome(s). The search was performed with no restriction to language, study type, or limit to the year of publication. The following keywords and medical subject heading (MeSH) terms were included: "atrial fibrillation," "Atrial Fibrillation (MeSH)," "CA," "CA (MeSH)," "ablation," "anticoagulation," "anticoagulant," "Anticoagulants (MeSH)," "warfarin," "Warfarin (MeSH)," "novel oral anticoagulants," "NOAC," "Off-OAC," and "Off-OAT." To ensure the inclusion of relevant studies, the reference lists of the identified studies, guidelines, and review articles were examined further.

Study Selection

Evaluation and selection of studies were undertaken independently by two authors (K.M and M.M). Studies were identified according to the following inclusion criteria: (1) compared continued anticoagulation and discontinued anticoagulation in AF patients after successful CA, (2) reported outcomes of interest. Primary outcomes: TE; ischemic stroke, TIA, systemic embolism (SE). Secondary outcome: MB; ICH, GI, IM and other (including retinal, genitourinary, rectal, retroperitoneal bleeding, splenic rupture, liver cyst hemorrhage, epistaxis, and bleeding from skin graft). The exclusion criteria: (1) Case reports, review articles, expert opinions, abstracts, and letters to the editor (2) failure to report the aforementioned outcomes of interest. Disagreements about study inclusion or exclusion were handled by the supervising author (J.Z).

Quality Assessment

Two authors independently assessed the quality of the titles, abstracts, and full texts from the literature. Disagreement was resolved by discussion and further evaluation by a third author. Quality assessment of selected studies was evaluated using the Newcastle-Ottawa scale (NOS),[11] which assigns points for the least risk of bias in three domains: (1) study group selection, (2) comparability of groups and (3) ascertainment of exposure and outcomes. The maximum score of these 3 domains is 9. A study score ≥7 is considered high-quality, with lower scores indicating potential bias in the study design. Funnel plots were visually inspected for asymmetry, and the Egger's test was used to measure publication bias due to small study effects ($P > .05$, no significant bias).[12]

Data Extraction

Relevant data were extracted independently by two authors from the studies that met the inclusion criteria; first author, publication year, study design, sample size, age, gender, mean follow-up, AF type, time of OAC discontinuation, $CHADS_2$ and CHA_2DS_2-VASc score, HAS-BLED score, blanking period, AF recurrence during follow-up, ablation energy, number of patients in the off-OAC/on-OAC group, and outcomes of interest (ie, TE, ischemic stroke, TIA, SE, MB, ICH, GI, IM and other bleeding events). The aforementioned data were entered into Tables 1 and 2.

Statistical Analysis

From the extracted data, thromboembolic and MB events form the cornerstone of this project, both of which were comparatively calculated from off-OAC and on-OAC groups. Raw data from the individual studies were reported as odds ratios and their respective 95% CI. The meta-analysis was calculated

Table 1. Baseline Characteristics of Included Studies.

Author (year) country	Study design	Type of OAC	Sample size	Age (years)	Male N (%)	Mean follow up (years)	Paroxysmal AF (%)	Time of OAC discontinuation (months)	$CHADS_2$/ CHA_2DS_2-VASc score Off-OAC (mean)	$CHADS_2$/ CHA_2DS_2-VASc score On-OAC (mean)	HAS-BLED score (mean)	Blanking period (months)	Ablation energy	AF recurrence during follow-up	Quality (NOS)
1.Hermida (2020) France	Prospective (Single center)	Warfarin/ DOACs	450	60 ± 9	351 (78%)	2.5	242 (54%)	3	0.7 ± 1.0[a]	1.8 ± 1.3[a]	NA	3	Cryo	180 (40%)	9
2.Yang (2019) China	Prospective (Multicenter)	Warfarin/ DOACs	4512	Off-OAC 62.8 ± 9.9 On-OAC 64.1 ± 9.8	2864 (63.5%)	Off-OAC 2.0 ± 1.2 On-OAC 1.9 ± 1.1	3119 (69.1%)	3	2.3 ± 1.3[a]	2.7 ± 1.4[a]	Off-OAC 1.7 ± 0.8 On-OAC 2.3 ± 1.3	NA	RF	Off-OAC 824 On-OAC 468	9
3.Winkle (2013) USA	Prospective (Single center)	Warfarin/ DOACs	108	66.2 ± 9.0	68 (62.9%)	2.8 ± 1.6	40 (37%)	3	NA	NA	NA	3	RF	37 (34.2%)	7
4.Hussein (2011) USA	Prospective (Single center)	Warfarin	831	58.7 ± 9.9	644 (77.5%)	4.6[b]	482 (58%)	NA	NA	NA	NA	2	RF	272 (32.7%)	9
5.Hunter (2011) (UK/Australia)	Prospective (Multicenter)	Warfarin	1273	58 ± 11	942 (74%)	3.1	(56%)	3	0.7 ± 0. 9 (71%)	0.9 ± 0.9 (69%)	NA	3	RF + Cryo	NA	5
6.Nademanee (2008) USA	Prospective (Single center)	Warfarin	635	67 ± 12	423 (66.5%)	2.3 + 1.7	254 (40%)	3	NA	NA	NA	3	RF	118 (18.5)	9
7. Oral (2006) USA	Prospective (Single center)	Warfarin	755	55 ± 11	577 (76.4%)	2.1 ± 0.7	490 (64.9%)	3	0 = 53% ≥1 = 47%	0 = 37% ≥1 = 63	NA	2	RF	233 (30.9%)	9
8.Yu (2020) China	Retrospective (Multicenter)	Warfarin/ DOACs	1491	59.6 ± 12.1	918 (61.6%)	2.3 ± 1.2	1491 (100%)	3	1.5 ± 1.4[a]	2.4 ± 1.7[a]	NA	NA	RF	159 (10.7%)	9
9.Arai (2019) Japan	Retrospective (Single center)	Warfarin/ DOACs	512	63.4 ± 10.4	389 (76%)	2.3 ± 1.4	278 (54%)	3	1.76 ± 1.40[a]	2.57 ± 1.55[a]	NA	3	RF + Cryo	200 (39.1%)	9
10. Kochhäuser (2017) Canada	Retrospective (Single center)	Warfarin/ DOACs	398	60.7 [b]	300(75.4%)	1.0 ± 3.0	279 (70.1%)	3	1 ± 1[a]	2.5 ± 1.3[a]	NA	3	RF	55 (13.8%)	7
11.Själander (2017) Sweden	Retrospective (Multicenter)	Warfarin	1175	59 ± 9.4	1157 (73%)	2.6[b]	NA	NA	NA	NA	Off-OAC+ On-OAC: 1.3	NA	NA	NA	9
12.Liang (2018) USA	Retrospective (Single center)	Warfarin/ DOACs	400	60.3 ± 9.7	162 (81%)	3.6 ± 2.4	0 (0%)	NA	0 or 1 = 46.5% ≥2 = 53.5%[a]	0 or 1 = 77.6% ≥2 = 22.4%[a]	Off-OAC 1.11 On-OAC 1.65	NA	NA	298 (72.3%)	8
13.Gallo (2016) Italy	Retrospective (Multicenter)	Warfarin	1000	Off-OAC 60 ± 10 On-OAC 64 ± 8	Off-OAC 361 On-OAC 323	5.0 ± 2.3	510 (51%)	3	1.9 ± 0.9[a]	2.4 ± 1[a]	NA	2-3	NA	299 (29.9%)	9
14.Riley (2014) USA	Retrospective (Single center)	Warfarin	1990	Off-OAC 55 ± 11 On-OAC 60 ± 9.6	Off-OAC 808 On-OAC 727	4.1 ± 2.4	1307 (65.7%)	NA	0 = 53% 1 = 37% ≥2 = 10% (0.6)	0 = 34% 1 = 48% ≥2 = 18% (0.9)	NA	NA	NA	NA	8
15.Gaita (2014) USA	Retrospective (Single center)	Warfarin	766	57 + 11	612 (79.9%)	5[b]	326 (42.6%)	3	≤1 = 92% ≥2 = 8% 1.3[a] (1.06)	≤1 = 70% ≥2 = 30% 2.6[a] (1.30)	Off-OAC ≤1 = 89.4% ≥2 = 10.6% On-OAC ≤1 = 59.6% ≥2 = 40.4%	3	RF	NA	9
16. Uhm (2014) Korea	Retrospective (Single center)	Warfarin	608	57.3 ± 10.9	468 (77%)	1.5 ± 1	(75.5%)	3	2.78 ± 1[a]	2.82 ± 0.98	Off-OAC 1.37 ± 0.83 On-OAC 1.45 ± 1.02	3	RF	NA	9
17.Guiot (2012) USA	Retrospective (Single center)	Warfarin	1016	70 ± 4	728	2.8 ± 2	613 (60.3%)	3	NA	NA	NA	3	RF	290 (28.5%)	8
18.Yagishita (2011) Japan	Retrospective (Single center)	Warfarin	524	60 ± 10	427 (81%)	3.6 ± 1.1	524 (100%)	3	0 = 49% 1 = 36% ≥2 = 15% (0.66)	0 = 46% 1 = 36% ≥2 = 18% (0.72)	NA	2	RF	95 (22%)	7
19.Themistoclakis (2010) USA	Retrospective (Multicenter)	Warfarin	3355	57 ± 11	2579 (77%)	2 + 1	2022 (60%)	3-6	0 = 60% 1 = 27% ≥2 = 13% (0.4)	0 = 23% 1 = 39% ≥2 = 38% (1.15)	NA	3	NA	552 (16.6%)	9
		Warfarin	630	Off-OAC	Off-OAC	0.1 ± 1.0	325 (51.6%)	3			NA	3	RF	NA	7

(continued)

Table 1. (continued)

Author (year) country	Study design	Type of OAC	Sample size	Age (years)	Male N (%)	Mean follow up (years)	Paroxysmal AF (%)	Time of OAC discontinuation (months)	$CHADS_2$/ CHA_2DS_2-VASc score Off-OAC (mean)	$CHADS_2$/ CHA_2DS_2-VASc score On-OAC (mean)	HAS-BLED score (mean)	Blanking period (months)	Ablation energy	AF recurrence during follow-up	Quality (NOS)
20. Bunch (2009) USA	Retrospective (Single center)			59.8 ± 10.7 On-OAC 66.0 ± 10.1	81 On-OAC 294				0 = 41% 1 = 59% (0.6)	0 = 14% 1 = 32% 2 = 25% ≥3 = 29.0%					

Abbreviations: Cryo, cryo-balloon; CHADS2, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/TIA/thromboembolism (2 points); CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, previous Stroke/TIA/thromboembolism (2 points), Vascular disease, Age 65 to 74 years, Sex category; DOAC, direct oral anticoagulation; NA, data not available; NOS, Newcastle-Ottawa Scale; OAC, oral anticoagulant; RF, radiofrequency.

[a]CHA2DS2-VASc score.

[b]Median.

Table 2. Summary of Outcomes of Included Studies.

Study (year) sample size	Post-ablation treatment	Total embolic events	Ischemic stroke	TIA	SE	Total major bleeding events	ICH	GI	IM	Other bleeding
1.Hermida (2020)	Warfarin/DOACS (375)	4	3	0	1	—	—	—	—	—
450	Off-OAC (75)	2	0	2	0	—	—	—	—	—
2.Yang (2019)	DOACS (1363)	22	19 (2 Fatal)	—	3	9	4	—	—	5
4512	Off-OAC (3149)	34	23	—	11	12	3	—	—	9
3.Winkle (2013)	Warfarin/DOACs (48)	1	0	0	1	9	—	2	—	7
108	Off-OAC (60)	0	0	0	0	0	—	0		0
4.Hussein (2011)	Warfarin (382)	0	0	—	—	—	—	—	—	—
831	Off-OAC (449)	1	1	—	—	—	—	—	—	—
5.Hunter (2011)	Warfarin (464)	16	—	—	—	10	5 (2 Fatal)	—	—	5
1273	Off-OAC (809)	4	—	—	—	2	1	—	—	1
6.Nademanee (2008)	Warfarin (201)	6	6	0	—	—	—	—	—	—
635	Off-OAC (434)	5	3	2	—	—	—	—	—	—
7. Oral (2006)	Warfarin (357)	2	1	—	1	2	—	—	—	—
755	Off-OAC (398)	0	0	—	0	0	—	—	—	—
8.Yu (2020)	Warfarin/DOACs (502)	11	—	—	—	13	—	—	—	—
1491	Off-OAC (989)	26	—	—	—	11	—	—	—	—
9.Arai (2019)	Warfarin/DOACS (282)	7	6	1	—	9	3	5	1	—
512	Off-OAC (230)	3	2	1	—	1	0	1	0	—
10. Kochhäuser (2017)	Warfarin/DOACs (122)	3	—	—	—	—	—	—	—	—
398	Off-OAC (276)	1	—	—	—	—	—	—	—	—
11.Själander (2017)	Warfarin (815)	5	5	—	—	3	3	—	—	—
1175	Off-OAC (360)	6	6	—	—	0	0	—	—	—
12.Gallo (2016)	Warfarin (500)	5	—	—	—	9	4	5	—	—
1000	Off-OAC (500)	7	—	—	—	0	0	0	—	—
13.Liang (2018)	Warfarin/DOACs (226)	4	3	1	—	14	3	9	1	1
400	Off-OAC (174)	3	2	1	—	0	0	0	0	0
14.Gaita (2014)	Warfarin (267)	6	—	—	—	7	5	2	—	—
766	Off-OAC (499)	5	—	—	—	0	0	0	—	—
15.Uhm (2014)	Warfarin (312)	3	1	2	—	2	—	—	—	—
608	Off-OAC (296)	1	1	0	—	2	—	—	—	—
16.Riley (2014)	Warfarin (959)	8	2	6	—	13 (1 Fatal)	7	—	1	5
1990	Off-OAC (1031)	8	4	4	—	1	1	—	0	0
17.Guiot (2012)	Warfarin (455)	10	—	—	—	4	4	—	—	—
1016	Off-OAC (561)	10	—	—	—	0	0	—	—	—
18.Yagishita (2011)	Warfarin (124)	2	2	0	—	2	—	1	1	—
524	Off-OAC (400)	1	0	1	—	0	—	0	0	—
19.Themistoclakis (2010)	Warfarin (663)	3	—	—	—	13	2	11	—	1
3355	Off OAC (2692)	2	—	—	—	1	0	0	—	0
20.Bunch (2009)	Warfarin (507)	5	4	0	1	2 (2 Fatal)	1	1	—	—
630	Off-OAC (123)	0	0	0	0	0	0	—	—	—

Abbreviations: DOAC, direct oral anticoagulation; OAC, oral anticoagulants; SE, systemic embolism; TIA, transient ischemic attack.

by the Mantel-Haenszel method using the DerSimonian and Laird random-effects model,[13] presented as forest plots. A subgroup analysis was performed comparing TE by CHA_2DS_2-VASc score stratification and TE, MB and ICH/GI events between studies reporting patients on direct-acting oral anticoagulants (DOACs) and warfarin versus warfarin alone. Assessment of heterogeneity was measured by Chi^2, Tau^2, and I^2, wherein I^2, 25–50%, 50–75%, and >75% indicated low, moderate, and high heterogeneity, respectively. Leave-one-out sensitivity analyzes were conducted to examine the robustness of the main findings. Statistical analyzes were performed using the Cochrane Collaborative

software, RevMan (5.4),[14] and STATA (17.0) (StataCorp, College Station, TX, USA). A P-value < .05 was indicative of statistical significance.

Results

Study Screening

Electronic database literature search and screening of reference lists yielded 9019 articles. After removing duplicates, a review of abstracts and titles of the remaining 3891 led to the exclusion of 3847 based on a lack of adherence to our inclusion criteria. Following title and abstract screening, 44 articles were considered potentially relevant and underwent full-text review. Finally, a total of 20 studies were included (n = 22 492), of which 7 were prospective,[15–21] and 13 were retrospective observational studies.[22–34] The search strategy is illustrated in a PRISMA flow diagram (Figure 1). The 2020 PRISMA abstract and main text checklist are available in Supplementary Table S1. The electronic database search strategy is illustrated in Supplementary Table S2.

Quality Assessment

The selected studies were evaluated using the NOS to assess the quality of study design and potential bias. The scores are summarized in Supplementary Table S3. Of the included twenty studies, thirteen were assigned a score of 9,[15,16,18,20–23,25–29,33] two assigned a score of 8,[30,31] four assigned a score of 7,[17,24,32,34] with the remaining assigned a score of 5.[19] Nineteen studies showed adequate representativeness of the exposed cohort.[15–30,32–34] Eighteen studies reported the absence of outcome at the start of the study.[15,16,18–33] Varied cohort comparability was observed in four studies.[17,19,24,34] Eighteen studies reported sufficient outcome assessment methods.[15–18,20–31,33,34] Follow-up rate was adequate within the cohorts in sixteen studies.[15–18,20–23,25–29,31,33,34]

Study Characteristics

The study characteristics of the 20 studies are presented in Table 1. All included studies were published between 2006 and 2020, comprising 22 429 individuals (13 505 patients off-OAC). The studies were conducted in diverse study populations, including patients from the USA, Canada, China, France, Italy, Korea, UK/Australia, Sweden, and Japan, of which fourteen are single-center,[15,17,18,20,21,23,24,27–32,34] and six multicenter.[16,19,22,25,26,33] Seven studies reported the administration of DOACs. The minimum follow-up was 12-months, with a total range of 1 to 5 years. Fifteen studies reported a 2-3 month blanking period. The most common decision to discontinue OAC therapy was sinus rhythm maintenance and a zero AF recurrence rate. All studies reported TE, including sixteen studies that documented MB events (Table 2). Seven studies that reported mean CHA_2DS_2-VASc scores showed patients in the on-OAC group had comparatively higher scores than those off-OAC 2.46 ± 1.32 versus 1.70 ± 1.14.[15,16,22–24,26,29] The included patients' age ranged from 55 to 79 years, with males making up 72.5% of the total patient population.

Thromboembolic Events

All 20 studies were included in the analysis. Among 22 429 patients, TE occurred in 242 (1.08%) patients during the follow-up, 119 (0.88%) patients in the off-OAC group and 123 (1.38%) in the on-OAC group. TE events were 0.50% more likely to occur in patients on-OAC; which did not differ in the meta-analysis, indicated by the greater odds of developing TE compared to those off-OAC (OR 0.65; 95% CI: 0.44-0.94; $P = .02$). Heterogeneity was low ($I^2 = 36\%$) (Figure 2). Based on the leave-one-out approach, this result was impacted by one study (Supplementary Table S4).[19]

Incidence of ischemic stroke, TIA, and SE were independently analyzed. By pooling the OR from 12 studies reporting ischemic stroke, an OR of 0.68 (OR 0.68; 95% CI: 0.39-1.17; $P = .16$) was derived. This demonstrated that the odds of ischemic stroke did not significantly differ between patients off-OACs and on-OACs. The same observations were made with regard to TIA and SE. The results from 7 studies that reported on TIA events and the 5 that reported on SE events exhibited no difference between the two treatment groups; (OR 1.05; 95% CI: 0.42-2.65; $P = .91$) and (OR 1.12; 95% CI: 0.41-3.05; $P = .82$), respectively (Supplementary Figure S1).

A subgroup analysis of 7 studies that reported the use of "DOACs + warfarin" did not favor either arm (OR 0.80; 95% CI: 0.52-1.23; $P = .31$) whereas, analysis of the 13 "warfarin alone" studies resulted in statistical significance among patients on-OAC (OR 0.55; 95% CI: 0.32-0.97; $P = .04$) (Supplementary Figure S2). This result points out that the odds of TE were significantly higher in studies that reported patients administered with warfarin alone.

The incidence of total TE was analyzed by stratification of the CHA_2DS_2-VASc score <2 and ≥2 in six studies. The analysis included 1930 patients off-OAC and 1363 on-OAC with a CHA_2DS_2-VASc score <2; 9 and 8 events occurred, respectively. CHA_2DS_2-VASc score ≥2 included 775 patients off-OAC and 1421 on-OAC; 21 and 23 events occurred, respectively. Generating a result supporting neither treatment arm in the < 2 group (OR 0.61; 95% CI: 0.15-2.42; $P = .48$). TE was significantly greater among patients off-OAC in the ≥2 group (OR 1.86; 95% CI: 1.02-3.40; $P = .04$) (Figure 3). The sensitivity analysis showed three studies impacted this result (Supplementary Table S5).[25,27,30]

Major Bleeding Events

Sixteen studies compared the risk of MB among the off-OAC and on-OAC groups. A total of 20 115 patients presented with an outcome of 151 (0.75%) MB events, 30 (0.24%) events in the off-OAC, and 121(1.54%) in the on-OAC group. The cumulative results showed a significantly higher

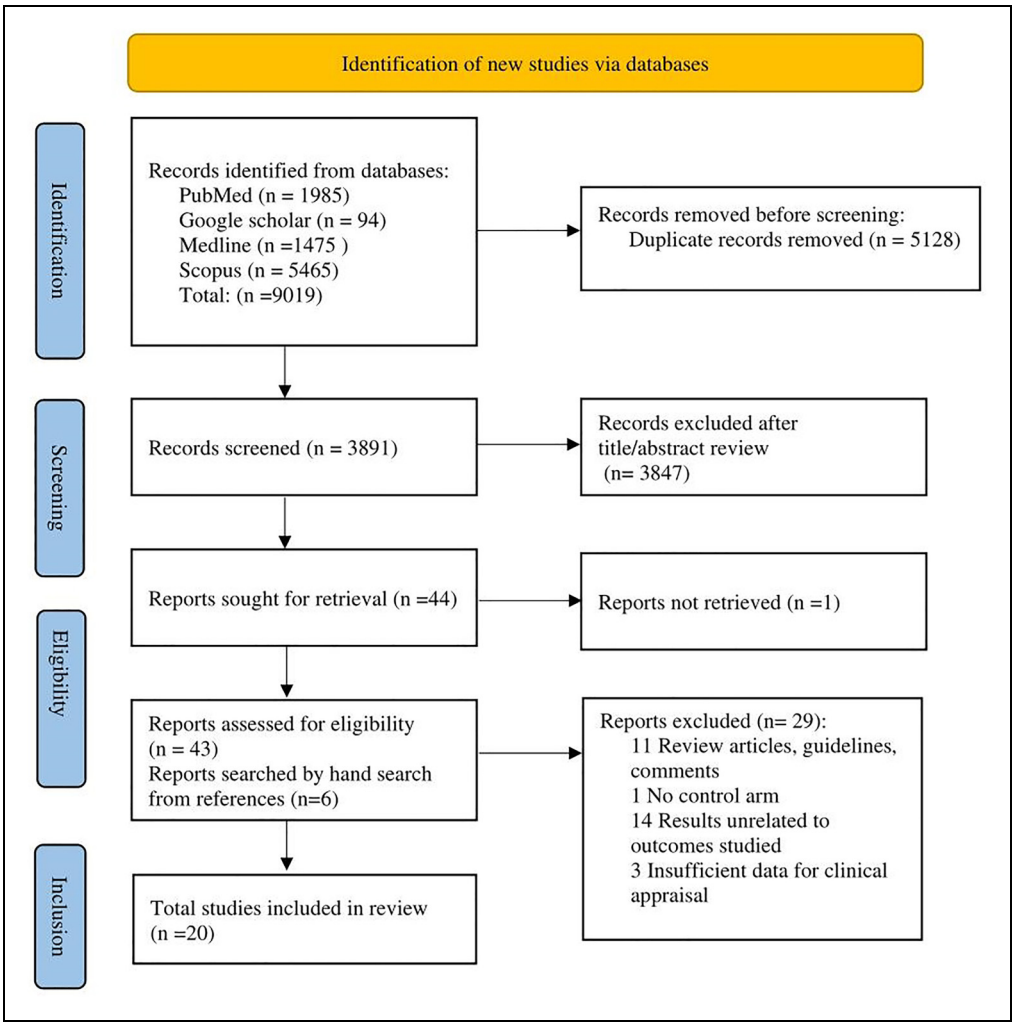

Figure 1. Search strategy and selection according to the PRISMA statement.

incidence of bleeding in the on-OAC group (OR 0.16; 95% CI: 0.08-0.31; $P < .00001$), demonstrating that patients on OACs were significantly more prone to experiencing bleeding episodes than those off-OACs. Heterogeneity was low ($I^2 = 44\%$) (Figure 4). The sensitivity analysis did not affect this result (Supplementary Table S6).

In comparison to patients off-OACs, the odds of ICH (OR 0.17; 95% CI: 0.08-0.36; $P < .00001$), GI (OR 0.12; 95% CI: 0.04-0.32; $P < .0001$) and other bleeding (OR 0.29; 95% CI: 0.10-0.85; $P = .02$) were significantly greater in patients on-OACs. IM bleeding did not favor either arm (OR 0.27; 95% CI: 0.06-1.36; $P = .11$), indicating that odds of its occurrence were not significantly attributed to OACs (Figure 5). Aside from "other bleeding" events, ICH and GI were not impacted by omitting studies during the sensitivity analysis (Supplementary Table S7).

An analysis comparing "DOACs + warfarin" versus "warfarin alone" showed MB events was greater among on-OACs in both subgroups (OR 0.26; 95% CI:0.10-0.67; $P = .005$ vs OR 0.12; 95% CI:0.05-0.26; $P < .00001$) (Supplementary Figure S3). This result illustrates that the odds of bleeding in patients on OACs were greater than those off OACs, irrespective of the inclusion of DOACs. Notably, this observation remained unchanged in a subgroup analysis of ICH and GI events. Subgroup analysis of ICH events in 3 "DOACs + warfarin" versus 9 "warfarin alone" studies (OR 0.26; 95% CI: 0.08-0.90; $P = .03$ vs OR 0.14; 95% CI: 0.05-0.34; $P < .0001$) demonstrated significant ICH in patients on-OAC in both subgroups (Supplementary Figure S4). This result did not remain robust in the sensitivity analysis as it received influence by all 3 "DOACs + warfarin" studies (Supplementary Table S8).[16,23,30] Similarly, subgroup analysis of GI events in 3 "DOACs + warfarin" (OR 0.15; 95% CI: 0.03-0.68; $P = .01$) and 5 "warfarin alone" studies (OR 0.10; 95% CI: 0.02-0.46; $P = .003$) both showed significance in the on-OAC group (Supplementary Figure S5). One study from the "DOACs + warfarin" subgroup influenced the robustness of the results (Supplementary Table S9).[30] The sensitivity analysis did not alter the results for both ICH and GI in the "warfarin alone" subgroup.

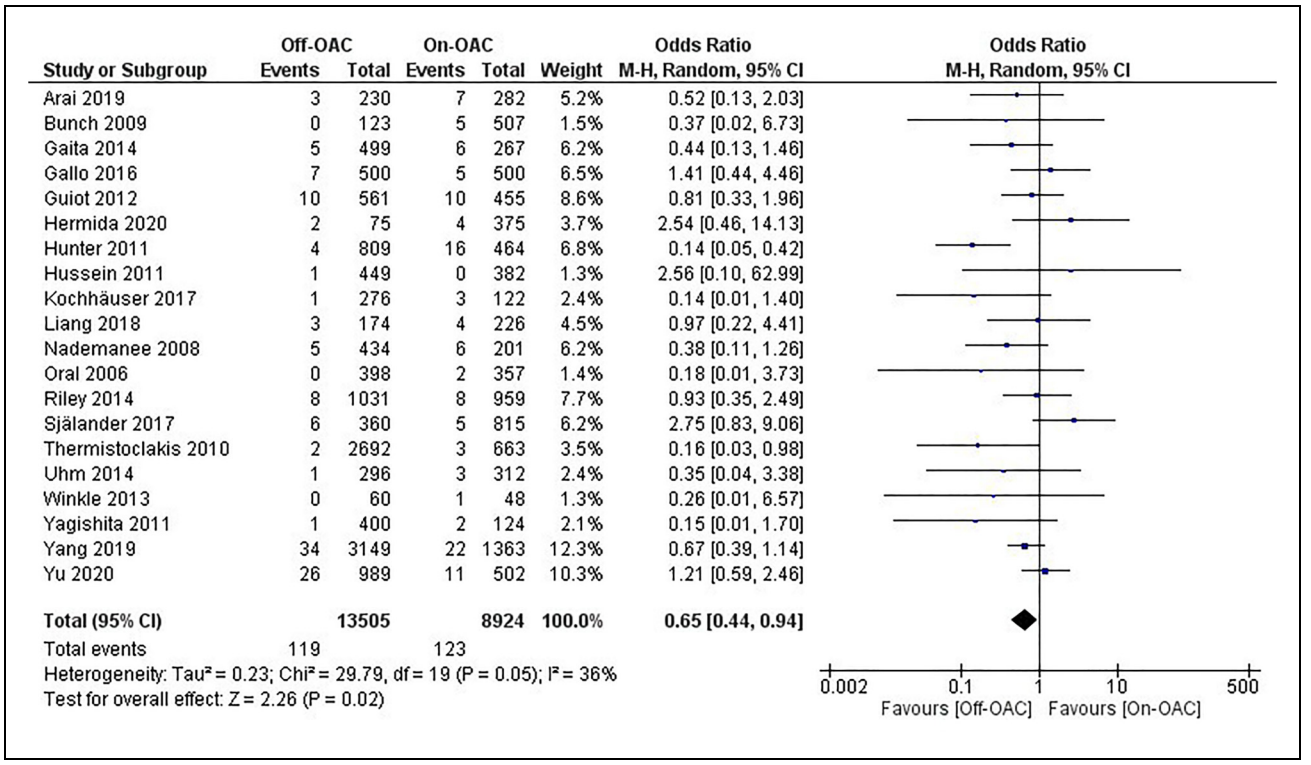

Figure 2. Forest plot analysis, incidence of total thromboembolic events.

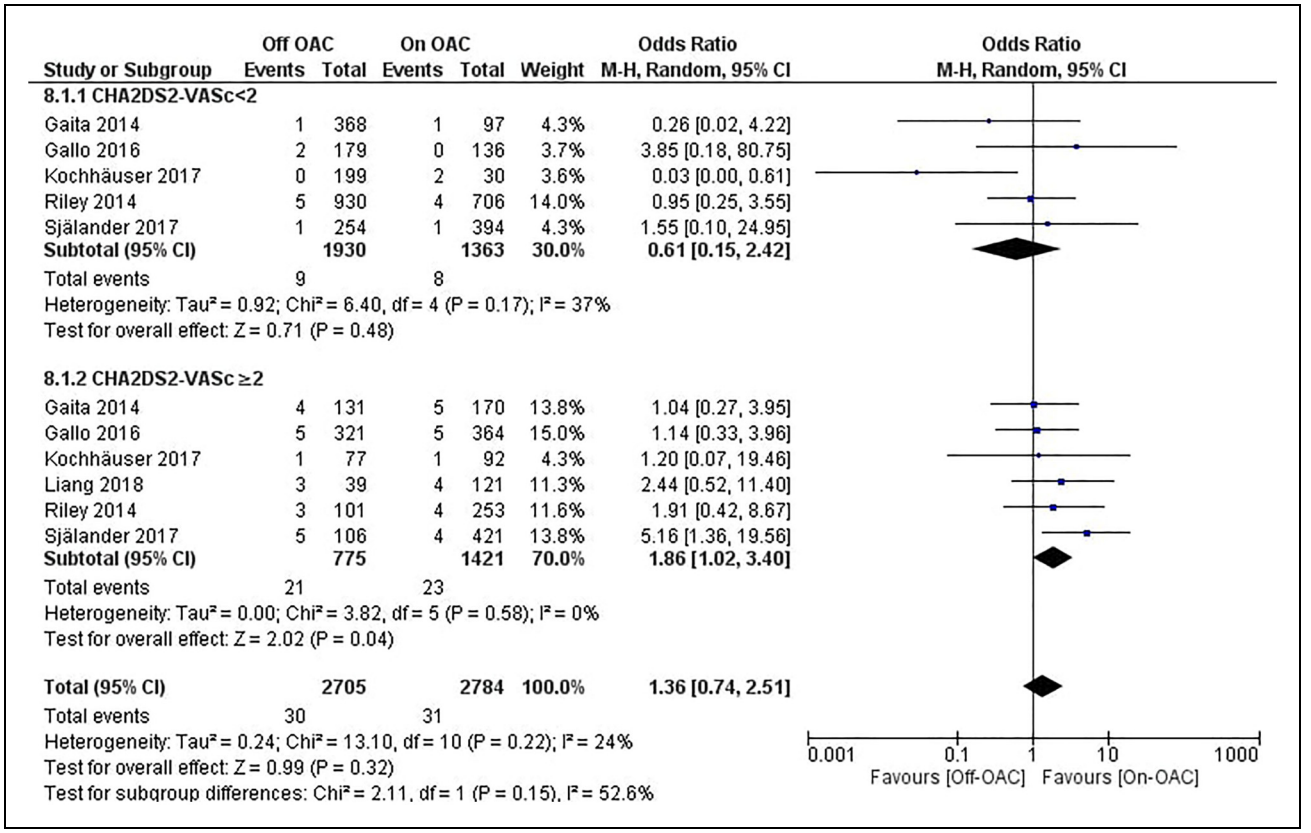

Figure 3. Forest plot analysis, incidence of thromboembolic events by CHA_2DS_2-VASc score stratification.

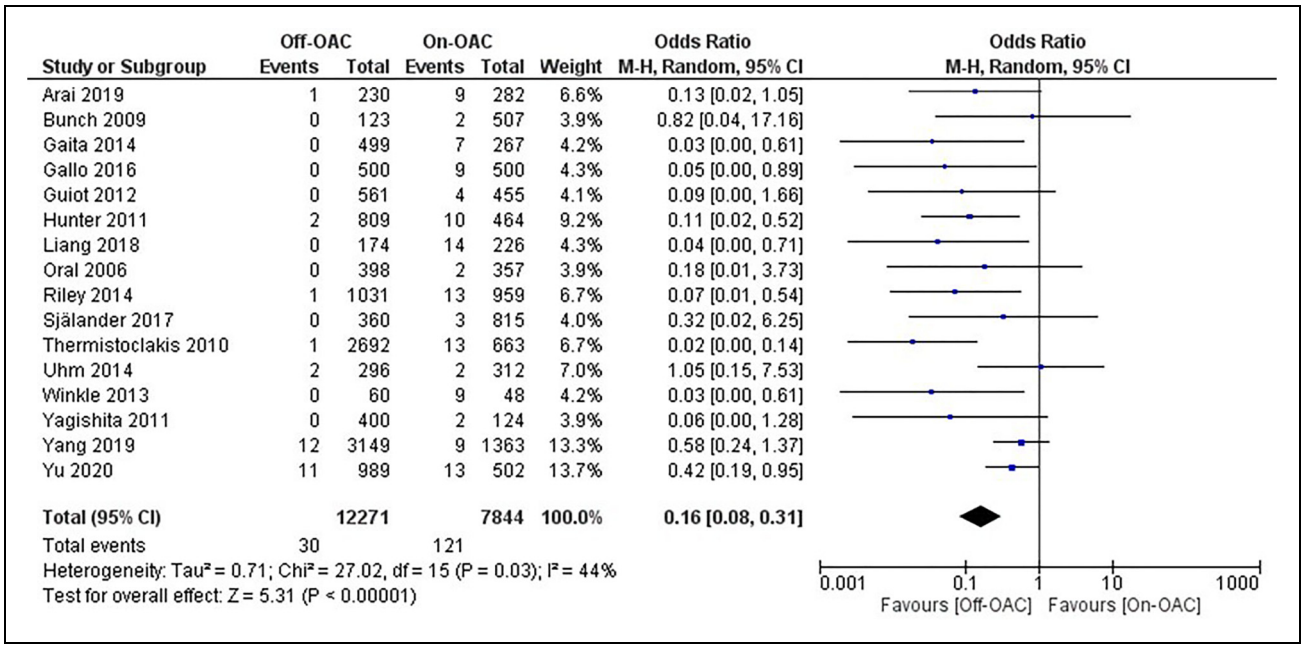

Figure 4. Forest plot analysis, incidence of major bleeding events.

Assessment of Publication Bias

Funnel plots were used to inspect for publication bias. Asymmetry was visible to a slight degree in both plots reporting TE and MB events. (Supplementary Figure S6) Egger's test showed no indication of publication bias in the reported incidence of TE ($P = .1857$); however, bias existed within the studies reporting MB events ($P = .0016$).

Discussion

CA is a mainstream alternative to antiarrhythmic therapy and surgical ablation.[35,36] This minimally invasive procedure involves the creation of lesions in the atria. However, scar tissue may activate the coagulation cascade, predisposing patients to periprocedural thromboembolism.[37] In light of this short-term risk, anticoagulants are recommended for a minimum of 2 months post-ablation.[3] Thereafter, physicians are required to decide on whether to continue/discontinue oral anticoagulants based on the patient's thromboembolic and bleeding risk scores (namely the CHA_2DS_2-VASc score and HAS-BLED score) irrespective of the patient's rhythm status. Due to the paucity of RCTs to guide OAC therapy, some clinicians believe that in chosen patients without AF who are closely monitored for AF recurrences, OAT therapy can be discontinued. This grey area is evident in the current CPG. To investigate the safety and efficacy of post-ablation long-term anticoagulation therapy, we analyzed 20 observational cohorts, making comparisons by pooling both embolic events and hemorrhagic events in patients who have discontinued (off-OAC) and continued (on-OAC) anticoagulation therapy.

Primary outcomes: Compared to the off-OAC group, patients on-OAC were 0.50% more likely to suffer from TE. A meta-analysis including all 20 studies confirmed this trend ($P = .02$). This outcome may be primarily attributed to the majority of patients in the on-OAC group who had comparatively higher CHA_2DS_2-VASc scores (off-OAC 2.46 ± 1.32 vs on-OAC 1.70 ± 1.14); hence are more predisposed to TE. Evaluation of embolic events, including ischemic stroke, TIA, and SE, showed no significant difference between the two treatment groups. Stratification of the CHA_2DS_2-VASc score aimed to understand the impact of stroke risk on the aforementioned results. In the CHA_2DS_2-VASc < 2 group, TE was not significantly greater in either arm. This suggests discontinuation could be beneficial in this group given risk of MB. Regarding patients with CHA_2DS_2-VASc score ≥ 2, Proietti et al analyzed three studies, and obtained results that did not significantly favor either treatment arm.[7] In this review, six studies were analyzed (including 2196 patients). Notably, patients with CHA_2DS_2-VASc score ≥ 2 benefited from OACs therapeutic effects. The analysis revealed a lower TE rate in patients on-OACs than off-OACs ($P = .04$), thereby supporting continued anticoagulation in high-stroke-risk males and intermediate/high-risk females. However, three studies were found to impact the pooled OR analysis based on the leave-one-out approach; hence physician discretion is still advised.[25,27,30]

Secondary outcomes: Long-term use of OACs and unnecessary administration can be life-threatening.[38] Our findings indicate that MB events were markedly increased in the long-term anticoagulated group, supporting discontinuation. These results coincide with those observed in previous systematic reviews.[7,8] Independent analysis showed that patients on OACs were significantly more prone to suffer from ICH, GI, and "other" bleeding events than those off-OACs. Current CPGs advocate efforts

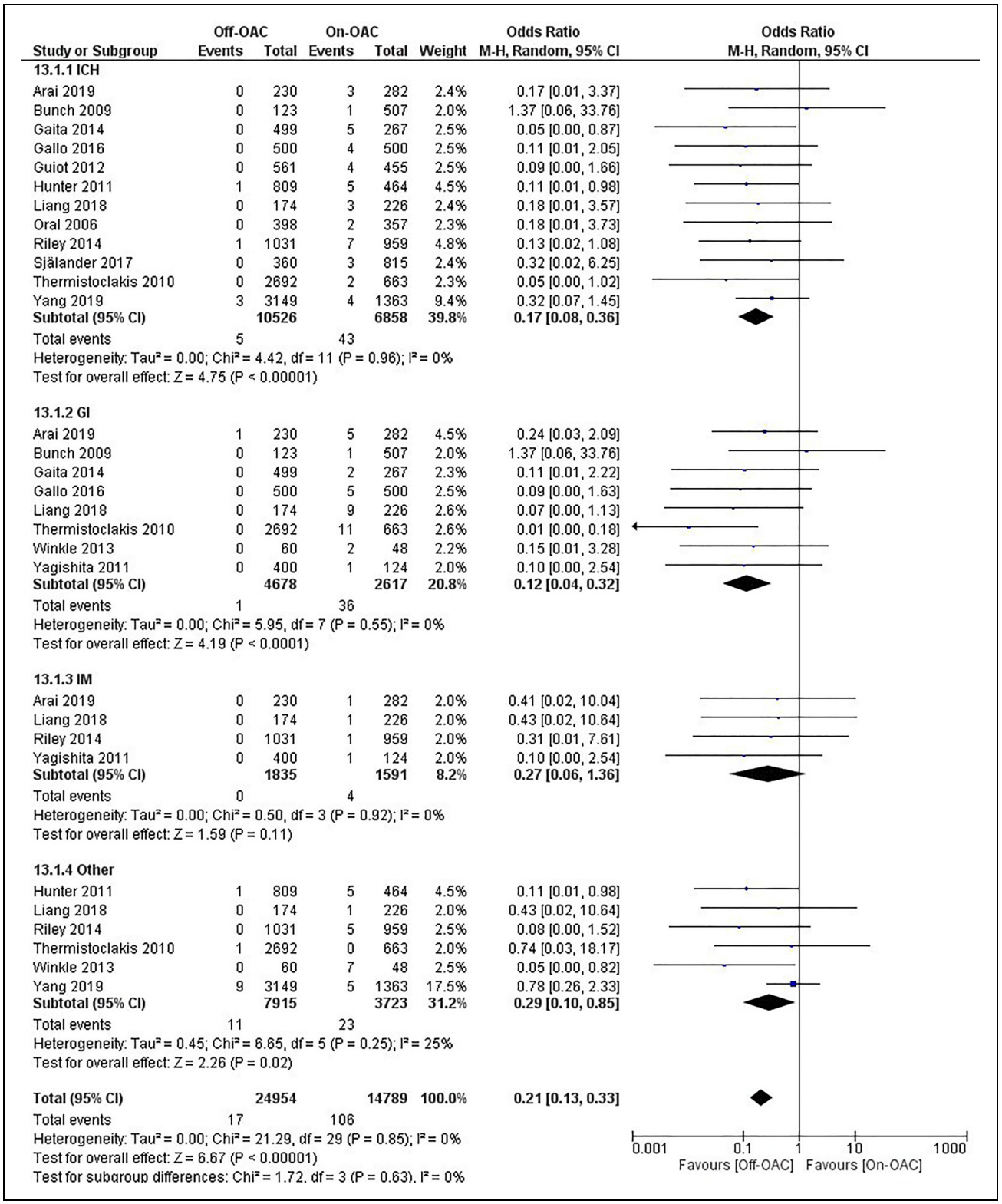

Figure 5. Forest plot analysis, incidence of ICH, GI, IM and other bleeding events.

to reduce bleeding, including prescribing the optimal OAC dose, evaluating alterable risk factors, and avoiding regular administration of nonsteroidal anti-inflammatory and antiplatelet medication in coagulated patients.[3] The search for effective bleeding-prevention techniques and safer anticoagulation methods should be pursued.

A subgroup analysis revealed that TE is more likely to occur in patients on "warfarin alone" than studies that reported administration of both "DOACs + warfarin". However, MB events were significantly increased in both subgroups treated with OACs. Analysis of ICH and GI events by subgrouping the studies into those including and excluding DOACs revealed that both subgroups experienced significant bleeding. After conducting a sensitivity analysis for both ICH and GI, robustness was reduced in the subgroup that included DOACs. Several studies have concluded a reduced risk of ICH associated with DOACs, particularly dabigatran and apixaban.[39–41] Regarding GI events, studies show risks were comparable with warfarin and DOAC use.[42,43] While rivaroxaban was associated with the most bleeding among DOACs,[44] events were shown to be completely dose-dependent.[45] The past decade has seen a considerable rise of DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) due to fewer drug interactions, fast onset and offset, and reduced need for constant monitoring.[46,47] Several studies examining anticoagulation strategies discovered minimal differences between DOACs and warfarin concerning TE, yet DOACs resulted in fewer MB events.[48–53] Studies that report post-ablation clinical outcomes and adverse effects specific to the type of OAC are in demand.

Rhythm status is an additional factor to consider when determining whether a patient should be kept on long-term anticoagulants. Sinus rhythm maintenance improves ventricular remodeling, left ventricular ejection fraction, and cardiac functional capacity, reducing stroke, TIA, and systemic embolisms.[54] Conversely, recurrent AF may lead to an increase in TE. In a retrospective analysis of 796 patients off-OACs, Rong *et al* reported the rate of thromboembolism was high in patients with intermediate and high CHA_2DS_2-VASc scores, concluding that the cessation of OACs in patients free from recurrence may be reasonable, particularly for those with contraindications for continuing OAC. They postulated that OAC discontinuation is unsafe in patients with recurrent AF and a high-risk stroke profile due to the high incidence rate of thromboembolism.[55]

Heedless of the current CPG recommendations for moderate to high-risk patients to remain on OACs, many patients fail to adhere mainly due to the risks and expenses involved.[56] As reported in previous studies, discontinuation of OACs occurred in about every one in four patients with a CHA_2DS_2-VASc score ≥ 2.[16,30] As an alternative to anticoagulants, monitoring strategies can be used after CA. In a prospective cohort, Zuern *et al* monitored the cardiac rhythm of 65 patients using intracardiac monitors. Two-thirds were able to remain off-OACs within 1.3 years after AF ablation.[57] Further research into such strategies can broaden treatment options in high-risk patients.

The current guidelines lack sufficient evidence to make a definitive decision on the continuation/discontinuation of OAC therapy after CA, warranting the need for large randomized control trials (RCT). A current ongoing international multicenter RCT, The Optimal Anticoagulation for Enhanced Risk Patients Post-CA for Atrial Fibrillation (OCEAN) trial (NCT02168829), is aimed to examine the role of long-term OAC (rivaroxaban 15 mg daily) against antiplatelet therapy (Aspirin 75-160 mg) in AF patients after a successful ablation procedure. The estimated time of completion is August 2025.

Limitations and Future Directions

The following caveats should be taken into account when interpreting the above results. First, all studies were nonrandomized; the inclusion of 13 retrospective studies raises the risk of confounding and reporting bias. Second, the differences in baseline characteristics, including follow-up, duration of the blanking period, and ablation methods, can prove potential bias. The findings of this study shines light on a pertinent topic; therefore, reduction of potential bias constitutes a mandate for prospective study design, randomization and blinded analysis, raising the need for high-quality RCTs. Third, covert strokes and asymptomatic events could have led to an underestimation of the reported results. In order to improve detection and assess symptoms, studies should implement monitoring techniques including; smart watches, wearable patch monitors, external loop recorders, or implantable devices for continuous cardiac monitoring as part of the study or as a subgroup analysis. Fourth, limited data prevented HAS-BLED stratification analysis. Similar to stroke risk assessment, researchers are encouraged to report bleeding risk scores which will provide clinicians with additional tools to guide clinical decisions. Fifth, only seven recent studies reported the use of DOACs; data specifying the drug the patient was administered, and the respective clinical outcomes were not provided, hindering deeper analysis. Following in the strides of the OCEAN trial, dose-specific and direct comparative studies of all DOACs are imperative in order to tailor an optimal personalized OAC treatment plan. Furthermore, studies are needed to examine the risks of long-term OACs in specific patient populations, including patients from specific geographical settings, ethnic groups, sex, and patients with valvular heart disease and chronic kidney disease.

Conclusions

Our findings support sustained anticoagulation in patients with a CHA_2DS_2-VASc score of ≥ 2 to minimize the risk of TE. The sensitivity analysis showed this association was attenuated after study exclusion; hence physician discretion is still advised. Long-term anticoagulation was associated with an increased risk of MB, predominantly ICH and GI, after successful atrial fibrillation CA. The search for effective bleeding-prevention techniques and safer anticoagulation methods should be pursued. Large RCT are required to validate our findings.

Author Contributions

Kellina Maduray contributed to the study concept, design, data analysis, organization and writing of the original manuscript. Md. Moneruzzaman contributed to the study selection and data collection. Geoffrey J. Changwe contributed to data processing and presentation. Jingquan Zhong supervised the project and gave the final approval for

publication. Manuscript final revision and submission was checked and approved by all authors.

Declaration of Conflicting Interests

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Ethics Approval and Consent to Participate

Our institution did not require informed consent or ethical approval from the patients for reporting a systematic review and meta-analysis.

Data Availability

All relevant data is presented in the review and Supplemental material.

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Supplemental Material

Supplemental material for this article is available online.

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