

Anticoagulation, Recurrent Thrombosis and Major bleeding in antiphospholipid syndrome: UK multicentre observational study

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Abstract:

Antiphospholipid syndrome (APS) is an acquired autoimmune disease characterised by presence of thrombosis and/or pregnancy morbidity with persistently positive antiphospholipid antibodies (aPL). Due to the heterogeneity and relative rarity of this disorder clinical practice in the management of APS remains varied. In this retrospective UK-wide multicentre study, we aimed to delineate clinical practice and outcomes in thrombotic APS to improve the areas of limited knowledge, particularly anticoagulant practice, thrombotic recurrence and bleeding. Anticoagulation in Antiphospholipid Syndrome (A2PLS) is the largest multicentre observational study to date spanning 20 national health service Trusts in the UK and including 500 adult patients (≥ 18 years) with thrombotic APS, on or off anticoagulation during the years 2012–2021. Thrombotic APS is primarily treated with vitamin K antagonists; however, the rates of recurrent thrombosis remain high. In the last decade, recurrent thrombosis occurred in 34.4% (43/125), 32.6% (31/95) and 39.8% (37/93) of single, dual and triple positive aPL patients respectively with a recurrence rate of 46%. There was no difference in the probability of recurrent thrombosis based on the number of positive aPL tests ($p=0.82$) especially in the first three years. However, the probability of recurrent thrombosis was significantly higher in patients with lupus anticoagulant ($p<0.01$) compared to presence of other antibodies. There was a higher probability of recurrence in patients with arterial than venous thrombosis ($p=0.03$). Overall, 10-year bleeding rate was 22.0% with 6.7% patients having major bleeding. Identifying APS patients at higher risk of recurrent thrombosis remains a challenge and current risk stratification is not adequate.

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Abstract

Antiphospholipid syndrome (APS) is an acquired autoimmune disease characterised by presence of thrombosis and/or pregnancy morbidity with persistently positive antiphospholipid antibodies(aPL). Due to the heterogeneity and relative rarity of this disorder clinical practice in the management of APS remains varied. In this retrospective UK-wide multicentre study, we aimed to delineate clinical practice and outcomes in thrombotic APS to improve the areas of limited knowledge, particularly anticoagulant practice, thrombotic recurrence and bleeding. Anticoagulation in Antiphospholipid Syndrome (A²PLS) is the largest multicentre observational study to date spanning 20 national health service Trusts in the UK and including 500 adult patients (≥18years) with thrombotic APS, on or off anticoagulation during the years 2012-2021. Thrombotic APS is primarily treated with vitamin K antagonists; however, the rates of recurrent thrombosis remain high. In the last decade, recurrent thrombosis occurred in 34.4% (43/125), 32.6% (31/95) and 39.8% (37/93) of single, dual and triple positive aPL patients respectively with a recurrence rate of 46%. There was no difference in the probability of recurrent thrombosis based on the number of positive aPL tests ($p=0.82$) especially in the first three years. However, the probability of recurrent thrombosis was significantly higher in patients with lupus anticoagulant ($p<0.01$) compared to presence of other antibodies. There was a higher probability of recurrence in patients with arterial than venous thrombosis ($p=0.03$). Overall, 10-year bleeding rate was 22.0% with 6.7% patients having major bleeding. Identifying APS patients at higher risk of recurrent thrombosis remains a challenge and current risk stratification is not adequate.

Running title: Recurrent thrombosis and bleeding in APS

Key words. Antiphospholipid syndrome; Thrombosis; bleeding; warfarin, direct acting oral anticoagulants

Key points

1. Due to the heterogeneity and relative rarity of this disorder clinical practice in the management of APS remains varied
2. 10-year recurrent thrombosis rate was 46% with a higher probability of recurrence in patients with lupus anticoagulant ($p<0.01$).

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Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune disease characterised by development of thrombosis and/or specifically defined pregnancy morbidity in association with persistently positive antiphospholipid antibodies (aPL). Various autoantibodies can be found in patients with APS but current clinical diagnosis of APS is based on the detection of one or more antibodies defined as 'criteria antibodies', namely lupus anticoagulant (LA), IgG and IgM anticardiolipin antibodies (aCL) and anti- β 2-glycoprotein I (anti- β 2GPI) antibodies at least two occasions > 12 weeks apart[1]. APS is a highly prothrombotic disease especially in patients with triple positive aPL (presence of all three criteria aPL) who are reported to be at highest risk of both a first thrombotic event and further recurrence[2].

Despite the autoimmune nature of the disease, the current mainstay of treatment in thrombotic APS is with anticoagulation. However, there is a clear difference in the efficacy of different anticoagulants, notably for triple positive aPL or patients with arterial thrombosis[3]. Vitamin K Antagonists (VKA) have been used in patients with thrombotic APS for many years but direct acting oral anticoagulants (DOACs) including rivaroxaban, apixaban, and edoxaban (direct FXa-inhibitors) and dabigatran (direct thrombin inhibitor) have been established as first line treatment for patients with venous thrombosis (VTE) without APS, owing to their safety data, ease of administration and lack of requirement for monitoring[4].

Consequently, the use of DOACs in patients with APS has been investigated. The trial of Rivaroxaban in AntiPhospholipid Syndrome (TRAPS), a randomized open-label multicentre noninferiority study comparing rivaroxaban to VKA in thrombotic triple positive APS was prematurely terminated due to excess arterial thrombotic events in patients receiving rivaroxaban (12%) compared to no recurrent thrombosis in VKA group[5]. Major bleeding events occurred in 7% and 3% of patients treated with rivaroxaban and VKA respectively[5]. This culminated in the Medicines and Healthcare Products Regulatory Agency and European Medicines Agency issuing recommendations that DOACs should not be used for treatment or secondary prevention of thrombosis in all APS patients, especially in those with triple positive APS[6, 7]. Subsequently, meta-analysis of four open-label randomised controlled trials (RCTs) [3, 5, 8, 9] comparing outcomes in 472 APS patients receiving DOACs or VKA

showed that DOACs were associated with an increased risk of arterial thrombotic events (OR 5.43, 95% CI 1.87-15.75, $p < 0.001$), especially stroke (OR 10.74, 95% CI 2.29-50.38)[10]. Importantly, this risk persisted regardless of aPL status (i.e. triple positive or not) and regardless of index thrombotic event (venous or arterial thrombosis). No difference in major bleeding between two anticoagulants was observed. Furthermore, there was only a trend toward a higher risk of recurrent arterial thrombosis in patients with single or dual positivity aPL treated with a DOAC compared to VKA (OR, 4.29; 95% CI, 0.75-24.43) [10]. As such, the British Society for Haematology (BSH) guidelines on APS in 2020 and updated in 2024, recommended against the use of DOACS, specifically following arterial thrombosis and VTE in '*triple positive*' individuals. Furthermore, in the absence of strong evidence for superior efficacy of VKA over DOACs in these groups, these guidelines suggested, rather than recommended, the use of VKA in thrombotic APS with single or dual positive aPL following VTE [6].

The prospect of further clinical trials investigating optimal therapy for thrombotic APS patients with non-triple positive aPL is limited due to concern over recurrent thrombosis with DOAC and also rarity of the disease. Furthermore, an important unresolved question in the management of APS is whether arterial thrombosis in APS patients is best managed with antiplatelet agents (single or dual) alone, anticoagulant therapy alone, or by a combination of the two.[11] Delineating clinical practice and outcomes in thrombotic APS in the UK would improve the current limited knowledge of anticoagulant safety and efficacy in this disorder.

In this retrospective UK-wide multicentre study, we aimed to evaluate anticoagulation practice, determine compliance with the current BSH guidelines and explore rates of thrombotic recurrence and bleeding in thrombotic APS.

Materials and Methods

Study design

Anticoagulation in Antiphospholipid Syndrome (A²PLS) is a multicentre observational study across 20 national health service (NHS) Trusts in the United Kingdom (UK). The study was

deemed an audit and not research by the NHS Health Research Authority (HRA) research decision tool. Therefore, formal ethics approval was not required. Results were compared to current BSH recommendations retrospectively. Data collection was approved by the audit departments at each participating centre prior to data entry (Audit registration number HAE_018). Data was collected retrospectively from patient clinical records by medical professionals with no breach of privacy or anonymity and allocating a unique study number. Inclusion criteria for the study were adult patients (≥ 18 years at the time of first thrombosis) with thrombotic APS on or off anticoagulation under clinical review between January 2012 and January 2022. Thrombotic events were objectively confirmed by radiological imaging and/or clinical review especially transient ischaemic attack. Minimal testing for APS comprised the testing for all three standard aPL (LA, IgM/IgG aCL and anti- $\beta 2$ GPI) and patients were only included in the 10-year event analysis after confirmation of aPL positivity following repeat testing at ≥ 12 weeks. Exclusion criteria were patients < 18 years of age and patients with only obstetric APS.

Data Collection

Data collection was facilitated nationally via the HaemSTAR network, a UK-wide network of clinical haematology trainees supported by the National Institute of Health Research non-malignant clinical research network (collaborators listed below). This project utilised the secure Research Electronic Data Capture (REDCap) database (REDCap v10.0.10; Vanderbilt University, Nashville, TN, USA) hosted by Imperial College London. Data were entered by clinicians responsible for patient care onto a bespoke standardised case report form (CRF). Baseline patient demographics, comorbidities, antiphospholipid antibody status and relevant clinical history including thrombotic, bleeding events and anticoagulation details were collected.

Outcomes

The primary outcome was to assess antithrombotic use according to type of initial thrombosis and triple vs non-triple APS type. Secondary outcomes were to assess thrombosis recurrence during follow-up according to APS testing patterns and type of antithrombotic. Major bleeding as a safety outcome was also assessed.

Statistical analysis

Categorical variables were reported as proportion and/or percentage. Continuous variables were reported as mean ($\pm$ SD) or median (range) value. The Fisher's exact test or chi-square test for categorical variables and the Student t-test or Wilcoxon-Mann-Whitney test for continuous variables were used as appropriate. Survival analysis was performed using Kaplan-Meier method and the log-rank test was used to examine the differences between curves. Multivariable Cox regression models were performed to determine the odds ratios (ORs) and 95% CIs of individual factors of interest. To identify factors associated with the probability of thrombosis-free survival, Kaplan-Meier curves were compared using the log-rank test. Factors found to be statistically significant at the $P < 0.2$ level were then entered into a stepwise Cox regression analysis, to produce a final model that encompassed all independent prognostic factors significant at $P < 0.05$. Tests of significance were two-sided and a p-value < 0.05 was considered significant. Analyses and figures were performed using R (R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org>).

Institutional Review Board has approved the study (Audit registration number HAE_018), which was conducted in accordance with the Declaration of Helsinki.

Results

Baseline Characteristics

500 patients with APS diagnosed after a first thrombosis from across 20 UK NHS Trusts were included in this study. The patients were predominantly female (58.6%) and the median age was 45.6 (IQR 18-87) years at the time of diagnosis. 37.4% of patients had co-existent autoimmune diseases. Baseline characteristics of the group including aPL profile and drug history are summarised in **Table 1**.

Anticoagulation Practice

Overall anticoagulation practice in the study group is summarised in **Figure 1**.

Thrombotic Events

Overall, 73.2% (366/500) patients had had VTE and 26.8% (134/500) arterial thrombosis at the time of APS diagnosis.

Arterial Thrombosis

Baseline characteristics of those with arterial thrombosis are summarised in **Table 1**. The sites of arterial thrombosis were stroke in 68.7% (92/134), myocardial infarction (MI) in 24.6% (33/134) and transient ischaemic attack in 6.7% (9/134). 68 (50.7%) of patients with arterial thrombosis were on an antiplatelet treatment in addition to anticoagulation. No patients were on antiplatelet treatment alone. On univariate analysis increasing age at diagnosis was associated with increased risk of arterial thrombosis between ages 40-60 (OR 4.12; 95% CI 1.71-11.6 $p=0.003$) and increased further in those over 60 (OR 7.74; 95% CI 3.25-21.6 $p<0.001$) compared to those between 18-40. In addition, male sex was also associated with increased risk of arterial thrombosis (OR 1.97; CI 1.19-3.29 $p=0.009$) on univariate analysis. Other parameters increasing risk of arterial thrombosis on univariate analysis included smoking (OR 3.22; CI 1.61-6.61 $p<0.001$) and hypocholesteremia (OR 5.02 CI 2.9-7.09 $p<0.001$). On univariate analysis triple positive antibody status did not significantly impact risk of arterial thrombosis (OR 1.17; 95% CI 0.69-2.0, $p=0.6$) although interestingly, double positive aCL and anti- β 2GPI was associated with increased risk of arterial thrombosis (OR 2.04; 95%CI 1.13-3.69, $p=0.01$). All parameters significant on univariate analysis were included in the multivariate analysis (MVA). Increased age of 40-60 remained significant on MVA (OR 4.43; 95% CI 1.65-13.7, $p=0.005$) as did age over 60 (OR 5.71; 95% CI 2.09-17.8, $p<0.001$). Smoking, hypercholesterolemia and double positivity for aCL and anti- β 2GPI also all remained positive on MVA; OR 3.11; 95% CI 1.36-7.36, $p<0.008$; OR 3.62; 95%CI 1.89-7.09, $p<0.001$ and OR 4.01; 95%CI 1.33-12.7, $p=0.015$, respectively. Male sex no longer remained significant on MVA. Taken together, those presenting with arterial thrombosis were more likely to be older males, with high cholesterol and a history of smoking and an antibody profile of dual aCL and anti- β 2GPI positivity.

Venous Thrombosis

Baseline characteristics of those with VTE are summarised in **Table 1**. The sites of VTE were deep vein thrombosis (DVT) in 42.6% (156/366), cerebral venous sinus thrombosis (in 27.3% (100/366), pulmonary embolism in 25.9% (95/366) and portal vein thrombosis in 4.1% (15/366). Unlike arterial thrombosis, age, atherosclerotic risk factors or any particular

antibody profile were not associated with VTE suggesting they may be a more heterogeneous group or more dependent on circumstantial factors.

Recurrent thrombosis

The Kaplan-Meier estimate of recurrence rate for all patients under follow up was 55% at 25 years. However, this value encompasses diagnoses of thrombotic APS as far back as 25 years and will be confounded by patients lost to follow up over that time. To explore this, further analyses were performed to compare recurrence between various of eras of diagnosis (Figure 2B). Complete follow up was available for 313/500 patients who were diagnosed within the last decade of the study criteria (2012-2022). The median duration of follow up for the 2012-2022 cohort was 1438 days. The K-M estimate of 10-year recurrence rate for this group was 46% (Figure 2B). Notably recurrence largely occurred within the first 5 years of diagnoses with very low recurrence rate after this point. There was overall no significance difference in recurrence between males and females ($p=0.6$) (Figure 3A). 10-year probability of recurrence was higher in patients with arterial thrombosis compared to VTE ($p=0.03$) (Figure 3B).

The recurrence rates for the 95/500 diagnosed between 2008 and 2012 and 92/500 diagnosed prior to 2008 were lower overall than in the study period 2012-2022. This was largely expected due to death, loss of follow-up and changes in diagnostic criteria and management of APS over time (Figure 2B).

Probability of Recurrent thrombosis according to aPL profile.

In the 2012-2022 cohort of patients, recurrent thrombosis occurred in 34.4% (43/125), 32.6% (31/95) and 39.8% (37/93) of single, dual and triple positive aPL patients respectively. There was no difference in the probability of recurrent thrombosis based on the number of aPL ($p=0.82$) especially in the first three years (Fig 4A). However, the probability of recurrent thrombosis was significantly higher in patients with LA ($p<0.01$) compared to other antibodies (Fig 4B). No difference in the probability of recurrent thrombosis was seen with patients positive for anti- $\beta 2$ GPI antibodies ($p=0.122$) (Figure 4C) or anti-cardiolipin antibodies only, compared to other antibodies($p=0.6$) (Figure 4D).

Given the significant association of LA with recurrence, it was then assessed in combination with either aCL or anti- β 2GPI. However, the recurrence rate was not altered by the combination of LA with anti- β 2GPI or aCL ($p=0.16$ combined with anti- β 2GPI and $p=0.06$ combined with aCL) supporting the role of LA as the primary driver of thrombotic recurrence (Figure 5 A and B). Furthermore, rates of recurrence with isolated LA positivity and triple antibody are almost identical, again suggesting that it is LA that is the most potent predictor of thrombosis (compare Figures 4A triple positive curve and 4B LA positive curve).

Management of recurrent thrombosis

Seventy-four of 192 patients who developed recurrent thrombosis (38.5%) switched to different anticoagulation or increased the intensity of their existing anticoagulation. Of these 74 patients, 87.9% (65/74) were on a DOAC and all of these switched to a VKA. Nine out of 74 (12.1%) who had recurrent thrombosis were on VKA: 5/9 who developed recurrence whilst on VKA had a target INR 2.5 (2.0-3.0) and subsequently had their target INR increased to 3.5 (3.0-4.0). The remaining 4 patients (4/9) were switched to a DOAC. Notably the 5 patients who had recurrence whilst on target INR of 2.5 were triple positive and the 4 patients who changed to a DOAC from VKA were non-triple positive and importantly these patients had time in therapeutic range of <50 % whilst on VKA. No second recurrences occurred following these described changes to anticoagulation within the study period.

Use of Hydroxychloroquine in thrombotic APS

Overall, 109 patients (21.8%) were treated with Hydroxychloroquine (HCQ) and of these, 60.6% (66/109) were given HCQ 200mg once daily whilst 39.4% (43/109) were given 200mg twice daily. Of the 109 patients on HCQ, in 13 % (14/109), the drug was started following the first thrombotic event and in 37% (40/109) following recurrent thrombosis. Of the remainder, HCQ was started with the concomitant diagnosis of other autoimmune disease (systemic lupus erythematosus and rheumatoid arthritis). It was found that patients with recurrent thrombosis were 13.8 times (95% CI 2.39-26, $P=0.01$) more likely to be started on HCQ compared to patients who had had a single thrombotic event suggesting it is used as an adjunct to treatment in recurrent thrombosis. Of the 13 patients commenced on HCQ after first thrombotic event, none developed recurrence within the study period.

Bleeding events whilst on anticoagulation

The 10-year bleeding rate between 2012-2022 (major or clinically significant non-major bleeding) whilst on anticoagulation was 22.0% (69/313). Major bleeding occurred in 6.7% (21/313) of patients and clinically significant non-major bleeding in 15.3 % (48/313) (as defined by International Society for Haemostasis and Thrombosis Scientific Standardization committee [12, 13]. Of these, 82.6% (57/69) occurred on VKA and 71.9% (41/57) occurred on standard intensity VKA . Intracranial haemorrhage was the most common major bleeding event, comprising 47.6% (10/21) followed by gastrointestinal bleeding comprising 28.6% (6/21). Increasing age was the only factor significantly associated with major bleeding on MVA. [OR) 1.05, 95% CI 1.01-1.10; P = 0.02]

Discussion

We report the largest study to date assessing the thrombosis and bleeding events in a nationwide cohort of patients with thrombotic APS in the United Kingdom. This study has some important key findings; notably the high recurrent thrombotic rate of 47% within 10-years), principally in the first 5 years from diagnosis, the strong association between LA and recurrent thrombosis and the relatively low bleeding rates in this cohort, 92% of whom were receiving antithrombotic therapy.

Our study provides valuable insight into management of venous and arterial thrombosis in APS nationally in the UK. Overall, we found that 95.1% of triple positive patients in the study were placed on VKA and 4.9% on DOACS. This contrasts with 54.1% of patients on VKA and 24.8% on DOACs in non-triple positive APS. Altogether this demonstrates that practice in the UK is largely in keeping with guidance for the highest risk APS cohort, but there remains a small group of triple positive patients on DOACS, in some cases due to poor time in therapeutic range INR.

Patients with arterial thrombosis and APS are an established high-risk group of patients with high rates of recurrence on standard anticoagulation or antiplatelet treatment and no agreed consensus of management to date. In the Euro-Phospholipid Project Group the most common arterial thrombotic manifestation was strokes and in another Polish cohort study

of 163 patients, arterial thrombosis manifested as stroke (65.3%), transient ischemic attacks (10.25%) and myocardial infarction (20.5%), which closely match the values in our own study (59.4%, 10.6% and 30% respectively)[14]. We did not find arterial thrombosis to occur more frequently in triple positive disease, but it was associated with increasing age, presence of atherosclerotic risk factors and dual aCL and anti- β 2GPI positivity. Other studies have also implicated IgG aCL antibodies in arterial thrombosis and it is plausible that anti- β 2GPI may further assist in identifying those at risk [15, 16]. When considering anticoagulation in this group, patients on DOACS consistently showed a significantly higher arterial recurrence [10]. In this study, although not statistically significant, the use of a DOAC showed a trend towards an increased risk of recurrence (OR 2.19 CI 0.52-11 p=0.3), compared to treatment with VKA (Table 2). We note that the UK practice has taken this concern into account and 81.3% of patients with arterial thrombosis were on VKA and 6.7% on DOACs with the remaining 11.9% patient on alternative anticoagulants. There was also a greater preference for higher intensity INR with VKA in this group compared with VTE (27.7% vs 14.7%).

There was a significantly increased risk of recurrence in those with arterial thrombosis compared to VTE confirming the need for more intensive antithrombotic regimens in this high-risk group (Figure 2B). Furthermore, there is little difference in the probability of recurrence between the non-triple and triple positive patients. This may be due to improved recognition of the highest risk triple positive patients resulting in more intensive anticoagulation and/or less frequent use of DOACs in triple positive patients (10.6% vs 88.4%).

The role of combined antiplatelet and anticoagulant therapy for arterial thrombosis remains unclear. In our study, 68 (50.7%) of patients with arterial thrombosis were on an antiplatelet treatment in addition to anticoagulation. A systematic review and meta-analysis of 13 studies including 719 patients, showed that combined antiplatelet and warfarin is associated with a significant reduction in the risk of recurrent overall thrombosis (relative risk [RR] of 0.41 [95% CI 0.20 to 0.85]) compared to single antiplatelet treatment (SAPT)[17]. DOAC use was associated with a significant increase in the risk of recurrent arterial thrombosis, with an RR of 4.06 (95% CI 1.33 to 12.40) when compared to SAPT. However,

there was no significant difference in major bleeding amongst various antithrombotic strategies[17]. As expected, atherosclerotic risk factors were more predominant in patients presenting with arterial thrombosis and associated with increased arterial thrombotic risk on MVA, highlighting the need for stringent cardiovascular risk factor management strategies; which was found to be suboptimal in the management of patients with APS[18] .

The most striking finding in this study was the confirmation of high probability of recurrence of 46% at 10-years. Pengo et al, in 2017 found the cumulative incidence of recurrent thromboembolic events to be 12.2% (95% CI, 9.6-14.8) after 1 year, 26.1% (95% CI, 22.3-29.9) after 5 years and 44.2% (95% CI, 38.6-49.8) after 10 years[2]. Similarly, in the 2015 Piedmont cohort study the cumulative incidence of thrombotic recurrences was 12.5% at one year, 29% after three -years, 38% after five years and 49% after ten years[19]. An interesting finding in our study was low rates of thrombosis recurrence after 5 years from diagnosis. RCTs have typically reviewed after shorter follow-up periods and may not have seen this phenomenon. Furthermore, we did not observe any second episodes of recurrence within the study period following the anticoagulation changes after initial recurrence. We speculate that could be due to improved standards of care especially vascular risk reduction, effective modification of therapy, including return to VKA for high risk (triple positive) patients, continuation of anticoagulation and combination with HCQ in a significant number. Furthermore, it could also imply that there is a subgroup of patients with high thrombotic risk who might benefit from alternative or more intensive therapy from diagnosis.

Not all aPL profiles have the same contribution to risk of developing thrombosis and LA positivity was defined as one of the high-risk aPLs profiles according to the EULAR recommendations and Global Anti-Phospholipid Syndrome Score [20, 21]. In a meta-analysis of 16,441 patients from 30 studies which reported an OR of 6.14 (95% CI 2.74–13.8, $P < 0.001$) for VTE associated with LA, compared with OR of 1.46 and 1.61 for aCL and anti- $\beta 2$ GPI, respectively[22]. For arterial thrombosis, the OR of LA was 3.58 (95% CI 1.29–9.92, $P=0.01$)[22]. Furthermore, LA has been identified as an independent risk factor for first thrombosis in aPLs carriers. Our study is in agreement with this, and LA positivity had a significantly higher probability of recurrence compared to any other antibody in isolation

($p < 0.01$) (Figure 4B). Furthermore, in our study, thrombosis free survival curves of isolated LA positivity and triple antibody are almost identical, suggesting that it is LA alone that is the most potent predictor of thrombosis (compare Figures 4A triple positive and 4B LA positive.) Whether this suggests that the presence of LA alone should warrant anticoagulation with VKA over DOAC remains to be determined, particular in non-triple positive APS however, consideration must be given to the possible lack of standardization in testing of solid phase antibodies across various labs in the UK that may make aCL and anti- β 2GPI less valuable in this context.

Interestingly, combined LA and aCL positivity (Figure 4B) had a trend towards an increased rate of recurrence ($p = 0.067$) which may delineate them as a higher risk group of dual positive thrombotic APS patients that may prove clinically valuable though further studies may be required to confirm this.

Strategies for managing recurrence in APS are limited but can include intensification of INR in the context of VKA, switch to LMWH or addition of an antiplatelet treatment, or an immunomodulatory drug, in particular HCQ [11, 23]. Although not established practice throughout the UK, HCQ has demonstrated antithrombotic effects in *in-vivo* and *in-vitro* studies[24]. Due to the small number of patients started on HCQ after a thrombotic event at APS diagnosis in this study ($n = 13$) we are unable to accurately assess its impact on recurrence however none of these 13 patients went on to develop recurrence during follow-up. We did however find patients with recurrent thrombosis were 13.8 times more likely to receive HCQ compared to patients without recurrent thrombosis[24, 25]. HCQ may be particularly of use in those with co-existent systemic lupus erythematosus (SLE), a group which this study identified as having a significantly increased probability of recurrence[26].

Clinically significant bleeding was experienced by 22.0% with 6.7% % patients having major bleeding. These figures are lower than the rate in large meta-analyses of anticoagulation for VTE which found the 5-year cumulative incidence of major bleeding with VKAs in the general population to be 6.3% (CI, 3.6% to 10.0%). This may reflect underreporting leading to bias or due to the underlying prothrombotic phenotype of this cohort[27]. Recent work by a single-centre group documented a major bleeding rate of 22.8% however this study included

24.9% of patients on combined antithrombotic therapy as well as 41.9% on high-intensity anticoagulation with target INR >3[28].

The strengths of the present study are that it is the largest study of APS in the UK documenting real-world data over a 10-year period representative of practice in the UK in both tertiary and non-tertiary centres. It had similar overall response rates to previously published data but provides more long-term follow up and detailed assessment of recurrence. This study has several limitations. Its retrospective, observational design limits causal inference and introduces potential confounding by indication, as treatment choices were influenced by clinician judgement and evolving guidelines. Although data was collected using a pre-designed eCRF to maintain uniformity, data was obtained from the routine clinical records across multiple centres, resulting in heterogeneity in follow-up, imaging practices and laboratory assays, particularly for aPL testing, which may have affected antibody classification. LA testing may have been influenced by concurrent anticoagulation, leading to possible misclassification. Recurrent thrombotic and bleeding events may have been under-ascertained if patients presented to other institutions and not reported to the managing centre. Follow-up duration varied, and as noted, longer-term recurrence estimates may be affected by loss to follow-up. Finally, subgroup analyses, particularly adjunctive therapies such as hydroxychloroquine were limited by small numbers and should be considered exploratory.

In conclusion, in the UK most APS patients with high-risk venous thrombotic and arterial thrombosis were treated with VKA. However, the rate of recurrent thrombosis remained high. Although the rate of major bleeding is low, increasing age was significantly associated with major bleeding. Taken together, there is an outstandingly high thrombotic risk in APS and identifying APS patients at higher risk of recurrent thrombosis is still an unsolved issue. This unacceptably high rate of recurrent thrombosis may further support the need to unravel and target alternative pathogenic mechanisms of thrombosis in APS in addition to anticoagulation to prevent recurrent thrombosis. Finally, LA has shown a significant association with recurrent thrombosis with both aCL and anti- β 2GPI having minimal impact. This highlights the importance of appropriate testing of LA in patients with suspected APS which is frequently affected by anticoagulation.

Author contributions: CCT designed the study, involved data verification, interpretation of data, writing and editing the manuscript. IR and ZO were involved in data verification, data analysis, figures, data interpretation and reviewing the manuscript. AD and KB contributed to data collection, interpretation of data and reviewing the manuscript. ML interpreted the data, reviewed, and edited the manuscript. DJA conceived the study, designed the study, involved in data verification, data interpretation, writing, reviewing and editing the manuscript. All authors reviewed and approved the final version of the manuscript.

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Legends to tables and figures

Table 1: Baseline characteristic including demographics, antiphospholipid antibody profile, vascular risk factors and antithrombotic treatment of the patients of all thrombotic APS patients in the study, those with venous thrombosis and those with arterial thrombosis.

LA : lupus anticoagulant, aCL: anticardiolipin antibody, anti- β 2GP1 – anti-beta-2-glycoprotein I antibody, IHD: Ischaemic Heart Disease INR: International Normalised Ratio.

Table 2. Factors included for the univariate analysis of probability of thrombosis recurrence in Thrombotic APS

Figure 1: Flow chart demonstrating anticoagulation practice in the 500 patients included in this study.

VKA : Vitamin K Antagonist, DOAC : Direct oral anticoagulant, LMWH : Low molecular weight heparin

Figure 2: K-M calculation of cumulative incidence of recurrent thrombosis from time of diagnosis in overall cohort of patients with thrombotic APS **(A)** and calculation by era of diagnosis **(B)**

Figure 3: K-M calculation of cumulative incidence of recurrent thrombosis from time of diagnosis with comparison between male and female sex **(A)** and comparison between those with arterial and venous thrombosis **(B)**

Figure 4. K-M calculation of cumulative incidence of recurrent thrombosis from time of diagnosis based on aPL profile comparing single, dual and triple positive groups **(A)** as well as each aPL (LA, aCL, anti- β 2GPI) individually **(B,C,D)**

Figure 5. Probability of recurrent thrombosis varies based on the combination of dual aPL. K-M calculation of cumulative incidence of recurrent thrombosis from time of diagnosis based on combinations of the two antibodies LA and anti- β 2GPI **(A)** and LA and aCL **(B)**

Table 1

		All thrombosis (n=500) (%)	Venous Thrombosis (n=366) (%)	Arterial Thrombosis (n=134) (%)
Total		500	366	134
Gender	Male	207 (41.4%)	125 (34.1%)	82 (61.2%)
	Female	293 (58.6%)	241 (65.8%)	52 (38.8%)
Age (Years)	IQR	18-88	18-76	22-88
	Median	45.6	42.3	55.7
	18-30	56 (11.2%)	45 (12.3%)	11 (8.2%)

	31-50	160 (32.2%)	128 (35.0%)	32 (23.9%)
	51-70	212 (42.4%)	164 (44.8%)	48 (35.8%)
	>71	72 (14.4%)	29 (7.9%)	43 (28.4%)
Antibody Status at time of diagnosis	Single Positive	155 (31%)	117 (31.9%)	38 (28.4%)
	Dual Positive	163 (32.6%)	114 (31.1%)	49 (36.6%)
	Triple Positive	182 (36.4%)	135 (36.9%)	47 (35.1%)
Anticoagulation Type initiated	VKA*	345 (69.0%)	236 (64.5%)	109 (81.3%)
	DOAC	85 (17.0%)	76 (20.8%)	9 (6.7%)
	Other/None	70 (14.0%)	54 (14.8%)	16 (11.9%)
INR of those on VKA	2.5-3.5	278 (80.6%)	167 (85.2%)	99 (72.3%)
	3.5-4.5	67 (19.4%)	29 (14.7%)	38 (27.7%)
Co-existent Autoimmune Disease		187 (37.4%)	139 (37.9%)	48 (35.8%)
	SLE	72 (39.6%)	50 (35.9%)	22 (45.8%)
	Rheumatoid Arthritis	38 (20.3%)	18 (12.9%)	20 (41.6%)
	Sjogren's	15 (8.0%)	9 (6.5%)	6 (12.5%)
	Hypothyroidism	10 (5.3%)	7 (5.0%)	3 (6.2%)
	Other	52 (27.8%)	32 (23.0%)	20 (41.6%)
Hydroxychloroquine	200mg OD	66 (13.2%)	37 (10.1%)	29 (21.6%)
	200mg BD	43 (8.6%)	19 (5.2%)	24 (17.9%)
Antiplatelet therapy initiated	Any antiplatelet	178 (35.6%)	110 (30.1%)	68 (50.7%)
	Single	147 (82.6%)	89 (80.9%)	58 (85.3%)
	Dual	31 (17.4%)	21 (19.1%)	10 (14.7%)
Arterial Risk Factors	Hypertension	212 (42.4%)	96 (27.1%)	116 (62%)
	Diabetes mellitus	194 (38.8%)	99 (28%)	95 (50.8%)
	IHD	50 (10%)	28 (8%)	22 (11.8%)
	Hypercholesterolaemia	124 (24.8%)	66 (18.6%)	58 (31%)
	Smoking	109 (21.8%)	44 (12.4%)	65 (34.7%)
	High BMI (>30)	64 (12.8%)	30 (8.5%)	34 (18.1%)

* 8/500 (1.6%) patients were on an alternative VKA that was not warfarin owing to allergic reactions

Table 2

	Subgroup	Odds Ratio for recurrence	95% Confidence-Interval	p-value
Age	40			
	40-60	0.58	0.28-1.22	0.15
	60+	1.23		0.6

Sex	Male			
	Female	1.03	0.61-1.74	0.9
Anticoagulation at time of recurrence	VKA			
	DOAC	2.19	0.02-0.37	0.3
Use of antiplatelet	No			
	Yes	1.69	0.97-2.92	0.062
Ischaemic Heart Disease	No			
	Yes	2.36	0.97-2.92	0.067
Hypercholesterolaemia	No			
	Yes	1.95	0.90-4.22	0.087
Smoking	No			
	Yes	1.48	0.73-2.93	0.3
High BMI	No			
	Yes	1.94	0.88-4.29	0.1
Additional autoimmune disease	Hypothyroidism			
	Sjogren's	1.28	0.57-2.8	0.5
	SLE	5.75	1.28-40.1	0.035
	ITP	0.85		0.6
Lupus Anticoagulant	No			
	Yes	2.61	1.49-4.69	<0.01
Triple positivity	No			
	Yes	1.3	0.76-2.23	0.3
Double positive : LA + aCL	No			
	Yes	3.37	1.44-8.35	0.006
Double positive : LA + anti-βGP1	No			
	Yes	1.21	0.67-7.4	0.8
Double positive : aCL + anti-β2GP1	No			
	Yes	1.35	0.16-1.68	0.004

Figure 1

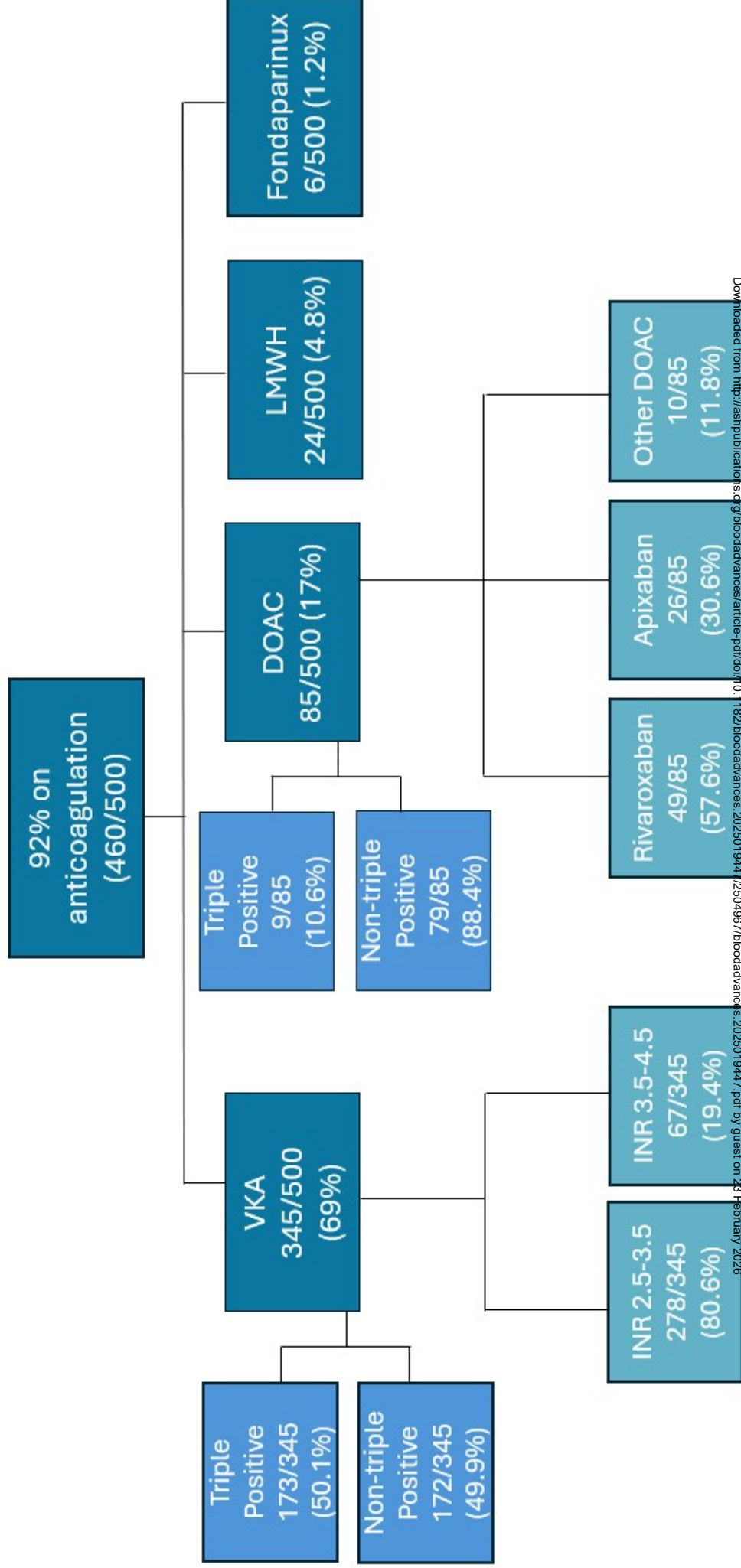


Figure 2

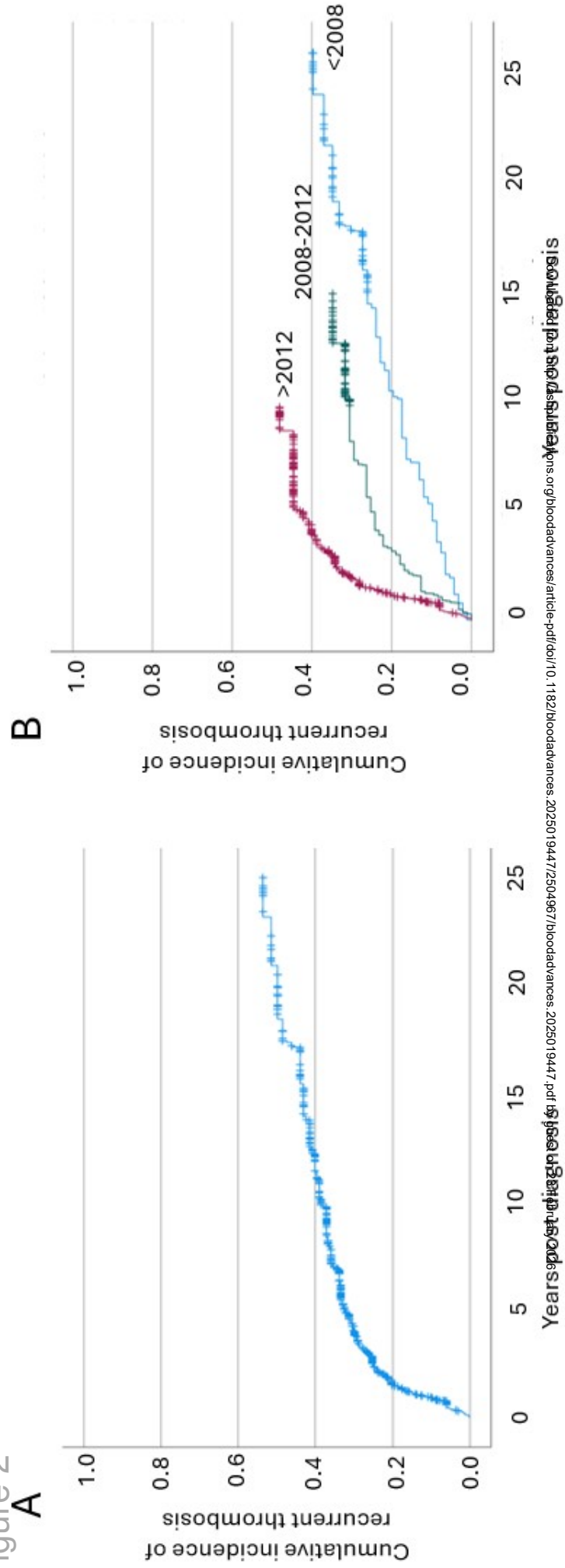
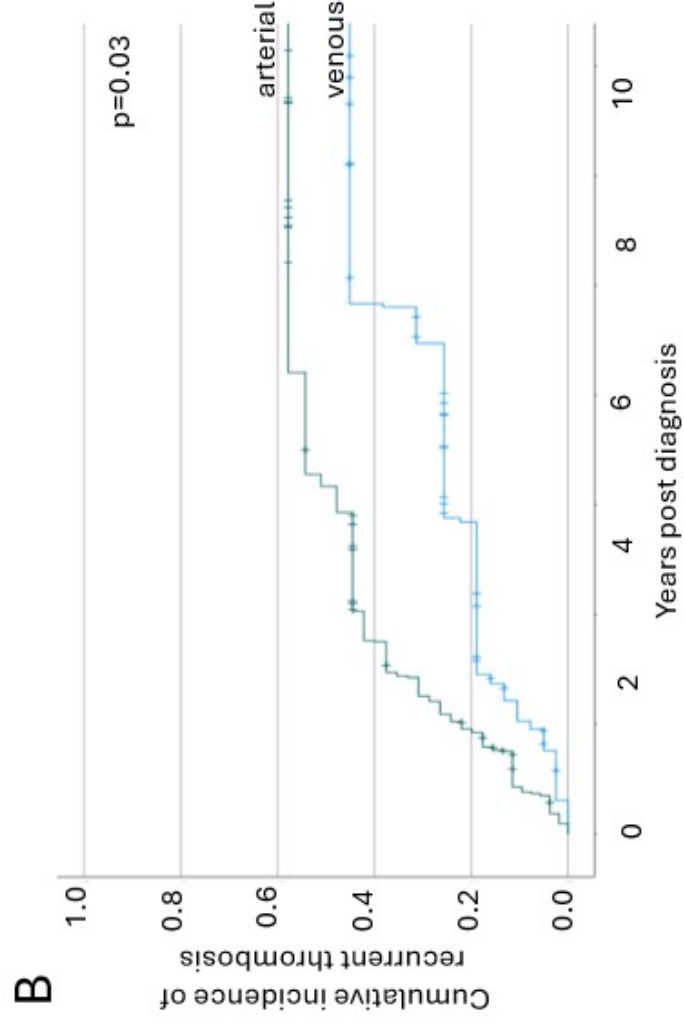
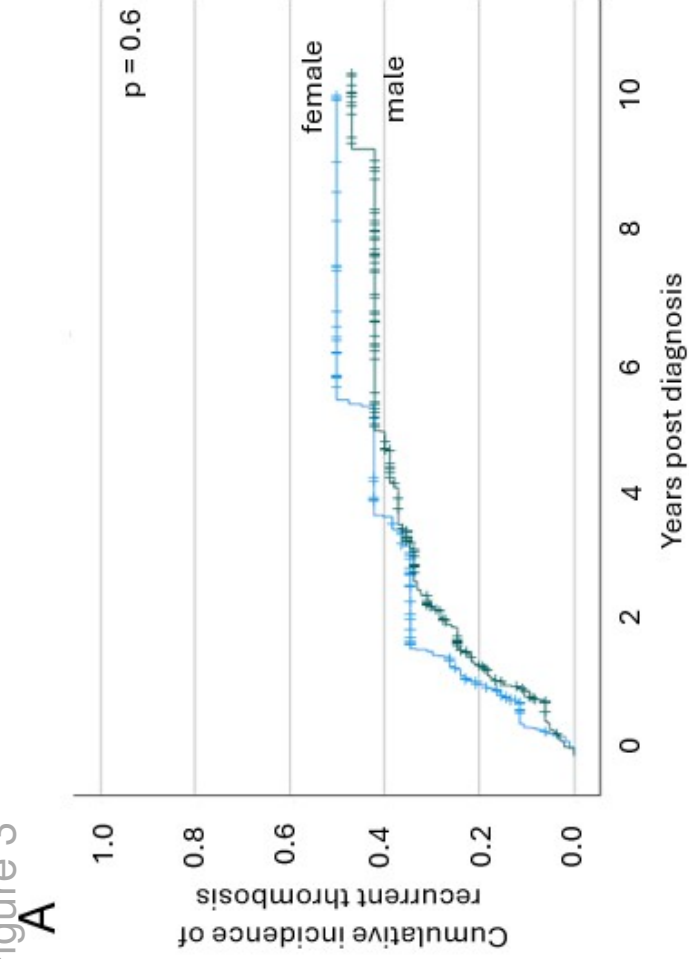


Figure 3



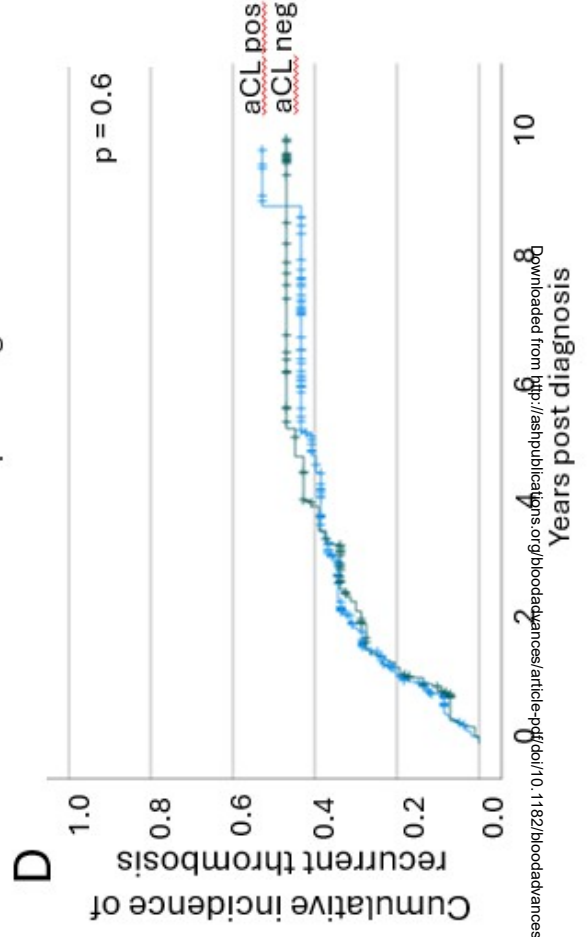
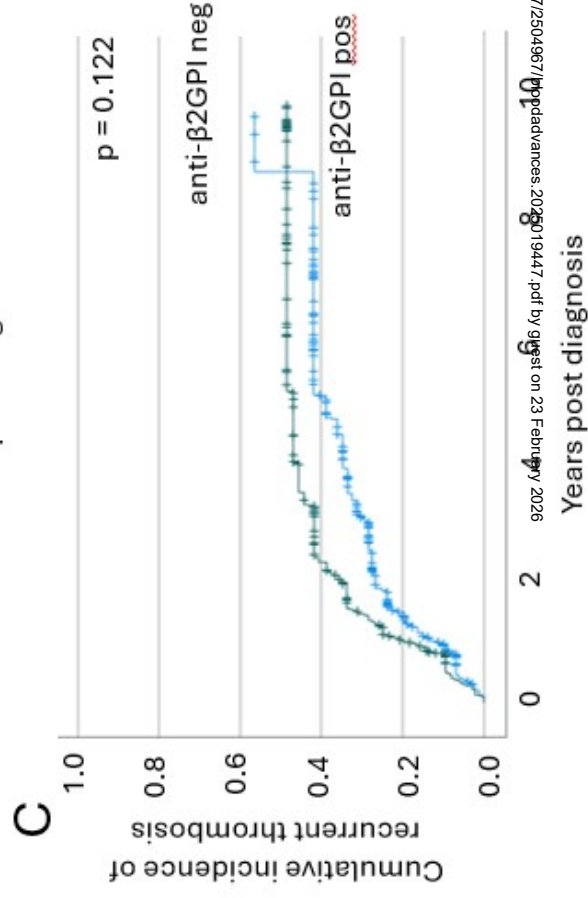
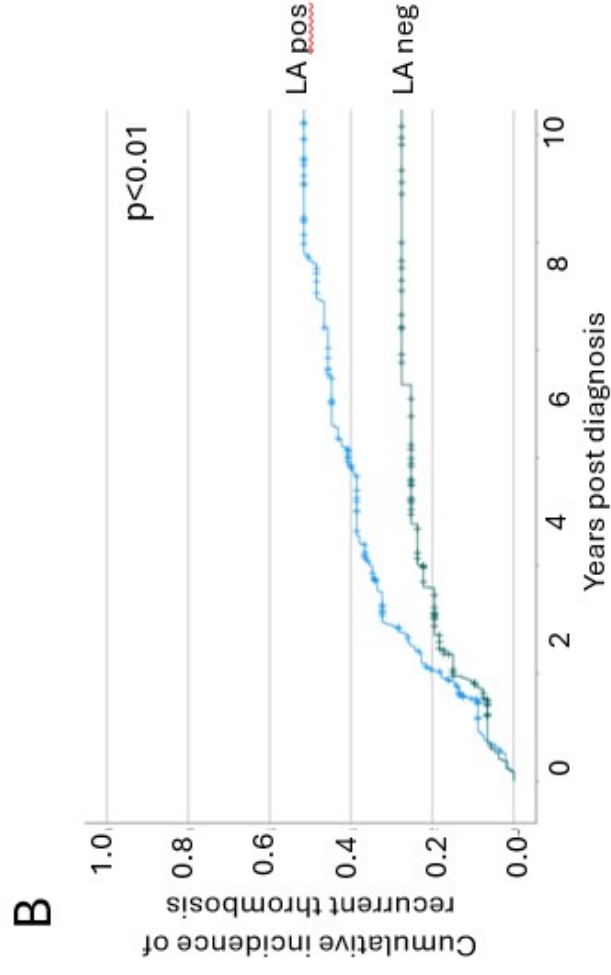
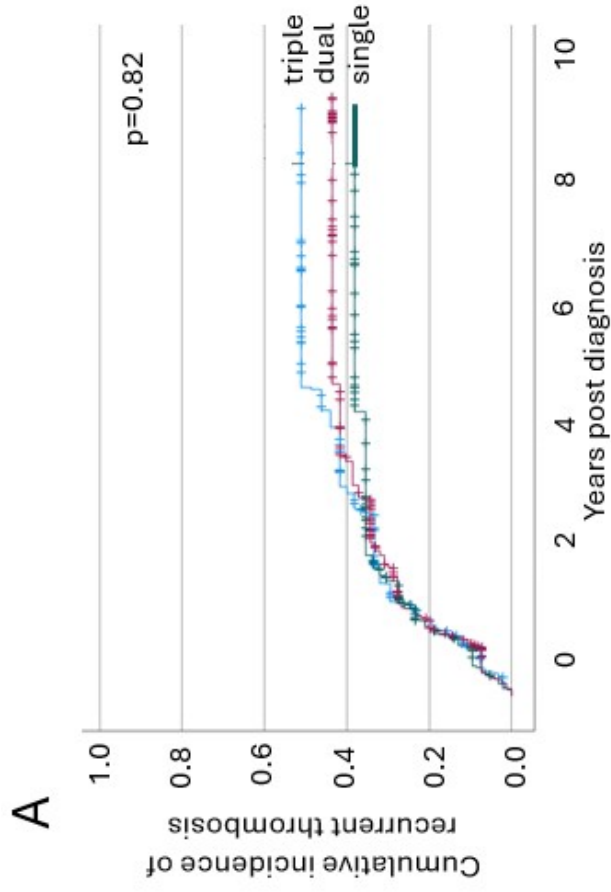


Figure 5

