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Commentary

OCEANIC-AF and the inferior efficacy of asundexian compared to apixaban in patients at high risk with atrial fibrillation: Have we come to the end of the road for factor XIa inhibitors?

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"The advances of science are so important to enhancing patient care over the long term" [1]
Gary H. Gibbons, M.D.
Director, National Heart, Lung, and Blood Institute

1. Introduction

Atrial fibrillation is the most common chronic cardiac arrhythmia and is associated with increased morbidity and mortality globally [2]. Unfortunately, despite the availability of proven, evidence-based medical treatment, >30 % of patients do not receive adequate anticoagulation therapy [3], placing them at unnecessary risk for stroke and thromboembolism. The development of direct oral anticoagulants (DOACs) was a major step forward in pharmacological therapy for patients at high risk for stroke with atrial fibrillation. These newer agents became clinically available after 50 years of using warfarin, which although effective, has a high degree of potential toxicity and difficulty with appropriate clinical use due to the need for close monitoring and multiple dosage adjustments.

Piccini et al. presented the results of the Asundexian vs. Apixaban in Patients with Atrial Fibrillation (OCEANIC-AF) at the European Society of Cardiology Late-Breaking Hotline Session on September 1, 2024. The trial results were simultaneously published in the New England Journal of Medicine [4]. The randomized cohort on asundexian demonstrated inferior efficacy to prevent stroke and thromboembolism and has led to questioning the viability of Factor XIa inhibition as a useful clinical tool to protect high-risk atrial fibrillation patients.

2. OCEANIC-AF: a large, international phase III study

This large, international phase III study planned to include a cohort of over 18,000 participants at high risk for stroke with atrial fibrillation, from 1069 locations globally. It sought to confirm that asundexian - a factor XIa inhibitor, in patients with atrial fibrillation who are at risk for stroke, would have similar efficacy with increased safety when compared to apixaban. The primary outcome measured was the time for the first occurrence of a stroke or systemic embolism. In the consideration of the need to determine the validity results in a widespread population, OCEAN-AF purposefully enrolled a diverse population, with a mean age of 73.9 ± 7.7 years, 5214 (35.2 %) were females, 10,427 (70.4 %) were white, and the patients were balanced geographically across Eastern Europe, North America, South America, Asia, Western EU, Australia, and Israel. The population was appropriately high risk with a mean CHA_2DS_2-VASc score was 4.3 ± 1.3. In addition, 13,123 (88.6 %) had hypertension, 9466 (63.9 %) had hyperlipidemia, 6929 (46.8 %) had heart failure, 4948 (33.4 %) had coronary artery disease, 5470 (36.9 %) had diabetes, and 2756 (18.6 %) had chronic kidney disease [4].

Disappointedly, asundexian, given at a dose of 50 mg once daily, was inferior to apixaban, 5 mg twice daily or 2.5 mg twice daily in patients with at least two of the following: an age of ≥80 years, a body weight of ≤60 kg, and a serum creatinine level of ≥1.5 mg per deciliter [133 μmol per liter]. With a population of approximately 14,000 patients, the

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steering committee was informed of the inferior asundexian results and deemed it necessary to stop the trial. The primary end point occurred in 98 patients (1.3 %) assigned to receive asundexian and in 26 (0.4 %) assigned to receive apixaban (hazard ratio [HR] 3.79; 95 % confidence interval [CI], 2.46 to 5.83). However, asundexian was associated with fewer major bleeding events which occurred in 17 patients (0.2 %) who received asundexian and in 53 (0.7 %) who received apixaban (HR 0.32; 95 % CI, 0.18 to 0.55) [4].

3. The ongoing need for a better antithrombotic drug for atrial fibrillation

Based on the preponderance of the evidence from multiple atrial fibrillation clinical trials, DOACs are now accepted as first-line therapy over warfarin, with lower rates of stroke, mortality, and intracranial hemorrhage. Nevertheless, patients receiving DOACs still face a bleeding risk of 2.7–3.5 % per year, a major challenge for maintaining therapy and adherence, resulting in undertreatment, underdosing, and poor treatment persistence [5]. Subsequently, <66 % of patients with atrial fibrillation and CHA_2DS_2-VASc score above 2 are prescribed an oral anticoagulant (OAC) at all and as much a 25 % of patients on DOACs are underdosed, with potential higher rates of thromboembolic events. Overall, as many as 1 in 3 patients adhere to their DOAC <80 % of the time, associated with potentially suboptimal clinical outcomes [6,7].

Moreover, although the factor Xa inhibitors provide a direct mean of stopping clot initiation, factor XIa inhibition uniquely works by decreasing clot promulgation versus clotting initiation. Factor XIa inhibitors promise to uncouple hemostasis from thrombosis. Pathological thrombi are prevented through inhibition of thrombin amplification, while hemostatic clots can still form as the tissue factor pathway would continue to produce thrombin. These considerations therefore reflected the potential of increased safety, with similar efficacy compared to the present well tolerated DOACs.

4. Was the tested asundexian dosage appropriate? - the rational for 50 mg

The chosen 50 mg asundexian, had previously achieved appropriate thrombi inhibition in prior basic science reports. This dose was based on basic clinical science and results of a phase 2 study in patients with atrial fibrillation, PACIFIC-AF. This was an active comparator-controlled, double-blind, double-dummy, parallel group for dose-finding to compare the safety of the oral factor XIa inhibitor asundexian with apixaban in patients with atrial fibrillation [8]. The primary objective was to evaluate whether the oral factor XIa inhibitor asundexian would lead to a lower incidence of bleeding in these patients. Quantification of factor XI inhibition was evaluated at peak and trough levels after 4 weeks of treatment with asundexian. The primary endpoint was bleeding, a composite of major bleeding or clinically relevant non-major bleeding according to International Society on Thrombosis and Hemostasis (ISTH) criteria. The exploratory efficacy composite endpoint was cardiovascular death, myocardial infarction, ischemic stroke, or systemic embolism.

Patients were eligible for the study if they have atrial fibrillation, with associated high risk for stroke or thromboembolism, with indication for indefinite treatment with an anticoagulant. Patients were not eligible for the study if, among other considerations, they had mechanical heart valve prosthesis (not including transcatheter aortic valve replacement); moderate-to-severe mitral stenosis at the time of inclusion into the study; atrial fibrillation only due to reversible cause (thyrotoxicosis, endocarditis, pneumonia, pulmonary embolism); participants after successful ablation therapy without documented recurrent atrial fibrillation or participants with LAA occlusion/exclusion or plan for ablation or LAA occlusion/exclusion within the next 6 months starting from randomization, or if they suffered a recent ischemic stroke.

The results of this trial revealed that asundexian resulted in 81 % and 90 % inhibition of factor XIa activity at trough and peak concentrations, respectively, when 20 mg dose was used, and in 92 % and 94 % inhibition at trough and peak concentrations; respectively, when 50 mg dose was used. The exploratory thrombotic composite endpoint occurred in two patients treated with asundexian 20 mg (both were ischemic strokes), four in those treated with asundexian 50 mg (one was ischemic stroke), and three in those treated with apixaban (none were ischemic stroke) (8). The authors of PACIFIC-AF concluded that anticoagulation with the factor XIa inhibitor oral asundexian at 20 mg and 50 mg was associated with less bleeding risk when compared to apixaban, with no signal for decreased efficacy.

Therefore, OCEANIC-AF was the first large phase III study, in patients with atrial fibrillation and high risk, to potentially translate these results eventually into clinical practice. Despite the encouraging results from the PACIFIC-AF trial, the OCEANIC-AF trial failed to show non-inferiority and The Independent Data Monitoring Committee (IDMC) recommended stopping the trial. Although the number of strokes may appear to have been small, there was a statistically and potentially clinically significant incidence, leading to the discontinuation of the medication and early termination of the trial. The curves separated earlier and stayed separated suggesting that this was a real effect of asundexian. At the time of trial termination, 14,830 of the planned 18,000 patients had been randomized and all sites were notified worldwide. Patients were transitioned to open-label therapy, close-out visits were conducted across the world, and all patients included into the study were scheduled to be switched to standard of care treatment, with direct communication sent out to all investigators.

Although OCEANIC-AF was stopped, research for asundexian in the OCEANIC-STROKE study was not affected and continues, with no stopping recommended by the IDMC. In addition, evaluation of factor XI and XIa inhibition is ongoing for other indications in patients in need of antithrombotic treatment.

5. OCEANIC-AF as a negative trial: what could have been done better?

The first analysis to understand the negative results of OCEANIC-AF was looking at the planned pharmacokinetic-pharmacodynamic (PK/PD) sub-study, with an evaluation at 4 weeks post randomization. The PK was similar between OCEANIC-AF and PACIFIC-AF, factor XI activity at trough was similar between OCEANIC-AF (8.1 %) and PACIFIC- AF (8.0 %). An analysis of subgroups based on a limited number of primary efficacy events showed no differences in response [9].

Moreover, participants who had not been on an anticoagulant were pre-specified as oral anticoagulant (OAC) naïve, and patients who were on OAC were pre-specified as OAC experienced. Regardless of the treatment arm, asundexian vs apixapan, the OAC naïve had a lower incidence of stroke or systemic embolization (HR 1.42, 95 % CI 0.54 to 3.73) when compared to OAC experienced (HR 4.66, 95 % CI 2.84 to 7.65). Although the HR of 1.42 was still inferior for asundexian in regard to the incidence of stroke or systemic embolism, it was encountered less often in the OAC experienced subgroup. Thus, this prespecified analysis suggests that those who had already been on OAC and have not suffered bleeding or stroke would have a lower risk of any complications with any form of therapy and have a lower risk than those who had not been treated or only recently diagnosed with atrial fibrillation. One consideration is that while 50 mg asundexian is inferior to apixaban, especially in those who have already been treated with an OAC, perhaps >92 % factor XIa would be needed to show equal efficacy to a DOAC.

6. There is no panacea for anticoagulation therapy. Is this the end of the road for factor XIa inhibitors?

Although DOACs are noninferior and even superior to vitamin K antagonists for preventing stroke in patients with atrial fibrillation, there are clinical scenarios where DOACs are not the first choice for

appropriate anticoagulation. Warfarin remains the first anticoagulant agent of choice for patients with mechanical heart valves, thrombotic antiphospholipid syndrome, and atrial fibrillation associated with rheumatic heart disease. In addition, warfarin may be considered a better clinical choice for anticoagulation for patients with left ventricular thrombus, catheter-associated deep vein thrombosis, cerebral venous sinus thrombosis, and for patients with atrial fibrillation or venous thrombosis who have end-stage renal disease [10,11].

The search for a new form of OAC contemporary treatment with atrial fibrillation can be reasonably argued against, considering that DOACs for atrial fibrillation are quite good with little margin for improvement, even with an agent which hypothetically would be safer and equal in efficacy. On the other hand, in addition to asundexian, factor XI and other factor XIa inhibitors, if in the future proven to have comparable efficacy and perhaps less potential complications compared with present DOACs, may overcome present real and perceived dangers as barriers to care.

The factor XIa inhibitor class is still undergoing phase II studies in other areas, including post myocardial infarction (PACIFIC-AMI) [12] and non-cardioembolic stroke (OCEANIC-STROKE) [13]. Factor XI pathway inhibitors are developed in different molecular forms, with different mechanism of action inhibiting the inactive factor XI alone, factor XIa alone, or both. This might render the potency of these agents in inhibiting the factor XI pathway different. Moreover, there is no standardized laboratory assay that would allow the direct comparison of the pharmacodynamic potency across these agents [14]. With that being said, future agents in the factor XI pathway, studied for different indications, may reveal different results. While this study may be described as a defeat for science, it's the essence of evidence-based research. The real goal of large, randomized outcome trials is to better inform the science and art of medicine and reveal ways to best to help our patients.

7. Conclusion: the struggle continues

The negative results of OCEAN-AF are a set-back for the clinical development of asundexian. However, correctly applied, medical research opens doors to understanding, and by doing randomized major trials, researchers seek to reveal both cardiovascular benefits and potential harms of newer approaches to therapy. Realistically, despite the best evidence of modern medical research, it is now clear that there is no panacea for the prevention of atrial fibrillation associated with ischemic stroke and thromboembolism. The essence of medicine is continuing evolution in scientific knowledge, based on basic research and randomized clinical trial evidence. The challenge, especially in the US, where disparities in medical care and outcomes are distressingly persistent, is to then apply the best evidence to all patients, regardless of race/ethnicity, socioeconomic status, sex/gender, geography, ability or disability.

Ethical statement

The authors declare the following:

- The work described has not been published previously.
- The article is not under consideration for publication elsewhere.
- The article's publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.
- If accepted, the article will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

CRediT authorship contribution statement

Keith C. Ferdinand: Conceptualization, Writing – original draft. **Asaad Nakhle:** Writing – review & editing.

Declaration of competing interest

Dr. Ferdinand is a member OCEANIC-AF Steering Committee. Consultant- Novartis, Medtronic, Eli Lilly, Boehringer Ingelheim, Janssen.

Dr. Nakhle has nothing to disclose.

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