ORIGINAL ARTICLE

Efficacy and safety of left atrial appendage closure versus medical treatment in atrial fibrillation: a network meta-analysis from randomised trials

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ABSTRACT

Background The effectiveness of vitamin K antagonist (VKA) versus placebo and antiplatelet therapy (APT) is well established for stroke prevention in atrial fibrillation (AF). Non-vitamin K antagonist oral anticoagulants (NOAC) are mostly superior to VKA in stroke and intracranial bleeding prevention. Recent randomised controlled trials (RCTs) suggested the non-inferiority of percutaneous left atrial appendage closure (LAAC) versus VKA. However, comparisons between LAAC versus placebo, APT or NOAC are lacking. The purpose of this network meta-analysis was to assess the efficacy and safety of LAAC compared with other strategies for stroke prevention in patients with AF.

Methods We pooled together all RCTs comparing warfarin with placebo, APT or NOAC in patients with AF using meta-analysis guidelines. Two major trials of LAAC were also included and a network meta-analysis was performed to compare the impact of LAAC on mortality, stroke/systemic embolism (SE) and major bleeding in relation to medical treatment.

Results The network meta-analysis included 19 RCTs with a total of 87 831 patients with AF receiving anticoagulants, APT, placebo or LAAC. Indirect comparison with network meta-analysis using warfarin as the common comparator revealed efficacy benefit favouring LAAC as compared with placebo (mortality: HR 0.38, 95% CI 0.22 to 0.67, p<0.001; stroke/SE: HR 0.24, 95% CI 0.11 to 0.52, p<0.001) and APT (mortality: HR 0.58, 95% CI 0.37 to 0.91, p=0.0018; stroke/SE: HR 0.44, 95% CI 0.23 to 0.86, p=0.017) and similar to NOAC (mortality: HR 0.76, 95% CI 0.50 to 1.16, p=0.211; stroke/SE: HR 1.01, 95% CI 0.53 to 1.92, p=0.969). LAAC showed comparable rates of major bleeding when compared with placebo (HR 2.33, 95% CI 0.67 to 8.09, p=0.183), APT (HR 0.75, 95% CI 0.30 to 1.88, p=0.542) and NOAC (HR 0.80, 95% CI 0.33 to 1.94, p=0.615).

Conclusions The findings of this meta-analysis suggest that LAAC is superior to placebo and APT, and comparable to NOAC for preventing mortality and stroke or SE, with similar bleeding risk in patients with non-valvular AF. However, these results should be interpreted with caution and more studies are needed to further substantiate this advantage, in view of the wide CIs with some variables in the current meta-analysis.

INTRODUCTION

Stroke prevention in the elderly patients with non-valvular atrial fibrillation (AF) is challenging due to associated high morbidity and mortality.[1] Although warfarin is highly effective in stroke and systemic embolism (SE) prevention, its use is limited by numerous food and drug interactions, narrow therapeutic range and increased bleeding risk.[2 3] Most of these disadvantages have been partially mitigated by non-vitamin K antagonist oral anticoagulants (NOAC), but the risk of gastrointestinal bleeding continues with some NOAC as compared with warfarin[4] and is definitely higher than in the absence of any antithrombotic therapy.

Left atrial appendage closure (LAAC) with the Watchman device (Boston Scientific, Marlborough, Massachusetts, USA) has been recently approved in the USA as an alternative to warfarin in patients with non-valvular AF[5] based on the results of two randomised trials.[6 7] As it obviates the need for long-term anticoagulation; the risk of bleeding is expected to be less with LAAC, in addition to maintaining the benefit of reduced stroke risk. However, direct comparison between NOAC and LAAC is lacking. In Europe, LAAC has a role in patients with thromboembolic risk who refuse or cannot be managed with any form of anticoagulation in the long term,[8] in whom antiplatelet therapy (APT) or no treatment is generally proposed. No direct comparison exists between LAAC and placebo or APT, and it is unlikely that a randomised controlled trial (RCT) will be performed in this setting. Thus, the aim of this analysis was to assess the efficacy (mortality and stroke/SE) and safety (major, intracranial and gastrointestinal bleeding) of LAAC as compared with medical prophylactic therapy for stroke prevention in patients with non-valvular AF.

METHODS

Objectives and study design

The population of interest included patients with non-valvular AF and the intervention was medical or percutaneous treatment for stroke prophylaxis assessed in RCT. Comparisons were performed between medical therapy (NOAC, APT or placebo) and percutaneous (LAAC) treatment, using vitamin K antagonist (VKA) as the common comparator.

The two primary efficacy endpoints were all-cause mortality and stroke or SE. The primary safety outcomes were the risk of major bleeding, intracranial bleeding and gastrointestinal bleeding. The study design was a network meta-analysis based on RCT. Two independent reviewers (SS and LN-F) searched MEDLINE/PubMed electronic databases using Cochrane highly sensitive search strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); PubMed format (supplemental material) and http://www.clinicaltrials.gov up to November 2015 to identify RCT comparing any treatment for stroke prevention in patients with AF. This included studies comparing VKA with placebo, APT (either single or dual) or NOAC. Also, all trials comparing LAAC with any percutaneous device against VKA were included. Keywords used for the search were "atrial fibrillation", "stroke", "stroke prophylaxis", "clinical trial", "phase III", "left atrial appendage closure", "non-vitamin K antagonist oral anticoagulants", "antiplatelet", "placebo" and "warfarin anticoagulation". The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses of RCT was used to extract data for this analysis.[9] The quality of the studies was scored using a checklist for the assessment of the methodological quality.[10]

Inclusion and exclusion criteria

The trials included in the meta-analysis met all the following criteria: RCTs, articles in English language, inclusion of patients with non-valvular AF, reporting one of the following outcomes —all-cause mortality, incidence of stroke and SE, major or gastrointestinal bleeding and intracranial haemorrhage. Trials with fixed-dose warfarin, a combination of APT with NOAC or any other comparison without including VKA were excluded from the analysis. Trials involving therapy that were commercially withdrawn (eg. ximelagatran) were excluded. Any percutaneous device for LAAC was considered eligible, although only Watchman device trials met the inclusion criteria. Two independent authors (SS and LN–F) determined whether trials met inclusion criteria, with discrepancies being resolved by joint review and consensus. Trials with inadequate data to extract the above outcomes, trials without availability of full-text article and ongoing trials were also excluded.

Statistical analysis

Categorical variables were expressed as n (percentage) and continuous variables as mean (standard deviation) or median (interquartile range, IQR: 25–75th percentile). Data were analysed according to intention-to-treat analysis, when available. For each direct comparison between treatments, where information from more than one trial was available, we performed a traditional random-effect model.[11] Q-statistic and Higgins' and Thompson's I^2 test[12] were calculated to evaluate heterogeneity among the studies. At least moderate heterogeneity was considered to be present for $p<0.10$ and an $I^2>50\%$. Publication bias was assessed by a funnel plot inspection and using the Begg and Egger's tests.[13 14] For indirect comparisons, network meta-analysis was performed within a Bayesian framework computing HR and 95% CIs with a random-effect hierarchical model by means of Markov chain Monte Carlo methods with Gibbs sampling from 1000 iterations obtained after a 5000 iteration training phase. Convergence was appraised graphically according to Gelman and Rubin.[15] Statistical significance was accepted at the 95% confidence level ($p<0.05$) and all data were analysed with the Stata Statistical Software: Release 14 (StataCorp. 2015; StataCorp, College Station, Texas, USA).

RESULTS

The flow diagram of the study analysis is shown in figure 1. A total of 2929 citations were identified using the search terms. Of these, 488 were screened at the abstract level and 413 records were excluded. The remaining 75 publications were carefully screened and after analysis of the full text (see online supplementary file table S1), 19 studies met the prespecified inclusion criteria and were included in the network meta-analysis.[6 7 16–32] The evidence network is shown in figure 2 before and after applying the inclusion and exclusion criteria. VKA were compared with NOAC in 6 studies, with APT in 10 studies, with LAAC with the Watchman device in 2 studies and with placebo in 3 studies. Of 87 831 randomised patients, 36 645 were assigned to warfarin, 43 314 to NOACs, 6215 to APT, 925 to placebo and 732 patients were assigned to Watchman device implantation (table 1). Relevant features (baseline characteristics and outcomes) of included studies are listed in tables 1 and 2. The median follow-up was 21.6 months.

Efficacy results

All-cause mortality and stroke/SE incidence was reported in 16 and 17 studies, with 81 316 and 86 013 patients, respectively. Direct comparison revealed a mortality benefit with NOAC (odds ratio, OR 0.89, CI 0.84 to 0.94) and no difference with LAAC (OR 0.68, CI 0.45 to 1.02) as compared with VKA. APT (OR 1.17, CI 0.97 to 1.40) and placebo (OR 1.75, CI 1.21 to 2.52) had worse mortality outcomes in comparison with warfarin (table 3, see online supplementary figure S1). While NOAC led to a significant reduction in the incidence of stroke or SE (OR 0.88, CI 0.81 to 0.95), LAAC led to a non-significant reduction (OR 0.84, CI 0.48 to 1.49) as compared with VKA. Both APT (OR 1.95, CI 1.59 to 2.40) and placebo (OR 3.54, CI 2.36 to 5.31) had higher risk of stroke in comparison with VKA (table 3, see online supplementary figure S2). The Begg ($Z=0.53$, $p=0.34$) and Egger's test ($t=1.72$, $p=0.103$) did not detect publication bias.

Indirect comparison revealed that LAAC was associated with lower rates of overall mortality than placebo (HR 0.38; CI 0.22 to 0.67; $p<0.001$) and APT (HR 0.58; CI 0.37 to 0.91; $p=0.018$). The mortality benefit of LAAC was not statistically significant in comparison with NOAC (HR 0.76; CI 0.50 to 1.16; $p=0.211$) (figure 3A). Similarly, pooled HR of stroke or SE outcomes of LAAC with placebo (HR 0.24; CI 0.11 to 0.52; $p<0.001$) and APT (HR 0.44; CI 0.23 to 0.86; $p=0.017$) showed a clear benefit in favour of LAAC. There was no difference in stroke or SE for LAAC compared with NOAC (HR 1.01; CI 0.53 to 1.92; $p=0.969$) (figure 3B).

Safety results

Major, intracranial and gastrointestinal bleedings were reported in 17 studies with 85,788, 85 713 and 77 116 patients, respectively. Direct comparison revealed a lower rate of major bleeding with NOAC (OR 0.77, CI 0.72 to 0.83) and placebo (OR 0.27, CI 0.12 to 0.63), and a non-significant difference with LAAC (OR 0.63, CI 0.33 to 1.19) and APT (OR 0.92, CI 0.74 to 1.14) as compared with warfarin (table 4, see online supplementary figure S3). Intracranial bleeding rate was reduced as compared with warfarin across all groups (table 4, see online supplementary figure S4). Gastrointestinal bleeding was significantly higher with NOAC as compared with warfarin (OR 1.12, CI 1.01 to 1.25), but lower with the other groups as compared with warfarin (table 4, see online supplementary figure S5).

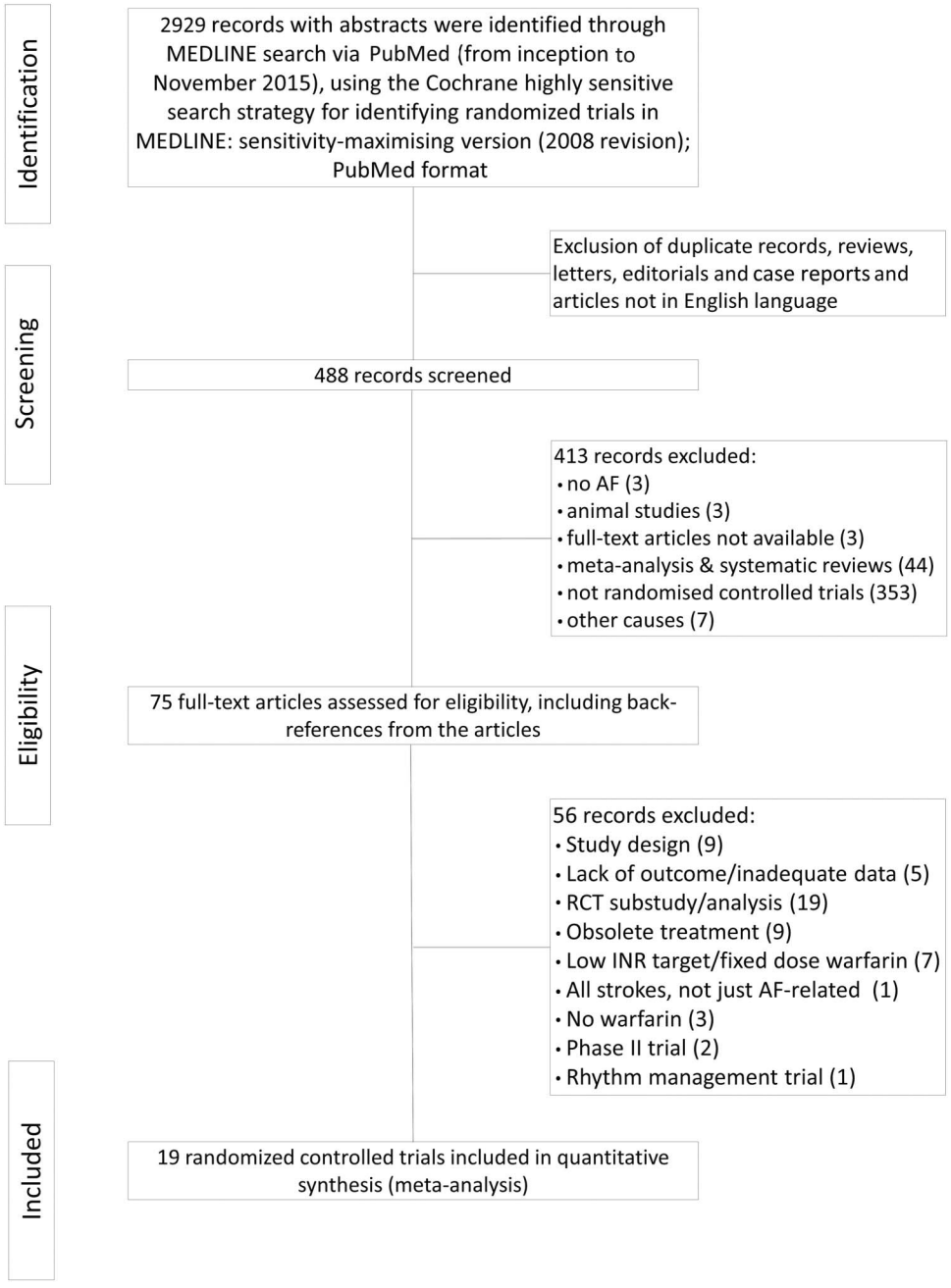

Figure 1 Flow chart of trials selection.

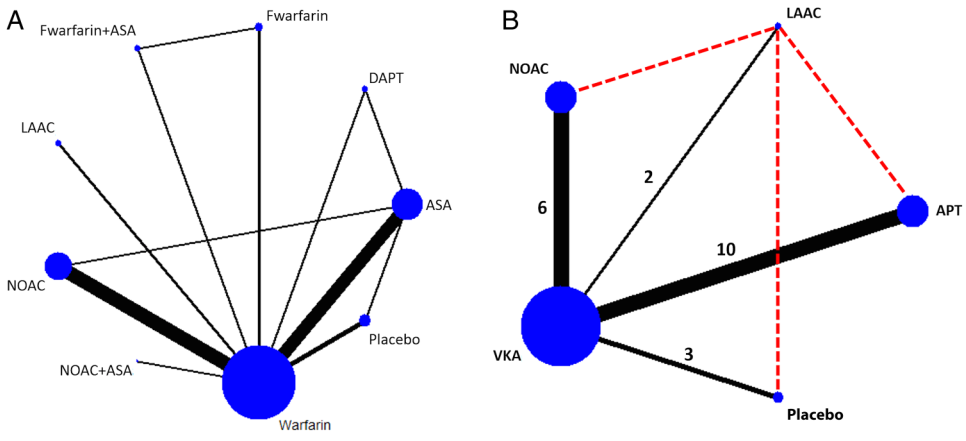

Figure 2 Network of antithrombotic treatment for patients with non-valvular atrial fibrillation with all searched studies (A) and network for selected studies and treatment comparisons for the meta-analysis (B). Dotted lines refer to indirect comparisons that have been performed.ASA, acetylsalicylic acid; APT, antiplatelet therapy; Fwarfarin, fixed dose of warfarin; DAPT, dual antiplatelet therapy; LAAC, left atrial appendage closure; NOAC, new oral anticoagulants; VKA, vitamin K antagonist.

Table 1 Baseline clinical characteristics of the population from selected studies

Trial	Year	Treatment	N	Age (mean±SD), median (IQR)	Age >75	Males	Hypertension	Diabetes	Heart failure	Stroke	$CHADS_2 \geq 2$	Control
LAAC trials												
PREVAIL	2014	Watchman	269	74.0±7.4	140	182	238	91	63	74	248	Warfarin
PROTECT-AF	2013	Watchman	463	71.7±8.8	190	326	415	113	124	82	307	Warfarin
NOAC trials												
ENGAGE-AF	2013	Edoxaban	14 069	72 (64–78)	5654	8670	13 166	5103	8076	3982	NA	Warfarin
J-ROCKET-AF	2012	Rivaroxaban	639	71 (34–89)	252	530	508	249	264	NA	639	Warfarin
ROCKET-AF	2011	Rivaroxaban	7131	73 (65–78)	NA	4300	6436	2878	4467	3916	7130	Warfarin
ARISTOTLE	2011	Apixaban	9120	70 (63–76)	2850	5986	7962	2284	3235	1748	6020	Warfarin
RELY	2009	Dabigatran	12 091	71.5±8.8	NA	7705	9533	2811	3871	2428	8174	Warfarin
PETRO	2007	Dabigatran	432	70.0±8.3	139	352	307	111	123	74	NA	Warfarin
WARFARIN trials												
PREVAIL	2014	Warfarin	138	74.9±7.2	78	103	134	41	32	39	126	LAAC
PROTECT-AF	2013	Warfarin	244	72.7±9.2	115	171	220	72	66	49	178	LAAC
ENGAGE-AF	2013	Warfarin	7036	72 (64–78)	2820	4575	6588	2521	4048	1991	NA	Edoxaban
J-ROCKET-AF	2012	Warfarin	639	71.2 (43–90)	246	500	508	237	257	NA	639	Rivaroxaban
ROCKET-AF	2011	Warfarin	7133	73 (65–78)	NA	4301	6474	2817	4441	3895	7131	Rivaroxaban
ARISTOTLE	2011	Warfarin	9081	70 (63–76)	2828	5899	7954	2263	3216	1790	5998	Apixaban
RELY	2009	Warfarin	6022	71.6±8.6	NA	3809	4750	1410	1922	1195	4163	Dabigatran
PETRO	2007	Warfarin	70	69.0±8.3	19	59	49	15	24	13	NA	Dabigatran
BAFTA	2007	Warfarin	488	81.5±4.3	488	267	259	68	96	64	139	Aspirin
WASPO	2007	Warfarin	36	83.5 (80–90)	NA	14	17	1	9	NA	NA	Aspirin
Vemmos *et al*[24]	2006	Warfarin	16	80.1±2.5	NA	7	10	2	1	NA	NA	Aspirin
ACTIVE-W	2006	Warfarin	3371	70.2±9.5	NA	2211	2767	717	1040	510	NA	DAPT
WARSS	2001	Warfarin	1103	63.3±11.2	NA	656	746	367	NA	321	NA	Aspirin
PATAF	1999	Warfarin	131	75.2	NA	58	46	25	NA	NA	NA	Aspirin
AFASAK II	1999	Warfarin	170	74.2±7.7	NA	97	80	NA	NA	9	NA	Aspirin
SPAF II	1994	Warfarin	197	64±8 80±3	NA	NA	NA	NA	NA	NA	NA	Aspirin
EAFT	1993	Warfarin	225	71.0±7.0	NA	124	97	27	18	NA	NA	Placebo/aspirin
SPAF	1991	Warfarin	210	67	17	155	103	25	29	17	NA	Placebo
AFASAK	1989	Warfarin	335	72.8 (41–88)	NA	176	108	25	168	16	NA	Placebo/aspirin
ANTIPLATELET trials												
BAFTA	2007	Aspirin	485	81.5±4.2	485	264	269	61	94	60	136	Warfarin
WASPO	2007	Aspirin	39	82.6 (80–90)	NA	21	18	2	10	NA	NA	Warfarin
Vemmos *et al*[24]	2006	Aspirin	15	79.5±2.9	NA	9	11	1	2	NA	NA	Warfarin
ACTIVE W	2006	DAPT	3335	70.2±9.4	NA	2219	2755	712	991	510	NA	Warfarin
WARSS	2001	Aspirin	1103	62.6±11.4	NA	653	753	338	NA	308	NA	Warfarin
PATAF	1999	Aspirin	141	75.2	NA	67	53	21	NA	NA	NA	Warfarin
AFASAK II	1999	Aspirin	169	73.1±7.2	NA	110	73	NA	NA	9	NA	Warfarin
SPAF II	1994	Aspirin	188		NA	NA	NA	NA	NA	NA	NA	Warfarin

Continued

Table 1 Continued

Trial	Year	Treatment	N	Age (mean±SD), median (IQR)	Age >75	Males	Hypertension	Diabetes	Heart failure	Stroke	$CHADS_2 \geq 2$	Control
				64±8 80±3								
EAFT	1993	Aspirin	404	73.0±8.0	NA	238	198	53	44	NA	NA	Warfarin
AFASAK	1989	Aspirin	336	75.1 (40–91)	NA	184	112	26	183	12	NA	Warfarin
PLACEBO trials												
EAFT	1993	Placebo	378	73.0±8.0	NA	200	178	49	45	NA	NA	Warfarin
SPAF	1991	Placebo	211	67.0	17	148	116	40	40	17	NA	Warfarin
AFASAK	1989	Placebo	336	74.6 (38–91)	NA	180	103	33	170	15	NA	Warfarin

DAPT, dual antiplatelet therapy; IQR, interquartile range; LAAC, left atrial appendage closure; NA, not available; SD, standard deviation.

Table 2 Characteristics and outcomes of selected studies

		Treatment			Mortality			Stroke or systemic embolism		Major bleeding		Intracranial bleeding		Gastrointestinal bleeding	
Study	Year	A	B	Total	A	B	Follow-up	A	B	A	B	A	B	A	B	A	B
AFASAK	1989	Warfarin	Placebo	671	335	336	2 years	3/335	17/336	5/335	21/336	21/335	0/336	1/335	0/336	NA	NA
SPAF	1991	Warfarin	Placebo	421	210	211	1.3 years	6/210	8/211	6/210	18/211	4/210	4/211	1/210	0/211	NA	NA
EAFT	1993	Warfarin	Placebo	439	225	378	2.3 years	41/225	99/378	21/225	99/378	13/225	4/378	0/225	1/378	4/225	1/378
AFASAK	1989	Warfarin	Aspirin	671	335	336	2 years	3/335	15/336	5/335	20/336	21/335	2/336	1/335	0/336	4/335	1/336
EAFT	1993	Warfarin	Aspirin	629	225	404	2.3 years	41/225	102/404	21/225	94/404	13/225	6/404	0/225	1/404	NA	NA
SPAF II	1994	Warfarin	Aspirin	385	197	188	2 years	26/197	24/188	21/197	21/188	NA	NA	7/197	3/188	NA	NA
AFASAK II	1999	Warfarin	Aspirin	339	170	169	3 years	17/170	14/169	12/170	10/169	4/170	5/169	1/170	1/169	NA	NA
PATAF	1999	Warfarin	Aspirin	729	131	141	2.7 years	12/131	17/141	6/131	9/141	2/131	11/141	1/131	0/141	0/131	0/141
WARSS	2001	Warfarin	Aspirin	2206	1103	1103	2 years	47/1103	53/1103	NA	NA	44/1103	30/1103	NA	NA	NA	NA
ACTIVE W	2006	Warfarin	DAPT	6706	3371	3335	1.28 years	NA	NA	63/3371	118/3335	93/3371	101/3335	15/3371	5/3335	NA	NA
Vemmos *et al*[24]	2006	Warfarin	Aspirin	45	16	15	3.7 months	0/16	0/15	0/16	2./15	0/16	0/15	NA	NA	0/16	0/15
WASPO	2007	Warfarin	Aspirin	75	36	39	1 year	1./36	2./39	0/36	0/39	0/36	3./39	0/36	0/39	NA	NA
BAFTA	2007	Warfarin	Aspirin	973	488	485	2.7 years	107/488	108/485	22/488	47/485	18/488	20/485	6/488	5/485	NA	NA
PETRO	2007	Warfarin	Dabigatran	334	70	264	12 weeks	NA	NA	0/70	1/264	0/70	0/264	0/70	0/264	NA	NA
RELY	2009	Warfarin	Dabigatran	18 113	6022	12 091	2 years	487/6022	884/12 091	199/6022	316/12 091	397/6022	697/12 091	45/6022	26/12 091	120/6022	315/12 091
ARISTOTLE	2011	Warfarin	Apixaban	18 201	9081	9120	1.8 years	669/9081	603/9120	265/9081	212/9120	462/9052	327/9088	78/9081	40/9120	119/9052	105/9088
ROCKET-AF	2011	Warfarin	Rivaroxaban	14 264	7133	7131	1.9 years	250/7133	208/7131	306/7090	269/7081	386/7125	395/7111	84/7125	55/7111	154/7125	224/7111
J-ROCKET-AF	2012	Warfarin	Rivaroxaban	1278	639	639	1.8 years	5/637	7/637	22/637	11/637	NA	NA	4/637	3/637	12/639	6/639
ENGAGE-AF	2013	Warfarin	Edoxaban	21 105	7036	14 069	2.8 years	839/7036	1510/14 069	337/7036	679/14 069	524/7012	672/14 014	90/7036	79/14 069	190/7012	361/14 014
PROTECT-AF	2013	Warfarin	Watchman	707	244	463	3.8 years	44/244	57/463	20/244	29/463	18/244	22/463	10/244	3/463	NA	NA
PREVAIL	2014	Warfarin	Watchman	407	138	269	1 year	3/138	7/269	1/138	7/269	NA	NA	0/138	1/269	NA	NA

DAPT, dual antiplatelet therapy.;
NA, not available.

Table 3 Pooled efficacy outcomes with stroke prevention strategies directly compared with warfarin

	Warfarin (events/n)	Comparator (events/n)	Pairwise meta-analysis, odds ratio (95% CI)	Heterogeneity, I^2, p value
All-cause mortality				
Warfarin vs NOAC	2250/29 909	3212/43 048	0.89 (0.84 to 0.94)	0.0%, p=0.881
Warfarin vs LAAC	47/382	64/732	0.68 (0.45 to 1.02)	0.0%, p=0.387
Warfarin vs APT	254/2685	335/2865	1.17 (0.97 to 1.40)	25.8%, p=0.223
Warfarin vs placebo	50/770	124/925	1.75 (1.21 to 2.52)	51.8%, p=0.126
Stroke or systemic embolism				
Warfarin vs NOAC	1129/29 936	1488/43 262	0.88 (0.81 to 0.95)	45.7%, p=0.101
Warfarin vs LAAC	21/382	36/732	0.84 (0.48 to 1.49)	50.6%, p=0.155
Warfarin vs APT	150/4933	321/5073	1.95 (1.59 to 2.40)	47.4%, p=0.065
Warfarin vs placebo	32/770	138/925	3.54 (2.36 to 5.31)	0.0%, p=0.883

APT, antiplatelet therapy; LAAC, left atrial appendage closure; NOAC, non-vitamin K antagonist oral anticoagulants.

Indirect comparison for major bleeding with LAAC versus placebo (HR 2.33; CI 0.67 to 8.09; p=0.183), APT (HR 0.75; CI 0.30 to 1.88; p=0.542) and NOAC (HR 0.80; CI 0.33 to 1.94; p=0.615) revealed no statistically significant differences (figure 4A). The risk of intracranial bleeding was not different between LAAC compared with APT (HR 0.42; CI 0.11 to 1.61; p=0.205) or NOAC (HR 0.44; CI 0.13 to 1.49; p=0.188) (figure 4B). Gastrointestinal bleeding was significantly lower with LAAC compared with NOAC (HR 0.22; CI 0.09 to 0.56; p=0.001) and similar to placebo (p=0.563) and APT (p=0.257) (figure 4C).

DISCUSSION

This network meta-analysis from RCTs showed that LAAC with the Watchman device is associated with higher survival and lower SE events compared with APT alone or placebo, with similar haemorrhagic outcomes. In comparison with NOAC, LAAC showed lower gastrointestinal bleeding risk with similar mortality and SE events.

Prevention of stroke in patients with AF is of high clinical relevance due to the disabling nature of stroke and associated high morbidity and mortality. Effective medical treatment consists of anticoagulation, the benefits of which have to be weighed against potential bleeding complications. Given the fact that AF population is usually elderly and has other pre-existing comorbidities, bleeding events tend to complicate anticoagulation management. In fact, patients with higher stroke risk are usually those at the highest risk for bleeding.[33] In clinical trials, around 20% of the patients discontinue antithrombotic therapy.[27–29] Eligible patients not receiving anticoagulation treatment are even higher in the real world.[34 35] LAAC has emerged as an alternative in patients with high-risk AF and contraindications to anticoagulation or high bleeding risk.[8] On the other hand, LAAC is not exempt from periprocedural and midterm complications that may counterbalance its clinical benefit compared with placebo or APT. Given that direct comparisons by clinical trials between LAAC and placebo or APT are currently unavailable (and unlikely to be performed in the near future), we applied network meta-analysis methodology to perform this comparison. In fact, the effectiveness of LAAC as compared with no anticoagulation treatment is only based on theoretical risk reduction of ischaemic and bleeding events determined by scores (such as CHA_2DS_2-VASc and HAS-BLED) in registries.[36–38] To the best of our knowledge, this is the first study to assess the efficacy and safety of LAAC compared with placebo or APT. Importantly, mortality and embolism events were significantly reduced with LAAC with no increase in safety events. These findings further support the evidence that LAAC may be recommended to patients deemed to be ineligible for oral anticoagulation. The rates of early ischaemic and bleeding complications in the two RCTs with LAAC were relatively high[39] compared with more recent registries.[40] Thus, the benefit of LAAC may be even superior after overcoming the learning curve with increased operator experience and decreased periprocedural complications. However, these findings should be interpreted with caution, as various heterogeneous trials were included in the meta-analysis and direct comparison from original RCT should not be substituted by network meta-analysis.[41]

In addition, LAAC with the Watchman device has recently been approved in the USA by the Food and Drug Administration for clinical use as an alternative to warfarin for stroke prevention.[5] The approval specific indications were in patients with non-valvular AF at increased risk of stroke or SE on the basis of $CHADS_2$ or CHA_2DS_2-VASc and deemed to be eligible for anticoagulation therapy. In parallel, recent RCTs have shown that NOAC are an alternative to VKA with mostly better outcomes in terms of mortality, stroke and intracranial bleeding, with occasionally relatively higher risk of gastrointestinal bleeding. Thus, the use of NOAC is increasing, as they

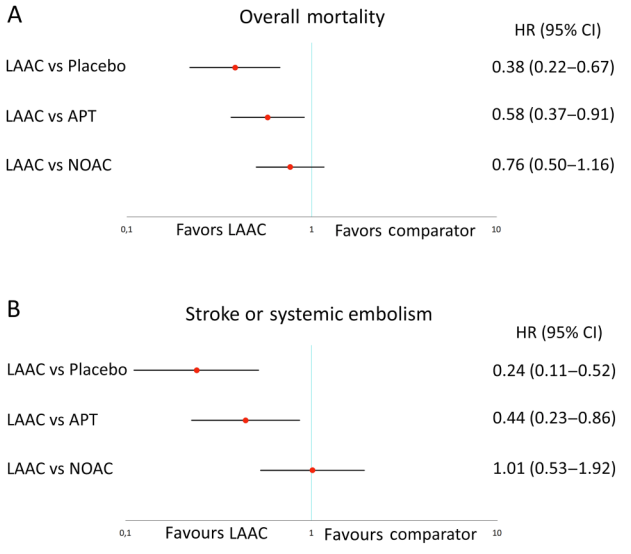

Figure 3 Pooled HR and 95% CIs determined by network meta-analysis for efficacy outcomes: overall mortality (A) and stroke or systemic embolism (B).

Table 4 Pooled safety outcomes with stroke prevention strategies directly compared with warfarin

	Warfarin (events/n)	Comparator (events/n)	Pairwise meta-analysis, odds ratio (95% CI)	Heterogeneity, I^2, p value
Major bleeding				
Warfarin vs NOAC	1769/29 211	2091/42 304	0.77 (0.72 to 0.83)	90.9%, p=0.001
Warfarin vs LAAC	18/244	22/463	0.63 (0.33 to 1.19)	-
Warfarin vs APT	195/5859	178/6012	0.92 (0.74 to 1.14)	74.6%, p=0.001
Warfarin vs placebo	38/770	8/925	0.27 (0.12 to 0.63)	71.4%, p=0.030
Intracranial bleeding				
Warfarin vs NOAC	301/29 901	203/43 028	0.48 (0.40 to 0.57)	52.0%, p=0.080
Warfarin vs LAAC	10/382	4/732	0.21 (0.06 to 0.71)	41.9%, p=0.190
Warfarin vs APT	33/4917	16/5058	0.50 (0.28 to 0.92)	0.0%, p=0.908
Warfarin vs placebo	2/770	1/925	0.58 (0.09 to 3.70)	0.0%, p=0.701
Gastrointestinal bleeding				
Warfarin vs NOAC	595/29 850	1011/42 943	1.12 (1.01 to 1.25)	77.9%, p=0.001
Warfarin vs LAAC	21/382	3/722	0.24 (0.11 to 0.51)	–
Warfarin vs APT	9/868	7/1065	0.56 (0.18 to 1.76)	53.9%, p=0.114
Warfarin vs placebo	8/560	1/714	0.13 (0.02 to 0.76)	0.0%, p=0.876

APT, antiplatelet therapy; LAAC, left atrial appendage closure; NOAC, non-vitamin K antagonist oral anticoagulants.

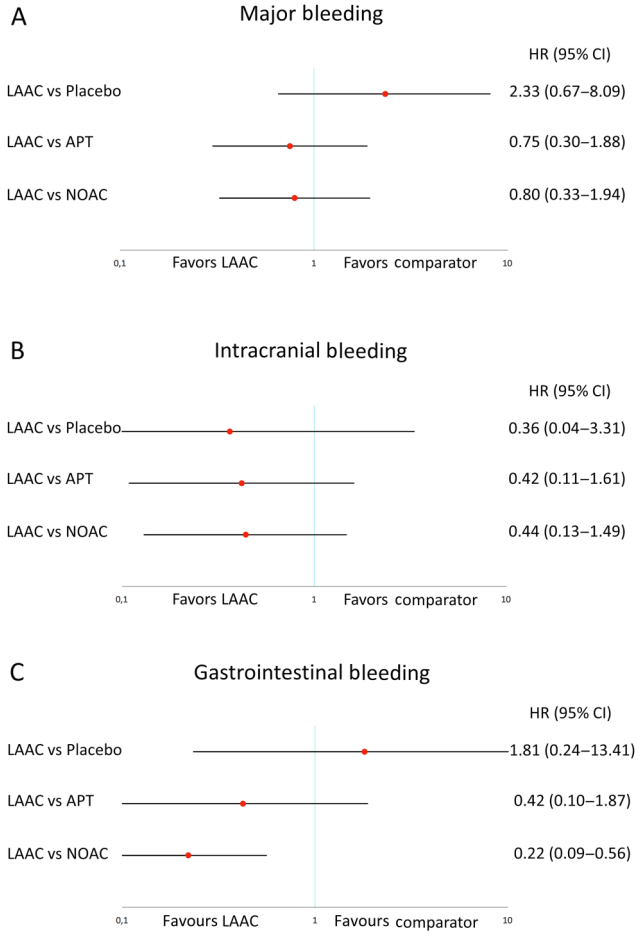

Figure 4 Pooled HR and 95% CIs determined by network meta-analysis for safety outcomes: major bleeding (A), intracranial bleeding (B) and gastrointestinal bleeding (C).

mitigate some disadvantages of VKA with better clinical outcomes. However, any type of anticoagulation still confers a permanent risk of bleeding, as compared with placebo, and NOAC are not indicated in patients with severe renal dysfunction. Furthermore, in clinical trials[27–29] and real-life registries,[35 42] there is a 13–25% discontinuation rate per 100 patient-year. The main reason for discontinuation was bleeding events, followed by NOAC side effects. Thus, in the absence of head-to-head comparison between NOAC and LAAC (and unlikely to have data in near future), it is clinically relevant to determine the clinical effects of both treatments. In accordance with previous studies,[43 44] our network meta-analysis demonstrated by indirect comparison that there was no significant difference between LAAC and NOAC in terms of mortality and stroke or SE prevention. Gastrointestinal bleeding was significantly lower with LAAC, with similar overall major bleeding rates. Although intracranial bleeding rate between LAAC compared with NOAC was not statistically different in our study, this was probably related to the small sample size in the LAAC arm and limited follow-up. Interestingly, Koifman *et al*[43] found a lower risk of haemorrhagic stroke with the Watchman device when including non-randomised trials in the analysis. Also, as anticoagulation confers ~2% annual risk of major bleeding, the differences may have been more evident with a longer follow-up period. Another issue when evaluating new therapies such as NOAC and LACC is cost. A recent study showed that both treatments were cost-effective relative to warfarin, but LAAC was found to offer a better value relative to NOAC.[45] On the contrary, Micieli *et al*[46] found that apixaban is the most cost-effective therapy in patients with AF compared with other NOAC and LAAC. Future studies are needed to clarify the benefits and the cost-effectiveness of LAAC compared with NOAC.

Limitations

This study, as with any meta-analysis, has the limitations of the original studies. Heterogeneity of the study designs and patient profile was present. Network meta-analysis assumes that patients enrolled in the different studies would have been sampled from the same theoretical population and, using VKA patients as bridge comparators, the indirect comparison may be biased. Moreover, we could not test inconsistencies between direct and indirect comparison, as no trials compare LAAC versus other medical treatment besides VKA. All patients with LAAC are treated with anticoagulants for the initial 45 days, dual APT for 6 months and single APT thereafter, which is a confounding factor when estimating the bleeding risk. However, this study

assesses the LAAC bleeding risk taking into account the LAAC plus the protocol-mandatory antithrombotic therapy, as a single intervention. Approximately, 95% of patients can be withdrawn from anticoagulation treatment after a follow-up transoesophageal echo at 6 weeks. There were only two RCTs comparing LAAC with VKA, and warfarin showed an unexpected low rate of stroke in one of them.[7] The relatively small sample size and the very low event rates of gastrointestinal and intracranial bleeding, with wide CIs, might underpower the comparison making it difficult to interpret the data. Finally, we have included some studies with low-dose warfarin, which can bias the safety as well as efficacy outcomes.

CONCLUSION

NOAC and LAAC are currently the two therapeutic strategies with the best efficacy and safety profile for embolism prevention in patients with non-valvular AF. LAAC obviates the need for life-long anticoagulation and the findings of this meta-analysis suggest that LAAC is associated with better efficacy and similar safety profiles, respectively, compared with placebo or APT. By indirect comparison, there seems to be no significant difference between LAAC and NOAC in terms of mortality and stroke/SE prevention, with similar major bleeding risk, making it a potent alternative to medical prophylaxis in patients with AF. Future studies will have to confirm these results.

Key messages

What is already known on this subject?

Vitamin K antagonists (VKA) are highly effective in patients with atrial fibrillation (AF) for stroke prevention, but its use is limited by drug interactions, narrow therapeutic range and increased bleeding risk. Non-vitamin K antagonist oral anticoagulants (NOAC) continue to have an increased risk of major bleeding as compared with placebo. Anticoagulation is frequently interrupted in a high proportion (~20%) of patients with AF with previous or high risk of bleeding, and antiplatelet therapy (APT) or no treatment is generally advised in this situation. Left atrial appendage closure (LAAC) has recently emerged as an effective treatment for stroke prevention in patients with AF. However, comparisons between LAAC versus medical treatment other than VKA are lacking.

What might this study add?

This network meta-analysis assessed the efficacy and safety of LAAC compared with medical therapy (NOAC, APT and placebo) for stroke prevention in patients with non-valvular AF. Importantly, LAAC was associated with higher survival and lower systemic embolism (SE) events compared with APT alone or placebo, with similar bleeding outcomes. In comparison with NOAC, LAAC showed lower gastrointestinal bleeding, with similar SE events.

How might this impact on clinical practice?

The results of this meta-analysis provide further insight into the clinical efficacy and safety of LAAC, which may be considered as a stroke prevention therapy in patients deemed to be ineligible for oral anticoagulation on long-term basis. This study could contribute to improving the treatment planning in this common group of patients.

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