Understanding the Effects of NOAC Combined with Antiplatelet Therapy on Clot Kinetics

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The pharmacodynamic effects of oral anticoagulants (OACs) on the coagulation pathway and the effect of antiplatelet therapy (APT) on platelet activation, used in isolation, have been extensively investigated. However, OAC and APT are now frequently used in combination, most commonly for the coexistence of atrial fibrillation and acute coronary syndrome (ACS) or percutaneous coronary intervention. Antiplatelet agents and OACs have therefore become unintended bedfellows.

In combination with dual APT (DAPT), the use of a non-vitamin K OAC (NOAC) has been shown to be superior to a vitamin K antagonist, with reduced bleeding and similar efficacy.[1,2] However, the combined effect of DAPT and NOAC on clot formation has hitherto been underinvestigated, and little is known about what effects the addition of either a NOAC or APT exert, over that which either would achieve alone.

In this issue of *Thrombosis and Haemostasis*, Franchi et al[3] set out to specifically address this issue, by investigating the effects of the combination of edoxaban, clopidogrel, and aspirin on markers of in vitro clot formation, including clot strength using the TEG6S system, and platelet reactivity. In the first phase of the study, 75 patients on DAPT, comprising aspirin and clopidogrel, were randomized to high dose (60 mg once daily) or low dose (30 mg once daily) edoxaban or DAPT only. In the second phase, aspirin was dropped from triple therapy. The primary endpoint was the assessment of clot strength, measured as maximal amplitude (MA) using thromboelastography (TEG), which represents the termination phase of clot formation and is an evaluation of the maximal thrombin-induced platelet–fibrin clot strength.

Surprisingly, while edoxaban dose-dependently prolonged the speed of thrombin generation, measured as the reaction time (TEG R) when added to DAPT, it had no effect on clot strength. Furthermore, clot stability was not influenced by whether DAPT or single APT (SAPT) was used, or by the addition of edoxaban to DAPT. As expected, discontinuation of aspirin resulted in an increase in the markers sensitive to cyclooxygenase-1 blockade but had no significant effect on markers of P2Y$_{12}$ reactivity or clot kinetics.

The authors conclude that although edoxaban delays thrombin generation, once thrombin is generated, the resultant clot has normal strength and stability.

Prior studies investigating the effect of NOACs, notably in the absence of APT, also showed that rivaroxaban, apixaban, and dabigatran caused significant elongation of R-time[4–7] with large interindividual variability.[5] Another consistent finding is that NOACs have little, if any effect on clot strength, although notably edoxaban had not been studied.[4,6,8] In fact, the group of Franchi et al have previously reported lack of any significant effect on in vitro clot strength when high dose dabigatran was added to DAPT.[9]

Nevertheless, the lack of effect of edoxaban on clot strength is surprising. NOACs have been shown to slow or block the amplification phase of coagulation, which can both delay and prevent large-scale thrombin generation.[10] Spiking of blood from patients already taking DAPT with the equivalent of very low ("vascular") dose (2.5 mg twice daily) rivaroxaban in vitro, led to significant reduction in coagulation-dependent thrombus formation and platelet-dependent thrombin generation,[11] an effect most pronounced in clopidogrel nonresponders.

Thrombin is the predominant determinant of arterial thrombosis and of the resistance of the arterial thrombus to thrombolysis. Despite DAPT, increased thrombin generation is documented in ACS patients,[12,13] and linked to recurrent myocardial infarction.[13,14] Inhibition of thrombin generation would therefore be expected to reduce arterial thrombosis. Indeed, the addition of rivaroxaban to DAPT in the ATLAS ACS 2-TIMI 51 study[15] and to SAPT in the COMPASS study[16] significantly reduced ischemic endpoints, albeit at a cost of increased bleeding, indicating that dual pathway inhibition may be attractive as a way of reducing thrombotic events in high-risk patients.[17]

Thus, the lack of effect of edoxaban (and other NOACs in previous studies) on MA is unexpected. Two possible
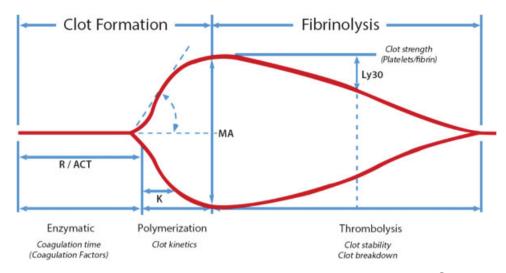
Fig. 1 Illustration of a thromboelastography tracing and interpretation of the main parameters assessed (TEGR® Hemostatis Analyzer tracings used by permission of Haemonetics Corporation). α, α angle; ACT, activated clotting time; K, coagulation time; LY30, percentage of lysis 30 minutes after MA; MA, maximum amplitude; R, reaction time.

explanations need to be considered. The first is that the additional benefit of NOACs on arterial thrombosis, over and above that of APT, is not mediated through an effect on clot strength, and second, that the TEG may not be the right test to assess these additional effects of NOAC on thrombus generation and susceptibility to lysis. A strength of the TEG is that a very large number of indices of clot formation and dissolution are measured, but this also becomes problematic when interpreting the meaning of any individual parameter in isolation. The difficulty is knowing which of more than 16 indices to consider, when in isolation, the interpretation of results is challenging. There are several measures that reflect clot strength (►**Fig. 1**) in addition to MA, including α (α) – the angle reflecting velocity of clot strength generation; kinetics (K) – a measure of the time to reach 20 mm of clot strength from reaction time; and amplitude (A) – reflecting clot strength. Which of these, if altered in isolation, reflects a clinically meaningful effect? One study showed that 11 of 16 TEG indices differed between patients on aspirin and those on OAC, including significant increase in R and reduction in MA in patients on NOAC or warfarin compared with those on aspirin.[7] Furthermore, the TEG employs low shear, more relevant to conditions of venous stasis than arterial thrombus formation under high flow conditions. There may also be differences between the NOACs, and dabigatran may reduce MA to a greater extent than apixaban or rivaroxaban.[6,7]

Second, clot strength may be better assessed by assessing the susceptibility of the formed thrombus to subsequent dislodgement or lysis under flowing conditions.[18] In the said paper, edoxaban did not affect clot lysis. In a murine model, dabigatran, but not rivaroxaban or apixaban, decreased venous thrombus stability[19] and enhanced the susceptibility of plasma clots to tissue plasminogen activator-induced lysis, as detected by a turbidimetric assay.[20,21] When flowing blood was subjected to high shear, apixaban, rivaroxaban, and dabigatran all exhibited a trend toward enhancing endogenous thrombolysis in vitro, although this was significant only for apixaban.[22] Recent work shows that while

apixaban had no effect on TEG lysis time, it significantly improved endogenous thrombolysis measured using the Global Thrombosis Test.[8]

The observation that after stopping aspirin, platelet reactivity increased to a greater extent with low dose edoxaban, should signal caution with regards to withdrawal of aspirin from triple therapy (DAPT plus NOAC), when less than full dose edoxaban is used. The contribution of platelets to thrombin generation was shown recently by the importance of platelet count, platelet volume, and platelet reactivity as determinants of thrombin generation.[23] Furthermore, the reduction in COX-1 blockade after aspirin withdrawal indicates, as expected, that edoxaban and clopidogrel do not affect this pathway. However, dabigatran was recently shown to inhibit glycoprotein Ibα-mediated platelet aggregation.[24] Although guidelines recommend avoidance of prolonged triple therapy[25,26] and reduction from triple therapy to OAC with clopidogrel whenever possible,[26–28] to reduce bleeding, caution should be exercised in high thrombotic risk groups when withdrawing aspirin.

The authors should be commended for a study that adds useful mechanistic insight into the effects of edoxaban on clot formation and lysis as assessed by TEG, in conjunction with DAPT or SAPT. However, the clinical value of these data are as yet unknown and can only be answered by prospective outcome studies linking these indices to clinical outcomes such as arterial thrombotic events. The findings also raise more questions as to how NOACs might exert their beneficial effect in reducing arterial events, if not through an effect on clot strength. Future studies to determine more precisely the mechanisms by which NOACs protect against arterial thrombosis, with and without concomitant APT, would be important to tailor such treatments to high-risk individuals, given that risk stratification for thrombosis and bleeding can be challenging.[29,30]

Conflict of Interest
None declared.

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