Application of EULAR and European Society of Cardiology recommendations with regard to blood pressure and lipid management in antiphospholipid syndrome

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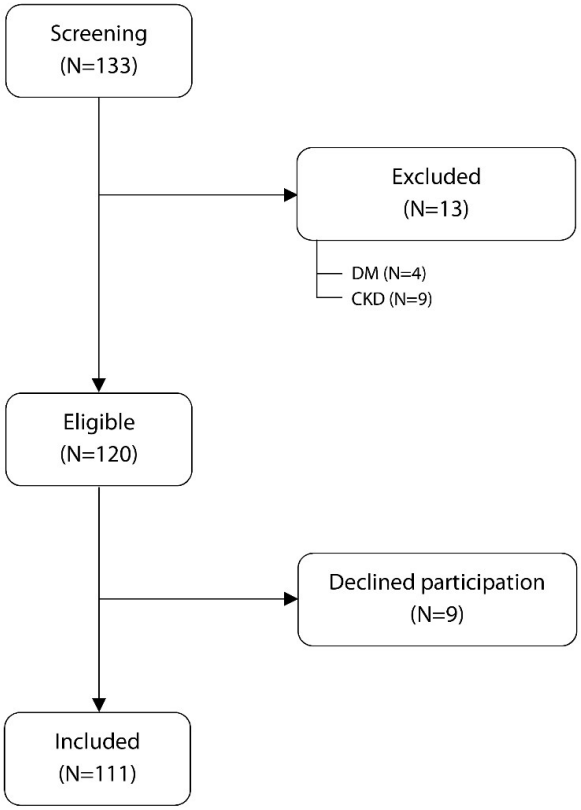
SUPPLEMENTAL DATA

SUPPLEMENTAL METHODS

Study population



Supplemental Figure S1

Flowchart of patient enrolment process. CKD, chronic kidney disease; DM, diabetes mellitus.

Cardiovascular risk assessment

Risk classification according to traditional atherosclerotic cardiovascular risk (ASCVR) factors

Age, gender, blood pressure (BP), cholesterol levels, and current smoking were used to calculate patients' Systemic Coronary Risk Evaluation (SCORE) estimates according to the European Society of Cardiology (ESC) guidelines.[1-3]

For primary antiphospholipid syndrome (APS) patients, modified SCORE was calculated by multiplying SCORE by a 1.5 factor as suggested by the ESC for autoimmune diseases.[1 3] A 2.0 multiplier was used for systemic lupus erythematosus (SLE)-associated APS cases owing to previous evidence suggesting a 2-fold higher risk of cardiovascular events in patients with SLE.[4 5]

As reported by the ESC,[1 6] the diabetes mellitus-equivalent ASCVR criteria (DIME) included disease duration, age, hypertension, atherogenic dyslipidaemia [defined as the concomitant presence of non-HDL-cholesterol ≥130 mg/dL and low HDL-cholesterol (men: <40 mg/dL; women: <50 mg/dL)], abdominal obesity (defined as waist circumference ≥94 cm for men and ≥80 cm for women), and current smoking.

Risk classification according to disease-related cardiovascular risk factors

Risk stratification according to the type of APS thrombotic event (APS_{events}) was based on the available evidence suggesting that patients with arterial thrombosis including major cardiovascular events (i.e. cerebrovascular, coronary or peripheral arterial events) would be at a higher risk compared to patients with venous events.[7-9] Thus, a three-strata risk classification system was devised with patients with major cardiovascular events assigned to very-high risk, those with arterial thrombosis other than major cardiovascular events to high risk, and cases with non-arterial events to low-moderate risk.

Following a similar approach, risk classification according to the antiphospholipid antibody (aPL) profile ($aPL_{profile}$) was based on the presence or absence of lupus anticoagulant, double or triple aPL positivity, and high/persistent levels of aPL titre.[8 10-12] This approach is consistent with the statements provided by the EULAR recommendations for the management of APS,[11 12] which, however, do not provide specific guidance on how to grade the clinical risk of events corresponding to the various combinations among aPL types, number and titres within the definition of the 'high-risk aPL profile', especially for very-high-risk and moderate-risk cases. Therefore, the $aPL_{profile}$ risk classes were stratified on the basis that the concomitant presence of multiple aPL types and elevated titres of aPL would signify a much higher risk.

Risk classes based on the $aGAPSS_{CVD}$ equation were grounded on the available literature on this prediction tool.[8 13] A >11 points threshold was used to identify patients at high-risk from those without. The very-high risk category pertaining to a cut-off of >16 points was derived from the observation in the original derivation study for $aGAPPS_{CVD}$,[8] where patients with triple aPL positivity (assigning a total of 13 points) in addition to at least one heavily weighted and one less weighted or >2 less weighted ASCVR factors would reach the aforementioned threshold.

Risk classification modalities are shown in Supplemental Box 1.

Definition of actual risk classes

Very-high actual risk—This class was defined by the presence of unequivocally documented plaques on vascular ultrasound (VUS) of the carotid and/or femoral arteries according to ESC guidelines.[1 3]

High actual risk—Based on the ESC recommendations about the risk enhancement provided by the presence or absence of a clinical ASCVR factor not included in the SCORE equations,[1] patients were deemed to be at actual high risk if plaques were absent on VUS imaging and ≥1 of the following were present: family history of premature cardiovascular disease and/or a single markedly elevated ASCVR factor, such as heavy smoking (≥20 pack-years), severe obesity (body mass index ≥40 kg/m^2), pronounced hypercholesterolaemia (non-high-density lipoprotein-cholesterol ≥160 mg/dL)[14 15] or extreme blood pressure levels (systolic/diastolic BP ≥180/≥110 mm Hg).

Low-moderate actual risk—Patients not satisfying the very-high or high-risk class criteria above.

Supplemental Box 1

Cardiovascular risk classification based on traditional and disease-related variables

Risk classifier	Low or moderate risk	High risk	Very-high risk
SCORE	<5%	5–9.9%	≥10%
mSCORE	<5%	5–9.9%	≥10%
DIME	<50 years old with disease duration <10 years	Disease duration ≥10 years plus one of the following*: age ≥50 years; hypertension; atherogenic dyslipidaemia; smoking; abdominal obesity.	Disease duration ≥20 years or three of the following: age ≥50 years; hypertension; atherogenic dyslipidaemia; smoking; abdominal obesity.
APS_{events}	Non-arterial events	Arterial events other than major cardiovascular events	Major cardiovascular events
$aPL_{profile}$	Single aCL or anti-β2GPI positivity	Isolated LA positivity, or double non-LA positivity with medium titre aCL and medium-titre anti-β2GPI, or triple positivity with medium-titre aCL and medium-titre anti-β2GPI	LA positivity with high-titre aCL or high-titre anti-β2GPI, or triple positivity with high-titre aCL and high-titre anti-β2GPI
$aGAPSS_{CVD}$	<11 points	>11–15 points	>16 points

*Hypertension: systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg; atherogenic dyslipidaemia: non-HDL-cholesterol ≥130 mg/dL and low HDL (women <50mg/dL; men <40 mg/dL); obesity: waist circumference ≥94 cm (men) or ≥80 cm (women).

aCL, anti-cardiolipin antibodies; $aGAPSS_{CVD}$, adjusted Global APS Score for cardiovascular disease; anti-β2GPI, anti-beta-2-glycoprotein I antibodies; aPL, antiphospholipid antibodies; $aPL_{profile}$, risk related to the aPL profile; APS, antiphospholipid syndrome; APS_{events}, risk related to the type of APS thrombotic events; BP, blood pressure; DIME, diabetes mellitus-equivalent risk; HDL, high-density lipoprotein; LA, lupus anticoagulant; mSCORE, modified SCORE; SCORE, Systematic Coronary Risk Evaluation.

BP and lipidaemia phenotypes

BP—Patients not receiving antihypertensives were assigned to one of the following categories: normotension (systolic/diastolic BP <130/<85 mm Hg), high-normal BP (systolic/diastolic BP 130–139/85–89

mmHg), or untreated hypertension (systolic/diastolic BP ≥140/≥90 mm Hg) according to the ESC guidelines.[2] Based on BP targets reported by the same set of recommendations, patients undergoing BP-lowering treatment were classified into an 'adequate treatment' or 'inadequate treatment' group.

Blood lipids—Risk stratification with SCORE tailored to lipid targets was used to discriminate between treatment-naïve patients with normolipidaemia and those with untreated hyperlipidaemia.[3] Patients receiving lipid-lowering treatment were designated as being under 'adequate' or 'inadequate treatment' according to attainment of non-HDL-cholesterol targets.

SUPPLEMENTAL RESULTS

Supplemental Table S1

Baseline characteristics of APS patients (N=111)

Age (years), mean ± SD	45.2 ± 11.7
Women, %	68.5
PAPS, %	64
SLE-APS, %	36
Disease duration (years), median (IQR)	7 (2–15)
Arterial events, %	48.6
Major cardiovascular events, %	36
Non-arterial events, %	51.4
Lupus anticoagulant, n %	71.2
Anticardiolipin antibodies, %	83.8
IgG, %	67.6
IgM, %	52.3
High-titre IgG and/or IgM, %	54.1
Anti-beta-2 glycoprotein I antibodies, %	64
IgG, %	45
IgM, %	39.6
High-titre IgG and/or IgM, %	39.6
High-titre aCL and high-titre anti-β2GPI, %	35.1
Double aPL positivity, %	34.2
Triple aPL positivity, %	42.3
SLEDAI-2K, mean ± SD	2.4 ± 2.1
Systolic blood pressure (mm Hg), mean ± SD	124 ± 13
Diastolic blood pressure (mm Hg), mean ± SD	75 ± 8
Hypertension, %	35.1
Total cholesterol (mg/dL), mean ± SD	185 ± 37
LDL-cholesterol (mg/dL), mean ± SD	110 ± 33
HDL-cholesterol (mg/dL), median (IQR)	52 (42–62)
Triglycerides (mg/dL), median (IQR)	96 (74–136)
Non-HDL-cholesterol (mg/dL), mean ± SD	131 ± 37
Hyperlipidaemia, %	45.9*, 46.8†
Atherogenic dyslipidaemia, %	19.8
Body mass index (kg/m^2), median (IQR)	28 (24–32)

Obesity, %	37.8
Waist circumference (cm), median (IQR)	91 (80–100)
Abdominal obesity, %	65.8
Smoking, current, %	36.9
Antihypertensives, %	27.9
Hypolipidaemics, %	17.1
Antiplatelets, %	40.5
Anticoagulants, %	82
Glucocorticoids, %	30.6
Mean daily dose (mg), median (IQR)	3.1 (0.5–7.8)
Cumulative dose (g), median (IQR)	7.1 (1.7–18.5)
Immunosuppressants, %	18.9
Hydroxychloroquine, %	45.1

Risk-stratified with SCORE (*) and mSCORE (†).

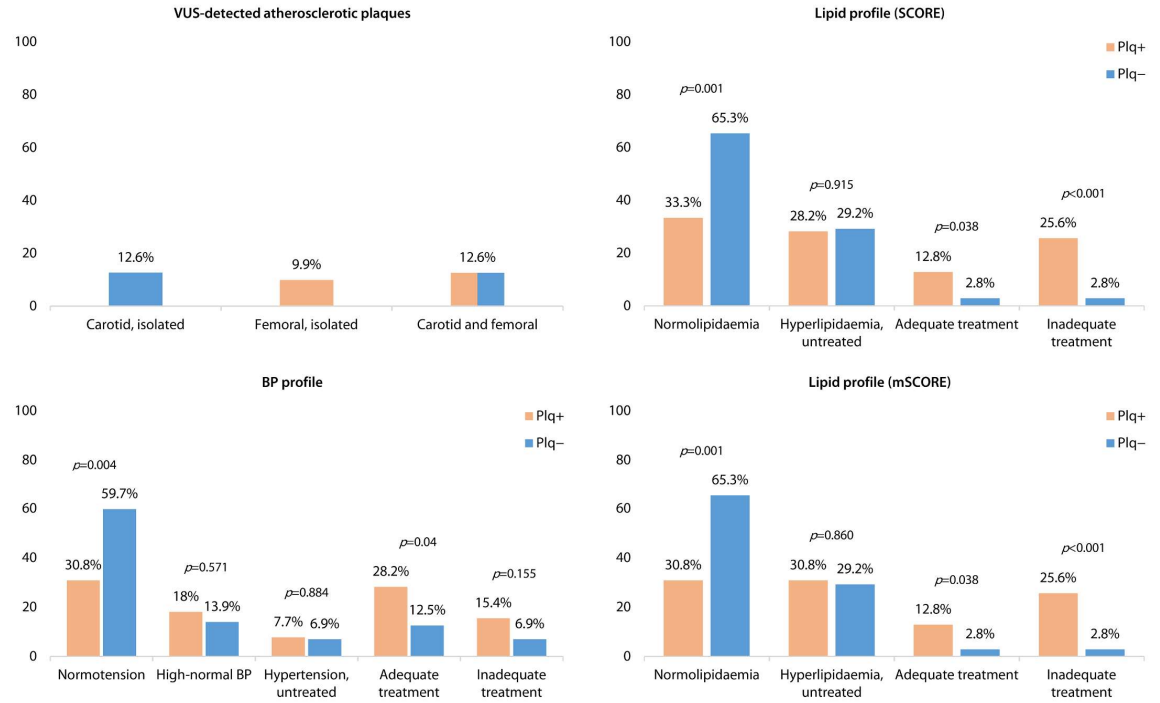
aCL, anticardiolipin antibodies; anti-β2GPI, anti-beta-2 glycoprotein I antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mSCORE, modified SCORE; PAPS, primary APS; SCORE, Systematic Coronary Risk Evaluation; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index-2000.

Supplemental Table S2

Associations of disease-related CVR features with very-high actual CVR in SLE-APS patients at low-moderate SCORE-predicted risk not receiving antihypertensives or hypolipidaemics (N=37)

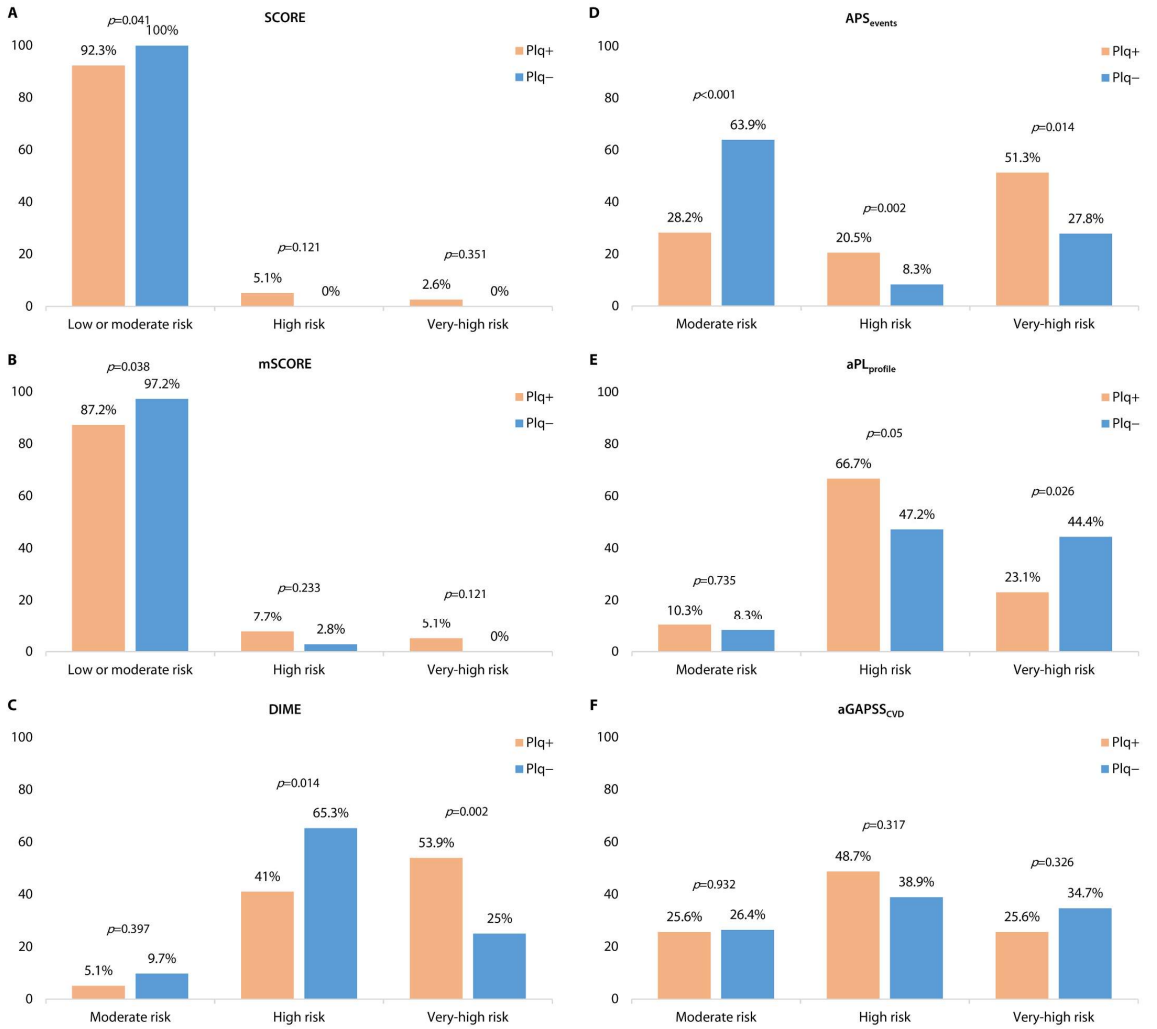
	OR (95% CI)	*p*-value
SLEDAI-2K ≥6	2.08 (0.31–14.2)	0.453
Glucocorticoids, mean daily dose (mg)	0.95 (0.83–1.08)	0.412
Glucocorticoids, mean daily dose ≥10 mg	0.55 (0.06–5.35)	0.605
Glucocorticoids, cumulative dose (g)	0.99 (0.96–1.04)	0.838
No use of hydroxychloroquine	0.85 (0.17–4.26)	0.843

CVR, cardiovascular risk; SCORE, Systematic Coronary Risk Evaluation; SLE-APS, systemic lupus erythematosus-associated antiphospholipid syndrome; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000.



Supplemental Figure S2

Cardiovascular risk assessment of APS patients according to vascular ultrasonography and BP and lipid profile. APS, antiphospholipid syndrome; BP, blood pressure; mSCORE, modified SCORE; Plq, presence (+) or absence (−) of atherosclerotic plaques; SCORE, Systematic Coronary Risk Evaluation; VUS, vascular ultrasound.



Supplemental Figure S3

Cardiovascular risk assessment of APS patients according to ASCVR classifiers (panels A–C), disease-related risk classifiers (panels D–E), and the $aGAPSS_{CVD}$ (panel F).

$aGAPSS_{CVD}$, adjusted Global APS Score for cardiovascular disease; $aPL_{profile}$, risk related to the antiphospholipid antibody (aPL) profile; APS, antiphospholipid syndrome; APS_{events}, risk related to the type of APS thrombotic events; ASCVR, atherosclerotic cardiovascular risk; DIME, diabetes mellitus-equivalent cardiovascular risk; mSCORE, modified SCORE; Plq, presence (+) or absence (−) of atherosclerotic plaques; SCORE, Systematic Coronary Risk Evaluation.

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