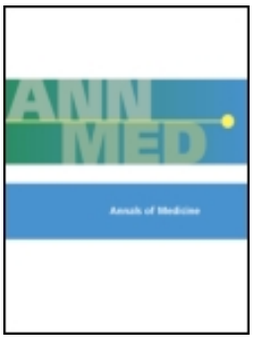

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ORIGINAL ARTICLE

Markers of cardiovascular risk in patients with antiphospholipid syndrome: A meta-analysis of literature studies

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Several studies reported on the association between antiphospholipid syndrome (APS) and venous thrombosis. In contrast, little is known about cardiovascular (CV) risk in APS. We performed a meta-analysis on the impact of APS on major markers of CV risk.

Studies on the relationship between APS and common carotid artery intima-media thickness (CCA-IMT), internal carotid artery IMT (ICA-IMT), carotid bifurcation IMT (BIF-IMT), prevalence of carotid plaques, flow-mediated dilation (FMD), nitrate-mediated dilation (NMD), and ankle-brachial index (ABI) were systematically searched in PubMed, Web of Science, Scopus, and EMBASE databases. Twenty case-control studies (668 cases, 678 controls) were included. Compared to controls, APS patients showed a higher CCA-IMT (mean difference [MD] 0.11 mm; 95% CI 0.07, 0.14), ICA-IMT (MD 0.08 mm; 95% CI 0.05, 0.11), BIF-IMT (MD 0.09 mm; 95% CI 0.06, 0.12) and a higher frequency of carotid plaques (OR 3.87; 95% CI 1.61, 9.31). Moreover, a lower FMD was found in APS subjects than in controls (MD −4.49%; 95% CI −6.20, −2.78), with no differences in NMD (MD −1.80%; 95% CI −4.01, 0.42). Finally, an increased prevalence of pathological ABI was found in APS patients compared to controls (OR 7.26; 95% CI 1.77, 29.71).

Despite heterogeneity among studies, APS appears significantly associated with markers of subclinical atherosclerosis and CV risk. These findings can be useful to plan adequate prevention strategies and therapeutic approaches.

Key words: Antiphospholipid syndrome, cardiovascular risk, endothelial dysfunction, intima-media thickness

Key messages

- Antiphospholipid syndrome (APS) is recognized as a major acquired thrombophilic condition associated with an increased risk of both venous and arterial events.
- The association of APS with markers of cardiovascular risk is widely discussed.
- We found that APS is associated with an increased subclinical atherosclerosis and with impaired endothelial function, both being recognized as markers of cardiovascular risk.

Introduction

The antiphospholipid syndrome (APS) is an acquired autoimmune disease characterized by the persistent presence of antiphospholipid antibodies (aPL) in patients with history of venous or arterial thrombosis and/or recurrent miscarriage (1,2). Antiphospholipid antibodies include lupus anticoagulant (LA), anticardiolipin (aCL), and anti-β_2 glycoprotein-I (β_2GPI) antibodies (3). With a prevalence of 40–50 cases per 100,000 persons (4), APS can occur in patients with systemic lupus erythematosus (SLE) or other autoimmune rheumatic diseases (secondary APS) or in patients without any concomitant clinical condition (primary APS) (5).

Overall, APS has been recognized as the most common acquired thrombophilic condition and, although associated with an increased risk of both venous and arterial events (6), some data suggest that venous thromboembolism represent $>60\%$ of vascular events secondary to APS (7), arterial thrombosis being less common in APS subjects (8,9).

Mechanisms leading to arterial thrombosis in APS are largely unknown (10), and the association between APS and subclinical atherosclerosis, known as a major marker of cardiovascular (CV) disease (11), is still controversial.

Carotid intima-media thickness (IMT) assessment is a non-invasive imaging test for subclinical atherosclerosis (12,13) and has been widely accepted as one of the strongest predictors of CV events (14,15). Similarly, flow-mediated dilation (FMD) and nitrate-mediated dilation (NMD), pulse-wave velocity (PWV), augmentation index (AIx), and ankle-brachial index (ABI) are considered surrogate markers of subclinical atherosclerosis and independent predictors of CV events (13,16,17), thus providing important prognostic data over and above traditional CV risk factors.

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During recent years, there has been growing interest in the relationship between these markers of CV risk and APS. In particular, some case-control studies reported accelerated atherosclerosis (18,19), impaired endothelial function (20), and increased arterial stiffness (21) in patients with primary or secondary APS. However, these data have been challenged in other studies (22,23), and no meta-analytical data providing an overall information about this issue are currently available.

The aim of the present study is to perform a systematic review and meta-analysis of all studies evaluating the impact of APS on the major markers of CV risk.

Methods

A protocol for this review was prospectively developed, detailing the specific objectives, the criteria for study selection, the approach to assess study quality, the outcomes, and the statistical methods.

Search strategy

To identify all available studies, a detailed search pertaining to APS and the markers of CV risk (i.e. IMT, FMD, NMD, PWV, AIx, and ABI) was conducted according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (24). A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search terms in all possible combinations: intima-media thickness, carotid plaques, flow-mediated dilation, nitrate-mediated dilation, endothelium-dependent dilation, endothelium-independent dilation, pulse wave velocity, tonometry, augmentation index, atherosclerosis, ankle-brachial index, antiphospholipid syndrome. The last search was performed on 10 March 2014. The search strategy was developed without any language restriction.

In addition, the reference lists of all retrieved articles were manually reviewed. In case of missing data, study authors were contacted by e-mail to try to retrieve original data. Two independent authors (P.A. and R.L.) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (M.N.D.D.M.). Discrepancies were resolved by consensus. Selection results have been reported according to PRISMA flowchart (Supplementary Appendix 1, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.959559).

Data extraction and quality assessment

According to the pre-specified protocol, all studies evaluating the impact of APS on the markers of CV risk were included. Case reports, case series without a control group, reviews, and animal studies were excluded. Only APS, both primary and secondary, was considered in this meta-analysis, while positivity of aPL without thrombotic history was not taken into account. To be included in the analysis, a study had to provide values (means with standard deviation) of at least one variable among the following: common carotid artery IMT (CCA-IMT), internal carotid artery IMT (ICA-IMT), carotid bifurcation IMT (BIF-IMT), brachial artery FMD or NMD, aortic PWV or AIx, and ABI. Studies reporting the prevalence of carotid plaques were also included.

In each study, data regarding sample size, major clinical and demographic variables, values of IMT, FMD, NMD, PWV, AIx, and ABI, and prevalence of carotid plaques in APS patients and healthy controls were extracted.

Given the characteristics of the included studies, the evaluation of methodological quality of each study was performed with the Newcastle–Ottawa Scale (NOS), which is specifically developed to assess quality of non-randomized observational studies (25). The scoring system encompasses three major domains (selection, comparability, exposure) and a resulting score range between 0 and 8, a higher score representing a better methodological quality. Results of the NOS quality assessment are reported in Supplementary Appendix 2 (to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.959559).

Statistical analysis and risk of bias assessment

Statistical analysis was carried out using Review Manager (Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark) provided by The Cochrane Collaboration.

Differences among cases and controls were expressed as mean difference (MD) with pertinent 95% confidence intervals (95% CI) for continuous variables, and as odds ratio (OR) with pertinent 95% CI for dichotomous variables.

IMT has been expressed in millimeters (mm), FMD, NMD, and AIx as percentage (%), PWV as mm per second (mm/s), and ABI as absolute number.

The overall effect was tested using Z scores, and significance was set at $P < 0.05$. Statistical heterogeneity between studies was assessed with chi-square, Cochran's Q test, and with I^2 statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25%–50% moderate, and 50% high heterogeneity (26).

Publication bias was represented graphically by funnel plots of the standard difference in means versus the standard error. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect (27).

In order to be as conservative as possible, the random-effect method was used to take into account the variability among included studies.

Sensitivity analyses

We repeated sensitivity analyses by including only the studies judged as 'high quality' according to NOS (i.e. NOS $\geq$ the median value found among included studies).

In order to avoid the risk of data overlap, a further analysis was performed after excluding studies involving same recruitment centers and enrolling patients in the same period time as other included studies.

Subgroup analyses

Given the potential influence of underlying clinical conditions on the outcomes, we planned to perform a separate subgroup analysis only including studies reporting on primary APS.

Meta-regression analyses

We hypothesized that changes in IMT, FMD, NMD, PWV, AIx, and ABI values, and number of carotid plaques may be affected by differences in baseline characteristics of patients included in different studies (mean age, percentage of male patients) or by the coexistence of other CV risk factors (hypertension, smoking, obesity, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia). To assess the possible effect of such variables in explaining the different results observed across studies, we planned to perform a meta-regression analysis after implementing a regression model with changes in IMT, FMD, NMD, PWV, AIx, and ABI values, or presence of carotid plaques as dependent variable (y) and the above-mentioned variables as independent variables

(x). This analysis was performed with STATA 11.1 (Stata Corp, Austin, TX, USA).

Results

After excluding duplicate results, the search retrieved 1071 articles. Of these studies, 683 were excluded because they were off the topic after scanning the title and/or the abstract, 358 because they were reviews/comments/case reports or they lacked of data of interest. For 1 study the online full-length version was not available, and another 9 studies were excluded after full-length paper evaluation.

Thus, 20 articles (on 668 APS patients and 678 healthy controls) were included in the final analysis (Supplementary Appendix 1, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.959559). In detail, we included 14 studies with data on CCA-IMT (19 data sets on 492 cases and 645 controls), 5 on ICA-IMT and BIF-IMT (6 data sets on 136 cases and 126 controls), 4 studies reporting on the prevalence of carotid plaques (6 data sets on 142 cases and 239 controls), 8 studies on FMD (10 data sets on 271 patients and 398 controls), and 4 on NMD (5 data sets on 154 cases and 257 controls).

The ABI has been tested in only 2 studies (73 cases and 79 controls) (19,28). No mean ABI values were reported for cases and controls, but only the prevalence of pathological ABI, defined as ABI < 1. No study on PWV and AIx could be included in the final analysis.

Study characteristics

All included studies had a case-control design, and major characteristics are shown in Table I.

The number of patients varied from 10 to 58, the mean age from 29.1 to 52.6 years, and the prevalence of male gender from 0% to 65%.

The presence of hypertension was reported by 0%–36% of patients, smoking habit by 4%–48%, diabetes mellitus by 0%–5%, obesity by 0%–54%, hypercholesterolemia by 0%–55%, and hypertriglyceridemia by 0%–25%.

Mean body mass index (BMI) varied from 22.8 kg/m^2 to 26 kg/m^2. Mean values of total cholesterol (TC) ranged from 175 to 211 mg/dL, of LDL-cholesterol (LDLc) from 97 to 132 mg/dL, of HDL-cholesterol (HDLc) from 37 to 66 mg/dL, and of triglycerides (TGs) from 89 to 137 mg/dL.

One study (29) provided separate data for three different age groups (< 30 years, 30–40 years, > 40 years). The first age group was excluded from our meta-analysis to avoid a potential source of bias secondary to the young age of patients as compared to the mean age reported in the other included studies. The remaining two groups were included as two different data sets. In addition, separate data for primary and secondary APS were reported by 3 studies for CCA-IMT (30–32), by 1 study for FMD (31), and by 2 studies (5,32) for the prevalence of carotid plaques. Finally, 1 study (21) provided separate data on CCA-IMT, FMD, and NMD for APS patients with pregnancy loss and those with venous thromboembolism. In all these cases, data were split into different data sets.

The NOS for quality assessment of included studies showed a median value of 6.

Intima-media thickness (IMT) (Figure 1)

In 14 studies (19 data sets) (5,18,21,22,29–38), we found that the 492 APS patients showed significantly higher CCA-IMT than the 645 controls (MD 0.11 mm; 95% CI 0.07, 0.14; $P < 0.00001$). Heterogeneity among these studies was statistically significant ($I^2 = 90\%$; $P < 0.00001$), and no reduction in the overall heterogeneity was found after excluding one study at time. Five studies (6 data sets) (18,29,34,35,39), evaluating a total of 136 cases and 126 controls, showed significantly higher ICA-IMT (MD 0.08 mm; 95% CI 0.05, 0.11; $P < 0.00001$) and BIF-IMT (MD 0.09 mm; 95% CI 0.06, 0.12; $P < 0.00001$) in APS subjects than in controls, without heterogeneity among studies ($I^2 = 0\%$; $P = 0.53$ and $I^2 = 0\%$; $P = 0.64$, respectively). Finally, in 4 studies (6 data sets) (5,22,32,38) 142 APS patients showed an increased prevalence of carotid plaques as compared to 239 controls (23.2% versus 8.37%), with a corresponding OR of 3.87 (95% CI 1.61, 9.31; $P = 0.0003$) and without a significant heterogeneity among studies ($I^2 = 35\%$; $P = 0.17$).

Flow-mediated dilation (FMD) and nitrate-mediated dilation (NMD) (Figure 2)

Eight studies (10 data sets) (20,21,31,33,35,37,40,41), evaluating a total of 271 cases and 398 controls, showed a significantly lower FMD in APS subjects as compared to controls (MD -4.49%; 95% CI -6.20, -2.78; $P < 0.00001$). Significant heterogeneity among studies was found ($I^2 = 92\%$; $P < 0.00001$), and it was not reduced by excluding one study at time.

Four studies (5 data sets) (20,21,33,41), evaluating a total of 154 APS subjects and 257 controls, showed a trend towards a lower NMD in APS patients than in controls (MD -1.80%; 95% CI -4.01, 0.42, $P = 0.11$). Although the difference was not significant and a high heterogeneity among studies was found ($I^2 = 66\%$; $P = 0.02$), after excluding one study (41), significantly lower values of NMD were found in APS subjects as compared to controls (MD -2.61%; 95% CI -4.06, -1.15; $P = 0.0004$) without heterogeneity among studies ($I^2 = 0\%$; $P = 0.49$).

Ankle-brachial index (ABI) (Figure 3)

Two studies (73 cases and 79 controls) (19,28) reported on the impact of APS on ABI. A pathological ABI (< 1) was found to be more frequent in APS subjects compared to controls (20.5% versus 2.5%), with a corresponding OR of 7.26 (95% CI 1.77, 29.71; $P = 0.006$), without heterogeneity among studies ($I^2 = 0\%$; $P = 0.44$).

Publication bias

Because it is recognized that publication bias can affect the results of meta-analyses, we attempted to assess this potential bias using funnel plots analysis.

Funnel plots of effect size versus standard error for studies evaluating CCA-IMT and FMD were rather symmetrical, suggesting the absence of publication bias and of small-study effect (Supplementary Appendix 3, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.959559).

In contrast, the small sample size and the low number of studies makes publication bias assessment unlikely to be performed for ICA-IMT, BIF-IMT, carotid plaques, NMD, and ABI.

Sensitivity analysis

The median value of NOS quality assessment was 6, and the analyses were repeated by including only the studies classified as 'high quality' (NOS ≥ 6) (Supplementary Appendix 2, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2014.959559) (5,18,21,22,29,31–35,38–41). For 1 study (37) the data of interest were extracted by the abstract, thus no quality assessment could be performed.

Table I. Characteristics of included studies.

Author		Pop (*n*)	M/F (*n*)	Age (y)	HT (%)	Smoking (%)	DM (%)	BMI (kg/m^2)	TC (mg/dL)	LDLc (mg/dL)	HDLc (mg/dL)	TGs (mg/dL)
Medina, 2003 (36)[a]	pAPS	28	12/16	40.0 ± 8.5	36	11	0	NA	NA	NA	NA	NA
	Controls	28	12/16	41.7 ± 6.3	0	14	0	NA	NA	NA	NA	NA
Vlachoyiannopoulus, 2003 (22)	pAPS/sAPS	33	0/33	33.9 ± 7.4	6	NA	0	26.0 ± 5.0	194 ± 34	120 ± 27	51 ± 14	89 ± 15
	Controls	33	0/33	33.3 ± 7.9	9	NA	3.0	24.0 ± 5.0	193 ± 37	117 ± 34	57 ± 12	47 ± 8
Roch, 2004 (30)	pAPS	20	4/16	44.0 ± 16.0	NA	NA	NA	NA	NA	NA	NA	NA
	sAPS	14	1/13	43.0 ± 16.0	NA	NA	NA	NA	NA	NA	NA	NA
	Controls	24	3/21	43.0 ± 9.0	NA	NA	NA	NA	NA	NA	NA	NA
Ames, 2005 (18)[b]	pAPS	20	13/7	35.0 ± 12.0	5	30	0	< 30.0	NA	NA	NA	NA
	Controls	20	13/7	34.0 ± 12.0	5	20	0	< 30.0	NA	NA	NA	NA
Ames, 2005 (39)	pAPS	18	5/13	42.0 ± 9.0	17	NA	NA	NA	NA	NA	NA	NA
	Controls	16	4/12	41.0 ± 8.0	0	NA	NA	NA	NA	NA	NA	NA
Barón, 2005 (28)[c]	pAPS	43	6/37	40.2 ± 7.9	35	23	NA	NA	NA	NA	NA	NA
	Controls	49	7/42	41.0 ± 11.7	6	27	NA	NA	NA	NA	NA	NA
Jimenez, 2005 (32)	pAPS	25	0/25	38.6 ± 11.4	4	36	0	24.2 ± 3.6	203 ± 36	121 ± 27	66 ± 14	91 ± 49
	sAPS	16	0/16	39.9 ± 10.3	NA	NA	NA	NA	NA	NA	NA	NA
	Controls	40	0/40	42.2 ± 11.2	10	37	5	24.9 ± 4.6	190 ± 50	109 ± 42	58 ± 26	78 ± 35
Chrsistodoulou, 2006 (19)	pAPS/sAPS	30	0/30	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Controls	30	0/30	NA	NA	NA	NA	NA	NA	NA	NA	NA
Stalc, 2006 (20)[d]	pAPS	25	15/10	47.0 ± 13.0	20	4	4	NA	NA	NA	NA	NA
	Controls	25	15/10	47.0 ± 13.0	12	4	4	NA	NA	NA	NA	NA
Der, 2007 (37)	pAPS	44	NA	52.0 ± 15.0	NA	NA	NA	NA	NA	NA	NA	NA
	Controls	36	NA	50.0 ± 11.0	NA	NA	NA	NA	NA	NA	NA	NA
Margarita, 2007 (29)	pAPS > 40 y	16	NA	> 40	NA	NA	NA	NA	NA	NA	NA	NA
	Controls	14	NA	> 40	NA	NA	NA	NA	NA	NA	NA	NA
	pAPS 30–40 y	17	NA	30–40	NA	NA	NA	NA	NA	NA	NA	NA
	Controls	11	NA	30–40	NA	NA	NA	NA	NA	NA	NA	NA
Belizna, 2008 (5)[e]	pAPS/sAPS	58	22/36	29.1 (21–45)	NA	48	0	NA	175 ± 19	101 ± 23	54 ± 3	137 ± 35
	Controls	58	16/42	28.1 (20–45)	NA	62	0	NA	174 ± 21	103 ± 12	56 ± 2	134 ± 27
Soltesz, 2008 (33)	pAPS	28	12/16	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Controls	38	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ames, 2009 (34)[f]	pAPS	49	18/31	37.0 ± 11.0	NA	37	0	25.3 ± 3.2	178 ± 35	97 ± 31	37 ± 11	106 ± 55
	Controls	49	18/31	37.0 ± 11.0	NA	24	0	23.4 ± 2.4	182 ± 29	110 ± 29	57 ± 14	83 ± 29
Bilora, 2009 (35)	pAPS	16	10/6	52.6 ± 3.1	31	NA	NA	25.5 ± 4.6	NA	NA	NA	NA
	Controls	16	10/6	52.9 ± 4.1	31	NA	NA	25.1 ± 4.4	NA	NA	NA	NA
Charakida, 2009 (21)[g]	pAPS abort	23	0/23	44.6 ± 9.2	26	43	0	26.1 ± 5.8	193 ± 44	132 ± 33	50 ± 17	76 (57–119)
	pAPS VTE	38	0/38	49.4 ± 10.8	32	16	3	25.2 ± 4.5	199 ± 45	126 ± 38	57 ± 13	78 (59–118)
	Controls	77	0/77	47.5 ± 10.4	25	22	2	24.5 ± 4.8	196 ± 39	129 ± 32	56 ± 11	73 (53–113)
Gresele, 2009 (40)[h]	pAPS	20	9/11	41.9 ± 4.0	NA	0	0	24.2 ± 0.9	NA	NA	NA	NA
	Controls	39	17/22	41.3 ± 2.9	NA	0	0	23.6 ± 0.7	NA	NA	NA	NA
Caraba, 2010 (38)	pAPS	10	2/8	41.4 ± 4.2	0	30	0	NA	211 ± 20	NA	NA	NA
	Controls	10	2/8	42.0 ± 4.0	0	40	0	NA	196 ± 29	NA	NA	NA
Cugno, 2010 (41)[i]	pAPS	40	7/33	38.0 ± 9.0	NA	17.5	NA	22.8 ± 3.4	188 ± 32	119 ± 26	58 ± 14	NA
	Controls	40	7/33	41.0 ± 12.0	NA	20	NA	23.7 ± 4.1	197 ± 32	115 ± 31	62 ± 13	NA
Conti, 2014 (31)[j]	pAPS	18	4/14	39.9 ± 11.5	NA	11	5	25.5 ± 3.3	191 ± 24	122 ± 19	49 ± 15	102 ± 59
	sAPS	19	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Controls	25	4/21	42.5 ± 12.0	NA	32	0	22.2 ± 3.1	203 ± 46	126 ± 43	58 ± 10	91 ± 47

abort = recurrent abortions; BMI = body mass index; DM = diabetes mellitus; HDLc = HDL-cholesterol; HT = hypertension; LDLc = LDL-cholesterol; M/F = male/female; NA = not assessed; pAPS = primary antiphospholipid syndrome; Pop = study population; sAPS = secondary antiphospholipid syndrome; TC = total cholesterol; TGs = triglycerides; VTE = venous thromboembolism.

[a]54% of patients and 39% of controls were obese; 29% of patients and 29% of controls had hypercholesterolemia; 25% of patients and 29% of controls had hypertriglyceridemia.

[b]5% of patients and 5% of controls had hypercholesterolemia; 15% of patients had hypertriglyceridemia.

[c]33% of patients and 6% of controls had BMI > 28; 26% of patients and 6% of controls had hypercholesterolemia.

[d]8% of patients and 8% of controls had BMI > 27; 28% of patients and 24% of controls had hyperlipidemia.

[e]Age is expressed as mean (range). Systolic blood pressure (mmHg, mean ± SD) was 110 ± 2.45 in cases and 109 ± 3.20 in controls; diastolic blood pressure (mmHg, mean ± SD) was 69 ± 1.68 in cases and 66.4 ± 1.59 in controls.

[f]Systolic blood pressure (mmHg, mean ± SD) was 125 ± 17.7 in cases and 123 ± 15.1 in controls; diastolic blood pressure (mmHg, mean ± SD) was 80 ± 9.6 in cases and 77 ± 7.9 in controls.

[g]Values of TGs are expressed as median (interquartile range).

[h]Systolic blood pressure (mmHg, mean ± SD) was 129 ± 4 in cases and 125 ± 3 in controls; diastolic blood pressure (mmHg, mean ± SD) was 77 ± 2 in cases and 74 ± 2 in controls; patients with dyslipidemia were excluded from the study.

[i]Systolic blood pressure (mmHg, mean ± SD) was 120 ± 15 in cases and 133 ± 24 in controls; diastolic blood pressure (mmHg, mean ± SD) was 78 ± 10 in cases and 88 ± 11 in controls; glycemia (mg/dL, mean ± SD) was 81 ± 10 in cases and 87 ± 10 in controls.

[j]Systolic blood pressure (mmHg, mean ± SD) was 127 ± 15 in cases and 115 ± 16 in controls; diastolic blood pressure (mmHg, mean ± SD) was 79 ± 11 in cases and 73 ± 9 in controls.

Of interest, after excluding studies classified as 'low quality' (19,20,28,30,36) and the one with only abstract available (37), all results were confirmed for IMT, FMD, and NMD (Table II). Both studies reporting on ABI (19,28) were classified as 'low quality', thus no data on sensitivity analysis are available for this outcome.

Similarly, results on IMT, FMD, NMD, and ABI were confirmed also after excluding studies (18,19,29,33,39) potentially

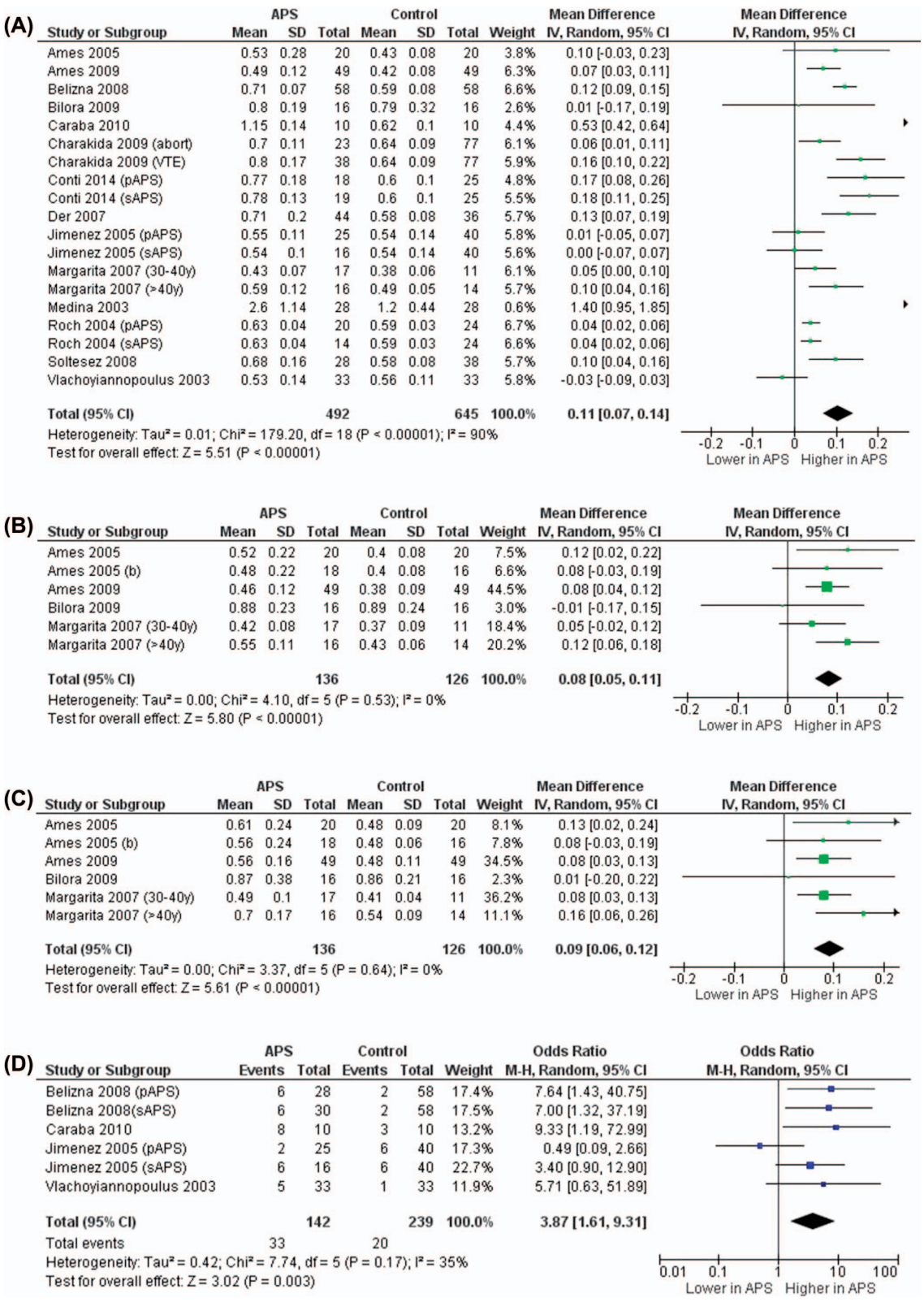

Figure 1. Intima-media thickness in antiphospholipid syndrome (APS) patients and controls. A: Common carotid artery intima-media thickness (CCA-IMT). B: Internal carotid artery IMT (ICA-IMT). C: Carotid bifurcation IMT (BIF-IMT). D: Prevalence of carotid plaques. (Abort = recurrent abortions; pAPS = primary antiphospholipid syndrome; sAPS = secondary antiphospholipid syndrome; VTE = venous thromboembolism; y = years of age).

reporting on the same population as other included studies (28,34,37) (Table III).

Subgroup analysis

With the exception of 2 studies (19,22), all studies reported on primary APS, and other 4 studies (5,30–32) provided separate data for primary and secondary APS for at least one outcome. When the analyses were repeated by including only data on primary APS (5,18,20,21,28–41), similar results were confirmed for all outcomes, with the only exception of prevalence of carotid plaques. This outcome has been reported by only 3 studies on primary APS (5,32,38), and the difference

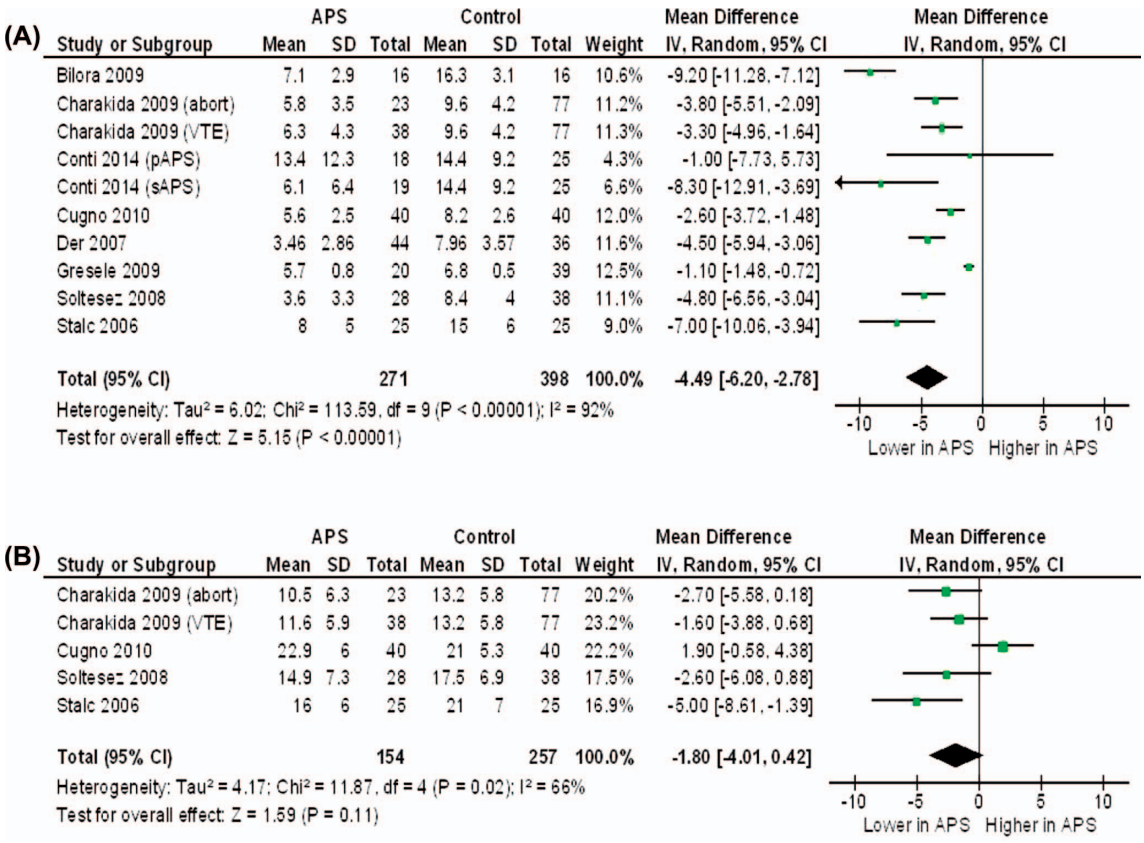

Figure 2. Flow-mediated dilation and nitrate-mediated dilation in antiphospholipid syndrome (APS) patients and controls. A: Flow-mediated dilation (FMD). B: Nitrate-mediated dilation (NMD). (Abort = recurrent abortions; pAPS = primary antiphospholipid syndrome; sAPS = secondary antiphospholipid syndrome; VTE = venous thromboembolism).

among APS subjects and controls was no longer significant (Table IV).

Meta-regression analyses

Regression models showed that none of the clinical and demographic variables influenced the association between APS and CCA-IMT. In contrast, increasing age ($P = 0.012$) and the presence of diabetes mellitus ($P = 0.011$) significantly impacted on FMD impairment.

According to Cochrane Collaboration guidelines (42), given the low number of studies, no meta-regression analysis was performed for ICA-IMT, BIF-IMT, prevalence of carotid plaques, NMD, and ABI.

Discussion

Results of the present meta-analysis show that APS is associated with subclinical atherosclerosis and endothelial dysfunction. In detail, we reported an increased carotid IMT, accompanied by impaired FMD, and increased prevalence of carotid plaques and of pathological ABI in APS subjects. In line with these findings, NMD was found to be lower in APS, but the difference did not reach statistical significance. Our findings are strengthened by the results of the subgroup and sensitivity analyses. Indeed, most results were confirmed after excluding the potential confounding effect due to other underlying medical conditions (i.e. systemic lupus erythematosus) and specifically evaluating data on patients with primary APS. Moreover, regression models have been performed to further assess any potential influence of clinical and demographic characteristics on evaluated outcomes

Overall, these data clearly show an increased CV risk in patients with APS and suggest a strict monitoring of cardiovascular risk factors and of subclinical signs of atherosclerosis in APS patients. The relevance of subclinical atherosclerosis lies in its ability to predict the CV risk and to contribute further to the morbidity of affected patients. This is in line with previously published studies reporting an increased CV risk in patients with other autoimmune and rheumatic diseases (43,44).

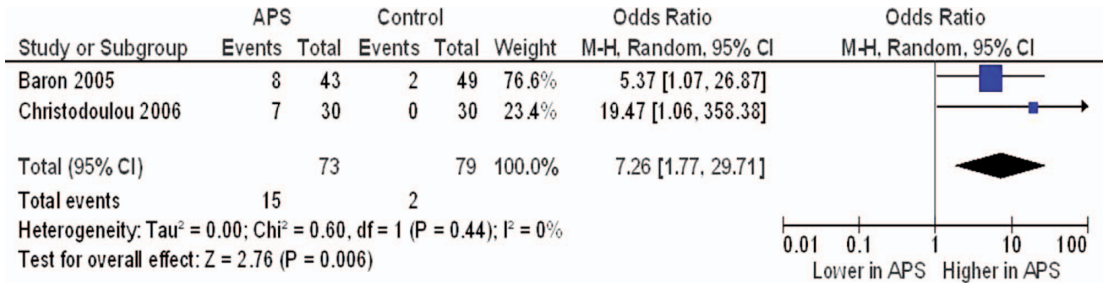

Figure 3. Prevalence of pathological ankle-brachial index in antiphospholipid syndrome (APS) patients and controls.

Table II. Sensitivity analysis including 'high-quality' studies (i.e. Newcastle–Ottawa Scale ≥ 6).

	Studies (*n*)	Patients (*n*)	Effect size MD or OR [95% CI]
CCA-IMT	12 (16 data sets)	430 patients 569 controls	MD: 0.11 [0.06, 0.15]; $P<0.00001$ $I^2=88\%$; $P<0.00001$
ICA-IMT	5 (6 data sets)	136 patients 126 controls	MD: 0.08 [0.05, 0.11]; $P<0.00001$ $I^2=0\%$; $P=0.53$
BIF-IMT	5 (6 data sets)	136 patients 126 controls	MD: 0.09 [0.06, 0.12]; $P<0.00001$ $I^2=0\%$; $P=0.64$
Carotid plaques	4 (6 data sets)	142 patients 239 controls	OR: 3.87 [1.61, 9.31]; $P=0.0003$ $I^2=35\%$; $P=0.17$
FMD	5 (6 data sets)	155 patients 274 controls	MD: − 3.66 [− 5.78, − 1.55]; $P=0.0007$ $I^2=93\%$; $P<0.00001$
NMD	2 (3 data sets)	101 patients 194 controls	MD: − 0.75 [–3.43, 1.92]; $P=0.58$ $I^2=70\%$; $P=0.04$
ABI < 1	No studies	–	–

95% CI = 95% confidence intervals; ABI = ankle-brachial index; BIF-IMT = carotid bifurcation intima-media thickness; CCA-IMT = common carotid artery intima-media thickness; FMD = flow-mediated dilation; ICA-IMT = internal carotid artery intima-media thickness; MD = mean difference; NMD = nitrate-mediated dilation; OR = odds ratio.

Many inherited and acquired risk factors are thought to have a causal role in the atherosclerotic process. However, the relationship between subclinical atherosclerosis and APS is complex, and the traditional CV risk factors do not seem to be the only parameters responsible for accelerated atherosclerosis in APS. Thus, inflammatory and immunological mechanisms have been proposed to explain the relationship between APS and atherosclerosis (22). Endothelial dysfunction, oxidative stress, increased expression of cell adhesion molecules, and platelet activation are common findings in this clinical setting (45). Moreover, growing evidence suggests that aPL are not only a marker of thrombophilia but play a direct pathogenic role (46–50). In keeping with this, some studies hypothesized a pro-atherogenic role of aPL and, in particular, of anti-β_2GPI antibodies (51,52). β_2GPI reduces the intake of oxidized LDL (oxLDL) by macrophages in the vessel wall (53), but this effect is blocked when anti-β_2GPI antibodies are present. Thus, macrophage uptake of oxLDL is increased, leading to accelerated atherosclerosis (28). In keeping with this, anti-β_2GPI antibodies have been found in atherosclerotic plaques obtained from human carotid endarterectomies (54). Other studies reported that aCL can cross-react with anti-oxLDL antibodies (55). Thus, aCL may have the same pro-atherogenic effect as anti-oxLDL antibodies (28).

Positivity to aPL has been associated also with reduced activity of paraoxonase, a HDL-related antioxidant enzyme (21). Animal models suggest that paraoxonase deficiency can lead to premature atherosclerosis (56).

Recently, an association between subclinical atherosclerosis and venous thrombosis has been reported, suggesting that the two conditions may share common risk factors (6,57).

Our findings are in line with this experimental and clinical evidence, supporting the hypothesis that, besides venous thrombosis (7), also premature atherosclerosis may be one of the main features of APS. The clinical relevance of our results can be better understood when we consider that the risk of myocardial infarction increases 43% with every 0.163 mm increase in carotid IMT (58). Moreover, each 1% decrease in FMD has been associated with a 12% increase of cardiovascular events (59). In order to provide a comprehensive overview of the relationship between APS and subclinical atherosclerosis, all the major recognized markers of CV risk were taken into account in the current meta-analysis. Although no meta-analytical evaluation was possible for arterial stiffness parameters (PWV and AIx), it is relevant that, in line with our findings, higher values of PWV have been documented in women with primary APS (21).

It is noteworthy that some data suggested that an unsolved issue is which of the carotid segments (CCA, ICA, or bifurcation) best predicts CV risk (60). Interestingly, in our meta-analysis, we found a wide agreement among different segments, consistently confirming an increased IMT in APS patients.

Table III. Sensitivity analysis: exclusion of studies potentially evaluating the same population as other included studies.

	Studies (*n*)	Patients (*n*)	Effect size MD or OR [95% CI]
CCA-IMT	11 (15 data sets)	411 patients 562 controls	MD: 0.11 [0.07, 0.16]; $P<0.00001$ $I^2=92\%$; $P<0.00001$
ICA-IMT	2 (2 data sets)	65 patients 65 controls	MD: 0.07 [0.02, 0.12]; $P=0.009$ $I^2=9\%$; $P=0.29$
BIF-IMT	2 (2 data sets)	65 patients 65 controls	MD: 0.08 [0.02, 0.13]; $P=0.005$ $I^2=0\%$; $P=0.53$
Carotid plaques	4 (6 data sets)	142 patients 239 controls	OR: 3.87 [1.61, 9.31]; $P=0.0003$ $I^2=35\%$; $P=0.17$
FMD	7 (9 data sets)	243 patients 360 controls	MD: − 4.46 [− 6.28, − 2.63]; $P<0.00001$ $I^2=92\%$; $P<0.00001$
NMD	3 (4 data sets)	126 patients 219 controls	MD: − 1.66 [− 4.35, 1.03]; $P=0.23$ $I^2=74\%$; $P=0.01$
ABI	1	43 patients 49 controls	OR: 5.37 [1.07, 26.87]; $P=0.04$ $I^2=$NA; $P=$NA

95% CI = 95% confidence intervals; ABI = ankle-brachial index; BIF-IMT = carotid bifurcation intima-media thickness; CCA-IMT = common carotid artery intima-media thickness; FMD = flow-mediated dilation; ICA-IMT = internal carotid artery intima-media thickness; MD = mean difference; NMD = nitrate-mediated dilation; OR = odds ratio.

Table IV. Subgroup analysis: studies on primary antiphospholipid syndrome.

	Studies (*n*)	Patients (*n*)	Effect size MD or OR [95% CI]
CCA-IMT	12 (14 data sets)	352 patients 465 controls	MD: 0.13 [0.08, 0.18]; $P<0.00001$ $I^2=90\%$; $P<0.00001$
ICA-IMT	5 (6 data sets)	136 patients 126 controls	MD: 0.08 [0.05, 0.11]; $P<0.00001$ $I^2=0\%$; $P=0.53$
BIF-IMT	5 (6 data sets)	136 patients 126 controls	MD: 0.09 [0.06, 0.12]; $P<0.00001$ $I^2=0\%$; $P=0.64$
Carotid plaques	3 (3 data sets)	63 patients 108 controls	OR: 3.14 [0.46, 21.32]; $P=0.24$ $I^2=71\%$; $P=0.03$
FMD	8 (10 data sets)	252 patients 373 controls	MD: -4.22 [-5.95, -2.49]; $P<0.00001$ $I^2=92\%$; $P<0.00001$
NMD	4 (5 data sets)	154 patients 257 controls	MD: -1.80 [-4.01, 0.42]; $P=0.42$ $I^2=66\%$; $P=0.02$
ABI	1	43 patients 49 controls	OR: 5.37 [1.07, 26.87]; $P=0.04$ $I^2=$NA; $P=$NA

95% CI = 95% confidence intervals; ABI = ankle-brachial index; BIF-IMT = carotid bifurcation intima-media thickness; CCA-IMT = common carotid artery intima-media thickness; FMD = flow-mediated dilation; ICA-IMT = internal carotid artery intima-media thickness; MD = mean difference; NMD = nitrate-mediated dilation; OR = odds ratio.

Some potential limitations of our study need to be discussed. First, studies included in our meta-analysis have different inclusion and exclusion criteria, and most of the patients included in the analysis had concomitant CV risk factors (hypertension, smoking, obesity, diabetes mellitus, dyslipidemia). Since meta-analysis is performed on aggregate data and some information is missing in each study, the multivariate approach allowed for the adjustment for some (but not all) potential confounders. Moreover, based on Cochrane Collaboration guidelines, a meta-regression approach is effective when a covariate is reported by at least 10 studies (42). Thus, because of the limited number of studies, a meta-regression analysis has been performed only for CCA-IMT and FMD, and we cannot exclude the influence of CV risk factors on the other outcomes. However, this issue cannot be fully addressed in a meta-analysis of aggregate data, making necessary an individual patient-level analysis.

As a further potential source of bias, we have to consider that some included studies presented data without making a distinction between patients with primary or secondary APS. Thus, we cannot exclude that the concomitant presence of systemic erythematosus lupus or other immune-mediated disorders might impact on our results. However, the large majority of studies reported separate data for primary APS, and the subgroup analysis confirmed all results. Thus, we are confident that the risk of bias due to the confounding effect of concomitant diseases could be low.

Finally, caution is necessary in the interpretation of the results on FMD and NMD. While IMT is a somewhat reproducible parameter, FMD and NMD measurements may be influenced by many confounding factors (61), significantly limiting reproducibility of FMD and NMD assessment and, in turn, the relevance of results. However, it is interesting to highlight that the effect of APS was consistently confirmed for all evaluated outcomes, strongly suggesting an increased CV risk in these patients.

Conclusions

In conclusion, in our meta-analysis APS appeared significantly associated with subclinical atherosclerosis, endothelial dysfunction, and, in turn, with an increased CV risk. Thus, patients with APS may benefit from a more meticulous screening for CV risk factors and more specific CV prevention strategy. However, additional and specifically designed studies are needed in order to establish the optimal management of these patients.

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Supplementary material available online

Supplementary Appendices 1–4.
Supplementary MOOSE checklist.