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Optimal duration of anticoagulation after left atrial appendage closure: a systematic review and meta-analysis

Xuan Lu[1], Zhenyu Yang[1], Wei Fang[1], Xiaona Niu[1], Qiuhe Wang[1*] and Yan Li[1*]

Abstract

Background Left atrial appendage closure (LAAC) has become the treatment of choice for stroke prevention in patients with nonvalvular atrial fibrillation who are at high risk of bleeding or with contraindications for anticoagulation. However, the optimal duration of anticoagulation after LAAC remains uncertain. The aim of this study was to evaluate the optimal duration of treatment with novel oral anticoagulants (NOACs) after LAAC.

Method We searched the PubMed, Embase, Cochrane Library, and Web of Science databases for studies related to LAAC published from inception to 20 December 2023, and performed a meta-analysis comparing the efficacy and safety of 45-day and 3-month postoperative NOAC treatment using R4.3.1 software.

Results A total of 14 studies were included in this study, of which 4 were prospective cohort studies and 10 were retrospective cohort studies. The incidence of stroke or transient ischaemic attack (0.018 [95% CI: 0.007–0.033] in the 3-month group and 0.005 [95% CI: 0.001–0.011] in the 45-day group; $P=0.07$) and the incidence of device-related thrombus (0.025 [95% CI: 0.002–0.065] in the 3-month group and 0.020 [95% CI: 0.007–0.037] in the 45-day group; $P=0.81$) were not significantly different. However, the incidence of major bleeding was significantly greater in the 3-month group than in the 45-day group (0.033 [95% CI: 0.018–0.053] in the 3-month group and 0.003 [95% CI: 0.000–0.008] in the 45-day group; $P<0.01$).

Conclusions Compared with the 3-month scheme, 45 days of postoperative anticoagulation significantly reduced the risk of major bleeding in patients without compromising the efficacy of preventing stroke or transient ischaemic attack and device-related thrombus.

Trial registration Our meta-analysis was registered in the PROSPERO international database (CRD42024524661).

Keywords Left atrial appendage closure, Novel oral anticoagulants, Stroke, Major bleeding

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Background

Left atrial appendage closure (LAAC) has been widely used as a treatment for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) [1–3]. Several previous studies have demonstrated that LAAC and oral anticoagulants (OACs) are similarly effective in preventing ischaemic stroke in patients at high risk of bleeding [1, 3, 4]. LAAC has been recommended by the 2023 ACC/AHA/ACCP/HRS guidelines as the treatment of choice for stroke prevention in patients with nonvalvular atrial fibrillation who are at high risk for bleeding or with contraindications for anticoagulation [5]. A short duration of antithrombotic therapy should be given after LAAC to allow complete endothelialization of the device and to prevent device-related thrombosis (DRT). Several studies have shown that NOACs better balance the risk of stroke and bleeding [6, 7], and an increasing number of large studies are adopting NOAC regimens (ADALA 2018–001013 - 32, ANDES NCT03568890, APPROACH NCT04550637). Nevertheless, the optimal postoperative anticoagulation regimen and the optimal duration of treatment remain subjects of debate [8].

Given the high risk of bleeding and thrombosis in patients undergoing LAAC, the ideal anticoagulation regimen should aim to achieve a balance between thromboprophylaxis and bleeding prevention. The 2023 SCAI/HRS expert consensus indicates that 45 days of OAC followed by long-term antiplatelet therapy is a standard recommendation following LAAC. Upon confirmation of successful endothelialization at 45 days, the regimen is transitioned to doublet antiplatelet therapy and subsequently to single-agent long-term antiplatelet therapy following a favourable review at six months [9]. While this short-term anticoagulation strategy offers theoretical advantages in reducing bleeding risk, concerns persist regarding the optimal treatment duration. The recommendation for 45-day therapy originates primarily from animal studies demonstrating complete endothelialization within this period [10]; however, human endothelialization processes may progress more slowly. In fact, 67.6–70% of patients cannot achieve complete endothelialization at 45 days postoperatively [11–14], and an increased risk of DRT as well as ischaemic events has been reported. Accordingly, a regimen of three months of NOACs followed by a switch to antiplatelet therapy has also been employed to ensure that anticoagulation encompasses the process of complete endothelialization of the device and to reduce the incidence of adverse events [15, 16]. However, this regimen may be associated with an increased risk of bleeding, particularly given that the target population of LAAC patients are already those with high bleeding risk or contraindications for OACs.

To address these controversies, we designed and conducted this meta-analysis to explore the optimal duration of treatment for NOACs after LAAC by comparing the effectiveness and safety of 45-day and 3-month anticoagulation regimens after LAAC in preventing stroke.

Methods

The study methodology followed the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. Our meta-analysis was registered in the PROSPERO international database (CRD42024524661).

Search strategy

Two researchers independently searched the PubMed, Embase, Cochrane Library, and Web of Science databases for studies published from inception to 20 December 2023. The following keywords and MeSH terms were used:'DOAC'or'NOAC'or'direct oral anticoagulant'or'nonvitamin K antagonist oral anticoagulant'or'novel oral anticoagulant'or'new oral anticoagulant'or'rivaroxaban'or'apixaban'or'edoxaban'or'dabigatran', and'LAAC'or'left atrial appendage closure'or'LAAO'or'left atrial appendage occlusion'. Further details of the search strategy are illustrated in Table S1.

Selection criteria

The inclusion criteria were as follows: (1) randomized controlled studies, randomized uncontrolled studies, prospective cohort studies, prospective single-arm cohort studies, retrospective cohort studies, or retrospective single-arm cohort studies; (2) postoperative treatment with the explicit use of NOACs or the percentage of patients receiving NOACs exceeding 65%; and (3) duration of postoperative NOAC treatment of either 45 days or 3 months. (4) If both sets of single arms in the same study are eligible, the single arm with the larger sample size will be selected.

The exclusion criteria were as follows: (1) animal experiments, case reports, systematic evaluations and meta-analyses, conference abstracts, letters, etc.; (2) no outcome metrics; (3) uncertainty about the duration of NOAC use; (4) NOAC cotreated with SAPT; (5) studies published in languages other than English; and (6) studies with a sample size of less than 30 cases.

Outcomes

The primary outcomes were as follows: (1) stroke or transient ischaemic attack (TIA), assessed according to the Munich consensus document on definitions, endpoints, and data collection requirements [17]; (2) DRT, defined as a thrombus attached to the surface of the

occluder found on transoesophageal echocardiography (TEE) or cardiac CT; and (3) major bleeding, on the basis of the International Society on Thrombosis definition (ISTH) definition: any fatal bleeding, bleeding in a critical organ or bleeding episode leading to a decrease in haemoglobin of ≥2 g/dl and/or transfusion of ≥2 units of whole blood or red cells [18]; or Bleeding Academic Research Consortium (BARC) type 3 or 5 [19]; or each study's own definition.

Literature screening and data extraction

Two researchers (Xuan Lu and Zhenyu Yang) independently screened the literature, extracted the data, and cross-checked the extracted information (including the baseline information, outcome events, etc.). In cases of disagreement (e.g., different data extraction methods due to ambiguous definitions of endpoints in the study), a third researcher (Wei Fang) resolved any disagreements. The following information was extracted: the name of the first author, publication year, country, study type, group, sample size, antithrombotic regimen, sex, age, mean CHA_2DS_2-VASc score, mean HAS-BLED score, clinical outcome, and duration of follow-up.

Quality assessment

A bias assessment was conducted independently and cross-checked by two researchers (Xuan Lu and Zhenyu Yang) on each of the included studies. The ROBINS-I tool was used to assess the quality of the cohort studies.

Statistical analysis

Statistical analysis was performed via the R software (version 4.3.1) package 'meta'. Event rates and 95% confidence intervals (CIs) were used as outcome indicators. The I^2 statistic was used to test for study heterogeneity. A random effects model was used if $I^2 \geq 50\%$ or $P < 0.05$. A fixed-effects model was used in the case of $I^2 < 50\%$ or $P \geq 0.05$. In addition, subgroup analyses were performed according to the Watchman device, a mean HAS-BLED score ≥3, age <75 years, different regions, and follow-up time ≥1 year, and $P < 0.05$ was considered a statistically significant difference between groups. We performed a "leave-one-out" sensitivity analysis to assess the impact of individual studies on the overall meta-analysis results. The symmetry of the funnel plots was analysed, and Egger's test was used to assess the publication bias of the included studies.

Results

Study selection and characteristics

A total of 1554 articles were identified after the search was performed on the abovementioned terms. Fourteen studies were included according to the inclusion/exclusion criteria (Fig. 1). A total of 10 studies were included in the 45-day group, 2 of which were prospective cohort

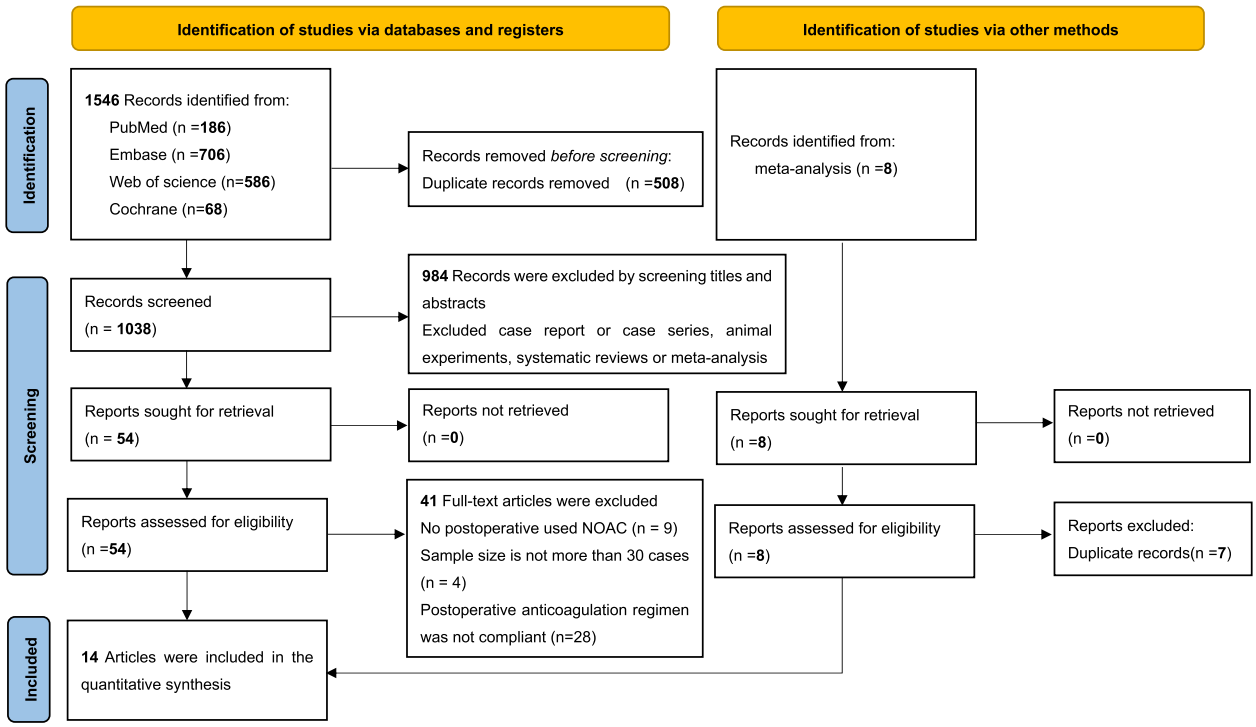

Fig. 1 PRISMA flow diagram

Table 1 Characteristics of the included studies

Study	Country	Design of the study	Group	Medication regimen		NOAC (numbers, dosage)		
Li, Wei 2022 [20]	China	retrospective, single-centre cohort	NOAC 3-month	OAC (3 months) + DAPT (6 months) + ASA (long time)		dabigatran (28, 110 mg); rivaroxaban (27, 15 mg); warfarin (27, NA)		
Bergmann, Martin W 2017 [21]	Germany	prospective, multicentre-centre cohort	NOAC 3-month	NOAC (3 months)		dabigatran (47, NA); rivaroxaban (39, NA); apixaban (23, NA)		
Li, Xiaoye 2021 [22]	China	prospective, single-centre cohort	NOAC 3-month	NOAC (3 months) + DAPT (6 months) + ASA (long time)		rivaroxaban (153, 15 mg)		
Ke, JinYan 2022 [23]	China	retrospective, single-centre cohort	NOAC 3-month	OAC (3 months) + ASA (long time)		dabigatran (1, NA); rivaroxaban (103, NA); warfarin (14, NA)		
Li, Xiaoye 2023 [24]	China	prospective, single-centre cohort	NOAC 45-day	NOAC (45 days) + DAPT (6 months) + ASA (long time)		rivaroxaban (NA, 10 mg); rivaroxaban (NA, 15 mg)		
Price, Matthew J 2020 [25]	USA	prospective, single-centre cohort	NOAC 45-day	NOAC (6 weeks)		edoxaban (NA, NA)		
Ajmal, Muhammad 2021 [26]	USA	retrospective, single-centre cohort	NOAC 45-day	NOAC (45 days) + DAPT (6 months) + ASA (long time)		rivaroxaban (23, NA); dabigatran (4, NA); apixaban (28, NA); edoxaban (2, NA)		
Zhou, XiaoDong 2023 [27]	China	retrospective, single-centre cohort	NOAC 45-day	NOAC (45 days) + DAPT (6 months) + ASA (long time)		rivaroxaban (178, 10 mg); rivaroxaban (164, 15 mg)		
Ge, Heng 2022 [28]	China	retrospective, single-centre cohort	NOAC 45-day	NOAC (45 days) + DAPT (6 months) + ASA (long time)		dabigatran (NA, 110 mg)		
Fu, Guohua 2021 [29]	China	retrospective, single-centre cohort	NOAC 45-day	NOAC (45 days) + DAPT (6 months)		dabigatran (165, NA)		
Chen, Yuyi 2021 [30]	China	retrospective, single-centre cohort	NOAC 45-day	NOAC (45 days) + DAPT (6 months) + ASA (long time)		NA		
Zhu, Jing 2021 [31]	China	retrospective, single-centre cohort	NOAC 45-day	NOAC (45 days) + DAPT (6 months) + ASA (long time)		dabigatran (16, 110 mg); rivaroxaban (24, 15 mg)		
Enomoto, Yoshinari 2016 [32]	USA	retrospective, multicentre-cohort	NOAC 45-day	NOAC (6 weeks)		apixaban (NA, NA); rivaroxaban(NA, NA); dabigatran(NA, NA); edoxaban (NA, NA)		
Tjoe, Benita 2021 [33]	USA	retrospective, single-centre cohort	NOAC 45-day	NOAC (45 days) + DAPT (6 months) + ASA (long time)		NA		
Patients (n)	Operation mode	Male, n (%)	Age, y (Mean ± SD)	CHA_2DS_2-VASc	HAS-BLED	Follow-up DRT (months)	Follow-up (months)	Type of LAAO device
82	NA	40 (49%)	68.55 ± 6.40	3.60 ± 1.14	4.11 ± 0.90	3	14.5 (9–21) *	Watchman
109	NA	NA	NA	4.1†	1.9†	3	3	Watchman
153	Non-one-stop	81 (52.9%)	69.9 ± 8.1	3.5 ± 1.4	3.2 ± 1.3	3	12	NA
118	One-stop	69 (58.5%)	67.4 ± 8.8	3.7 ± 1.5	2.5 ± 1.1	3–6	25.2 ± 15.6	Watchman
280	NA	180 (64.3%)	69.0 ± 8.3	3.7 ± 1.9	3.0 ± 1.2	12 (11–14) *	12 (11–14)*	Watchman
75	NA	50 (66.7%)	79.6 ± 8.0	4.54 ± 1.36	2.6 ± 0.79	1.5	1.5	Watchman
57	NA	32 (56%)	75.3 ± 7.0	4 (3–4) *	4 (3–4) *	18.6 ± 4.3	18.6 ± 4.3	Watchman
342	NA	229 (67.0%)	71.9 ± 7.2	4.5 ± 1.5	3.8 ± 1.0	32.4	32.4	Watchman/ACP/ LAmbre
38	NA	27 (71.1%)	66.1 ± 10.9	3.8 ± 1.4	2.7 ± 0.8	12	12	Watchman
165	NA	106 (64.2%)	68.9 ± 7.8	4.6 ± 1.5	3.0 ± 1.0	1.5	1.5	Watchman
170	NA	101 (59.4%)	65.6 ± 7.7	3.3 ± 1.6	1.9 ± 1.1	1.5	28.9†	Watchman/ACP
40	NA	21 (52.5%)	67 (80, 50) ‡	4.05 ± 1.09	3.18 ± 0.59	1.5	1.5	Watchman
214	NA	134 (62.6%)	76 ± 8	3.8 ± 1.4	2.4 ± 1.0	1.5–4	1.5–4	Watchman
71	NA	41 (57.7%)	79 (8.7) *	4.0 (3.5–5) *	3.0 (3–4) *	1.5	1.5	Watchman

NOAC novel oral anticoagulation, *NA* not applicable

* The median (with interquartile range) was reported

† The means are reported

‡ The median (with maximum and minimum values) is reported

studies and 8 of which were retrospective cohort studies; 4 studies were included in the 3-month group, 2 of which were prospective cohort studies and 2 of which were retrospective cohort studies. These studies were conducted mainly in Asia, North America, and Europe. The detailed characteristics of the included studies are shown in Table 1. In all the included studies, patients were given either short-term NOAC therapy for 45 days

Table 2 Differences in characteristics between the 3-month group and 45-day group studies at baseline

Characteristics	3-month group	45-day group	*p* value
Age (years)	68.78 ± 8.02*	71.46 ± 8.9	< 0.001
Male (%)	190/353(53.8%)*	921/1452(63.4%)	0.001
CHA_2DS_2-VASc score	3.71 ± 1.23	4.0 ± 1.59	< 0.001
HAS-BLED score	2.88 ± 1.23	2.99 ± 1.19	0.892
Hypertension (%)	235/353(66.6%)*	950/1452(65.4%)†	0.716
Diabetes mellitus (%)	89/353(25.2%)*	290/1452(20.0%)†	0.038
Prior stroke/TIA (%)	121/353(34.3%)*	640/1452(44.1%)†	0.001

* Bergmann, Martin W et al. 2017 lacked baseline information and was not included in the calculations

† Enomoto, Yoshinari et al. 2016 lacked baseline information and was not included in the calculations

or 3 months followed by antiplatelet therapy. DRT was measured by transoesophageal echocardiography (TEE) or CTA. We extracted data from 1910 patients treated with NOACs (45-day group: n = 1448; 3-month group: $n = 462$) (Table 1).

Differences in baseline characteristics between the 3-month group and 45-day group are presented in Table 2. Age was significantly lower in the 3-month group than in the 45-day group (68.78 vs. 71.46 years, $P < 0.001$). The percentage of males was significantly lower in the 3-month group than in the 45-day group (53.8% vs. 63.4%, $P = 0.001$). The CHA_2DS_2-VASc score was significantly lower in the 3-month group than in the 45-day group (3.71 vs. 4.0, $P < 0.001$). The HAS-BLED score was comparable between the two groups (2.88 vs. 2.99, $P = 0.892$). The percentage of patients with hypertension was comparable between the two groups (66.6% vs. 65.4%, $P = 0.716$). The percentage of patients with diabetes mellitus was significantly greater in the 3-month group than in the 45-month group (25.2% vs. 20.0%, $P = 0.038$). The percentage of patients with prior stroke/TIA was significantly lower in the 3-month group than in the 45-day group (34.3% vs. 44.1%, $P < 0.001$).

Risk assessment

The 14 included cohort studies were evaluated using the ROBINS-I tool. Based on the grading criteria, 8 studies were evaluated as low-risk studies and 6 studies were evaluated as moderate-risk studies. Notably, most of the studies were single-arm studies that selected only one of the time points, 3 months or 45 days, without prospective calculation of sample size and unbiased assessment of endpoint events (Table S2).

Primary outcomes

The incidence of stroke or TIA was reported in 13 studies, with 4 studies ($n = 462$) in the 3-month group and 9 studies ($n = 1106$) in the 45-day group, with a total of 1568 patients enrolled. The mean CHA_2DS_2-VASc score was 3.7 in the 3-month group and 4.0 in the 45-day group. In the 3-month group, there were 10 stroke or TIA events, predominantly stroke events. In the 45-day group, there were 10 stroke or TIA events, predominantly stroke events, for a total of 9 events (Table S3). Interstudy heterogeneity was low ($P = 0.11$, $I^2 = 49.73\%$ in the 3-month group; $P = 0.36$, $I^2 = 9.31\%$ in the 45-day group), and both groups were analysed using fixed effects models. The incidence of stroke or TIA events was comparable between the two groups (0.018 [95% CI: 0.007–0.033] vs. 0.005 [95% CI: 0.001–0.011], $P = 0.07$) (Fig. 2, Table S3).

All 14 studies reported the incidence of DRT, with a total of 1910 patients enrolled. There was heterogeneity between studies ($P = 0.01$, $I^2 = 72.96\%$ in the 3-month group; $P < 0.01$, $I^2 = 64.49\%$ in the 45-day group), and both groups were analysed using a random effects model. The results revealed that there was no significant difference in the incidence of DRT between the 3-month group and the 45-day group (0.025 [95% CI: 0.002–0.065] in the 3-month group vs. 0.020 [95% CI: 0.007–0.037] in the 45-day group; $P = 0.81$) (Fig. 3, Table S4).

The incidence of major bleeding events was also reported in all 14 studies. The mean HAS-BLED score in the 3-month group was 2.88, and in the 45-day group, the mean HAS-BLED score was 2.99. The percentage of postoperative NOAC use was approximately 91.1% in the 3-month group and 100% in the 45-day group. With respect to the definition of major bleeding, 3 studies in the 3-month group used BARC type 3 or 5, and 1 study used the ISTH criteria; 6 studies in the 45-day group used the ISTH criteria, 1 study used BARC type 3 or 5, and the other 3 studies defined major bleeding (1 instance of intracranial or gastrointestinal bleeding, 1 instance of haemorrhagic stroke, and 1 instance of cerebral haemorrhage) (Table S3). Interstudy heterogeneity was low ($P = 0.55$, $I^2 = 0\%$ in the 3-month group; $P = 0.38$, $I^2 = 6.66\%$ in the 45-day group), and both groups were analysed using fixed effects models. The incidence of major bleeding events was significantly greater in the 3-month group than in the 45-day group (0.033 [95% CI: 0.018–0.053] vs. 0.003 [95% CI: 0.000–0.008], $P < 0.01$) (Fig. 4).

Subgroup analyses

The difference in the incidence of stroke or TIA between the 3-month group and the 45-day group was not statistically significant regardless of the Watchman device used; whether the HAS-BLED score was < 3; whether the study was conducted in Europe and the United States; and whether the follow-up time was ≥ 1 year. The significantly greater incidence of

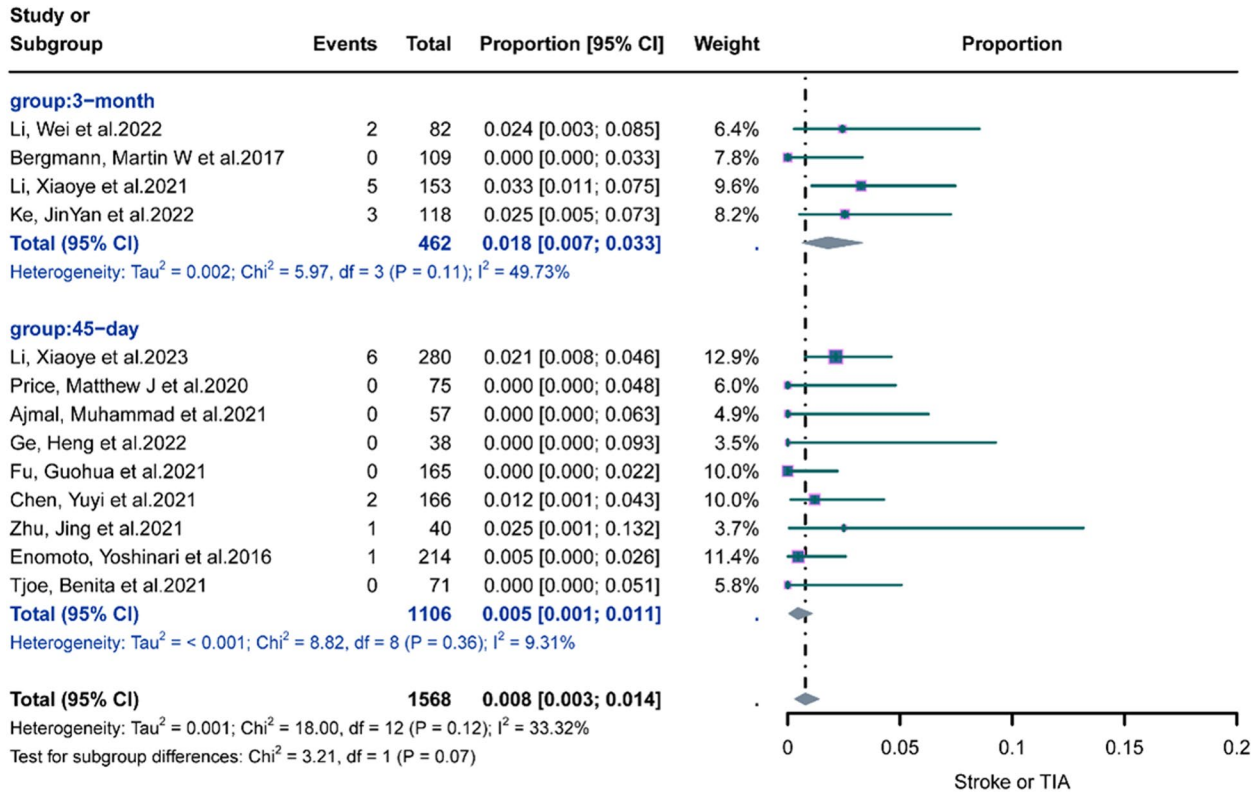

Fig. 2 Forest plots to compare the incidence of stroke or TIA between the 3-month and 45-day NOAC schemes. There was no significant difference in the incidence of stroke or TIA between the two groups (0.018 [95% CI: 0.007–0.033] in the 3-month group vs. 0.005 [95% CI: 0.001–0.011] in the 45-day group; *P* = 0.07)

stroke or TIA in the 3-month group was consistent with the HAS-BLED score being ≥ 3 (0.029 [95% CI: 0.010–0.056] vs. 0.004 [0.000; 0.015]), whether the patients were aged < 75 years (0.028 [0.011; 0.045] vs. 0.006 [0.000; 0.012]), and whether the patient sample was from the Asian population (0.028 [0.011; 0.045] vs. 0.017 [0.001;0.032]) (Tables S5). The difference in the incidence of DRT between the 3-month group and the 45-day group was not statistically significant, regardless of the Watchman device used, whether the HAS-BLED score was ≥ 3, whether the patients were age < 75 years, the region, or whether the follow-up time ≥ 1 year (Table S6). The significantly greater incidence of major bleeding in the 3-month group was consistent with the Watchman device (0.024 [95% CI: 0.007–0.041] vs. 0.002 [95% CI: 0.000–0.006]); whether the HAS-BLED score was ≥ 3 (0.038 [95% CI: 0.013–0.062] vs. 0.002 [95% CI: 0.000–0.006]); whether the patients were aged < 75 years (0.039 [95% CI: 0.020–0.062] vs. 0.0022 [95% CI: 0.000–0.007]); whether the patients were part of the Asian population (0.039 [95% CI: 0.020–0.062] vs. 0.002 [95% CI:0.000–0.007]); and whether the follow-up time was ≥ 1 year (0.036 [95% CI: 0.017–0.056] vs. 0.002 [95% CI: 0.000–0.006]). The incidence of major bleeding in the 3-month group was numerically greater than that in the 45-day group in the subgroup whose HAS-BLED score was < 3 as well as in Europe and United States subgroups; however, the difference was not statistically significant (Table S7).

Sensitivity analyses

A sensitivity analysis of clinical outcome indicators was conducted to assess the robustness of the results by sequentially excluding one study.

The incidence of stroke or TIA was robust in the 3-month group and in the 45-day group after excluding the studies on a case-by-case basis. The incidence of DRT was 0.013 ([95% CI: 0.003–0.028], $I^2 = 0\%$) in the 3-month group after excluding the study by Li, Wei 2022 [20], and 0.015 ([95% CI: 0.006–0.026], $I^2 = 40\%$) in the 45-day group after excluding the study by Ge, Heng 2022

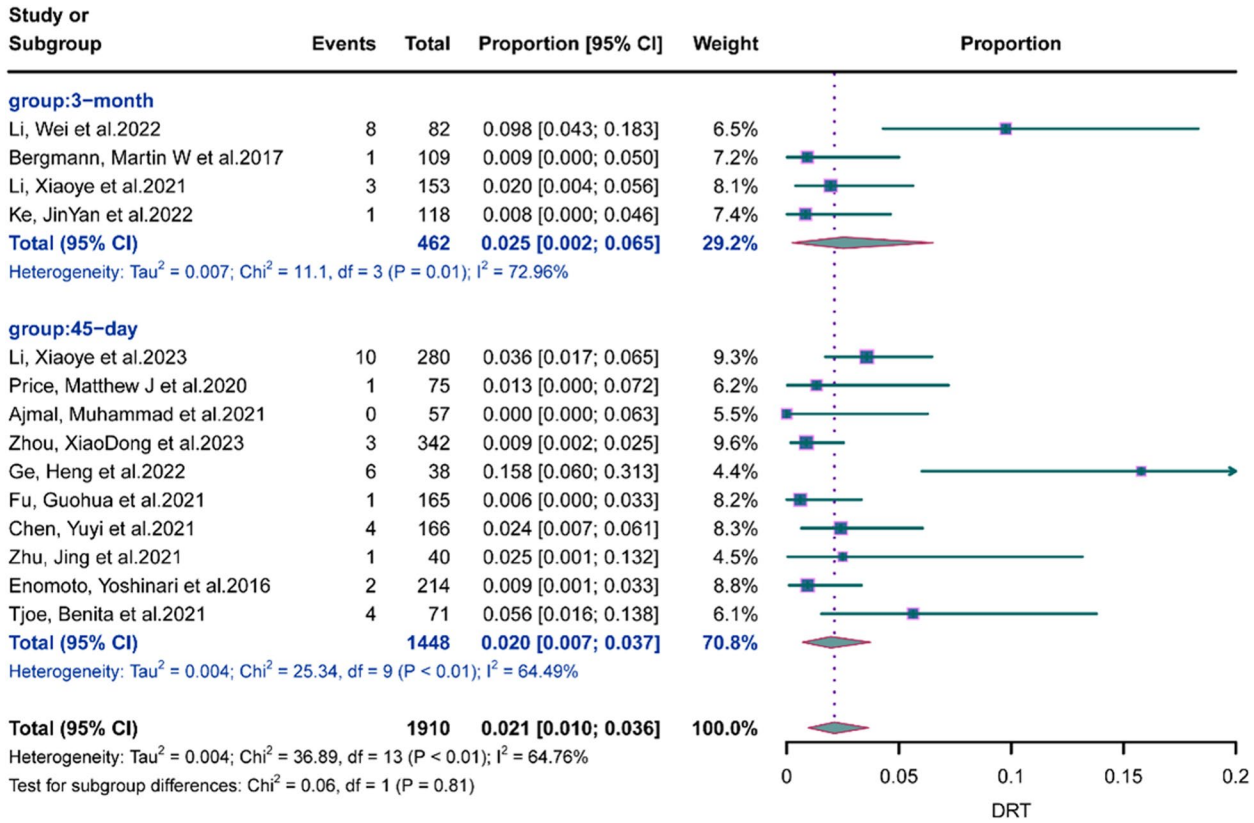

Fig. 3 Forest plots to compare the incidence of DRT between the 3-month and 45-day NOAC schemes. There was no significant difference in the incidence of DRT between the two groups (0.025 [95% CI: 0.002–0.065] in the 3-month group vs. 0.020 [95% CI: 0.007–0.037] in the 45-day group; $P = 0.81$)

[28], with reduced interstudy heterogeneity and a nonsignificant difference between the two groups. The incidence of major bleeding was robust in the 3-month group and in the 45-day group after excluding studies on a case-by-case basis. These analyses indicate that our results are robust (Figures S1 and S2).

Publication bias

Egger's test and funnel plots were used to assess publication bias. The small number of studies available in the 3-month group hindered the assessment of publication bias. The funnel plots were largely symmetrical in the 45-day group in terms of the primary outcome indicators of stroke or TIA, DRT, and major bleeding, with Egger's test results of $P = 0.5401$, $P = 0.1884$, and $P = 0.2999$, respectively, and no significant risk of bias (Figure S3).

Discussion

In this systematic review and meta-analysis, we examined 14 cohort studies with a total of 1910 patients. We found that there were no significant differences between 3-month and 45-day anticoagulation use in terms of the incidence of stroke or TIA and DRT. However, the 45-day group presented a significantly lower incidence of major bleeding than did the 3-month group. Our analysis suggests that short-term anticoagulation use with a 45-day NOAC regimen after LAAC might be a safer choice to control major bleeding without compromising the efficacy of preventing embolism.

Controlled studies on the optimal duration of anticoagulation use with head-to-head comparisons of 45-day and 3-month schemes in the same population after LAAC occlusion are lacking. Therefore, only single-arm studies with either 3-month or 45-day OAC use durations could be identified and selected for the meta-analysis in this study. Nevertheless, this study is the first to analyse and compare the optimal anticoagulation time after LAAC occlusion, providing a reference for future study design and clinical practice.

Stroke or TIA

In this study, there was no significant difference in the incidence of stroke or TIA between the two groups, with ischaemic stroke events being the most commonly reported embolism events in each study. The CHA_2DS_2-VASc score was significantly lower in the

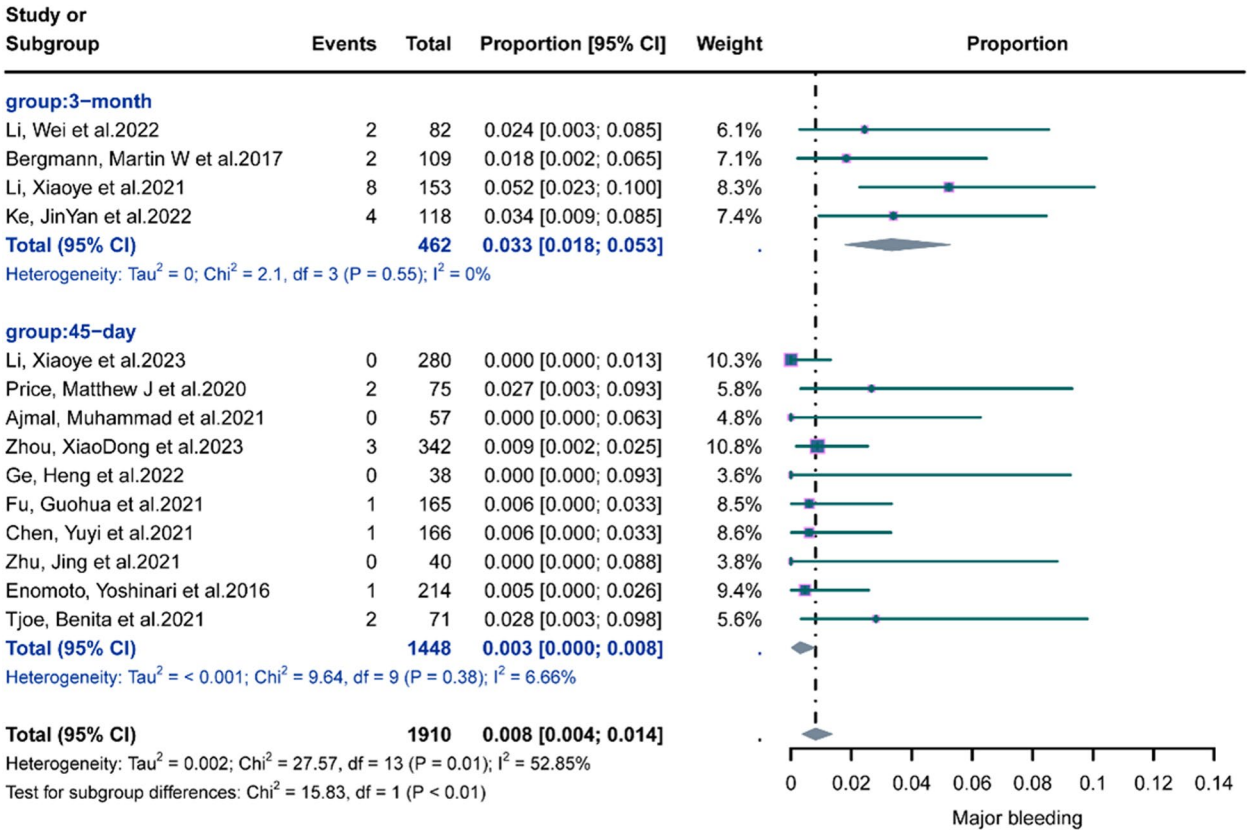

Fig. 4 Forest plots to compare the incidence of major bleeding between the 3-month and 45-day NOAC schemes. The incidence of major bleeding events was significantly greater in the 3-month group than in the 45-day group (0.033 [95% CI: 0.018–0.053] vs. 0.003 [95% CI: 0.000–0.008], $P < 0.01$)

3-month group than in the 45-day group (3.71 vs. 4.0, $P < 0.001$). The postoperative antithrombotic regimen in the 3-month group was mainly postoperative 3-month NOAC +6-month DAPT +long-term SAPT, and the postoperative antithrombotic regimen in the 45-day group was mainly postoperative 45-day NOAC +6-month DAPT +long-term SAPT. The main difference between the two regimens was the difference in the medication used between 45 days and 3 months postoperatively, i.e., NOACs versus DAPT, during the period from 45 days to 3 months (Figure S4). A meta-analysis of 83 studies including 12,326 patients by Mohammed Osman et al. revealed that there was no difference in stroke incidence at the midterm follow-up (1.5 to 12 months) between patients treated with short-term OAC or APT after LAAC [34]. In a meta-analysis of 32 studies including 4474 patients, Shuyue Li et al. found no significant difference in the incidence of SE (0.00–0.18%, 0.00–1.10%) or stroke/TIA (0.00–2.65%, 0.81–2.26%) treated with short-term NOACs versus DAPT after LAAC in a subgroup analysis [35]. Thus, the reason for the lack of difference between the two groups may be that continuation of 45-day DAPT therapy after anticoagulation in the 45-day group did not significantly affect the occurrence of ischaemic events compared with NOAC therapy in the 3-month group (Figure S4), which is consistent with the findings of Pedro E.P. Carvalho et al. [7]. Additionally, research has indicated that shortening the duration of postoperative antithrombotic therapy may help reduce the incidence of bleeding events without increasing the risk of stroke [36]. DRT is considered one of the major risk factors for stroke/SE after LAAC and is associated with a higher incidence of stroke/SE [37]. The absence of a significant difference in the incidence of DRT between the two groups in the present study similarly supports this conclusion. These findings suggest that prolonged postoperative anticoagulation does not reduce the risk of ischaemic events.

Given that the difference in the duration of follow-up between the 3-month and 45-day groups may have affected the results, we performed a subgroup analysis of studies with more than 1 year of postoperative follow-up. The results revealed that the incidence of stroke or TIA in the 3-month group was not significantly different from that in the 45-day group (0.028 [0.011;0.045] vs. 0.012 [0.002;0.022]). We also performed subgroup

analyses that considered the incidence of stroke or TIA in the groups of patients with different devices, in the group with a mean HAS-BLED score was ≥3, in the group aged <75 years, and in the groups from different regions. Most of the subgroup analyses yielded consistent results (Table S5).

DRT

In this study, the incidence of DRT was not significantly different between the two groups. The initial phase of DRT formation can begin at the early peak of coagulation activation. The risk of DRT is greater in the early postimplantation stages of endothelial cell activation, coagulation activation, and early endothelialization, with a large bare leakage area of the device [38]. Postoperative assessment of coagulation biomarkers and platelet activation markers in the study by Josep Rodés-Cabau et al. revealed that LAAC is associated with significant activation of the coagulation system, reaching peak levels on postoperative Day 7 and partially returning to baseline levels by Day 30 [39]. Therefore, it is possible that 45 days of postoperative anticoagulation therapy, where the coagulation system is largely restored and major endothelialization of the device is completed, could control the risk of early DRT, and the remaining risk difference in DRT caused by the subsequent time gap between 45 days and 3 months was insignificant. Moreover, this time gap was filled with DAPT. These results suggest that prolonged postoperative anticoagulation does not reduce the occurrence of DRT. The highest incidence of DRT in the included studies was 9.8% in the 3-month group and 15.8% in the 45-day group, both of which involved the use of a Watchman device, possibly due to differences in the use of different diagnostic devices and diagnostic criteria in different centres.

Sensitivity analysis revealed that the heterogeneity in DRT events was attributable primarily to two studies. Specifically, in the 3-month group, heterogeneity significantly decreased following the exclusion of Li, Wei 2022 [20], whereas a similar reduction was observed in the 45-day group after removing the study by Ge, Heng 2022 [28]. Importantly, no statistically significant differences in DRT event rates were identified between the two groups in either the original or adjusted analyses, further supporting the robustness of our findings (Figure S1, S2). In addition, we performed subgroup analyses that considered the incidence of DRT in patients with different devices, whether the mean HAS-BLED score was ≥3, whether the patients were aged <75 years, and the groups of patients from different regions. The subgroup analyses showed consistent results (Table S6).

Major bleeding

Major bleeding in this study was based mainly on BARC type 3 or 5 or ISTH-specific major bleeding events. The mean HAS-BLED score was 2.88 in the 3-month group and 2.99 in the 45-day group, indicating similar bleeding risk. The difference in the incidence of major bleeding may be because prolonged anticoagulation may increase the risk of bleeding. In the ADRIFT randomized pilot study comparing reduced-dose rivaroxaban and DAPT after LAAC, the risk of major bleeding in the half-dose (10 mg) rivaroxaban group was comparable to that of the DAPT group at the 3-month postoperative follow-up, and the rate of major bleeding was numerically slightly higher in the half-dose rivaroxaban group (21.62%) than in the DAPT group (21.21%) [16]. In a meta-analysis of 32 studies including 4474 patients, Shuyue Li et al. found in a subgroup analysis that the incidence of major haemorrhage was numerically higher in LAAC than in DAPT when patients were treated with short-term NOACs (5.05% and 2.12%, respectively) [40]. Especially in regions such as Europe, short-term DAPT after LAAC is widely used instead of OACs to reduce the risk of bleeding while balancing the reduction in thromboembolic events [41]. DAPT is primarily used to reduce the risk of bleeding after LAAC compared with OACs, and as shown in the NCDR's LAAC Registry study, patients treated with DAPT demonstrated higher HAS-BLED scores and a more frequent history of prior major bleeding [6]. In conclusion, the risk of bleeding is lower with DAPT than with NOACs, and the present study suggests that prolonged anticoagulation may increase the incidence of major bleeding. However, this finding still needs to be confirmed in larger randomized controlled studies.

Given that the difference in follow-up time between the 3-month group and the 45-day group may have affected the results, we performed a subgroup analysis for studies with more than one year of postoperative follow-up. The results revealed that the incidence of major bleeding remained significantly greater in the 3-month group than in the 45-day group (0.036 [0.017; 0.056] vs. 0.002 [0.000; 0.006]) (Table S7). We also performed subgroup analyses that considered the incidence of the primary outcome in patients with different devices, whether the mean HAS-BLED score was ≥3, whether the patients were aged <75 years, and whether the patients were from different regions. Most subgroup analyses yielded consistent results. Notably, in the HAS-BLED <3 subgroup, the difference between the two groups did not reach statistical significance, probably because prolonged anticoagulation did not significantly increase the risk of bleeding in the low-bleeding-risk population. The 3-month group also exhibited a significantly greater incidence of major bleeding events than did the 45-day group in Asia but this was not observed in patients from Europe or the U.S., possibly due to poorer tolerance of anticoagulation therapy in the Asian population [42, 43, 44].

Limitations

Our meta-analysis has several limitations. The main limitation is that no studies with head–to-head comparisons have been conducted, and we could include only studies with either one anticoagulation scheme or another. The final results of this meta-analysis are affected by the heterogeneity of the different study populations. Owing to the lack of original data, this meta-analysis was not conducted at the patient level. This massively increases the susceptibility to systematic errors. However, we used subgroup analyses to reduce the heterogeneity of the populations during the analysis, which helped to reduce bias. Moreover, although analysing the events occurring within the time frame of 45–90 days would be helpful to further compare the differences between DAPT and OAC, the lack of data in the studies of interest made such analyses difficult. Further individual patient data analyses would help solve this issue. The current study is the first to provide results of comparisons as a reference. Nevertheless, meta-analyses of data from individualized patients or head-to-head clinical studies are still needed to confirm these conclusions in the future. In addition, the type and dose of NOACs varied across the studies, and the efficacy and safety of different NOAC regimens may vary. For example, one study reported a greater incidence of DRT with dabigatran than with rivaroxaban [22]. However, since some studies did not provide detailed NOAC information, further analyses could not be performed, which may have biased the results. Finally, different definitions of major bleeding were used across studies. This inconsistency might impact pooled estimates.

Conclusion

In conclusion, this meta-analysis is the first to investigate the optimal duration of anticoagulation after LAAC. Compared with the 3-month scheme, 45-day anticoagulation significantly reduced the risk of major bleeding events, and there were no significant differences in the rates of stroke or TIA events and DRT between the two groups. Therefore, our study suggests that a 45-day NOAC regimen may offer comparable stroke prevention with improved safety compared with extended anticoagulation. However, these findings require confirmation in randomized trials accounting for baseline risk differences.

Abbreviations

DRT	Device-related thrombosis
LAAC	Left atrial appendage closure
NOAC	Novel oral anticoagulants
NVAF	Nonvalvular atrial fibrillation
OACs	Oral anticoagulants
SE	Systemic embolism
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3: Tables S1–S7 and Figures S1–S4.

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Authors' contributions

Xuan Lu: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review and editing. Zhenyu Yang: Conceptualization, Data curation, Formal analysis, Writing – original draft. Wei Fang: Data curation, Formal analysis. Xiaona Niu: Data curation, Formal analysis. Qiuhe Wang: Conceptualization, Supervision, Writing – review and editing. Yan Li: Conceptualization, Supervision, Writing – review and editing. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical and IRB approval of this analysis were not required as no human or animal subjects were involved.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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