

Addendum to British Society for Haematology Guidelines on Investigation and Management of Antiphospholipid syndrome, 2012 (*Br. J. Haematol.* 2012; 157: 47–58): use of direct acting oral anticoagulants

Deepa R. J. Arachchillage,^{1,2}  Keith Gomez,³ Raza Alikhan,⁴  Julia A. M. Anderson,⁵ Will Lester,⁶  and Mike Laffan^{1,2}  On behalf of British Society for Haematology Haemostasis and Thrombosis Taskforce

¹Department of Haematology, Imperial College Healthcare NHS Trust, ²Centre for Haematology, Imperial College London, ³Katherine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London, ⁴Haemophilia and Thrombosis Centre, University Hospital of Wales, Cardiff, ⁵Department of Haematology, Royal Infirmary of Edinburgh, Edinburgh and ⁶Centre for Clinical Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Keywords: Antiphospholipid syndrome; direct acting oral anticoagulants; lupus anticoagulant, venous thrombosis, arterial thrombosis.

Until recently, data on the role of direct acting oral anticoagulants (DOACs) in treatment of thrombotic antiphospholipid syndrome (APS) have been limited and derived from case reports, cohort studies and small prospective open-labelled randomised controlled studies. In a meta-analysis of 47 studies comprising a total of 447 APS patients who received DOACs, 73 patients (16%) developed a recurrent thrombosis after a mean period of 12.5 months (Dufrost *et al.*, 2018). The recurrent thrombosis occurred in 16.9% and 15% of patients receiving a factor Xa inhibitor (FXa; rivaroxaban or apixaban) or a factor IIa inhibitor (dabigatran) respectively. Presence of all three antiphospholipid antibodies (aPL): lupus anticoagulant (LA), IgG and/or IgM anti-beta-2 glycoprotein-1 and anticardiolipin antibodies, defined as 'triple positivity' was associated with a fourfold increased risk of recurrent thrombosis compared to patients with single or dual positive positivity [56% vs. 23%; OR = 4.3 (95% CI; 2.3–7.7), $P < 0.0001$]. Patients treated for arterial thrombosis with rivaroxaban or apixaban had a higher risk of recurrent thrombosis compared to those with venous thrombosis (32% vs. 14%; OR = 2.8 [95% CI; 1.4–5.7], $P = 0.006$) (Dufrost *et al.*, 2018).

Recently, the results of a randomised controlled trial (RCT) in which rivaroxaban was compared to warfarin in

triple positive APS patients with a history of thrombosis have been reported (Pengo *et al.*, 2018). The trial was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Thromboembolic events occurred in 12% of patients randomised to rivaroxaban while there were no thrombotic events in the warfarin arm at mean follow-up of 19 months. Major bleeding occurred in four patients (7%) in the rivaroxaban arm and two patients (3%) in the warfarin arm.

In May 2019, the European Medicines Agency (EMA) (<https://www.ema.europa.eu>, 2019) recommended that DOACs should not be used for secondary prevention in APS patients. In June 2019, the Medicines and Healthcare Products Regulatory Agency (MHRA) (<https://www.gov.uk/drug-safety-update>, 2019) issued similar recommendations. These recommendations drew specific attention to high-risk patients but were not limited to this group and referred to APS patients in general. Guidelines from the European League Against Rheumatism (EULAR) also adopted a similar approach (Tektonidou *et al.*, 2019).

It is notable that the EMA and MHRA extended the results from the RCT of rivaroxaban to make a recommendation for all DOACs and from a study of triple positive patients to a recommendation including all patients with APS. Importantly, four out of a total of seven recurrent thrombotic events (57.1%) in the rivaroxaban arm in Pengo *et al.* (2018) were in patients who received rivaroxaban for arterial thrombosis, which was an unlicensed indication. In the RAPS (Rivaroxaban in Antiphospholipid Syndrome) trial, APS patients with at least one venous thromboembolism or recurrence whilst off anticoagulation were randomised to receive rivaroxaban 20 mg or to continue on warfarin. In this study, 12% (7/57) receiving rivaroxaban and 20% (12/59) receiving warfarin were triple positive while the

Correspondence: BSH Administrator, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK.
E-mail: bshguidelines@b-s-h.org.uk

© 2020 The Authors. *British Journal of Haematology* published by British Society for Haematology and John Wiley & Sons Ltd

doi: 10.1111/bjh.16308

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

remainder were single or double positive. Although not the primary outcome measure, none of the patients had recurrent thrombosis or major bleeding in either arm of the study (secondary outcome) at six months follow-up (Cohen *et al.*, 2016). Irrespective of the type of anticoagulant, all patients should be reminded about the importance of adherence, the signs of symptoms of venous and arterial thrombosis and the risks of bleeding.

The ASTRO-APS study (<https://clinicaltrials.gov/ct2/show/NCT02295475>) is comparing apixaban 5 mg bd and warfarin [international normalized ratio (INR) 2.0–4.0] in patients previously anticoagulated for APS and venous thromboembolism (VTE) for more than six months. However, this trial has stopped recruiting.

Approximately 10% of patients with VTE have APS (Andreoli *et al.*, 2013), and less than 50% of these are triple positive (Pengo *et al.*, 2010). Unselected screening of patients with VTE will therefore be inefficient but there are several features that may help to identify those patients more likely to have APS (Cervera *et al.*, 2002).

The British Society for Haematology (BSH) has decided to add the following recommendations regarding the use of DOACs in patients with thrombotic APS.

RECOMMENDATIONS

Patients with arterial thrombosis

For anticoagulation for treatment and secondary prophylaxis of arterial thrombosis in patients with APS, we recommend vitamin K antagonists (VKAs) and do not recommend DOACs (Grade 1B).

Patients with triple positive APS and venous thrombosis

We recommend against the initiation of DOACs for treatment or secondary prophylaxis in patients with venous thrombosis and known triple positive APS (Grade 1B).

For patients with triple positive APS who are currently on a DOAC, we recommend switching from the DOAC to a VKA after discussion with patients regarding the available evidence. For those patients who do not wish to switch, we recommend continuation of the DOAC over no anticoagulation (Grade 1B).

Patients with non-triple positive APS and venous thrombosis

There is insufficient evidence to make strong recommendations in this group of patients.

We suggest against the initiation of DOACs for treatment or secondary prophylaxis in patients with venous thrombosis and known non-triple positive APS (Grade 2C).

Patients who are already on a DOAC may continue or switch to a VKA after discussion with the patient taking into account their clinical history, treatment adherence and previous experience. For those patients who do not wish to switch, we recommend continuation of the DOAC over no anticoagulation (Grade 2C).

Testing for lupus anticoagulant in the presence of direct acting oral anticoagulants

The presence of DOAC in a sample, even if present at trough levels, may result in a false positive test result when dilute Russell viper venom time (dRVVT)- or activated partial thromboplastin time (APTT)-based methods are used (Meriman *et al.*, 2011). One study indicated that this effect may be lost when rivaroxaban concentration is <50 ng/ml (Arachchillage *et al.*, 2015). A combination of Taipan snake venom and ecarin clotting times may provide a possible alternative method to detect LA in samples containing direct FXa inhibitors because they are direct activators of prothrombin (Arachchillage *et al.*, 2015). However, these tests are not widely available. No alternatives exist for LA detection in samples containing direct thrombin inhibitors. Some studies have suggested that absorption methods to remove the DOACs are effective (Exner *et al.*, 2018; Cox-Morton *et al.*, 2019; Platton & Hunt, 2019; Zabczyk *et al.*, 2019) but none of these methods are validated in a large number of samples from true positive and negative patients with APS.

Although low molecular weight heparins (LMWH) have little effect on APTT and DRVVT this may be dependent on LMWH type and APTT reagent (Liestol & Wisloff, 2005). Therefore, the possible effect of LMWH should be taken into account even if reagents with heparin neutralisers are used (Moore, 2016). Samples should be taken just before the next dose of LMWH to minimise the effect of LMWH.

Recommendations

APTT or DRVVT based tests should not be used to detect LA on samples from patients taking DOACs when there is a detectable drug level (Grade 1A).

There is insufficient evidence to recommend alternative tests for detection of LA in the presence of DOACs.

Patients with newly diagnosed provoked venous thromboembolism

We do not recommend testing for antiphospholipid antibodies in these patients (Grade 1B).

Patients with newly diagnosed unprovoked venous thromboembolism

We do not recommend testing for LA at diagnosis because this can be confounded by acute changes and the effects of anticoagulants (Grade 1A).

We suggest testing for solid phase aPL (IgG and IgM anti-beta-2 glycoprotein-1 and anticardiolipin antibodies) in selected patients at the time of diagnosis and if positive, repeating at 12 weeks to confirm persistence (Grade 2C).

Features indicating an increased likelihood of APS are listed below:

- History of systemic lupus erythematosus (SLE) or other autoimmune disease
- Presence of livedo reticularis
- Prolonged APTT prior to starting anticoagulation
- Recurrent thrombosis
- VTE at unusual sites
- History of arterial thrombosis without clear risk factors
- Thrombocytopenia
- Recurrent miscarriages/still birth/severe pre-eclampsia
- Cardiac valve abnormalities in the absence of other explanations

Patients who are positive for one or two solid phase antibodies at presentation should be considered for LA testing at three months, after switching to LMWH (Grade 2C).

If both antibody types are positive and LA testing is not performed, we recommend long term oral anticoagulation using a VKA rather than a DOAC (Grade 2C).

When patients are switched to LMWH, samples for LA testing should be taken just before the next dose of LMWH (Grade 1C).

References

- Andreoli, L., Chighizola, C.B., Banzato, A., Pons-Estel, G.J., de Ramire, J.G. & Erkan, D. (2013) Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. *Arthritis Care & Research*, **65**, 1869–1873.
- Arachchillage, D.R., Mackie, I.J., Efthymiou, M., Isenberg, D.A., Machin, S.J. & Cohen, H. (2015) Interactions between rivaroxaban and antiphospholipid antibodies in thrombotic antiphospholipid syndrome. *Journal of Thrombosis and Haemostasis*, **13**, 1264–1273.
- Cervera, R., Piette, J.C., Font, J., Khamashta, M.A., Shoenfeld, Y., Camps, M.T., Jacobsen, S., Lakos, G., Tincani, A., Kontopoulou-Griva, I., Galeazzi, M., Meroni, P.L., Derksen, R.H., de Groot, P.G., Gromnica-Ihle, E., Baleva, M., Mosca, M., Bombardieri, S., Houssiau, F., Gris, J.C., Quere, I., Hachulla, E., Vasconcelos, C., Roch, B., Fernandez-Nebro, A., Boffa, M.C., Hughes, G.R. & Ingelmo, M. (2002) Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1000 patients. *Arthritis and Rheumatism*, **46**, 1019–1027.
- Cohen, H., Hunt, B.J., Efthymiou, M., Arachchillage, D.R., Mackie, I.J., Clawson, S., Sylvestre, Y., Machin, S.J., Bertolaccini, M.L., Ruiz-Castellano, M., Muirhead, N., Dore, C.J., Khamashta, M. & Isenberg, D.A. (2016) Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. *The Lancet Haematology*, **3**, e426–e436.
- Cox-Morton, S., MacDonald, S. & Thomas, W. (2019) A diagnostic solution for haemostasis laboratories for patients taking direct oral anticoagulants using DOAC-Remove. *British Journal of Haematology*, **187**, 377–385.
- Dufrost, V., Risse, J., Reshetnyak, T., Satybaldyeva, M., Du, Y., Yan, X.X., Salta, S., Gerotziafas, G., Jing, Z.C., Elalamy, I., Wahl, D. & Zuily, S. (2018) Increased risk of thrombosis in antiphospholipid syndrome patients treated with direct oral anticoagulants. Results from an international patient-level data meta-analysis. *Autoimmunity Reviews*, **17**, 1011–1021.
- Exner, T., Michalopoulos, N., Pearce, J., Xavier, R. & Ahuja, M. (2018) Simple method for removing DOACs from plasma samples. *Thrombosis Research*, **163**, 117–122.
- Liestol, S. & Wisloff, F. (2005) Effect of subcutaneous administration of dalteparin on lupus anticoagulant assays. *Thrombosis Research*, **115**, 509–517.
- Merriman, E., Kaplan, Z., Butler, J., Malan, E., Gan, E. & Tran, H. (2011) Rivaroxaban and false positive lupus anticoagulant testing. *Thrombosis and Haemostasis*, **105**, 385–386.
- Moore, G.W. (2016) Current controversies in lupus anticoagulant detection. *Antibodies*, **5**, 22.
- Pengo, V., Ruffatti, A., Legnani, C., Gesele, P., Barcellona, D., Erba, N., Testa, S., Marongiu, F., Bison, E., Denas, G., Banzato, A., Padayattil, J.S. & Iliceto, S. (2010) Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *Journal of Thrombosis and Haemostasis*, **8**, 237–242.
- Pengo, V., Denas, G., Zoppellaro, G., Jose, S.P., Hoxha, A., Ruffatti, A., Andreoli, L., Tincani, A., Cenci, C., Prisco, D., Fierro, T., Gesele, P., Cafolla, A., De Micheli, V., Ghirarduzzi, A., Tosetto, A., Falanga, A., Martinelli, I., Testa, S., Barcellona, D., Gerosa, M. & Banzato, A. (2018) Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*, **132**, 1365–1371.
- Platton, S. & Hunt, C. (2019) Influence of DOAC Stop on coagulation assays in samples from patients on rivaroxaban or apixaban. *International Journal of Laboratory Hematology*, **41**, 227–233.
- Tektonidou, M.G., Andreoli, L., Limper, M., Amoura, Z., Cervera, R., Costedoat-Chalumeau, N., Cuadrado, M.J., Dörner, T., Ferrer-Oliveras, R., Hambly, K., Khamashta, M.A., King, J., Marchiori, F., Meroni, P.L., Mosca, M., Pengo, V.,

Acknowledgements

The authors wish to thank Peter Baker, Elaine Gray, Ian Jennings and Sean Platton for their comments.

Conflict of interest

All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request.

Review process

The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search for any RCT or other high-quality data that is either new or that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk).

Disclaimer

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

Guideline

Raio, L., Ruiz-Irastorza, G., Shoenfeld, Y., Stojanovich, L., Svenungsson, E., Wahl, D., Tincani, A. & Ward, M.M. (2019). EULAR recommendations for the management of

antiphospholipid syndrome in adults. *Annals of the Rheumatic Diseases*, **78**, 1296–1304.
Zabczyk, M., Kopytek, M., Natorska, J. & Undas, A. (2019) The effect of DOAC-Stop on lupus

anticoagulant testing in plasma samples of venous thromboembolism patients receiving direct oral anticoagulants. *Clinical Chemistry and Laboratory Medicine*, **57**, 1374–1381.