ORIGINAL RESEARCH

Cardiovascular risk assessment in patients with antiphospholipid syndrome: a cross-sectional performance analysis of nine clinical risk prediction tools

George C Drosos,1 George Konstantonis,1 Petros P Sfikakis,1,2 Maria G Tektonidou 1,2

ABSTRACT

Objectives This study aimed to assess the performance of cardiovascular risk (CVR) prediction models reported by European Alliance of Associations for Rheumatology and European Society of Cardiology recommendations to identify high-atherosclerotic CVR (ASCVR) patients with antiphospholipid syndrome (APS).

Methods Six models predicting the risk of a first cardiovascular disease event (first-CVD) (Systematic Coronary Risk Evaluation (SCORE); modified-SCORE; Framingham risk score; Pooled Cohorts Risk Equation; Prospective Cardiovascular Münster calculator; Globorisk), three risk prediction models for patients with a history of prior arterial events (recurrent-CVD) (adjusted Global APS Score (aGAPSS); aGAPSSCVD; Secondary Manifestations of Arterial Disease (SMART)) and arterial/femoral artery vascular ultrasound (VUS) were used to assess ASCVR in 121 APS patients (mean age: 45.8±11.8 years; women: 68.6%). We cross-sectionally examined the calibration, discrimination and classification accuracy of all prediction models to identify high ASCVR due to VUS-detected atherosclerotic plaques, and risk reclassification of patients classified as non-high-risk according to first-CVD/recurrent-CVD tools to actual high risk based on VUS.

Results Spiegelhalter’s z-test p values 0.47–0.57, area under the receiver-operating characteristics curve (AUROC) 0.56–0.75 and Matthews correlation coefficient (MCC) 0.01–0.35 indicated moderate calibration, poor-to-acceptable discrimination and negligible-to-moderate classification accuracy, respectively, for all risk models. Among recurrent-CVD tools, SMART and aGAPSSCVD (for non-triple antiphospholipid antibody-positive patients) performed better (AUROC/MCC: 0.47/0.64/0.29 and 0.52/0.69/0.29, respectively) than aGAPSS. VUS reclassified 34.2%–47.9% and 40.5%–52.6% of patients classified as non-high-ASCVR by first-CVD and recurrent-CVD prediction models, respectively. In patients aged 40–54 years, >40% VUS-guided reclassification was observed for first-CVD risk tools and >50% for recurrent-CVD prediction models.

Conclusion Clinical CVR prediction tools underestimate actual high ASCVR in APS. VUS may help to improve CVR assessment and optimal risk factor management.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with antiphospholipid syndrome (APS) are at high cardiovascular risk (CVR), including accelerated atherosclerosis. To date, the performance of first-cardiovascular disease (CVD) and recurrent-CVD event risk prediction models reported by European Alliance of Associations for Rheumatology and the European Society of Cardiology (ESC) recommendations to assess CVR has yet to be examined in patients with APS.

WHAT THIS STUDY ADDS

⇒ Most of the examined nine risk prediction tools showed inadequate performance in calibration, discrimination and classification accuracy to identify actual high CVR as documented by vascular ultrasound (VUS)-detected atherosclerotic plaques (a risk assessment modality endorsed by the ESC), even in younger patients and those without APS-related high-CVR factors such as triple antiphospholipid antibody positivity.

⇒ Risk reclassification of patients to high risk due to VUS-detected plaques amounted to up to 50% of non-high-risk cases according to clinical risk prediction tools.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ VUS in addition to the use of risk prediction tools may assist clinicians to optimise CVR assessment in apparently non-high-risk patients with APS.

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune rheumatic and musculoskeletal disorder (RMD) characterised by recurrent arterial and/or venous thrombosis and obstetric morbidity in the presence of persistently circulating antiphospholipid antibodies (aPL).1 2 Cardiovascular disease (CVD) events represent the most devastating manifestations of this rare disorder affecting
primarily young adults, either in its primary form (‘primary APS’, PAPS) or in association with systemic lupus erythematosus (SLE). Stroke is the most frequent arterial event and, along with myocardial infarction (MI), are the most common causes of death in APS.

A high risk of premature and accelerated subclinical atherosclerosis has been also described in APS compared with the general population and at comparable rates to established high-cardiovascular risk (CVR) diseases such as diabetes mellitus (DM). CVD pathophysiology in APS is characterised by an interplay between aPL-mediated thrombosis, inflammation and atherogenesis. Traditional atherosclerotic CVR (ASCVR) factors are more prevalent in patients with APS versus other high-CVR RMDs such as rheumatoid arthritis (RA) and have been independently associated with incident and recurrent vascular events in APS. Hence, the recent European Alliance of Associations for Rheumatology (EULAR) recommendations for CVR management in RMDs prompted for joint assessment of ASCVR and disease-related features to reduce cardiovascular harm in APS.

ASCVR can be assessed by clinical prediction tools such as the Systematic Coronary Risk Evaluation (SCORE) and modified SCORE (mSCORE), Framingham risk score (FRS), Pooled Cohort Risk Equations (PCRE), Prospective Cardiovascular Münchner study risk tool (PROCAM) and Globorisk. The Secondary Manifestations of Arterial disease (SMART) prediction model has been developed to calculate residual ASCVR in patients with previous arterial events. A disease-specific risk tool for the prediction of recurrent thrombotic events in APS has been developed, the adjusted Global APS Score (aGAPSS), which includes weights for the three major aPL used in the classification criteria for APS, along with hypertension and hyperlipidaemia. A derivative equation that incorporates additional ASCVR factors such as obesity, smoking and DM, the aGAPSS for CVD (aGAPSSCVD), has also been tested for the prediction of recurrent arterial events in APS.

The presence of subclinical atherosclerotic plaques on vascular ultrasound (VUS) classifies patients at a CV event-equivalent risk. Thus, according to the European Society of Cardiology (ESC), VUS-detected carotid and/or femoral plaques should be considered as an ASCVR modifier for patients classified as non-high risk by clinical prediction tools. Cumulative evidence indicates that most generic CVR models may miss actual risk in patients with RMDs for whom VUS screening in addition to clinical assessment could help to optimise risk factor management.

Currently, there is no evidence on the performance of risk prediction tools for ASCVR assessment in APS. Therefore, we designed a study encompassing two clinically relevant topics: (1) the performance of six first CVD event (first-CVD) risk prediction models (SCORE, mSCORE, FRS, PCRE, PROCAM, Globorisk) and three recurrent CVD event (recurrent-CVD) risk prediction tools (SMART, aGAPSS, aGAPSSCVD) to identify high-risk patients as defined by the presence of atherosclerotic plaques on VUS and (2) the impact of VUS on ASCVR classification by clinical prediction tools.

**METHODS**

**Study population**

All adult patients with APS followed up at the Rheumatology Unit of our Department were screened for their eligibility to participate in the study. Exclusion criteria included a history of symptomatic atherosclerotic CVD events, high-ASCVR comorbidities including DM and chronic kidney disease (CKD) and acute illness (see online supplemental data). All APS patients fulfilled the updated Sapporo classification criteria and, those with SLE/APS, the SLE International Collaborating Clinics classification criteria.

**Clinical and laboratory parameters**

Eligible patients were referred for assessment to the Cardiovascular Risk Research laboratory of our Department. The following baseline clinical parameters were cross-sectionally collected during the first visit of patients: sociodemographic data, medical history and current medications; weight, height and body mass index and averaged blood pressure (BP) levels according to ESC guidelines. Laboratory variables included blood cholesterol fractions and triglycerides; the type, number and titres of aPL, that is, IgG and IgM anticardiolipin antibodies (aCL), and IgG and IgM anti-beta-2-glycoprotein I antibodies (anti-β2GPI) and lupus anticoagulant (LA) tested according to International Society on Thrombosis and Haemostasis guidelines. The presence of atherosclerotic plaques on VUS of the carotid and femoral arteries was determined according to a standardised protocol. Details about the recorded parameters are reported in online supplemental data.

**CVR assessment**

Nine CVR prediction tools were used to classify patients in high-risk versus non-high-risk categories according to established risk cut-offs reported in the literature for each of the examined risk prediction models (see also online supplemental data). Specifically, six prediction models designed to assess the risk of a first CVD event (SCORE, mSCORE, FRS, PCRE, PROCAM and Globorisk) and three risk prediction models developed for patients with a previous history of arterial events (SMART, aGAPSS and aGAPSSCVD) were assessed regarding their performance to identify actual ASCVR due to the presence of atherosclerotic plaques. Since atherosclerosis is a disease of the arteries, SMART and the two aGAPSS equations were specifically examined in patients with a previous arterial event (see the Sensitivity analyses section). Following the ESC recommendations on the use of VUS in ASCVR assessment, patients initially classified by clinical prediction tools as non-high...
risk were reclassified as high risk after detecting atherosclerotic plaques on VUS.

**Statistical analysis**
Categorical variables were assessed with \( \chi^2 \) test or Fisher’s exact test and are presented as percentages. Student’s t-test and Mann-Whitney U test were used to compare subgroup characteristics for normally and non-normally distributed continuous data, respectively, and are displayed as mean±SD or median and IQR according to data distribution profile.

Performance measures tested for all risk models included calibration, discrimination and classification accuracy according to Spiegelhalter’s \( \hat{z} \)-test, receiver operating characteristics (ROC)/area under the curve (AUC), and Matthews’ correlation coefficient (MCC), respectively. Sensitivity and specificity were examined at established high-risk cut-offs for each risk prediction model, while the Youden index was used to test the performance of risk tools regarding maximum accuracy corresponding to optimal high-risk cut-offs to identify high ASCVR due to the presence of VUS-detected atherosclerotic plaques. Fleiss kappa was used to examine the agreement between the recurrent-CVD risk tools. Statistical significance was set at a \( p \leq 0.05 \). All statistical analyses were performed with Stata V.13.0 (StataCorp).

**Sensitivity analyses**
Five sensitivity analyses were included in the study, as follows:
1. Considering that recurrent-CVD risk prediction tools are designed to predict different types of recurrent vascular events, the performance of SMART and the aGAPSS models was separately examined in patients with (a) arterial with or without venous events (‘arterio-venous’ group) and (b) isolated arterial events (‘arterial only’ group).
2. According to the weights employed in the aGAPSS equations, triple aPL positivity for LA, aCL and anti-β2GPI classifies by default patients at high risk.\(^{12,13}\) Thus, performance metrics for aGAPSS and aGAPSScvD were tested both before and after excluding triple aPL-positive patients (‘non-triple aPL’ group).
3. To better delineate the performance of risk prediction tools to identify actual high-ASCVR as documented by VUS-detected plaques in the absence of major CVD events, a sensitivity analysis that further excluded patients with non-atherosclerotic MI or stroke on treatment with antihypertensives and/or hypolipidaemics was carried out for all risk models.
4. The nine risk prediction tools examined in this study employ different lower age limits for clinical application. Furthermore, the classification criteria for APS\(^4\) suggested that in patients older than 55 years, a high impact of traditional ASCVR factors on thrombotic events would be expected. To satisfy both conditions, risk reclassification by VUS was additionally explored in a subgroup of patients aged 40–54 years.

5. Based on current evidence suggesting that patients with PAPS may have a different ASCVR compared with those with SLE-APS,\(^4,5\) VUS-guided risk reclassification was separately examined in these two patient subpopulations.

**RESULTS**

**Baseline characteristics**
One hundred and twenty-one patients (mean age 45.8±11.8 years; 68.6% women; 62.8% PAPS; 37.2% SLE-APS) were included in the study (online supplemental figure S1). Median systolic BP was 123 (IQR 116–131) mm Hg, mean LDL-cholesterol 111±34 mg/dL and 34.7% of patients were current smokers. Two-thirds of patients had high-titre aPL, while triple aPL positivity was noted in 44.6% of cases. Atherosclerotic plaques were observed in 35.5% of patients (carotid: 12.4%; femoral: 9.9%; both arteries: 13.2%). Baseline characteristics of study participants are shown in table 1.

**CVR estimates**
Baseline risk estimates according to first-CVD and recurrent-CVD risk tools in patients with and without plaques are shown in table 2. All first-CVD prediction models assigned significantly higher risks (\( p<0.05 \)) to patients with plaques compared with patients without plaques, except for SCORE and mSCORE. In the ‘arterial only’ group, SMART scored patients with plaques at risks above the established high-risk threshold and significantly higher than patients without plaques (23.2%±12.2% vs 16.5%±7.5%; \( p=0.033 \)); a similar result was observed in the ‘arterio-venous’ group, though it did not reach statistical significance (\( p=0.078 \)). No difference was noted for risk estimates calculated with aGAPSS and aGAPSScvD between patients with and without plaques in ‘arterio-venous’ or ‘arterial only’ and ‘non-triple aPL/arterial only’ groups.

**Performance of risk prediction models**
The performance of clinical prediction models is shown in table 3. Results for a sensitivity analysis of performance measures after excluding patients with MI and/or stroke treated with antihypertensives and/or hypolipidaemics agents are included in online supplemental table S2.

**Assessment of first-CVD risk prediction models**
Spiegelhalter’s \( \hat{z} \)-test \( p \) values ranged from 0.47 to 0.57, indicating moderate calibration. ROC analysis revealed a poor-to-acceptable discriminatory power (AUC 0.59–0.75). MCC values for classification accuracy were 0.11, 0.10, 0.10, 0.22, 0.27 and 0.11 for SCORE, mSCORE, FRS, PCRE, Globorisk and PROCAM, respectively, suggesting no improvement of classification by using mSCORE versus SCORE. Sensitivity ranged from 9.5% to 41.5% and specificity from 82.9% to 96.1%. Optimal high-risk cut-offs to identify high-risk cases due to the presence of VUS-detected plaques according to the highest Youden
## Table 1  Baseline characteristics of study participants (N=121)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>45.8±11.8</td>
</tr>
<tr>
<td>Women, %</td>
<td>68.6%</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years), median (IQR)</td>
<td>7 (2–16)</td>
</tr>
<tr>
<td>PAPS, %</td>
<td>62.8%</td>
</tr>
<tr>
<td>SLE-APS, %</td>
<td>37.2%</td>
</tr>
<tr>
<td>Thrombotic events, %</td>
<td>98.4%</td>
</tr>
<tr>
<td>Venous, %</td>
<td>59.5%</td>
</tr>
<tr>
<td>Arterial, %</td>
<td>49.6%*</td>
</tr>
<tr>
<td>Obstetric events, % (N=83)</td>
<td>37.4%</td>
</tr>
<tr>
<td>Family history of MI, %</td>
<td>8.3%</td>
</tr>
<tr>
<td>Smoking, current, %</td>
<td>34.7%</td>
</tr>
<tr>
<td>Systolic BP (mm Hg), median (IQR)</td>
<td>123 (116–131)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg), mean±SD</td>
<td>75±8</td>
</tr>
</tbody>
</table>

### Laboratory variables

- **aPL profile**
  - Lupus anticoagulant, %: 71.9%
  - Anticardiolipin antibodies, IgG, %: 67.8%
  - Anticardiolipin antibodies, IgM, %: 52.1%
  - High-titre aCL, %: 54.6%
  - Anti-beta2 glycoprotein I antibodies, IgG, %: 45.5%
  - Anti-beta2 glycoprotein I antibodies, IgM, %: 40.5%
  - High-titre anti-b2GPI, %: 39.7%
  - High-titre aPL, %: 58.7%
  - Double aPL positivity, %: 32.2%
  - Triple aPL positivity, %: 44.6%
  - Double or triple aPL positivity, %: 76.9%

- **Lipid profile**
  - Total cholesterol (mg/dL), mean±SD: 188±37
  - LDL-cholesterol (mg/dL), mean±SD: 111±34
  - HDL-cholesterol (mg/dL), median (IQR): 52 (43–63)
  - Triglycerides (mg/dL), median (IQR): 97 (75–139)

- **Treatment, current**
  - Antihypertensives, %: 30.6%
  - Hypolipidaemics, %: 17.4%
  - Antiplatelets, %: 41.3%
  - Anticoagulants, %: 81%
  - Hydroxychloroquine, %: 44.6%
  - Glucocorticoids, %: 32.2%
  - Immunosuppressants, %: 19.8%

### Ultrasound findings for atherosclerotic plaques

- Carotid or femoral, %: 35.5%
- Carotid, %: 12.4%
- Femoral, %: 9.9%
- Carotid and femoral, %: 13.2%

*8.3% of patients with arterial thrombosis had a history of recurrent arterial-to-arterial events; all of them were on anticoagulation treatment. 60% were receiving antiplatelets and 80% had ultrasonographic evidence of atherosclerotic plaques. aCL, anti-cardiolipin antibodies; anti-b2GPI, anti-beta-2 glycoprotein I antibodies; aPL, antiphospholipid antibodies; BP, blood pressure; HDL, high-density lipoprotein; LA, lupus anticoagulant; LDL, low-density lipoprotein; MI, myocardial infarction; PAPS, primary antiphospholipid syndrome; SLE-APS, systemic lupus erythematosus-associated antiphospholipid syndrome.

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**Assessment of recurrent-CVD risk prediction models**

Moderate calibration was observed for all recurrent-CVD prediction models across all groups (p value range 0.47–0.52). For SMART, AUC and MCC were 0.64 and 0.29 in the ‘arterial only’ group and 0.66 and 0.33 in the ‘arterial±venous’ group, respectively, while the optimal high-risk cut-off was identical in both groups.

aGAPSS and aGAPSS<sub>CVD</sub> showed marginally poor-to-good discrimination (AUC 0.56–0.69) in all groups and negligible-to-low classification accuracy (MCC 0.01–0.08) in ‘arterial±venous’ and ‘arterial only’ groups. In ‘non-triple aPL/arterial±venous’ and ‘non-triple aPL/arterial only’ groups, MCC was better for aGAPSS<sub>CVD</sub> (0.29 and 0.28, respectively) compared with aGAPSS (0.16 and 0.17, respectively). Optimal high-risk cut-offs for aGAPSS and aGAPSS<sub>CVD</sub> were 14 and 16 points in ‘arterial±venous’ and ‘arterial only’ groups, and 9 and 10 points in ‘non-triple aPL/arterial±venous’ and ‘non-triple aPL/arterial only’ groups, respectively.

Fleiss kappa for SMART, aGAPSS and aGAPSS<sub>CVD</sub> was 0.30 in the ‘arterial only’ group and 0.44 in the ‘non-triple aPL/arterial only’ group, indicating fair and moderate agreement, respectively, between recurrent-CVD risk prediction models to predict high CVR.

**Impact of VUS on risk classification**

Figure 1 shows high-risk versus non-high-risk classification of patients by first-CVD and recurrent-CVD risk prediction models. Risk reclassification of patients from non-high risk according to risk prediction models to high risk based on the presence of VUS-detected atherosclerotic plaques is displayed in figures 2 and 3.

**VUS plus first-CVD risk prediction models**

High-risk classification before applying the results of vascular imaging ranging from 5.8% to 29.3%. VUS-based risk reclassification was 48% for both SCORE and mSCORE, 37.8% for FRS, 44.8% for PCRE, 41.4% for Globorisk and 34.2% for PROCAM; reclassification rates were similar for all risk prediction models in the 40–54 years old subgroup.

When examined separately, VUS reclassified PAPS versus SLE-APS patients from non-high risk to high risk as follows: SCORE: 52.2% versus 40%; mSCORE: 54.5% versus 34.8%; FRS: 44.3% versus 27%; PCRE: 50% versus 36%; Globorisk: 47.2% versus 31.8%; and PROCAM: 40.3% versus 23.1%, respectively.

**VUS plus recurrent-CVD risk prediction models**

SMART, aGAPSS and aGAPSS<sub>CVD</sub> assigned 36.8% and 31.3%, 66.7% and 59.6% and 66% of patients to high risk in the ‘arterial±venous’ and ‘arterial only’ groups, respectively. VUS-guided risk reclassification rates of non-high-risk patients in ‘arterial±venous’ versus ‘arterial only’ groups for SMART, aGAPSS and aGAPSS<sub>CVD</sub> were 41.7% versus 40.7%, 40.5% versus 52.6% and 50% respectively.
versus 50% for all patients, respectively. In the 40–54 years old subgroup, VUS reclassified ≥50% of apparently non-high-risk cases according to SMART, aGAPSS or aGAPSS<sub>CVD</sub> in both the ‘arterial±venous’ and ‘arterial only’ groups. Risk reclassification was higher among PAPS (50%–70.6%) compared with SLE-APS (0%–25%) patients for recurrent-CVD risk prediction tools also. Application of VUS findings to ‘non-triple aPL/arterial±venous’ and ‘non-triple aPL/arterial only’ groups returned similar reclassification results to those in ‘arterial±venous’ and ‘arterial only’ groups for aGAPSS and aGAPSS<sub>CVD</sub> in the entire cohort (all APS patients) and in the PAPS and SLE-APS subgroups (online supplemental figures S2 and S3).

**DISCUSSION**

To our knowledge, this is the first study in APS to assess multiple types of CVR assessment tools along with complementary risk classification modalities such as VUS according to EULAR<sup>15</sup> and ESC recommendations.<sup>16,19,29</sup>

Our findings showed inadequate performance of clinical tools alone to identify actual CVR, affecting optimal CVR management to prevent cardiovascular harm in patients with APS.<sup>2,15</sup>

Mounting evidence suggests that first-CVD risk prediction models underestimate actual risk in patients with RMDs.<sup>15,21,28,30</sup> Our results about SCORE, FRS, PCRE, PROCAM and Globorisk in APS are in line with these observations. Although demonstrating moderate calibration, all models showed low classification accuracy to identify patients at actual high risk. Remarkably, identification of high-risk cases would require to use cut-offs corresponding to very low estimates compared with the thresholds recommended in the general population. Consequently, pragmatic use of these CVR assessment tools to guide CVR management tailored to risk class<sup>15,19</sup> seems challenging in APS.

Failure of generic first-CVD risk models to capture actual ASCVR in RMDs may arise out of biases related to a higher risk attributed to older age and the higher prevalence of traditional CVR factors in RMDs compared with the general population.<sup>15,21,28,30</sup> Previous evidence showed that SLE<sup>31,32</sup> and RA<sup>32</sup> are independently associated with premature atherosclerotic CVD. In our study, marked reclassification of younger non-high-risk patients to high

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**Table 2** Cardiovascular risk estimates of 121 APS patients by clinical prediction models

<table>
<thead>
<tr>
<th></th>
<th>Patients with atherosclerotic plaques (N=43)</th>
<th>Patients without atherosclerotic plaques (N=78)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First CVD event risk tools</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCORE, %, median (IQR)</td>
<td>0.6 (0.3–1.7)</td>
<td>0.4 (0.2–1)</td>
<td>0.123</td>
</tr>
<tr>
<td>mSCORE, %, median (IQR)</td>
<td>1.2 (0.6–2.55)</td>
<td>0.75 (0.3–2)</td>
<td>0.177</td>
</tr>
<tr>
<td>FRS, %, median (IQR)</td>
<td>8 (4.1–12.9)</td>
<td>3.4 (2.05–7.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCRE, %, median (IQR)</td>
<td>4.3 (1.6–8.7)</td>
<td>2 (0.9–4.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Globorisk, %, median (IQR)</td>
<td>7.7 (4–11)</td>
<td>4 (2–7)</td>
<td>0.002</td>
</tr>
<tr>
<td>PROCAM, %, median (IQR)</td>
<td>4.3 (1.9–9.4)</td>
<td>1.5 (0.6–4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Recurrent CVD event risk tools</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMART,* %, median (IQR)</td>
<td>20.3 (11.3–30.1)</td>
<td>14.3 (9.9–19.3)</td>
<td>0.078</td>
</tr>
<tr>
<td>SMART,† %, mean±SD</td>
<td>23.2±12.2</td>
<td>16.5±7.5</td>
<td>0.033</td>
</tr>
<tr>
<td>aGAPSS,* points, mean±SD</td>
<td>11.5±3.5</td>
<td>12.7±3.8</td>
<td>0.185</td>
</tr>
<tr>
<td>aGAPSS,† points, mean±SD</td>
<td>11.4±3.5</td>
<td>12.4±3.9</td>
<td>0.395</td>
</tr>
<tr>
<td>aGAPSS&lt;sub&gt;CVD&lt;/sub&gt;,* points, mean±SD</td>
<td>13.1±3.5</td>
<td>13.8±4.2</td>
<td>0.468</td>
</tr>
<tr>
<td>aGAPSS&lt;sub&gt;CVD&lt;/sub&gt;,† points, mean±SD</td>
<td>13.2±3.5</td>
<td>13.7±4.2</td>
<td>0.614</td>
</tr>
<tr>
<td><strong>Patients without triple aPL positivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aGAPSS,* points, mean±SD</td>
<td>9.8±2.9</td>
<td>9.1±2.2</td>
<td>0.469</td>
</tr>
<tr>
<td>aGAPSS,† points, mean±SD</td>
<td>10.1±3.0</td>
<td>9.3±2.4</td>
<td>0.469</td>
</tr>
<tr>
<td>aGAPSS&lt;sub&gt;CVD&lt;/sub&gt;,* points, mean±SD</td>
<td>11.7±3.0</td>
<td>10.0±3.0</td>
<td>0.126</td>
</tr>
<tr>
<td>aGAPSS&lt;sub&gt;CVD&lt;/sub&gt;,† points, mean±SD</td>
<td>12.0±3.1</td>
<td>10.4±3.1</td>
<td>0.177</td>
</tr>
</tbody>
</table>

*Patients with arterial with or without venous events.
†Patients with isolated arterial events.
aGAPSS, adjusted Global Antiphospholipid Syndrome Score; aGAPSS<sub>CVD</sub>, aGAPSS for CVD; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CVD, cardiovascular disease; FRS, Framingham Risk Score; mSCORE, modified SCORE; PCRE, Pooled Cohorts Risk Equation; PROCAM, Prospective Cardiovascular Muncher Study calculator; SCORE, Systematic Coronary Risk Evaluation; SMART, Secondary Manifestations of Arterial Disease risk score.
Table 3  Performance measures of cardiovascular risk prediction tools to identify high ASCVR in patients with APS (N=121)

<table>
<thead>
<tr>
<th>First CVD event risk prediction tools</th>
<th>Spiegelhalter's z-test p value</th>
<th>AUC (95% CI)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>MCC</th>
<th>Highest Youden index</th>
<th>Optimal high-risk cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORE</td>
<td>0.47</td>
<td>0.60 (0.49 to 0.71)</td>
<td>17.1 (7.2 to 32.1)</td>
<td>90.2 (76.9 to 97.3)</td>
<td>0.11</td>
<td>0.15</td>
<td>0.2%</td>
</tr>
<tr>
<td>mSCORE</td>
<td>0.47</td>
<td>0.59 (0.47 to 0.70)</td>
<td>22 (10.6 to 37.6)</td>
<td>85.4 (70.8 to 94.4)</td>
<td>0.10</td>
<td>0.20</td>
<td>1%</td>
</tr>
<tr>
<td>FRS</td>
<td>0.48</td>
<td>0.72 (0.63 to 0.81)</td>
<td>9.8 (2.7 to 23.1)</td>
<td>95.3 (86.9 to 99)</td>
<td>0.10</td>
<td>0.36</td>
<td>3.2%</td>
</tr>
<tr>
<td>PCRE</td>
<td>0.49</td>
<td>0.68 (0.57 to 0.78)</td>
<td>26.8 (14.2 to 42.9)</td>
<td>90.2 (76.9 to 97.3)</td>
<td>0.22</td>
<td>0.29</td>
<td>5.3%</td>
</tr>
<tr>
<td>Globorisk</td>
<td>0.57</td>
<td>0.70 (0.59 to 0.80)</td>
<td>41.5 (26.3 to 57.9)</td>
<td>82.9 (67.9 to 92.8)</td>
<td>0.27</td>
<td>0.27</td>
<td>3%</td>
</tr>
<tr>
<td>PROCAM</td>
<td>0.50</td>
<td>0.75 (0.66 to 0.83)</td>
<td>9.5 (2.7 to 22.6)</td>
<td>96.1 (88.9 to 99.2)</td>
<td>0.11</td>
<td>0.41</td>
<td>1.7%</td>
</tr>
<tr>
<td>Recurrent CVD event risk prediction tools</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMART*</td>
<td>0.47</td>
<td>0.64 (0.50 to 0.76)</td>
<td>50 (31.3 to 68.7)</td>
<td>77.8 (57.7 to 91.4)</td>
<td>0.29</td>
<td>0.35</td>
<td>20.3%</td>
</tr>
<tr>
<td>SMART†</td>
<td>0.49</td>
<td>0.66 (0.51 to 0.79)</td>
<td>56 (34.9 to 75.6)</td>
<td>76.2 (52.8 to 91.8)</td>
<td>0.33</td>
<td>0.42</td>
<td>20.3%</td>
</tr>
<tr>
<td>aGAPSS*</td>
<td>0.50</td>
<td>0.59 (0.46 to 0.72)</td>
<td>58.1 (39.1 to 75.5)</td>
<td>34.5 (17.9 to 54.3)</td>
<td>0.08</td>
<td>0.29</td>
<td>14 points</td>
</tr>
<tr>
<td>aGAPSS†</td>
<td>0.50</td>
<td>0.56 (0.41 to 0.71)</td>
<td>60 (38.7 to 78.9)</td>
<td>40.9 (20.7 to 63.6)</td>
<td>0.01</td>
<td>0.24</td>
<td>14 points</td>
</tr>
<tr>
<td>aGAPSSCVD*</td>
<td>0.50</td>
<td>0.57 (0.44 to 0.70)</td>
<td>67.7 (48.6 to 83.3)</td>
<td>34.5 (17.9 to 54.3)</td>
<td>0.02</td>
<td>0.25</td>
<td>16 points</td>
</tr>
<tr>
<td>aGAPSSCVD†</td>
<td>0.50</td>
<td>0.56 (0.41 to 0.70)</td>
<td>68.0 (46.5 to 85.1)</td>
<td>36.4 (17.2 to 59.3)</td>
<td>0.05</td>
<td>0.24</td>
<td>16 points</td>
</tr>
<tr>
<td>Patients without triple aPL positivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aGAPSS*</td>
<td>0.49</td>
<td>0.60 (0.42 to 0.76)</td>
<td>38.1 (18.1 to 61.6)</td>
<td>76.9 (46.2 to 95)</td>
<td>0.16</td>
<td>0.22</td>
<td>9 points</td>
</tr>
<tr>
<td>aGAPSS†</td>
<td>0.49</td>
<td>0.62 (0.42 to 0.79)</td>
<td>44.4 (21.5 to 69.2)</td>
<td>72.7 (39 to 94)</td>
<td>0.17</td>
<td>0.25</td>
<td>9 points</td>
</tr>
<tr>
<td>aGAPSSCVD*</td>
<td>0.52</td>
<td>0.69 (0.50 to 0.83)</td>
<td>52.4 (29.8 to 74.3)</td>
<td>76.9 (46.2 to 95)</td>
<td>0.29</td>
<td>0.36</td>
<td>10 points</td>
</tr>
<tr>
<td>aGAPSSCVD†</td>
<td>0.51</td>
<td>0.68 (0.48 to 0.84)</td>
<td>55.6 (30.8 to 78.5)</td>
<td>72.7 (39.0 to 94)</td>
<td>0.28</td>
<td>0.36</td>
<td>10 points</td>
</tr>
</tbody>
</table>

Results about Spiegelhalter’s z-test, AUC, sensitivity, specificity and MCC computed according to established high-risk cut-offs for each risk prediction model.
*Patients with arterial with or without venous events.
†Patients with isolated arterial events.
aGAPSS, adjusted Global Antiphospholipid Syndrome Score; aGAPSSCVD, aGAPSS for CVD; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; ASCVR, atherosclerotic cardiovascular risk; AUC, area under the curve; CVD, cardiovascular disease; FRS, Framingham Risk Score; MCC, Matthews’ correlation coefficient; mSCORE, modified SCORE; PCRE, Pooled Cohorts Risk Equation; PROCAM, Prospective Cardiovascular Muncher Study calculator; SCORE, Systematic Coronary Risk Evaluation; SMART, Secondary Manifestations of Arterial Disease risk score.
risk was observed with use of VUS for all generic risk models. These findings indicate that earlier and stricter CVR screening and risk factor management may be required in younger APS patients compared with same age individuals in the general population.

Modifications of baseline risk assessed by generic models using multipliers has been proposed by the ESC to improve CVR assessment in RMDs, with mixed results. Our results suggest that mSCORE does not perform better than SCORE to predict actual high risk in APS patients. Nevertheless, incorporation of appropriately weighted disease-related risks into existing prediction models, as the inclusion of SLE into QRISK3, instead of applying multiplication factors, could help to...
Figure 2  Risk reclassification by vascular ultrasound of APS patients classified as non-high-risk according to first CVD event (A1, A2) and recurrent CVD event (B1, B2) clinical risk prediction tools. *Patients with arterial with or without venous events. †Patients with isolated arterial events. aGAPSS, adjusted Global Antiphospholipid Syndrome Score; aGAPSS-CVD, aGAPSS for CVD; CVD, cardiovascular disease; FRS, Framingham Risk Score; mSCORE, modified SCORE; PCRE, Pooled Cohorts Risk Equation; PROCAM, Prospective Cardiovascular Muncher Study calculator; SCORE, Systematic Coronary Risk Evaluation; SMART, Secondary Manifestations of Arterial Disease risk score.
optimise the use of measures of association computed to calculate risk of CVD events in APS.

APS is characterised by a wide range of vascular manifestations. From a clinical standpoint, it is unclear whether patients with venous versus those experiencing arterial events should be assessed differently. In our study, this issue was addressed using recurrent-CVD risk prediction tools. SMART and the aGAPSS equations showed comparable calibration, but SMART had considerably greater classification accuracy against aGAPSS and aGAPSSCVD, and high-risk cut-offs of maximum accuracy corresponded to thresholds validated in the general population. Results about cut-off points for SMART were similar also after excluding patients with non-atherosclerotic stroke and/or MI, but only in the ‘arterial only’ group. Our findings suggest that both models perform poorly to identify actual high ASCVR in APS. This observation may be related to the weighting of aPL relative to traditional ASCVR factors in the aGAPSS and aGAPSSCVD equations. Indeed, exclusion of triple aPL-positive patients substantially improved the performance of both risk prediction tools. Therefore, use of these models to assess CVR may not apply to all aPL profiles encountered in clinical practice.

Earlier evidence reported that aGAPSS and aGAPSSCVD estimates do not associate with progression of ASCVR in APS, while a recent study examining aGAPSS found a
thrombotic recurrence cut-off similar to the high-ASCVR threshold identified in our study. Interestingly, both in the latter study and ours, the decision thresholds to assign a patient to high CVR were similar, as well as corresponding to a higher threshold compared with the cut-off reported in the aGAPSS derivation study.\(^\text{12}\) Nevertheless, in the sensitivity analysis of our study excluding triple aPL positivity as a potential shortcoming of the aGAPSS and aGAPSS\(_{\text{CVD}}\) equations, aGAPSS\(_{\text{CVD}}\) performed better compared with aGAPSS in both ‘arterial’ and ‘arterial only’ groups, as well as in patients with and without stroke and/or MI, to identify high-risk patients with plaques. Since both models assign equal weights to aPL, this difference could be attributed to the inclusion of a greater number of ASCVR factors into the aGAPSS\(_{\text{CVD}}\). Risk estimates calculated with aGAPSS\(_{\text{CVD}}\) also correlate with measures of subclinical atherosclerosis such as intima–media thickness,\(^\text{13}\) but further validation of both aGAPSS is needed to better elucidate their role in identifying high ASCVR groups in APS.\(^\text{15,16}\)

CVR management in APS may need to address unique aspects of CVD pathophysiology in the syndrome.\(^\text{5}\) Besides their role in immune-mediated thrombosis, aPL has been shown to also have a proatherogenic effect even in the absence of comorbidities or concomitant ASCVR factors.\(^\text{6,35}\) Importantly, comprehensive aPL profiling\(^\text{2,5,35}\) according to the type, titres and number of autoantibodies may be necessary to improve CVR assessment strategies in APS. Likewise, traditional ASCVR factors generally recognised as promoters of atherosclerosis may also act as precipitating factors for first and recurrent thrombotic events in APS.\(^\text{3,9}\) Therefore, studies examining revisions of existing disease-related risk prediction models or additional risk modifiers to CVR estimates by generic models would help to prevent cardiovascular damage in APS. This line of research would be consistent with EULAR recommendations for CVR management in APS\(^\text{36}\) and has been introduced for other high-CVR diseases such as DM or CKD.\(^\text{16,19}\)

VUS has been proposed by the ESC\(^\text{16}\) to refine CVR estimation in non-high-risk patients. Increasing evidence has also highlighted the importance of VUS for CVR assessment in RMDs.\(^\text{22,28,36}\) Risk reclassification by VUS in our study ranged from two-fifths of all patients to more than half of the younger subgroup population, indicating that this risk assessment modality may significantly impact CVR management in patients with APS misclassified as non-high risk by clinical risk prediction alone. VUS reclassification was less pronounced in SLE-APS cases, but this finding is most likely related to the smaller representation of this disease subgroup (37%) in our study sample. However, optimal use of VUS to inform CVR prevention in RMDs is currently unclear.\(^\text{15,36}\) Awaiting further investigation, employment of VUS-guided risk assessment in APS could be reserved for clinical phenotypes expected to be misidentified as non-high risk by risk prediction models such as younger patients or those with PAPS, as shown in this study.

Strengths of our study include testing a wide range of clinical risk prediction models to identify APS patients at actual high risk as documented by the presence of atherosclerotic plaques in multiple anatomical sites of the carotid and femoral arteries on VUS, as recommended by the ESC.\(^\text{16,19}\) Assessment of risk prediction tools was examined in a well-characterised, relatively large sample considering the rarity of APS, without high-ASCVR comorbidities. Additionally, performance analysis of risk prediction models incorporated different clinical scenarios, as suggested by EULAR,\(^\text{15}\) including patients with and without major CVD events in the presence or absence of triple aPL positivity.

We acknowledge that our study has certain limitations. The cross-sectional design does not allow deducing definite conclusions about the performance of risk models on par with prospectively recorded CVD events over a 10-year interval, particularly regarding calibration. Accounting for the fact that VUS-detected plaques are a surrogate measure of ASCVR,\(^\text{16}\) our results should be approached with caution, especially considering the complex interplay between aPL and traditional risk factors in both ASCVR and immune-mediated CVR in APS. Nevertheless, in terms of risk-stratified ASCVR factor modification,\(^\text{19,20}\) the presence of atherosclerotic plaques on VUS has equivalent importance to incident cardiovascular events.\(^\text{16,19,20}\) Additionally, aGAPSS and aGAPSS\(_{\text{CVD}}\) have not been specifically designed to assess ASCVR, though our results—considering also the inclusion of traditional ASCVR factors in these models and the high ASCVR in APS\(^\text{6}\)—suggest that recalibration based on studies comprising prospectively recorded atherosclerotic and non-atherosclerotic thrombotic events could help to improve the use of these risk tools in patients with APS. Our study population included only white Europeans and was recruited in an academic hospital centre, limiting conclusive validity and generalisation of our findings permitted by ethnic diversity and primary care settings.

To conclude, our study showed that generic first-CVD risk prediction models misidentify actual ASCVR in APS without the use of additional risk assessment modalities such as VUS. Among recurrent-CVD risk tools, SMART had acceptable performance only for patients with isolated arterial events, while CVR assessment incorporating disease-related features may require an update of the relative contribution of each of aPL based on the new American College of Cardiology/EULAR classification criteria for APS\(^\text{37}\) and each of traditional ASCVR factors. Studies further exploring the complexities of CVR assessment in APS are urgently needed.
investigation, resources, writing–review and editing, supervision and project administration; guarantor. All authors contributed to data interpretation and gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Laiko General Hospital Scientific Board (SB number 1790). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. The data underpinning this article will be shared on reasonable request to the corresponding author.

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**REFERENCES**


29 Rossello X, Dorrestein JA, Janssen A, et al. Risk prediction tools in cardiovascular disease prevention: a report from the ESC prevention of CVD programme led by the European association of preventive cardiology (EAPC) in collaboration with the acute cardiovascular care association (ACCA) and the association of cardiovascular


