Accepted manuscript.
Article accepted for publication in Journal of the American College of Cardiology, 21/01/2019.

Differential effects of oral anticoagulation on thrombotic and fibrinolytic profile in Asian and non-Asian patients with non-valvular atrial fibrillation

Brief title: Thrombotic profile of Asians versus non-Asians with AF

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Word count: 800

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Acknowledgement and funding

In the United Kingdom, this study was supported by a grant from ERISTA (BMS/Pfizer European Thrombosis Investigator Initiated Research Program, BMS protocol number: CV185-622). The investigators acknowledge the support of the U.K. National Institute for Health Research Clinical Research Network (NIHR CRN).

Disclosures

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.
DAG: Related through family to a director in Thromboquest Ltd. but no personal or institutional research sponsorship received from this company, and instrument and consumables purchased through normal commercial transactions. Speaker fees/honoraria from Bayer, BMS, Abbott. Other co-authors have no conflicts to declare.

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Abbreviations

ICH = intracranial haemorrhage

INR = international normalized ratio

LT = lysis time

NOAC = non-vitamin K antagonist oral anticoagulant

NVAF = non-valvular atrial fibrillation

OAC = oral anticoagulant

OT = occlusion time

VKA = vitamin K antagonist

vWF = von Willebrand factor

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Asian patients with non-valvular atrial fibrillation (NVAF) have a higher risk of stroke and systemic embolism than non-Asians, but experience more frequent major bleeding on oral anticoagulation (OAC), including intracranial haemorrhage (ICH). Although Asians constituted only a minority of patients in large trials comparing VKA and non-vitamin K antagonist oral anticoagulants (NOACs), the magnitude of stroke reduction with NOACs appears greater in Asians than non-Asians(1,2). The pathophysiological mechanisms underlying these ethnic differences are unclear. We hypothesised that differences in thrombotic and fibrinolytic profiles, specifically in response to OAC use, may be responsible.

In a prospective observational study, thrombotic status was assessed in 127 Japanese and 120 white European patients with NVAF, anticoagulated with apixaban or warfarin. Patients with hepatic or renal impairment; malignancy; blood dyscrasias; coagulopathy; alcohol/substance abuse; taking antiplatelets, steroids or immunosuppression, were excluded. The choice of oral anticoagulation was decided by the clinical teams. Patients taking apixaban (Eliquis, Bristol-Myers Squibb Pharmaceuticals Limited) 5mg b.i.d. (or 2.5mg b.i.d. if two or more of: age ≥80 years, weight ≤60 kg, creatinine ≥133μmol/L) were tested after uninterrupted treatment for ≥4 weeks, ~4 hours post-dose. Patients taking warfarin were tested after ≥3 consecutive therapeutic INRs (2.0-3.0). Venous blood samples were assessed with the Global Thrombosis Test (GTT) (Thromboquest Ltd., London, UK), an *in vitro* point-of-care technique assessing platelet reactivity to high shear (time to occlusive thrombus formation, occlusion time [OT]) and subsequent spontaneous endogenous fibrinolysis (lysis time [LT])(3).

Platelet reactivity was lower (OT 675.8s[525–806.7] vs. 513.2s[419.6–642.2], p<0.0001) and endogenous fibrinolysis faster (LT 1553s[835–2191] vs. 2157s[172 –2841], p<0.0001) in Japanese than in white Europeans on OAC.

On apixaban, platelet reactivity was lower (difference in OT +245s[186.4-304], p<0.0001) and faster fibrinolysis (LT –532s[-866 – -198], p=0.002) in Japanese than European subjects. On warfarin, platelet reactivity was similar but fibrinolysis faster (LT –983s[-1484.7 – -481.3], p<0.0001) in Japanese than Europeans.

In European patients, platelet reactivity was increased (OT 463s[372-535] vs. 590s[487-679], p<0.0001) and fibrinolysis was more rapid (1850s[1591-2300] vs. 2758s[2014-3502], p <0.0001) on apixaban compared to warfarin. Among Japanese patients, platelet reactivity was similar on apixaban and warfarin (OT 711s[604.2-789] vs. 615s[474.2-822], p=0.231), but fibrinolysis was more rapid on apixaban compared to warfarin (LT 1302s[805.5-1847] vs. 1854s[1017-2823], p=0.009).

Differences in OT and LT remained significant after accounting for baseline differences and confirmed with sensitivity analyses.

The effects of OAC on platelet reactivity and endogenous fibrinolysis are greater in Japanese patients than white Europeans. Whilst all patients on apixaban exhibited more efficient endogenous fibrinolysis than those on warfarin, the effect was particularly marked in Japanese patients, which may explain the greater stroke risk-reduction seen in Asians with NOACs(1). On warfarin, fibrinolysis was more efficient in Japanese than in Europeans. This may explain the increased risk of ICH, which is 3-4 times more frequent in East-Asians compared to non-East Asians(1).

Impaired endogenous fibrinolysis is an emerging risk factor for thrombotic cardiovascular events(3), that may be modifiable by NOAC(4). The more efficient

fibrinolysis seen in Japanese patients on apixaban may explain the greater benefit of apixaban in East Asians compared to Westerners. Ethnic differences in thrombotic and fibrinolytic profiles have been documented, with greater prevalence of high on-treatment platelet reactivity and lower factor VIII, plasmin-antiplasmin, vWF, D-dimer and fibrinogen in East Asians than Europeans(5). This is the first study to investigate inter-ethnic differences in thrombosis and fibrinolysis in NVAF. Limitations include small sample size, non-randomised drug allocation, single timepoint on-treatment assessment, and lack of compliance assessment. Furthermore, data on Japanese patients may not be applicable to other East Asian subjects.

In conclusion, the effects of OAC on platelet reactivity and endogenous fibrinolysis are greater in Japanese patients than white Europeans. Apixaban is associated with greater platelet inhibition and more rapid fibrinolysis in Japanese patients, which may explain the greater stroke risk-reduction in Asians with NOACs, and potentially aid bleeding risk-stratification of Japanese patients.

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Figure 1. Differential effects of OAC on thrombosis/fibrinolysis in Japanese and white Europeans with NVAF

OAC is associated with lower platelet reactivity and faster fibrinolysis in Japanese than European NVAF patients, and this differential effect is greater for apixaban than warfarin [arrow breadth denotes effect-size].