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Review

Immunoglobulin G (IgG) anticardiolipin antibodies and recurrent cardiovascular events. A systematic review and Bayesian meta-regression analysis

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ABSTRACT

Background: Anticardiolipin antibodies of the immunoglobulin G isotype (IgG aCL) have been suggested as risk factor for arterial and venous thrombosis. No conclusive data in patients with coronary artery disease (CAD) do exist. We investigate the risk of recurrent CAD according to the presence of IgG aCL.

Methods: We performed a systematic review and meta-analysis to evaluate the risk of recurrent major adverse cardiac events (MACE) associated with the presence of IgG aCL in patients with CAD. MEDLINE and Cochrane databases were searched. We conducted a meta-analysis of the relative risk (RR) both at 12 and 24 months.

Results: We included 11 eligible studies with a total of 2425 patients, 283 IgG aCL+ and 2142 IgG aCL-. The prevalence of IgG aCL+ ranged from 6.1% to 43.3%. A total of 341 cardiac events were reported: 71 (25.1%) in IgG aCL+ and 270 (12.6%) in IgG aCL- patients. We found an increased risk of recurrent MACE in patients with high IgG aCL both at 12 (RR 2.17, 2.5–97.5%CI, 1.54–3.00) and 24 months (RR 2.11, 2.5–97.5%CI, 1.62–2.66). This association was even stronger in patients with juvenile CAD (i.e. < 50 years) at both 12 (RR 3.21, 2.5–97.5%CI, 1.74–5.41) and 24 months (RR 3.24, 2.5–97.5%CI, 1.84–5.21).

Conclusion: Patients with CAD and elevated IgG aCL have a doubled risk of recurrent MACE at 12 and 24 months. The presence of aCL should be suspected in patients with recurrent CAD events or in patients with juvenile CAD.

1. Introduction

Anti-phospholipid antibodies (aPL) are a heterogeneous group of antibodies, the most common being represented by anticardiolipin (aCL) and anti β2 glycoprotein I antibodies. The prevalence of aPL in the general population has been poorly estimated due to the absence of symptoms in aPL carriers and due to the lack of persistent aPL positivity over time in the majority of asymptomatic aPL carriers. However, a study on healthy donors showed a prevalence of 6.5% for IgG aCL, and 9.4% for IgM aCL [1]. Moreover, a study performed on a general Australian population cohort showed that low levels of at least one autoantibody may be detected in 51.5% of patients, the most frequent being represented by anti β2 glycoprotein I antibodies (12.1%) [2]. The presence of aPL has been detected also in other autoimmune [3] and non-autoimmune diseases [4].

The risk of a first thrombotic event in asymptomatic aPL-positive subjects is low (< 1%/year), but it significantly increases from carriers with single to those with triple positivity [5]. However, after a first episode of venous thromboembolism, or after cessation of oral anticoagulation the risk increases by 10–67% [6,7]. A previous metanalysis carried out on patients with several different underlying conditions, such as systemic lupus erythematosus, arterial thrombosis, and venous thrombosis, showed also an increased thrombotic risk in patients with LAC or aCL [8].

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The pathogenesis of coronary artery disease (CAD) is multifactorial, including metabolic, genetic, inflammatory and immunological factors [9]. Despite recent advance in diagnostic techniques, antithrombotic treatments and new-generation stents and antithrombotic treatments, the risk of recurrent cardiac events after a first myocardial infarction (MI) or coronary revascularization remains elevated [10]. In the AMI-QUEBEC Study, that involved 858 patients with ST-segment elevation MI, 42% of patients suffered a recurrent major adverse cardiac event (MACE) at 10 years (88% were recurrent episodes of ischaemic heart disease), the risk being higher during the first year (incidence rate of 23.5 per patient-year) [11]. Even the strongest antithrombotic combination such as dual antiplatelet therapy plus oral anticoagulant (the so-called "dual-pathway" approach) [12] only reduced the rate of re-infarction from 10.7% to 8.8% as demonstrated by the ATLAS ACS 2–TIMI 51 [13].

This suggests the presence of some non-traditional risk factors causing persistent inflammation and atherosclerotic vasculopathy, thus contributing to this residual cardiovascular risk, such as oxidative stress and oxidized low density lipoprotein [14,15].

So far, the role of aPL, and in particular aCL, in patients with pre-existing CAD has been not systematically assessed, and the prognostic value of aCL in this setting is unclear.

For our analysis, we focused on immunoglobulin (Ig)G aCL for a number of reasons: 1) they have been the most widely studied in patients with CAD; 2) after the production by the IgM-complement- antigene complex, IgG persistence in the human circulation is higher than IgM, and 3) the onset of autoimmune diseases has been shown to correlate with a switch from IgM to IgG autoantibodies [16].

The aim of this systematic review and metanalysis was to evaluate the association between IgG aCL and risk of recurrent MACE in patients with CAD.

2. Methods

2.1. Eligibility criteria and research strategy

We performed a systematic review of the literature searching MEDLINE via PubMed and Cochrane database using a combination of the following keywords antiphospholipid antibodies, anticardiolipin, myocardial infarction, coronary artery disease, ischemic heart disease, acute coronary syndrome, and cardiovascular events.

The research strategy was performed according to PRISMA guidelines with no time restrictions. (Supplementary Fig. S1) [17].

We included only observational (both prospective/retrospective) cohort studies or randomized clinical trials (RCT) performed in patients with coronary artery disease (CAD), acute coronary syndrome (ACS), or undergoing cardiac revascularization (PCI and or CABG) in whom IgG aCL antibodies were measured. We included only journal articles in English language with full text available. As principal endpoint we considered the recurrence of MI, coronary restenosis, cardiovascular death or a combination of them.

We excluded the following: (1) case reports, cross-sectional, case-control studies, editorials/comments, letters; (2) studies which reported only cerebrovascular events as outcome, (3) studies not reporting specific data on IgG aCL.

2.2. Study selection and quality assessment

The study selection was performed in multiple phases. In the first phase, potentially relevant studies were obtained by combined searches of electronic databases using the selected above-mentioned keywords. Then, studies not in English language, not involving humans, or not addressing study question were excluded. In the second phase, studies were reviewed and selected according to the inclusion exclusion criteria. The third phase consisted in a detailed analysis of full-text articles to assess if they provided necessary data to be included in the metanalysis (Supplementary Fig. S1). Quality assessment of studies included in the metanalysis was performed by using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized cohort studies (Supplementary Fig. S1) [18]. Studies with a score ≥ 7 were considered good quality.

2.3. Data retrieval

Two physicians (DP, TB) independently screened the titles and abstracts of manuscripts identified through the database searches to identify studies potentially eligible for further assessment.

For each eligible study we collected the following information: first author, year of publication, study typology, antithrombotic treatment, number of participants included in each group, percentage of men/women, age, percentage of patients with elevated IgG aCL titres, thresholds used to define aCL positivity, follow-up (months), number and percentage of events (n/%) and a brief summary of the main findings of each study.

2.4. Methods for meta-analysis

We conducted a meta-analysis of the relative risk (RR) of recurrent MACE both at 12 and 24 months. All studies reported RR or data needed to compute it, but that was referred to the total follow-up time of the study. Hence, we did not perform a meta-analysis which would have combined RR at different follow-up times, but a meta-regression where the moderator was the study follow-up. This allowed us to predict the pooled RR and study RR at desired follow-up times (12 and 24 months). Since the final number of studies was low, a reliable assessment of study heterogeneity was not possible. Therefore, according to Higgins et al. [19], we performed Bayesian meta-regression with informative priors, assuming heterogeneity in order to be conservative. Each log-RR was assumed to be Gaussian distributed centred on a study-specific effect, and whose standard deviation was the study standard error, inflated by 25%, in order to be conservative. The study-specific effect was assumed to be Gaussian, centred on a pooled effect. A linear model was used for describing the pooled effect as a function of moderators (in our case, follow-up time). An informative prior was used for the variance of the regression coefficients, as an inverse Gamma centered on an estimator obtained with a moment- based approach (inflated by 25% to be conservative). The predictive distribution was used to assess the outcome at the desired time-horizon for each study. Finally, a bivariate meta-regression was estimated using both total follow-up time and basal age as moderators. We also performed a subgroup analysis including only the studies with a mean age < 50 years.

2.5. Ethical review

Given the study type (review article), an ethical approval was not required.

3. Results

3.1. Study characteristics and results of individual studies

After applying the inclusion and exclusion criteria, we found 25 potentially eligible studies pertinent to the study question and with full-text available (Table 1).

Of these, 9 were not performed in patients with CAD (in detail, one in VTE [20], one in the general population [21], one in peripheral artery disease patients [22], one in patients with ischaemic stroke [23], 1 in patients with dyslipidemia [24], and 4 in APS patients [25–28]), and 5 did not report data on IgG aCL [29–33]. These studies were not considered, and the remaining 11 observational studies performed in patients with CAD were used for the metanalysis, (Table 2). Of these, 7 were prospective, 2 RCT or post-hoc of RCT, and 1 retrospective. Of

Table 1
Observational studies evaluating the relationship between anticardiolipin antibodies and cardiac outcomes.

Year Author	Type of study	Population	Age *years*	Sex M/F	aPL evaluation	aPL/technique	Endpoint	Prevalenc e of aPL+	Definition of IgG aCL+	Results
1986 Hamsten [38]	P	62 MI survivors	40.7	56/6	aCL measured at 3,12 and 36 months	aCL IgG/IgM 'Titertek' multiscan photometer	MACE	13/62 (21%) had aCL+	≥3 SD of the mean of healthy controls	20/62 patients had CVEs. 8/20 were aCL+ ($p < .05$). (3/8 had MI).
1986 Morton [39,49]	RCT	76 patients undergoing CABG	55	69/14	aCL: 2 days before, 7–10 days, 3 months, 11-12.5 months after CABG.	aCL IgG/IgM 'Titertek' multiscan photometer	Thromboti c events	16/76 (21%) were aCL+	> 2 SD of aCL of controls	8 patients had thrombotic events. 4/8 were aCL+.
1990 De Caterina [35]	P	119 patients: 75 stable and 29 unstable CAD, 15 non-cardiac chest pain	–	–	aCL measured before coronary angiography	aCL IgG/IgM"Titertek' multiscan photometer	MI and death	50/119 (42%) patients and 45/104 with proven CAD had IgG aCL +	> 1 U	There were 8 deaths and 1 MI: 5 in patients aCL+ and 4 in aCL-.
1990 Sletnes [34]	R	49 patients admitted with MI	–	–	aCL measured at admittance after 1 and 6 weeks, 9 months	aCL IgG ELISA	Previous MI	3/49 (6.1%) patients were IgG aCL +	> 97.5th percentile of controls	14/49 had previous MI; 2/3 patients with aCL+ had previous MI.
1992 Sletnes [36]	Post-hoc of RCT	597 MI survivors from the Warfarin Reinfarction Study [50]	61.6	Ratio 3,3/1	At randomisation (27.6 days after MI)	aCL IgG/IgM ELISA	*Re*-MI	37/594 (6.2%) patients were aCL +	> 5 U	120 (20.1%) had new MI. IgG aCL RR 0.89 (0.74–1.08).
1992 Eber [37]	P	65 patients undergoing PTCA for CAD	55	All M	At follow-up angiography	aCL IgG/IgM ELISA	Coronary restenosis	IgG aCL+ in 7 patients (3 with restenosis and 4 without)	> 2 SD mean of controls, GPL- > 12 U/ml	34 patients had restenosis: 3/34 were IgG aCL+ (p = NS).
1992 Cortellaro [29]	P	74 patients with previous TIA/MI from PLAT study [51]	< 45	N/A	3 months after the last ischaemic event	IgG aCL	Thromboti c events	IgG aCL+ in 3 (25%) TIA patients and in 8 (13%) MI survivors	N/A	3 thrombotic events all in aPL -patients.
1992 Tsakiris [52]	P	232 patients with angina pectoris	Male: 55 Female:5 6	198/34	At admission	aCL IgG/IgM ELISA	Coronary restenosis	35/232 (15.1%) aCL+, 12 IgG, 20 IgM, 3 IgA 2 both IgG/IgA.	> 3.6 GPL	14.3% of aCL + and 12.2% of aCL – had restenosis ($p = .73$). No data on IgG aCL.
1993 Phadke [31]	P	307 patients with MI + 160 with UA	52	MI: 245/62 UA: 99/61	aCL measured at day 1 and 5	aCL IgG/IgM ELISA	Re-MI and death	6.8% ($n = 20$) of MI patients IgG aCL+.5% IgM aCL + in each group	≥5 GPL	19 patients died and 28 had re- MI. No data on IgG aCL and follow-up outcomes.
1993 Raghavan [53]	P	111 patients: 83 with (MI group) 28 without MI (non-MI group)	MI group 61	83/28	aPL on admission, 24 h later, 5–7 days, 6–8 weeks after admission.	aCL IgG/IgM ELISA	*Re*-MI	20 (18%) aCL+ at admission. 7 (35%) of aCL+ and 22 (24.2%) of aCL-had previous MI	> 10 U	4/91 aCL-and 1/20 aCL+ had re- MI.
1994 Yilmaz [54]	P	76 patients with CHD (71 with follow- up)	aCL+: 42.33 aCL- 41.25	65/11	3rd, 14th, and 90th day after acute MI	aCL IgG/IgM ELISA	Re-MI	32/76 patients were IgG aCL+	11.3 GPL U/ml	32 patients with IgG aCL +levels had re-MI (3.1%), No re-MI in 39 patients IgG aCL –.
1995 Vaarala [24]	Post-hoc of RCT	133 patients (MI or cardiac death) and 133 controls	Patients 49.2 controls 47.2	N/A	At baseline prior to randomizatio n	aCL IgG ELISA	MI/Cardiac death	15 patients and 2 controls were IgG aCL+	> 0.650 OD unit	26 fatal cases, 4 with aCL+.

(*continued on next page*)

Table 1 (*continued*)

Year Author	Type of study	Population	Age *years*	Sex M/F	aPL evaluation	aPL/technique	Endpoint	Prevalenc e of aPL+	Definition of IgG aCL+	Results
1996 Zuckerman [40]	P	124 MI survivors	55.5	90/34	Upon admission	aCL IgG/IgM ELISA	Re-MI	Patients: 17/124 (14%) aCL+: 12 IgG and 5 IgM (> 8 MPL)	> 10 GPL	17 re-MI: 6 (35%) IgG aCL+; 11 (10%) IgG aCL- $p < .01$.
1998 Ludia [55]	P	60 patients with CHD	64.5	50/10	Baseline	aCL IgM/IgG ELISA LAC	Restenosis	15/60 aPL+: IgG aCL+ in 7/60, LAC in 5/60 and IgG aCL+and LAC in 3/60.	> 20 GPL	13/60 restenosis: 7/45 in IgG aCL-; 6/15 IgG aCL+.3 in LAC + only 4 in LAC/IgG aCL+.
1998 Shulmann [20]	RCT	1124 VTE patients	N/A	N/A	After randomisation	aCL IgG ELISA	MI	aCL IgG+ ($n = 150$) aCL – ($n = 871$)	≥5 GPL	5 (3%) MI in aCL + and 11(1.3%) in aCL – $p = .007$.
2000 Bili [56]	P	1150 patients with acute MI from the Thrombo study	48% had age > 60 years	75% M	Before hospital discharge and at 2 months	aCL IgG, IgM aβ2GI IgG, IgM ELISA	MACE (non-fatal MI + cardiac death)	78 patients with aCL IgG + 9 patients with aβ2GI IgG, + (defined by ≥20 SGU)	≥23 GPL	131 events: 84 cardiac deaths and 47 nonfatal MI. 14 (11%) in IgG aCL + and 64 (6%) in aCL-($p = .06$) No association between aβ2GI IgG and events.
2000 Pusieux [22]	P	232 patients with PAD	aCL+ 59 aCL- 58	aCL+ 22 F; aCL- 1 F	Baseline	aCL IgG, IgM ELISA	Fatal MI	44/232 (18.9%) were aCL + (36 IgG and 8 IgM).	> 15 U	8 fatal MI: 2/35 (5,7%) in IgG aCL+ and 6/194 (3%) in IgG aCL-. HR of aCL IgG for fatal MI: 4.4 (1,6–12) ($p = .001$).
2001 Chiarugi [57]	P	167 patients undergoing PTCA	64	130/37	Before the procedure	aCL IgG, IgM ELISA	*Re*-stenosis	18 (10.8%) patients were aCL+	> 20 IU	Restenosis in 29/167 (17%). Association of aCL with restenosis only when elevated Lp(a).
2004 APASS Investigators [23]	Post-RCT	Recurrent stroke	aPL + 63.1 aPL – 62.2	aPL + 38%F aPL – 45%F	Baseline	aCL IgG, IgM IgA ELISA	MACE+ death	Of the 926 patients 330 (35.6%) IgG+, 88 (9.5%) IgM+ and 169 (18.3%) IgA+	IgG + > 21 μg IgG aCL per deciliter of serum	aCL were not associated with events in patients treated with warfarin or ASA. No data on IgG aCL.
2005 Erkkila [32]	P	413 patients with CHD from EUROASPIRE study	61	NR	Baseline	aCL ELISA	MI, CHD-death	Patients divide in tertiles of aCL.	> 0.96 (mean + 2 SD)	35 CHD-death and MI at follow-up: 29/35 in the second and third tertile of aCL. No data on IgG aCL.
2005 Gurlek [41]	P	80 patients with ACS	Group I: 61 Group II: 58	N/A	Before hospital discharge	IgM and IgG aCL ELISA	MI re- infarction, restenosis	aCL IgG+(group I, $n = 30$); aCL IgG –(group II, $n = 50$)	≥ 40 IgG GPL	Re-stenosis in 40% aCL+ and 14% aCL- ($p < .01$). *Re*-MI in 26% vs 10% ($p > .05$).
2007 Greco [33]	P	232 patients with CAD	63	116/116	At admission	aCL	MACE	aCL was found in 7.4% of patients with CAD	N/A	No data on IgG aCL.
2009 Greco [30]	P	215 patients with CAD	aPL +: 63.7 aPL -: 61	aPL +: 52/94M aPL –: 80/ 121 M	Admission	aCL, aβ2GPI, anti-phosphatidylserin e antibodies IgG/IgM/IgA Anti-prothrombin and anti-ox LDL IgG/IgM	AEs: death + vascular events.	Overall, 94 were aPL + and 121 were aPL – aCL was in 6/94 (1 IgG and 4 IgM, 1 IgA) aβ2GPI + in 51/ 94 aPL + patients with CAD	N/A	AEs in 27% of aPL + patients and 9% in aPL -The risk for AEs in aPL + patients was 3 times higher than aPL – (RR, 2.9; 1.5–5.6; $p = .0006$).

Study design: CC = case-control; CS = cross-sectional, P = Prospective; R = Retrospective; RCT = randomized clinical trials.

Abbreviations: aβ2GI: anti-beta2-glycoprotein I; aCL: anticardiolipin antibodies; ACS: acute coronary syndrome; aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; APT: antiplatelet; ASA: aspirin; CABG: coronary artery bypass graft; CAD: coronary artery disease; CVA: cerebrovascular accident; CVE: cardiovascular events; GPL: gamma-phospholipid units/ml; HR: hazard ratio; Ig: immunoglobulin; LAC: lupus anticoagulant; MACE: major adverse cardiac events; MI: myocardial infarction; MPL: μ-phospholipid units/ml; OAC: oral anticoagulation; OD: optical density; OR: odds ratio; PCI: percutaneous coronary intervention; PE: pulmonary embolism; PTCA: percutaneous transluminal coronary angioplasty; RR: relative risk; SD: standard deviation; SLE: systemic lupus erythematosus; STEMI: ST-Elevation MI; UA: unstable angina; VTE: venous thromboembolism.

Table 2
Studies included in the metanalysis reporting on the association between recurrent cardiac outcomes and anticardiolipin IgG antibodies in patients with ischemic heart disease.

Study/Author (Year)	Study design (P = prospective, R = retrospective, RCT = randomize d clinical trial)	GROUPS 1 = IgG aCL + 2 = IgG aCL -	Patients in each group	Number of events in each group	% of events	Follow-up (months)
1 Hamsten (1986)	P	1	13	8	61,50	36–64
		2	49	12	24,50	
2 Morton (1986)*	RCT	1	16	4	25,00	12,00
		2	60	4	6,70	
3 De Caterina** (1990)	P	1	45	5	11,10	24,00
		2	59	4	6,80	
4 Sletnes (1990)	R	1	3	2	66,70	9,00
		2	46	12	26,10	
5 Sletnes (1992)	Post hoc RCT	1	37	6	16,20	39,00
		2	557	113	20,30	
6 Eber (1992)	P	1	7	3	42,90	12,00
		2	58	31	53,40	
7 Yilmaz (1994)	P	1	32	1	3,10	10–22
		2	39	0	0,00	
8 Zuckerman (1996)	P	1	17	6	35,30	19,00
		2	107	11	10,30	
9 Ludia (1998)	P	1	5	2	40,00	2,20
		2	45	7	15,50	
10 Bili (2000)	P	1	78	14	17,95	24,60
11 Gurlek (2005)		2	1072	64	5,97	
	P	1	30	20	66,70	12,00
		2	50	12	24,00	

* Assuming that the 1 patient excluded from the original group of 17 was free from events.
** Considering only 104 patients with proven CAD.

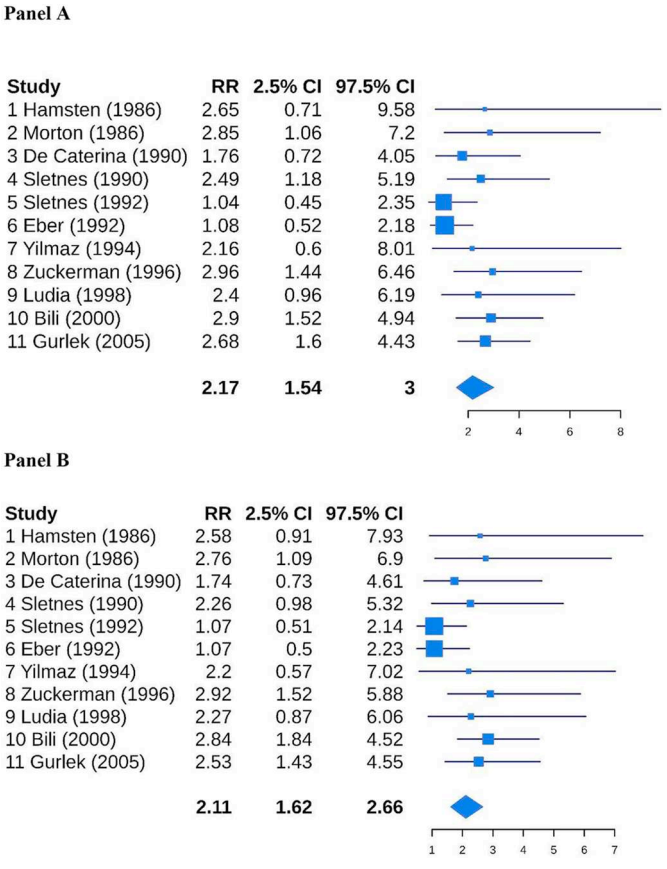

Fig. 1. Forest plot showing relative risk (RR) or recurrent major adverse cardiac events at 12 months (Panel A) or 24 months (Panel B) of follow-up in patients aged < 50 years.

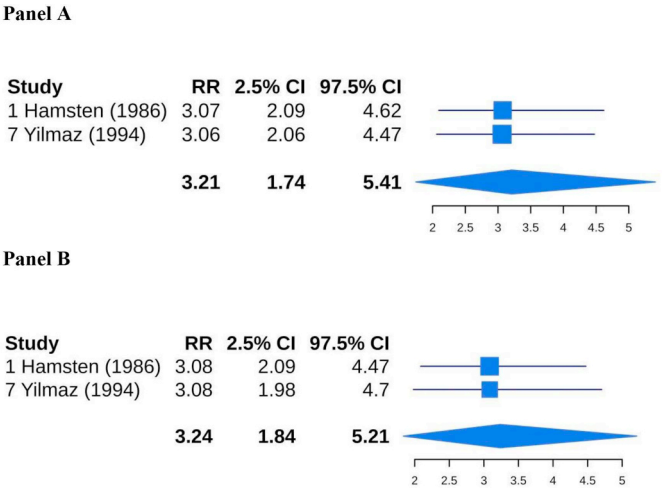

Fig. 2. Forest plot showing relative risk (RR) or recurrent major adverse cardiac events at 12 months (Panel A) or 24 months (Panel B) of follow-up in patients aged < 50 years.

these, 8 had a NOS score ≥7.

A total of 2425 patients were included, 283 were IgG aCL+ and 2142 were IgG aCL-. The reported prevalence of IgG aCL+ ranged from 6.1% [40] to 43.3% [35]; however, this latter study used a very low cut-off to define IgG aCL positivity (> 1 U).

The follow-up period ranged from 1.4 to 64 months. The most common outcomes considered were re-MI, coronary restenosis and cardiac death. A total of 341 cardiac events were reported: 71 (25.1%) in IgG aCL+ and 270 (12.6%) in IgG aCL- patients.

Overall, 9 studies reported a positive association between IgG aCL titers and recurrent cardiac outcomes (Table 2), while only two showed negative results [36,37]. Of note, the study by Sletnes et al. [36] had a very low prevalence of IgG aCL + patients (only 6.2%), and the study by Eber et al. [37] involved 65 patients, of whom only 7 were IgG aCL +.

Once data were pooled, we found an increased risk of recurrent MACE in patients with CAD and high IgG aCL both at 12 (Fig. 1 Panel A, RR 2.17, 2.5–97.5%CI, 1.54–3.00) and 24 months (Fig. 1 Panel B, RR 2.11, 2.5–97.5%CI, 1.62–2.66).

Results were consistent both at 12 and 24 months after excluding the retrospective study by Sletnes [34] (Supplementary Fig. S2).

A meta-regression analysis showed no association between IgG aCL positivity and cardiovascular risk according to age (beta = 0.068, $p = .779$) (Supplementary Fig. S3).

In particular, the association between aCL IgG and recurrent ischemic cardiac events was even stronger in patients with juvenile CAD (i.e. < 50 years) at both 12 (Fig. 2 Panel A, RR 3.21, 2.5–97.5%CI, 1.74–5.41) and 24 months (Fig. 2 Panel B, RR 3.24, 2.5–97.5%CI, 1.84–5.21).

4. Discussion

This is the first metanalysis reporting a significant association between high IgG aCL titers and risk of recurrent MACE in patients with CAD. In particular, we found that after a first MI or coronary revascularization, the risk of a second cardiac event is at least doubled in patients with high IgG aCL levels at 12 and 24 months.

Of particular interest is that this positive association was present also in studies including young patients (i.e. < 50 years) [24,38–40], suggesting that aCL should be regarded to as an additional risk factor for coronary events independently from classical cardiovascular risk factors, thus being responsible for a proportion of early MI occurring in young patients.

Finally, only one study used the cut-off of ≥40 GPL to define the positivity for aCL [47], which is the current threshold used to define the antiphospholipid syndrome. This study showed a higher rate or coronary restenosis or re-MI in patients with high IgG aCL compared to those with negative aCL [41].

The apparent pro-thrombotic role of IgG aCL in patients with CAD is in keeping with the “two hit” model of thrombosis associated with aPL syndrome [42]. Thus, the presence of aCL represents the “first hit” by inducing a pro-thrombotic and pro-inflammatory state [43,44], which is, however, not enough to trigger alone thrombus formation [42]. When a second inflammatory/pro-coagulant event occurs (the “second hit”), which is represented in this setting by endothelial/plaque disruption at coronary level, the presence of IgG aCL amplifies the platelet and coagulation response contributing to thrombus formation and growth. Thus, the β2 glycoprotein I, which is the main component of aCL may induce platelet and coagulation activation [45]. Another potential “second hit” in patients with CAD is represented by circulating lipopolysaccharide (LPS). In mice injected with aCL, none of the injected IgG samples had an overt pro-coagulant effect alone, while when the rats were intraperitoneally injected with LPS 3 h prior to infusion of aPL-positive IgG, the formation of platelets-leukocytes aggregates and thrombi was observed [46]. These findings were recently confirmed by a human study showing that LPS localizes into human atherosclerotic plaques [47], being an important trigger for platelet activation [48]. We could therefore hypothesize that also in patients with aPL the presence of LPS may contribute to coronary damage by amplifying platelet and coagulation response in response of endothelial injury.

Our study has clinical implications. Our findings indicate that patients with CAD and raised aCL represent a subgroup of patients at higher risk for recurrent coronary disease, for whom a more tailored antithrombotic strategy is needed. For instance, extended dual antiplatelet therapy or addition of anticoagulation to single antiplatelet therapy in the first year after an acute episode of CAD in patients positive for IgG aCL could be tested to reduce the incidence of recurrent MI.

5. Limitations

The present meta-analysis has a number of limitations that should be acknowledged. Most studies included in the meta-analysis are not randomized clinical trials but prospective observational studies with relatively small samples, which allow only an associative observation between high IgG aCL titer and recurrent MACE. In this context, the definition of MI changed over time and could be overestimated in the earlier studies not using high-sensitive troponin for the diagnosis of MI. Furthermore, not all studies reported antithrombotic regimens, which may influence outcomes rate and none reported the proportion of events according to treatment.

Of note, the proportion of males included in the studies is remarkably higher than females, thus our results should be considered with caution at this regard. Finally, despite most studies used ELISA method, the cut-off used to define the positivity of IgG aCL differed among studies.

6. In conclusion

The risk of recurrent MACE in patients with CAD is doubled when high IgG aCL titers are present. The presence of aCL should be regarded to as an additional risk factor for recurrent CAD and should be suspected especially in young patients experiencing MI, and in those with no significant cardiovascular risk factors.

Conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2019.03.005.

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