What is the appropriate anticoagulation strategy for thrombotic antiphospholipid syndrome?

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune prothrombotic disorder mediated by a heterogeneous group of autoantibodies collectively known as antiphospholipid antibodies (aPL). They include lupus anticoagulant (LA), IgG and IgM anticardiolipin antibodies (aCL) and anti-β2-glycoprotein-I (anti-β2GPI) antibodies. It has been shown that those patients with all three aPL (triple-positive), are at highest risk of both a first thrombotic event and of a recurrence, despite anticoagulation. In response to publication of a meta-analysis and a randomised controlled trial assessing the safety and efficacy of rivaroxaban vs warfarin in triple positive APS with venous and/or arterial thrombosis, the Medicines and Healthcare Products Regulatory Agency (MHRA) and European Medicines Agency (EMA) issued recommendations that direct acting oral anticoagulant (DOACs) should not be used for secondary prevention of thrombosis in all APS patients; although they did draw specific attention to the high-risk of triple positive patients. As there is less evidence for patients with single or dual positive patients with APS, this may be an over-interpretation of the data. In this review we explore the available evidence on safety and efficacy of DOACs in thrombotic APS, the problem of detecting LA whist on DOAC and provide some practical guidance for managing this problem.

Key words: antiphospholipid syndrome, triple positive, venous thrombosis, arterial thrombosis, warfarin, direct acting oral anticoagulant, lupus anticoagulant

Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune disease defined by objectively confirmed thromboembolic events (arterial, venous, or small vessel, in any tissue or organ) or specified pregnancy morbidity, associated with the presence of antiphospholipid (aPL) antibodies (Miyakis *et al*, 2006). aPL are a heterogeneous group of autoantibodies, including lupus anticoagulant (LA), IgG and IgM anticardiolipin antibodies (aCL) and anti-β2-glycoprotein-I (anti-β2GPI) antibodies. Their primary targets are phospholipid-binding proteins, although antibodies directed against phospholipids and other proteins also occur. Laboratory diagnosis of APS requires the presence of LA in plasma or aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titre (i.e. >40 GPL or MPL, or >the 99th centile) or anti-β2GPI of IgG and/or IgM isotype in serum or plasma (in titre >the 99th centile). The positive results must be obtained on two or more occasions, at least 12 weeks apart (Miyakis *et al*, 2006). Currently, thromboprophylaxis is not recommended for asymptomatic, aPL positive individuals because there is no convincing evidence of benefit. Subjects who are triple positive aPL (presence of all three antibodies: LA, aCL and anti-β2GPI antibodies) have been shown to have a much higher risk of thrombosis than controls but whether this warrant different treatment remains to be established. Consequently, secondary prevention of thromboembolic events is the primary therapeutic goal in these patients and choice of anticoagulant is a key question.

Vitamin K antagonists (VKA) are an established therapy for anticoagulation in APS but is complicated by a narrow therapeutic range and interactions with drugs and diet. In APS patients, it may be further complicated by the effect of the LA on certain thromboplastins,

leading to misleading international normalized ratio (INR) results. (Isert *et al*,2015 ;Tripodi *et al*,2001).

Direct acting oral anticoagulants (DOACs; rivaroxaban, apixaban, edoxaban and dabigatran) are approved for treatment and prevention of venous thromboembolism (VTE) and have largely displaced warfarin as the standard treatment for this indication by virtue of their lack of need for monitoring, fewer drug and food interactions and lower rate of intracranial bleeding. However, patients with thrombotic APS are a heterogeneous group whose thrombotic risk varies widely and are unusual in developing arterial as well as venous thrombosis (Bazzan *et al*, 2013). Only limited information is available for this patient subgroup. Post hoc analysis of a small group of patients (70) with uncharacterized possible APS who received dabigatran vs VKA showed no difference in recurrence of VTE (Goldhaber *et al*, 2016). To date, only one study has directly compared VKA and DOAC for thrombotic APS and this was terminated prematurely due to an excess of thrombotic events in the rivaroxaban arm (Pengo *et al*, 2018)**.** As a result, in May 2019, the European Medicines Agency (EMA) (ema, 2019) advised that DOACs are not recommended for patients with a history of thrombosis and APS, 'in particular for patients who are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies)'. In June 2019, the Medicines and Healthcare Products Regulatory Agency (MHRA) (drug-safety-update/,2019) issued similar recommendations.

In this review we will explore the available evidence in detail on safety and efficacy of DOACs in thrombotic APS, the problem of detecting LA whist on DOAC and provide some practical guidance for anticoagulation of patients with APS and detection of LA whilst on DOACs.

APS and thrombosis

APS is an autoimmune prothrombotic disorder mediated by autoantibodies but it appears that a 'second hit' or 'trigger' is required to precipitate thrombosis. This may be infection, endothelial injury, inflammation, immunological or other non-immunological procoagulant factors such as hormonal therapy, surgery or immobility (Pengo *et al*, 2011) in interaction with the patient's genetic constitution. Nonetheless, anticoagulation rather than immunosuppression remains the mainstay of management. Although the prevalence of aPL in the general population ranges between 1 and 5%, clinical manifestations of APS occur in only a proportion of individuals (Mehrania T & Petri M., 2009). The reported annual risk of thrombosis in asymptomatic aPL-positive individuals ranges from 0% to 3.8% (Barbhaiya & Erkan, 2011), but for those positive for all three antibodies it is 5.3% per year (Pengo *et al*, 2011).

In a study of 1000 patients with APS ("Euro-Phospholipid Project") the prevalence of clinical manifestations were as follows: 38.9% DVT, 19.8% stroke, 11.1% transient ischemic attack (TIA), 11.6% valve thickening/dysfunction, 5.5% MI, 24.1% livedo reticularis, 29.6% thrombocytopenia ($<100x10^9/L$) and 9.7% haemolytic anemia (Cervera *et al*, 2009). In the same group, the prevalence of recurrent miscarriages (<10 weeks) and fetal losses (>10 weeks) were 35.4% and 16.9% respectively. The prevalence of APS is higher in patients with autoimmune disease than the general population with approximately 30-40% of patients with systemic lupus erythematosus have aPL and around 20 % of these have APS (Cervera *et al*, 2009).

Although deep vein thrombosis (DVT) is the most common thrombotic event in patients with APS, it may arise anywhere in the body including pulmonary embolism (PE) and unusual sites

such as cerebral venous thrombosis (CVT) and splanchnic vein thrombosis (SVT), including portal vein (PVT), mesenteric (MVT) and splenic vein thrombosis and the Budd–Chiari syndrome (BCS) (Shatzel *et al*, 2019). In addition, a very small proportion of patients with APS can develop the rare but potentially fatal variant of APS called Catastrophic APS (CAPS), characterized by sudden onset of extensive microvascular thrombosis at multiple sites leading to multi-organ failure (Cervera *et al*,2014).

Although only one persistently positive antiphospholipid antibody with either thrombosis or pregnancy complication is required to fulfill the criteria for diagnosis of APS, patients may have more than one aPL in different combinations. It has been shown that those presenting with triple-positive aPL are at highest risk of both a first thrombotic event (de Groot *et al*, 2005) and of a recurrence, despite anticoagulation (Pengo *et al*, 2005;Zoghlami-Rintelen *et al*, 2005). The reported risk of thrombosis in patients with an incidental finding of single positive antibody is <1% per year but the risk may be as high as 40% within 10 years in a person with triple positive antibodies (Reynaud *et al*, 2014;Forastiero *et al*, 2005;Lim, 2016;Pengo *et al*, 2011b). Approximately 10% of patients with a first episode unprovoked venous thromboembolism (VTE) have aPL (Andreoli *et al*, 2013), and less than 50% of these are triple positive (Pengo *et al*, 2010)**.**

Despite warfarin anticoagulation, 30% of triple positive patients have recurrent thrombotic events within 10 years and is significantly higher in patients without anticoagulation (P =0.002) (Pengo *et al*, 2010). A retrospective study in a tertiary referral centre of 147 APS patients with thrombosis (80/147 venous and 67/147 arterial) found a recurrent thrombosis rate of 69% over a 10-year period. Recurrence was significantly lower in patients with a target INR ≥3.0 (+/- low

dose aspirin) compared those with a target INR of 2.5, aspirin alone or no anticoagulant treatment. In the same period 20% suffered bleeding episodes (all with INR >3) and 5% had severe bleeding. Triple positive patients were not identified but the study confirms that some APS patients are very high risk and may require intensive warfarin anticoagulation with target INR of ≥ 3.0 with or without low-dose aspirin.

Venous thrombosis

Management of a first episode of venous thrombosis or recurrence whilst off anticoagulation or with subtherapeutic anticoagulation

The high rate of recurrence both on and off anticoagulation makes it important to identify APS patients with thrombosis at their first clinical presentation. Clinical and laboratory features that may help to detect those with an increased likelihood of having APS and which should prompt testing are summarised in table 1.

Vitamin K antagonists

At present, the standard treatment for APS patients after a first episode of VTE or recurrence whilst off anticoagulation or with subtherapeutic anticoagulation is with an immediate short period of treatment with heparin, followed by long term anticoagulation with VKA, usually warfarin, with a target INR of 2.5 (2.0-3.0).

This is based on two randomised controlled trials which showed that high-intensity warfarin was not superior to standard intensity warfarin (INR 2.0-3.0) for the prevention of recurrent VTE (Crowther *et al*, 2003;Finazzi *et al*, 2005). In Crowther et al, a total of 114 patients with

objectively confirmed arterial or venous thrombosis and positive LA or IgG aCL antibody, or both were randomized (double-blind) to receive warfarin to achieve an INR of 2.0 to 3.0 (standard intensity) or 3.1 to 4.0 (high intensity) with follow up for a mean of 2.7 years. Recurrent thrombosis occurred in 6 of 56 patients (10.7%) in the high-intensity arm and in 2 of 58 patients (3.4 %) in the standard-intensity arm (hazard ratio [HR] for the high-intensity group, 3.1; 95% confidence interval [CI] 0.6 to 15.0). Major bleeding occurred in 3 and 4 patients on high-intensity and standard intensity warfarin respectively.

In Finazzi et al, 109 patients with thrombotic APS were randomized to receive either high-intensity warfarin (INR 3.0–4.5, 54 patients) or standard intensity (INR 2.0–3.0, 52 patients. During followed up for a median 3.6 years, mean INRs were 3.2 (standard deviation [SD] 0.6) and 2.5 (SD 0.3), in the high and standard intensity warfarin groups respectively, (P<0.0001). Recurrent thrombosis occurred in six of 54 patients (11.1%) in high-intensity warfarin and in three of 55 patients (5.5%) in standard intensity arm [hazard ratio for the high intensity group, 1.97; 95% confidence interval (CI) 0.49–7.89]. Major bleeding occurred in 2 patients (3.7%) in high-intensity warfarin and 3 (5.8%) in standard intensity arm (hazard ratio 0.66 (0.11–3.96). Both studies concluded that high-intensity warfarin was not superior to standard treatment in preventing recurrent thrombosis in patients with APS.

These studies were carried out prior to introduction of the concept of triple positive APS with the updated Sapporo Criteria (The International Consensus Criteria) in 2006 (Miyakis *et al*, 2006) and so the triple positive proportions in the studies are unknown. Nonetheless, the recurrent thrombotic rates on anticoagulation of 3.4% to 11.1% in the two studies are much higher than in non-APS patients treated with VKAs which in a Cochrane meta-analysis was 1.6%

(Middeldorp *et al*, 2014). These data in combination with the high risk of recurrence noted above are the basis for the current recommendation that patients with APS and otherwise un-precipitated VTE should remain on anticoagulants indefinitely with a target INR of 2.5. This reduces recurrent VTE by 80-90% compared to no treatment (Danowski *et al*,2013 ;Ruiz-Irastorza *et al*,2007).

Direct acting oral anticoagulants

Data on the safety and efficacy of DOACs in treatment of thrombotic APS have been largely limited to case reports, cohort studies and small prospective open labeled randomized controlled studies using rivaroxaban only. In a meta-analysis of 47 studies comprising 447 APS patients treated with a DOAC (290 rivaroxaban, 144 dabigatran and 13 apixaban) 73 patients (16%) experienced one or more recurrent thrombotic events while on DOACs after a mean period of 12.5 months (Dufrost *et al*, 2018). Recurrent thrombosis was identified in 16.9% and 15% receiving either a factor Xa inhibitor (rivaroxaban or apixaban) or a direct thrombin inhibitor (dabigatran) respectively. Triple positivity was associated with a 4-fold increased risk of recurrent thrombosis compared to single or dual positive positivity (OR=4.3 [95%CI; 2.3–7.7], $p < 0.0001$) (Dufrost *et al*, 2018). It is important to highlight that three patients treated with DOACs developed catastrophic APS.

The only randomised controlled study in the meta-analysis was the RAPS (Rivaroxaban in antiphospholipid syndrome) trial. This included patients with APS (at least one venous thromboembolism when taking no or subtherapeutic anticoagulant therapy) taking warfarin with target INR of 2·5 for at least 3 months since the last VTE event. The majority of patients

were single or dual positive for aPL but 12% (7/57) of patients on rivaroxaban and 20 % (12/59) on warfarin arm were triple positive. Thrombosis was only a secondary outcome but there were no thrombotic events in either arm up to the end of the study at 210 days after randomisation (Cohen *et al*, 2016).

The only randomized open-label multicentre study to date assessing the clinical endpoints of safety and efficacy of DOACs in patients with APS is the study by Pengo et al, in which rivaroxaban was compared to warfarin in patients with a history of thrombosis and triple positive APS (Pengo *et al*, 2018). This was terminated prematurely after recruiting only 120 patients, due to an excess of events in the rivaroxaban arm. With a mean follow-up of 569 days, 12% of patients randomized to rivaroxaban developed recurrent thrombotic events (4 ischaemic strokes and 3 myocardial infarctions). Interestingly, in contrast to previous studies of VKAs, none of the patients randomised to warfarin in this study had recurrence. Major bleeding occurred in 4 patients (7%) in the rivaroxaban group and 2 patients (3%) in the warfarin group. A comparison of the two randomised controlled studies is presented in table 2.

ASTRO-APS (Apixaban for Secondary Prevention of Thrombosis Among Patients with Antiphospholipid Syndrome) (https: & clinicaltrials.gov/ct2/show/NCT02295475) is investigating apixaban 5 mg bd versus Warfarin (INR 2.0-3.0) in patients with APS (definite, likely, or historical) and VTE ≥ 6 months ago, on anticoagulation. The initial apixaban dose of 2.5mg BD was increased to 5mg bd following the preplanned data safety monitoring board review after the first 25 patients, and the entry criteria were changed to include patients with VTE only and to perform brain MRI at enrollment to exclude evidence of stroke or white matter changes

(Woller *et al*, 2018). However, this trial has stopped recruiting. Currently, there are no other on-going studies investigating this area.

Following publication of the meta-analysis (Dufrost *et al*, 2018) and the TRAPS study (Pengo *et al*, 2018) the MHRA (drug-safety-update, 2019) and EMA (ema.europa.eu, 2019) both issued statements that DOACs should not be used for secondary prevention in APS patients. Although they drew specific attention to triple positive high-risk patients, the recommendations make two generalisations from the single RCT: firstly, from rivaroxaban to all DOACs and secondly from 'triple positive' to all patients with APS. As earlier studies had shown that triple positive patients are at especially high risk of thrombosis and there is a lack of data for single or dual positive APS patients, the recommendation to avoid DOACs in all APS patients may represent over-interpretation of the data. Taking this into account and the data from RAPS, it may be reasonable to retain DOACs as an option for some non-triple positive patients, particularly when there are problems with warfarin such as poor INR control or drug interactions. Moreover, some patients may have already been on a DOAC for some time without problems and patient preference may be an important factor. It is important to make patients aware of available evidence and the EMA and MHRA recommendations.

The identification of triple positive patients as a distinct group with higher risk of thrombosis is well established. They appear to have a different antibody profile with higher levels of antibodies against 2GPI-domain 1, which is thought to be important in pathogenesis of thrombosis (Pengo et al,2015) and also against phosphatidylserine/prothrombin (Hoxha et al, 2017). However, it is not clear how this may alter their susceptibility to different anticoagulants. All clinical studies to date have used rivaroxaban 15 or 20mg daily in patients with APS and

whether higher or more frequent doses will prove effective in triple positive APS patients remains to be seen. The direct inhibitory action of rivaroxaban or other DOACs against factor Xa or thrombin compared to the indirect VKA effect of lowering multiple coagulation factors in both intrinsic and extrinsic pathways may determine the difference in efficacy between the two classes of anticoagulant, but this may also arise from their different time course of anticoagulant effect. The endogenous thrombin potential (ETP) was higher in patients on rivaroxaban compared to warfarin (Cohen et al, 2016) and raised ETP has been demonstrated to be an independent predictor of recurrent venous thromboembolism (Eichinger et al, 2008).

An unfortunate consequence of the EMA and MHRA warnings on use of DOACs in APS will be to greatly reduce the likelihood of further clinical studies and so we may be left with incomplete evidence to guide treatment of thrombotic APS (Table 2).

Arterial thrombosis

The most frequent site of arterial thrombosis in APS is in the cerebral vasculature, resulting in stroke/transient ischaemic attacks (TIA) (Cervera *et al*, 2009) but can occur anywhere in the body including coronary and renal arteries.

Vitamin K antagonists

Arterial events can be thrombotic or embolic. In general, for patients without APS, antiplatelet therapy (single or dual) is the recommended treatment for thrombotic stroke (without atrial fibrillation). In patients with APS, recurrent thrombosis frequently occurs in the previous

distribution (arterial vs. venous) but cross-over may occur in around 30-40% of patients (Pengo *et al*, 2010). There are relatively limited data available on management of arterial thrombosis with definite APS from RCT and no satisfactory RCTs comparing standard intensity VKAs with antiplatelet treatment in APS and stroke. Current therapeutic recommendations range from single or dual antiplatelet treatment to VKA with a target INR of 2.5 (2.0-3.0) or 3.5 (3.0-4.0).

Although two prospective randomized controlled trials (Crowther *et al*, 2003;Finazzi *et al*, 2005) concluded that warfarin with standard intensity INR was appropriate for thrombotic APS to prevent recurrence for both venous and arterial thrombosis, only 24% (27/114) and 40% (44/109) patients with arterial thrombosis respectively were included in these two trials. Therefore, it is questionable whether the results can be generalised to patients with arterial thrombosis. The Antiphospholipid Antibodies and Stroke Study (APASS), was a prospective cohort study within the Warfarin versus Aspirin Recurrent Stroke Study (WARSS) (Levine *et al*, 2004). It studied patients with aPL detected at the time of an initial ischemic stroke and found no benefit of warfarin anticoagulation (target INR 1.4–2.8) over aspirin (325 mg/day) in prevention of stroke. aPL status was tested within 90 days of the index stroke by a central independent laboratory. However, this study has major limitations. The mean age in the study population was 60 years; therefore, patients were likely to have multiple risk factors for the development of stroke, such as hypertension, diabetes and cardiovascular disease, independent of aPL. More importantly, (ref) aPL were tested only once and may therefore have been only transiently positive. Of 726 aPL-positive patients, 52.6% had low positive aCL including IgA aCL which are not a recognised APS laboratory criterion.

In a systematic review of 16 studies (9 retrospective cohort studies, 3 prospective cohort studies and 4 RCT), APS patients with first episode of VTE had lower recurrence rates compared to patients with arterial and/or previous recurrent events, with and without anticoagulant therapy (Ruiz-Irastorza et al, 2007). Out of 180 recurrent thrombotic events identified from this systematic review, 57% occurred when patients were on neither anticoagulant nor anti-platelet treatment (28% arterial vs 72% venous), 15% whilst on low dose aspirin (83% arterial vs 17% venous), 23 % whilst on warfarin with target INR <3.0 (45% arterial vs 55% venous) and only 3.8% of events with target INR of >3.0 (80% arterial vs 20% venous) (Ruiz-Irastorza et al, 2007). However, these were not the rates of thrombosis and studies were not randomised studies comparing specific anticoagulant regimens and therefore are of limited use in guiding therapy. Bleeding rates were reported in only 8 studies. Only seven studies reported the INR measured at the time of bleeding: of the total of 93 bleeding episodes reported, 24 (26%) occurred when INR was <3.0 and 69 (74%) when INR >3.0 (Ruiz-Irastorza *et al*, 2007). Based on these data, the authors recommended that APS with arterial thrombosis and/or recurrent venous events should be treated with warfarin at an INR >3.0. However, this is supported only by cohort studies and the two RCTs, albeit with limited numbers, agreed that this was without benefit compared to standard INR target. (Ruiz-Irastorza *et al*, 2007).

In a retrospective study of 139 APS patients with arterial thrombosis, patients treated with antiplatelet therapy had a 2.1-fold increase of recurrence compared to anticoagulation whilst patients on combined antiplatelet and anticoagulant treatment had a 70% lower risk of recurrent event (HR 0.30, 95% CI (0.08, 0.83, p<0.025) (Jackson *et al*, 2017). However, lack of data on bleeding events was a major limitation of this study.

The lack of robust evidence for optimal anticoagulant intensity in patients with arterial thrombosis is reflected in national and international guidelines. The 13th International Congress on Antiphospholipid Antibodies task force recommended an INR >3.0 or combined antiplatelet-anticoagulant (INR 2.0–3.0) therapy for arterial thrombosis (Ruiz-Irastorza *et al*, 2011). However, 5 out 13 panel members suggested that either anti-platelet treatment alone or VKAs with target INR 2.5 (2.0-3.0) were equally effective for patients with arterial thrombosis. The British Society for Haematology (BSH) guidelines recommend that due to lack of strong evidence, anticoagulation with warfarin should be considered in patients <50 years with stroke and APS using a target INR of 2.5 (2.0-3.0) but that there is no strong evidence to recommend it over antiplatelet therapy. Standard practice is to maintain a target INR of 2.5, with escalation to a higher target INR should thrombosis recur (Keeling *et al*, 2012) although some suggest beginning with a higher target INR (Cohen *et al*, 2018).

In a retrospective cohort study of 90 APS patients evaluating secondary prevention of arterial thrombosis, it was found that dual antiplatelet treatment (DAPT) significantly reduced the rate of recurrence compared with warfarin with INR of 1.5-2.5 (log-rank P = 0.001)(Ohnishi *et al*, 2019). There were no significant differences in the rate of serious adverse events (major bleeding and deaths) between groups. However, small numbers and retrospective design are major limitations of this study. In elderly patients with atrial fibrillation antiplatelet therapy had a similar rate of major but lower rate of intracranial bleeding (RR, 0.46; 95% CI, 0.30-0.73) compared to anticoagulants (Melkonian *et al*, 2017). Therefore, in older population at high risk of intracranial bleeding and additional risk factors for ischemic stroke, single or dual anti-platelet treatment may be suitable alternative to warfarin.

Direct acting oral anticoagulant and arterial thrombosis

At present, DOACs are not licensed for use in arterial thrombosis with or without APS except for low dose rivaroxaban with or without aspirin for secondary prevention of cardiovascular events. (Eikelboom *et al*, 2017). However, patients with APS were not included and patients with or without APS should still be stratified for other cardiovascular risk factors such as smoking, hypertension and diabetes.

There are very limited data on the use of DOACs in patients with APS and arterial thrombosis. In a meta-analysis of 303 patients with APS, 48 and 8 patients were treated with either rivaroxaban or apixaban for arterial or small vessel thrombosis (Dufrost *et al*, 2018). These patients had a 3 to 5-fold increased risk of recurrent thrombosis compared to patients treated for venous thrombosis; odds ratio (OR) =2.8 (95%CI: 1.4-5.7) and OR =5.3 (95% CI: 1.3-23.2) for arterial or small vessel thrombosis respectively. The rate of recurrence was particularly high in 'triple positive' patients, (56% vs 23%; OR=4.3 [95%CI; 2.3–7.7], $p < 0.0001$). This group has previously been identified as having a high thrombotic risk and was studied further in randomised trial comparing standard dose rivaroxaban (20mg od) with standard intensity warfarin (INR target 2.0 – 3.0) (Pengo *et al*, 2018). 120 patients with triple positive APS were randomised, including 11 patients (11/59, 19%) with arterial thrombosis randomised to rivaroxaban and 14 patients (14/61, 23%) to receive warfarin. The trial was stopped prematurely due to an excess of thrombotic events in the rivaroxaban arm. Interestingly, 4 out of the 7 patients (57%) who developed recurrent thrombotic events on rivaroxaban had had previous arterial thrombosis. None of the patients on warfarin had a recurrence.

In summary patients with APS and arterial thrombosis should not be treated with DOACs. Patients in whom APS is the clear reason for arterial thrombosis and have no additional risk factors for thrombosis irrespective of the age, VKA with a target INR of 2.5 (2.0-3.0) is the preferred option over antiplatelet treatment. If there are additional risk factors for bleeding with anticoagulation, single or dual antiplatelet treatment should be given rather than no treatment (Ruiz-Irastorza *et al*, 2007). Modifiable risk factors for arterial thrombosis should be addressed adequately.

Management of recurrent thrombosis despite therapeutic anticoagulation

There are no prospective studies to guide the management of these patients; clearly some intensification of therapy is required. The recurrence thrombosis should be confirmed objectively. If the patient was on a DOAC at the time of recurrent thrombosis, they should be switched to LWMH followed by warfarin. We aim for a higher target INR than 2.5 in these patients on the grounds that all DOACs were compared with warfarin target INR of 2.5 in phase III clinical studies for VTE. If a patient developed recurrence whilst on a VKA, it is important determine the INR at the time and the overall time in therapeutic range. The sensitivity of the thromboplastin reagent used to the presence of LA should be reviewed (Robert *et al*, 1998;Tripodi *et al*, 2001). If this is likely to have affected the INR estimation then changing thromboplastin or measuring amidolytic factor X (FX) assays may be helpful (Keeling *et al*, 2012). FX levels of 20–40% are expected with INR of 2.0-3.0 (Rosborough *et al*, 2010). However, if a recurrent thrombotic event occurred whilst on established therapeutic anticoagulation with

VKA, the INR target should be increased to 3.5 (3.0-4.0) with an initial short period of treatment with LMWH (until the required target INR is achieved). Although long term LMWH is an option it is seldom practical but in a small group of patients, may be the preferred choice. This has been shown to be effective for VTE and in cancer. In the latter case there is some evidence that standard doses can be increased by 25% for recurrent event (Carrier et al, 2009). Adding antiplatelet agent to VKAs is another option whilst keeping the target INR of 2.5 (2.0-3.0) especially in patients with arterial thrombosis. Hydroxychloroquine (HCQ) is another adjuvant treatment for patients with recurrent thrombosis whilst on anticoagulant (Nuri *et al*, 2017;Petri, 2011). The recommendation for use of HCQ as an adjuvant treatment is based on studies demonstrating its inhibitory effect on platelet aggregation and arachidonic acid release and protection of the Annexin V anticoagulant shield, reducing thrombus size in mice models of APS (Espinola et al, 2002; Rand et al,2010). It has also demonstrated efficacy as thromboprophylaxis after hip surgery (Johansson et al, 1981). In patients with SLE and aPL, treatment with HCQ was associated with a reduction in thrombotic risk (Ho et al. 2005). In a prospective nonrandomized study with 40 APS patients without SLE (20 patients in each arm), addition of HCQ to VKA reduced thrombosis compared to VKA alone (Schmidt-Tanguy et al. 2013). Consensus guidelines also support its use as an adjuvant to anticoagulation in patients with recurrent thrombosis despite anticoagulation (Ruiz-Irastorza et al, 2011). More importantly, modifiable risk factors for arterial thrombosis such as smoking, hypertension and diabetes should be addressed adequately in all patients. Hypercholesterolemia should be treated with statins and dietary modifications.

For those who develop recurrent thrombosis despite high-intensity warfarin (INR of 3.0-4.0), only limited options are available. These include addition of an antiplatelet agent or substituting warfarin with high-intensity LMWH (maintaining peak anti Xa levels 1.6 – 2.0IU/ml for once daily dosing and peak 0.8 – 1.0IU/ml for twice daily dosing (Arachchillage & Laffan, 2017) or using a combination of direct thrombin inhibitor (dabigatran) and a factor Xa inhibitor (rivaroxaban or apixaban) (Arachchillage et al, 2016). Failure of high intensity antithrombotic therapy suggests that other mechanisms may be important and combined anticoagulation with immunosuppression and/or immunomodulation with modalities such as rituximab, complement inhibitors and mTOR inhibitors such as sirolimus should be considered in such patients. (Arachchillage & Laffan, 2017). Management of patients with recurrent thrombosis despite on therapeutic anticoagulation is summarized in Figure 1.

DOACs and detection of Lupus anticoagulant

The presence of anticoagulants can interfere with detection of LA, mainly by producing false positive results. Samples taken at the time of acute thrombosis may also be unreliable due to acute phase reactants and anticoagulant therapies. Subsequent interruption of anticoagulation for several days to allow testing for LA is not a safe option as this can exposure the patient to risk of recurrent thrombosis and is therefore not recommended if APS is suspected, especially in patients with positive solid phase antibodies (aCL and anti-beta 2GPI). However, identifying those with triple positive APS is important because it will affect the choice of anticoagulant. Patients who are positive for both solid phase antibodies should be switched to warfarin if they

are on a DOAC and the LAC status cannot be determined. Advice on LA detection in patients on long-term VKA can be found in ISTH guidelines (Pengo *et al*, 2009). DOACs, even at trough levels can produce false-positive LA (Merriman *et al*, 2011), although some studies suggest that this may not occur at rivaroxaban levels <50ng/mL ((Arachchillage *et al*, 2015). A possible method to detect LA in samples containing direct factor Xa inhibitors is the Taipan snake venom time/Ecarin clotting time combination, as these tests are insensitive to factor Xa-inhibitors (Arachchillage *et al*, 2015). However, these tests are not readily available in many routine hospital laboratories and require further validation studies with large number of samples from true positive and negative patients with APS before recommending for routine use. No alternatives exist for LA detection in samples containing direct thrombin inhibitors. Some studies have shown that absorption methods to remove the effect of DOACs are useful for avoiding the false positive DRVVT whilst on DOACs (Cox-Morton *et al*, 2019;Exner *et al*, 2018;Platton & Hunt, 2019;Zabczyk *et al*, 2019) and are currently being used in clinical practice in some centres. However, prior to recommendation of these methods for routine use, they should be validated in large enough numbers of samples from true positive and negative patients with APS. Temporary switching to LMWH is an option but depending on the renal function, the DOAC should be discontinued for 48-72-hours before the sample is taken for analysis (or DOACs levels should be measured). Interference from the LMWH can be minimised by taking the sample just before the next dose of LMWH and using a kit containing polybrene to neutralize residual heparin.

Summary: detection of LA whilst on anticoagulant

Whilst on VKAs, ISTH guidelines are to be followed (Pengo *et al*, 2009)

Patients on DOACs

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

2) Although Taipan snake venom time/Ecarin clotting time combination has been suggested to detect LA in patients on direct factor Xa inhibitors, further studies assessing and sensitivity for LAC of this test combination are required before recommending for routine use.

3) Although methods absorb DOACs from plasma samples are used to allow testing for LA in some centres, they need further validation studies before recommending for routine clinical use

4. Testing of LA using APTT and DRVVT based test can be performed at 3 months, after switching to LMWH (sample taken just before the next dose of LMWH) after an adequate washout period for oral anticoagulant depending on renal function.

In conclusion, VKA warfarin remains the standard long-term anticoagulant for APS patients with triple positive VTE and arterial thrombosis patients irrespective of the site of thrombosis. One randomized open-label multicentre study showed that rivaroxaban was ineffective for patients with high risk triple positive APS and mixed arterial and venous thromboses but this does not allow generalisation to all patients with other degrees of thrombotic APS. Nonetheless the results of this study and the regulatory responses may make it an extra challenge to conduct future studies in this area. Based on current evidence, patients with triple positive APS and VTE and all APS patients with arterial thrombosis should not treated with DOACs. There is insufficient evidence to make recommendations for those with venous thrombosis and single or

dual positive APS. Data from other trials suggest it is reasonable to consider DOACs in this group of patients and to continue DOACs if they have been on them without recurrence. However, it is important to educate the patients on available evidence and to discuss the recommendations from EMA and the MHRA.

Authorship

D.R.J.A performed the literature search and wrote the first draft. M.L and D.R.J.A reviewed and approved the final manuscript

Disclosure of conflict of interest

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Legends to tables and figures

Table 1. Clinical and laboratory features suggestive an increased likelihood of having antiphospholipid syndrome

Table 2. Comparison of two randomised controlled studies investigating the use of direct acting oral anticoagulants in antiphospholipid syndrome

Figure 1: Management of patients with recurrent thrombosis in antiphospholipid syndrome despite therapeutic anticoagulation

Table 1.

Features indicating an increased likelihood of APS and therefore should be tested for aPL at the diagnosis of unprovoked thrombosis
• ***Idiopathic VTE <50 years old*** • ***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 other explanation***

APS=antiphospholipid syndrome; aPL=antiphospholipid antibodies; APTT= activated partial thromboplastin time; VTE= venous thromboembolism

Table 2

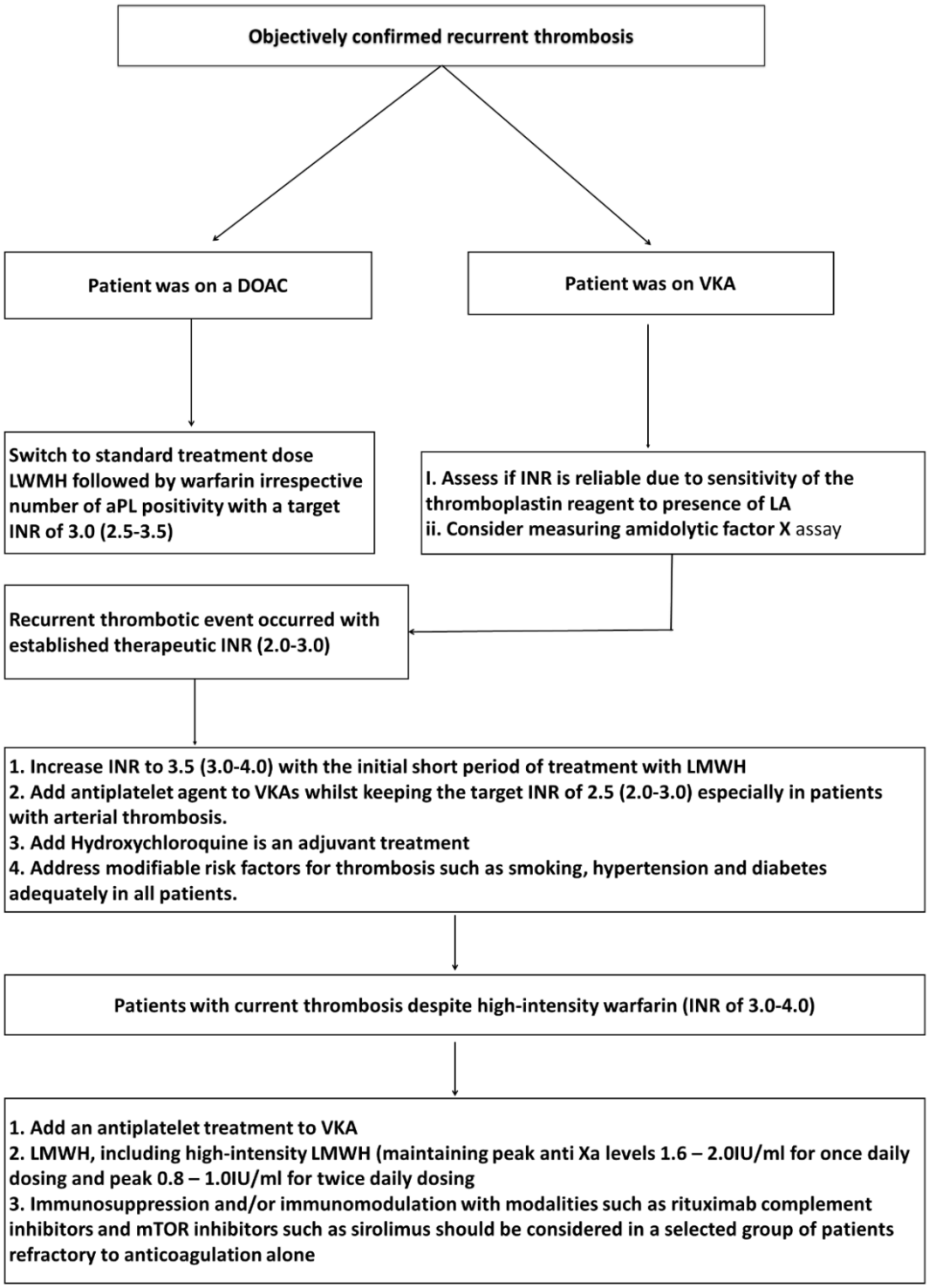
Characteristics	**Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (Cohen *et al*, 2016)**	**Rivaroxaban vs warfarin in high- risk patients with antiphospholipid syndrome (Pengo *et al*, 2018)**
Trial design	Randomised open-label, phase 2/3, non-inferiority trial in two UK hospitals	Randomized open-label multicentre noninferiority study in Italy
Number of patients (total)	116	120
Rivaroxaban arm	57	59
Warfarin arm	59	61
Age		
Rivaroxaban arm	47 ±17	46.5 ±10.2
Warfarin arm	50 ±14	46.1 ± 13.2
Male/female		
Rivaroxaban arm	15/42	20/39
Warfarin arm	17/42	23/38
Primary outcome measure	Percentage change in ETP from randomisation to day 42	Cumulative incidence of thromboembolic events, major bleeding, and vascular death
Secondary outcome measures	Recurrence of thromboembolism or bleeding up to day 210 after randomisation parameters of thrombin generation (lag time, time to peak thrombin generation, peak thrombin generation, and ETP), markers of in-vivo coagulation activation at baseline and on day 42, INR and amidolytic factor X for warfarin and anti-factor Xa rivaroxaban level	Incidence of any individual component of the composite end point
APL status (Miyakis categories*) I (excluding triple positive) I (triple-positive) IIa IIb	 35/116 19/116 53/116 4/116	 - 120 - -

IIc	5/116	-
Previous thrombotic events Rivaroxaban arm	DVT 32 (56%) PE 25 (44%)	Stroke 8/59 (14%) Acute MI 0/59 (0%) Arterial thrombosis in other sites 3/59 (5%) DVT and/or PE 36/59 (61%) VTE in other sites 2/59 (3%) VTE and arterial thrombosis 10/59 (17%)
Warfarin arm	DVT 37 (63%) PE 22 (37%)	Stroke 8/61 (13%) Acute MI 2/61 (3%) Arterial thrombosis in other sites 4/61 (7%) DVT and/or PE 32/61(52%) VTE in other sites 7/61 (12%) VTE and arterial thrombosis 8/61 (13%)
Follow up	210 days	569 days
Recurrent thrombotic events Rivaroxaban arm	None	Arterial thrombosis 12% (7/59 which include 4 ischemic strokes and 3 myocardial infarction)
Warfarin arm	None	None
Study conclusions	ETP for rivaroxaban did not reach the non-inferiority threshold, no increase in thrombotic risk compared with standard-intensity warfarin	Rivaroxaban in high-risk patients with APS was associated with an excess of thrombotic events compared to warfarin
Comments	Study population was homogeneous in terms of clinical events prior to entering the trial (only VTE) either one-episode VTE or recurrence whilst off anticoagulant. However, only 12% (7/5) in rivaroxaban arm and 20% (12/59) in warfarin arm were triple positive and majority of the patients were positive for only one antibody. Although laboratory outcome was the primary outcome measure, the absence of recurrent events at 6 months, may provide reassurance for use of rivaroxaban in this low risk APS population.	Study population was homogeneous for aPL status (triple positive) but clinical events prior to entering the trial were heterogeneous and included thrombosis at venous sites, arterial or both sites. Four out of 7 patients had recurrent thrombosis on rivaroxaban arm had previous arterial thrombosis. Therefore, results are less powerful than it appears. The study data cannot be applied to patients with single or dual positive APS and thrombosis

*Category I, presence of more than one aPL in any combination; category IIa, presence of lupus anticoagulant alone; category IIb, presence of antibodies against cardiolipin alone; category IIc, presence of antibodies against β2 glycoprotein I alone

ETP = endogenous thrombin potential; INR = international normalised ratio; DVT= deep venous thrombosis; PE= pulmonary embolism; MI= myocardial infarction; VTE= venous thromboembolism; aPL = antiphospholipid antibodies; APS= antiphospholipid syndrome

Figure 1:



DOAC= direct acting oral anticoagulant, aPL= antiphospholipid antibodies; VKA= vitamin K antagonist; INR= international normalized ratio ; LMWH= Low molecular weight heparin; mTOR= mammalian target of rapamycin