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Atrial fibrillation (AF), left atrial appendage occlusion (LAAO), Direct oral anticoagulant (DOAC), stroke, vitamin K antagonist (VKA)

Abstract

Introduction Existing randomised controlled trials assessing the safety and efficacy of left atrial appendage occlusion (LAAO) in atrial fibrillation (AF) were of relatively small sample size, or included patients who could receive oral anticoagulant treatment after device implantation. We compared the outcomes of patients with newly diagnosed AF who received percutaneous LAAO or direct oral anticoagulants (DOAC) treatment, in a large population from a global federated health network (TriNetX).

Methods Patients with AF treated with percutaneous LAAO were matched with those treated with DOAC between 1st December 2010 and 1st October 2018. Outcomes were all-cause mortality, ischaemic stroke and intracranial haemorrhage (ICH) at 5 years.

Results We included 200 patients with AF, who received either LAAO or DOAC. The risk of all-cause mortality, ischaemic stroke and ICH at 5 years was not significantly different between the two groups (Risk Ratio [RR] for all-cause mortality: 1.52, 95% confidence interval (CI): 0.97- 2.38, RR for ischaemic stroke: 1.09, 95% CI: 0.51- 2.36, and RR for ICH: 1.0, 95% CI: 0.44- 2.30).

Conclusion

Patients newly diagnosed with AF, eligible for DOAC, showed similar 5-year risk of death, ischemic stroke, and ICH when comparing those who underwent percutaneous LAAO to those receiving DOAC. Future randomised controlled trials are needed to confirm the findings and advise changes in guidelines.

Introduction

Atrial fibrillation (AF) is a major risk factor for ischaemic stroke which occurs in 5% of non-anticoagulated individuals every year[1]. Previous studies estimated that the risk of ischaemic stroke in patients with AF treated with warfarin is about 1% - 4% per year, increasing to 4.5% - 7% per year for untreated individuals, and to 12% per year for those who are intolerant of warfarin[1,2].

Despite the substantial reduction in the stroke risk with oral anticoagulation, the rate of recurrent or "breakthrough" stroke remains high at 3.0% at 3 months, 7.0% at 1 year, and 10.3% at 2 years[3]. Not only that direct oral anticoagulants (DOACs) are similar or better than vitamin K antagonists (VKAs), namely warfarin, in reducing the risk of thromboembolism with AF[4], their use versus VKA use after an index stroke was found to be associated with lower odds of recurrent ischaemic stroke within 3 months, and lower odds of a composite endpoint of recurrent ischaemic stroke, intracranial haemorhage (ICH), and all-cause death at 3 months[5].

Evidence to date suggests a higher risk of recurrent stroke among those with AF who had already been on oral anticoagulants (OACs) prior to their index stroke[6]. Hence, deciding on the best anticoagulation strategy for secondary prevention is of paramount importance. In a pooled analysis (from 7 prospective cohort studies) of about 5000 patients with AF and recent ischaemic stroke or transient ischaemic attack, the risk of recurrent stroke at 3 months after the index event was not different between those who remained on the same OAC and those who had it changed (ie, from VKA to DOAC, vice versa, or from DOAC to DOAC)[5,6]. In contrast, in a recent retrospective cohort study including larger number of patients[7], it has been demonstrated that switching to a different DOAC or to warfarin is associated with significantly increased risk of recurrent ischaemic stroke[7].

Despite extenuating the risk of stroke associated with AF, the use of OAC does not come risk free, especially from bleeding[8]. With VKA, the annual incidence of major bleeding ranges from 1.3% to 7.2%[9]. DOAC, namely apixaban, low/ high dose dabigatran, and low/ high dose edoxaban, were associated with lower annual risk of major bleeding compared to warfarin (2.13%, 2.71%/3.11%, and 1.61% /2.75% respectively)[10–12], while rivaroxaban use was associated with similar risk of major bleeding to warfarin at 3.6%[13].

The most feared complication of OAC use is intracranial haemorrhage, which confers major challenges in decision-making for stroke prevention[14]. More recently, percutaneous left atrial appendage occlusion (LAAO) has been suggested as a reasonable means of reducing stroke risk in individuals at high risk but with contraindication to systemic oral anticoagulation[15]. Prior studies compared LAAO

to VKA, but it was not until 2020 that data were published showing non-inferiority of LAAO to NOAC for stroke prevention in AF patients[16]. In clinical practice, LAAO tends to be reserved for AF patients with contraindications to OAC or with a perceived high bleeding risk[17].

In this analysis, we aim to evaluate the benefits and risks of percutaneous LAAO over DOAC in a contemporary cohort of patients with AF using a global federated research network.

Methods and materials

We conducted a retrospective observational study using data within the TriNetX platform. TriNetx, (https://live.trinetx.com), is a global health research network that provides access to anonymised electronic medical records of multiple health care organisations (HCOs) predominantly in the United States.

We ran our query on the network (83 HCOs). The TriNetX platform only uses aggregated data of de-identified information; neither the patients' nor the participating organisations' identifiable information are published in this platform. Therefore, any research using TriNetX does not require ethical approvals from any review boards.

Search was conducted on the 25th of December 2023 using the International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] codes (Table S1 in the Supplementary Material). The index date for each patient within a cohort is the day on which they first met the selected criteria for the cohort. The index event defines the earliest time point after which outcomes are analysed. Hence, we searched for patients aged 18 years and above meeting the following inclusion criteria: (1) have a diagnosis of AF, and (2) either received percutaneous LAAO or DOAC therapy on or within 12 months after the first instance of AF diagnosis, (3) included in the register and met all the above criteria between the 1st of December 2010 (as DOAC were first introduced in the ESC guidelines for AF management in 2010 as an alternative to VKA[18]) and the 1st of October 2018; allowing for five years of follow up for all participants even for those meeting the criteria on the last day of the inclusion period. Patients who had surgical occlusion or exclusion of the LAA, mechanical valve replacement, mitral stenosis, or history of gastrointestinal bleeding were excluded.

At the time of the search, 24 participating HCOs had data available for patients meeting the required study inclusion criteria for the LAAO group, while 71 responded with data for the DOAC group (Figure S1 and Figure S2 in the Supplementary Material). The outcomes of interest were: 1. All-cause mortality, 2. Ischaemic stroke, or 3. Spontaneous intracranial haemorrhage (ICH) at 5 years of follow up.

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Table S2 in the Supplementary Material).

Statistical analysis

Statistical analysis was performed using the TriNetX platform. Before comparing outcomes in cohorts, control for differences was done using propensity score matching (PSM) in a 1:1 ratio. Within the prespecified time window, both cohorts of this analysis were balanced using propensity score matching in a 1:1 ratio (Table S3 in the Supplementary Material) for age at index, sex, race, valvular heart disease, cardiomyopathy, hypertension and hypertensive heart and chronic kidney disease, dyslipidaemia, diabetes mellitus, high body mass index (BMI), chronic ischaemic heart disease (IHD), acute myocardial infarction (MI), heart failure, asthma, chronic obstructive pulmonary disease, peripheral vascular disease, thyroid disease, neoplasms, and use of antiplatelet therapy, beta-blocker, calcium channel blocker, anti-arrhythmic drug therapy, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker and lipid lowering agents. These variables were selected as they were not well matched between the two cohorts and or they are perceived to influence the clinical outcome of interest.

All categorical variables were expressed as frequencies and percentages, and were compared using Chi-squared $\chi 2$ test. All continuous variables were expressed as mean and standard deviation (SD), and were compared using independent-sample t test. Kaplan–Meier curves for the intended outcomes were created and survival distributions were assessed using log-rank test. Risk ratio (RR) with 95% confidence intervals (CIs) were calculated using logistic regression.

Outcomes of interest were assessed in the LAAO versus DOAC cohort. Statistical significance was set at $p < 0.05$.

A subgroup analysis excluding patients with history of ICH prior to the time window was also performed.

Results

The first cohort consisted of patients who received percutaneous LAAO in the 12 months following the diagnosis of AF (n=101). The second cohort had AF patients eligible for oral anticoagulation and received a DOAC on or within one year after AF diagnosis (n= 176,478). Most patients were Caucasian

(82.2% in the LAAO group and 78.6% in the DOAC group) and males (58.4% in LAAO group, 56.2% in DOAC group).

Compared to patients receiving DOAC, patients in the LAAO group were older (mean age ± standard deviation (SD)= 75 ± 8 years vs 71 ± 12 years), and had higher incidence of comorbidities such as diabetes mellitus, dyslipidaemia, peripheral vascular disease, asthma, emphysema, valvular disease, history of MI, chronic IHD, cardiomyopathy, or heart failure. More patients in the LAAO group were prescribed antiarrhythmic drugs (Table 1).

After PSM, 100 patients were included in each cohort. When assessing outcomes at 5 years, there was no difference between the two cohorts for all-cause mortality (RR: 1.52, 95% confidence interval (CI): 0.97- 2.38), rates of ischaemic stroke (RR: 1.09, 95% CI: 0.51- 2.36) or ICH (RR: 1.0, 95% CI: 0.44- 2.30) (Figures 1-3). Compared to the DOAC group, the hazard ratio (HR) for ICH in the LAAO group was 8.52 with 95% CI: 1.07- 68.23, $p = 0.36$.

Subgroup analysis

In a subgroup analysis, patients with history of ICH prior to the index event were excluded. In doing this, 16 patients were excluded from the results in the LAAO group and 10 were excluded in the DOAC group. There remained to be no statistical difference in the risk of ICH between the two groups (RR: 1.17, 95% CI: 0.51- 2.67) (Figure 4).

Discussion

Our study shows that there was no difference in the risk of death, ischaemic stroke or ICH between percutaneous LAAO and DOAC use for patients with newly diagnosed AF who are eligible for DOAC. The risk of ICH remained consistent and showed no variation between the groups, even after the exclusion of patients with prior events.

Two trials, Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) trial[19,20] and Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy (PREVAIL) trial[21], compared the efficacy and safety of LAAO to warfarin in non-valvular AF patients. However, the cohorts were relatively small (n= 463 and 269 in the intervention group, respectively). The trials only included patients who were eligible for warfarin therapy. Our study included patients using DOAC in accordance with the standard of care for stroke prophylaxis in AF.

Those in the LAAO group were not on anticoagulant treatment representing most patients in real world data who are at risk of stroke but unable to have OAC. This approach is also in line with the contemporary guidelines[17,22,23] which suggests consideration of LAAO in AF patients with perceived high bleeding risk or with a contraindication to OAC. A similar design to our registry analysis was adopted in the ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology (ASAP) trial[15] which included patients ineligible for warfarin therapy. Patient receiving LAAO in the ASAP trial did not receive warfarin at any point post device implantation. ASAP proved the safety of closing the LAA with Watchman device without oral anticoagulation cover. In contrast, in the LAAO III trial[24], a randomised trial assessing the outcomes of surgical LAAO in patients with AF undergoing cardiac surgery, patients continued on OAC after receiving surgical LAAO. Such approach was proved to result in lower risk of ischemic stroke or systemic embolism than OAC alone. Similar trial assessing concomitant percutaneous LAAO might be challenging given the current guidelines for the use of percutaneous LAAO in AF patients.

Our study had comparable cohort characteristics to those included in the PROTECT-AF and PREVAIL trials[19–21], such as mean age, sex, race, and co-morbidities.

Turagam et al.[25] performed a metanalysis including data from the 3 main randomised controlled trials- PROTECT-AF, PREVAIL, and PRAGUE-17. While a mortality benefit of LAAO over OAC was observed in this meta-analysis, this benefit was mainly observed with warfarin, and was mainly driven by the 78% reduction in haemorrhagic stroke and the 47% reduction in non-procedure-related bleeding[25]. Similar effects of VKA therapy were observed in the intention to treat analysis of the 5-year outcomes of the combined data of PROTECT-AF and PREVAIL trials[26]. In contrast, all-cause mortality was similar between both groups in our study. No difference in the risk of ischaemic stroke between our study groups was observed either.

The Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation (PRAGUE-17)[16] is the only published randomised trial to date comparing LAAO to DOAC for stroke prevention in AF patients. All participants in PRAGUE-17 had high risk for stroke and increased risk of bleeding, and LAAO was found noninferior to DOAC in preventing major AF-related cardiovascular, neurological, and bleeding events. The primary end point in the PRAGUE-17 trial was a composite (of stroke, transient ischaemic attack, systemic embolism, cardiovascular death, major or non-major clinically relevant bleeding, or procedure-/device-related complications), to take into consideration the associated long term increased risk of bleeding with DOAC use and the procedure related complication risk with LAAO[16]. However, only one patient in the DOAC group and none in the LAAO had ICH in the PRAGUE-17 trial. The analysis of the 4-year outcomes of PRAGUE-17 trial[27] showed that

LAAO was associated with lower rates of nonprocedural bleeding, but only 1 patient in the LAAO and 2 patients in the DOAC group had haemorrhagic strokes. Furthermore, the study was not powered to evaluate the individual components of the primary composite end point[27]. In contrast, the risk of ICH in our study was not significantly different between the study groups with comparable event rates in both even after excluding patients with history of ICH (n=10 in each group). On the other hand, the survival probability at the end of the follow up time window for those who had ICH was numerically lower in the LAAO group (89.30% vs 98.86%, HR: 8.52 with 95% CI: 1.07- 68.23, p= 0.36). This may be secondary to inherent characteristics of the population in the LAAO cohort with more significant comorbidities contributing to the indication for the procedure in the first instance. However, the design of our study does not allow for exploration of other possible confounders.

Strengths and limitations

The main strengths of this study are the number of individuals included in the analysis, the follow up period of five years, and the use of propensity score matching to control for clinically and prognostically relevant factors and minimise the risk of bias from confounding.

Nonetheless, our study has a few limitations. The analysis was based on data derived from administrative database (TriNetX). Hence, it is susceptible to errors related to coding. The retrospective nature of the database extracted from electronic medical records is prone to risk of bias. The database also lacks the level of granularity seen in trials and registries. For example, there were no specific data on cause of death. The data included in this cohort were predominantly from the United States health care organisations, which may not be representative of the wider global population. This may limit the study generalisability. We were also unable to explore or alleviate the impact of confounders that might have contributed to outcomes described, for example the adherence of patients to anticoagulation. Finally, as the output from TriNetx database represent an aggregate anonymised data, it does not take into account loss to follow up where some patients might have been registered as “event free” during the follow up period.

Conclusion

Among patients with newly diagnosed AF who were eligible for DOAC, those who received percutaneous LAAO had similar risk of death, ischaemic stroke and ICH at 5 years of follow up compared to those who received DOAC. While the results raise no safety concern for the use of percutaneous LAAO in the selected population, they should be used for hypothesis generation only. Future randomised controlled trials are needed to confirm the findings and advise changes in guidelines.

Statement of Ethics

Ethical approval and consent were not required as this study was based on publicly available data.

The TriNetX federated network collects aggregated data from different health-care organisations, but the identity of the participating organisations and their detailed contribution remain anonymous as well as any patients' identifiable data. As a result, any research studies using TriNetX platform do not require ethical approvals.

Conflict of Interest Statement

Sandra Elsheikh: has no conflict of interest to declare.
Tommaso Bucci: has no conflict of interest to declare.
Muath Alobaida: has no conflict of interest to declare.
Benjamin JR Buckley has received research funding from Bristol-Myers Squibb (BMS)/Pfizer.
Dhiraj Gupta: has received proctor fees from Abbott for LAAO implants.
Greg Irving: has no conflict of interest to declare.
Andrew Hill: has no conflict of interest to declare.
Gregory Y.H. Lip: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. He is also a co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871. No fees are received personally.
Azmil H. Abdul-Rahim: has no conflict of interest to declare.

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Author Contributions

Sandra Elsheikh conceived and designed the research; Gregory Y.H. Lip and Azmil H. Abdul-Rahim handled the supervision. Sandra Elsheikh conducted the analysis. Muath Alobaida, Tommaso Bucci, and Benjamin J.R Buckley verified the analytical methods and results. Sandra Elsheikh drafted the initial manuscript. Muath Alobaida, Tommaso Bucci, Benjamin J.R Buckley, Dhiraj Gupta, Greg Irving, Andrew Hill, Gregory Lip and Azmil Abdul-Rahim reviewed the results, made critical revision of the manuscript for key intellectual content and approved the final version.

Data Availability Statement

To gain access to TriNetX data, a request can be made (https://live.trinetx.com), but costs may be incurred, a data sharing agreement would be necessary, and no patient identifiable information can be obtained. Further enquiries can be directed to the corresponding author.

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