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Editorial

Lowering the risk of stroke prevention: Managing bleeding complications

Diana A. Gorog *

Postgraduate Medical School, University of Hertfordshire, Hertfordshire, UK
National Heart & Lung Institute, Imperial College, London, UK

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Oral anticoagulation is increasingly used, predominantly for thromboprophylaxis of atrial fibrillation and the prevention and treatment of venous thromboembolism. With an ageing population, increasing burden, and earlier recognition of atrial fibrillation, the number of patients taking oral anticoagulation is increasing year on year.

The journey of anticoagulation in the last decade has been punctuated by two major milestones. Firstly, the development, validation and roll out of simple risk scoring systems that allow identification of patients with atrial fibrillation at risk of stroke, which in turn allowed targeted thromboprophylaxis. Second, the development of novel non-vitamin K oral anticoagulants (NOAC), that are easy to use and shown in landmark randomised clinical trials to be at least as effective as vitamin K antagonists in preventing stroke, but with half the risk of intracranial haemorrhage, has led to the establishment of these agents in pole position as oral thromboprophylaxis of stroke and systemic embolism [1].

However, widespread roll-out of NOACs was hampered initially by the cost of these newer agents and the perceived risks from bleeding. Healthcare provider organisations and indeed cautious physicians cited the lack of a reversal agent as the rationale for scepticism and caution in NOAC prescribing, and perhaps to mask economic incentives for ongoing warfarin use.

The last few years have, however, seen an insurgence with widespread accelerated adoption of NOACs as first line treatment, fuelled by ease-of-use in primary care, reduction in hospital stay in secondary and tertiary care, familiarity with prescribing and falling costs, leading to breakdown of perceived barriers to use (lower bleeding, comfort with lower overall fatal bleeding events, general familiarity, potential reversal agents). Cardiologists, internists, stroke physicians and primary care physicians managing patients with atrial fibrillation, as well as surgeons prescribing post-operative thromboprophylaxis, are now very comfortable prescribing NOACs.

All anticoagulation however, carries a risk of bleeding and enthusiasm for NOAC uptake has not been matched by prescribers' awareness of optimal strategies to manage bleeding complications in such anticoagulated patients.

Although fortunately rare, major bleeding can be life-threatening in patients with AF, occurring in approximately 1.6–3.6 per 100 patients per year, varying with the oral anticoagulant used. Whilst no head-to-head comparisons between NOACs exist, major bleeding was significantly reduced with dabigatran 110 mg b.i.d., apixaban, and both doses of edoxaban whilst the bleeding rates for dabigatran 150 mg b.i.d. and rivaroxaban appear similar to those with warfarin. Notably, the risk of intracranial haemorrhage is almost half that with all NOACs compared to vitamin K antagonists (0.2–0.5 *vs.* 0.7–0.85 per 100 patient years).

The latest international recommendations for managing such bleeding emergencies were published in 2017. The European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis published a position paper on Reversal strategies for non-vitamin K antagonist oral anticoagulants [2] and was followed by the American College of Cardiology Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants [3]. The ACC guidelines already incorporated the use of idarucizumab for specific reversal of dabigatran effect.

This issue of the journal sees the publication of two papers on the management of bleeding in patients on oral anticoagulants; general measures [4] and specific reversal agents [5]. The papers are timely and comprehensive, and will provide a very useful overview to practicing clinicians. The scope is broad, ranging from empiric measures in common scenarios that include gastrointestinal, retroperitoneal, and intracranial haemorrhage, as well as bleeding complicating trauma, to specific laboratory studies to assess the intensity of anticoagulant effect with different NOACs. The papers cover manoeuvres for reversal of anticoagulation that include, *inter alia*, tranexamic acid, activated charcoal, dialysis, fresh frozen plasma, prothrombin complex concentrates as well as specific reversal agents for dabigatran and factor X inhibitors. The inclusion of specific reversal agents is important and very pertinent, since 2017 saw the publication of the RE-VERSE AD (Reversal of Dabigatran Anticoagulant Effect with Idarucizumab) study, assessing

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* National Heart and Lung Institute, Imperial College, Dovehouse Street, London SW3 6LR, UK.
E-mail address: d.gorog@imperial.ac.uk.

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the effect of idarucizumab, a humanized anti-dabigatran monoclonal antibody fragment in dabigatran-treated patients with either ongoing severe haemorrhage or requiring emergency surgical procedures [6]. The primary endpoint of maximum reversal of dabigatran's anticoagulant effect within 4 h was 100% and was achieved in all patients. Among patients with bleeding, cessation was achieved within a median time of 3.5–4.5 h. This year, 2018, has seen the FDA approval of andexanet alfa, a reversal agent for the factor Xa inhibitors rivaroxaban and apixaban, a recombinant modified human, catalytically-inactive form of factor Xa that acts as a "decoy" to bind and sequester the anticoagulant. Two phase III studies, ANNEXA-R and ANNEXA-A, evaluated the safety and efficacy of andexanet alfa in healthy volunteers, showing a median decrease in anti-Factor Xa activity of 97% from baseline for those on rivaroxaban and 92% for those on apixaban [7]. In an open-label study of 67 patients with acute major bleeding, andexanet given 4.8 ± 1.8 h after presentation reduced anti-factor Xa activity by 89% in rivaroxaban-treated and by 93% in apixaban-treated patients [8]. Designated an orphan drug by the FDA, it was cleared through the agency's accelerated approval pathway. It remains under review by the European Medicines Agency, with a final decision expected in early 2019.

The articles by Di Fusco et al. give practical advice on how to handle life-threatening bleeding in patients receiving OAC and, in particular, on NOAC treatment. The papers also serve as a timely reminder to all clinicians prescribing oral anticoagulants of the importance of prompt recognition and optimal treatment of intracranial or other life-threatening bleeding in patients receiving oral anticoagulation to improve the otherwise bleak prognosis associated with such events. Following the transformative decade that helped identify patients at risk of stroke and target them appropriately with anticoagulation to reduce that risk, we must now learn to close the loop of risk by improving recognition and effective management of bleeding on anticoagulation optimally.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] M.V. Huisman, K.J. Rothman, M. Paquette, C. Teutsch, H.C. Diener, S.J. Dubner, J.L. Halperin, C.S. Ma, K. Zint, A. Elsaesser, D.B. Bartels, G.Y. Lip, GLORIA-AF Investigators, The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry Phase 2, J. Am. Coll. Cardiol. 69 (7) (2017) 777–785.

[2] A. Niessner, J. Tamargo, J. Morais, L. Koller, S. Wassmann, S.E. Husted, C. Torp-Pedersen, K. Kjeldsen, B.S. Lewis, H. Drexel, J.C. Kaski, D. Atar, R.F. Storey, G.Y.H. Lip, F.W.A. Verheugt, S. Agewall, Reversal strategies for non-vitamin K antagonist oral anticoagulants: a critical appraisal of available evidence and recommendations for clinical management-a joint position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis, Eur. Heart J. 38 (22) (Jun 7 2017) 1710–1716.

[3] G.F. Tomaselli, K.W. Mahaffey, A. Cuker, P.P. Dobesh, J.U. Doherty, J.W. Eikelboom, R. Florido, W. Hucker, R. Mehran, S.R. Messé, C.V. Pollack Jr., F. Rodriguez, R. Sarode, D. Siegal, B.S. Wiggins, 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: a report of the American College of Cardiology Task Force on expert consensus decision pathways, J. Am. Coll. Cardiol. 70 (24) (Dec 19 2017) 3042–3067.

[4] S.A. Di Fusco, F. Luca, Benvenuto, et al., Major bleeding with old and novel oral anticoagulants: how to manage it: focus on general measures, Int. J. Cardiol. (2018).

[5] S.A. Di Fusco, F. Luca, Benvenuto, et al., Major bleeding with old and novel oral anticoagulants: how to manage it: focus on reversal agents, Int. J. Cardiol. (2018).

[6] C.V. Pollack Jr., P.A. Reilly, J. van Ryn, J.W. Eikelboom, S. Glund, R.A. Bernstein, R. Dubiel, M.V. Huisman, E.M. Hylek, C.W. Kam, P.W. Kamphuisen, J. Kreuzer, J.H. Levy, G. Royle, F.W. Sellke, J. Stangier, T. Steiner, P. Verhamme, B. Wang, L. Young, J.I. Weitz, Idarucizumab for dabigatran reversal - full cohort analysis, N. Engl. J. Med. 377 (5) (2017) 431–441.

[7] R. Tummala, A. Kavtaradze, A. Gupta, R.K. Ghosh, Specific antidotes against direct oral anticoagulants: a comprehensive review of clinical trials data, Int. J. Cardiol. 214 (2016) 292–298.

[8] S.J. Connolly, T.J. Milling Jr., J.W. Eikelboom, et al., Andexanet alfa for acute major bleeding associated with factor Xa inhibitors, N. Engl. J. Med. 375 (2016) 1131–1141.