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Review

14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends

Doruk Erkan [a,*], Cassyanne L. Aguiar [a], Danieli Andrade [b], Hannah Cohen [c,d], Maria J. Cuadrado [e], Adriana Danowski [f], Roger A. Levy [g], Thomas L. Ortel [h], Anisur Rahman [c,d], Jane E. Salmon [a], Maria G. Tektonidou [i], Rohan Willis [j], Michael D. Lockshin [a]

[a] Hospital For Special Surgery, Weill Cornell Medical College, New York, NY, USA
[b] Department of Rheumatology, University of São Paulo School of Medicine, São Paulo, Brazil
[c] Department of Hematology, University College London Hospitals NHS Foundation Trust, London, UK
[d] University College London, London, UK
[e] Lupus Unit, Guys' and St Thomas Foundation Trust, London, UK
[f] Department of Rheumatology, Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil
[g] Department of Rheumatology, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil
[h] Hemostasis and Thrombosis Center, Duke University Medical Center, Durham, NC, USA
[i] First Department of Medicine, University of Athens School of Medicine, Athens, Greece
[j] University of Texas Medical Branch, Galveston, TX, USA

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ABSTRACT

Antiphospholipid Syndrome (APS) is characterized by vascular thrombosis and/or pregnancy morbidity occurring in patients with persistent antiphospholipid antibodies (aPL). The primary objective of the APS Treatment Trends Task Force, created as part of the 14th International Congress on aPL, was to systematically review the potential future treatment strategies for aPL-positive patients. The task force chose as future clinical research directions: a) determining the necessity for venous thrombosis controlled clinical trials with the new *oral direct thrombin or anti-factor Xa inhibitors* pending the results of ongoing rivaroxaban in APS (RAPS) trial, and designing controlled clinical trials in other forms of thrombotic APS; b) systematically analyzing the literature as well as aPL/APS registries, and creating specific registries for *non-warfarin/heparin anticoagulants*; c) increasing recruitment for an ongoing primary thrombosis prevention trial, and designing secondary thrombosis and pregnancy morbidity prevention trials with *hydroxychloroquine*; d) determining surrogate markers to select patients for *statin* trials; e) designing controlled studies with *rituximab* and other *anti-B-cell* agents; f) designing mechanistic and clinical studies with *eculizumab* and other *complement inhibitors*; and g) chemically modifying *peptide therapy* to improve the half-life and minimize immunogenicity. The report also includes recommendations for clinicians who consider using these agents in difficult-to-manage aPL-positive patients.

Contents

* Corresponding author at: Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery, 535 E70th Street, New York, NY, USA. Tel.: +1 212 774 2291; fax: +1 212 774 2374.
E-mail address: erkand@hss.edu (D. Erkan).

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1. Introduction

Antiphospholipid Syndrome (APS) is characterized by thrombosis and/or pregnancy morbidity occurring in patients with persistent antiphospholipid antibodies (aPL) [1]. Clinical manifestations of aPL represent a broad spectrum: a) asymptomatic aPL positivity (no history of thrombosis or pregnancy morbidity); b) non-criteria manifestations of aPL, e.g., livedo retucularis, thrombocytopenia, hemolytic anemia, cardiac valve disease, aPL-associated nephropathy, skin ulcers, or cognitive dysfunction; c) pregnancy morbidity (recurrent embryonic or fetal loss, preeclampsia, and growth restriction); d) venous, arterial, or small vessel thrombosis; and e) catastrophic APS (multiple organ thromboses commonly associated with microangiopathy).

The current mainstay of treatment for thrombotic APS is heparin followed by long-term anticoagulation with vitamin K antagonists (VKA) such as warfarin. Treatment with VKA in general is problematic because of numerous drug and food interactions, which necessitate frequent monitoring and potential under- or over-anticoagulation. Furthermore, monitoring of anticoagulation may be complicated by variable responsiveness of thromboplastin reagents to aPL, which may invalidate the prothrombin time (PT)/International Normalized Ratio (INR) [2].

The 14th International Congress on aPL was held in Rio de Janeiro, Brazil in September 2013. The APS Treatment Trends Task Force was one of five task forces developed by the meeting organization committee. The goal of the task force was to review potential new treatment strategies for aPL-positive patients rather than traditional anticoagulants or antiplatelet agents. Six subgroups of task force members systematically reviewed in vitro, animal, and completed and ongoing clinical studies in aPL-positive patients; following open discussions before and presentations during the 14th International Congress on aPL, the task force report was finalized.

2. Oral direct thrombin or anti-factor Xa inhibitors (new generation oral anticoagulants)

The oral direct inhibitors (ODI), also known as new generation oral anticoagulants (NOAC), include the direct thrombin inhibitor (DTI) dabigatran etexilate (Pradaxa®) [3], and the direct anti-factor Xa inhibitors rivaroxaban (Xarelto®) [4], apixaban (Eliquis®) [5], and

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Table 1
Oral direct thrombin and anti-factor Xa inhibitors (new generation oral anticoagulants).

Drug	Class	Therapeutic dose*
Rivaroxaban[a,b,c]	Factor-Xa inhibitor	20 mg once daily
Apixaban[a,b,d]	Factor-Xa inhibitor	5 mg twice daily
Edoxaban[d]	Factor-Xa inhibitor	60 mg once daily
Dabigatran[a,b,d]	Thrombin inhibitor	150 mg twice daily

Currently licensed by the European Medical Agency and approved by the Food and Drug Administration for:

a. The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
b. The prevention of stroke and systemic embolism in eligible adult patients with non-valvular atrial fibrillation
c. The treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent DVT and PE following an acute DVT in adults
d. Phase III trials on treatment of DVT and PE completed and published

* Dose reduction for renal impairment, age, and interacting drugs are defined in the individual package inserts.

edoxaban (Lixiana®) [6] (www.emc.medicines.org.uk) (Table 1). These agents, unlike warfarin, are fixed dose with predictable anticoagulant effect, do not interact with dietary constituents or alcohol, and have few reported drug interactions that affect anticoagulant intensity. Furthermore, monitoring of anticoagulant intensity of ODIs is not routinely required due to their predictable anticoagulant effects.

The efficacy of ODIs for venous thromboembolism (VTE) has been demonstrated in large Phase III clinical trials [7–10]. Rivaroxaban, dabigatran, and apixaban have been licensed by the European Medicines Agency (EMA) and approved by the United States Food and Drug Administration (FDA) for several indications (Table 1).

2.1. In vitro and/or animal antiphospholipid syndrome studies

No studies.

2.2. Completed clinical studies in antiphospholipid antibody-positive patients

There are no completed studies of ODI in aPL-positive patients. A small subset of patients with known thrombophilic conditions (5–7%) were included in the randomized open-label non-inferiority trials of rivaroxaban versus enoxaparin followed by VKA (EINSTEIN DVT/PE), including a subset of patients with aPL (personal communication with Janssen Scientific Affairs, LLC). These patients were not identified as "APS" in the analyses, no information about the aPL profile, e.g., persistence of aPL, LA test, is available, and therefore the results of these ODI trials are not generalizable to APS patients.

2.3. Ongoing interventional clinical studies in antiphospholipid antibody-positive patients

The Rivaroxaban in AntiPhospholipid Syndrome (RAPS) trial is an open label prospective non-inferiority randomized controlled trial (RCT) in patients with thrombotic APS, with or without systemic lupus erythematosus (SLE), who have had either a single episode of VTE while not on anticoagulation or recurrent episode(s) which occurred while off anticoagulation or on sub-therapeutic anticoagulant therapy. Following at least three months of warfarin, patients are randomized to remain on warfarin (target INR 2.5) or to switch to rivaroxaban 20 mg once daily (with consideration of dose reduction to 15 mg once daily for renal insufficiency [creatinine clearance 30–49 ml/min] in accordance with the package insert) [4]. The primary aim of the RAPS trial is to demonstrate that the intensity of anticoagulation achieved with rivaroxaban is not inferior to that of warfarin in patients with thrombotic APS. The thrombin generation test, as a global measure of anticoagulation, assesses the anticoagulant effects of both rivaroxaban and warfarin. The hypothesis is that rivaroxaban induces more predictable anticoagulation and, therefore, a greater sustained reduction in thrombin generation, than warfarin. If the trial demonstrates that: a) the anticoagulant effect of rivaroxaban is not inferior to that of warfarin; and b) there are no adverse effects that cause concern, it will suggest that rivaroxaban can be an alternative to VKA in APS. The trial is currently open to recruitment (http://www.controlled-trials.com/ISRCTN68222801).

2.4. Future clinical research directions

It is unclear if ODIs can replace warfarin for the long-term secondary thrombosis prevention in APS patients with VTE even if the RAPS trial achieves its primary objectives. The necessity for controlled outcome trials of ODIs in APS patients with venous thrombosis will depend on the results of the RAPS trial; in addition, controlled outcome trials of ODIs in other forms of APS, e.g., obstetrical and microthrombotic, should be considered.

2.5. Recommendations for clinicians

The task force recommends that warfarin or other VKA remains the mainstay of anticoagulation in thrombotic APS. Oral direct inhibitors can be considered in APS patients with a first or recurrent VTE occurring off or on subtherapeutic anticoagulation, only when there is known VKA allergy/intolerance or poor anticoagulant control. There are no data to recommend ODI in APS patients with recurrent VTE occurring on therapeutic anticoagulation or with APS-related arterial thrombosis. Clinicians should keep in mind that:

- The International Society of Thrombosis and Hemostasis (ISTH) Scientific Subcommittee (SSC) guidance on practical aspects related to patient selection, use of concomitant drugs, follow-up modalities, and assessment of patients' adherence provides useful information for ODI use [12].
- The Phase III VTE trials of ODIs in general population patients have compared these agents with VKA at a target INR of 2.5 (2.0–3.0).
- Measurement of the anticoagulant effect of ODIs, which is challenging, may be needed in clinical circumstances such as bleeding, potential drug interactions, extreme body weight, deteriorating renal function, perioperative management, reversal of anticoagulation, suspicion of overdose, and assessment of adherence [13]. Some of the basic coagulation screening tests provide an assessment of ODI activity, however some prothrombin time reagents show very poor sensitivity, and the activated partial thromboplastin time (aPTT) may also be prolonged because of lupus anticoagulant (LA) [14,15]. A chromogenic anti-factor Xa and chromogenic anti-IIa assays in combination with appropriate specific calibrators provide a quantitative measure of rivaroxaban or apixaban and dabigatran activity, respectively, but these assays are not widely available [16–18].
- As with warfarin or heparin (unfractionated or low-molecular-weight), ODIs can result in false positive LA test results in assays done with aPTT and dilute Russell viper venom time (dRVVT) reagents [19]. Limited observations on the addition of the rivaroxaban in vitro to from aPL-positive plasma suggest that ratios using Taipan/Ecarin and snake venoms, which directly activate prothrombin and which can be used to detect LA, are not affected by rivaroxaban [14,15].
- There are no pharmacological reversal agents for ODIs; 4-factor prothrombin complex concentrate (PCC) completely reverses the anticoagulant effect of rivaroxaban in healthy subjects, but had no influence on the anticoagulant effect of dabigatran [20]. The management of major bleeding in patients receiving ODIs requires supportive measures, which include transfusion of blood components. Hemostatic support with PCC, activated PCC, e.g. factor VIII inhibitor bypass activity (FEIBA), or recombinant factor VIIa (rVIIa) as well as antifibrinolytic

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therapy (tranexamic acid) may be useful. Renal replacement therapy should be considered for dabigatran (not useful for rivaroxaban, which is highly protein bound in the circulation) and activated charcoal for recent ingestion of dabigatran or rivaroxaban.

- In the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) study, dabigatran (150 mg to 300 mg twice daily) was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk [21].
- Patient adherence is critical in ODI-receiving patients, even more so than in VKA-receiving patients, because of the lack of routine anticoagulant monitoring in patients on ODI. Thus, non-adherence with VKA is not a reason to switch APS patients to an ODI.
- There have been anecdotal reports of thrombosis occurring shortly after switching APS patients from warfarin to ODI (personal communication with Congress attendees).

3. Older non-heparin/warfarin anticoagulants

Older anticoagulants are the indirect anti-factor Xa inhibitors (fondaparinux, idraparinux, idrabiotaparinux, and danaparoid) and the non-oral direct thrombin inhibitors (argatroban, lepirudin, and bivalirudin) [22].

3.1. In vitro and/or animal antiphospholipid syndrome studies

Although heparin prevents aPL-induced fetal loss by inhibiting complement activation, fondaparinux is ineffective in murine models of obstetric APS [23] as it has no molecular interactions with complement.

3.2. Completed clinical studies in antiphospholipid antibody-positive patients

Data are limited to anecdotal case reports and small case series of successful use of fondaparinux in APS patients with heparin-induced thrombocytopenia [24,25].

3.3. Ongoing interventional studies in antiphospholipid antibody-positive patients

No studies.

3.4. Future clinical research directions

Given the difficulty of conducting controlled studies in a small group of APS patients receiving older non-heparin/warfarin anticoagulants, systematic analysis of the literature as well as the large scale aPL/APS registries, e.g., APS Alliance for Clinical Trials and International Networking (APS ACTION) International Clinical Database and Registry, International Web-based Catastrophic APS Registry, or European Forum on aPL, may provide useful information.

3.5. Recommendations for clinicians

The task force recommends that danaparoid, fondaparinux, and argatroban can be considered in APS patients with heparin-induced thrombocytopenia. In addition, creation of specific registries of APS patients who are treated with conventional parenteral non-heparin/warfarin anticoagulants should be considered. Clinicians should keep in mind that:

- The evidence in favor of fondaparinux as a treatment of heparin-induced thrombocytopenia is of low quality [22], however, many consider the therapeutic dose of fondaparinux as an acceptable alternative anticoagulant for this indication [26].
- There have been case reports of fondaparinux-induced heparin-induced thrombocytopenia, however the evidence for fondaparinux-induced heparin-induced thrombocytopenia is of low quality [27–29] and experts dispute its existence [22,30,31].
- Novel parenteral anticoagulants in development for general population patients include new indirect activated factor Xa inhibitors, ultra-low-molecular-weight heparins, direct FXa inhibitors, direct FIIa inhibitors, direct FXIa inhibitors, direct FIXa inhibitors, FVIIIa inhibitors, FVIIa/tissue factor inhibitors, FVa inhibitors and dual thrombin/FXa inhibitors.

4. Hydroxychloroquine

Hydroxychloroquine (HCQ) is an important treatment in rheumatic diseases, particularly in SLE, due to its anti-inflammatory, immunomodulatory, and metabolic effects.

4.1. In vitro and/or animal antiphospholipid syndrome studies

Hydroxychloroquine reduces the extent and the time of thrombus persistence in aPL-injected mice [32], reverses thrombogenic properties of aPL in mice, and reverses aPL-mediated platelet activation. Hydroxychloroquine also reduces the attachment of aPL–β_2GPI complexes to phospholipid bilayers and cells [33], reverses the binding of aPL to human placental syncytiotrophoblasts, restores annexin A5 expression [34,35], and inhibits Toll-like receptors [36].

4.2. Completed clinical studies in antiphospholipid antibody-positive patients

4.2.1. Primary thrombosis prevention in the general population

In the 1970s to early-1980s, several placebo-controlled studies showed that 600–1200 mg of HCQ daily prevents postoperative thrombosis after hip replacement [37].

4.2.2. Primary thrombosis prevention in SLE patients with/without aPL

Hydroxychloroquine reduces flares, damage, cardiovascular events, and mortality in lupus patients [38]. Lupus patients have a higher risk of developing vascular thrombosis due to multiple factors including corticosteroids, hypertension, renal disease, and hyperlipidemia; a protective effect of HCQ against thrombosis was first reported by Wallace [39] and then later confirmed by several prospective [40–43] and retrospective studies [44–46], with some exceptions [47,48]. Tektonidou et al. examined the effect of HCQ in lupus patients with positive and negative aPL, with similar beneficial effects in both groups [43]. Petri et al. showed a reduction in both arterial and venous thrombosis rate in aPL-positive SLE patients [49]. However, it is not clear if the protective role of HCQ against thrombosis in SLE is associated with its effect on aPL, lupus activity, or traditional cardiovascular disease risk factors. Of note, based on experimental and clinical studies, antimalarials have lipid and glucose lowering effects.

4.2.3. Primary thrombosis prevention in aPL-positive individuals

Erkan et al. observed a decreased risk of thrombosis in asymptomatic aPL-positive individuals (no history of thrombosis or fetal loss) treated with HCQ; however 78% of 56 aPL-positive patients included in the cross-sectional study had SLE [50].

4.2.4. Secondary thrombosis prevention in APS

The only prospective non-randomized trial comparing oral anticoagulation plus HCQ (400 mg daily) versus oral anticoagulation alone in primary APS patients was recently published. Patients had history of one or two episodes of venous thrombosis (no obstetrical/arterial events except two patients with stroke) and were on

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anticoagulation with fluindione. No patients received platelet aggregation inhibitors. There were six (30%) venous events in the monotherapy group (n: 20) despite therapeutic range INR and none in the HCQ group (n: 20) during the six month and 36 month follow-up, respectively [51]. Given the small number of patients that were included, the short follow-up, and the methodological limitations of the study, it is difficult to derive meaningful conclusions.

4.2.5. Role of HCQ on the aPL titers

Based on limited number of studies, HCQ may decrease antibody levels in aPL positive persons [52]; HCQ use was also associated with lower odds of having persistently positive aPL, adjusted for age, ethnicity, and gender [53]. However, a retrospective study found no variation of aPL levels over time in patients receiving aspirin, warfarin, or HCQ [54].

4.3. Ongoing interventional clinical studies in antiphospholipid antibody-positive patients

One study is currently investigating the effect of HCQ on the annexin A5 resistance assay in persistently aPL-positive patients, with and without SLE, at six and 12 weeks after initiation of treatment (clinicaltrials.gov #: NCT01475149) [55]. The secondary objectives of this study include the effects of HCQ on other prothrombotic markers (D-Dimer, Activated Protein C Resistance) and on aPL titers/status.

Another multicenter, international, prospective, randomized controlled trial of HCQ for primary thrombosis prevention in persistently aPL-positive but thrombosis-free patients without other systemic autoimmune diseases ("HCQ Trial") is currently taking place under the auspices of the APS ACTION (www.apsaction.org) (clinicaltrials.gov #: NCT01784523). The primary objective is to determine the efficacy of HCQ for primary thrombosis prevention over the five year study period. Patients are randomized to receive HCQ or no treatment in addition to their standard regimen.[1]

4.4. Future clinical research directions

Every effort should be taken to increase the number of patients and centers participating in the primary thrombosis prevention trial discussed above. Long-term prospective controlled studies are needed to determine the role of HCQ in secondary thrombosis and pregnancy morbidity prevention as an adjunctive treatment. Another important question is whether HCQ significantly affects the aPL profile; larger scale controlled studies are needed to investigate the role of HCQ on aPL profile of the patients.

4.5. Recommendations for clinicians

The task force recommends HCQ in all aPL-positive SLE patients. The role of HCQ for primary thrombosis prevention in asymptomatic aPL-positive individuals without an underlying autoimmune disease remains to be elucidated. There are no strong data to recommend HCQ in persistently aPL-positive persons without other autoimmune diseases; given that HCQ may reduce the risk of thrombosis in experimental models and SLE patients as well as its multiple-targeted effects and good safety profile, HCQ may be considered as an adjunctive treatment in refractory cases. Clinicians should keep in mind that:

- Adherence to HCQ in SLE varies from 7% to 51%, depending on the methodology selected to evaluate compliance [56,57].
- The frequency of adverse events related with HCQ (mostly gastrointestinal and cutaneous) is low; however, the use of HCQ for more than 10 years increases the risk of skin (hyperpigmentation), eye, and muscle toxicity.
- The risk of retinal toxicity increases toward 1% after five to seven years of use or a cumulative dose of 1000 g. After the baseline examination, a five year screening-free interval is recommended by the American Academy of Ophthalmology for low-risk patients (no liver or kidney disease, no retinal or macular disease, and age less than 60); after five years of use, annual screening is recommended [58].
- Hydroxychloroquine cardiotoxicity has been rarely described and the rate of heart conduction disorders is similar to what is expected in the general population [59].

5. Statins

Statins are potent inhibitors of cholesterol synthesis in the mevalonate pathway.

Their observed benefits in primary and secondary prevention of coronary heart disease in the general population are based not only on their lipid lowering effect but also on their pleiotropic immunomodulatory, anti-inflammatory, and anti-thrombotic properties [60]. These additional properties also provide the rationale for their potential application in APS, in which inflammation and the immune-mediated cell activation represent key pathogenic mechanisms.

5.1. In vitro and/or animal antiphospholipid syndrome studies

In-vitro studies utilizing human umbilical vein endothelial cells (HUVECs) demonstrate that fluvastatin, simvastatin, and rosuvastatin reduce aPL-mediated tissue factor (TF) and cell adhesion molecule (CAM) expression as well as monocyte adhesion to endothelial cells (EC) [61–63]. In mouse models of APS, simvastatin and pravastatin reduce fetal death [64], and fluvastatin reduces the CAM expression, thrombus size, and leukocyte adhesion to EC [65]. In contrast, based on in-vitro data, pravastatin does not prevent aPL-mediated changes in human trophoblast function [66].

In APS, statins have multiple profound effects on monocytes, lymphocytes, and endothelial cell activities, all of which may contribute to thrombosis prevention in APS patients. These immunomodulatory and anti-thrombotic effects result in: a) correcting dyslipidemia; b) modulating the proinflammatory profile; c) downregulating the prothrombotic status; and d) preventing atherosclerosis even if the association between aPL and atherosclerosis is controversial [67,68].

In addition, the most frequent cardiovascular risk factors found in APS patients are hypertriglyceridemia and low HDL cholesterol levels [69]. Antibodies to HDL and apolipoprotein A (ApoA-I) have been described in APS patients [70]. Immunoglobulin-G anti-high density lipoprotein antibodies (IgG anti-HDL) may substantially reduce the antioxidant and anti-inflammatory effect of HDL, favoring low-grade inflammation and enhanced oxidation in thrombotic APS.

5.2. Completed clinical studies in antiphospholipid antibody-positive patients

In the first human mechanistic study, utilizing a proteomic analysis, López-Pedrera et al. showed that inflammatory proteins can be reversed in APS patients following one month of daily 20 mg fluvastatin treatment [71]. One of the most prominent mechanisms linking aPL to thrombosis is the upregulation of TF expression, the major initiator of coagulation in vivo [72]. In 2003, Gharavi et al. proposed a hypothetical model in which aPL activate nuclear factor-kB (NFkB) expression through the mitogen-activated protein (MAP) kinase) p38 pathway leading to TF overexpression [73], which was confirmed by others. In the study by López-Pedrera et al., fluvastatin downregulated tissue factor and other prothrombotic markers in APS patients [71].

In the second human study by Erkan et al., the treatment with fluvastatin was extended to three months, and patients were

[1] Physicians or patients interested in participating in the "HCQ Trial" can contact Joann Vega, CCRC at vegaj@hss.edu.

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monitored for proinflammatory and prothrombotic biomarkers for additional three months after discontinuation of the treatment [74]. Based on the comparison of the baseline samples of 41 aPL-positive patients with 30 healthy controls, 9/12 (75%) biomarkers (interleukin [IL]-6, IL1β, vascular endothelial growth factor [VEGF], tumor necrosis factor [TNF]-α, interferon [IFN]-α, inducible protein-10 [IP10], soluble CD40 ligand [sCD40L], soluble tissue factor [sTF], and intracellular adhesion molecule [ICAM]-1) were significantly elevated. Twenty-four patients completed the study; fluvastatin significantly and reversibly reduced the levels of 6/12 (50%) biomarkers (IL1β, VEGF, TNFα, IP10, sCD40L, and sTF).

5.3. Ongoing interventional clinical studies in antiphospholipid antibody-positive patients

No studies.

5.4. Future clinical research directions

Statin-induced modulation of the aPL effects on target cells can be a valuable approach in the management of aPL-positive patients. Ideally, future research should focus on clinical trials designed to determine the role of statins in primary thrombosis prevention of aPL-positive patients. Additional investigations should focus on determining if statins could be an effective additional treatment to anticoagulation in patients with recurrent thrombosis despite adequate anticoagulation. However, the large number of patients and the long-term follow-up time necessary to find statistically significant differences between current treatment and new therapeutic approaches are the limiting factors for those trials. Thus, it is important to determine relevant surrogate markers involved in the mechanisms of aPL-mediated thrombosis and downregulated by statins, which can be used to select patients for statin trials and stratify patients in terms of the potential benefits of statin therapy.

5.5. Recommendations for clinicians

The task force recommends that although statins ameliorate the proinflammatory profile and down-regulate the prothrombotic stage found in APS patients, based on the available data, statins cannot be recommended in APS patients in the absence of hyperlipidemia. However, a subgroup of aPL-positive patients with recurrent thrombosis despite adequate anticoagulation might derive benefits from statins. Clinicians should keep in mind that:

- Because of the disruption of gonadal stem cell development and theoretical long-term fetal neurological damage [75], statins are classified as Category X (contraindicated) for pregnancy by FDA.
- In healthy persons with normal low-density-lipoprotein levels of less than 130 mg/dl and elevated C-reactive protein levels greater than 2.0 mg/dl, rosuvastatin 20 mg daily significantly reduced the occurrence of the first major cardiovascular event and symptomatic venous thromboembolism [76,77].
- Recent studies also suggest that perioperative statin use provides a cardio-protective effect; statins can be considered during the perioperative period in high thrombosis risk APS patients. In a meta-analysis, Hindler et al. reported a 44% reduction in mortality associated with preoperative statin therapy [78]. Although most of the current data is observational, the American College of Cardiology/American Heart Association recommends that patients currently taking statins should continue the drug for non-cardiac surgery; it is reasonable for patients undergoing vascular surgery with or without clinical risk factors to initiate statin therapy; and statins should be considered for patients with at least one clinical risk factor who are undergoing intermediate-risk procedures [79].

6. B-cell inhibition

B cells play an important role in APS [80] and are key players in the development, re-activation, and persistence of autoimmune diseases beyond the production of autoantibodies. B-cells orchestrate the immune response by producing antibodies, germinal centers, and cytokines, as well as by their roles in antigen recognition and presentation (independent or dependent of T-cells).

6.1. In vitro and/or animal antiphospholipid syndrome studies

Based on the in vitro experience B cells are involved in aPL-related clinical events [80,81]: a) blocking B-cell activating-factor (BAFF) prevents disease onset and prolongs survival in APS murine models [82]; and b) cytotoxic T-lymphocyte antigen 4 immunoglobulin (CTLA4-Ig) prevents initiation but not development of APS, in the NZW × BXSB F1 APS mouse model [83].

Rituximab is an anti-CD20 chimeric monoclonal antibody that is effective against B-cell non-Hodgkin's lymphomas and chronic lymphocytic leukemias. Rituximab is also approved by the FDA for rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis), and microscopic polyangiitis (MPA). In K/BxN mouse model of inflammatory arthritis, rituximab decreases the titer of antibodies targeting glucose-6-phosphate isomerase, but not the total antibody titer probably because glucose-6-phosphate isomerase specific plasma cells reside primarily in the spleen and lymph nodes, have shorter half-lives, and express CD20. These plasma cells are rapidly depleted by rituximab in comparison to most CD20 negative plasma cells which have longer half-lives and are found in the bone marrow [84].

6.2. Completed clinical studies in antiphospholipid antibody-positive patients

Several case reports and review articles [85–90] have described rituximab use in APS patients with severe thrombocytopenia [91–94], hemolytic anemia [86], skin ulcers or necrosis [90,95], aPL nephropathy [96], and catastrophic APS [97] with variable responses. The summary of these cases can be found elsewhere [81,85,87,88,97].

Rituximab in Antiphospholipid Syndrome (RITAPS) trial was a pilot open-label Phase II study, the primary objective of which was to evaluate the safety of rituximab in adult APS with no other systemic autoimmune diseases patients (up to 12 months). The secondary objectives were to evaluate the effect of rituximab on aPL profile (up to 12 months) and non-criteria aPL manifestations (up to 6 months). Patients received two doses of IV rituximab (1000 mg) on Days 1 and 15. The RITAPS trial suggested that rituximab in APS patients is safe, and that even without inducing substantial change in aPL profiles, rituximab may be effective in controlling some non-criteria manifestations of aPL. The numbers of patients with a complete response, a partial response, no response, and recurrence for the clinical outcome measures at 24 weeks were as follows: for thrombocytopenia (n: 4), 1, 1, 2, and 0, respectively; for cardiac valve disease (n: 3), 0, 0, 3, and not analyzed, respectively; for skin ulcer (n: 5), 3, 1, 0, and 1, respectively; for aPL nephropathy (n: 1), 0, 1, 0, and 0, respectively; and for cognitive dysfunction (n: 5), 3, 1, 1, and not analyzed, respectively [98].

Regarding the effect of RTX on aPL profiles, based on the PubMed/Ovid search for “RTX” and “aPL”, “APS”, “LA”, “aCL”, or “aβ_2GPI” [85], 50 articles describing 90 aPL-positive patients treated with RTX were reported (as of May 2013). Of 42/90 patients tested for three aPL (LA, anticardiolipin antibody [aCL], aβ_2GPI) pre-RTX, 37/42 (88%) were tested twice 6–12 weeks apart. Of 28/90 patients tested for any two aPL pre-RTX, 7/28 (25%) were tested twice. Of 20/90 patients tested for only one aPL pre-RTX, 2/20 (10%) were tested twice. This analysis concluded that: a) no case report has described a

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patient with a clinically significant persistently positive aPL profile (LA and/or moderate-to high titer aCL/aβ_2GPI) who became negative for aPL (LA, aCL, and aβ_2GPI) following treatment only with rituximab; and b) the literature is heterogeneous with the reporting of aPL type, isotype, titer, and persistency with significant amount of missing data.

In the international web-based catastrophic APS registry, of 20 rituximab-treated patients, 15 recovered and five died [97]. The authors concluded that rituximab might have a role in the management of refractory catastrophic APS patients.

Belimumab (Benlysta®) [99] is a fully human recombinant immunoglobulin G (IgG) 1λ monoclonal antibody to soluble B-lymphocyte stimulator (BLyS), which blocks the crucial survival signal in early stages of B-cell development and decreases the survival of autoreactive B-cells. There are no reports of belimumab use for aPL-manifestations; however, Stohl et al. [100] completed a pooled analysis of RCTs to determine the effect of belimumab (1 mg/kg and 10 mg/kg doses) on autoantibody levels at 52 weeks. The median percentage changes for aCL IgG, IgM, and IgA were −29, −47, and −40, respectively for the 1 mg/kg group and −28, −32, and −41, respectively for the 10 mg/kg group. However, no other aPLs were checked and the definitions of aCL positivity in terms of titers were not described. The only statistically significant change was seen in IgA (−41) at the 10 mg/kg dose when compared to placebo.

6.3. Ongoing interventional clinical studies in antiphospholipid antibody-positive patients

No studies.

6.4. Future clinical research directions

Given the successful case reports of rituximab use in APS patients and one Phase II pilot study, controlled studies with rituximab and other anti-B cell agents are needed. The observation that treatment with belimumab reduced B-cells and serum immunoglobulins and autoantibodies suggests that belimumab may be beneficial in other B cell-mediated autoimmune diseases beyond SLE.

6.5. Recommendations for clinicians

The task force recommends that B-cell inhibition may have a role in difficult-to-treat APS patients, possibly in those with hematologic and microthrombotic/microangiopathic manifestations. Clinicians should keep in mind that:

- The FDA-approved dose of rituximab for RA 1000 mg intravenous infusions separated by 2 weeks every 24 weeks or based on clinical evaluation, and dose for GPA and MPA is 375 mg/m^2 once weekly for 4 weeks, but no studies have compared different dosing regimens. It is unknown if the effectiveness of these dosing regimens is different in aPL-positive patients.
- Methylprednisolone 100 mg intravenous or equivalent glucocorticoid is recommended 30 min prior to each infusion.
- Belimumab was not studied for preventing thrombosis and other aPL manifestations in SLE patients with aPL, but with the increasing experience we expect to learn more about its action in this population.

7. Complement inhibition

Passive transfer of human aPL demonstrates that aPL are pathogenic in vivo in animal models of thrombosis, endothelial cell activation, and pregnancy loss [101,102]. Endothelial cell activation correlates with a prothrombotic phenotype in vitro and enhances thrombus formation in vivo [102,103]. Complement activation, specifically C5, is a necessary intermediary event in thrombosis associated with aPL in rodent models [104].

7.1. In vitro and/or animal antiphospholipid syndrome studies

Complement is implicated in APS via generation of the potent inflammatory mediator C5a, which contributes to vascular inflammation [105,106]. Complement 5a is a potent anaphylatoxic and chemotactic molecule. It interacts with its receptor, C5aR, to promote recruitment and activation of neutrophils (PMN) and monocytes and mediate EC activation [101]. Complement 5a–C5aR ligation also up-regulates neutrophil-derived TF expression, thought to be one mechanism of aPL-mediated coagulation and disseminated thrombosis [107]. Treatment with anti-C5 monoclonal antibody or C5aR antagonist peptides attenuates thrombosis in mouse models of APS [101,102].

In a mouse model of APS, interaction of C5a with its receptor C5aR is necessary for aPL-induced placental insufficiency, inflammation, and thrombosis [101]. Complement 5a-induced recruitment and activation of neutrophils lead to trophoblast injury and angiogenic factor imbalance in aPL-induced fetal injury [108]. Anti-C5 antibody, C5aR antagonist peptides, and complement deficiency experiments prevent pregnancy loss [101]. That heparin has anti-complement effects, as well as acting as an anticoagulant, may explain some of its efficacy in APS [23].

Mouse studies demonstrate that the absence of complement regulatory proteins is associated with microangiopathy and pregnancy loss [109–111]. Recent reports in patients have demonstrated association of loss-of-function mutations in complement regulatory proteins and atypical hemolytic uremic syndrome (aHUS), pre-eclampsia (PEC), and paroxysmal nocturnal hemolysis (PNH). These diseases have microvascular endothelial cell activation, cell injury, and thrombosis in common [112].

7.2. Completed clinical studies in antiphospholipid antibody-positive patients

Clinical studies in APS patients are limited to a small number of case reports. A case report described improvement of post kidney transplant thrombotic microangiopathy in an eculizumab-treated APS patient [113]. In another catastrophic APS patient resistant to anticoagulation, immunosuppression, plasmapheresis, and rituximab, eculizumab successfully blocked complement activity, aborted progressive thrombosis, and reversed thrombocytopenia [114]. Another case report [115] and personal communications describe catastrophic APS patients who failed to respond to eculizumab.

Considering other complement-mediated diseases, eculizumab, a recombinant humanized monoclonal antibody that binds to the terminal complement protein C5and inhibits its cleavage to C5a and C5b, reduces the frequency of episodes of hemolysis, hemoglobinuria, transfusion, and thrombosis in patients with PNH [116]. Responses can vary and may depend on underlying marrow failure, underlying inflammatory conditions, and red cell clone size following treatment [117].

In aHUS, eculizumab improves renal transplantation outcomes and allows plasma exchange-dependent patients to stop this treatment [118,119]. Of note, some aHUS patients with thrombomodulin mutations are refractory to eculizumab [120].

7.3. Ongoing interventional clinical studies in antiphospholipid antibody-positive patients

One study is investigating if blocking the complement cascade in patients with a prior history of catastrophic APS who are undergoing kidney transplant will allow for increased transplant success (clinicaltrials.gov #: NCT01029587).

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7.4. Future clinical research directions

Animal and human studies have confirmed the value of complement inhibition in many inflammatory and microthrombotic diseases. Potential targets include C5aR antagonists (antibodies or peptides) and soluble and targeted complement regulatory proteins. Future mechanistic and clinical studies of eculizumab and other complement inhibitors will help individualize treatment.

7.5. Recommendations for clinicians

The task force recommends that complement inhibition may have a role as an adjuvant or main therapy for APS patients refractory to anticoagulation; however more clinical data are needed before this medication can be recommended. Clinicians should keep in mind that:

- The infection risk of eculizumab is mainly with encapsulated organisms, specifically meningococcal. Patients must be immunized against *Neisseria meningitidis* before treatment with this drug.

8. Peptide therapy

β_2-Glycoprotein-I consists of five homologous domains (DI to DV) [121]; Domain V binds to negatively charged molecules, most specifically exteriorized phosphatidylserine in phospholipid bilayers in cell membranes of activated or apoptotic cells [122]. Alternatively, it may bind to a specific receptor. Antibodies to different domains exist in patients with APS. Most evidence suggests that anti-DI antibodies are most closely related to pathogenicity, but binding of DV to its receptor is required as well. Proposed peptide therapies mainly target the DI–aPL interaction or the DV–phospholipid interaction. However, all studies so far are either in-vitro or in mouse models.

8.1. In vitro and/or animal antiphospholipid syndrome studies

8.1.1. Targeting the aPL–DI interaction

Two groups have studied the effect of deletion or mutation of DI on binding to IgG antibodies from patients with APS (APS-IgG). Both Iversen et al. [123,124] and Ioannou et al. [125] noted an important epitope for binding APS-IgG between residues 39 and 43 of DI. Mutating R39 to serine (variant DI (R39S)) abolished binding [125]. Mutating aspartic acid residues at positions 8 and 9 to serine and glycine produced variant DI (D8S,D9G), which bound more strongly to APS-IgG than wild-type DI [125]. Using the Pierangeli mouse femoral vein thrombosis model, it was then shown that both wild-type DI and DI (D8S,D9G) inhibited thrombosis caused by human APS-IgG in a dose-dependent manner whereas DI (R39S) had no inhibitory effect [126]. Modeling [125] and nuclear magnetic resonance [127] studies suggest that the key epitopes on DI are conformational. Linear peptides containing the R39–R43 epitope do not bind APS-IgG as well as whole DI [128]. Domain I inhibition also reduces IgG-aPL induced TF expression in murine peritoneal macrophages and VCAM-1 expression on thoracic murine aorta EC ex vivo. It therefore seems likely that a future therapy directed at DI will be based on the whole domain.

8.1.2. Targeting the DV–phospholipid interaction

Studies on DV have used short peptides rather than the whole domain. Krilis and colleagues studied a range of peptides derived from DV and showed that those containing the octapeptide CKNKEKKC were best at inhibiting binding of monoclonal and polyclonal aPL to cardiolipin [122]. A 15-amino acid peptide containing CKNKEKKC has been particularly widely used as an inhibitor. This peptide (GDKV) shows strong homology to a cytomegalovirus peptide TIFI. Both TIFI and GDKV, when joined to larger proteins, can be used to immunize mice leading to aPL formation [129]. TIFI has been used as an inhibitor of thrombosis in the mouse femoral vein pinch model. In comparison to a control peptide, TIFI reduced the size of the thrombus produced in response to human APS-IgG [130] and reduced binding of fluorosceinated β_2GPI to human umbilical vein endothelial cells. de la Torre et al., showed that TIFI inhibits binding of aPL to human trophoblast cells in-vitro and also reduces fetal loss in mice induced by injection of aPL [131].

8.1.3. Targeting other domains

It is important to note that not all aPL bind to DI. By screening a phage display library, Blank et al. identified three peptides (designated peptides A, B and C) that bound human monoclonal IgM aβ_2GPI [132]. Peptide A shares homology with the DI/DII interlinker region of β_2GPI. In comparison to a scrambled version of the same peptide used as a control, peptide A reduced thrombosis induced by APS-IgG in the murine femoral vein pinch model [133].

8.2. Completed clinical studies in antiphospholipid antibody-positive patients

No studies.

8.3. Ongoing interventional clinical studies in antiphospholipid antibody-positive patients

No studies.

8.4. Recommendations for clinicians

The task force recommends that at present, none of these peptides is ready for trials in patients; however peptide therapy is potentially an important future targeted treatment for aPL-positive patients. Chemical modification to improve half-life and minimize immunogenicity will be required. Different peptides may be needed for different aPL manifestations. Clinicians should be aware that:

- Based on in-vitro and murine data, peptide therapy may target aPL specifically and thus offer a new paradigm for APS therapeutics.
- There are no peptide therapies currently available or in trials for aPL-positive patients; the task force predicts that peptide therapy will be ready to be tested in aPL-positive patients in the next five years.

9. Vitamin D

Although the goal of the task force was to review potential new medications for aPL-positive patients, the members also decided to briefly comment on the vitamin D supplementation.

Vitamin D has important immunomodulatory functions; vitamin D deficiency (<10–20 ng/ml) and insufficiency (<30 ng/ml) are relatively common in autoimmune diseases [134]. Based on in vitro APS studies, vitamin D may function as an anti-thrombotic immunomodulator by inhibiting β_2GPI-mediated TF expression [135]. Retrospective studies indicate that the prevalence of vitamin D deficiency in APS patients ranges from 10 to 50%, while insufficiency may occur in up to 70% of patients [135–139]. Low vitamin D levels correlate with arterial and venous thrombosis as well as the non-criteria APS manifestations [135,136,139]. In contrast, although most of the studies indicate no association between low vitamin D levels and obstetric APS [135,136,139], a recent cross-sectional study of women with recurrent pregnancy loss reported an association between low vitamin D levels and increased odds of positive aPL [140].

The task force recommends that vitamin D deficiency and insufficiency should be corrected in all aPL-positive patients based on the general population guidelines. The prognostic role of vitamin D deficiency and therapeutic value of supplementation (including the dosage and

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Table 2
In vitro/Animal Antiphospholipid Syndrome (APS) studies, completed and ongoing clinical interventional studies in antiphospholipid antibody-positive patients, and future clinical research directions.

Treatment	In vitro/Animal APS studies	Completed clinical APS studies	Ongoing interventional APS studies	Future clinical research directions
Oral direct thrombin and anti-factor Xa inhibitors	No	No	RAPS	Determining the necessity for venous thrombosis controlled clinical trials pending the results of RAPS trial; designing controlled trials in other forms of thrombotic APS
Older non-warfarin/heparin anticoagulants	Yes	No	No	Systematically analyzing the literature and the aPL/APS registries; creating specific registries
Hydroxychloroquine (HCQ)	Yes	Yes	APS ACTION "HCQ Trial"	Increasing recruitment for an ongoing primary thrombosis prevention trial; designing secondary thrombosis and pregnancy morbidity prevention trials
Statins	Yes	Yes	No	Determining surrogate markers to select aPL-positive patients for statin trials
B-cell inhibition	Yes	RITAPS	No	Designing controlled studies with rituximab and other anti B-cell agents
Complement inhibition	Yes	No	No	Designing mechanistic and clinical studies with eculizumab and other complement inhibitors
Peptide therapy	Yes	No	No	Chemical modification to improve half-life and minimize immunogenicity

APS ACTION: Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking; RAPS: Rivaroxaban in AntiPhospholipid Syndrome; RITAPS: Rituximab in Antiphospholipid Syndrome.

definition of treatment goals) in aPL-positive patients should be clarified with prospective studies that include appropriate control groups and standardized definitions of "vitamin D deficiency".

10. Antiphospholipid Syndrome Treatment Trends Task Force conclusion

The management of the aPL-positive patients with or without APS is currently sub-optimal due to: a) the fact that anticoagulation is not fully effective; and b) given our limited understanding of the origin, specificities, and biologic activities of aPL, new drug development for aPL-positive patients is challenging.

Barriers to the development of new treatment strategies in APS include the multifactorial nature of thrombosis; controversies about the strength of association between aPL and clinical events; the relatively low risk of thrombosis in a randomized controlled trial; and poor understanding of mechanisms of aPL-induced thrombosis.

Recent studies, based on newly understood mechanisms, suggest new treatments that target new coagulation and immunomodulatory pathways. It is tempting to speculate that the current antithrombotic approach to APS patients may be replaced by a potentially safer immunomodulatory approach in the future as our understanding of the molecular mechanisms of aPL-mediated thrombosis grows.

We hope that this report will guide basic and clinical researchers to design future collaborative trials of APS patients (Table 2). At the next International Congress (September 2016 in Istanbul, Turkey — (www.apsistanbul2016.org) we will update this report.

Take-home messages

- Antiphospholipid Syndrome (APS) is characterized by thrombosis and/or pregnancy morbidity occurring in patients with persistent antiphospholipid antibodies (aPL).
- The current treatment for thrombotic APS is heparin followed by long-term anticoagulation with vitamin K antagonists, which is problematic because of numerous drug and food interactions that necessitate frequent monitoring; furthermore, anticoagulation is not effective for all aPL manifestations.
- Recent studies, based on newly understood mechanisms, suggest new treatments for aPL-positive patients that target new coagulation and immunomodulatory pathways.
- The APS Treatment Trends Task Force was one of five task forces developed by the 14th International Congress on aPL Organization Committee with the goal of reviewing potential new treatment strategies (oral direct thrombin or anti-factor Xa inhibitors, non-warfarin/heparin anticoagulants, hydroxychloroquine, statins, B-cell inhibitors, complement inhibitors, and peptide therapy) for aPL-positive patients.
- We hope that this report will guide basic and clinical researchers to design future collaborative trials of APS patients. At the next International Congress (September 2016 in Istanbul, Turkey — www.apsistanbul2016.org), we will update this report.

Uncited reference

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