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EDITORIAL COMMENT

LAAO in Cardio-Oncology

Protecting the Delicate Balance Between Stroke and Bleeding?*

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Cancer is well recognized as an independent risk factor for atrial fibrillation (AF),[1,2] and cancer therapies may increase the risk of AF through cardiotoxic effects.[2] Malignancy, particularly upper gastrointestinal and hematological malignancies,[3] increase the risk of arterial and venous thrombosis and thereby raises the ischemic stroke risk. The cornerstone of stroke prevention in AF remains systemic anticoagulation, which may promote bleeding because of the presence of metastases, thrombocytopenia, and drug-drug interactions with chemotherapeutic agents.[2] Left atrial appendage occlusion (LAAO) has emerged as a means to mitigate stroke risk without the bleeding risk of anticoagulation. Since approval of the first-generation Watchman (Boston Scientific) by the Food and Drug Administration in 2015, LAAO is now widely performed and has a 2B recommendation for stroke prevention in patients with AF and contraindications to long-term anticoagulation in the American College of Cardiology/American Heart Association/Heart Rhythm guideline update.[4] However, cancer patients were excluded from the original clinical trials demonstrating the safety and efficacy of Watchman LAAO,[5,6] and outcomes in these patients remain unclear.

To explore the role of LAAO in this population, Shabtaie et al[7] studied LAAO in 55 cancer patients at 2 experienced centers as published in this issue of *JACC: CardioOncology*. The authors interrogated an institutional cancer registry and abstracted the CHA_2Ds_2-VASc score, cardiovascular comorbidities, and bleeding risk factors from the National Cardiovascular Data Registry (NCDR). After a median of 1.6 years of follow-up, they compared incident mortality, stroke, bleeding, and device-related complications in this group with 212 matched control patients without cancer. Inverse probability weights were calculated to adjust for the effects of age and sex between cancer patients and controls.

The cancer cohort had a mean age of 79 ± 6 years, was predominantly male (80%), and was high risk for both ischemic events (median CHA_2DS_2-VASc of 5) and major bleeding (median Hypertension, Abnormal renal/liver function, Stroke, Bleeding score of 3), with 85.5% having prior significant bleeding. Compared with the landmark PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation)[6] and PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy)[8] trials that excluded patients who were significantly anemic, thrombocytopenic, or had contraindications to anticoagulation or antiplatelet therapy, this cohort was at higher bleeding risk. However, the bleeding risk was comparable to that in the more contemporary PRAGUE-17 (Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation) trial and the real-world NCDR LAAO registry.[9,10] Of note, this retrospective study is limited by a small sample size and patient heterogeneity, with a lower representation of malignancies that carry higher thrombotic risk. Furthermore, few (n = 12) were receiving active cancer treatment.

One-year mortality was only 6.5%, although the 5-year mortality rate was 50% and largely unrelated to LAAO or AF; instead, it was driven by cancer progression and infection. In this population with life

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expectancy limited by cancer, metrics that determine quality of life, such as freedom from stroke, major bleeding, and device-related complications, may be more meaningful outcomes than long-term survival when considering LAAO.

Ischemic stroke occurred in 1 patient at 1 year (1.4%) and an additional patient at 5 years (3.4%), which was not significantly different from the noncancer control group. The rate of ischemic stroke events was similar to the NCDR LAAO registry[9] as well as PROTECT-AF (2.2 per 100 person-years in 2 years of follow-up) and PREVAIL (1.9% in 12 months of follow-up).[6,8]

Major bleeding at 1-year post-LAAO occurred in 10.7% of patients, which did not differ significantly from the noncancer cohort or the small (n = 12) subset actively receiving cancer treatment at the time of device implantation. The rate of major bleeding was comparable to the real-world NCDR registry (7.85%).[9] The vast majority of study patients (84%) continued warfarin or direct oral anticoagulant therapy for the first 45 days after LAAO implantation (as defined by PROTECT-AF to allow for device endothelization) followed by lifelong aspirin. Hence, unsurprisingly, most of the major bleeding events occurred while receiving initial anticoagulation. Increasing evidence from ASAP, EWOLUTION, and other studies suggest that a short duration of dual antiplatelet therapy post-LAAO without anticoagulation is safe[11-13] and may be more likely used in cancer patients with high bleeding risk. Additionally, the cancer patients studied by Shabtaie et al[7] were neither profoundly anemic nor thrombocytopenic (median platelet count = 186,000). Whether overall outcomes are similar in patients who are more thrombocytopenic or receiving cancer therapies that cause bone marrow suppression was not answered by this study even though bleeding rates would most certainly be lower with LAAO than lifelong anticoagulation.

Device-related thrombosis (DRT) and peridevice leak (PDL) are notable complications of LAAO. DRT, which is associated with a 4- to 5-fold higher risk of ischemic events,[14,15] was found in 4.2% at 1 year, similar to rates in clinical trials and real-world registries,[14] and 7.2% at 5 years. In the cancer cohort, PDL >5 mm was found in only 1 (1.1%) patient at 1 year. Smaller leaks, which are more common and may be underdiagnosed depending on the mode of surveillance imaging (transesophageal echocardiography vs computed tomography),[16] were not reported but may increase ischemic stroke risk.[17] Importantly, this retrospective study did not include patients implanted with the newer-generation Watchman FLX (Boston Scientific) or the Amulet (Abbott Laboratories) devices, which were only recently approved by the Food and Drug Administration, and the incidence of DRT and PDL may be lower in these newer devices.[18]

Based on the findings of this retrospective study by Shabtaie et al,[7] Watchman LAAO appears safe in cancer patients without increased ischemic stroke, procedural complications, or cardiovascular mortality compared with noncancer patients. Although LAAO vs anticoagulation was not directly evaluated in this study, LAAO appears to be a reasonable alternative for stroke prevention in cancer patients in whom the bleeding risk with anticoagulation may be potentially prohibitive. Oncologists and primary care providers for these cancer patients with AF should be aware of the option of LAAO, which may be underutilized in this population. Nonetheless, not all cancer patients carry the same risk for bleeding or other types of clotting (such as venous thromboembolism), which influences the risk-benefit equilibrium of anticoagulation. A patient-centered approach with a multidisciplinary care team is especially important for cancer patients in deciding to pursue LAAO given the delicate balance between the risks of ischemic stroke and bleeding. More studies are needed to refine our understanding of which cancer patients may derive the greatest benefit from LAAO and the optimal anticoagulation/antiplatelet regimen post-device implantation.

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