Direct oral anticoagulants for thromboprophylaxis in patients with antiphospholipid syndrome

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ABSTRACT

The current mainstay of the treatment and secondary thromboprophylaxis of thrombotic APS is anticoagulation with warfarin or other vitamin K antagonists (VKAs). In addition to their well known limitations, VKAs are often problematic in APS patients because of the variable sensitivity of thromboplastins to lupus anticoagulant. As a result, the International Normalised Ratio (INR) may not accurately reflect the intensity of anticoagulation. Direct oral anticoagulants (DOACs) are established as therapeutic alternatives to VKAs for a wide range of indications, including the treatment and secondary prevention of venous thromboembolism. Definition of the role of DOACs in the treatment of thrombotic APS is emerging with the results of recent and ongoing clinical studies. This review focuses on the current situation with regard to DOACs for secondary thromboprophylaxis in APS and issues pertinent to DOAC use in APS patients, as well as potential future directions.

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

INTRODUCTION

Thrombotic antiphospholipid syndrome (APS) is clinically heterogenous, with thrombotic manifestations spanning a broad spectrum. These encompass mild to potentially life-threatening episodes, including refractory thrombosis despite adequate anticoagulation and the rare catastrophic APS. Thrombosis may occur in one or more of any vascular sites - venous, arterial or microvascular.

The current mainstay of the treatment and secondary thromboprophylaxis of thrombotic APS is anticoagulation with warfarin or other vitamin K antagonists (VKAs) [1]. However, treatment with VKAs is often problematic. Warfarin, the most widely used VKA worldwide, has a slow onset of action of several days, a narrow therapeutic window, numerous drug and dietary interactions, the potential for variation of action with alcohol, intercurrent illness, exercise and smoking, and requires regular blood test monitoring of the International Normalised Ratio (INR).

Direct oral anticoagulants (DOACs) provide an effective, safe and convenient therapeutic alternative to warfarin and other VKAs and are becoming the standard of care for a wide range of indications [2-5]. Definition of the role of DOACs in the treatment of thrombotic APS is emerging with the results of recent and ongoing clinical studies. This review focuses on the current situation with regard to DOACs for secondary thromboprophylaxis in APS and issues pertinent to DOAC use in APS patients, as well as potential future directions.

ANTIPHOSPHOLIPID SYNDROME

Definition of antiphospholipid syndrome

APS is defined as the presence of thrombosis (venous, arterial, microvascular or a

combination of these) and/or pregnancy loss or late obstetric morbidity in association with persistently positive antiphospholipid antibodies (aPL), i.e. present on two or more occasions at least 12 weeks apart. APS may occur in isolation or in association with other conditions, notably systemic lupus erythematosus (SLE). aPL are heterogeneous, with current laboratory criteria for diagnosis of APS based on the presence of one or more of lupus anticoagulant (LA), IgG and/or IgM anticardiolipin antibodies (aCL) and anti-β2 glycoprotein-I (aβ2GPI) antibodies [6].

Clinical relevance of thrombotic antiphospholipid syndrome.

Thrombotic APS is of major clinical relevance, particularly because thrombotic events may be potentially devastating and life-threatening and it mainly affects relatively young individuals: in a cohort of 1000 patients (over 70% with thrombotic manifestations), although the age range at the onset of symptoms was wide (0-81 years), the median age was 31 years, with 85% of patients diagnosed to have APS between 15 and 50 years [7]. APS is classified as a rare disease [8], however it has been estimated that aPL are present in approximately 10% of patients with deep vein thrombosis (DVT) and 14% of all patients with stroke [9]. These are both conditions that are potentially life-threatening with major impact on health. Given that there are an estimated 10 million new venous thromboembolism (VTE) cases and 17 million new stroke cases worldwide each year [10;11], the estimated prevalence figures may imply that APS is underdiagnosed and is more common than may be appreciated. In addition, 15% of patients with SLE have thrombotic APS, which is a major adverse prognostic factor [12]. Appropriate management of thrombotic APS is vital to minimize its deleterious impact.

Anticoagulation for thrombotic antiphospholipid syndrome

Venous thromboembolism

Retrospective studies have shown a high incidence of thrombosis recurrence in patients with aPL [13-15]. In these studies, 80/147 [15], 39/70 [14] and 23/61 [13] had VTE. In the prospective Duration of Anticoagulation (DURAC) study on 412 patients with VTE, a single aCL positive test doubled the risk of a recurrence in the first six months after cessation of anticoagulation: 29% (20 of 68) in patients with aCL and 14% (47 of 334) in patients without aCL (P = 0.0013), for a risk ratio of 2.1 (95% CI 1.3 to 3.3). It should be noted that the study included patients defined to have low positive aPL (5 to 35 GPL units): the risk of recurrence in this group was 28% (17 of 60)) and 38% (3 of 8) in patients with moderate or high positive aCL (defined as >35 GPL units) [16].

It takes about three months to complete "active treatment" of VTE, with further treatment aimed at prevention of new episodes of thrombosis ("secondary prevention") [17;18]. The risk of recurrent VTE is significantly higher after an unprovoked episode [19], and in patients with unprovoked proximal deep venous thrombosis (DVT) or pulmonary embolism (PE), where there is low or moderate bleeding risk, extended anticoagulant therapy is advised by the American College of Chest Physicians (ACCP) [18]. The decision to continue anticoagulation indefinitely after a first unprovoked proximal DVT or PE is strengthened if the patient is male, the index event was PE rather than DVT, and/or D-dimer testing is positive one month after stopping anticoagulant therapy [17;18].

The paucity of robust prospective data on the influence of aPL status on VTE recurrence in patients with unprovoked or provoked VTE does not enable definitive evidence based recommendations for those whom to test for aPL after a VTE episode or the duration of anticoagulation in individuals with persistent aPL who have had an episode of VTE,

unprovoked or provoked. Thrombotic APS is clinically heterogeneous, with the risk of recurrent thrombosis and intensity of anticoagulation required dependent on the clinical phenotype. A particularly high risk group is triple positive APS patients (who have LA, aCL and aβ2GP1 antibodies). The risk of recurrent thrombosis, both venous and arterial, is high in such patients - 45% over 6 years - despite standard intensity anticoagulation (INR 2.0-3.0) [20]; therefore, aPL testing would be expected to at least identify this triple positive thrombotic APS subgroup where anticoagulation could potentially prevent recurrent thrombosis.

Untreated thrombotic APS may result in further thrombotic episodes, arterial or venous, which may be potentially life-threatening or have major adverse impact on health. A pragmatic approach, in view of the potentially severe potentially life-threatening consequences of thrombotic APS, including in patients with SLE, is to undertake aPL testing in all patients with a first unprovoked DVT or PE, with consideration of extended duration anticoagulation in all those identified to have APS. 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.

Ischaemic stroke and cerebral ischaemic lesions in APS patients

Retrospective and observational studies suggest that ischaemic stroke in APS patients carries a high risk of recurrence and should be treated with life-long warfarin. In a systematic review of 16 studies on secondary thromboprophylaxis in patients with aPL [21], ten studies reported the INR measured at the time of recurrent thrombotic events [13;14;22-28].

In three additional studies, thrombotic events occurred only among patients who were not receiving anticoagulant treatment [16;29;30]. Of the 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 with only 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 [21].

There is a lack of well-designed prospective studies to guide optimal antithrombotic treatment in APS patients with ischaemic stroke or cerebral ischaemic lesions. The risk of bleeding with increasing anticoagulant intensity needs to be balanced against the risk of profound permanent disability and death, or irreversible neurological deterioration as a result of recurrent stroke.

Three major prospective studies have addressed the key issue of the optimal antithrombotic treatment for stroke patients with aPL, however, these have major limitations as regards informing definitive conclusions on the use or intensity of anticoagulation. Crowther *et al* [24] and Finazzi *et al* [31] 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, in both studies patients with recurrent thrombosis while on therapeutic anticoagulation or with arterial thrombosis were poorly represented, with the latter comprising only 24% and 32% of a total of 114 and 109 patients, respectively. Notably, patients in the high-intensity INR arm had INR values below the target range of 3.1-4.0 for over 40% of the follow up time. In addition, six of eight recurrent thrombotic events (six in the high-intensity and two in the standard-intensity group) in the study by Crowther *et al* [24] occurred either while the INR was <3.0 (five out of

six patients) or while off warfarin (the sixth patient had not taken warfarin for 137 days before the recurrent event); 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* did not report on this issue [31].

A third study, the Antiphospholipid Antibodies and Stroke Study (APASS), 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 [32]. In the general stroke and TIA population, aspirin plus dipyridamole, or clopidogrel alone, are superior to aspirin alone[33]. APASS participants were those in the WARSS study who also consented to enrol in APASS, with usable baseline blood samples, drawn prior to randomization to WARSS and analysed for aPL status within 90 days of the index stroke by a central independent laboratory. However, laboratory criteria for aPL were not compliant with the international consensus criteria for a diagnosis of APS [6] as aPL testing was done only on a single occasion and persistence of aPL was not established. Approximately 50% of patients had low positive aCL, which do not appear to be relevant in the context of thrombosis [6]; and in 25% of aCL positive patients the presence of IgA aCL, which is not a recommended criterion for APS diagnosis [6], was stated to denote aPL positivity. In addition, aβ2GPI levels were not measured, so that some APS patients were not identified, as isolated aβ2GPI do occur in a proportion of APS patients, reported to be approximately 30% in one study [34]. The results of these three prospective studies do not, therefore, enable valid conclusions about the optimal antithrombotic treatment in APS, in particular in ischaemic stroke patients with APS.

The lack of robust data on the optimal anticoagulant intensity in ischaemic stroke patients with APS is reflected in national and international guidelines: current British Committee for Standards in Haematology (BCSH) [35] and ACCP guidelines [36] or 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 Antiphospholipid Antibodies 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 (range 2.0–3.0)) therapy [37]. This suggestion was a non-graded recommendation due to lack of consensus within the Task Force, and many physicians treating APS patients use high-intensity warfarin (target INR 3.5) for APS patients with ischaemic stroke, cerebral ischaemic lesions or arterial thrombosis in other sites.

VITAMIN K ANTAGONISTS FOR THE TREATMENT OF ANTIPHOSPHOLIPID SYNDROME

Anticoagulation with warfarin, or other VKAs, is the current mainstay of the treatment and secondary thromboprophylaxis of thrombotic APS. VKAs may present particular problems in patients with APS. First, VKA monitoring in patients with aPL can be complicated by the variable responsiveness of thromboplastin reagents to LA, which may in turn potentially influence the validity of the prothrombin time (PT) –INR in monitoring oral VKA treatment in patients with APS. A multisite study of laboratory INR testing in patients with APS concluded that LA interference with the PT-INR measured with the majority of commercial thromboplastins is not enough to cause concern if insensitive thromboplastins, properly calibrated to assign them an instrument-specific International Sensitivity Index (ISI) are used. The investigators also suggested that new thromboplastins, especially those made of

relipidated recombinant human tissue factor, should be checked to ensure that they are insensitive to the effects of aPL before they are used to monitor oral anticoagulant treatment in patients with APS [38]. Whilst these procedures are generally routine in specialist centres, they may not be as easily undertaken in other institutions and thus as a result the INR may not accurately reflect the true degree of anticoagulation. The variable responsiveness of aPL to LA can result in instability of the INR, which necessitates frequent anticoagulant monitoring with the attendant inconvenience to the patient, adverse impact on quality of life and increased costs. It may also be associated with potential thrombotic or bleeding complications. A systematic review reported that approximately 2.8% of APS patients on VKA had recurrent thrombotic events, and bleeding rates of up to 10% per year [21]. Secondly, LA detection in patients on warfarin may be problematic because of the prolonged basal clotting time [39]. This restriction limits the ability to diagnose APS in patients on VKA and complicates monitoring of aPL status in those with an established diagnosis. The limitations of warfarin and other existing anticoagulants have driven a search for alternative anticoagulant options.

DIRECT ORAL ANTICOAGULANTS (DOACs)

Currently available DOACs include dabigatran etexilate (Pradaxa®), a direct thrombin inhibitor, and apixaban (Eliquis®); edoxaban (Lixiana®) and rivaroxaban (Xarelto®), direct factor Xa inhibitors [2-5]. DOACs are established as therapeutic alternatives to VKAs, and are becoming the standard of care for a wide range of indications, detailed in the summary of product characteristics (SPC) [2-5]; 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 non-valvular atrial fibrillation; and acute

coronary syndromes. DOACs, in contrast to VKAs, are at a fixed dose with predictable effect, therefore do not require regular anticoagulant monitoring. They also have a rapid onset of action thus do not require bridging anticoagulation with LMWH at the initiation of anticoagulation. In addition, they are not affected by changes in diet and alcohol intake and have fewer drug interactions than VKAs that affect anticoagulant intensity [40-42], which would be expected to result in improved quality of life for patients. (Table 1 summarises the differential pharmacology and pharmacokinetics of DOACs).

Safe DOAC administration requires special consideration in several populations of individuals, including those with renal or hepatic impairment, extremes of body weight, the elderly, or those on potentially interacting medication through which DOACs are metabolised [2-5]. Drug interactions and the potential for gastrointestinal bleeding are pertinent in some APS patients where an antiplatelet agent is considered in addition to anticoagulation, or in those with SLE or other autoimmune diseases where a variety of other drugs may be considered, including non-steroidal anti-inflammatory drugs (NSAIDs). These situations and the use of DOACs in women of childbearing potential are addressed below. Other considerations in the use of DOACs include the management of bleeding and reversal of anticoagulant effect, which are the same as for non-APS patients, and are addressed elsewhere [43;44].

Drug interactions

One of the advantages of DOACs is that compared to VKAs such as warfarin, fewer drug interactions are believed to exist. A consequence of this however, is that unlike VKAs, the anticoagulant effect cannot routinely be monitored when a potentially interacting drug is

co-prescribed. Clear contraindications exist for certain drug-drug combinations (e.g. systemic ketoconazole or itraconazole with dabigatran), while the concurrent use of other drugs is generally best avoided (e.g. rifampicin, carbamazepine, phenytoin). Some potential interactions may become clinically relevant in certain situations:factors that may increase DOAC plasma levels and therefore increase the risk of bleeding could include for example, two or more potentially interacting drugs, renal impairment, frail elderly, acute illness and low body weight. Management strategies should include the review of DOAC dose and agent or even the temporary cessation of DOAC, e.g. in acute illness where renal function hasor may deteriorate. Where ongoing potential drug interactions with additional risk factors exist, it may be prudent to use VKA rather than a DOAC.

Gastrointestinal bleeding

Gastrointestinal bleeding (GIB) causes considerable morbidity and mortality (5%–15%) and contributes greatly to health care use [45]. APS patients, particularly those with SLE or other autoimmune diseases may be prescribed steroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or antiplatelet agents, all of which could potentially increase the risk of gastrointestinal side effects, including GIB. The addition of an anticoagulant would therefore be expected to increase the risk further, but in this respect warfarin and DOACs do not necessarily demonstrate equivalent risks.

The four pivotal DOAC trials in non-valvular atrial fibrillation (NVAF) [46-49] contained a common comparator (adjusted dose warfarin, target INR 2.5), allowing indirect comparison of the relative impact of DOACs on GIB. It should be noted that there were differences in the study populations and definitions of major bleeding events, thus limiting the robustness of such comparisons. Rivaroxaban and dabigatran 150mg bd increased the risk of major GI

bleeding approximately 1.5 fold compared to warfarin, whereas the risk associated with dabigatran 110mg bd or apixaban was comparable. The risk of GIB was higher with edoxaban 60mg OD vs. warfarin, but lower with 30mg OD. Dyspepsia was significantly more common with both dabigatran 150mg and 110mg bd compared to warfarin (11.3%, 11.8% and 5.8% respectively). Major GI bleeding was significantly lower for all patient groups in the VTE trials [50-54] compared to the NVAF trials [46-49], perhaps highlighting the difference in patient populations and associated risk factors for bleeding.

It should be noted that the pivotal trials of DOAC use in NVAF and VTE treatment or prevention excluded patients thought to be at a higher risk of gastrointestinal complications. Use of DOACs in daily clinical practice, often in higher risk individuals with multiple co-morbidities, would therefore be expected to influence the incidence of GI adverse events. Where possible, the additional use of drugs with known GI toxicities (e.g. NSAIDs, antiplatelets, steroids etc) should be avoided, but if this is not possible then a potentially "lower risk" DOAC should be selected and the dose optimised; the co-prescription of a proton pump inhibitor for gastroprotection is advised in this situation.

DOACs in relation to pregnancy and lactation

Animal studies have shown DOAC-related reproductive toxicity and secretion into milk [5]. The potential for reproductive toxicity of DOACs in humans is unknown, and there are no substantive data on the use of DOACs in pregnant women via maternal or paternal exposure. Consequently, the DOAC SPCs recommend against their use in pregnancy and during breast-feeding [2-5]. Many women receiving DOACs for VTE are in their reproductive years and may become pregnant while on DOAC therapy. Guidance is available from the

International Society of Thrombosis and Haemostasis (ISTH) [55]. The key recommendations can be summarised as follows: a) women of childbearing potential should receive documented counselling prior to commencement of DOACs; b) should pregnancy be desired, the DOAC should be switched to an alternative anticoagulant pre-conceptually, with the main alternative anticoagulant options be VKAs (to be switched to LMWH as soon as possible when pregnant and before six weeks of gestation), or LMWH, with cognisance that the latter may result in prolonged subcutaneous injections until pregnancy is achieved; in women who become pregnant while on a DOAC, DOAC should be discontinued immediately and LMWH commenced; d) inadvertent exposure to a DOAC would not in itself be regarded as medical grounds for termination of pregnancy - this is supported by limited pregnancy outcome data on DOAC exposure during pregnancy in 137 women [56]; e) 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; f) breast-feeding women should not be treated with DOACs [55]. The ISTH guidance on DOACs in women of childbearing potential also recommends that clinicians should collect data on the course and outcomes of pregnancy after DOAC exposure and report these to DOAC manufacturers and responsible health and regulatory authorities, to improve knowledge on potential risks and harms; all cases of DOAC exposure during pregnancy should be reported to the international ISTH registry to ensure consistency of data collection [55]:

http://www.surveygizmo.com/s3/2394649/International-registry-of-pregnancy-during-NOAC-use-Inclusion.

DIRECT ORAL ANTICOAGULANTS (DOACs) FOR SECONDARY THROMBOPROPHYLAXIS IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

It is likely that patients with thrombotic APS were included in the study populations in the major phase 3 clinical trials of DOACs versus warfarin in patients with VTE [2-5;51-54]. However, aPL status was not systematically documented in these trials, so confirmation of the utility of DOACs in secondary prevention of VTE in APS is required.

Anecdotal clinical reports and case series on DOAC use in patients with thrombotic APS

Anecdotal clinical reports and case series have reported on DOAC use in APS patients, with approximately 100 cases reported at the time of writing this review. Several have suggested thromboembolism recurrence following switching APS patients from warfarin to a DOAC. Schaefer et al reported one patient who developed thrombotic endocarditis with symptomatic cerebral emboli after switching from warfarin to dabigatran; and two cases of thrombosis, one with ischemic arterial strokes and right transverse-sigmoid sinus thrombosis, and the second with porto-mesenteric VTE, after switching from warfarin to rivaroxaban 20mg daily. Two of the three patients reported had previous arterial events (cerebral infarction and radial artery thrombosis) [57]. Win and Rodgers reported three cases of recurrent thrombosis in patients with APS after switching from warfarin to NOAC; two patients had superficial VTEwhile on rivaroxaban 20mg daily (one of these patients had previous transient ischaemic attacks (TIAs) and stroke) and one patient who was taking dabigatran developed recurrent TIA [58].

Son et al reported that two out of 12 patients developed recurrent VTE after switching from warfarin to rivaroxaban 20mg daily [59]. These treatment failures occurred in patients with SLE combined with triple aPL positivity that has been demonstrated to be associated with a very high risk of recurrent thrombosis, despite anticoagulation [20]. Noel et al reported on 26 APS

patients (14/26 had associated autoimmune disease, SLE in seven cases) enrolled in a French multicenter observational cohort, treated with DOACs for a median duration of 19 months [60]. In four patients the therapy was discontinued due to: one relapse of arterial thrombosis, two bleeding events (hypermenorrhoea and rectal bleeding on rivaroxaban) and one recurrent migraine. The conclusion of this study was that DOACs might be an alternative therapeutic option in APS and that prospective studies are warranted to evaluate their safety in this condition [60]. Signorelli et al reported failure of thrombosis prevention in eight APS patients; three of these patients had a previous history of arterial thrombosis (renal infarction, mesenteric ischaemia and stroke) [61]. The Antiphospholipid Syndrome Alliance for Clinical trials and International Networking (APS ACTION) group analysed DOAC use among 19 (17 on rivaroxaban and 2 on dabigatran) of 428 thrombotic APS patients, with a mean follow up of 23 (range 1-84) months. Recurrent thrombotic events were reported in six of these patients; three had previous arterial events (one microthrombosis and two arterial thrombosis) and two others were triple positive APS patients [62].

There are also reports of DOAC use in thrombotic APS unassociated with recurrent thrombosis. Scascia et al reported a series of 35 patients with APS, 24 with a history of previous DVT and 11 with DVT and PE. All had been on VKA, target INR 2.5; those requiring a higher target INR were excluded. The indication for switching from VKA to rivaroxaban for secondary prevention of VTE was erratic INR. There was no VTE recurrence, major bleeding or serious side-effects over a median follow up of 10 (range 6-24) months [63]. Betancur et al reported on eight patients with APS that switched from warfarin (after treatment for a mean of 71 (range 17-153) months to rivaroxaban 20mg OD. None of these patients had recurrent thrombosis on rivaroxaban over a mean follow up period of 19 (range 2-36)

months. Three of these patients had previous arterial events: recurrent TIA, stroke and common femoral artery thrombosis [64]. Bachmeyer and Elalamy reported a patient with recurrent superficial lower limb thrombophlebitis who did not experience any recurrence on rivaroxaban 20mg OD [65].

These anecdotal reports and case series, with recognition of their inherent limitations, nevertheless suggest that recurrent thrombotic events with DOACs in APS patients mainly occur when DOACs are used for APS-related arterial thrombosis (where DOACs are unlicensed) and where many APS treaters use high-intensity anticoagulation, or in APS patients with triple aPL positivity. They highlight the need for randomised controlled trials (RCTs) to guide the use of DOACs in thrombotic APS.

RAPS (Rivaroxaban in Antiphospholipid Syndrome) Trial

RAPS (Rivaroxaban versus warfarin in patients with thrombotic antiphospholipid syndrome, with or without SLE: a randomised, controlled, open label, phase 2/3, non-inferiority trial), included APS patients on warfarin for previous VTE, target INR 2·5 (range 2.0-3.0) (ISRCTN68222801; http://www.ucl.ac.uk/cctu/researchareas/other/othertrials) [66;67].

Participants were randomised 1:1 to warfarin or rivaroxaban 20mg daily, at two UK hospitals, stratified by centre and patient type (SLE/non-SLE). The primary outcome measure was percentage change in endogenous thrombin potential (ETP), a thrombin generation test parameter, from randomisation to day 42, with rivaroxaban non-inferior if the percentage change in ETP was not more than 20% higher than for warfarin. Other thrombin generation parameters, markers of *in vivo* coagulation activation (prothrombin fragment F1.2, thrombin-antithrombin complex and D-dimer), thrombosis and bleeding

were also assessed [66,67].

Thrombin generation

Thrombin is a pivotal component of the haemostatic mechanism, with thrombin generation (TG) via the tissue factor pathway been integral to blood coagulation [68]. The TG assay, a global assay, measures the overall tendency of a plasma sample to form thrombin after initiation of coagulation. The thrombin generation curve is quantified in terms of the lag time, time to peak, peak thrombin and endogenous thrombin potential (ETP), the area under the thrombin generation curve [69]. The ETP, a key parameter of TG, is derived from the end amount of free thrombin produced and incorporates all phases from activation to final endpoint [70].

In recent years TG testing has increasingly been transformed from a research only tool to a useful and sensitive assay for clinical use for haemophilias [71;72], and with the ETP identified having predictive value for the development of recurrent VTE [73-76]. TG might be an assay of particular importance in APS, as it has been shown to be informative in regard to APS status and identification of LA [77;78].

TG testing has been used to assess the inhibitory effects of anticoagulants with the ETP demonstrated to provide a good measure of anticoagulant intensity in both patients with APS and non-APS [79;80]. Warfarin has been shown to reduce ETP by 30%–50% [81;82]. Direct FXa inhibitors such as rivaroxaban can downregulate and completely suppress the process of TG in whole blood, platelet-rich plasma [83;84] and platelet poor plasma [85;86]. The ETP has been shown to be an appropriate measure of the intensity of the anticoagulant effect in patients receiving rivaroxaban for VTE prophylaxis and rivaroxaban-treated healthy normal subjects

[80;87-89], and other DOACs such as dabigatran and apixaban also inhibit TG [90-93].

RAPS results and conclusions

One-hundred and sixteen patients were randomised. At day 42 the ETP was significantly higher on rivaroxaban, indicating rivaroxaban was inferior to warfarin. However, peak thrombin was significantly lower on rivaroxaban. Clinical outcomes over six months treatment showed no thrombosis or major bleeding and there were no differences in clinically relevant or minor bleeding in the two groups. Quality of life assessment showed a small but significant improvement on rivaroxaban. The overall thrombogram and clinical outcomes suggest that APS patients with previous VTE who require standard intensity warfarin (i.e. target INR 2·5), had no increase in thrombotic risk on rivaroxaban compared to warfarin. This conclusion is supported by the *in vivo* coagulation activation markers, which were elevated in only a minority of patients in both arms. Rivaroxaban thus may offer an effective and safe alternative to warfarin in this APS patient subgroup. The trial was designed with a laboratory surrogate outcome measure, since this reflects the mechanism of action of the interventions in these patients. A trial with a primary end point of recurrent thrombosis would require a much larger sample size of several thousand patients, unfeasible in this patient group, with a much longer follow up period. There was an intended selection bias: patients with VTE who developed recurrent events while on standard intensity anticoagulation and thus required higher intensity anticoagulation were excluded, as were patients with arterial events [66].

The absence of new thrombotic events during six months treatment in RAPS justifies selection of this APS subgroup and puts into context anecdotal case reports and small case series, of recurrent thrombosis after switching APS patients from warfarin to a DOAC.

Notably, almost one-third of the RAPS patient population, (28%), had triple positive aPL at baseline, so RAPS included many patients with a particularly high-risk aPL profile [20,66].

Both rivaroxaban and warfarin inhibit TG in non-APS patients compared to normal controls [80], indicative of effective anticoagulation. However, the mechanism of TG inhibition of these two agents differs: warfarin inhibits TG by reducing functional vitamin K-dependent coagulation factor levels, while rivaroxaban directly inhibits FXa through specific binding to its active site [84;94]. Warfarin therefore affects all TG parameters equally, whereas rivaroxaban mainly affects the initiation and propagation phases of TG with delay in formation of the prothrombinase complex [89]. As a result, rivaroxaban induces protraction of the TG curve, which in turn results in prolonged lag time and time to peak,[80;89] and also a relatively greater ETP than would be expected for the degree of anticoagulation with rivaroxaban [80]. This is depicted in Figure 1 and reflected in the RAPS results [66]. The higher ETP on rivaroxaban is thus explained by altered reaction kinetics, with the overall thrombogram indicating no increase in thrombotic risk. This conclusion has been demonstrated clinically in the major phase 3 DOAC RCTs [2-5;50-54], which are likely to have included a proportion of APS patients [9]. The ETP and peak thrombin findings in RAPS patients at day 42 can be attributed to anticoagulant rather than aPL effects. This is supported by observations that aPL effects on TG parameters *in vitro* are limited to prolongation of lag time and time to peak [95]. aPL could potentially interfere with the anticoagulant action of DOACs, however we have demonstrated in *in vitro* studies that this is not the case, based on aPL positive IgG spiking of PNP on rivaroxaban's anticoagulant action on thrombin generation or rivaroxaban anti-Xa levels [95].

Ongoing studies of direct oral anticoagulants in thrombotic antiphospholipid syndrome

Ongoing DOAC studies include two randomised controlled trials (RCTs): TRAPS (Rivaroxaban in Thrombotic Antiphospholipid Syndrome; ClinicalTrials.gov: NCT02157272) and ASTRO-APS (Apixaban for the Secondary Prevention of Thromboembolism Among Patients With the AntiphosPholipid Syndrome; ClinicalTrials.gov: NCT02295475); and a subsequent study also entitled RAPS (Rivaroxaban for Antiphospholipid Syndrome; ClinicalTrials.gov: NCT02116036), a phase 4 pilot feasibility study. The salient features of our completed RAPS trial (ISRCTN68222801) [66,67] and these ongoing studies are summarised in Table 2.

Lupus anticoagulant testing in the presence of direct oral anticoagulants

False positive DRVVT may occur in rivaroxaban-treated patients, mainly at peak therapeutic levels. The Taipan venom time (TVT)/Ecarin clotting time (ECT) ratio and Textarin time are not affected, irrespective of the rivaroxaban levels, enabling detection of LA in patients receiving rivaroxaban. In thrombotic APS patients treated with rivaroxaban, the TVT/ECT appears reliable even at peak therapeutic plasma levels of rivaroxaban. The DRVVT may be acceptable at trough rivaroxaban plasma levels, in samples taken at least 18 hours following the previous dose of rivaroxaban. However, a rivaroxaban anti-Xa assay should be done in parallel to ensure a trough level [95-98].

CONCLUSIONS AND FUTURE DIRECTIONS

Much progress has been made with regard to the use of DOACs in patients with thrombotic APS. The RAPS trial and ongoing studies will provide a wealth of information to help us define the role of DOACs in these patients. It should be appreciated that 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. It follows that the optimal dose of DOACs in patients who experience recurrent VTE whilst on standard intensity VKA is not established. The RAPS trial results are not applicable to APS patients with VTE who require higher intensity anticoagulation (i.e. those with recurrent VTE while on standard intensity anticoagulation) or APS patients with stroke or other arterial thrombosis.

Studies are required to define the role of DOACs, including with regard to optimal anticoagulation intensity, in APS patients with stroke or cerebral ischaemic lesions, as well as arterial thrombosis in other sites, where DOACs are currently unlicensed.

Addendum

Hannah Cohen, Maria Efthymiou, Carolyn Gates and David Isenberg were involved in collecting literature, interpretation of data and revising the manuscript.

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Disclosure of Conflict of Interests

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Table 1: Differential pharmacology and pharmacokinetics of direct oral anticoagulants
Comments within the table relate specifically to venous thromboembolism

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Mode of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Bioavailability	Approx 7%	Approx 50%	Approx 62%	Approx 66% in absence of food[a]; ≥80% in presence[a,b]
Time to	0.5-2 hours	3-4 hours	1-2 hours	2-4 hours

Peak levels				
Approximate half-life	13 hours (CrCL>80mL/min)	12 hours	10-14 hours	5-9 hours (young) 11-13 hours (elderly)
Metabolism	• Not metabolised by CYP450 • Dabigatran etexilate is a substrate of the efflux transport protein P-gp	• Mainly metabolized by CYP3A4/5 • Substrate of the efflux transport proteins P-gp and BCRP	• CYP3A4/5 weekly involved with metabolism (<10%) • Substrate of the efflux transport protein P-gp	• Metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms • Substrate of the efflux transport proteins P-gp and BCRP
% dose renally eliminated	85%	27%	35% renal	66% (half as inactive metabolite)
Drug interactions	Strong P-gp inhibitors or inducers	Strong inhibitors/ inducers of both CYP3A4 and P-gp pathways	Strong P-gp inhibitors or inducers	Strong inhibitors / inducers of both CYP3A4 and P-gp pathways
Standard VTE treatment dose and prevention of recurrence *(refer to SPC for dosing in NVAF)*	Acute VTE: Other parenteral agent for at least 5 days, then 150mg bd	Acute VTE: 10mg bd for 7 days, then 5mg bd. Prevention of recurrence after 6mths treatment: 2.5mg bd	Acute VTE: Parenteral agent for at least 5 days, then 60 mg od	Acute VTE: 15mg bd for 3 weeks, then 20 mg od
Dose reductions as per SPC	110 mg bd if: • ≥80 years or • on verapamil Consider 110mg bd • 75-80 years or • CrCL 30-50mL/min or • at increased risk of bleeding (e.g. gastrointestinal) *(Note: 110mg bd based on PK/PD data only)*	None specified for VTE, but caution if CrCL 15-29ml/min *(Note: different advice for NVAF; refer to SPC)*	30 mg od if: • CrCL 15-50 mL/min or • ≤ 60kg or • taking any of ciclosporin dronedarone erythromycin ketoconazole	Consider 15 mg od after the first 3 weeks of 15mg bd, if CrCL 15-49 mL/min and risk of bleeding outweighs risk of VTE recurrence. *(NB: dosing based on PK modeling only; limited VTE clinical data for CrCL 15-29mL/min)*
Renal impairment (CrCL mL/min)	*VTE trials excluded CrCL <30mL/min* • CrCL 30-50 caution • CrCL <30 contraindicated	*VTE trials excluded CrCL <25mL/min or Cr > 220µmol/L* • CrCL 15-29 caution *(for NVAF: refer to SPC)* • CrCL <15 not advised	*VTE trials excluded CrCL <30mL/min* • CrCL 15-50 caution • CrCL <15 not advised	*VTE trials excluded CrCL <30mL/min* • CrCL 15-29 caution • CrCL <15 not advised
Drug interactions and SPC recommend-ations (not exhaustive) *Refer to SPC and other*	*Contraindicated* • Other AC agents (unless switching agents, or if using UFH to maintain patency of CV/ arterial lines) • systemic	*Contraindicated* • Other AC agents (unless switching agents, or if using UFH to maintain patency of CV/ arterial lines) *Not recommended*	*Contraindicated* • Other AC agents (unless switching agents, or if using UFH to maintain patency of CV/ arterial lines) *Reduce edoxaban*	*Contraindicated* • Other AC agents (unless switching agents, or if using UFH to maintain patency of CV/ arterial lines) *Avoid:*

suitable drug interaction tables for further info *Also, consider <u>additional risk factors for bleeding</u> which may merit ↓dose, alternative agent or DOAC avoidance* • *Age* • *Frailty* • *Renal function*	cyclosporine dronedarone itraconazole ketoconazole (↑DOAC levels) *SPC advises caution* • amiodarone, posaconazole, quinidine, verapamil (↑DOAC levels) *Not recommended* • tacrolimus (↑DOAC levels)	• systemic, itraconazole ketoconazole posaconazole voriconazole HIV protease inhibitors (e.g. ritonavir) (↑DOAC levels) • rifampicin carbamazepine phenobarbital St. John's Wort (↓DOAC levels)	*dose with:* • ciclosporin dronedarone erythromycin ketoconazole (↑DOAC levels) *SPC advises caution* • rifampicin carbamazepine phenytoin phenobarbital St. John's Wort (↓DOAC levels) *No data* • HIV protease inhibitors - avoid	• rifampicin phenytoin carbamazepine phenobarbital St. John's Wort (↓DOAC levels) *Not recommended*: • systemic ketoconazole itraconazole voriconazole posaconazole HIV protease inhibitors (e.g. ritonavir) (↑DOAC levels)
Aspirin / clopidogrel	↑risk of major bleeding. Authors' advice: stop antiplatelet agent if possible. If concomitant therapy unavoidable (and a careful risk-benefit assessment has been made) then (1) review the most appropriate drug combination (2) review DOAC dose* and (3) PPI cover advised. Close clinical monitoring required. *(*SPC for dabigatran - consider ↓110mg bd, but note lack of clinical VTE data at this dose)*			
Prasugrel / ticagrelor	Potent antiplatelet agents. Clinical data for concurrent use lacking. Very high risk of major bleeding expected *(Ticagrelor ↑ AUC and Cmax of dabigatran, extent depends on dosing regimen; see SPC)*			
NSAIDs	↑risk of bleeding. Authors' advice: careful risk-benefit assessment required. If benefit of chronic NSAID outweighs risk of bleeding then (1) review DOAC dose* (2) PPI cover advised. Close clinical monitoring required *(*SPC for dabigatran - consider ↓110mg bd, but note lack of clinical VTE data at this dose; SPC for edoxaban states chronic NSAID use not recommended)*			
Obese	SCC of ISTH suggests not to use in BMI >40 kg/m^2 or >120 kg (limited clinical data and available PK/PD data raises concerns for under-dosing)			
Low body weight	Exposure increase of ~ 30 % if <50 kg; SPC only states dose reduction for <u>≤</u> 60kg in NVAF with additional risk factors; *authors advise caution*	Limited clinical data <50kg; plasma levels increased; SPC states dose adjustment unnecessary; *authors advise caution*	Dose reduction required if <u>≤</u> 60kg; *authors advise caution < 50kg*	Exposure increase of ~25% if <50kg‡. SPC states dose adjustment unnecessary; *authors advise caution*

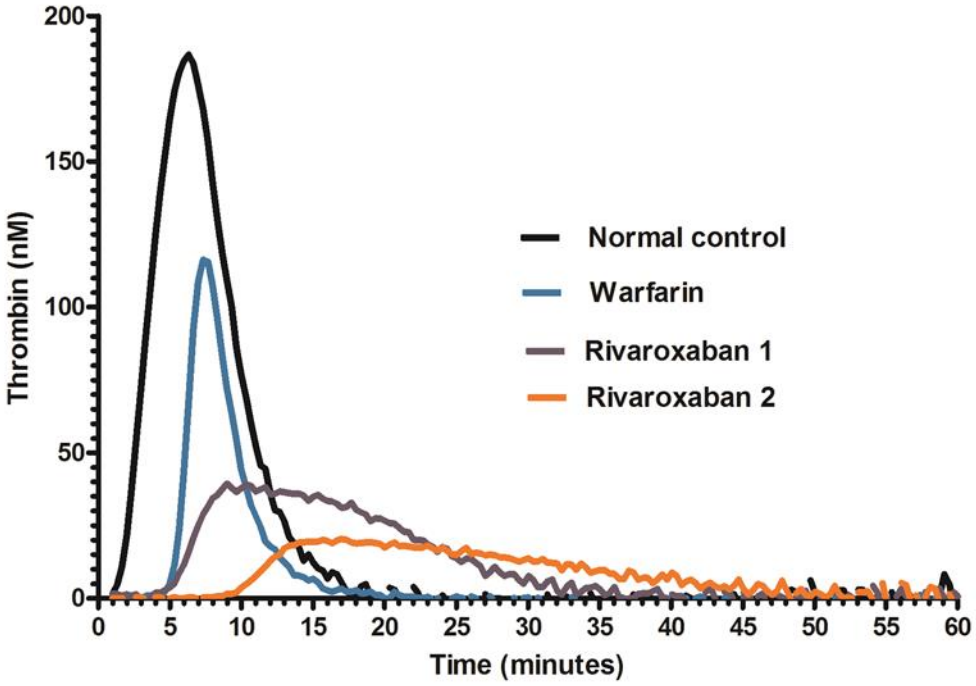
a: 20 mg oral dose; b: Taking 15mg and 20 mg doses with food corrects pharmacokinetic parameters
‡Based on a single 10mg dose study in healthy subjects
AC=anticoagulant; bd=twice daily; BRCP=breast cancer resistance protein; Cr=serum creatinine; CrCL=creatinine clearance; CYP=cytochrome P450; ISTH=International Society on Thrombosis and Haemostasis; NSAIDs=nonsteroidal anti-inflammatory drugs; NVAF=non-valvular atrial fibrillation; od=once daily; P-gp=P-gycoprotein inhibitor; PD=pharmacodynamic; PK=pharmacokinetic; SCC = Scientific and Standardization Committee; SPC=summary of product characteristics [2-5]

Table 2: Current status of studies of direct oral anticoagulants in thrombotic antiphospholipid syndrome (APS)

	RAPS	TRAPS	ASTRO-APS	RAPS
Study design	Phase 2/3 RCT	Phase 3 RCT	Phase 2/3 RCT	Phase 4 pilot feasibility study
Number of patients	116	536	200	150
APS subgroups	Previous VTE, target INR 2.5No thrombosis ≥3 mths Patients with arterial thrombosis excluded	Triple positive thrombotic APS Arterial, venous, and/or biopsy proven microthrombosis	Thrombotic APS VTE or arterial Target INR 2.5, 3.0, 3.5 No thrombosis ≥6 mths	VTE with/without arterial thrombosis
Intervention	Rivaroxaban 20mg OD vs warfarin target INR 2.5	Rivaroxaban 20mg OD vs warfarin target INR 2.5	Apixaban 5mg BD vs warfarin target INR 2.5	Rivaroxaban 20mg OD
Primary outcome(s)	Thrombin generation – endogenous thrombin potential (ETP)	Thrombosis – arterial or venous Major bleeding Death	Thrombosis - arterial and/or venous Bleeding	Identification of 150 patients consent in 135, compliance in 95%
Duration	Jun 13 – Nov 14	Dec 14 – Dec 18	Feb 15 – Dec 17	Sep 14 – Dec 16
Status	Completed	Recruiting	Recruiting	Recruiting

RAPS*=Rivaroxaban in Antiphospholipid Syndrome (ISRCTN68222801)[66,67]; TRAPS=Rivaroxaban in Thrombotic Antiphospholipid Syndrome (ClinicalTrials.gov: NCT02157272); ASTRO-APS=Apixaban for the Secondary Prevention of Thromboembolism Among Patients With the AntiphosPholipid Syndrome (ClinicalTrials.gov: NCT02295475); RAPS**=Rivaroxaban for Antiphospholipid Syndrome (ClinicalTrials.gov: NCT02116036); BD=twice daily; OD=once daily; RCT=randomised controlled trial

Figure 1: Typical examples of thrombograms in RAPS* trial patients on warfarin and rivaroxaban



Legend to Figure 1: The normal control thrombin generation (TG) curve has a sharp peak and short tail. Warfarin typically has a similar shape with a lower peak. However, with rivaroxaban the TG curve is protracted with a much lower peak and longer tail. RAPS*=Rivaroxaban in Antiphospholipid Syndrome (ISRCTN68222801)[66].