ESC European Society of Cardiology

European Heart Journal (2025) **46**, 69–71
https://doi.org/10.1093/eurheartj/ehae795

EDITORIAL
Thrombosis and antithrombotic treatment

Oral anticoagulation and non-steroidal anti-inflammatory drugs: a recipe for bleeding

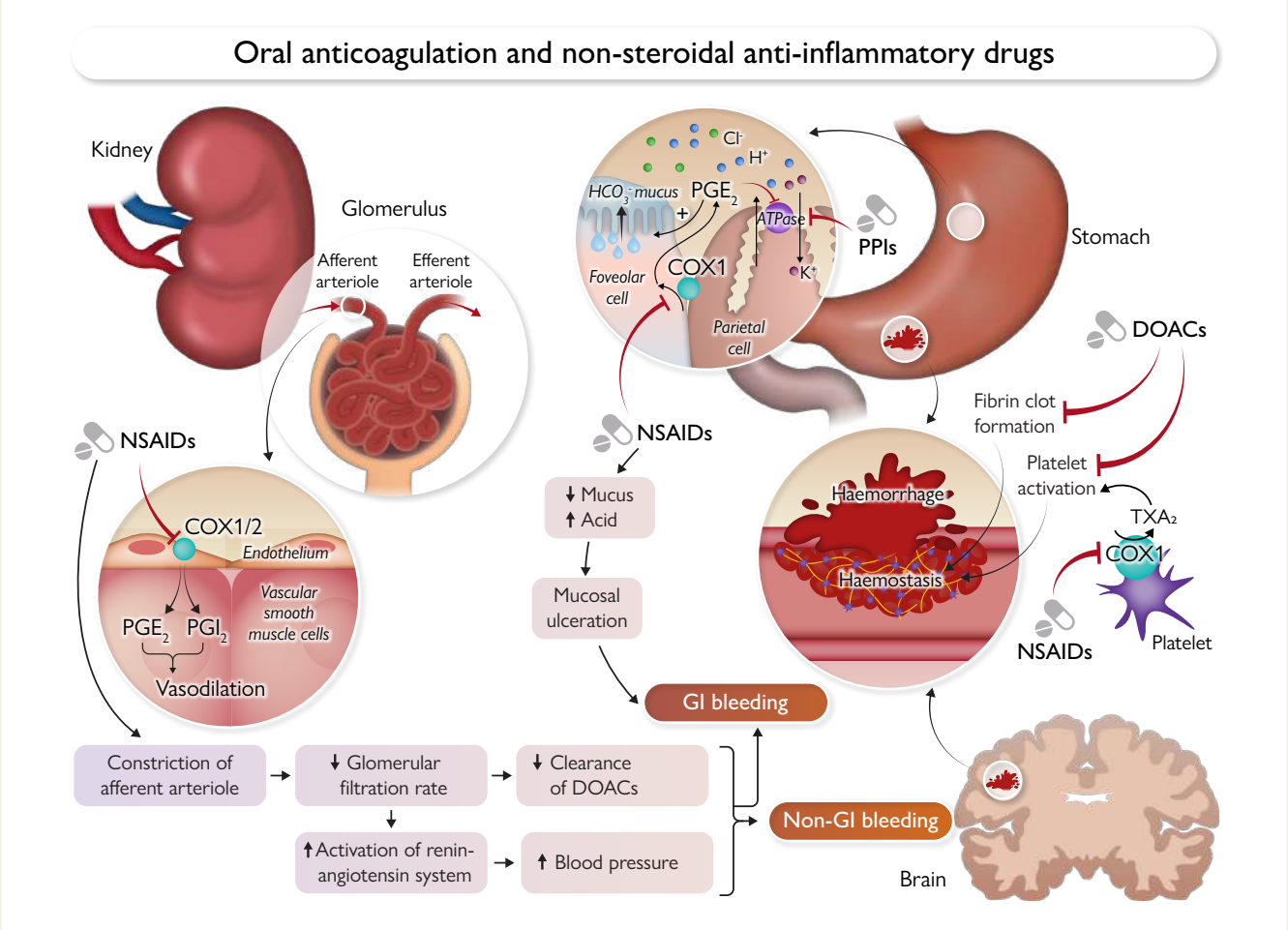
William A.E. Parker [1,2,3] **and Robert F. Storey** [1,2,3,*]

[1]Cardiovascular Research Unit, Division of Clinical Medicine, University of Sheffield, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK; [2]NIHR Sheffield Biomedical Research Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; and [3]Department of Cardiology, South Yorkshire Cardiothoracic Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Online publish-ahead-of-print 18 November 2024

This editorial refers to 'Bleeding risk using non-steroidal anti-inflammatory drugs with anticoagulants after venous thromboembolism: a nationwide Danish study', by S.R. Petersen *et al.*, https://doi.org/10.1093/eurheartj/ehae736.

Graphical Abstract



Interactions between non-steroidal anti-inflammatory drugs (NSAIDs) and oral anticoagulants (OACs) that may contribute to excess risk of gastrointestinal (GI) and non-GI bleeding. ATPase, adenosine triphosphatase; COX, cyclo-oxygenase; DOAC, direct-acting OAC; PG, prostaglandin; PPI, proton pump inhibitor; TX, thromboxane.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +44 114 2266159, Fax: +44 114 3052008, Email: r.f.storey@sheffield.ac.uk

Oral anticoagulants (OACs), including vitamin K antagonists (VKAs) such as warfarin and the direct-acting oral anticoagulants (DOACs) apixaban, dabigatran, edoxaban, and rivaroxaban, are central to the treatment and prevention of a range of thrombotic conditions, including venous thromboembolism (VTE), a term encompassing deep vein thrombosis and pulmonary embolism.[1]

All currently available OACs increase the risk of bleeding. In the management of VTE, a significant proportion of patients are recommended long-term OAC, meaning that cumulative risk can be considerable.[2] OAC-related bleeding can range from events that are usually termed trivial, for example superficial bruising or gum bleeding, through to major bleeding, associated with significant disability or even death.[3] Any grade of bleeding can lead to significant patient distress and increase the chance of either poor adherence to therapy or physician-directed discontinuation, with a resulting loss of therapeutic effect that increases the risk of a recurrent thrombotic event. Most major bleeding episodes are gastrointestinal (GI), whilst intracranial events have the highest risk of mortality. Through data from clinical trials and observational studies, we are building good understanding of how a range of risk factors contribute to bleeding risk during treatment with OACs.

The use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, and diclofenac, has been appreciated as a risk factor for bleeding events for a long time. For example, large-scale registry data have shown that NSAIDs increase the risk of upper GI bleeding ~4-fold in the general population, increased by co-prescription with other drugs known to cause bleeding.[4] Furthermore, in the recently derived VTE-PREDICT score, developed to guide OAC duration in VTE by providing an assessment of net thrombotic and bleeding risk, NSAID use is incorporated as a risk factor for bleeding, based on data from trials and cohort studies, including from Denmark.[2] However, detailed large-scale analysis of the interaction between NSAID use and OAC-related bleeding during VTE treatment, including during VKA and DOAC use, has not been available.

NSAIDs are very commonly used for their analgesic, antipyretic, and anti-inflammatory properties. Making up 8% of prescriptions worldwide, but also available without prescription, they are consumed in huge quantities every year.[4] Non-prescription use usually ranges from single doses to short courses for transient illnesses such as viral upper respiratory tract infections or tension headache. NSAID prescriptions are usually for musculoskeletal complaints, particularly osteoarthritis. Whilst they do not slow progression of the disease, they can be effective for symptom relief and remain prominent in current guidelines.[5]

NSAIDs act by inhibiting cyclo-oxygenase (COX) enzymes, responsible for the conversion of arachidonic acid, formed by the action of phospholipase A_2 on the phospholipid bilayer of the cell membrane, to prostaglandin H_2, which is then converted by other enzymes to a range of prostanoids that act as thromboinflammatory modulators.[6]

In this issue of the *European Heart Journal*, Petersen *et al*. present analyses of 51 794 Danish patients initiating OAC for VTE during an 11-year period that saw a switch from near universal VKA to near universal DOAC use, primarily rivaroxaban or apixaban.[7] The Danish civil registration and healthcare record system is impressive in allowing comprehensive assimilation of clinical events with prescription data, though it must be noted that unprescribed medication use, which the authors estimate to make up ~25% of NSAID consumption, is not recorded. The primary endpoint was defined as a composite of hospital-diagnosed GI bleeding, intracranial bleeding, thoracic and respiratory tract bleeding, urinary tract bleeding, or anaemia caused by bleeding. The analysis demonstrated, after adjustment for a range of covariates, a significantly increased risk of this composite bleeding endpoint in those receiving NSAIDs (2.09, 95% confidence interval [CI] 1.67–2.62) compared with those who did not. This risk appears to be of a clinically meaningful magnitude: the number needed to cause one additional bleeding event during 1 year with NSAID use vs. no use was 36 (95% CI 24–72), and yearly event rates were as high as 15% in those who had received naproxen, the NSAID associated with the greatest excess risk in this study.

Treatment with DOACs has been associated with a reduced risk of bleeding events compared with VKAs.[8] In this analysis, however, the overall rate of bleeding appeared similar between the two groups of OAC. Likewise, the increase in bleeding risk when receiving NSAIDs appeared similar between the two groups, meaning we need to be at least as vigilant in the DOAC era about NSAID-associated bleeding.

As well as confirming the association between NSAID use and bleeding in patients receiving OAC for VTE, these data provide some insights into how NSAIDs might be causing bleeding events (*Graphical Abstract*). Mechanistically, understanding of NSAID-associated bleeding has largely focussed on toxic effects on the upper GI tract. COX1-dependent prostaglandin E_2 is responsible for promoting alkaline mucus secretion and suppressing acid production by the parietal cells of the stomach. Inhibition of COX1 by NSAIDs therefore leads to less mucus and more acid, creating an environment promoting mucosal ulceration of the stomach and duodenum.[9] The frequency and severity of bleeding from these is enhanced significantly by co-administration with an antithrombotic drug such as an OAC. Yet, a striking finding in the study by Petersen *et al*. was that the increase in risk applied not only to GI bleeding, but also to intracranial events, consistent with data from other settings of OAC and NSAID use in combination, such as during the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.[10]

Whilst, in this observational analysis, confounders such as use of NSAIDs for symptoms relevant to causes of intracranial bleeding cannot be excluded, there are several potential explanations for why NSAIDs increase non-GI as well as GI bleeding. Inhibition of platelet COX1 by NSAIDs can exert an antiplatelet effect by reducing release of thromboxane A_2, though this may be counteracted by inhibition of COX1/2-mediated endothelial prostacyclin generation.[6] Whilst not a strong and irreversible effect like that of aspirin, another COX inhibitor generally regarded as an antiplatelet drug rather than an NSAID at low doses, combination with anticoagulants, which can also inhibit thrombin-mediated platelet activation, might potentiate this action.[11] Furthermore, 19% of patients in this analysis were receiving antiplatelet therapy (APT) in addition to OAC. It is now generally acknowledged that prescribing APT to those with an indication for therapeutic OAC should only be considered in those at very high atherothrombotic risk, such as those with a recent acute coronary syndrome event or percutaneous coronary intervention.[12] It is not clear what proportion received both APT and NSAID in the cohort analysed by Petersen *et al*., but, despite evidence that the acetylation of platelet COX1 by aspirin can be blocked by NSAIDs,[6] representing a thrombotic risk, combining NSAIDs, OAC, and APT is likely to be particularly hazardous for bleeding. This is especially the case when the APT consists of a platelet $P2Y_{12}$ receptor antagonist, leading to blockade of three pathways of platelet activation.

Similarly, inhibition of renal prostanoid generation leads to constriction of the afferent arterioles and a compensatory increase in blood pressure mediated by activation of the renin–angiotensin system.[13] Whilst generally modest, the magnitude of this effect is variable between individuals and, furthermore, a small increase in blood pressure may be of greater significance in those who are already hypertensive. Hypertension leads to increased bleeding risk due to mechanical stress on the arterial wall and is particularly associated with intracranial

haemorrhage. The same renal actions of NSAIDs lead to a reduced glomerular filtration rate, which has also been associated with bleeding risk, potentially mediated by effects on blood pressure but also uraemic coagulopathy and, in the case of concomitant DOACs, which are renally eliminated, higher drug levels. Reduced renal function is a recognized independent risk factor for bleeding, including when receiving OAC.[14]

It seems clear that avoiding NSAIDs in combination with OAC is the safest strategy to avoid excess bleeding risk. However, if this is not possible, what mitigation can be put in place? NSAID prescription should obviously be at the lowest dose and for the shortest time possible, but choice of agent and route may also be important. The present analysis suggests that the excess risk with ibuprofen may be considerably less than that with diclofenac or naproxen, and, though the authors acknowledge limitations that may lead to imprecision, this is supported by other data.[4] Though not explored in the present study, current guidelines place strong emphasis on a preference for topical rather than systemic administration of NSAIDs for musculoskeletal conditions where the drug is likely to penetrate significantly into the affected area, e.g. knee or hand osteoarthritis, leading to lower plasma drug levels and better safety.[5] Co-prescription of a proton pump inhibitor, received by 28% of those in the current study, is also known to reduce risk of GI bleeding during OAC or NSAID use.[4,15]

An episode of VTE mandates initiation of anticoagulation, usually an OAC, in all but the rarest of circumstances. However, when doing so, physicians must consider the full context of a patient's bleeding risk factors, including NSAID use. It is important to appropriately counsel the patient, consider alternatives to NSAIDs, including non-pharmacological therapies, and pursue all possible mitigation strategies to reduce the chance of an adverse outcome.

Declarations

Disclosure of Interest

W.A.E.P. reports research support and personal fees from AstraZeneca. R.F.S. reports institutional research grants/support from AstraZeneca and Cytosorbents; and personal fees from Abbott, Alfasigma, AstraZeneca, Boehringer Ingelheim/Lilly, Bristol Myers Squibb/Johnson & Johnson, Chiesi, Cytosorbents, Daiichi Sankyo, Idorsia, Novartis, Novo Nordisk, Pfizer, PhaseBio, and Tabuk.

References

1. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, *et al.* 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2020;**41**:543–603. https://doi.org/10.1093/eurheartj/ehz405
2. de Winter MA, Büller HR, Carrier M, Cohen AT, Hansen J-B, Kaasjager KAH, *et al.* Recurrent venous thromboembolism and bleeding with extended anticoagulation: the VTE-PREDICT risk score. *Eur Heart J* 2023;**44**:1231–44. https://doi.org/10.1093/eurheartj/ehac776
3. De Marco F, Valli G, Ancona C, Ruggieri MP. Management of bleeding in patients on direct oral anticoagulants in emergency department: where we are and where we are going. *Eur Heart J Suppl* 2023;**25**:C15–9. https://doi.org/10.1093/eurheartjsupp/suad004
4. Tai FWD, McAlindon ME. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. *Clin Med (Lond)* 2021;**21**:131–4. https://doi.org/10.7861/clinmed.2021-0039
5. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, *et al.* OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;**27**:1578–89. https://doi.org/10.1016/j.joca.2019.06.011
6. Driver B, Marks DC, van der Wal DE. Not all (N)SAID and done: effects of nonsteroidal anti-inflammatory drugs and paracetamol intake on platelets. *Res Pract Thromb Haemost* 2020;**4**:36–45. https://doi.org/10.1002/rth2.12283
7. Petersen SR, Bonnesen K, Grove EL, Pedersen L, Schmidt M. Bleeding risk using nonsteroidal anti-inflammatory drugs with anticoagulants after venous thromboembolism: a nationwide Danish study. *Eur Heart J* 2025;**46**:58–68. https://doi.org/10.1093/eurheartj/ehae736
8. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, *et al.* 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;**35**:3033–69. https://doi.org/10.1093/eurheartj/ehu283
9. Parker WAE, Storey RF. Combining DAPT with a PPI faces the acid test of real-world use. *Eur Heart J* 2019;**40**:1971–4. https://doi.org/10.1093/eurheartj/ehz102
10. Dalgaard F, Mulder H, Wojdyla DM, Lopes RD, Held C, Alexander JH, *et al.* Patients with atrial fibrillation taking nonsteroidal anti-inflammatory drugs and oral anticoagulants in the ARISTOTLE trial. *Circulation* 2020;**141**:10–20. https://doi.org/10.1161/CIRCULATIONAHA.119.041296
11. Sumaya W, Parker WAE, Fretwell R, Hall IR, Barmby DS, Richardson JD, *et al.* Pharmacodynamic effects of a 6-hour regimen of enoxaparin in patients undergoing primary percutaneous coronary intervention (PENNY PCI study). *Thromb Haemost* 2018;**118**:1250–6. https://doi.org/10.1055/s-0038-1657768
12. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, *et al.* 2024 ESC guidelines for the management of chronic coronary syndromes: developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2024;**45**:3415–537. https://doi.org/10.1093/eurheartj/ehae177
13. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994;**121**:289–300. https://doi.org/10.7326/0003-4819-121-4-199408150-00011
14. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, *et al.* Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011;**32**:2387–94. https://doi.org/10.1093/eurheartj/ehr342
15. Komen J, Pottegård A, Hjemdahl P, Mantel-Teeuwisse AK, Wettermark B, Hellfritzsch M, *et al.* Non-vitamin K antagonist oral anticoagulants, proton pump inhibitors and gastrointestinal bleeds. *Heart* 2022;**108**:613–8. https://doi.org/10.1136/heartjnl-2021-319332