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Head-to-Head Comparison of Auto-Antibodies for Cardiovascular Outcome Prediction after Myocardial Infarction: a Prospective Study

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Abstract

Background: Atherosclerosis-related inflammation fulfils the three required Koch's postulates to be considered as an autoimmune disease. Accordingly, several auto-antibodies have been associated with an increased cardiovascular (CV) risk suggesting that they could be of help for cardiovascular risk stratification in the future.

Aims: to compare the prognostic accuracies of auto-antibodies to β_2 glycoprotein I (anti-β_2GPI) domain I and IV, cardiolipin, apolipoproteinA-1 (anti-apoA-1 IgG), heat-shock protein 60 (anti-HSP-60), and to phosphorylcholine (anti-PC IgM) for 12-months major cardiovascular events (MACE) prediction after myocardial infarction (MI).

Methods: Auto-antibodies were prospectively assessed by ELISA in 221 MI patients without autoimmune diseases who all completed the 12-months follow-up. Prognostic accuracies were evaluated by receiving operating characteristic (ROC) curve analyses, and risk analyses were performed using Cox regression model.

Results: MACE rate was 14% during follow-up. Among the tested auto-antibodies, anti-apoA-1 IgG antibodies were found to be the only candidate significantly predicting subsequent MACE ((Area Under the Curve (AUC):0.65; p=0.007)). A non-significant trend was observed for anti-cardiolipin (AUC: 0.59; p=0.05) and anti-HSP-60 (AUC:0.58; p=0.06) antibodies. No association was retrieved for others auto-antibodies. Cox regression analyses indicated that anti-apoA-1 IgG positivity was associated to a 4-fold MACE risk increase, independently of the 10-year global Framingham risk-score (Hazard Ratio: 3.8; p=0.002)

Conclusions: In this head-to-head prospective comparison study performed on secondary prevention patients anti-apoA-1 IgG appeared as the candidate with the strongest and independent MACE prognostic accuracy in non-autoimmune settings.

Keywords: Auto-antibodies; Myocardial infarction; Prognosis

Introduction

Cardiovascular diseases (CVD) account for the majority of morbidity and mortality in Western countries, and are often clinically manifest as acute coronary syndromes (ACS), including myocardial infarction (MI) [1]. The underlying mechanism of ACS is atherosclerotic plaque rupture, in which vascular immune-mediated inflammation has been recognized of major importance [2], and atherosclerosis-related inflammation even fulfils the required "Koch's postulates" to be considered as an autoimmune disease [3]. Consistent with this hypothesis, there is a growing body of biological evidences demonstrating that auto-antibodies could modulate inflammation through innate immune receptor signalling which can either stimulate or inhibit atherogenesis-related processes, as reviewed elsewhere [4]. Accordingly, different clinical trials have demonstrated that high levels of anti-cardiolipin, anti-β_2 glycoprotein-I (anti-β_2 GPI), anti-heat shock protein 60 (anti-HSP-60), anti-apolipoproteinA-1 (apoA-1) auto-antibodies were associated with an increased CV risk [5,6-11], whereas other studies demonstrated that high levels of auto-antibodies of IgM subtype against phosphorylcholine (anti-PC IgM), the immunodominant epitope of oxidised Low-Density Lipoprotein (oxLDL), protected against CVD [4,12-13]. Given their relative independence toward classical cardiovascular risk factors, those auto-antibodies have been proposed as emergent tools for cardiovascular risk stratification [4]. Nevertheless, on top of being debated, knowing which among those auto-antibodies would yield the strongest prognostic value for CVD prediction in non autoimmune settings has never been evaluated. Therefore, we compared in a head-to-head manner the respective prognostic accuracies of those auto-antibodies for major cardiovascular event (MACE) prediction one year after MI, in order to identify the autoantibody with the best prognostic accuracy for MACE recurrence. We also tested the prognostic value of anti-β_2 GPI antibodies of IgA subtype directed against domain IV, as to our knowledge, those auto-antibodies have not been tested for MACE prediction in non-autoimmune settings so far. Finally, we challenged the prognostic accuracy independence of the best candidate towards the 10-year global Framingham risk score, one of the most commonly used cardiovascular risk stratification algorithm [14].

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Patients and Methods

Myocardial infarction patients

Data of this ancillary study are derived from a previous prospective study aiming at evaluating the prognostic value of anti-ApoA-1 IgG for MACE prediction at one year with a power of 80% to detect a three-fold difference in MACE rate, and involves 221 consecutive MI patients who all completed one-year follow-up [9]. The Local Ethical Committee approved this study conducted in conformity with Helsinki Declaration. Briefly, all patients gave their informed consent before enrolment. Exclusion criteria consisted in the presence of Takotsubo disease, any known auto-immune disease except diabetes mellitus, and inability to give informed consent for any reason, including oro-tracheal intubation. Conventional left ventricular ejection fraction (LVEF) evaluation by echocardiography was performed within 5 days of admission by experienced cardiologists.

Endpoint definition

The primary endpoint definition was the occurrence of MACE at one year after the acute event, defined by the presence of death of any cause, fatal/non fatal ACS, fatal/non fatal stroke or hospitalization for heart failure, which was independently determined by two experienced cardiologists blinded to the biochemical results. The information was obtained by checking patients' medical file, by contacting patients by telephone and was further confirmed by contacting the physician in charge of the patient.

Biochemical analyses

To avoid interference with the door-to-revascularization policy, samples were taken after percutaneous coronary intervention within the first 24 h of hospitalization. Blood samples were then immediately centrifuged, stored at -80°C, until analyses. Anti-apoA-1 IgG were assessed according to our previously described in house ELISA, and anti-apoA-1 IgG positivity was pre-specified by an Absorbance (405nm) >0.6 optical densities (OD) and ≥37% of the positive control (corresponding to the 97.5th centile of a normal distribution, assessed on 140 healthy blood donors) according to our previous studies [9-11]. Anti-HSP-60 antibodies were assessed using commercially available ELISA kits HSP- 60 from Stressgen Biotechnologies (Ann Arbor, MI, USA), anti-PC IgM kits were obtained from Athera Biotechnologies (CVDefine™, Upsala, Sweden). Anti-cardiolipin, anti-anti-β_2 GPI antibodies (IgG, IgM and IgA), and anti-anti-β_2 GPI IgA against domain 4 were from INOVA Diagnostics (San Diego, CA, USA). All analyses were performed according to manufacturer's instruction. The other conventional biochemical parameters were determined as described before [9].

Statistical analyses

Bilateral Fischer exact test was used for nominal variables comparison. For continuous variables, results were presented as median and interquartile range and difference were computed with U-Mann Whitney test. Prognostic accuracies were assessed by receiver operating characteristics (ROC) curve analyses providing 95% confidence intervals (95%CI). Area under the curve (AUC) comparison was performed using a nonparametric approach as proposed by Delong [15]. Due to the limited sample size, Cox regression analyses were performed with the best candidate in unadjusted mode and after the adjustment for the 10-years global Framingham risk score [14], allowing adjusting for most traditional cardiovascular risk factors within a single continuous variable. Analyses were performed using Statistica™ software (StatSoft, Tulsa, OK, USA) and Analyse-It™ software. P-value <0.05 was considered as significant.

Results

14% of patients developed a MACE during the one year follow-up, corresponding to the expected complication rate in this population [16]. As expected [1,16], those patients also had lower LVEF, were more likely to be known for coronary heart disease, to be smoker, and had lower kidney function as reflected by increased creatinine levels (Table 1). No difference in creatine kinase (CK) peak was observed between patients with and without MACE, and there was no difference in MACE recurrence between patients with or without ST-elevation upon admission (Table 1).On the other hand, patients with MACE had higher levels of anti-apoA-1 IgG than patients without MACE during follow-up as well as a higher anti-apoA-1 IgG positivity rate, whereas no significant differences were observed between those two groups for the other antibodies (Table 1). No differences in auto-antibodies levels were observed between STEMI and NSTEMI patients (data not shown), whereas significant differences were observed for LVEF (respective medians: 50 % against 55%, p=0.03), CK peak (respective medians: 1262 IU/L against 366 IU/L), and CRP (respective medians: 5 mg/L against 7.8 mg/L; p=0.04) between those two groups of patients.

When considering each endpoints separately, at the exception of death due to the too low events rate (n=3) in this subgroup, the results were the following. For heart failure requiring hospitalization (n=9), there was no significant differences nor a trend for all the auto-antibodies tested between patients with or without the event during follow-up (data not shown), whereas significant differences were observed for CRP (respective medians: 15.2 mg/L against 6 mg/L; p=0.008), NT-proBNP (respective medians: 3179 pg/ml against 743 pg/ml; p=0.01) and LVEF (respective medians; 35% against 50%; p=0.0001) between those two subgroups. When considering only patients with ACS relapse during follow-up (n=19), patients with the event had higher levels of anti-cardiolipin IgM when compared to patients without (respective medians: 5.3 GPL against 3.7 GPL; p=0.02), and there was a non-significant trend between those two groups of patients for both anti-apoA-1 IgG (respective medians: 24 index against 21 index; p=0.08) and anti-cardiolipin IgG (median 4.8 GPL against 3.5 GPL p=0.08). No significant differences were retrieved for the other auto-antibodies, CRP, NT-proBNP and LVEF (data not shown). ROC curve analyses pointed to anti-apoA-1 IgG as the autoantibody with the best prognostic accuracy with a statistically significant AUC of 0.65 (p=0.007; Table 2). Anti-cardiolipin antibodies of IgM and IgG subtype, as well as anti-HSP-60 displayed AUCs close to significance (0.59; p=0.05; 0.58, p=0.08 and 0.58, p=0.06, respectively; Table 2). The result of the sum of anti-cardiolipin IgM units and anti-apoA-1 IgG index did not significantly increased the prognostic accuracy of anti-apoA-1 IgG alone according to the non parametric method (AUC 0.65 to 0.67, p=0.28). Given the fact that anti-apoA-1 IgG was the only autoantibody with significant prognostic accuracy fro MACE prediction, risk analyses were performed only with this autoantibody, using the prospectively defined and previously validated cut-off [9-11]. As shown in the Table 2, adjusted Cox regression analyses indicated that anti-apoA-1 IgG positivity was associated with a 4-fold risk of MACE occurrence at one year, independently of the 10-year Framingham risk global score. For MACE prediction, the pre-specified anti-apoA-1 IgG cut-off had a specificity of 87% (95%CI: 82-92), and a sensitivity of 36% (95%CI: 19-55).

Discussion

The main result of this head-to-head auto-antibody comparison

Demographic characteristics

	MI patients (n=221)	MACE at 12 months (n=31)	No MACE at 12 months (n=190)	*P value
Age, year	64 (55–74)	67 (55-80)	63 (55-74)	0.43
Sex				
Male, % (n)	78 (173)	90 (28)	76 (145)	0.10
Female, % (n)	22 (48)	10 (3)	24 (45)	
Systolic BP, mmHg	120 (110-130)	120 (100-130)	120 (110-130)	0.52
Diastolic BP, mmHg	70 (60-80)	70 (60-80)	70 (60-80)	0.93
BMI, kg/m^2	25.8 (24–29)	26.5 (24.5-29.5)	25.8 (23.7-28.4)	0.18
Creatinin, µmol/L	84 (73–98)	95 (77-114)	83 (72-96)	0.01
cTnI, ng/mL	0.50 (5–7)	0.84 (0.10-3.42)	0.38 (0.09-2.98)	0.36
CRP, mg/L	6.0 (2.85-14)	10.9 (3-31.4)	5.9 (2.7-13)	0.11
NT-proBNP, pg/ml	785 (283-2057)	1503 (475-3500)	771 (271-1641)	0.07
LVEF, %	50 (45-55)	45 (35-50)	50 (45-60)	0.0003
Total CK, IU/L	687 (273-1873)	509 (264-1168)	703 (280-1818)	0.49
STEMI, % (n)	54 (120)	43 (13)	56 (107)	0.17
NSTEMI, % (n)	46 (101)	58 (18)	44 (83)	-
MACE rate, % (n)	14 (31)	-	-	-
MACE details, % (n***):***			-	
-Deaths	1 (3)	-	-	-
-Heart Failure related hospitalisations	4 (9)	-	-	-
-Non fatal ACS	9 (19)	-	-	-
-Non fatal stroke	0 (0)	-	-	-
Comorbidities, % (n)				
Hypertension	53 (117)	51 (18)	52 (99)	0.56
Diabetes	19 (43)	32 (10)	17 (33)	0.08
Dyslipidaemia	46 (102)	42 (13)	47 (89)	0.70
Smoker	45 (99)	23 (7)	5 (9)	0.003
Obesity	16 (35)	23 (7)	15 (28)	0.29
Known CAD	29 (65)	52 (16)	26 (49)	0.005
Stroke	5 (12)	13 (4)	4 (8)	0.06
Positive familial history	31 (69)	29 (9)	32 (60)	0.84
Atrial fibrillation	5 (11)	13 (4)	4 (7)	0.06
Auto-Antibodies				
Anti-apoA-1 IgG, Index	22.2 (15.9-31.3)	31.4 (20.7-41.2)	20.6 (15.5-29.9)	0.009
Anti-HSP-60 antibodies, ng/ml	18.5 (11.5-37.1)	22.5 (15.6-43)	17.8 (11.2-36.5)	0.14
Anti-β_2GPI IgG, GPL units	1.1 (0.9-1.3)	1.1 (1.0-1.4)	1.0 (0.9-1.3)	0.46
Anti-βGPI IgM, GPL units	2.1 (1.3-3.5)	2.4 (1.2-3.6)	2.1 (1.3-3.4)	0.82
Anti-βGPI IgA, GPL units	4.5 (3.5-6.1)	4.8 (3.5-6.5)	4.5 (3.5-6.1)	0.58
Anti-cardiolipin IgG, GPL units	3.6 (2.4-5.4)	4.4 (6.2-2.6)	3.5 (2.4-5.4)	0.17
Anti-cardiolipin IgM, GPL units	3.9 (2.5-5.7)	4.0 (3.0-7.2)	3.9 (2.5-5.7)	0.12
Anti-cardiolipin IgA, GPL units	2.7 (1.9-4.1)	3.2 (1.7-4.9)	2.7 (1.9-4.0)	0.50
Anti-β_2GPI D4D5 IgA, GPL units	7.3 (4.9-10.4)	7.8 (5.6-11.1)	7.2 (4.8-10.4)	0.38
Anti-PC IgM, U/ml	33.1 (22.5-55.2)	37.9 (17-45.9)	32.8 (22.9-57.8)	0.73

Table 1: All continuous variables are reported as median with interquartile range. *P-value was calculated according to Mann–Whitney U-test for continuous variable and according to exact bilateral Fischer test for proportions. P values were computed by comparing groups of patients with and without MACE during the follow-up.

study in MI is that anti-apoA-1 IgG appears as the auto-antibodies with the strongest MACE prognostic accuracy in non autoimmune patients one year after a MI. Those results are in line with our recent data demonstrating that anti-apoA-1 IgG was a good predictor of Non ST-segment elevation in patients presenting to the emergency room for acute chest pain without electrocardiographic changes, even when initial cardiac troponin I values were normal [17], and were associated with carotid atherosclerosis vulnerability in patients with severe carotid stenosis [11]. From a pathophysiological point of view, anti-apoA-1 IgG have been shown *in vitro* to act as a strong positive chronotropic agent [9], and to promote sterile inflammation and atherogenesis *in vitro* and in apoE knockout mice [10-11]. Whether the superimposition of those deleterious effects could explain the worse CV prognosis affecting MI patients with high levels of anti-apoA-1 IgG remains a hypothesis to be demonstrated.

ROC curve and Risk Analyses

Autoantibodies Prognostic Accuracies	*AUC*	*95% CI*	*P*	
Anti-apoA-1 IgG, Index	0.65	0.53-0.76	0.007	
Anti-HSP-60 antibodies, ng/ml	0.58	0.48-0.69	0.06	
Anti-β_2GPI IgG, units	0.54	0.43-0.65	0.23	
Anti-βGPI IgM, units	0.51	0.40-0.63	0.41	
Anti-βGPI IgA, units	0.53	0.42-0.64	0.29	
Anti-cardiolipin IgG, units	0.58	0.47-0.69	0.08	
Anti-cardiolipin IgM, units	0.59	0.48-0.70	0.05	
Anti-cardiolipin IgA, units	0.54	0.42-0.66	0.27	
Anti-β_2GPI D4/5 IgA, units	0.55	0.45-0.65	0.16	
Anti-PC IgM, U/ml	0.52	0.37-0.59	0.37	
Cox Regression analyses for MACE prediction	***Unadjusted Hazard Ratio***	***P***	****Adjusted Hazard Ratio***	***P***
Anti-apoA-1 IgG positivity	3.92	0.001	3.80	0.002

*Adjusted for the 10-year global Framingham risk score

Table 2:

A close to significance trend for MACE prediction was observed for anti-cardiolipin and anti-HSP-60 antibodies, which corroborates the data in the literature indicating that those auto-antibodies are associated to CV events [4,5,8]. On the other hand, we were not able to reproduce the CVD associations previously described for anti-β_2GPI antibodies, and anti-PC IgM antibodies [4,6,8,12,13]. There are several factors that may explain this discrepancy. Firstly, this can be due to a study population and study design differences. Indeed, most studies reported so far for anti-β_2GPI and anti-PC IgM antibodies were case-control studies performed on primary prevention patients [4-8,12,13], whereas our cohort consisted in secondary prevention patients, which were all longitudinally followed-up over a period of 1 year. Secondly, this discrepancy could also be explained by the limited sample size of this study. If appropriately powered to detect a 3-fold difference between groups (MACE versus no MACE) for anti-apoA-1 antibodies (power of 80%) [9], this sample size could not have been sufficient to detect a less important association for anti-PC IgM, anti-HSP-60 and anti-phospholipid antibodies. The close to significant trend observed for anti-cardiolipin and anti-HSP-60 autoantibodies supports this hypothesis. Due to the absence of significant difference upon ROC curve analyses, choosing a cut-off for subsequent risk analyses appeared irrelevant in the present study. Thirdly, when it comes to anti-HSP-60 and anti-β_2GPI antibodies, this divergence could also be due to analytical differences between commercially available kits, as there is currently no standardisation of those auto-antibody assays. For anti-PC IgM, this analytical matter can be ruled-out as we used the same ELISA kit than what has been used in previous studies [3,11,12]. Finally, because the anti-apoA-1 IgG AUC for MACE prediction was relatively modest (0.65), it could be considered as clinically uninteresting. Nevertheless, because this AUC was of the same order of magnitude than what has been reported for the 10-year global Framingham risk score (in the Cardiovascular Health Study, AUC=0.68) which determines patient management [18], we believe that the potential clinical applications of such prognostic accuracy must be further evaluated, especially in terms of specific therapy orientation. Taken together with our unpublished data indicating that the pro-arythmogenic effects of anti-apoA-1 IgG could be abrogated by a specific mineralocorticoid receptor (MR) antagonist *in vitro* (Rossier M et al. Under review), the relatively good specificity of anti-apoA-1 IgG positivity to predict MACE occurrence (87%) suggests that this test could be of interest to identify MI patients who could benefit from MR inhibition in secondary prevention. Further randomized control trials are needed to confirm this hypothesis.

This study has several limitations. The most important one as already mentioned above is its relative limited sample size. Although adequately powered (80%) to detect differences of 3-fold, our study could have been underpowered to detect smaller associations. In turn, this could explain the close to significant associations retrieved for anti-cardiolipin and anti-HSP-60 auto-antibodies. Nevertheless, we believe that this limitation is very unlikely to affect our conclusions about the superiority of anti-apoA-1 IgG over other antibodies for MACE prediction after MI. Another limitation of this study is that we could not evaluate the appropriateness of conventional diagnostic anti-phospholipid antibodies cut-offs for MACE prediction. Indeed, the number of patients presenting MACE during follow-up that were tested positive for anti-phospholipid antibodies at study inclusion was too small to perform meaningful statistical analyses. Further studies are warranted to explore this aspect. Finally, it can be argued that we did not assess anti-oxLDL antibodies on this cohort. Nevertheless, given their controversial association to CVD [3], and the fact that PC is recognized as the immunodominant epitope of oxLDL [4,14], we considered assessing anti-PC IgM instead of anti-oxLDL as a more relevant option.

In conclusion, to the best of our knowledge, this is the first prospective study evaluating in a head-to-head approach the respective prognostic accuracies of the most promising humoral autoimmune candidates for MACE prediction in secondary prevention settings. Those preliminary results point toward anti-apoA-1 IgG as the autoantibody with the strongest prognostic accuracy for MACE prediction after MI, independently of the 10-year global Framingham Risk Score. Further larger multicentre randomized control trials are needed to determine whether an anti-apoA-1 IgG-based CV risk stratification algorithm could reach any clinical decisions making, especially in terms of patient specific therapy orientation.

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