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Asundexian and apixaban exert differential effects on thrombin generation: insights from OCEANIC-AF

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In patients with atrial fibrillation (AF), direct oral anticoagulants (DOACs) reduce the risk of stroke and systemic embolism but increase the risk of major bleeding. Since coagulation factor XI (FXI) plays a major role in thrombus amplification, but only a minor role in haemostasis, strategies that inhibit FXI are attractive to reduce bleeding risk associated with DOACs.[1]

The only published Phase 3 trial evaluating FXI inhibition in patients with AF, OCEANIC-AF, comparing the oral small molecule FXIa inhibitor asundexian with the FXa inhibitor apixaban,[2] was stopped prematurely because of a higher incidence of stroke or systemic embolism with asundexian compared to apixaban, despite less bleeding. The reason behind the lower effectiveness of asundexian for stroke prevention remains unclear, with little data on the differential effects of these drugs on key markers of coagulation and fibrinolysis.

In a small cohort of patients participating in OCEANIC-AF (n = 20), who were also enrolled in a prospective, observational study evaluating thrombotic markers (IRAS ID 301851 and 328110), we assessed markers of thrombus formation and lysis under static and high shear conditions (*Figure 1*), with ethical and regulatory approval. Following informed consent, patients were randomized centrally, and after taking blinded trial medication with apixaban or asundexian for at least 2 weeks, blood samples were taken ∼3 h after the last anticoagulant dose. Citrated blood was centrifuged at 2300 × g for 10 min to yield platelet-poor plasma. Native whole blood was evaluated using the Global Thrombosis Test (Thromboquest Ltd.) to measure shear-induced occlusion time and endogenous lysis time.[3] D-dimer, urokinase-type plasminogen activator (uPA), and plasminogen activator inhibitor (PAI)-1 antigen concentrations were measured in platelet-poor plasma using Simple Plex™ assays on Ella system™.[4] Fibrinogen, FXI antigen, thrombin-antithrombin complex (TAT), soluble glycoprotein VI (GPVI), and PAI-1 activity were measured by ELISA. Thrombin generation was assessed using calibrated automated thrombography (Diagnostica Stago). Turbidity assays, lysis, and plasmin generation were quantified.[4] Samples were analysed blinded to treatment allocation.

Following trial termination and official unblinding, thrombotic profiles were compared by drug allocation. Patients on asundexian and apixaban were well matched for clinical characteristics (see Supplementary data online, *Table S1*).

Patients on asundexian exhibited ∼4-fold higher endogenous thrombin potential (ETP) and peak thrombin generation (TG) compared to those on apixaban (760.5 ± 411.7 vs 199.8 ± 123.0 nM.minute, P = 0.002 and 81.8 ± 55.6 vs 17.4 ± 11.1 nM, P =0.005, respectively), with no difference in lag time or time to peak TG (*Figure 1*). Compared to healthy volunteers on no medication, in AF patients, ETP was reduced 29% by asundexian (1078 ± 237.8 vs 760.5 ± 237.8 nM/min, P = 0.049) and 81% by apixaban (1078 ± 237.8 vs 99.8 ± 123 nM/min, P < 0.0001), and peak TG reduced 38% by asundexian (133 ± 49.53 vs 82 ± 55.6 nM P = 0.0367) and 87% by apixaban (133 ± 49.53 vs 17.5 ± 11.2 nM, P < 0.0001).

Patients on asundexian exhibited longer activated partial thromboplastin time, higher international normalized ratio, and similar thrombin time compared to those on apixaban, with no difference in fibrinogen, FXI antigen, D-dimer, TAT, GPVI, PAI-1 antigen or activity, plasmin generation with tPA or uPA, plasma clot lysis, whole blood high-shear occlusion, or endogenous lysis times. We show, for the first time, that in patients with AF, asundexian is less effective at inhibiting TG than apixaban. The 4-fold greater TG on asundexian may reflect reduced protection against thrombus formation in low-shear environments, such as the left atrium of patients with AF, and could explain the

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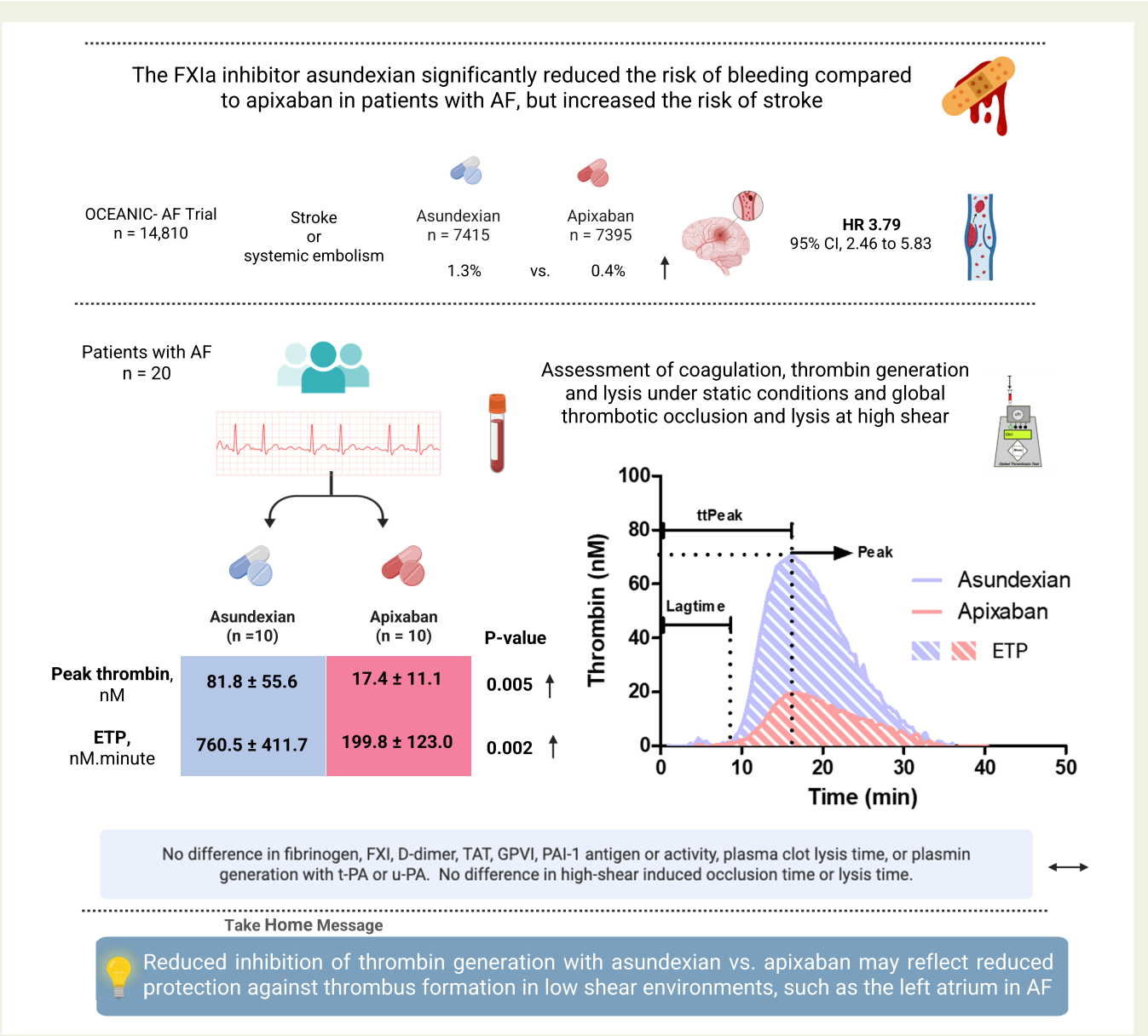

Figure 1 In a small sub-study of patients taking part in the OCEANIC-AF trial, peak thrombin generation and endogenous thrombin potential were significantly higher in patients on asundexian than in patients on apixaban. AF = atrial fibrillation, ETP = endogenous thrombin potential, FXIa = activated factor XI, glycoprotein VI (GPVI), PAI-1 = plasminogen activator inhibitor 1, thrombin-antithrombin complex (TAT), t-PA = tissue plasminogen activator, u-PA = urokinase plasminogen activator.

higher incidence of stroke on asundexian 50 mg daily in OCEANIC-AF.[2] In the phase 2 PACIFIC-AF trial,[5] asundexian reduced FXIa activity by 92% at trough and 94% at peak concentrations, which was used to indicate the drug effect. However, the pharmacodynamic profiles of asundexian and apixaban with respect to TG were not assessed. FXIa inhibition attenuates TG via the intrinsic coagulation pathway, while FXa inhibition targets the common pathway, therefore assessment of TG may be superior to FXIa activity as a measure of anticoagulation effectiveness. Others have shown a weak correlation of TG with DOAC drug concentrations,[6] and asundexian achieved only limited inhibition of TG *in vitro*.[7] Once daily dosing has been proposed as a possible explanation for reduced clinical efficacy of asundexian compared to apixaban (twice daily). Importantly, we assessed thrombosis markers in the peak therapeutic window, and since asundexian has a terminal half-life of 14–17 h, we can infer that as drug concentration falls, inhibition of thrombin may be further compromised.

These distinct differences in pharmacodynamic profiles between asundexian and apixaban are apparent under static conditions but not at high shear. At high shear, thrombus formation is driven by von Willebrand factor and shear-dependent platelet aggregation, whereas fibrin-rich clots dominate in venous thrombosis. In whole blood under high shear, thrombotic occlusion time and lysis time were similar on apixaban and asundexian. This could be pertinent for applications of FXI inhibition

to high-shear environments, such as coronary disease or stroke, where asundexian could prevent thrombosis without ncreasing bleeding. This is supported by the results of the OCEANIC-STROKE trial in patients with non-cardioembolic ischaemic stroke or TIA, where addition of asundexian to aspirin reduced the rate of ischaemic stroke, without increasing major bleeding.[8] In patients with recent acute coronary syndrome (ACS), addition of DOAC to antiplatelet therapy (APT) reduced ischaemic risk, but greatly increased bleeding.[9] In the phase 2 PACIFIC-AMI trial, addition of asundexian to dual APT did not increase bleeding, but the trial was not powered to detect a reduction in ischaemic endpoints.[10] The ongoing LIBREXIA-ACS trial (NCT05754957), evaluating the FXIa inhibitor milvexian as an adjunct to APT in ACS, may shed further light on the efficacy of these inhibitors in a high shear context. FXIa inhibition may also be an attractive strategy to prevent contact pathway activation with artificial surfaces (mechanical circuits) or for thrombosis driven by complement activation or neutrophil extracellular traps (e.g. sepsis). Conversely, thrombus formation on artificial valves is driven by activation of both the contact (foreign material) and tissue factor (shear stress) pathways, particularly in low-flow environments, requiring intense anticoagulation, unlikely to be afforded by FXI inhibition.

The main limitation of our study is the small sample size. The groups in our study were well matched and broadly similar to the OCEANIC-AF cohort, although older, entirely white, with lower CHA_2DS_2-VASc score and rates of diabetes, hypertension, and hyperlipidaemia (see Supplementary data online, *Table S1*). Blood samples were taken in the peak therapeutic time window, but pharmacokinetics or drug levels were not measured and so compliance is a possible confounder. Our results are hypothesis generating, and the impact of FXIa inhibition on TG may vary by drug, by mechanism of action and by disease state.

In conclusion, in this proof-of-concept study, TG was significantly higher on asundexian than on apixaban, which may explain the higher stroke rate with asundexian compared to apixaban in OCEANIC-AF. Coupled with similar high shear-induced thrombotic occlusion times on apixaban and asundexian, these exploratory findings could inform future clinical applications of FXI/FXIa inhibitors.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

D.A.G. has received honoraria from Chiesi, J&J and BMS, unrelated to this work. The other authors have no disclosures to report.

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Data Availability

The data may be made available upon suitable request.

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Ethical Approval

The study was approved by the UK Health Research Authority and the local Research and Development Board of East and North Hertfordshire NHS Trust.

Pre-registered Clinical Trial Number

Not applicable.

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