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Meta-analysis of Left Atrial Appendage Closure Versus Anticoagulation in Patients With Atrial Fibrillation

Oral anticoagulation (OAC) (vitamin-K-antagonists or direct oral anticoagulants) is the standard-of-care to prevent systemic thromboembolism in patients with atrial fibrillation (AF). However, a growing number of patients have a contraindication or are deemed inappropriate for long-term OAC therapy[1] and therefore an alternative mechanical strategy to prevent left atrial appendage (LAA) thrombus migration has emerged to treat this population. We conducted a meta-analysis of all randomized clinical trials (RCTs) to assess the safety and efficacy of LAA closure (LAAC) versus anticoagulation in high-risk AF patients.

We performed a comprehensive electronic databases search for RCTs. Two authors extracted and analyzed the data using R v3.3.1 and STATA v15.1 software. The primary outcome was all-cause death. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) to account for differences in follow-up duration using a random-effects model. A unique Kaplan-Meier curve for all-cause death was reconstructed from the included trials and a Cox proportional-hazards model was calculated. The proportional-hazards assumption was tested using the residual Schoenfeld test.

We identified 3 RCTs with 1,516 total patients (age 73.0 ± 8.1 years; females 31%), randomizing 5,038.9 patient-years of follow-up.[2,3] The mean CHA2DS2-VASc score was 4.0 ± 1.5 and 31.1% of the patients had permanent AF. Successful device deployment was achieved in 91.9% of the study participants. Early procedural complications (within 7 days) included 3.1% pericardial effusion, 0.6% device embolization, 0.5% major bleeding, 0.5% stroke, and 0.1% death (combined risk of serious complications 5.0%).

Compared with OAC, LAAC was associated with a statistically significant reduction of all-cause death (incident-rate-ratio = 0.74, 95% CI 0.56 to 0.99, p = 0.02; HR 0.73, 95% CI 0.56 to 0.97, p = 0.03; absolute-risk-difference = 2.6%) and cardiovascular death (HR 0.63, 95% CI 0.42 to 0.94, p = 0.02). There were no significant differences between groups in terms of all stroke or systemic embolism (HR 0.99, 95% CI 0.65 to 1.50, p = 0.96) or overall bleeding (HR 0.88, 95% CI 0.65 to 1.20, p = 0.43). However, LAAC was associated with a significant reduction of nonprocedural bleeding compared with OAC (HR 0.49; 95% CI 0.35 to 0.70; p <0.01) (Figure 1). Subgroup analysis of all-cause mortality based on the type of anticoagulants (vitamin-K-antagonists vs direct oral anticoagulants) showed no significant interaction.

This investigation demonstrated for the first time that LAAC was associated with a significant reduction of all-cause death. LAAC was also associated with a significant reduction in cardiovascular death and nonprocedural related bleeding.

The observation of lower mortality in the LAAC group is paramount considering 2/3 of the enrolled population were above 75 years which may impose significant competing mortality risks in this population. The primary driver for the lower mortality could be explained by the significant reduction in bleeding.

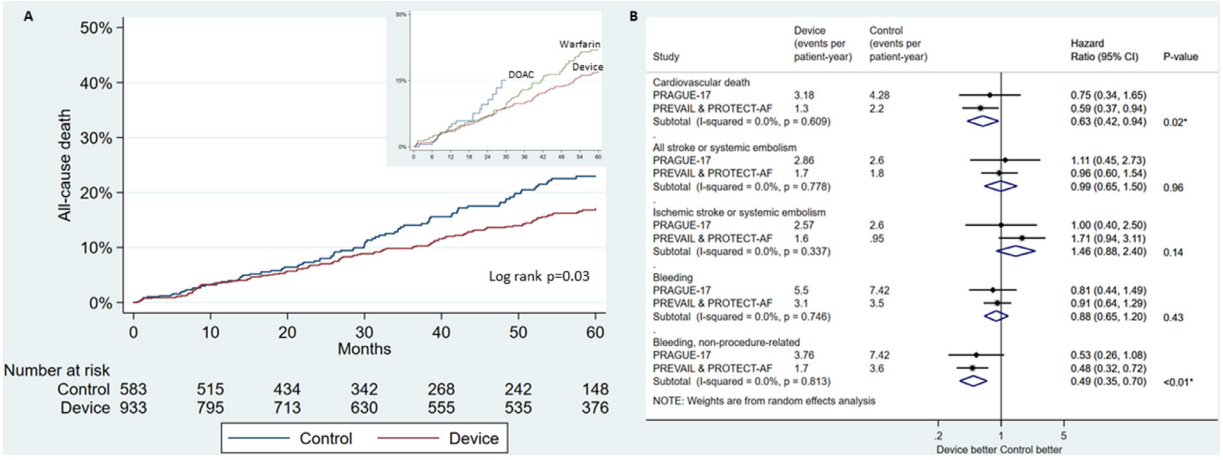

Figure 1. Kaplan Meier curve for all-cause death *(A)* and forest plot for clinical outcomes *(B)*. DOAC = direct oral anticoagulants; PRAUGE-17 = Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation; PREVAIL = Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy; PROTECT AF = WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation.

The divergence of mortality curves is notable beyond follow-up duration of 1 year − the time where most of the LAAC arm discontinued anticoagulant therapy. It is noteworthy in the PRAGUE-17 trial, the LAAC group did not require anticoagulation (only 13.8% of the patients received apixaban for 3 months).[3] This observation might indeed favor lower bleeding in the device arm, and therefore conferred a lower mortality.

The nonstatistically significant trend toward higher ischemic stroke or systemic embolism in the LAAC arm warrants further investigation. This observation is mainly derived from the lower-than-expected ischemic stroke events in the warfarin group of the PREVAIL trial at a rate of 0.73%. This rate could be partially explained by the relatively high appropriate time-in-therapeutic range for warfarin (68%) and/or low sample size, which is reflected by the wide confidence interval in our analysis.[2]

Although serious early procedure-related complications were not infrequent (5.0%) these complications occurred predominantly in earlier RCTs, with more contemporary data demonstrating a lower complication risks and higher success rates, perhaps due in part to improvements in patient selection and/or operator experience.[4] Nevertheless, the decision of LAAC should be individualized in a shared decision-making process with appropriately selected patients, considering the short-term procedural complications, long-term thromboembolism risk absent therapy, and bleeding risks while on anticoagulation.

In conclusion, in selected patients with nonvalvular AF, LAAC is associated with lower all-cause and cardiovascular death, and nonprocedural bleeding without increased ischemic events. Further long-term adequately powered trials assessing ischemic endpoints are needed.

Disclosures

The authors have no conflicts of interest to disclose.

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Letter to the Editor in Response to Nous et al 2020

Dear Editor,—

We were interested to read Nous et al's[1] recent article which described the prognostic benefits of using coronary computed tomography angiography (CCTA) to identify subclinical coronary artery disease (CAD) in patients with atrial fibrillation (AF). The addition of the calcium score and CCTA resulted in the re-classification of 47 patients' cardiovascular risk stratification score. Twenty-eight of these moved up in classification with 8 becoming very high-risk due to obstructive CAD. Initiation of secondary prevention (statin therapy) in these patients was concluded to be beneficial.[2]

Dunleavy et al[3] investigated patients undergoing computed tomography of the pulmonary veins prior to AF ablation therapies. They identified 131 patients with undiagnosed coronary artery calcification, yet none of these patients were prescribed a statin upon discharge. Thus, whilst CCTA may enhance risk stratification of AF patients it is apparent that this does not always translate to a change in clinical practice.

Nous et al[1] also states that the observed radiation dose of CCTA was high, limiting its use in asymptomatic patients. Cori et al[4] noted that in symptomatic patients undergoing radiofrequency ablation the use of CT compared to no CT resulted in a significantly higher effective radiation dose with no improvements in clinical outcomes for AF. Whilst it is worth noting that Nous et al[1] identified benefit in stratification for cardiovascular risk, it raises the point as to whether the benefits of routine CT in all AF patients would justify the radiation exposure.

Despite these limitations, the authors introduce a novel way in which CT in AF could be of prognostic benefit.[1] As the identification and management of CAD to improve AF burden is already recommended in the international guidelines,[5] this approach may be useful prior to catheter ablation given that patients are likely to undergo a CT. The true impact CT scans could have on stratifying the medical management of AF patients requires further investigation with larger sample sizes.

Disclosures

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