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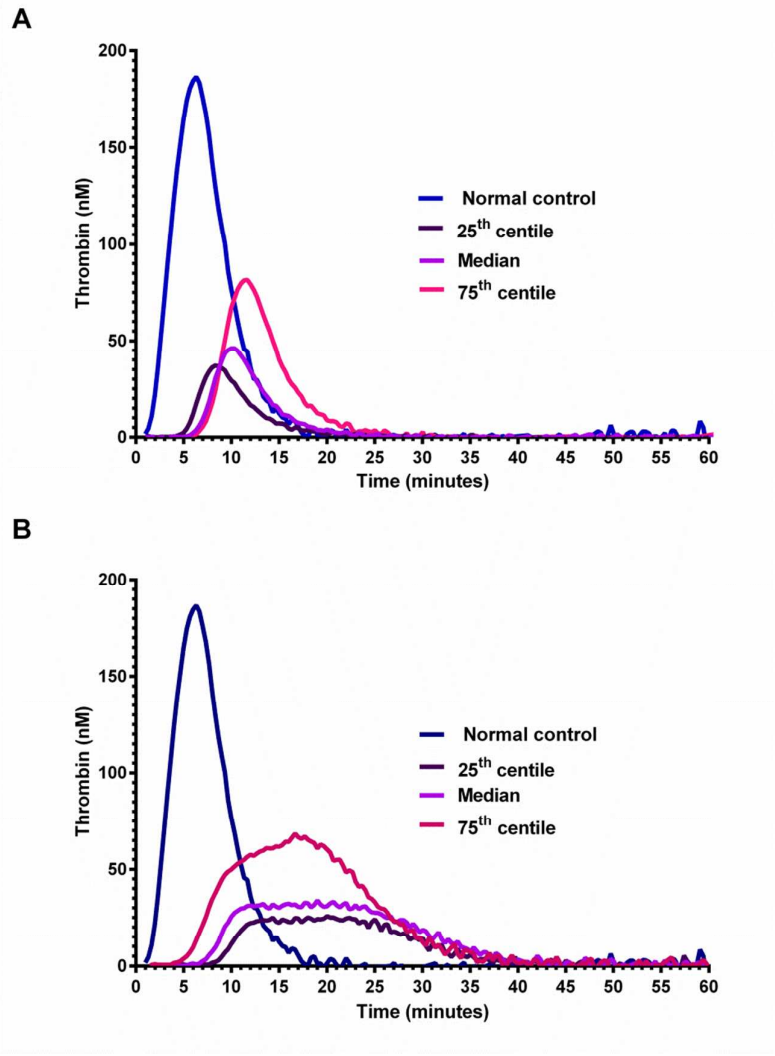
Figure 1: RAPS (Rivaroxaban in Antiphospholipid Syndrome) trial thrombograms for median (25th and 7th percentiles) ETP values in patients on rivaroxaban or warfarin compared with a typical normal control value [46]



Use of direct oral anticoagulants in antiphospholipid syndrome

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Abstract

The direct oral anticoagulants (DOACs) are therapeutic alternatives to warfarin and other vitamin K antagonists (VKAs), and the standard of care for many indications. VKAs are conventional therapy for the treatment and secondary thromboprophylaxis of thrombotic antiphospholipid syndrome (APS), but are often problematic due to the variable sensitivity of thromboplastins to lupus anticoagulant. Thus, the International Normalised Ratio may not accurately reflect anticoagulation intensity, or be clinically effective. Definition of the current role of DOACs in APS is based on limited clinical trial data and information from other sources, including manufacturers' data, case series or cohort studies and expert consensus. The RAPS randomised controlled trial (RCT), that had a laboratory surrogate primary outcome measure, suggests that rivaroxaban offers the potential to be an effective and convenient alternative to warfarin in thrombotic APS patients with a single VTE event requiring standard intensity anticoagulation. However, further studies, in particular, acquisition of better long-term efficacy and safety data, are needed before it can be widely recommended. APS patients are clinically heterogeneous, with the risk of recurrent thrombosis and the intensity of anticoagulation influenced by their clinical phenotype and risk profile. DOAC trials involving homogeneous thrombotic APS populations, with aPL status well defined, will help to optimise the appropriate treatment in APS patient subgroups. Ongoing and emerging DOAC RCTs should provide further information to guide the use of DOACs in APS. Optimal identification of APS patients is a key step in working towards improved therapeutic strategies in these individuals.

Keywords: direct oral anticoagulants, antiphospholipid syndrome, venous thromboembolism, ischaemic stroke, thrombin generation

Introduction

Antiphospholipid syndrome (APS) is manifested by thrombosis (arterial, venous or microvascular) and/or obstetric morbidity in association with persistent antiphospholipid antibodies (aPL), i.e. lupus anticoagulant (LA), anticardiolipin (aCL) and/or anti-beta 2 glycoprotein 1 antibodies (aβ2GP1) [1]. Thrombotic APS is clinically heterogenous, with thrombotic episodes ranging from mild to potentially life-threatening, refractory thrombosis despite adequate anticoagulation; and the rare catastrophic APS. Thrombotic events may be venous, arterial, or microvascular. APS mainly affects relatively young individuals. The median age at study entry in the Euro-Phospholipid Project of 1,000 patients, more than 70% of whom had stroke or VTE, was 40 (range 0-82) years [2]. Among systemic lupus erythematosus (SLE) patients, 30-40% have aPL [3], with estimates of the frequency with which APS occurs in patients with SLE ranging from 7% to 22% [4,5]. SLE patients with APS are often difficult to manage with complex clinical problems [6]. Warfarin or other vitamin K antagonists (VKAs) are conventional therapy for the treatment and secondary thromboprophylaxis of thrombotic APS [7]. However, treatment with VKAs is often problematic as they have a slow onset of action of several days, a narrow therapeutic window, numerous drug and dietary interactions; and the potential for variation of action with alcohol, intercurrent illness, exercise, and smoking. Patients require regular monitoring of the International Normalised Ratio (INR). The direct oral anticoagulants (DOACs), dabigatran, a direct thrombin inhibitor, and apixaban, edoxaban and rivaroxaban, direct factor Xa inhibitors, represent a major milestone in anticoagulation. They are therapeutic alternatives to VKAs and the standard of care for many indications, detailed in the summary of product characteristics (SPC) [8-11]. DOACs, in contrast to VKAs, are prescribed at a fixed dose with a more predictable anticoagulant effect and do not routinely require regular

anticoagulant monitoring. They have a rapid onset of action which generally obviates the need for bridging anticoagulation with low-molecular-weight heparin (LMWH) [9,11], are not affected by dietary changes and alcohol intake and have fewer drug interactions than VKAs that affect anticoagulant intensity. These features should improve patient quality of life. The SPCs for the licensed DOACs [8-11] do not contain information regarding the use of DOACs in patients with APS. Definition of the current role of DOACs in APS is based on limited clinical data and information from other sources, including manufacturers' data, case series or cohort studies and expert consensus.

Warfarin and other vitamin K antagonists for antiphospholipid syndrome

Approximately 10% of APS patients overall [2] and 30% of those who are triple aPL positive, i.e. have LA, aCL and aβ2GP1 [12], have recurrent thrombotic events, arterial or venous, on VKAs (at standard intensity, target INR 2.5) at 5 years follow up. The high thrombotic risk of triple aPL positive patients is also observed in asymptomatic individuals, where the risk of thrombosis is significantly higher than in those with single aPL positivity. The annual rate of first cardiovascular event is 5.3% in triple aPL positive (cumulative incidence 37% at 10 years) vs 1.36% in single aPL positive individuals vs ~0.4% in the normal population [13]. A systematic review of 16 studies indicated that APS patients on anticoagulation experience major bleeding rates of 0.57% to 10% per year [14].

Venous thromboembolism

Retrospective studies have shown a high incidence of thrombosis recurrence in patients with aPL [15-17]. In these studies, 54% (80/147), 56% (39/70) and 38% (23/61) of patients

had VTE. In the prospective Duration of Anticoagulation (DURAC) study on 412 patients with VTE, a single aCL-positive test doubled the risk of recurrence in the first 6 months after cessation of warfarin: 29% (20/68) in patients with aCL and 14% (47/334) in patients without aCL (p=0.0013), for a risk ratio of 2.1 (95% confidence interval [CI]: 1.3–3.3) [18]. Current recommendations on the duration of anticoagulation in individuals with VTE who have APS are extrapolated from studies in the general VTE population [19-21]. Although indefinite anticoagulation is suggested for APS patients with unprovoked VTE and temporary anticoagulation for those with a provoked VTE [19,22], there are no specific substantive data on the optimal duration of anticoagulation for APS patients with VTE. A pragmatic approach is to test for aPL in patients who have had a first unprovoked VTE, as aPL positivity strengthens the decision for indefinite anticoagulation. It also identifies women who require higher than standard prophylactic dose anticoagulation with LMWH during pregnancy [23-25], and who also require low dose aspirin and monitoring for placental insufficiency [26], to guide optimal timing of delivery, reducing the risk of perinatal morbidity and mortality. Testing for aPL is recommended in patients with unprovoked VTE [19], however aPL testing should also be considered in patients with provoked VTE, particularly if the provoking factor for VTE appears disproportionately mild.

Stroke and other arterial thrombosis

APS patients with ischaemic brain manifestations also require identification in contrast to non-APS stroke patients where antiplatelet treatment is the standard of care. Anticoagulation is a rational treatment for patients with APS and stroke, TIA or other ischaemic brain manifestations since it can lead to resolution of in situ arterial thrombosis or prevent cardioembolic events. UK national clinical guidelines for stroke recommend aPL

testing in individuals under 50 years [27]. There are few data to guide the optimal anticoagulation intensity in APS patients with stroke or other arterial thrombosis. Ruiz-Irastorza et al [14] reviewed 16 studies (4 randomised controlled trials (RCTs) and 12 prospective or retrospective cohort studies) on secondary thromboprophylaxis in patients with aPL. Of 180 thrombotic events reported, 104 (57%) occurred when patients were not taking any anticoagulant or antiplatelet agent. Only 7 of 49 recurrences (27%) on warfarin occurred in patients when the INR was >3.0; of these, in the five cases where specified, 4 were arterial and one venous.

Three prospective studies have addressed the key issue of the optimal antithrombotic treatment for stroke patients with aPL, however, these have major limitations. Two RCTs on standard vs high intensity warfarin in patients with thrombotic APS, Crowther et al [28] and Finazzi et al [29] concluded that the optimal target INR for both venous and/or arterial thromboembolism, including stroke, in APS is 2.5 (range 2.0–3.0) (standard-intensity) rather than 3.5 (range 3.0-4.0) (high-intensity). However, patients with recurrent thrombosis history while on therapeutic anticoagulation or with arterial thrombosis were poorly represented in both studies, with the latter comprising only 24% and 32% (62 of 223 patients across both studies). Notably, 6/8 recurrent thrombotic events in Crowther et al's study [28] occurred while the INR was <3.0 (5/6) or while off warfarin (1/6). The study by Finazzi et al did not detail the INR at the time of thrombosis [29]. The Antiphospholipid Antibodies and Stroke Study (APASS) [30], a prospective cohort study within the Warfarin versus Aspirin Recurrent Stroke Study (WARSS), reported no benefit of warfarin anticoagulation (target INR 1.4–2.8) over aspirin (325 mg/day) in stroke prevention.

However, laboratory criteria for aPL were not compliant with the international consensus criteria for APS diagnosis [30].

The lack of robust data on the optimal anticoagulant intensity in ischaemic stroke patients with APS is reflected in national and international guidelines. British Society for Haematology [19] and American College of Chest Physicians guidelines [31] on APS associated ischaemic stroke include warfarin (or other VKA) at a target INR of 2.5 (range 2.0-3.0). The Task Force at the 13th International Congress on aPL recommended that patients with definite APS and arterial thrombosis should be treated with warfarin at an INR >3.0 or combined antiplatelet-anticoagulant (target INR 2.5) therapy [21]. This suggestion was a non-graded recommendation due to lack of consensus within the Task Force. Many physicians treating APS patients use high-intensity warfarin (target INR 3.5; range 3.0-4.0) for APS patients with ischaemic stroke or other arterial thrombosis.

Laboratory issues in antiphospholipid syndrome patients on vitamin K antagonists or direct oral anticoagulants

Laboratory monitoring of anticoagulation on warfarin

VKAs can be problematic in APS patients because of variable sensitivity of thromboplastins to LA [32,33]. A multicentre study indicated that LA interference with the prothrombin time-INR measured with the majority of commercial thromboplastins is insufficient to cause concern if insensitive thromboplastins, properly calibrated to assign them an instrument-specific International Sensitivity Index (ISI), are used. The investigators suggested that new thromboplastins, especially those made of relipidated recombinant human tissue factor,

should be checked ensuring that they are insensitive to the effects of aPL before being used to monitor oral anticoagulant treatment in APS patients [33]. These procedures are generally routine in specialist centres, but may not available elsewhere. Thus, the INR might not accurately reflect anticoagulation intensity and, as a result, could be associated with potential thrombotic or bleeding complications. Amidolytic factor X assays, as a LA-independent measure of anticoagulation intensity, may be useful in such cases, although this is rarely practicable [32,34]. The variable sensitivity of thromboplastins to LA may also be associated with instability of the INR, necessitating frequent anticoagulant monitoring causing inconvenience to the patient, adversely impacting on quality of life and increasing costs. Warfarin also interacts with many other drugs altering the INR and complicating the treatment of APS patients with other disorders, including SLE.

Testing for antiphospholipid antibodies

LA testing in patients on VKAs isaddressed in national and international guidelines [19, 35]. Tests for LA detection should include screening, mixing and confirmation ones assessed with at least two different methodologies [19,35]. Many studies have reported DOAC interference with assays for LA leading to false positive and unreliable results [36;37-39]. Dabigatran and apixaban interfere with both the activated partial thromboplastin time (APTT) and the dilute Russell Viper Venom time (dRVVT) assays, with false positive resultsreported with a hexagonal phase lipid neutralisation assay using the Staclot LA assay [40-43]. False positive tests for PTT LA, Silica Clotting Time screens and dRVVT have also been reported for rivaroxaban, particularly at peak plasma levels [36;41;44-46]. However, the Taipan Venom Time/Ecarin Clotting Time (TVT/ECT) ratio and Textarin time assays

perform better and are unaffected by rivaroxaban, irrespective of concentration. In thrombotic APS patients treated with rivaroxaban, the TVT/ECT appears reliable even at peak therapeutic plasma levels, while the dRVVT may be acceptable at trough rivaroxaban plasma levels (>18 hours after the last dose of rivaroxaban), although a rivaroxaban anti-Xa should be performed in parallel to ensure that the result is not a false positive [36,43,46]. No interference has been reported by any DOACs on solid phase assays or enzyme–linked immunosorbent assays (ELISAs) for anti-β2GPI or aCL [42,44,46] .

Thrombin generation and direct oral anticoagulants

Thrombin generation (TG), assessed by calibrated automated thrombography, represents a global dynamic assay that measures the overall ability of plasma to form thrombin after initiation of coagulation using a thrombin-sensitive fluorogenic substrate. The TG curve, quantified in terms of the lag time, time to peak TG, peak TG, and endogenous thrombin potential (ETP), the area under the TG curve [47], is informative in regard to APS status and LA detection [48,49]. TG can be used to assess the effects of anticoagulants in platelet poor (PPP) and rich plasma (PRP) and in both APS and non-APS patients [34,50,51,52,]. Rivaroxaban can downregulate and completely suppress TG in whole blood, PRP [53,54] and PPP [55,56], while dabigatran can significantly inhibit TF-induced TG in a concentration-dependent manner, but with weaker inhibitory effects than rivaroxaban [57]. Apixaban affects all TG parameters with prolonged lag time, ETP and peak TG (the latter showing greater reduction than the ETP) [58]. Antiphospholipid antibodies might interfere with the anticoagulant action of DOACs, however no effect with rivaroxaban was observed in *in-vitro* studies which showed that aPL did not affect its anticoagulant action at peak or trough

levels, based on TG testing and anti-Xa levels [36]. This was predictable as rivaroxaban is a small molecule with high specificity and affinity for its target [53,59].

Observational data on the use of direct oral anticoagulants in antiphospholipid syndrome

Patients with aPL or APS were neither specifically included nor excluded from the phase 3 RCTs that demonstrated that DOACs are effective and safe compared with warfarin for the treatment and secondary prevention of VTE after a first VTE event or prevention of stroke or systemic embolism in patients with atrial fibrillation [8-11]. APS is classified as a rare disease in the USA [60]. Systematic reviews suggest that aPL are present in 10% of patients with deep vein thrombosis and 14% of patients with stroke [61], although this is not reflected in thrombotic APS patient numbers in clinical practice, suggesting likely underdiagnosis.

Data on antiphospholipid syndrome derived from phase 3 randomised controlled trials of direct oral anticoagulants in the general population

Dabigatran

A post hoc analysis of pooled data on patients with aPL (LA and/or aCL) from the RE-COVER, RE-COVER II and RE-MEDY studies was undertaken [62]. aPL testing was not mandatory, but when performed, the data were captured. Of 6,822 patients in the pooled analysis, 151 (2.2%) had LA and/or aCL at baseline. In aPL positive patients, there was no significant difference in VTE/VTE-related deaths or major or clinically relevant non-major bleeding events between the two treatment arms. However, this study was heavily underpowered.

Apixaban

In the AMPLIFY RCT of apixaban 5mg twice daily versus enoxaparin followed by warfarin target INR 2.5, relevant baseline risk factors for recurrent VTE included known thrombophilia: 74 (2.85%) patients in the apixaban arm and 59 (2.2%) patients in the enoxaparin followed by warfarin arm. No separate analysis on the safety and efficacy in this specific patient population was performed [63].

Edoxaban

The phase 3 ENGAGE-AF TIMI-48 AF study included one patient with aPL, one with APS and approximately five with SLE or other autoimmune disease [64].

Rivaroxaban

In the EINSTEIN Phase 3 clinical trial programme, adult patients with known thrombophilic conditions (antithrombin, protein C or S deficiency, factor V or prothrombin gene mutations, or aPL) were not excluded [65,66]. In the EINSTEIN DVT and PE pooled analysis patients had a mean age of 57.0 ± 17.0 years. A total of 5.9% of patients in the rivaroxaban group and 5.7% in the enoxaparin/VKA group, respectively, had a known thrombophilic disorder (6.2% vs 6.8% in EINSTEIN DVT [65] and 5.7% vs. 5.0% in EINSTEIN PE [66], respectively). The

relative primary efficacy and principal safety outcomes across the pre-specified subgroups (including the subgroup of patients with a known thrombophilic disorder) in the EINSTEIN DVT and the EINSTEIN PE studies were consistent with the observed overall effects.

Case series and cohort studies of direct oral anticoagulants in antiphospholipid syndrome

Case reports, series and cohort studies have reported on DOAC use in APS patients, with approximately 200 cases reported. Several authors have reported case series and cohort studies describing thromboembolism recurrence in APS patients switched from warfarin to a DOAC [67-72] (Table 1). Other case series report that DOAC use in thrombotic APS has been unassociated with recurrent thrombosis [73,74]; Sciascia et al, reported a case series of 36 patients with APS and VTE requiring standard intensity warfarin, who were switched to rivaroxaban 20mg once daily, and followed for a median of 10 (range 6-24) months. None of these patients had recurrent thrombosis [73]. These data, with their inherent limitations, including selection bias, lack of a comparator arm and in some studies, retrospective design, suggest that recurrent thrombotic events with DOACs in APS patients mainly occur when DOACs are used for secondary prevention of APS-related arterial or microvascular thrombosis, where DOACs are unlicensed and where many APS treaters use high-intensity anticoagulation [22], or in triple aPL positive APS patients (Table 1).

RAPS (Rivaroxaban for Antiphospholipid Syndrome Pilot Feasibility Study) prospective cohort study

The RAPS pilot feasibility study (ClinicalTrials.gov:NCT02116036) was a prospective cohort study for patients with confirmed APS and prior VTE, with or without prior arterial thrombosis, allocating them to receive rivaroxaban 20 mg daily. Patients were followed for thrombosis. Recruitment was closed on 30th September 2016 with a plan to follow all patients for one year. Seventy-nine patients were identified, with the recruitment target 150. Available information indicates that few complications, and no recurrent thromboses, occurred. One patient suffered unexplained hepatitis [7]. This study provides additional data on the efficacy and safety of DOACs in APS patients.

Randomised controlled trials of direct oral anticoagulants in antiphospholipid syndrome

A challenge in DOAC APS studies is ensuring sufficient statistical power. Trials with clinical outcomes are ideal, however, where APS trials with clinical outcomes have succeeded, numbers have been relatively small, 334 patients in 5 RCTs on treatment for APS-associated recurrent miscarriage in the meta-analysis by Mak et al [75], while trials with larger recruitment targets have proved challenging [76,77]. The appropriateness or otherwise, of the use of surrogate markers in clinical trials was considered in an editorial review by Svennson et al who, after supporting their use in fatal diseases like amyotrophic lateral sclerosis, went onto say they felt this approach was justified: “in the case of very rare diseases, (where) validation of hard end points may take an unreasonable time to complete” [78].

The characteristics and status of completed and recruiting RCTs of DOACs in thrombotic APS are summarised in Table 2.

RAPS: Rivaroxaban in Antiphospholipid Syndrome trial

The RAPS trial is the only completed RCT of DOAC use in APS patients. This phase 2/3 non-inferiority RCT compared rivaroxaban to warfarin (target INR of 2.5; range 2.0-3.0) to treat patients with previous VTE [79] on standard-intensity warfarin for at least three months after the last VTE. Warfarin-treated APS patients with previous VTE, with or without SLE, were randomized 1:1 to warfarin or rivaroxaban, 20 mg once daily, stratified by center and SLE/non-SLE.

The primary outcome measure was percentage change in ETP in the TG assay from randomisation to day 42, with treatment continued for 180 days and follow-up for 210 days. 116 patients were randomised, of whom 19% had SLE. When anticoagulation intensity was assessed by ETP alone, rivaroxaban was inferior to warfarin. However, peak thrombin generation was lower with rivaroxaban (Figure 1). Warfarin affects all phases of thrombin generation equally, whereas rivaroxaban directly inhibits factor Xa through specific binding to its active site [53,59] and mainly affects the initiation and propagation of thrombin generation leading to a delay in the formation of the prothrombinase complex [59]. Consequently, the TG curve becomes protracted, lengthening the lag time and time to peak TG [50,52], and leading to greater ETP than would be expected for the degree of anticoagulation [52]. RAPS concluded that, taking into account the altered reaction kinetics with rivaroxaban, the overall thrombogram indicated no difference in thrombotic risk. This conclusion was supported by in vivo coagulation activation marker concentrations (thrombin–antithrombin complexes, prothrombin fragment 1.2 and D-dimer) being slightly raised in few patients in both treatment groups. Furthermore, no new thrombotic events were seen during 6 months of treatment. No major bleeding episodes were noted. Clinically

relevant and minor bleeding rates were similar in the two groups. Quality of life was significantly improved in patients on rivaroxaban.

RAPS was not designed to confirm clinical efficacy and long-term safety. Rather, the trial was designed pragmatically with a laboratory surrogate outcome measure to assess the mechanism of action of the interventions in the two patient groups. Recurrent thrombosis in the APS population selected for RAPS is rare and a primary endpoint of recurrent thrombosis would necessitate several thousand patients and a follow up period of several years, which is impractical. The trial had an intended selection bias, ensuring a clinically homogenous study population with definite APS [1]. Patients who had VTE and developed recurrent VTE while taking standard-intensity anticoagulation (i.e. needing higher-intensity anticoagulation) and those with arterial events were excluded. The proportion of triple positive aPL patients included, 28%, was representative of VTE patients requiring standard-intensity anticoagulation in the investigators' APS population and consistent with the proportion in APS patients suggested in a large multicentre study [2]. The conclusions from the RAPS trial were generally supported by the independent expert comment [80].

Exploratory post-hoc analysis in the RAPS trial patients showed no significant interactions between the effects of rivaroxaban and LA positivity on TG. Coagulation proteases such as factor Xa can activate complement proteins. In a RAPS translational study, APS patients had significantly higher complement activation markers at baseline and day 42 compared to normal controls. Patients randomised to rivaroxaban showed a significant reduction in levels

of C3a, C5a, terminal complement complex [SC5b-9], with levels of Bb fragment, a marker of alternative complement pathway activation, unchanged. These results suggest that rivaroxaban may provide additional benefit to its anticoagulant effect in APS patients by limiting complement activation [81].

TRAPS: Rivaroxaban in Thrombotic Antiphospholipid Syndrome trial

The objective of the TRAPS multicentre phase 3 RCT is to demonstrate non-inferiority of rivaroxaban 20 mg (15 mg in patients with moderate renal insufficiency) once daily versus warfarin (target INR 2.5; range 2.0-3.0) with respect to cumulative incident thrombosis (arterial or venous) confirmed by imaging studies, major bleed, and death in triple aPL-positive APS patients. The trial plans to recruit 536 patients [7,82].

ASTRO-APS: Apixaban for The Secondary Prevention of Thrombosis among patients with Antiphospholipid Syndrome (ASTRO-APS) trial

The ASTRO-APS RCT is comparing apixaban with warfarin (target INR 2.5; range 2.0-3.0) for the secondary prevention of thromboembolism among patients with a history of APS and thrombosis [83]. ASTRO-APS was originally designed to compare apixaban 2.5 or 5 mg twice a day with warfarin, enrolling patients with a history of arterial or venous thromboses receiving indefinite anticoagulation. APS patients are categorized as having definite, likely or historic APS and therefore ASTRO-APS may include patients who do not meet the International Consensus Criteria for APS diagnosis [1]. After accrual of the first 25 patients, a

pre-specified Data Safety Monitoring Board (DSMB) review recommended the protocol be modified to use apixaban 5mg twice a day. In this context, patients with indications for long-term treatment with a VKA, such as aPL, were excluded from AMPLIFY-EXT in which a dose of 2.5mg twice daily was used [84]. After five more patients were enrolled, a potential safety signal led to an ad hoc DSMB re-review, which recommended continuing ASTRO-APS, excluding patients with prior arterial thrombosis; and undertaking brain magnetic resonance imaging with stroke protocol for all otherwise eligible candidates to exclude prior silent stroke. ASTRO-APS plans to enroll 200 patients [7,83].

RISAPS: Rivaroxban for Stroke Patients with Antiphospholipid Syndrome trial

The RISAPS open-label, phase 2/3 non-inferiority RCT [Chief Investigator H Cohen], funded by Arthritis Research UK (reference: 21517), will assess the efficacy of rivaroxaban versus warfarin in adult patients with APS, with or without SLE, who have ischaemic stroke or other ischaemic brain manifestations.

Use of direct oral anticoagulants in antiphospholipid syndrome patients in clinical practice

The RAPS trial suggests that rivaroxaban offers the potential to be an effective and convenient alternative to warfarin in thrombotic APS patients with a single VTE event requiring standard intensity anticoagulation [79]. Further studies, in particular, acquisition of better long-term efficacy and safety data, are needed before it can be widely recommended. Of note, the major phase 3 clinical trials that established the use of DOACs

versus warfarin for the treatment and secondary prevention of VTE used warfarin at a target INR of 2.5 (range 2.0–3.0) as the comparator. The optimal intensity of DOACs in patients who experience recurrent VTE on standard-intensity VKA, in whom it is usual to switch to high intensity VKA (target INR 3.5; range 3.0-4.0), is not established, therefore DOAC use should be avoided in such patients. The 15th International Congress on Antiphospholipid Antibodies Task Force on Treatment Trends Recommendations stated: "Insufficient evidence to make recommendations at this time regarding DOAC use in APS. The RAPS trial suggests that rivaroxaban might be useful in selected APS patients with single venous thrombosis requiring standard intensity anticoagulation; however, this needs to be confirmed with additional studies using clinical outcome measures" [7].

The case series and cohort studies of DOAC use in APS patients, suggest that recurrent thrombotic events with standard intensity DOACs in APS patients mainly occur when DOACs are used for secondary prevention of APS-related arterial or microvascular thrombosis [67-72], where DOACs are unlicensed [8-11]. We believe these patient groups should not be treated with DOACs until further trial data are available.

Practical clinical issues

The potential use of DOACs in APS patients requires comparative considerations as for their use in non-APS patients, including in those with renal or hepatic impairment, the elderly, or those on potentially interacting drugs, in accordance with the DOAC SPCs [8-11]. Drug interactions and the potential for gastrointestinal bleeding are of particular relevance in APS where an antiplatelet agent is considered in addition to anticoagulation, or in patients with

SLE or other autoimmune diseases where other drugs may be considered, including nonsteroidal anti-inflammatory drugs and steroids. Proton pump inhibitor cover is advisable. The optimal dosing strategy for DOACs in patients at extremes of body weight, >120 kg or <50 kg, has raised concern. Several studies, including a review of Phase 1-3 studies of rivaroxaban [85], measurement of rivaroxaban levels at various weight ranges [86] and a pharmacokinetic study [87], suggest that standard dose rivaroxaban can be used safely in patients of all weights, however, further data are required. International Society of Thrombosis and Haemostasis Scientific and Standardisation Committee (ISTH SSC) guidance recommends that DOACs should not be used for standard indications in obese patients, >120 kg, however, if used, to check drug-specific peak and trough levels. If the drug is within the expected range, the DOAC can continue, and if not, it should be switched to a VKA [88]. The management of bleeding in patients on DOACs is addressed elsewhere [89]. Idarucizumab, an antibody fragment which binds to and neutralizes dabigatran, is licensed for rapid reversal of dabigatran [90] and andexanet-alfa has been shown to be effective for reversal of factor Xa inhibitors [91].

While the use of warfarin offers the advantage that its regular monitoring helps to determine the degree of patient adherence, its many complications drive the need to assess alternative therapies. The development of DOACs now provides such alternatives, however, good adherence to anticoagulation is essential, particularly as the risk of thrombosis is compounded by the short half-lives of DOACs compared to VKAs. A systematic review indicated that poor adherence to INR monitoring on VKA is a risk factor for recurrent thrombosis following a switch to a DOAC [92] and therefore such a switch is probably best avoided where there is pre-existing poor adherence. Measurement of DOAC concentration

may be helpful in certain circumstances, including extremes of body weight and to confirm absorption, however, routine anticoagulant monitoring of DOAC levels is generally not practicable or feasible.

Women's health issues

There is a preponderance of women with APS, female to male ratio approximately 5:1, many of whom have thrombotic as well as obstetric APS [2]. Vaginal bleeding complications are a common complication of oral anticoagulation [93] and appear to occur more often with direct oral factor Xa inhibitors than with VKAs [94]. Beyer-Westendorf et al reported vaginal bleeding events in 57 of 178 women of reproductive age in the Dresden DOAC registry, with recurrent bleeding in 23%. Patients with anatomic abnormalities had more intense bleeding and more needed surgical treatment [95]. A proactive approach, with gynaecological input, is required. A temporary interruption or dose reduction of DOAC on days when bleeding is heaviest, can be sufficient to prevent recurrent heavy menstrual bleeding (HMB). A levonorgestrel intrauterine system (LNG-IUS Mirena) is the most effective medical intervention for HMB [96] and avoids potential thrombogenic effects of oral hormonal preparations. Tranexamic acid is an effective alternative or adjunct [96]. A switch to split dose LMWH may need consideration pending definitive gynaecological treatment.

The potential for reproductive toxicity of DOACs in humans, via maternal or paternal exposure, is undefined. Consequently, the DOAC SPCs recommend avoiding them during pregnancy and breast-feeding [8-11]. Limited data suggest embroyopathy occurs in

approximately 2% of women who experience DOAC exposure in pregnancy [97]. ISTH SSC guidance recommendations can be summarized as follows: (1) women of childbearing potential should receive documented counselling prior to commencement of DOACs; (2) should pregnancy be desired, the DOAC should be switched to an alternative anticoagulant pre-conceptually, with the main options being VKAs (to be switched to LMWH as soon as possible when pregnant and before 6 weeks of gestation), or LMWH, with cognizance that the latter may result in prolonged subcutaneous injections until pregnancy is achieved; (3) in women who become pregnant while on a DOAC, DOAC should be discontinued immediately and LMWH commenced; (4) inadvertent exposure to a DOAC would not in itself be regarded as medical grounds for termination of pregnancy; (5) in women who become pregnant while on a DOAC and who decide to continue with pregnancy, there should be early obstetric review and fetal monitoring; and (6) breast-feeding women should not be treated with DOACs [98]. The ISTH SSC guidance on DOACs in women of childbearing potential also recommends that all cases of DOAC exposure during pregnancy should be reported to the international ISTH registry to ensure consistency of data collection: http://www.survey-gizmo.com/s3/2394649/International-registry-of-pregnancy-during-NOAC-use-Inclusion.

Conclusions

The RAPS trial, that had a surrogate laboratory primary outcome measure, suggests that rivaroxaban offers the potential to be an effective and convenient alternative to warfarin in thrombotic APS patients with a single VTE event requiring standard intensity anticoagulation. However, further studies, in particular, acquisition of better long-term efficacy and safety data, are needed before it can be widely recommended. APS DOAC RCTs

with clinical primary outcomes represent the gold standard, however, a primary endpoint of recurrent thrombosis would require a larger sample size than has been achieved to date. APS patients are clinically heterogeneous, with the risk of recurrent thrombosis and the intensity of anticoagulation influenced by their clinical phenotype and risk profile. Thus, DOAC trials involving homogeneous thrombotic APS populations, with aPL status well defined, will help to optimise the appropriate treatment in APS patient subgroups. Ongoing and emerging RCTs should provide further information to guide the use of DOACs in APS. Optimal identification of APS patients merits attention as this is a key step in working towards improved therapeutic strategies in these individuals.

Addendum

Hannah Cohen wrote the first draft of the manuscript and was involved in collecting literature, interpretation of data and revising the manuscript. Maria Efthymiou and David Isenberg were involved in collecting literature, interpretation of data and revising the manuscript.

Disclosure of Conflict of Interests

Hannah Cohen reports receiving institutional research support and honoraria (diverted to local Charity) for lectures and Advisory Board from Bayer. Maria Efthymiou and David Isenberg have no conflicts of interest to disclose.

Table 1: Case series and cohort studies in which thrombotic antiphospholipid syndrome patients treated with direct oral anticoagulants developed recurrent thrombosis

	Case Series [67]	Case Series [68]	Case Series [69]	Cohort[70]	Cohort[71]	Case Series [72]
Number of patients	8	12	23	26	56	19
Thrombosis history	VTE: 6 VTE+AT: 2	VTE: 10 VTE+AT: 2	VTE: 19 AT: 2 VT+AT: 1 CAPS: 1	VTE: 13 VTE+AT/MT: 4 AT: 9	VTE:19 AT:2 VTE+AT:1	VTE: 3 VTE+AT: 2 VTE+MT: 1
DOAC given: number of patients	R: 8	R: 12		R: 15 D: 11	R: 49 D: 4 A: 3	R: 17 D: 2
Systemic lupus erythematosus	0	4	5	9	33	NS
Outcome: DOAC given	5 VTE: R 2 VTE+AT: R 1 AT: R	2 VT: R	1 VTE: R	1 MT: NS	4 VTE: R* 1 SVT: R 1 AT: R	2 AT: D 1VTE+?AT: R 1 AT: R 1 MT: R
Time to thrombosis (months)	Median 3 (range 0.2-12)	5, 2	20	Median 10 (range 8-29)	Mean 46.7 (range 6-144)	Mean+/-SD: 23.3+/-22.3 (range 1-84)
Previous thrombosis history in patients who developed recurrent thrombosis on DOAC Triple aPL positivity in patients with recurrent thrombosis (where stated)	2/3 had previous AT; the third patient had previous VTE and was triple aPL positive	Both triple aPL positive	VTE+OM, triple aPL positive	Previous MT	2/6 had VTE+AT 4/6 were triple aPL positive	2/6 had previous AT 1/6 ad previous MT 2 others were triple aPL positive

Abbreviations: aPL, antiphospholipid antibodies; AT, arterial/transient ischemic attack; CAPS, catastrophic antiphospholipid syndrome; D, dabigatran; DOAC, direct oral anticoagulant; MT, microvascular thrombosis; NS, not stated; OM, obstetric morbidity; r, range; R, rivaroxaban 20 mg once daily; SVT, superficial vein thrombosis; triple aPL positive, presence of lupus anticoagulant + IgG/IgM anticardiolipin + IgG/IgM anti-β2 glycoprotein 1 antibodies; VT, venous thromboembolism; *nonadherence

Table 2: Characteristics and status of completed and recruiting randomised controlled trials of direct oral anticoagulants in thrombotic antiphospholipid syndrome

	RAPS [79]	TRAPS [7,82]	ASTRO-APS [7,83]
Chief Investigator	H Cohen	V Pengo	S Woller
Study design	Phase 2/3 RCT	Phase 3 RCT	Phase 2/3 RCT
Number of patients	116	536	200
APS subgroups	Previous VTE, target INR of 2.5; no thrombosis >3 m; patients with arterial thrombosis excluded	Triple positive thrombotic APS; arterial, venous, and/or biopsy-proven microthrombosis	Thrombotic APS VTE target INR 2.5; no thrombosis >6 m; definite, likely or historic APS
Intervention	Rivaroxaban 20 mg od vs. warfarin target INR of 2.5	Rivaroxaban 20 mg od vs. warfarin target INR of 2.5	Apixaban 2.5 mg or 5 mg bd vs. warfarin target INR of 2.5
Primary outcome(s)	Thrombin generation - endogenous thrombin potential (ETP)	Thrombosis - arterial or venous Major bleeding Death	Thrombosis - arterial and/or venous Bleeding
Duration of recruitment	Jun 13 – Nov 14	Dec 14 – Dec 18	Feb 15 - ongoing
Status	Completed and results published	Ongoing	Ongoing: protocol modified after potential safety signal (see text)

Abbreviations: ASTRO-APS, Apixaban for the Secondary Prevention of Thromboembolism Among Patients with AntiPhospholipid Syndrome (ClinicalTrials.gov:NCT02295475) ; bd, twice daily; m, months; od, once daily; RAPS, Rivaroxaban in Antiphospholipid Syndrome (ISRCTN68222801); RCT, randomized controlled trial; TRAPS, Rivaroxaban in Thrombotic Antiphospholipid Syndrome (ClinicalTrials.gov:NCT02157272)

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Use of direct oral anticoagulants in antiphospholipid syndrome

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Abstract

The direct oral anticoagulants (DOACs) are therapeutic alternatives to warfarin and other vitamin K antagonists (VKAs), and the standard of care for many indications. VKAs are conventional therapy for ~~, the traditional mainstay of~~ the treatment and secondary thromboprophylaxis of thrombotic antiphospholipid syndrome (APS), are often problematic due to the variable sensitivity of thromboplastins to lupus anticoagulant. Thus,~~, so that~~ the International Normalised Ratio may not accurately reflect anticoagulation intensity, or be~~not be~~ clinically effective. Definition of the current role of DOACs in APS is ~~necessarily~~ based on limited clinical trial data and ~~as well as~~ information from other sources, including manufacturers' data, case series or cohort studies and expert consensus. The RAPS randomis~~z~~ed controlled trial (RCT), that had a laboratory surrogate primary outcome measure, suggests that rivaroxaban offers the potential to be an effective and convenient alternative to warfarin in thrombotic APS patients with a single VTE event requiring standard intensity anticoagulation. However, further studies, in particular, acquisition of better long-term efficacy and safety data, are needed before it can be widely recommended. APS patients are clinically heterogeneous, with the risk of recurrent thrombosis and the intensity of anticoagulation influenced by their clinical phenotype and risk profile. DOAC trials involving homogeneous thrombotic APS populations, with aPL status well defined, will help to optimise the appropriate treatment in APS patient subgroups. ~~Available data support the concept that rivaroxaban offers an effective, safe and convenient alternative to VKA in APS patients with a history of venous thromboembolism (VTE) requiring standard intensity anticoagulation, i.e. with a single VTE episode or recurrent VTE while unanticoagulated or on subtherapeutic anticoagulation.~~ Ongoing and emerging DOAC RCTs should provide further information to guide the use of DOACs in APS. Optimal

identification of APS patients is a key step in working towards the provision of improved therapeutic strategies in these individuals

~~future clinical studies, particularly those in clinically homogenous APS patient subgroups, are essential to define the role of DOACS in thrombotic APS patients, including those who need higher intensity anticoagulation after recurrent thrombotic events while they were taking standard-intensity anticoagulation for VTE, and those with stroke or other arterial thrombosis. The need for these studies is highlighted by recent observations suggesting that recurrent thrombosis occurs particularly when DOACs are used for secondary prevention of APS related arterial or microvascular thrombosis or in APS patients with triple aPL positivity.~~

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Keywords: direct oral anticoagulants, antiphospholipid syndrome, venous thromboembolism, thrombin generation, ischaemic stroke

Introduction

Antiphospholipid syndrome (APS) is manifested by thrombosis (arterial, venous or microvascular) and/or obstetric morbidity in association with persistent antiphospholipid antibodies (aPL), i.e. lupus anticoagulant (LA), anticardiolipin (aCL) and/or anti-beta 2 glycoprotein 1 antibodies (aβ2GP1) [1]. Thrombotic APS is clinically heterogenous, with thrombotic episodes ranging from mild to potentially life-threatening, refractory thrombosis despite adequate anticoagulation; and the rare catastrophic APS. Thrombotic events may be venous, arterial, or microvascular. APS mainly affects relatively young individuals. The

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median age at study entry in the Euro-Phospholipid Project of 1,000 patients, more than 70% of whom had stroke or VTE was 40 (range 0-82) years [2]. Among systemic lupus erythematosus (SLE) patients, 30-40% have aPL [3], with estimates of the frequency with which APS occurs in patients with SLE ranging from 7% to 22%, of whom approximately half have thrombotic APS [4,5]. SLE patients with APS~~Thirty About 30-40% of patients with systemic lupus erythematosus (SLE) patients have aPL [3], approximately , and approximately 15% half of whom have thrombotic APS . The~~[14]. These patients are often difficult to manage with complex clinical problems [~~3,4~~14,~~15~~]. Warfarin or other vitamin K antagonists (VKAs) are conventional therapy for ~~The mainstay of~~ the treatment and secondary thromboprophylaxis of thrombotic APS ~~is warfarin or other vitamin K antagonists (VKAs)~~ [5]. However, treatment with VKAs is often problematic as they have a slow onset of action of several days, a narrow therapeutic window, numerous drug and dietary interactions; and the potential for variation of action with alcohol, intercurrent illness, exercise, and smoking. Patients require regular monitoring of the international normalized ratio (INR). The direct oral anticoagulants (DOACs), dabigatran~~etexilate (Pradaxa)~~, a direct thrombin inhibitor, and apixaban ~~(Eliquis)~~, edoxaban ~~(Lixiana)~~ and rivaroxaban ~~(Xarelto)~~, direct factor Xa inhibitors, represent a major milestone in anticoagulation. They are therapeutic alternatives to ~~warfarin and other vitamin K antagonists (~~VKAs~~),~~ and the standard of care for many indications, detailed in the summary of product characteristics (SPC) [6-9]. ~~; these include primary thromboprophylaxis for major lower limb orthopaedic surgery, the treatment and secondary prevention of VTE, the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF), and acute coronary syndromes [1-4]. The~~ DOACs, in contrast to VKAs, are prescribed at a fixed dose with a more predictable anticoagulant effect and do not routinely require regular anticoagulant

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monitoring. They have a rapid onset of action which generally obviates the need for bridging anticoagulation with low-molecular-weight heparin (LMWH) ~~at the initiation of anticoagulation or post-procedures~~ [7,9], are not affected by dietary changes and alcohol intake and have fewer drug interactions than VKAs that affect anticoagulant intensity. These features should ~~, which should~~ improve patient quality of life.

The SPCs for the licensed DOACs [6-9] do not contain information regarding the use of DOACs in patients with APS ~~antiphospholipid antibodies (aPL), i.e. lupus anticoagulant (LA), anticardiolipin (aCL) and/or anti-beta 2 glycoprotein 1 antibodies (aβ2GP1) or antiphospholipid syndrome (APS), defined as thrombosis (arterial, venous or microvascular) and/or obstetric morbidity in association with persistent aPL [5]. Major phase 3 randomised controlled trials (RCTs) have demonstrated that DOACs are effective and safe compared with warfarin for the treatment and secondary prevention of venous thromboembolism (VTE) in VTE patients who require standard intensity anticoagulation, i.e. target International Normalised Ratio (INR) 2.5 [6-13]. The use of DOACs in APS patients was not specifically investigated in these studies. About 30-40% of patients with systemic lupus erythematosus (SLE) have aPL, approximately half of whom have APS [14]. These patients are often difficult to manage with complex clinical problems [14,15]. APS is classified as a rare disease [16]. Systematic reviews suggest that aPL are present in 10% of patients with deep vein thrombosis [17], although this is not reflected in thrombotic APS patient numbers in clinical practice, suggesting likely underdiagnosis.~~ Definition of the current role of DOACs in APS is ~~necessarily~~ based on limited clinical ~~trial~~ data and information from other sources, including manufacturers' data, case series or cohort studies and expert consensus.

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Antiphospholipid syndrome patients in phase 3 trials of direct oral anticoagulants

Patients with aPL or APS were not specifically included or excluded from the phase 3 clinical trials that compared the use of individual DOACs with warfarin for the treatment of acute VTE and prevention of recurrent VTE, as well as the atrial fibrillation trials [6-13,18-21]. Details on these trials, which include information from the manufacturers on patients with aPL, are summarised below.

Dabigatran

The efficacy and safety of dabigatran compared with warfarin for the treatment of VTE and prevention of recurrent VTE were investigated in a post hoc analysis of pooled data on patients with aPL (LA and/or aCL) from the RE-COVER, RE-COVER II and RE-MEDY studies [22]. aPL testing was not mandatory, but when performed, the data were captured. Of the 6,822 patients in the pooled analysis, 151 (2.2%) had LA and/or aCL at baseline. Patients with aPL (n=151; 71 treated with dabigatran 150mg twice daily vs 80 treated with warfarin target INR 2.5) were slightly younger than those without aPL and those not tested. In aPL positive patients, there was no significant difference in VTE/VTE-related deaths between the two treatment arms: dabigatran (3 [4.2%]) vs warfarin (4 [5%]); hazard ratio (95% CI): 0.43 (0.08-2.38). Rates of bleeding events were significantly lower with dabigatran than with warfarin for any bleeding event, i.e. major, clinically relevant or minor: dabigatran (14 [20%]) vs warfarin (31 [40.3%]), hazard ratio (95% CI): 0.53 (0.26-0.95). Major or clinically relevant non-major bleeding events showed no significant difference between the two

treatment groups 6 [8.6%] and 14 [18.2%]) respectively; hazard ratio (95% CI): 0.53 (0.20-1.41) [18].

Apixaban

In AMPLIFY of apixaban 5mg twice daily versus enoxaparin followed by warfarin target INR 2.5, relevant baseline risk factors for recurrent VTE included known thrombophilia: 74 (2.85%) patients in the apixaban arm and 59 (2.2%) patients in the enoxaparin followed by warfarin arm. Further information about thrombophilia or other hypercoagulable conditions in these patients was unknown. No separate analysis on the safety and efficacy in this specific patient population was performed [9]. In AMPLIFY EXT, of apixaban 2.5mg twice daily versus apixaban 5mg twice daily versus placebo, in patients where there was equipoise after a period of therapeutic anticoagulation, relevant baseline risk factors for recurrent VTE included known prothrombotic genotype: 32 (3.8%) patients in the 2.5 mg apixaban arm, 26 (3.2%) patients in the 5 mg apixaban arm and 36 (4.3%) patients in the placebo arm [10].

Edoxaban

The phase 3 ENGAGE AF TIMI 48 AF study included 1 patient with aPL, one with APS and approximately five with SLE or other autoimmune disease [21].

Rivaroxaban

In the EINSTEIN Phase 3 clinical trial programme, adult patients with known thrombophilic conditions (antithrombin, protein C or S deficiency, factor V or prothrombin gene mutations, or aPL) were not excluded [12,13]. In the EINSTEIN DVT and PE pooled analysis patients had

a mean age of 57.0 ± 17.0 years. A total of 5.9% of patients in the rivaroxaban group and 5.7% in the enoxaparin/VKA group, respectively, had a known thrombophilic disorder (6.2% vs. 6.8% in EINSTEIN DVT [12] and 5.7% vs. 5.0% in EINSTEIN PE [13], respectively). The relative primary efficacy and principal safety outcomes across the pre-specified subgroups (including the subgroup of patients with a known thrombophilic disorder) in the EINSTEIN DVT and the EINSTEIN PE studies were consistent with the observed overall effects, but the proportion of these patients in the EINSTEIN trials was too low to provide any specific recommendations about the use of rivaroxaban in these patients.

Warfarin and other vitamin K antagonists for thrombotic antiphospholipid syndrome

These agents can be particularly problematic in APS patients because of variable sensitivity of thromboplastins to LA, which is often present. A multicentre study indicated that LA interference with the prothrombin time-INR measured with the majority of commercial thromboplastins is insufficient to cause concern if insensitive thromboplastins, properly calibrated to assign them an instrument specific International Sensitivity Index (ISI), are used. The investigators suggested that new thromboplastins, especially those made of relipidated recombinant human tissue factor, should be checked ensuring that they are insensitive to the effects of aPL before they are used to monitor oral anticoagulant treatment in APS patients [23]. While these procedures are generally routine in specialist centres, they may not available in other institutions. Thus, the INR might not accurately reflect anticoagulation intensity and, as a result, could be associated with potential thrombotic or bleeding complications. Amidolytic factor X assays, as a LA-independent measure of anticoagulation intensity, may be useful in such cases, although this is generally

~~not practicable [24,25]. The variable sensitivity of thromboplastins to LA may also be associated with instability of the INR, necessitating frequent anticoagulant monitoring with the attendant inconvenience to the patient, adverse impact on quality of life, and increased costs. Warfarin also interacts with many other drugs altering the INR and complicating the treatment of APS patients with other disorders, including SLE.~~

Approximately 10% of APS patients overall [2] and 30% of those who are triple aPL positive, i.e. have LA, aCL and aβ2GP1 [10], have recurrent thrombotic events, arterial or venous, on VKAs (at standard intensity, target INR 2.5) at 5 years follow up. ~~;~~ The high thrombotic risk of triple aPL positive patients is also observed in asymptomatic individuals, where the risk of thrombosis is significantly higher than in those with single aPL positivity. The annual rate of first cardiovascular event is 5.3% in triple aPL positive (cumulative incidence 37% at 10 years) vs 1.36% in single aPL positive individuals vs ~0.4% in the normal population [11]Ref]. A systematic review of 16 studies indicated that APS patients on anticoagulation experience ~~and~~ major bleeding rates of 0.57% to 10% per year [12]. ~~There are no substantive data on the influence of aPL status on VTE recurrence, and therefore the need for indefinite anticoagulation, in patients with VTE, unprovoked or provoked. Current recommendations on the duration of anticoagulation in individuals with VTE who have APS are extrapolated from studies in general VTE patient populations [29-31]. A pragmatic approach is to test for aPL in patients who have had a first unprovoked VTE, as aPL positivity strengthens the decision for indefinite anticoagulation. It also identifies women who require higher than standard prophylactic dose anticoagulation during pregnancy [32-34], with the addition of low dose aspirin, and monitoring for placental insufficiency with fetal growth restriction [35], to guide optimal timing of delivery and reduce the risk of perinatal morbidity and~~

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~~mortality [36]. aPL testing should also be considered in patients with provoked VTE, particularly if the provoking factor for VTE appears disproportionate to the severity of the episode.~~

Venous thromboembolism

~~Warfarin and other VKAs have been the mainstay for the treatment and secondary prevention of VTE in patients with thrombotic APS for over 30 years.~~ Retrospective studies have shown a high incidence of thrombosis recurrence in patients with aPL [13-15~~37-39~~]. In these studies, 54% (80/147), 56% (39/70) and 38% (23/61) of patients had VTE. In the prospective Duration of Anticoagulation (DURAC) study on 412 patients with VTE, a single aCL-positive test doubled the risk of recurrence in the first 6 months after cessation of warfarin~~anticoagulation~~: 29% (20/68) in patients with aCL and 14% (47/334) in patients without aCL (p=0.0013), for a risk ratio of 2.1 (95% confidence interval [CI]: 1.3–3.3) [16~~40~~]. Current recommendations on the duration of anticoagulation in individuals with VTE who have APS are extrapolated from studies in the general VTE population [17-19]. Although indefinite ~~long term~~ anticoagulation is suggested for APS patients with unprovoked VTE and temporary anticoagulation ~~a limited duration course~~ for patients with a provoked VTE [17, 20], there are no specific substantive data on the optimal duration of anticoagulation for APS patients with VTE~~, unprovoked or provoked~~. A pragmatic approach is to test for aPL in patients who have had a first unprovoked VTE, as aPL positivity strengthens the decision for indefinite anticoagulation. It also identifies women who require higher than standard prophylactic dose anticoagulation with LMWH during pregnancy [21-23], and also require low dose aspirin and monitoring for placental insufficiency [24], to guide optimal timing of delivery, reducing the risk of perinatal morbidity and mortality ~~[25]~~. aPL testing should also

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be considered in patients with provoked VTE, particularly if the provoking factor for VTE appears disproportionately mild.

Stroke and other arterial thrombosis

APS patients with ischaemic brain manifestations also require identification in contrast to non-APS stroke patients where antiplatelet treatment is the standard of care. Anticoagulation is a rational treatment for patients with APS and stroke, TIA or other ischaemic brain manifestations since it can lead to resolution of in situ arterial thrombosis or prevent cardioembolic events. UK national clinical guidelines for stroke recommend aPL testing in individuals under 50 years [26][REF]. There are few data to guide the optimal anticoagulation intensity in APS patients with stroke or other arterial thrombosis. Ruiz-Irastorza et al [122] reviewed 16 studies (4 randomised controlled trials (RCTs) and 12 prospective or retrospective cohort studies) on secondary thromboprophylaxis in patients with aPL ~~that included prospective randomised controlled trials (RCTs), prospective and retrospective cohort studies~~. Of 180 thrombotic events reported, 104 (57%) occurred when patients were not taking any anticoagulant or antiplatelet agent. ~~An additional 27 events (15%), with the majority arterial, occurred among patients treated only with aspirin. The remaining 49 recurrences (27%) were seen in patients treated with warfarin, with the INR at the time of the event <3.0 in 42/49 cases.~~ Only 7 of 49 recurrences (27%) on warfarin ~~nly seven of 180 recurrent thrombotic events~~ occurred in patients when the INR was >3.0; of these, in the five cases where specified, 4 ~~recurrences~~ were arterial and one venous.

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Three prospective studies have addressed the key issue of the optimal antithrombotic treatment for stroke patients with aPL, however, these have major limitations. Two RCTs ~~randomised, controlled trials~~ on standard vs high intensity warfarin in patients with thrombotic APS, Crowther et al [27~~41~~] and Finazzi et al [28~~42~~] concluded that the optimal target INR for both venous and/or arterial thromboembolism, including stroke, in APS is 2.5 (range 2.0–3.0) (standard-intensity) rather than 3.5 (range 3.0-4.0) (high-intensity). However, patients with recurrent thrombosis history while on therapeutic anticoagulation or with arterial thrombosis were poorly represented in both studies, with the latter comprising only 24% and 32% (62 ~~of a total of 223 114 and 109~~ patients across both studies~~, respectively~~. Notably, 6/8 recurrent thrombotic events ~~(six on high-intensity and 2 on standard-intensity warfarin)~~ in Crowther et al's ~~'s~~ study [27~~41~~] occurred while the INR was <3.0 (5/6) or while off warfarin (1/6)~~; only two of the recurrent thrombotic events, both in patients randomised to high-intensity warfarin, occurred while the INR was 3.1–4.0~~. The study by Finazzi et al ~~reported recurrent thrombosis was observed in 6/54 (11.1%) assigned to high-intensity warfarin and 3/55 (5.5%) to standard-intensity. This study~~ did not ~~report detail~~on the INR at the time of thrombosis [28~~42~~].

The Antiphospholipid Antibodies and Stroke Study (APASS) [29~~43~~], a prospective cohort study within the Warfarin versus Aspirin Recurrent Stroke Study (WARSS), reported no benefit of warfarin anticoagulation (target INR 1.4–2.8) over aspirin (325 mg/day) in stroke prevention. However, laboratory criteria for aPL were not compliant with the international consensus criteria for APS diagnosis [29~~43~~].

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The lack of robust data on the optimal anticoagulant intensity in ischaemic stroke patients with APS is reflected in national and international guidelines. British Society for Haematology [1729] and American College of Chest Physicians guidelines [3044] on APS associated ischaemic stroke include warfarin (or other VKA) at a target INR of 2.5 (range 2.0-3.0). The Task Force at the 13th International Congress on aPL recommended that patients with definite APS and arterial thrombosis should be treated with warfarin at an INR >3.0 or combined antiplatelet-anticoagulant (target INR 2.5) therapy [2045]. This suggestion was a non-graded recommendation due to lack of consensus within the Task Force. Many physicians treating APS patients use high-intensity warfarin (target INR 3.5; range 3.0-4.0) for APS patients with ischaemic stroke ~~, cerebral ischaemic lesions~~ or other arterial thrombosis ~~in other sites~~.

Laboratory issues in antiphospholipid syndrome patients on vitamin K antagonists or direct oral anticoagulants

Laboratory monitoring of anticoagulation on warfarin

VKAs can be problematic in APS patients because of variable sensitivity of thromboplastins to LA [31,32]. A multicentre study indicated that LA interference with the prothrombin time-INR measured with the majority of commercial thromboplastins is insufficient to cause concern if insensitive thromboplastins, properly calibrated to assign them an instrument-specific International Sensitivity Index (ISI), are used. The investigators suggested that new thromboplastins, especially those made of relipidated recombinant human tissue factor, should be checked ensuring that they are insensitive to the effects of aPL before being used

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to monitor oral anticoagulant treatment in APS patients [32]. These procedures are generally routine in specialist centres, but may not available elsewhere. Thus, the INR might not accurately reflect anticoagulation intensity and, as a result, could be associated with potential thrombotic or bleeding complications. Amidolytic factor X assays, as a LA-independent measure of anticoagulation intensity, may be useful in such cases, although this is rarely practicable [31,-33]. The variable sensitivity of thromboplastins to LA may also be associated with instability of the INR, necessitating frequent anticoagulant monitoring causing inconvenience to the patient, adversely impacting on quality of life and increasing costs. Warfarin also interacts with many other drugs altering the INR and complicating the treatment of APS patients with other disorders, including SLE.

Testing for antiphospholipid antibodies

LA testing in patients on VKAs are addressed in national and international guidelines [197, 354]. Tests for LA detection should include screening, mixing and confirmation ones assessed with at least two different methodologies [17,34][Refs]. ~~LA testing in patients on VKAs are addressed in national and international guidelines [17,34].~~ Many studies have reported DOAC interference with assays for LA leading to false positive and unreliable results [35;36-38~~52; 74-76~~]. Dabigatran and apixaban interfere with both the activated partial thromboplastin time (APTT) and the dilute Russell Viper Venom time (dRVVT) assays, with false positive results also been reported with a hexagonal phase lipid neutralization assay using the Staclot LA assay [39-42~~77-81~~]. False positive tests for PTT LA, Silica Clotting Time screens and ~~D~~dRVVT have also been reported for rivaroxaban, particularly at peak plasma levels [35; 40;43-45~~52; 78; 82; 83, 84~~]. However, the Taipan Venom Time/Ecarin

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Clotting Time (TVT/ECT) ratio and Textarin time assays perform better and are unaffected by rivaroxaban, irrespective of concentration. In thrombotic APS patients treated with rivaroxaban, the TVT/ECT appears reliable even at peak therapeutic plasma levels, while the ~~D~~dRVVT may be acceptable at trough rivaroxaban plasma levels (>18 hours after the last dose of rivaroxaban), although a rivaroxaban anti-Xa should be performed in parallel to ensure that the result is not a false positive- [36,45,42~~52,84,85~~]. No interference has been reported by any DOACs on solid phase assays or enzyme–linked immunosorbent assays (ELISAs) for anti-β2GPI or aCL [41,43,45~~79,82,84~~] .

Thrombin generation and direct oral anticoagulants

Thrombin generation (TG), assessed by calibrated automated thrombography, represents a global dynamic assay that measures the overall ability of plasma to form thrombin after initiation of coagulation using a thrombin-sensitive fluorogenic substrate. ~~TG investigates all stages of TG and subsequent inactivation~~T. ~~T~~he TG curve, quantified in terms of the lag time, time to peak TG, peak TG, and endogenous thrombin potential (ETP), the area under the TG curve [~~4~~86], is informative in regard to APS status and LA detection [47,48~~87,88~~]. TG can be used to assess the effects of anticoagulants in platelet poor (PPP) and rich plasma (PRP) and in both APS and non-APS patients [33,49,51,51~~25,50,89,90~~]. Rivaroxaban can downregulate and completely suppress TG in whole blood, PRP [52,53~~48,91~~] and PPP [54,55~~97,93~~], while dabigatran can significantly inhibit TF-induced TG in a concentration-dependent manner, but with weaker inhibitory effects than rivaroxaban [56~~94~~]. Apixaban affects all TG parameters with prolonged lag time, ETP and peak TG (the latter showing greater reduction than the ETP)- [57]~~[95]~~. Antiphospholipid antibodies might interfere with the anticoagulant

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action of DOACs, however no effect with rivaroxaban was observed in *in-vitro* studies which showed that aPL did not affect itsthe anticoagulant action ~~of rivaroxaban~~ at peak or trough levels, based on TG testing and anti-Xa levels [3552]. This was predictable as rivaroxaban is a small molecule with high specificity and affinity for its target [52,58].~~[47,48].~~

~~There is a preponderance of women with APS, female:male ratio approximately 5:1, many of whom have thrombotic as well as obstetric APS [26]. The potential for reproductive toxicity of DOACs in humans, via maternal or paternal exposure, is undefined. Consequently, the DOAC SPCs recommend against their use in pregnancy and during breast-feeding [1-4]. Limited data suggest embryopathy occurs in approximately 2% of women who experience DOAC exposure in pregnancy [98]. APS mainly affects relatively young individuals, with the median age at study entry in the Euro-Phospholipid Project of 1,000 patients, more than 70% of whom had stroke or VTE, 40 (range 0-82) years [26]. International Society of Thrombosis and Haemostasis (ISTH) guidance on the management of DOACs in women of childbearing potential should be followed by women in their reproductive years who are receiving DOACs for thrombotic APS [99].~~

Observational data on the use of direct oral anticoagulants in antiphospholipid syndrome

Patients with aPL or APS were neither specifically included nor excluded from the phase 3 RCTs that demonstrated that DOACs are effective and safe compared with warfarin for the treatment and secondary prevention of VTE after a first VTE event or prevention of stroke or systemic embolisation in patients with atrial fibrillation [6-9]~~[1-4]~~. APS is classified as a rare disease in the USA [5916]. Systematic reviews suggest that aPL are present in 10% of

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patients with deep vein thrombosis and 14% of patients with stroke [6017], although this is not reflected in thrombotic APS patient numbers in clinical practice, suggesting likely underdiagnosis.

~~Major phase 3 randomised controlled trials (RCTs) have demonstrated that DOACs are effective and safe compared with warfarin for the treatment and secondary prevention of venous thromboembolism (VTE) in VTE patients who require standard intensity anticoagulation, i.e. target International Normalised Ratio (INR) 2.5 [6-13]. The use of DOACs in APS patients was not specifically investigated in these studies~~***Data on antiphospholipid syndrome derived from phase 3 randomised controlled trials of direct oral anticoagulants in the general population***

Dabigatran

A post hoc analysis of pooled data on patients with aPL (LA and/or aCL) from the RE-COVER, RE-COVER II and RE-MEDY studies was undertaken [6122]. aPL testing was not mandatory, but when performed, the data were captured. Of 6,822 patients in the pooled analysis, 151 (2.2%) had LA and/or aCL at baseline. In aPL positive patients, there was no significant difference in VTE/VTE-related deaths or major or clinically relevant non-major bleeding events between the two treatment arms. However, this study was heavily underpowered.

Apixaban

In the AMPLIFY RCT of apixaban 5mg twice daily versus enoxaparin followed by warfarin

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target INR 2.5, relevant baseline risk factors for recurrent VTE included known thrombophilia: 74 (2.85%) patients in the apixaban arm and 59 (2.2%) patients in the enoxaparin followed by warfarin arm. No separate analysis on the safety and efficacy in this specific patient population was performed [62]. ~~[9], [10], Just 92~~

Edoxaban

The phase 3 ENGAGE-AF TIMI-48 AF study included one~~1~~ patient with aPL, one with APS and approximately five with SLE or other autoimmune disease [63~~21~~].

Rivaroxaban

In the EINSTEIN Phase 3 clinical trial programme, adult patients with known thrombophilic conditions (antithrombin, protein C or S deficiency, factor V or prothrombin gene mutations, or aPL) were not excluded [64,65~~12,13~~]. In the EINSTEIN DVT and PE pooled analysis patients had a mean age of 57.0 ± 17.0 years. A total of 5.9% of patients in the rivaroxaban group and 5.7% in the enoxaparin/VKA group, respectively, had a known thrombophilic disorder (6.2% vs 6.8% in EINSTEIN DVT [64~~12~~] and 5.7% vs. 5.0% in EINSTEIN PE [65~~13~~], respectively). The relative primary efficacy and principal safety outcomes across the pre-specified subgroups (including the subgroup of patients with a known thrombophilic disorder) in the EINSTEIN DVT and the EINSTEIN PE studies were consistent with the observed overall effects.

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Case series and cohort studies of direct oral anticoagulants in antiphospholipid syndrome

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Case reports, series and cohort studies have reported on DOAC use in APS patients, with approximately 200 cases reported. Several authors have reported case series and cohort studies describing thromboembolism recurrence in APS patients switched from warfarin to a DOAC [66-71] (Table 1). Other case series report that DOAC use in thrombotic APS has been unassociated with recurrent thrombosis [72,73]; Sciascia et al, reported a case series of 36 patients with APS and VTE requiring standard intensity warfarin, who were switched to rivaroxaban 20mg once daily, and followed for a median of 10 (range 6-24) months. None of these patients had recurrent thrombosis. These data, with their inherent limitations, including selection bias, lack of a comparator arm and in some studies, retrospective design, suggest that recurrent thrombotic events with DOACs in APS patients mainly occur when DOACs are used for secondary prevention of APS-related arterial or microvascular thrombosis, where DOACs are unlicensed and where many APS treaters use high-intensity anticoagulation [208], or in triple aPL positive APS patients (Table 1).

RAPS (~~:~~ Rivaroxaban for Antiphospholipid Syndrome Pilot Feasibility Study) prospective cohort study

The RAPS pilot feasibility study (ClinicalTrials.gov:NCT02116036) wa~~s~~ is a prospective cohort study for patients with confirmed APS and prior VTE, with or without prior arterial thrombosis, allocating them to receive rivaroxaban 20 mg daily. Patients we~~a~~re followed for thrombosis. ~~The study is designed as a feasibility study with clinical outcomes as secondary endpoints (thrombosis; minor, major, and fatal bleeding).~~ Recruitment was closed on 30th

September 2016 with a plan to follow all patients for one year. Seventy-nine patients were identified, with the ~~expected~~ recruitment target~~of~~ 150. Available information indicates that few complications, and no recurrent thromboses, ~~have~~ occurred. One patient suffered unexplained hepatitis [74~~5~~]. This study ~~is underpowered but will~~ provides additional data on the efficacy and safety of DOACs in ~~patients with~~ APS patients.

Randomised controlled trials~~Clinical studies~~ of direct oral anticoagulants ~~direct oral anticoagulants~~ in ~~thrombotic~~ antiphospholipid syndrome

A challenge in DOAC APS studies is ensuring sufficient statistical power. Trials with clinical outcomes are ideal, however, where APS trials with clinical outcomes have succeeded, numbers have been relatively small, 334 patients in 5 RCTs on treatment for APS-associated recurrent miscarriage in the meta-analysis by Mak et al [75~~57-62~~], while trials with larger recruitment targets have proved challenging [76,77~~63,64~~]. The appropriateness or otherwise, of the use of surrogate markers in clinical trials was considered in an editorial review by Svennson et al who, after supporting their use in fatal diseases like amyotrophic lateral sclerosis, went onto say they felt this approach was justified: “in the case of very rare diseases, (where) validation of hard end points may take an unreasonable time to complete” [78~~65~~].

The characteristics and status of completed and recruiting RCTs of DOACs in thrombotic APS are summarised in Table 2.

RAPS: Rivaroxaban in Antiphospholipid Syndrome trial~~Trial~~

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The RAPS trial is the only completed RCT of DOAC use in APS patients. This phase 2/3 non-inferiority RCT compared rivaroxaban to warfarin (target INR of 2.5; range 2.0-3.0) to treat patients with previous VTE [7946] on . Eligible patients had taken standard-intensity warfarin for at least three months after the last VTE. Warfarin-treated APS patients with previous VTE, with or without SLE, were randomized 1:1 to warfarin or rivaroxaban, 20 mg once daily, stratified by center and SLE/non-SLE.

The primary outcome measure was percentage change in endogenous thrombin potential (ETP , the area under the thrombin generation [TG] curve) in the TG assay from randomiszation to day 42, with treatment continued for 180 days and follow-up for 210 days. 116 patients were randomised, of whom 19% had SLE. When anticoagulation intensity was assessed by ETP alone, rivaroxaban was inferior to warfarin. However, peak thrombin generation was lower with rivaroxaban (Figure 1). Warfarin affects all phases of thrombin generation equally, whereas rivaroxaban directly inhibits factor Xa through specific binding to its active site [52,5847,48] and mainly affects the initiation and propagation of thrombin generation leading to a delay in the formation of the prothrombinase complex [8049]. Consequently, the TG curve becomes protracted, lengthening the lag time and time to peak TG [49,5149,50], and leading to greater ETP than would be expected for the degree of anticoagulation [49]. The RAPS concludedsion was that, taking into account the altered reaction kinetics with rivaroxaban, the overall thrombogram indicated no difference in thrombotic risk. This conclusion was supported by in vivo coagulation activation marker concentrations (thrombin–antithrombin complexes, prothrombin fragment 1.2 and D-dimer) being slightly raised in few patients in both treatment groups. Furthermore, no new thrombotic events were seen during 6 months of treatment. No major bleeding episodes

were noted. C ~~and c~~linically relevant and minor bleeding rates were similar in the two groups. Quality of life was significantly improved in patients on rivaroxaban.

~~A limitation of~~ RAPS ~~is that it~~ was not designed to confirm clinical efficacy and long-term safety. Rather, the trial was designed pragmatically with a laboratory surrogate outcome measure to assess the mechanism of action of the interventions in the two patient groups. Recurrent thrombosis in the APS population selected for RAPS is rare and ~~thus,~~ a primary endpoint of recurrent thrombosis would necessitate ~~require a sample of~~ several thousand patients and a follow up period of several years, which is impractical ~~for these patients~~. The trial had an intended selection bias, ensuring a clinically homogenous study population with definite APS [15~~]~~. Patients who had VTE and developed recurrent VTE while taking standard-intensity anticoagulation (i.e. needing higher-intensity anticoagulation) and those with arterial events were excluded. The proportion of triple positive aPL patients included, 28%, was representative of VTE patients requiring standard-intensity anticoagulation in the investigators' APS population and consistent with the proportion in APS patients suggested in a large multicentre study [2~~6~~]. The conclusions from the RAPS trial we~~a~~re generally supported by the independent expert comment [8~~5~~1]. ~~RAPS and ongoing studies of DOACs in APS patients are summarised in Table 1.~~

Exploratory post-hoc analysis in the RAPS trial patients showed no significant interactions between the effects of rivaroxaban and LA positivity on TG. ~~Antiphospholipid antibodies might interfere with the anticoagulant action of DOACs, however no effect with rivaroxaban~~

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~~was observed in in-vitro studies which showed that aPL did not affect the anticoagulant action of rivaroxaban at peak or trough levels, based on TG testing and anti-Xa levels [52]. This was predictable as rivaroxaban is a small molecule with high specificity and affinity for its target [47,48].~~ Coagulation proteases such as factor Xa can activate complement proteins. In a RAPS translational study, APS patients had significantly higher complement activation markers at baseline and day 42 compared to normal controls. Patients randomised to rivaroxaban ~~, a direct factor Xa inhibitor,~~ showe~~d~~ing a significant reduction in levels of C3a, C5a, terminal complement complex [SC5b-9], with levels of Bb fragment, a marker of alternative complement pathway activation, unchanged. These results suggest that r~~R~~ivaroxaban may provide additional benefit to its anticoagulant effect in APS ~~this~~ patient~~s group~~ by limiting complement activation [82~~53~~].

TRAPS: Rivaroxaban in Thrombotic Antiphospholipid Syndrome trial~~Trial~~

The objective of the TRAPS multicentre phase 3 RCT is to demonstrate non-inferiority of rivaroxaban 20 mg (15 mg in patients with moderate renal insufficiency) once daily versus warfarin (target INR 2.5; range 2.0-3.0) with respect to cumulative incident thrombosis (arterial or venous) confirmed by imaging studies, major bleed, and death in triple aPL-positive APS patients. The trial plans to recruit 536 patients [7~~5~~4,83~~55~~] ~~[113 recruited by July 2017: personal communication, Prof V Pengo]~~.

ASTRO-APS: Apixaban for The Secondary Thrombosis Prevention in Antiphospholipid Syndrome (ASTRO-APS) trial

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The ASTRO-APS RCT is comparing apixaban with warfarin (target INR 2.5; range 2.0-3.0) for the secondary prevention of thromboembolism among patients with a history of APS and thrombosis [8456]. The intentions of this phase IV pilot study are to provide data on feasibility of enrolling APS patients and to estimate efficacy and safety of apixaban compared with usual care. ASTRO-APS was originally designed to compare apixaban 2.5 or 5 mg twice a day with warfarin, enrolling patients with a history of arterial or venous thromboses receiving indefinite anticoagulation. In this context, patients with aPL, as well as those with high risk heritable thrombophilias, were excluded from AMPLIFY-EXT in which a dose of 2.5mg twice daily was used [10]. APS patients are categorized as having definite, likely or historic APS and therefore ASTRO-APS may include patients who do not meet the International Consensus Criteria for APS diagnosis [15]. The primary clinical outcomes are rates at one year of arterial or venous thrombosis, death caused by thrombosis, major bleeding, and clinically relevant non-major bleeding. After accrual of the first 25 patients, a pre-specified Data Safety Monitoring Board (DSMB) review recommended the protocol be modified to use apixaban 5mg twice a day. In this context, patients with indications for long-term treatment with a VKA, such as aPL, , as well as those with high risk heritable thrombophilias, were excluded from AMPLIFY-EXT in which a dose of 2.5mg twice daily was used [8510]. After five more patients were enrolled, a potential safety signal led to an ad hoc DSMB re-review, which recommended , first, to continuinge ASTRO-APS, ; second, excludinge patients with prior arterial thrombosis;, and, undertaking third, obtain brain magnetic resonance imaging (MRI) with stroke protocol for all otherwise eligible candidates to exclude prior silent stroke. ASTRO-APS plans to enroll 200 patients [74,8455,56].

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RISAPS: Rivaroxban for~~in~~ Stroke Patients with Antiphospholipid Syndrome trial

The RISAPS open-label, phase 2/3 non-inferiority RCT [Chief Investigator H Cohen], funded by Arthritis Research UK (reference: 21517), will assess the efficacy of rivaroxaban versus warfarin in adult patients with APS, with or without SLE, who have ischaemic stroke or other ischaemic brain manifestations.

~~*RAPS: Rivaroxaban for Antiphospholipid Syndrome Pilot Feasibility Study*~~

~~The RAPS pilot feasibility study (ClinicalTrials.gov:NCT02116036) is a prospective cohort study for patients with confirmed APS and prior VTE, with or without prior arterial thrombosis, allocating them to receive rivaroxaban 20 mg daily. Patients are followed for thrombosis. The study is designed as a feasibility study with clinical outcomes as secondary endpoints (thrombosis; minor, major, and fatal bleeding). Recruitment was closed on 30th September 2016 with a plan to follow all patients for one year. Seventy-nine patients were identified, with the expected recruitment of 150. Available information indicates that few complications, and no recurrent thromboses, have occurred. One patient suffered unexplained hepatitis [55]. This study is underpowered but will provide additional data on the efficacy and safety of DOACs in patients with APS.~~

~~A challenge in DOAC APS studies is ensuring sufficient statistical power. Trials with clinical outcomes are ideal, however, where APS trials with clinical outcomes have succeeded,~~

numbers have been relatively small, 334 patients in 5 RCTs on treatment for APS-associated recurrent miscarriage in the meta-analysis by Mak et al [57-62], while trials with larger recruitment targets have proved challenging [63,64]. The appropriateness or otherwise, of the use of surrogate markers in clinical trials was considered in an editorial review by Svennson et al who, after supporting their use in fatal diseases like amyotrophic lateral sclerosis, went onto say they felt this approach was justified: "in the case of very rare diseases, (where) validation of hard end points may take an unreasonable time to complete" [65].

Case series and cohort studies of direct oral anticoagulants in thrombotic antiphospholipid syndrome

Case reports or series and cohort studies have reported on DOAC use in APS patients, with approximately 200 cases reported. Several authors have reported case series and cohort studies in which there has been thromboembolism recurrence in APS patients switched from warfarin to a DOAC [66-71], summarised in Table 2. Other case series report that DOAC use in thrombotic APS has been unassociated with recurrent thrombosis [72,73]. These data, with their inherent limitations, including selection bias, lack of a comparator arm and in some studies, retrospective design, suggest that recurrent thrombotic events with DOACs in APS patients mainly occur when DOACs are used for secondary prevention of APS-related arterial or microvascular thrombosis, where DOACs are unlicensed and where many APS treaters use high-intensity anticoagulation [28], or in triple aPL positive APS patients.

Testing for antiphospholipid antibodies in patients on direct oral anticoagulants

Many studies have reported DOAC interference with assays used for diagnosis of LA [74-76]. Dabigatran interferes with both the activated partial thromboplastin time (APTT) and the dilute Russell Viper Venon time (dRVVT) assays, inducing a concentration dependent prolongation in both assays, a proportional increase in the dRVVT screen and confirm results and a corresponding increase in the dRVVT screen:confirm normalised ratio [77]. Dabigatran also induces prolongation of the silica clotting time (SCT) screen and confirmatory test [78]. Normalisation of the dRVVT results does not correct the false-positive LA results at high dabigatran concentrations [79], while false positive results have also been reported with a hexagonal phase lipid neutralization assay using the Staclot LA assay with the effect been dependent on dabigatran concentration [80]. Similarly, apixaban induces a concentration dependent prolongation on the PTT-LA, Staclot LA, and dRVVT screen and confirm assays [81]. False positive tests for LA, based on the DRVVT have also been reported for rivaroxaban. Goralczyk et al showed false positive results with both the PTT-LA and dRVVT assays in 10 patients receiving rivaroxaban [82], while Mani et al reported a significant increase in dRVVT 2 hours after administration of low dose rivaroxaban compared to results prior to administration or 12 hours after administration [83]. False positive dRVVT screen, mixing and confirmatory tests, SCT screens, and prolonged APTT has also been reported by Martinuzzo et al [78] and in the 21 patients in the EINSTEIN study that were tested for LA while on rivaroxaban with only partial or no correction with 1:1 mixing [84].

The Taipan Venom Time/Ecarin Clotting Time (TVT/ECT) ratio and Textarin time assays have been shown to perform better and be unaffected by rivaroxaban, irrespective of

concentration. In thrombotic APS patients treated with rivaroxaban, the TVT/ECT appears reliable even at peak therapeutic plasma levels, while the DRVVT may be acceptable at trough rivaroxaban plasma levels, although an anti-Xa should be performed in parallel to ensure that the result is not a false positive [52,84,85]. No interference has been reported by any DOACs on solid phase assays or enzyme-linked immunosorbent assays (ELISAs) for anti-β2GPI or aCL [79,82,84] .

Thrombin generation and direct oral anticoagulants

The CAT TG represents a global dynamic assay that measures the overall tendency of a plasma sample to form thrombin after initiation of coagulation using a thrombin-sensitive fluorogenic substrate and investigates all stages of TG and inactivation. The TG curve is quantified in terms of the lag time, time to peak TG, peak TG, and ETP, the area under the TG curve [86]. TG testing has been shown to be informative in regard to APS status and LA diagnosis [87,88]. While traditional assays such as PT and aPTT are not sensitive enough for assessment of anticoagulant intensity of DOACs, TG can be used to assess the effects of anticoagulants in platelet poor (PPP) and rich plasma (PRP), and in both APS and non-APS patients [25,50,89,90]. Rivaroxaban can downregulate and completely suppress TG in whole blood, PRP [48,91] and PPP [92,93]. Dabigatran can significantly inhibit TF-induced TG in a concentration-dependent manner but with weaker inhibitory effects than rivaroxaban [94]. Apixaban affects all TG parameters with prolonged lag time, ETP and peak TG (the latter showing greater reduction than the ETP)[95]. TG testing has been used to establish the effect of prothrombin complex concentrate in reversing the anticoagulant effect of rivaroxaban and dabigatran [96,97].

Use of direct oral anticoagulants in antiphospholipid syndrome patients~~DOACs for APS~~ in clinical practice

The RAPS trial suggests ~~supports the view~~ that rivaroxaban offers the potential to be ~~is~~ an effective ~~, safe~~ and convenient alternative to warfarin in ~~adult patients with~~ thrombotic APS patients with a single VTE event requiring standard intensity anticoagulation~~who require standard intensity warfarin following a single VTE event or recurrent VTE while unanticoagulated or on subtherapeutic anticoagulation~~ [7946]. Further studies ~~and~~, in particular, acquisition of better long-term safety data, are needed before it can be widely recommended. ~~There is no evidence to support the current use of other DOACs in this situation.~~ Of note, the major phase 3 clinical trials that established the use of DOACs versus warfarin for the treatment and secondary prevention of VTE used warfarin at a target INR of 2.5 (range 2.0–3.0) as the comparator. The optimal intensity of DOACs in patients who experience recurrent VTE on standard-intensity VKA, in whom it is usual to switch to high intensity VKA (target INR 3.5; range 3.0-4.0), is not established, therefore DOAC use should be avoided in such patients. The 15th International Congress on Antiphospholipid Antibodies Task Force on Treatment Trends Recommendations stated: "Insufficient evidence to make recommendations at this time regarding DOAC use in APS. The RAPS trial suggests that rivaroxaban might be useful in selected APS patients with single venous thrombosis requiring standard intensity anticoagulation; however, this needs to be confirmed with additional studies using clinical outcome measures" [7455].

The case series and cohort studies of DOAC use in APS patients, suggest that recurrent thrombotic events with standard intensity DOACs in APS patients mainly occur when DOACs

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are used for secondary prevention of APS-related arterial or microvascular thrombosis [66-713-68], where DOACs are unlicensed [6-9] ~~and many APS physicians use high-intensity anticoagulation [45,66-71], or in APS patients with triple aPL positivity [66-71]~~. ~~These data emphasise the need for avoidance of DOACs in APS patients with arterial or microvascular thrombosis and detailed assessment of APS patients with VTE, including those with triple aPL positivity who are at highest risk of recurrent thrombosis [27]. Careful enquiry about any symptoms that suggest arterial thrombosis, including "brain fog" and a low threshold for MRI brain imaging with SWI 3D flair sequences, are needed to establish whether there is evidence of cerebral ischaemia.~~ We believe these patient groups~~s~~ should not be treated with DOACs until further trial data are available.

Practical clinical issues

The potential use of DOACs in APS patients requires comparative considerations for the use of DOACs in non-APS patients, including those with renal or hepatic impairment, the elderly, or those on potentially interacting drugs, in accordance with the DOAC SPCs [6-9]~~1-4~~.~~.~~ Drug interactions and the potential for gastrointestinal bleeding are of particular relevance as APS where an antiplatelet agent is considered in addition to anticoagulation, or in those with SLE or other autoimmune diseases where other drugs may be considered, including nonsteroidal anti-inflammatory drugs and steroids. Cover with a proton pump inhibitor is usual. The optimal dosing strategy for DOACs in patients at extremes of body weight, >120 kg or <50 kg, has raised concern. Several studies, including a review of Phase 1-3 studies of rivaroxaban [86], ~~[Ref],~~ measurement of rivaroxaban levels at various weight ranges [87~~[Ref]~~] an~~a~~nd a pharmacokinetic study [88] s~~[Ref]~~ suggest that standard dose rivaroxaban can be

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used safely in patients of all weights, however, further data are required. International Society of Thrombosis and Haemostasis Scientific and Standardisation Committee (ISTH SSC) guidance recommends that DOACs should not be used for standard indications in obese patients, >120 kg, however, if used, to check drug-specific peak and trough levels. If the drug is within the expected range, the DOAC can continue, and if not, it should be switched to a VKA [89]. ~~[Ref]~~ The management of bleeding in patients on DOACs is addressed elsewhere [90]. I~~[REF]~~. Idarucizumab, an antibody fragment which binds to and neutralizes dabigatran, is licensed for rapid reversal of dabigatran [91] a~~[Ref]~~ and andexanet-alfa has been shown to be effective for reversal of factor Xa inhibitors [92]. W~~[Ref]~~. While the use of warfarin offers the advantage that its regular monitoring helps to determine the degree of patient adherence, its many complications drive the need to assess alternative therapies. The development of DOACs now provides such alternatives, however, good adherence to anticoagulation is essential, particularly as the risk of thrombosis is compounded by the short half-lives of DOACs compared to VKAs. A systematic review indicated that poor adherence to INR monitoring on VKA is a risk factor for recurrent thrombosis following a switch to a DOAC [93] a~~[Ref]~~ and therefore such a switch is probably best avoided where there is pre-existing poor adherence. Measurement of DOAC concentration may be helpful in certain circumstances, including extremes of body weight and to confirm absorption, however, routine anticoagulant monitoring of DOAC levels is generally not practicable or feasible.

Women's health issues

There is a preponderance of women with APS, female to male ratio approximately 5:1,

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many of whom have thrombotic as well as obstetric APS [26]. Vaginal bleeding complications are a common complication of oral anticoagulation [94] a[Ref] and appear to occur more often with direct oral factor Xa inhibitors than with VKAs [95] [Refs]. Beyer-Westendorf et al reported vaginal bleeding events in 57 of 178 women of reproductive age in the Dresden DOAC registry, with recurrent bleeding in 23%. Patients with anatomic abnormalities had more intense bleeding and more needed surgical treatment [96]. [Ref]. A proactive approach, with gynaecological input, is required. A temporary interruption or dose reduction of DOAC on days when bleeding is heaviest, can be sufficient to prevent recurrent heavy menstrual bleeding (HMB). A levonorgestrel intrauterine system (LNG-IUS Mirena) is the most effective medical intervention for HMB [97] [Ref] and avoids potential thrombogenic effects of oral hormonal preparations. Tranexamic acid, is an effective alternative or adjunct [97]. [Ref]. A switch to split dose LMWH may need consideration pending definitive gynaecological treatment.

The potential for reproductive toxicity of DOACs in humans, via maternal or paternal exposure, is undefined. Consequently, the DOAC SPCs recommend avoiding them during pregnancy and breast-feeding [6-9].[1-4]. Limited data suggest embryopathy occurs in approximately 2% of women who experience DOAC exposure in pregnancy [98]. ISTH SSC guidance recommendations can be summarized as follows: (1) women of child- bearing potential should receive documented counselling prior to commencement of DOACs; (2)

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should pregnancy be desired, the DOAC should be switched to an alternative anticoagulant pre-conceptually, with the main options being VKAs (to be switched to LMWH as soon as possible when pregnant and before 6 weeks of gestation), or LMWH, with cognizance that the latter may result in prolonged subcutaneous injections until pregnancy is achieved; (3) in women who become pregnant while on a DOAC, DOAC should be discontinued immediately and LMWH commenced; (4) inadvertent exposure to a DOAC would not in itself be regarded as medical grounds for termination of pregnancy; (5) in women who become pregnant while on a DOAC and who decide to continue with pregnancy, there should be early obstetric review and fetal monitoring; (6) breast-feeding women should not be treated with DOACs [99]. The ISTH SSC guidance on DOACs in women of childbearing potential also recommends that all cases of DOAC exposure during pregnancy should be reported to the international ISTH registry to ensure consistency of data collection: http://www.survey-gizmo.com/s3/2394649/International-registry-of-pregnancy-during-NOAC-use-Inclusion.

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~~*RISAPS: Rivaroxban in Stroke Patients with Antiphospholipid Syndrome trial*~~

~~The RISAPS trial, recently funded by Arthritis Research UK with support from Bayer, is a non-inferiority, open-label, phase 2/3 RCT [Chief Investigator H Cohen], that will assess the efficacy of rivaroxaban versus warfarin in adult patients with APS, with or without SLE, who have one or more of: a) ischaemic stroke; b) transient ischaemic attack (one or more episodes) with evidence of tissue injury on diffusion weighted imaging and diagnosed by a clinician with expertise in stroke; c) brain infarcts (territorial or subcortical) or white matter~~

~~hyperintensities of presumed vascular origin on brain MRI, with or without cognitive impairment; and an expert clinical opinion that anticoagulation is a reasonable treatment option for the secondary prevention of stroke in these patients. Patients will be randomized to either rivaroxaban 15 mg twice daily or warfarin target INR 3.5 (range 3.0-4.0). This study will inform the utility of rivaroxaban in APS patients post stroke or other brain ischaemic lesions.~~

~~There is a preponderance of women with APS, female:male ratio approximately 5:1, many of whom have thrombotic as well as obstetric APS [26]. The potential for reproductive toxicity of DOACs in humans, via maternal or paternal exposure, is undefined. Consequently, the DOAC SPCs recommend against their use in pregnancy and during breast-feeding [1-4]. Limited data suggest embryopathy occurs in approximately 2% of women who experience DOAC exposure in pregnancy [98]. APS mainly affects relatively young individuals, with the median age at study entry in the Euro-Phospholipid Project of 1,000 patients, more than 70% of whom had stroke or VTE, 40 (range 0-82) years [26]. International Society of Thrombosis and Haemostasis (ISTH) guidance on the management of DOACs in women of childbearing potential should be followed by women in their reproductive years who are receiving DOACs for thrombotic APS [99].~~

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Conclusions

The RAPS trial, that had a surrogate laboratory primary outcome measure, suggests that rivaroxaban offers the potential to be an effective and convenient alternative to warfarin in

thrombotic APS patients with a single VTE event requiring standard intensity anticoagulation. However, further studies and, in particular, acquisition of better long-term efficacy and safety data, are needed before it can be widely recommended. ~~The RAPS trial findings support the concept that rivaroxaban offers an effective, safe and convenient alternative to VKA in APS patients with a history of VTE who require standard intensity anticoagulation, i.e. with a single VTE episode or recurrent VTE while unanticoagulated or on subtherapeutic anticoagulation. Further clinical studies are essential to define the role of DOACs in the treatment of APS patients, including those who need higher-intensity anticoagulation after recurrent thrombotic events while they were taking standard-intensity anticoagulation for VTE, and those with stroke or other arterial thrombosis.~~ APS DOAC RCTs with clinical primary outcomes represent the gold standard, however, a primary endpoint of recurrent thrombosis would require a larger sample size than has been achieved to date. APS patients are clinically heterogeneous, with the risk of recurrent thrombosis and the intensity of anticoagulation influenced by~~dependent on~~ their clinical phenotype and risk profile. Thus, DOAC trials involving ~~clinically~~ homogeneous thrombotic APS populations, with aPL status well defined, ~~,~~ will help to optimise the appropriate treatment in APS patient subgroups. ~~The need for further APS DOAC trials is highlighted by recent observations suggesting that recurrent thrombosis occur particularly when DOACs are used for secondary prevention of APS-related arterial or microvascular thrombosis or in APS patients with triple aPL positivity.~~Ongoing and emerging RCTs should provide further information to guide the use of DOACs in APS. Optimal identification of APS patients merits attention as this is a key step in working towards ~~the provision of~~ improved therapeutic strategies in these individuals.

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Addendum

Hannah Cohen wrote the first draft of the manuscript and was involved in collecting literature, interpretation of data and revising the manuscript. Maria Efthymiou and David Isenberg were involved in collecting literature, interpretation of data and revising the manuscript.

Disclosure of Conflict of Interests

Hannah Cohen reports receiving institutional research support and honoraria (diverted to local Charity) for lectures and Advisory Board from Bayer. Maria Efthymiou and David Isenberg have no conflicts of interest to disclose.

Table 1: Current status of randomised controlled trials of direct oral anticoagulants in thrombotic antiphospholipid syndrome

	RAPS	TRAPS	ASTRO-APS
Chief Investigator	H Cohen	V Pengo	S Woller
Study design	Phase 2/3 RCT	Phase 3 RCT	Phase 2/3 RCT
Number of patients	116	536	200
APS subgroups	Previous VTE, target INR of 2.5 No thrombosis >3 mo Patients with arterial thrombosis excluded	Triple positive thrombotic APS; arterial, venous, and/or biopsy-proven microthrombosis	Thrombotic APS VTE target INR 2.5, No thrombosis >6 mo; Definite, likely or historic APS
Intervention	Rivaroxaban 20 mg od vs. warfarin target INR of 2.5	Rivaroxaban 20 mg od vs. warfarin target INR of 2.5	Apixaban 2.5 mg or 5 mg bd vs. warfarin target INR of 2.5
Primary outcome(s)	Thrombin generation – endogenous thrombin potential (ETP)	Thrombosis – arterial or venous Major bleeding Death	Thrombosis – arterial and/or venous Bleeding
Duration of recruitment	Jun 13 – Nov 14	Dec 14 – Dec 18	Feb 15- ongoing
Status	Completed and results published[46]	Ongoing: 113 patients recruited July 2017	Ongoing: protocol modified after potential safety signal (see text)

Abbreviations: ASTRO-APS, Apixaban for the Secondary Prevention of Thromboembolism Among Patients With the AntiPhospholipid Syndrome (ClinicalTrials.gov:NCT02295475) [55,56]; bd, twice daily; od, once daily; RAPS, Rivaroxaban in Antiphospholipid Syndrome (ISRCTN68222801) [46]; RCT, randomized controlled trial; TRAPS, Rivaroxaban in Thrombotic Antiphospholipid Syndrome (ClinicalTrials.gov:NCT02157272) [54,55]; *Rivaroxaban for Antiphospholipid Syndrome (ClinicalTrials.gov:NCT02116036)

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Table 12: Case series and cohort studies in which thrombotic antiphospholipid syndrome patients treated with direct oral anticoagulants developed recurrent thrombosisREFS

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	Case Series [66]	Case Series [67]	Case Series [68]	Cohort [69]	Cohort [70]	Case Series [71]
Number of patients	8	12	23	26	56	19
Thrombosis history	VTE: 6 VTE+AT: 2	VTE: 10 VTE+AT: 2	VTE: 19 AT: 2 VT+AT: 1 CAPS: 1	VTE: 13 VTE+AT/MT: 4 AT: 9	VTE:19 AT:2 VTE+AT:1	VTE: 3 VTE+AT: 2 VTE+MT: 1
DOAC given: number of patients	R: 8	R: 12		R: 15 D: 11	R: 49 D: 4 A: 3	R: 17 D: 2
Systemic lupus erythematosus	0	4	5	9	33	NS
Outcome: DOAC given	5 VTE: R 2 VTE+AT: R 1 AT: R	2 VT: R	1 VTE: R	1 MT: NS	4 VTE: R* 1 SVT: R 1 AT: R	2 AT: D 1VTE+?AT: R 1 AT: R 1 MT: R
Time to thrombosis (months)	Median 3 (range 0.2-12)	5, 2	20	Median 10 (range 8-29)	Mean 46.7 (range 6-144)	Mean+/-SD: 23.3+/-22.3 (range 1-84)
Previous thrombosis history in patients who developed recurrent thrombosis on DOAC Triple aPL positivity in patients with recurrent thrombosis (where stated)	2/3 had previous AT; the third patient had previous VTE and was triple aPL positive	Both triple aPL positive	VTE+OM, triple aPL positive	Previous MT	2/6 had VTE+AT 4/6 were triple aPL positive	2/6 had previous AT 1/6 ad previous MT 2 others were triple aPL positive

Abbreviations: aPL, antiphospholipid antibodies; AT, arterial/transient ischemic attack; CAPS, catastrophic antiphospholipid syndrome; D, dabigatran; DOAC, direct oral anticoagulant; MT, microvascular thrombosis; NS, not stated; OM, obstetric morbidity; r, range; R, rivaroxaban 20 mg once daily; SVT, superficial vein thrombosis; triple aPL positive, presence of lupus anticoagulant + IgG/IgM anticardiolipin + IgG/IgM anti-β2 glycoprotein 1 antibodies; VT, venous thromboembolism; *nonadherence

Table 2: Characteristics and status of completed and recruiting randomised controlled trials of direct oral anticoagulants in thrombotic antiphospholipid syndrome

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	RAPS	TRAPS	ASTRO-APS
Chief	H Cohen	V Pengo	S Woller

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Investigator			
Study design	Phase 2/3 RCT	Phase 3 RCT	Phase 2/3 RCT
Number of patients	116	536	200
APS subgroups	Previous VTE, target INR of 2.5 No thrombosis >3 mo Patients with arterial thrombosis excluded	Triple positive thrombotic APS; arterial, venous, and/or biopsy-proven microthrombosis	Thrombotic APS VTE target INR 2.5, No thrombosis >6 mo; Definite, likely or historic APS
Intervention	Rivaroxaban 20 mg od vs. warfarin target INR of 2.5	Rivaroxaban 20 mg od vs. warfarin target INR of 2.5	Apixaban 2.5 mg or 5 mg bd vs. warfarin target INR of 2.5
Primary outcome(s)	Thrombin generation—endogenous thrombin potential (ETP)	Thrombosis—arterial or venous Major bleeding Death	Thrombosis—arterial and/or venous Bleeding
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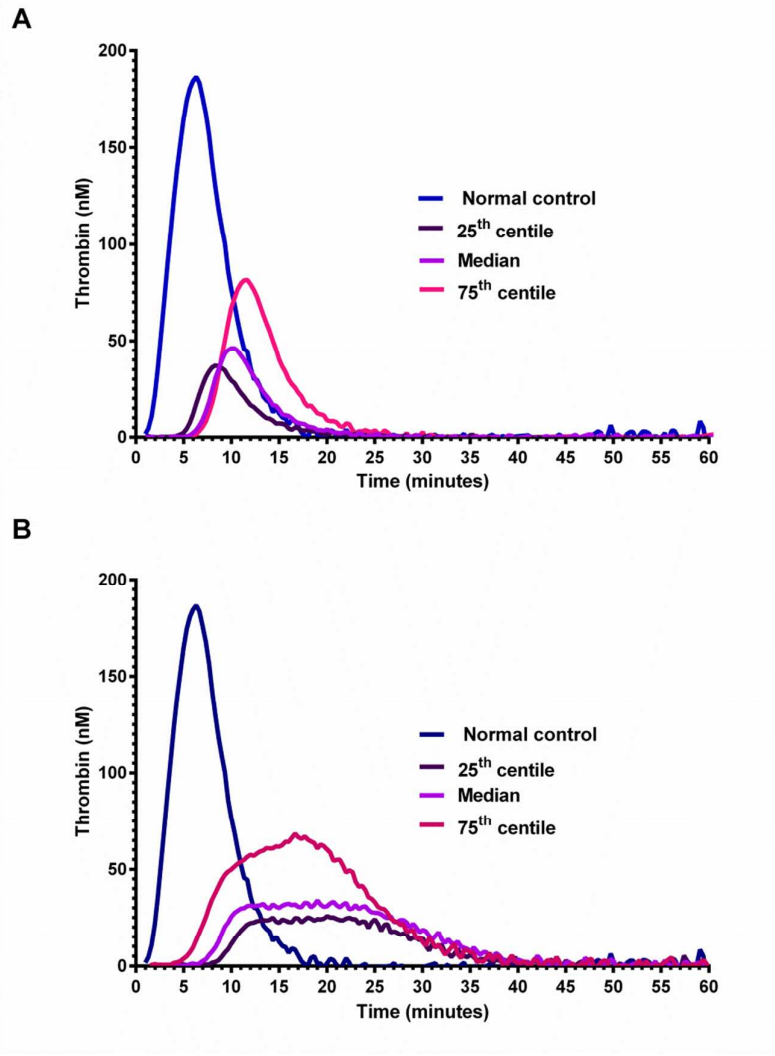
Figure 1: RAPS (Rivaroxaban in Antiphospholipid Syndrome) trial thrombograms for median (25th and 7th percentiles) ETP values in patients on warfarin (A) or rivaroxaban (B) compared with a typical normal control value [79]



Use of direct oral anticoagulants in antiphospholipid syndrome

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Abstract

The direct oral anticoagulants (DOACs) are therapeutic alternatives to warfarin and other vitamin K antagonists (VKAs), and the standard of care for many indications. VKAs are conventional therapy for the treatment and secondary thromboprophylaxis of thrombotic antiphospholipid syndrome (APS), but are often problematic due to the variable sensitivity of thromboplastins to lupus anticoagulant. Thus, the International Normalised Ratio may not accurately reflect anticoagulation intensity, or be clinically effective. Definition of the current role of DOACs in APS is based on limited clinical trial data and information from other sources, including manufacturers' data, case series or cohort studies and expert consensus. The RAPS randomised controlled trial (RCT), that had a laboratory surrogate primary outcome measure, suggests that rivaroxaban offers the potential to be an effective and convenient alternative to warfarin in thrombotic APS patients with a single VTE event requiring standard intensity anticoagulation. However, further studies, in particular, acquisition of better long-term efficacy and safety data, are needed before it can be widely recommended. APS patients are clinically heterogeneous, with the risk of recurrent thrombosis and the intensity of anticoagulation influenced by their clinical phenotype and risk profile. DOAC trials involving homogeneous thrombotic APS populations, with aPL status well defined, will help to optimise the appropriate treatment in APS patient subgroups. Ongoing and emerging DOAC RCTs should provide further information to guide the use of DOACs in APS. Optimal identification of APS patients is a key step in working towards improved therapeutic strategies in these individuals.

Keywords: direct oral anticoagulants, antiphospholipid syndrome, venous thromboembolism, ischaemic stroke, thrombin generation

Introduction

Antiphospholipid syndrome (APS) is manifested by thrombosis (arterial, venous or microvascular) and/or obstetric morbidity in association with persistent antiphospholipid antibodies (aPL), i.e. lupus anticoagulant (LA), anticardiolipin (aCL) and/or anti-beta 2 glycoprotein 1 antibodies (aβ2GP1) [1]. Thrombotic APS is clinically heterogenous, with thrombotic episodes ranging from mild to potentially life-threatening, refractory thrombosis despite adequate anticoagulation; and the rare catastrophic APS. Thrombotic events may be venous, arterial, or microvascular. APS mainly affects relatively young individuals. The median age at study entry in the Euro-Phospholipid Project of 1,000 patients, more than 70% of whom had stroke or VTE, was 40 (range 0-82) years [2]. Among systemic lupus erythematosus (SLE) patients, 30-40% have aPL [3], with estimates of the frequency with which APS occurs in patients with SLE ranging from 7% to 22% [4,5]. SLE patients with APS are often difficult to manage with complex clinical problems [6]. Warfarin or other vitamin K antagonists (VKAs) are conventional therapy for the treatment and secondary thromboprophylaxis of thrombotic APS [7]. However, treatment with VKAs is often problematic as they have a slow onset of action of several days, a narrow therapeutic window, numerous drug and dietary interactions; and the potential for variation of action with alcohol, intercurrent illness, exercise, and smoking. Patients require regular monitoring of the International Normalised Ratio (INR). The direct oral anticoagulants (DOACs), dabigatran, a direct thrombin inhibitor, and apixaban, edoxaban and rivaroxaban, direct factor Xa inhibitors, represent a major milestone in anticoagulation. They are therapeutic alternatives to VKAs and the standard of care for many indications, detailed in the summary of product characteristics (SPC) [8-11]. DOACs, in contrast to VKAs, are prescribed at a fixed dose with a more predictable anticoagulant effect and do not routinely require regular

anticoagulant monitoring. They have a rapid onset of action which generally obviates the need for bridging anticoagulation with low-molecular-weight heparin (LMWH) [9,11], are not affected by dietary changes and alcohol intake and have fewer drug interactions than VKAs that affect anticoagulant intensity. These features should improve patient quality of life. The SPCs for the licensed DOACs [8-11] do not contain information regarding the use of DOACs in patients with APS. Definition of the current role of DOACs in APS is based on limited clinical data and information from other sources, including manufacturers' data, case series or cohort studies and expert consensus.

Warfarin and other vitamin K antagonists for antiphospholipid syndrome

Approximately 10% of APS patients overall [2] and 30% of those who are triple aPL positive, i.e. have LA, aCL and aβ2GP1 [12], have recurrent thrombotic events, arterial or venous, on VKAs (at standard intensity, target INR 2.5) at 5 years follow up. The high thrombotic risk of triple aPL positive patients is also observed in asymptomatic individuals, where the risk of thrombosis is significantly higher than in those with single aPL positivity. The annual rate of first cardiovascular event is 5.3% in triple aPL positive (cumulative incidence 37% at 10 years) vs 1.36% in single aPL positive individuals vs ~0.4% in the normal population [13]. A systematic review of 16 studies indicated that APS patients on anticoagulation experience major bleeding rates of 0.57% to 10% per year [14].

Venous thromboembolism

Retrospective studies have shown a high incidence of thrombosis recurrence in patients with aPL [15-17]. In these studies, 54% (80/147), 56% (39/70) and 38% (23/61) of patients

had VTE. In the prospective Duration of Anticoagulation (DURAC) study on 412 patients with VTE, a single aCL-positive test doubled the risk of recurrence in the first 6 months after cessation of warfarin: 29% (20/68) in patients with aCL and 14% (47/334) in patients without aCL (p=0.0013), for a risk ratio of 2.1 (95% confidence interval [CI]: 1.3–3.3) [18]. Current recommendations on the duration of anticoagulation in individuals with VTE who have APS are extrapolated from studies in the general VTE population [19-21]. Although indefinite anticoagulation is suggested for APS patients with unprovoked VTE and temporary anticoagulation for those with a provoked VTE [19,22], there are no specific substantive data on the optimal duration of anticoagulation for APS patients with VTE. A pragmatic approach is to test for aPL in patients who have had a first unprovoked VTE, as aPL positivity strengthens the decision for indefinite anticoagulation. It also identifies women who require higher than standard prophylactic dose anticoagulation with LMWH during pregnancy [23-25], and who also require low dose aspirin and monitoring for placental insufficiency [26], to guide optimal timing of delivery, reducing the risk of perinatal morbidity and mortality. Testing for aPL is recommended in patients with unprovoked VTE [19], however aPL testing should also be considered in patients with provoked VTE, particularly if the provoking factor for VTE appears disproportionately mild.

Stroke and other arterial thrombosis

APS patients with ischaemic brain manifestations also require identification in contrast to non-APS stroke patients where antiplatelet treatment is the standard of care. Anticoagulation is a rational treatment for patients with APS and stroke, TIA or other ischaemic brain manifestations since it can lead to resolution of in situ arterial thrombosis or prevent cardioembolic events. UK national clinical guidelines for stroke recommend aPL

testing in individuals under 50 years [27]. There are few data to guide the optimal anticoagulation intensity in APS patients with stroke or other arterial thrombosis. Ruiz-Irastorza et al [14] reviewed 16 studies (4 randomised controlled trials (RCTs) and 12 prospective or retrospective cohort studies) on secondary thromboprophylaxis in patients with aPL. Of 180 thrombotic events reported, 104 (57%) occurred when patients were not taking any anticoagulant or antiplatelet agent. Only 7 of 49 recurrences (27%) on warfarin occurred in patients when the INR was >3.0; of these, in the five cases where specified, 4 were arterial and one venous.

Three prospective studies have addressed the key issue of the optimal antithrombotic treatment for stroke patients with aPL, however, these have major limitations. Two RCTs on standard vs high intensity warfarin in patients with thrombotic APS, Crowther et al [28] and Finazzi et al [29] concluded that the optimal target INR for both venous and/or arterial thromboembolism, including stroke, in APS is 2.5 (range 2.0–3.0) (standard-intensity) rather than 3.5 (range 3.0-4.0) (high-intensity). However, patients with recurrent thrombosis history while on therapeutic anticoagulation or with arterial thrombosis were poorly represented in both studies, with the latter comprising only 24% and 32% (62 of 223 patients across both studies). Notably, 6/8 recurrent thrombotic events in Crowther et al's study [28] occurred while the INR was <3.0 (5/6) or while off warfarin (1/6). The study by Finazzi et al did not detail the INR at the time of thrombosis [29]. The Antiphospholipid Antibodies and Stroke Study (APASS) [30], a prospective cohort study within the Warfarin versus Aspirin Recurrent Stroke Study (WARSS), reported no benefit of warfarin anticoagulation (target INR 1.4–2.8) over aspirin (325 mg/day) in stroke prevention.

However, laboratory criteria for aPL were not compliant with the international consensus criteria for APS diagnosis [30].

The lack of robust data on the optimal anticoagulant intensity in ischaemic stroke patients with APS is reflected in national and international guidelines. British Society for Haematology [19] and American College of Chest Physicians guidelines [31] on APS associated ischaemic stroke include warfarin (or other VKA) at a target INR of 2.5 (range 2.0-3.0). The Task Force at the 13th International Congress on aPL recommended that patients with definite APS and arterial thrombosis should be treated with warfarin at an INR >3.0 or combined antiplatelet-anticoagulant (target INR 2.5) therapy [21]. This suggestion was a non-graded recommendation due to lack of consensus within the Task Force. Many physicians treating APS patients use high-intensity warfarin (target INR 3.5; range 3.0-4.0) for APS patients with ischaemic stroke or other arterial thrombosis.

Laboratory issues in antiphospholipid syndrome patients on vitamin K antagonists or direct oral anticoagulants

Laboratory monitoring of anticoagulation on warfarin

VKAs can be problematic in APS patients because of variable sensitivity of thromboplastins to LA [32,33]. A multicentre study indicated that LA interference with the prothrombin time-INR measured with the majority of commercial thromboplastins is insufficient to cause concern if insensitive thromboplastins, properly calibrated to assign them an instrument-specific International Sensitivity Index (ISI), are used. The investigators suggested that new thromboplastins, especially those made of relipidated recombinant human tissue factor,

should be checked ensuring that they are insensitive to the effects of aPL before being used to monitor oral anticoagulant treatment in APS patients [33]. These procedures are generally routine in specialist centres, but may not available elsewhere. Thus, the INR might not accurately reflect anticoagulation intensity and, as a result, could be associated with potential thrombotic or bleeding complications. Amidolytic factor X assays, as a LA-independent measure of anticoagulation intensity, may be useful in such cases, although this is rarely practicable [32,34]. The variable sensitivity of thromboplastins to LA may also be associated with instability of the INR, necessitating frequent anticoagulant monitoring causing inconvenience to the patient, adversely impacting on quality of life and increasing costs. Warfarin also interacts with many other drugs altering the INR and complicating the treatment of APS patients with other disorders, including SLE.

Testing for antiphospholipid antibodies

LA testing in patients on VKAs isaddressed in national and international guidelines [19, 35]. Tests for LA detection should include screening, mixing and confirmation ones assessed with at least two different methodologies [19,35]. Many studies have reported DOAC interference with assays for LA leading to false positive and unreliable results [36;37-39]. Dabigatran and apixaban interfere with both the activated partial thromboplastin time (APTT) and the dilute Russell Viper Venom time (dRVVT) assays, with false positive resultsreported with a hexagonal phase lipid neutralisation assay using the Staclot LA assay [40-43]. False positive tests for PTT LA, Silica Clotting Time screens and dRVVT have also been reported for rivaroxaban, particularly at peak plasma levels [36;41;44-46]. However, the Taipan Venom Time/Ecarin Clotting Time (TVT/ECT) ratio and Textarin time assays

perform better and are unaffected by rivaroxaban, irrespective of concentration. In thrombotic APS patients treated with rivaroxaban, the TVT/ECT appears reliable even at peak therapeutic plasma levels, while the dRVVT may be acceptable at trough rivaroxaban plasma levels (>18 hours after the last dose of rivaroxaban), although a rivaroxaban anti-Xa should be performed in parallel to ensure that the result is not a false positive [36,43,46]. No interference has been reported by any DOACs on solid phase assays or enzyme–linked immunosorbent assays (ELISAs) for anti-β2GPI or aCL [42,44,46] .

Thrombin generation and direct oral anticoagulants

Thrombin generation (TG), assessed by calibrated automated thrombography, represents a global dynamic assay that measures the overall ability of plasma to form thrombin after initiation of coagulation using a thrombin-sensitive fluorogenic substrate. The TG curve, quantified in terms of the lag time, time to peak TG, peak TG, and endogenous thrombin potential (ETP), the area under the TG curve [47], is informative in regard to APS status and LA detection [48,49]. TG can be used to assess the effects of anticoagulants in platelet poor (PPP) and rich plasma (PRP) and in both APS and non-APS patients [34,50,51,52,]. Rivaroxaban can downregulate and completely suppress TG in whole blood, PRP [53,54] and PPP [55,56], while dabigatran can significantly inhibit TF-induced TG in a concentration-dependent manner, but with weaker inhibitory effects than rivaroxaban [57]. Apixaban affects all TG parameters with prolonged lag time, ETP and peak TG (the latter showing greater reduction than the ETP) [58]. Antiphospholipid antibodies might interfere with the anticoagulant action of DOACs, however no effect with rivaroxaban was observed in *in-vitro* studies which showed that aPL did not affect its anticoagulant action at peak or trough

levels, based on TG testing and anti-Xa levels [36]. This was predictable as rivaroxaban is a small molecule with high specificity and affinity for its target [53,59].

Observational data on the use of direct oral anticoagulants in antiphospholipid syndrome

Patients with aPL or APS were neither specifically included nor excluded from the phase 3 RCTs that demonstrated that DOACs are effective and safe compared with warfarin for the treatment and secondary prevention of VTE after a first VTE event or prevention of stroke or systemic embolism in patients with atrial fibrillation [8-11]. APS is classified as a rare disease in the USA [60]. Systematic reviews suggest that aPL are present in 10% of patients with deep vein thrombosis and 14% of patients with stroke [61], although this is not reflected in thrombotic APS patient numbers in clinical practice, suggesting likely underdiagnosis.

Data on antiphospholipid syndrome derived from phase 3 randomised controlled trials of direct oral anticoagulants in the general population

Dabigatran

A post hoc analysis of pooled data on patients with aPL (LA and/or aCL) from the RE-COVER, RE-COVER II and RE-MEDY studies was undertaken [62]. aPL testing was not mandatory, but when performed, the data were captured. Of 6,822 patients in the pooled analysis, 151 (2.2%) had LA and/or aCL at baseline. In aPL positive patients, there was no significant difference in VTE/VTE-related deaths or major or clinically relevant non-major bleeding events between the two treatment arms. However, this study was heavily underpowered.

Apixaban

In the AMPLIFY RCT of apixaban 5mg twice daily versus enoxaparin followed by warfarin target INR 2.5, relevant baseline risk factors for recurrent VTE included known thrombophilia: 74 (2.85%) patients in the apixaban arm and 59 (2.2%) patients in the enoxaparin followed by warfarin arm. No separate analysis on the safety and efficacy in this specific patient population was performed [63].

Edoxaban

The phase 3 ENGAGE-AF TIMI-48 AF study included one patient with aPL, one with APS and approximately five with SLE or other autoimmune disease [64].

Rivaroxaban

In the EINSTEIN Phase 3 clinical trial programme, adult patients with known thrombophilic conditions (antithrombin, protein C or S deficiency, factor V or prothrombin gene mutations, or aPL) were not excluded [65,66]. In the EINSTEIN DVT and PE pooled analysis patients had a mean age of 57.0 ± 17.0 years. A total of 5.9% of patients in the rivaroxaban group and 5.7% in the enoxaparin/VKA group, respectively, had a known thrombophilic disorder (6.2% vs 6.8% in EINSTEIN DVT [65] and 5.7% vs. 5.0% in EINSTEIN PE [66], respectively). The

relative primary efficacy and principal safety outcomes across the pre-specified subgroups (including the subgroup of patients with a known thrombophilic disorder) in the EINSTEIN DVT and the EINSTEIN PE studies were consistent with the observed overall effects.

Case series and cohort studies of direct oral anticoagulants in antiphospholipid syndrome

Case reports, series and cohort studies have reported on DOAC use in APS patients, with approximately 200 cases reported. Several authors have reported case series and cohort studies describing thromboembolism recurrence in APS patients switched from warfarin to a DOAC [67-72] (Table 1). Other case series report that DOAC use in thrombotic APS has been unassociated with recurrent thrombosis [73,74]; Sciascia et al, reported a case series of 36 patients with APS and VTE requiring standard intensity warfarin, who were switched to rivaroxaban 20mg once daily, and followed for a median of 10 (range 6-24) months. None of these patients had recurrent thrombosis [73]. These data, with their inherent limitations, including selection bias, lack of a comparator arm and in some studies, retrospective design, suggest that recurrent thrombotic events with DOACs in APS patients mainly occur when DOACs are used for secondary prevention of APS-related arterial or microvascular thrombosis, where DOACs are unlicensed and where many APS treaters use high-intensity anticoagulation [22], or in triple aPL positive APS patients (Table 1).

RAPS (Rivaroxaban for Antiphospholipid Syndrome Pilot Feasibility Study) prospective cohort study

The RAPS pilot feasibility study (ClinicalTrials.gov:NCT02116036) was a prospective cohort study for patients with confirmed APS and prior VTE, with or without prior arterial thrombosis, allocating them to receive rivaroxaban 20 mg daily. Patients were followed for thrombosis. Recruitment was closed on 30th September 2016 with a plan to follow all patients for one year. Seventy-nine patients were identified, with the recruitment target 150. Available information indicates that few complications, and no recurrent thromboses, occurred. One patient suffered unexplained hepatitis [7]. This study provides additional data on the efficacy and safety of DOACs in APS patients.

Randomised controlled trials of direct oral anticoagulants in antiphospholipid syndrome

A challenge in DOAC APS studies is ensuring sufficient statistical power. Trials with clinical outcomes are ideal, however, where APS trials with clinical outcomes have succeeded, numbers have been relatively small, 334 patients in 5 RCTs on treatment for APS-associated recurrent miscarriage in the meta-analysis by Mak et al [75], while trials with larger recruitment targets have proved challenging [76,77]. The appropriateness or otherwise, of the use of surrogate markers in clinical trials was considered in an editorial review by Svennson et al who, after supporting their use in fatal diseases like amyotrophic lateral sclerosis, went onto say they felt this approach was justified: “in the case of very rare diseases, (where) validation of hard end points may take an unreasonable time to complete” [78].

The characteristics and status of completed and recruiting RCTs of DOACs in thrombotic APS are summarised in Table 2.

RAPS: Rivaroxaban in Antiphospholipid Syndrome trial

The RAPS trial is the only completed RCT of DOAC use in APS patients. This phase 2/3 non-inferiority RCT compared rivaroxaban to warfarin (target INR of 2.5; range 2.0-3.0) to treat patients with previous VTE [79] on standard-intensity warfarin for at least three months after the last VTE. Warfarin-treated APS patients with previous VTE, with or without SLE, were randomized 1:1 to warfarin or rivaroxaban, 20 mg once daily, stratified by center and SLE/non-SLE.

The primary outcome measure was percentage change in ETP in the TG assay from randomisation to day 42, with treatment continued for 180 days and follow-up for 210 days. 116 patients were randomised, of whom 19% had SLE. When anticoagulation intensity was assessed by ETP alone, rivaroxaban was inferior to warfarin. However, peak thrombin generation was lower with rivaroxaban (Figure 1). Warfarin affects all phases of thrombin generation equally, whereas rivaroxaban directly inhibits factor Xa through specific binding to its active site [53,59] and mainly affects the initiation and propagation of thrombin generation leading to a delay in the formation of the prothrombinase complex [59]. Consequently, the TG curve becomes protracted, lengthening the lag time and time to peak TG [50,52], and leading to greater ETP than would be expected for the degree of anticoagulation [52]. RAPS concluded that, taking into account the altered reaction kinetics with rivaroxaban, the overall thrombogram indicated no difference in thrombotic risk. This conclusion was supported by in vivo coagulation activation marker concentrations (thrombin–antithrombin complexes, prothrombin fragment 1.2 and D-dimer) being slightly raised in few patients in both treatment groups. Furthermore, no new thrombotic events were seen during 6 months of treatment. No major bleeding episodes were noted. Clinically

relevant and minor bleeding rates were similar in the two groups. Quality of life was significantly improved in patients on rivaroxaban.

RAPS was not designed to confirm clinical efficacy and long-term safety. Rather, the trial was designed pragmatically with a laboratory surrogate outcome measure to assess the mechanism of action of the interventions in the two patient groups. Recurrent thrombosis in the APS population selected for RAPS is rare and a primary endpoint of recurrent thrombosis would necessitate several thousand patients and a follow up period of several years, which is impractical. The trial had an intended selection bias, ensuring a clinically homogenous study population with definite APS [1]. Patients who had VTE and developed recurrent VTE while taking standard-intensity anticoagulation (i.e. needing higher-intensity anticoagulation) and those with arterial events were excluded. The proportion of triple positive aPL patients included, 28%, was representative of VTE patients requiring standard-intensity anticoagulation in the investigators' APS population and consistent with the proportion in APS patients suggested in a large multicentre study [2]. The conclusions from the RAPS trial were generally supported by the independent expert comment [80].

Exploratory post-hoc analysis in the RAPS trial patients showed no significant interactions between the effects of rivaroxaban and LA positivity on TG. Coagulation proteases such as factor Xa can activate complement proteins. In a RAPS translational study, APS patients had significantly higher complement activation markers at baseline and day 42 compared to normal controls. Patients randomised to rivaroxaban showed a significant reduction in levels

of C3a, C5a, terminal complement complex [SC5b-9], with levels of Bb fragment, a marker of alternative complement pathway activation, unchanged. These results suggest that rivaroxaban may provide additional benefit to its anticoagulant effect in APS patients by limiting complement activation [81].

TRAPS: Rivaroxaban in Thrombotic Antiphospholipid Syndrome trial

The objective of the TRAPS multicentre phase 3 RCT is to demonstrate non-inferiority of rivaroxaban 20 mg (15 mg in patients with moderate renal insufficiency) once daily versus warfarin (target INR 2.5; range 2.0-3.0) with respect to cumulative incident thrombosis (arterial or venous) confirmed by imaging studies, major bleed, and death in triple aPL-positive APS patients. The trial plans to recruit 536 patients [7,82].

ASTRO-APS: Apixaban for The Secondary Prevention of Thrombosis among patients with Antiphospholipid Syndrome (ASTRO-APS) trial

The ASTRO-APS RCT is comparing apixaban with warfarin (target INR 2.5; range 2.0-3.0) for the secondary prevention of thromboembolism among patients with a history of APS and thrombosis [83]. ASTRO-APS was originally designed to compare apixaban 2.5 or 5 mg twice a day with warfarin, enrolling patients with a history of arterial or venous thromboses receiving indefinite anticoagulation. APS patients are categorized as having definite, likely or historic APS and therefore ASTRO-APS may include patients who do not meet the International Consensus Criteria for APS diagnosis [1]. After accrual of the first 25 patients, a

pre-specified Data Safety Monitoring Board (DSMB) review recommended the protocol be modified to use apixaban 5mg twice a day. In this context, patients with indications for long-term treatment with a VKA, such as aPL, were excluded from AMPLIFY-EXT in which a dose of 2.5mg twice daily was used [84]. After five more patients were enrolled, a potential safety signal led to an ad hoc DSMB re-review, which recommended continuing ASTRO-APS, excluding patients with prior arterial thrombosis; and undertaking brain magnetic resonance imaging with stroke protocol for all otherwise eligible candidates to exclude prior silent stroke. ASTRO-APS plans to enroll 200 patients [7,83].

RISAPS: Rivaroxban for Stroke Patients with Antiphospholipid Syndrome trial

The RISAPS open-label, phase 2/3 non-inferiority RCT [Chief Investigator H Cohen], funded by Arthritis Research UK (reference: 21517), will assess the efficacy of rivaroxaban versus warfarin in adult patients with APS, with or without SLE, who have ischaemic stroke or other ischaemic brain manifestations.

Use of direct oral anticoagulants in antiphospholipid syndrome patients in clinical practice

The RAPS trial suggests that rivaroxaban offers the potential to be an effective and convenient alternative to warfarin in thrombotic APS patients with a single VTE event requiring standard intensity anticoagulation [79]. Further studies, in particular, acquisition of better long-term efficacy and safety data, are needed before it can be widely recommended. Of note, the major phase 3 clinical trials that established the use of DOACs

versus warfarin for the treatment and secondary prevention of VTE used warfarin at a target INR of 2.5 (range 2.0–3.0) as the comparator. The optimal intensity of DOACs in patients who experience recurrent VTE on standard-intensity VKA, in whom it is usual to switch to high intensity VKA (target INR 3.5; range 3.0-4.0), is not established, therefore DOAC use should be avoided in such patients. The 15th International Congress on Antiphospholipid Antibodies Task Force on Treatment Trends Recommendations stated: "Insufficient evidence to make recommendations at this time regarding DOAC use in APS. The RAPS trial suggests that rivaroxaban might be useful in selected APS patients with single venous thrombosis requiring standard intensity anticoagulation; however, this needs to be confirmed with additional studies using clinical outcome measures" [7].

The case series and cohort studies of DOAC use in APS patients, suggest that recurrent thrombotic events with standard intensity DOACs in APS patients mainly occur when DOACs are used for secondary prevention of APS-related arterial or microvascular thrombosis [67-72], where DOACs are unlicensed [8-11]. We believe these patient groups should not be treated with DOACs until further trial data are available.

Practical clinical issues

The potential use of DOACs in APS patients requires comparative considerations as for their use in non-APS patients, including in those with renal or hepatic impairment, the elderly, or those on potentially interacting drugs, in accordance with the DOAC SPCs [8-11]. Drug interactions and the potential for gastrointestinal bleeding are of particular relevance in APS where an antiplatelet agent is considered in addition to anticoagulation, or in patients with

SLE or other autoimmune diseases where other drugs may be considered, including nonsteroidal anti-inflammatory drugs and steroids. Proton pump inhibitor cover is advisable. The optimal dosing strategy for DOACs in patients at extremes of body weight, >120 kg or <50 kg, has raised concern. Several studies, including a review of Phase 1-3 studies of rivaroxaban [85], measurement of rivaroxaban levels at various weight ranges [86] and a pharmacokinetic study [87], suggest that standard dose rivaroxaban can be used safely in patients of all weights, however, further data are required. International Society of Thrombosis and Haemostasis Scientific and Standardisation Committee (ISTH SSC) guidance recommends that DOACs should not be used for standard indications in obese patients, >120 kg, however, if used, to check drug-specific peak and trough levels. If the drug is within the expected range, the DOAC can continue, and if not, it should be switched to a VKA [88]. The management of bleeding in patients on DOACs is addressed elsewhere [89]. Idarucizumab, an antibody fragment which binds to and neutralizes dabigatran, is licensed for rapid reversal of dabigatran [90] and andexanet-alfa has been shown to be effective for reversal of factor Xa inhibitors [91].

While the use of warfarin offers the advantage that its regular monitoring helps to determine the degree of patient adherence, its many complications drive the need to assess alternative therapies. The development of DOACs now provides such alternatives, however, good adherence to anticoagulation is essential, particularly as the risk of thrombosis is compounded by the short half-lives of DOACs compared to VKAs. A systematic review indicated that poor adherence to INR monitoring on VKA is a risk factor for recurrent thrombosis following a switch to a DOAC [92] and therefore such a switch is probably best avoided where there is pre-existing poor adherence. Measurement of DOAC concentration

may be helpful in certain circumstances, including extremes of body weight and to confirm absorption, however, routine anticoagulant monitoring of DOAC levels is generally not practicable or feasible.

Women's health issues

There is a preponderance of women with APS, female to male ratio approximately 5:1, many of whom have thrombotic as well as obstetric APS [2]. Vaginal bleeding complications are a common complication of oral anticoagulation [93] and appear to occur more often with direct oral factor Xa inhibitors than with VKAs [94]. Beyer-Westendorf et al reported vaginal bleeding events in 57 of 178 women of reproductive age in the Dresden DOAC registry, with recurrent bleeding in 23%. Patients with anatomic abnormalities had more intense bleeding and more needed surgical treatment [95]. A proactive approach, with gynaecological input, is required. A temporary interruption or dose reduction of DOAC on days when bleeding is heaviest, can be sufficient to prevent recurrent heavy menstrual bleeding (HMB). A levonorgestrel intrauterine system (LNG-IUS Mirena) is the most effective medical intervention for HMB [96] and avoids potential thrombogenic effects of oral hormonal preparations. Tranexamic acid is an effective alternative or adjunct [96]. A switch to split dose LMWH may need consideration pending definitive gynaecological treatment.

The potential for reproductive toxicity of DOACs in humans, via maternal or paternal exposure, is undefined. Consequently, the DOAC SPCs recommend avoiding them during pregnancy and breast-feeding [8-11]. Limited data suggest embroyopathy occurs in

approximately 2% of women who experience DOAC exposure in pregnancy [97]. ISTH SSC guidance recommendations can be summarized as follows: (1) women of childbearing potential should receive documented counselling prior to commencement of DOACs; (2) should pregnancy be desired, the DOAC should be switched to an alternative anticoagulant pre-conceptually, with the main options being VKAs (to be switched to LMWH as soon as possible when pregnant and before 6 weeks of gestation), or LMWH, with cognizance that the latter may result in prolonged subcutaneous injections until pregnancy is achieved; (3) in women who become pregnant while on a DOAC, DOAC should be discontinued immediately and LMWH commenced; (4) inadvertent exposure to a DOAC would not in itself be regarded as medical grounds for termination of pregnancy; (5) in women who become pregnant while on a DOAC and who decide to continue with pregnancy, there should be early obstetric review and fetal monitoring; and (6) breast-feeding women should not be treated with DOACs [98]. The ISTH SSC guidance on DOACs in women of childbearing potential also recommends that all cases of DOAC exposure during pregnancy should be reported to the international ISTH registry to ensure consistency of data collection: http://www.survey-gizmo.com/s3/2394649/International-registry-of-pregnancy-during-NOAC-use-Inclusion.

Conclusions

The RAPS trial, that had a surrogate laboratory primary outcome measure, suggests that rivaroxaban offers the potential to be an effective and convenient alternative to warfarin in thrombotic APS patients with a single VTE event requiring standard intensity anticoagulation. However, further studies, in particular, acquisition of better long-term efficacy and safety data, are needed before it can be widely recommended. APS DOAC RCTs

with clinical primary outcomes represent the gold standard, however, a primary endpoint of recurrent thrombosis would require a larger sample size than has been achieved to date. APS patients are clinically heterogeneous, with the risk of recurrent thrombosis and the intensity of anticoagulation influenced by their clinical phenotype and risk profile. Thus, DOAC trials involving homogeneous thrombotic APS populations, with aPL status well defined, will help to optimise the appropriate treatment in APS patient subgroups. Ongoing and emerging RCTs should provide further information to guide the use of DOACs in APS. Optimal identification of APS patients merits attention as this is a key step in working towards improved therapeutic strategies in these individuals.

Addendum

H. Cohen wrote the first draft of the manuscript and was involved in collecting literature, interpretation of data and revising the manuscript. M. Efthymiou and D. Isenberg were involved in collecting literature, interpretation of data and revising the manuscript.

Disclosure of Conflict of Interests

H. Cohen reports receiving institutional research support and honoraria for lectures and Advisory Board from Bayer. The other authors state that they have no conflict of interest.

Table 1: Case series and cohort studies in which thrombotic antiphospholipid syndrome patients treated with direct oral anticoagulants developed recurrent thrombosis

	Case	Case	Case	Cohort[70]	Cohort[71]	Case

	Series [67]	Series [68]	Series [69]			Series [72]
Number of patients	8	12	23	26	56	19
Thrombosis history	VTE: 6 VTE+AT: 2	VTE: 10 VTE+AT: 2	VTE: 19 AT: 2 VT+AT: 1 CAPS: 1	VTE: 13 VTE+AT/MT: 4 AT: 9	VTE:19 AT:2 VTE+AT:1	VTE: 3 VTE+AT: 2 VTE+MT: 1
DOAC given: number of patients	R: 8	R: 12		R: 15 D: 11	R: 49 D: 4 A: 3	R: 17 D: 2
Systemic lupus erythematosus	0	4	5	9	33	NS
Outcome: DOAC given	5 VTE: R 2 VTE+AT: R 1 AT: R	2 VT: R	1 VTE: R	1 MT: NS	4 VTE: R* 1 SVT: R 1 AT: R	2 AT: D 1VTE+?AT: R 1 AT: R 1 MT: R
Time to thrombosis (months)	Median 3 (range 0.2-12)	5, 2	20	Median 10 (range 8-29)	Mean 46.7 (range 6-144)	Mean+/-SD: 23.3+/-22.3 (range 1-84)
Previous thrombosis history in patients who developed recurrent thrombosis on DOAC Triple aPL positivity in patients with recurrent thrombosis (where stated)	2/3 had previous AT; the third patient had previous VTE and was triple aPL positive	Both triple aPL positive	VTE+OM, triple aPL positive	Previous MT	2/6 had VTE+AT 4/6 were triple aPL positive	2/6 had previous AT 1/6 ad previous MT 2 others were triple aPL positive

Abbreviations: aPL, antiphospholipid antibodies; AT, arterial/transient ischemic attack; CAPS, catastrophic antiphospholipid syndrome; D, dabigatran; DOAC, direct oral anticoagulant; MT, microvascular thrombosis; NS, not stated; OM, obstetric morbidity; r, range; R, rivaroxaban 20 mg once daily; SVT, superficial vein thrombosis; triple aPL positive, presence of lupus anticoagulant + IgG/IgM anticardiolipin + IgG/IgM anti-β2 glycoprotein 1 antibodies; VT, venous thromboembolism; *nonadherence

Table 2: Characteristics and status of completed and recruiting randomised controlled trials of direct oral anticoagulants in thrombotic antiphospholipid syndrome

	RAPS [79]	TRAPS [7,82]	ASTRO-APS [7,83]
Chief Investigator	H Cohen	V Pengo	S Woller
Study design	Phase 2/3 RCT	Phase 3 RCT	Phase 2/3 RCT
Number of patients	116	536	200
APS subgroups	Previous VTE, target INR of 2.5; no thrombosis >3 m; patients with arterial thrombosis excluded	Triple positive thrombotic APS; arterial, venous, and/or biopsy-proven microthrombosis	Thrombotic APS VTE target INR 2.5; no thrombosis >6 m; definite, likely or historic APS
Intervention	Rivaroxaban 20 mg od vs. warfarin target INR of 2.5	Rivaroxaban 20 mg od vs. warfarin target INR of 2.5	Apixaban 2.5 mg or 5 mg bd vs. warfarin target INR of 2.5
Primary outcome(s)	Thrombin generation - endogenous thrombin potential (ETP)	Thrombosis - arterial or venous Major bleeding Death	Thrombosis - arterial and/or venous Bleeding
Duration of recruitment	Jun 13 – Nov 14	Dec 14 – Dec 18	Feb 15 - ongoing
Status	Completed and results published	Ongoing	Ongoing: protocol modified after potential safety signal (see text)

Abbreviations: ASTRO-APS, Apixaban for the Secondary Prevention of Thromboembolism Among Patients with AntiPhospholipid Syndrome (ClinicalTrials.gov:NCT02295475) ; bd, twice daily; m, months; od, once daily; RAPS, Rivaroxaban in Antiphospholipid Syndrome (ISRCTN68222801); RCT, randomized controlled trial; TRAPS, Rivaroxaban in Thrombotic Antiphospholipid Syndrome (ClinicalTrials.gov:NCT02157272)

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Figure 1: RAPS (Rivaroxaban in Antiphospholipid Syndrome) trial thrombograms for median (25th and 7th percentiles) ETP values in patients on warfarin (A) or rivaroxaban (B) compared with a typical normal control value [79]