# **SUPPLEMENTAL MATERIAL**

NON STANDARD ABBREVIATIONS AND ACRONYMS

AA – African American

Anti β2GP1 – Anti Beta 2 glycoprotein 1 autoantibodies

Anti CCP – Anti cyclic citrullinated protein autoantibodies

Anti HSP – Anti heat shock protein autoantibodies

Anti HSP65 – Anti heat shock protein 65 autoantibodies

Anti LDL – Anti low density lipoprotein autoantibodies

Anti OxLDL – Anti oxidised low density lipoprotein autoantibodies

Anti OxLDL/ β2GP1 – Anti atherox

Anti PC – Anti phosphorylcholine autoantibodies

AAT – Asymptomatic autoimmune thyroiditis

Ab / Abs – Antibody / Antibodies

aCL – Anti cardiolipin autoantibodies

ACS – Acute coronary syndrome

AF – Amaurosis fugax

AMA – Anti myosin antibodies

AMI – Acute myocardial infarction

ANA – Anti nuclear autoantibodies

AO – Arterial occlusion

aOxCL - Antibodies against oxidised cardiolipin

AP – Angina pectoris

APAs – Anti phospholipid autoantibodies

aPL – Anti phospholipid syndrome

aPT/PS – Phosphatidylserine dependent antiprothrombin antibodies

AS – Atherosclerosis

β2GP1 – Beta 2 glycoprotein 1

Ca 2+ - Calcium ions

CABG – Coronary artery bypass graft

CAC – Coronary artery calcification

CAD – Coronary artery disease

CBV – Cerebrovascular disease

CHD – Coronary heart disease

CI – Cerebral infarction

95% CI – 95% Confidence interval

cIMT – Carotid intima media thickness

CL - Cardiolipin

CMV – Cytomegalovirus

Cpn – Chlamydia pneumoniae

CRP – C reactive protein

Cu - Copper

Cu oxLDL – Copper oxidised low density lipoprotein

CV - Cardiovascular

CVD – Cardiovascular disease

CVE – Cardiovascular event

dsDNA – Double stranded deoxyribonucleic acid

DVT – Deep vein thrombosis

ECG – Electrocardiogram

E.F - Eastern Finland

EPIC Norfolk study - European prospective investigation of cancer, Norfolk study

EUROASPIRE - A European Society of Cardiology survey of secondary prevention of coronary heart disease

Fcγ receptors – Fc gamma receptors

FcγR1 – Fc gamma receptor 1

F/U – Follow up

F - Female

GENICA study - Gene environment interaction and breast cancer study

GPL – Immunoglobulin G phospholipid units

HF – Heart failure

H pylori – Helicobacter pylori

HR – Hazard ratio

hsCRP – High sensitivity C reactive protein

HSP60 – Heat shock protein 60

HSP65 – Heat shock protein 65

HSP70 – Heat shock protein 70

huHSP60 – Human heat shock protein 60

IC – Immune complex

IgA – Immunoglobulin A

IgG – Immunoglobulin G

IgM – Immunoglobulin M

IHD – Ischeamic heart disease

IMT – Intima media thickness

LAC – Lupus anticoagulant

LDL – Low density lipoprotein

MACE – Major adverse cardiovascular events

MDA LDL – Malondialdehyde modified low density lipoprotein

MESA - Multi ethnic study of atherosclerosis

MESH – Medical subject headings

mHSP65 – Mycobacterial heat shock protein 65

MI – Myocardial infarction

mmol/L - Millimole per litre

MONICA - Monitoring and Determinants in Cardiovascular Disease project

M –Male

MDA P210 - Malondialdehyde P210 autoantibody

MDA P45 - Malondialdehyde P45 autoantibody

N/A – Not applicable

NOS – Newcastle Ottawa scale

NS – Not significant

OR – Odds ratio

OxCL – Oxidised cardiolipin

OxLDL – Oxidised low density lipoprotein

OxPLs – Oxidised phospholipids

PAD enzymes – Peptidylarginyl deaminase enzymes

PAF – Platelet activating factor

PCI – Percutaneous coronary intervention

PE – Pulmonary emboli

PI – Pro-inflammatory

PRISMA – Preferred reporting items for systematic reviews and meta-analyses

PTCA – Percutaneous transluminal coronary angioplasty

PTE – Pulmonary thromboembolism

PVD – Peripheral vascular disease

Q1 – Quartile 1

Q2 – Quartile 2

Q3 – Quartile 3

Q4 – Quartile 4

RA – Rheumatoid arthritis

RCTs – Randomised control studies

RF – Rheumatoid factor

RHR – Resting heart rate

RR – Relative risk

SD – Standard deviation

SM – Smooth muscle

SR – Screening ration

TIA – Transient ischeamic attack

TNF α – Tumor necrosis factor alpha

TSH – Thyroid stimulating hormone

T1 –Tertile 1

T2 – Tertile 2

T3 – Tertile 3

U/ml – Units per millilitre

VIP - Vasterbotten Intervention Program

W.F - Western Finland

METHODS

**Search Strategy**

A computer assisted search across 5 databases (MEDLINE, EMBASE, SCIENCE DIRECT, SCOPUS, and PUBMED) was carried out up to JUNE 2016, to identify published observational and experimental studies investigating an association between the presence of autoantibodies and the subsequent occurrence of cardiovascular disease (CVD) morbidity and mortality in populations with and without clinical disease. Index words and key terms utilised in this search included: (‘autoantibody’ or ‘autoimmunity’ or ‘auto reactivity’ or ‘antibodies’) AND (‘atherosclerosis’ or ‘cardiovascular disease’ or ‘angina’ or ‘stroke’ or ‘heart attack’ or ‘coronary heart disease’ or ‘atherogenesis’ or ‘myocardial infarction’). All searches were limited to human studies and papers published in English. Though we were targeting original research studies, bibliographies of reviews and editorials that aligned with our objectives were also examined to identify additional studies. Though studies examining the association between autoantibodies and the subsequent occurrence of cardiovascular disease amongst clinical populations were initially extracted they were not included in this review as our focus was to formally establish the strength of the association between autoantibodies and atherosclerosis without the confounding effect of immunosuppressive agents.

**Study Selection**

Titles and abstracts of all articles retrieved in the initial comprehensive search were evaluated independently by two reviewers (RI and TH). Studies that were not clearly aligned with our objective were excluded. Full-text articles that fulfilled this initial screening were subjected to a second evaluation for relevance by the same two reviewers using a hierarchical approach: study population, exposure, and outcome on the basis of a predefined set of eligibility criteria as illustrated in **Table 1** below.

***Table 1:* Predetermined inclusion and exclusion criteria for selection of articles**

\*A non-clinical sample was deemed present where researchers did not clearly identify their study sample as suffering with a particular autoimmune condition based on clearly defined diagnostic criteria. Specific autoantibodies are not listed to avoid missing any not notoriously linked to the occurrence of atherosclerotic related cardiovascular diseases (AS related CVDs) in past literature that may still represent novel biomarkers. AS related CVD outcomes included angina pectoris (AP), myocardial infarction (MI), coronary artery disease (CAD), and atherosclerosis ischaemic stroke.

CRITERIA FOR SELECTION OF RESEARCH ARTICLES CONSISTING OF A NON-CLINICAL SAMPLE.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **POPULATION** | **EXPOSURE** | **OUTCOME** |
| **INCLUSION**  **CRITERIA** | * ≥ 18 years * \*Non-clinical sample. | Any autoantibody. | * Atherosclerotic-related cardiovascular disease mortality/morbidity |
| **EXCLUSION**  **CRITERIA** | * ≤18 years * Clinical autoimmune sample. | No autoantibodies measured. | * All-cause mortality. |

Any disagreements were discussed and resolved by consensus. Studies included in this review consisted of full text, published, observational or experimental studies addressing the presence of autoantibodies and the subsequent occurrence of AS related CVD morbidity and mortality in populations with and without clinical autoimmune disease. Only autoantibodies with estimates for more than two studies were considered for meta-analysis.

**Quality Assessment**

Studies deemed relevant after full screening were subjected to quality assessment for methodological rigor. The quality of all observational studies was assessed using the Newcastle – Ottawa Scale (NOS) for assessing the quality of non-randomized studies, whilst, the quality of experimental studies was assessed using the Cochrane Risk of Bias Quality Assessment Tool (1,2). (see **Appendix 1 and 2)**. Articles with 6 or more stars in the NOS scale were considered to be methodologically sound. Similarly, articles with ‘low risk’ of bias across all domains in the Cochrane Risk of Bias Quality Assessment Tool were considered to be good quality.

**Data Extraction**

Data extraction was performed independently by the two reviewers and entered into a uniform data extraction sheet. Information that was extracted from the relevant papers included; study reference, study design, source population, sample size, sample characteristics (Gender, Age, Ethnicity of sample [where available]), type of CVD outcome, autoantibodies measured, and the results observed including the estimates of association. Multiple publications from the same study during the same follow up period (i.e. study of the same group of individuals) were combined unless different autoantibodies were measured. Where several risk estimates were provided, results were reported for the one adjusting for the largest number of factors. Moreover, where provided all adjusted risk estimates for varying autoantibody titers were reported. Discrepancies in data extraction were discussed and resolved by consensus by the reviewers.

**Data Synthesis**

We followed a standardised protocol and reported this analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (3). Study results were grouped and reported according to autoantibody of interest. Only the results for key autoantibodies whose results could be combined in a meta-analysis were presented in the main text with the remainder contained in the supplementary material.

**Statistical Analysis**

The meta analyses evaluated the effect of each autoantibody (highest versus lowest quartiles of autoantibody titer) on cardiovascular outcomes. All AS related CVD outcomes were combined on the basis of the common underlying pathology, namely ischeamic heart disease. Studies reporting Odds ratios (ORs), Relative risks (RRs) and Hazard ratios (HRs) and their associated 95% confidence intervals (95% CI) were pooled separately and then a final overall effect measure was also pooled across the three types of effect sizes.

Estimates from each study and their standard errors were pooled on the log-scale using random effects models (the method of DerSimonian and Laird). The I² statistic (and significance test) was used to assess between-study heterogeneity. Due to a lack of adequate study numbers further analysis comprising meta- regression could not be carried out to identify potential sources of heterogeneity. Publication bias was explored by examining funnel plot asymmetry only for autoantibodies with at least five studies. All statistical analysis was carried out using Stata Version 11 (4).

# RESULTS

A total of 113 primary articles were retrieved for full text examination with 62 articles subsequently being excluded as illustrated in **Figure 1** below.

***Figure 1:* Flow chart illustrating the study selection process**

MEDLINE; EMBASE; SCIENCE DIRECT; SCOPUS; PUBMED

n = 7,205

TOTAL OF 55 STUDIES INCLUDED IN REVIEW

51 STUDIES INCLUDED IN THIS REVIEW

3 ARTICLES EXCLUDED FOR NOT MEETING CRITERIA

42 ARTICLES EXCLUDED:

9 DUPLICATES

33 DID NOT MEET CRITERIA

FULL TEXTS ASSESSED FOR METHODOLOGICAL QUALITY n = 15

FULL TEXT PRIMARY RESEARCH ARTICLES RETRIEVED FOR DETAILED EXAM

n = 18

HANDSEARCHING OF REVIEWS IDENTIFIED 60 ARTICLES FOR FURTHER ASSESSMENT

FULL TEXT ARTICLES ASSESSED FOR METHODOLIGICAL QUALITY

n = 36

FULL TEXT ARTICLES RETRIEVED FOR DETAILED EXAMINATION

n = 95 (primary articles)

n = 54 (reviews)

=

CITATIONS AND ABSTRACTS ASSESSED AFTER REMOVAL OF DUPLICATES

n = 6,874

N =

6,725 RECORDS EXCLUDED.

NOT MEETING CRITERIA FOR:

STUDY DESIGN n = 1,050

POPULATION / EXPOSURE

n = 3,200

NON ENGLISH n = 30

OUTCOME n = 2,445

59 RECORDS EXCLUDED.

NOT MEETING CRITERIA FOR:

STUDY DESIGN n = 17

POPULATION n = 14

ABSTRACT/POSTER n = 6

OUTCOME n = 22

Only one observational study was deemed poor quality according to the NOS scale (5). The latter was not excluded, instead we highlighted its limitations. Additionally, all identified experimental studies were deemed to be of fair quality. **Appendix 3 and 4** illustrates the quality analysis findings of the observational and experimental studies respectively. The characteristics of the 51 studies included in this review are presented in **Appendix 5**. A summary of the extracted information emphasizing the number of positive and negative studies for each autoantibody is presented in **Appendix 6**. The information contained in this section consists of a summary of the key findings for the autoantibodies whose data could not be pooled in a meta-analysis. The remainder of the results were previously presented in the main text.

**Anti-Heart Muscle Autoantibodies**

Two studies were identified that examined the association between autoantibodies targeting cardiac antigens and the subsequent occurrence of AS related CVDs (5, 6). The autoantibody of interest was anti-cardiac myosin (AMA). Whilst Dangas et al (2000) focused on the recurrence of an ischaemic event as the outcome of interest, Pang et al (2000) examined the association of the latter autoantibody with mortality following an initial MI (5, 6). The latter study however failed to identify precise cause of death in its study participants (5). Both studies reported higher CVD events amongst patients positive for the latter autoantibody at baseline though neither study provided an effect size.

**Thyroid Autoantibodies**

Only two studies investigating the association between the presence of thyroid autoantibodies and the subsequent occurrence of AS related CVDs were identified during our literature search (7, 8). Both studies examined the latter association amongst the Finnish population. Bastenie et al 1977 utilised a male only cohort while Aho et al (1984) also examined the association in a mixed gender Finnish cohort (7, 8). In both studies, study participants testing positive for either thyroglobulin or thyroid microsomal autoantibodies were deemed positive for thyroid autoantibodies. Both studies reported an increased risk of cardiovascular related morbidity and mortality amongst subjects’ positive for thyroid autoantibodies when compared to the rest of the cohort. Additionally, in both studies, participants were classified as having asymptomatic autoimmune thyroiditis.

**Anti-Nuclear Autoantibodies (ANA) AND Rheumatoid Factor (RF)**

Three studies examining a range of ANAs and their relationship with the subsequent development of AS related CVD were identified (9, 10, 11). Similarly, three studies examined the latter association with regards to RF exposure (9, 10, 12). Only three studies utilized primary CVD events as the study outcomes of interest (9, 11, 12). The majority of studies failed to specify the autoantibody isotype of interest. Only three studies provided an effect size quantifying the relationship between their specified autoantibody and related CVD outcomes (10, 11, 12). Moreover, the latter three studies reported that ANA and RF positivity significantly predicted cardiovascular morbidity and mortality amongst study participants (10, 11, 12).

# DISCUSSION

**Anti-Heart Muscle Autoantibodies**

Smooth muscle (SM) responsible for involuntary movement of organs such as blood vessels, plays a crucial role in the development of AS (5). Myosin is the main contractile protein in muscle cells (5, 13). Exogenous stimuli such as hypercholesterolemic diets are reported to provoke abnormal antigenic properties such as differentiation of medial SM cells to assume antigenic properties such as increased proliferation and alterations in phenotype from contractile to synthetic, prior to migrating into thickening intima (5, 13). The latter change is reportedly induced by oxLDL which is associated with sustained and intense calcium dependent retraction of vascular SM cells, stimulation of collagen production in SM cells as well as formation of substances such as lysophosphatidylcholine which affect the growth of SM cells (5, 13). Antibodies to myosin are postulated to be indicative of this phenotypic modulation in atherogenesis.

Conversely, as an intracellular protein, an absence of immune tolerance likely exists towards myosin. Tissue damage following acute MI (AMI) or ACS can lead to myocardial necrosis and subsequent presentation of intracellular proteins to the immune system in turn triggering an autoimmune response. Evidence suggests myosin is an important antigen in the process of inflammation either by directly evoking an immune response or acting as a cross-reactive epitope of other proteins (group A streptococci M protein and Coxsackie B virus) (13). It is therefore proposed that AMA might play an important role in the development of myocardial lesion and ventricular remodeling. It could also affect cardiac function and prognosis of patients following heart muscle trauma. It is important to note that the few studies identified highlighted significant limitations that would affect our interpretation of their results.

Unfortunately, existing animal studies examining the role of these autoantibodies have largely focused on delineating anti cardiac myosin autoantibody mediated induction of heart failure. One in vitro study that attempted to examine the functional effects of anti myosin autoantibodies observed altered calcium ion (Ca 2+) sensitivity of myofilaments and reduction of contractility of cardiomyocytes following exposure of isolated cardiomyocytes to affinity purified anti cardiac myosin autoantibodies from patients suffering from dilated cardiomyopathy or ischeamic heart disease (14). Nonetheless, the molecular mechanisms leading to AS related CVDs mediated by anti myosin autoantibodies still remain poorly understood.

**Thyroid Autoantibodies**

It is well established that hypothyroidism has been observed to favour the development of coronary heart disease (CHD) (7). The latter is driven by high cholesterol levels that are characteristic of this condition (7). Asymptomatic autoimmune thyroiditis (AAT) precedes overt hypothyroidism (7). The few existing studies have established a positive association between the former condition and CHD development. Interestingly studies have shown unchanged cholesterol levels in these ostensibly healthy subjects with thyroid autoantibodies hence it seems unlikely that the same mechanisms highlighted in hypothyroidism to contribute to AS related CVDs take part in AAT (7). This is further supported by the fact that lipid alterations are highlighted as significant risk factors for AS related CVD development in men before the age of 60 years but not after, whilst the importance of thyroid autoimmunity as a CHD risk factor apparently increases with advancing age (8). It is important to note that AAT is often accompanied by high concentrations of thyroid stimulating hormone (TSH) despite no signs of pronounced thyroid failure, which is often indicative of a latent thyroid dysfunction (8). Nonetheless it is increasingly argued that it isn’t the subclinical thyroid failure proposed to occur in AAT but rather the autoimmune process per se that appears to be responsible for vascular degeneration (8)**.** This is further supported by the fact that elevated TSH did not appear to be a better indicator of CVD related mortality or morbidity than the autoantibodies. The lack of a large number of studies examining this association highlights the need to clarify the possible effect of thyroid antibodies on atherogenesis. We therefore cannot disregard the possibility that thyroid antibodies are in fact innocent bystanders in the latter disease process. In addition, though it has been suggested that the effect of thyroid autoimmunity on cardiovascular outcomes is believed to be mediated through immune complexes the potential mechanisms underlying thyroid antibody immune pathogenesis in AS has not been elucidated (8).

**Anti-Nuclear Autoantibody (ANA) AND Rheumatoid Factor (RF)**

ANAs comprise a range of antibodies that target normal proteins located within the nucleus of a cell. Studies have highlighted an association between ANA and several traditional CVD risk factors, particularly anti dsDNA and smoking (9). Similarly, RF has been shown to be associated with high blood pressure (9). Nonetheless evidence exists to suggest these autoantibodies may also be independent risk factors for AS related CVD events.

ANAs have been linked to reduced arterial wall elasticity an early structural change in AS (15). Studies observing ANA in apparently healthy young individuals have proposed that these autoantibodies are indicators of latent autoimmunity that may determine premature disease occurrence (15). Environmental influences such as viral infections as well as defective clearance of apoptotic cells and misregulation of the inflammatory response are also linked to ANA production (15, 16). As such the association between ANA and AS is said to be correlative rather than causative. Alternatively, CAD is also proposed to lead to ANA seroconversion (15, 16). It is suggested that repeated myocardial necrosis during MI may lead to leakage of intracellular antigens that subsequently induce ANA production in turn aiding local inflammatory responses at the site of lipid deposition into the vascular wall where cellular necrosis is known to occur (16).

Even less is understood of the role RF plays in the pathogenesis of AS. Studies examining the latter relationship amongst RA patients have concluded that the increased prevalence of cardiovascular morbidity and mortality rates in RA cannot be explained by the presence of traditional AS risk factors (10). Nonetheless we cannot disregard the possibility that RF could merely be a by-product of a chronic inflammatory response that is responsible for promoting the development of accelerated AS in these patients. Researchers have observed a relationship between disease activity amongst RA patients and endothelial dysfunction. It is therefore poorly understood whether or not RF plays a causative role in AS development and progression.

Studies examining the association of either group of autoantibodies in relation to AS related CVD events are few and often examine the latter association with RF and ANAs included as possible confounding factors and not the main exposure of interest (17, 18, 19).

***Appendix 1:* Criteria utilized in Newcastle-Ottawa Scale for Assessing the Quality of Non Randomised studies in meta-analysis to evaluate methodological rigor of Observational Studies.**

Studies are assigned a star indicating the presence of sufficient information describing measures put in place, if any, to ensure each domains requirements were fulfilled in each study. In the case of ascertainment of exposure, a star was awarded for the use of a standardised laboratory procedure. In addition, any loss to follow-up less than 20% was considered to be unlikely to introduce any bias. Particular emphasis was placed on ensuring studies control for traditional cardiovascular disease risk factors. Studies acquiring less than 6 stars overall are considered to be of poor quality.

Selection:

1. Representativeness of exposed cohort / cases.
2. Selection of non-exposed cohort / controls.
3. Ascertainment of exposure / Is the case definition adequate?
4. Demonstration that outcomes of interest not present at start of study / Definition of controls

Comparability:

1. Comparability of cohort on basis of design or analysis.
   1. Are exposed / cases and non-exposed / controls matched.
   2. Does the study control for confounding in the analysis?

Outcome:

I. Assessment of outcome / exposure.

1. Was follow up long enough for outcome to occur? / Same method of ascertainment for cases and controls?
2. Adequacy of follow up of cohort. / Non response rate.

***Appendix 2*: Criteria utilized in Cochrane Risk of Bias Quality Assessment Tool to evaluate methodological rigor of Randomised Control Studies.**

An assessment is made for each outcome domain. A judgement of ‘Low risk’, ‘High risk’ or ‘Unclear risk’ is made based on the presence or absence of sufficient information describing measures put in place, if any, to ensure each domains requirements were fulfilled in each study. Articles with ‘low risk’ of bias across all domains are considered to be good quality research papers, those with ‘uncertain risk’ of bias for one or more domains and no known important limitation that could invalidate the results are deemed to be of fair quality and those with ‘high risk’ of bias in one or more domain are considered to be of poor methodological quality.

Selection bias:

1. Random sequence generation.
2. Allocation concealment.

Performance bias:

1. Blinding of participants and personnel.

Detection bias:

1. Blinding of outcome assessment.

Attrition bias:

1. Incomplete outcome data.

Reporting bias:

1. Selective reporting

Other bias:

1. Anything else, ideally prespecified such as failure to describe guidelines for monitoring the uptake of the therapeutic drug as per physician’s recommendations which could result in performance bias.

***Appendix 3*: Quality analysis of observational studies examining the association between presence of autoantibodies and occurrence of Atherosclerosis related Cardiovascular events using the Newcastle-Ottawa Scale**.

Underlined references represent studies consisting of community / population samples. References in italics represent mixed samples of those with and without autoimmune disease. Other studies consist of clinical samples of patients suffering some form of CVD or other non-autoimmune condition (outcome is secondary events).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **REFERENCE** | **SELECTION** | **COMPARABILITY** | **EXPOSURE** |
| 1 | Wilson PWF et al 2006 | \*\*\* | \* | \*\* |
| 2 | Erkkila AT et al 2005 | \*\*\* | \* | \*\*\* |
| 3 | Wu R et al 1997 | \*\*\*\* | \* | \*\* |
| 4 | Vaarala O et al 1995 | \*\*\* | \*\* | \*\*\* |
| 5 | Ahmed E et al 1999 | \*\*\*\* | \*\* | \*\*\* |
| 6 | Salonen JT et al 1992 | \*\*\*\* | \*\* | \*\* |
| 7 | Tsimikas S et al 2012 | \*\*\*\* | \* | \*\*\* |
| 8 | Caidahl K et al 2012 | \*\*\* | \* | \*\*\* |
| 9 | De Faire U et al 2010 | \*\*\*\* | \*\* | \*\* |
| 10 | Fiskesund R et al 2012 | \*\*\* | \* | \*\* |
| 11 | Sjoberg BG et al 2009 | \*\*\*\* | \*\* | \*\*\* |
| 12 | Cambridge G et al 2013 | \*\*\* | \*\* | \*\* |
| 13 | Majka DS et al 2016 | \*\*\*\* | \* | \* |
| 14 | Majka DS et al 2013 | \*\*\*\* | \* | \*\* |
| *15* | *Liang KP et al 2009* | \*\*\*\* | \*\* | \*\*\* |
| 16 | Mathews DJ et al 1973 | \*\*\* | \* | \*\*\* |
| 17 | Zielinska J et al 1999 | \*\*\* | \*\* | \* |
| 18 | Aho K et al 1984 | \*\*\*\* | \*\* | \*\* |
| 19 | Ahmed E et al 2000 | \*\*\*\* | \*\* | \*\*\* |
| 20 | Bastenie PA et al 1977 | \*\*\*\* | \* | \*\* |
| 21 | Bili A et al 2000 | \*\*\* | \* | \*\*\* |
| 22 | Birnie DH et al 2005 | \*\*\* | \* | \*\*\* |
| 23 | Brey RL et al 2001 | \*\*\*\* | \* | \*\*\* |
| 24 | Kiechl S et al 2001 | \*\*\*\* | \* | \*\*\* |
| 25 | Heinzlef O et al 2001 | \*\*\* | \* | \*\* |
| 26 | Huittinen T et al 2002 | \*\*\*\* | \*\* | \*\* |
| 27 | Huittinen T et al 2003 | \*\*\* | \*\* | \*\*\* |
| 28 | Janardhan V et al 2004 | \*\*\*\* | \* | \*\* |
| 29 | Kervinen H et al 2003 | \*\*\*\* | \*\* | \*\* |
| 30 | Greco TP et al 2007 | \*\*\* | \* | \*\* |
| 31 | Mayr M et al 2000 | \*\*\*\* | \* | \*\*\* |
| 32 | Su J et al 2013 | \*\*\*\* | \*\* | \*\*\* |
| 33 | Tanne D et al 2002 | \*\*\* | \* | \*\* |
| 34 | Xu Q et al 1999 | \*\*\*\* | \* | \*\*\* |
| 35 | Veres A et al 2002 | \*\*\*\* | \*\* | \*\* |
| 36 | Pang H et al 2000 | \*\* | \* | \* |
| 37 | Dangas G et al 2000 | \*\*\* | \*\* | \*\* |
| 38 | Gurlek A et al 2005 | \*\*\* | \*\* | \*\* |
| 39 | Hamsten A et al 1986 | \*\*\* | \*\* | \*\* |
| 40 | Maiolino G et al 2013 | \*\*\* | \*\* | \*\*\* |
| 41 | Tsimikas S et al 2007 | \*\*\* | \*\* | \*\*\* |
| 42 | Carrerro JJ et al 2009 | \*\*\* | \* | \*\*\* |
| 43 | Ravandi A et al 2011 | \*\*\*\* | \*\* | \*\*\* |
| 44 | Gigante B et al 2014 | \*\*\* | \* | \*\*\* |
| *45* | *Aho K, et al 1982* | \*\*\*\* | \*\* | \*\*\* |
| *46* | *Asciutto G, et al 2015* | \*\*\* | \*\* | \*\*\* |
| *47* | Bjorkbacka H, et al 2016 | \*\*\*\* | \*\* | \*\*\* |
| *48* | Fredrikson GN, et al 2007a | \*\*\*\* | \*\* | \*\*\* |
| *49* | *McLeod O, et al 2014* | \*\*\* | \*\* | \*\* |

***Appendix 4:* Quality assessment of Randomised Control Studies examining the association between autoantibodies and the occurrence of cardiovascular events utilising the Cochrane Risk of Bias Quality Assessment Tool.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
| Fredrikson GN 2007 | + | ? | + | + | + | + | ? |
| Puurunen M 1994 | + | ? | + | + | + | + | + |

**Key**

+ Low risk of bias

─ High risk of bias

? Uncertain risk of bias

***Appendix 5:* Data extraction table describing various features of the full-texts included in this review.**

Follow up ranged from 6 months to 20 years. Study participants were aged between 20 to 79 years. Only one study restricted their research to females while 11 studies focused only on males. Cardiovascular disease (CVD) death, angina pectoris (AP), myocardial infarction (MI), stroke, and carotid intima media thickness progression (cIMT progression) was included as a CVD outcome of interest in 31, 6, 36, 24, and 9 studies respectively. In total, this review included two randomised control trials (RCTs), 24 prospective nested case control studies (PNCCs) and 25 cohort studies. The majority of studies were carried out across various European countries and the United States of America.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **REFERENCE** | **STUDY DESIGN** | **SAMPLING FRAME** | **SAMPLE SIZE** | **SAMPLE CHARACTERISTICS** | **AS RELATED CVD OUTCOMES** | **AUTOANTIBODY EXPOSURE** | **FOLLOW – UP PERIOD** | **RESULTS** |
| Ahmed E, et al 2000 | Prospective nested case control study  (PNCC) | Population sample from Sweden. Study nested in MONICA and Vasterbotten Cohort Project. | Cases  = 123  (46/123 -females)  Controls = 241  (89/241 – females) | Males and females;  Mean age 55.2 ± 7.6 years (cases);  Mean age 55.1 ± 7.6 (controls). | Stroke  (Primary event) | Immunoglobulin G (IgG) Anti Cardiolipin (aCL),  Immunoglobulin A (IgA) aCL,  Immunoglobulin M (IgM) aCL Antibody (Ab). | 3 years | **Odds ratio (OR) IgG:**  1; p= Not significant (NS); 95% Confidence interval (95% CI) 0.79 – 1.26)  **OR IgM:**  1.24; p=0.077;  95% CI: 0.98 – 1.56  **OR IgA:**  1.05; p=NS;  95% CI: 0.88 – 1.24 |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Brey RL, et al 2001 | PNCC | Population sample of American men of Japanese ancestry born from 1900 – 1919 and residing on the island of Oahu in 1965. Study nested in Honolulu Heart Program. | Stroke cases  = 259  MI cases = 379  Controls  = 1,360 | Male only sample  Age range 48 – 70 years. | Stroke  Myocardial infarction (MI)  (Primary event) | Beta 2 glycoprotein 1 (β2GP1) dependent aCL IgG;  β2GP1 dependent aCL IgM;  β2GP1 independent aCL IgG;  β2GP1 independent aCL IgM,  Unique IgG antibodies to  β2GP1 alone in the absence of  Cardiolipin. | 5, 10, 15 and 20 year follow up (F/U) | β2GP1 dependent aCL IgG: Stroke, OR 2.2 (95% CI 1.5 to 3.4) at 15 years and 1.5 (95% CI 1.0 to 2.3) at 20 years. MI, OR 1.8 (95% CI 1.2 to  2.6) at 15 years and 1.5 (95% CI 1.1 to 2.1) at 20 years. (Data on shorter periods not described due to limited numbers of events.). Results only presented for β2GP1 dependent aCL IgG. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Janardhan V, et al 2004 | Longitudinal study | Community based population sample  (USA – Framingham heart study) | Original cohort:  562 men and 815 women.  Offspring cohort:  1700 men and 1897 women | Original cohort:  562 men (69.1 ± 6.7 years) &  815 women (70.1 ± 7.1 years).  Offspring cohort:  1700 men (54.8 ± 9.9 years) &  1897 women (54.6 ± 9.8 years) | Incident ischaemic stroke or Transient Ischaemic Attack (TIA)  (Primary event) | aCL IgG, IgA and IgM | 11 years | An aCL screening ration (SR) of  0.4 (78% of sample) significantly associated with an increased risk of ischemic stroke/TIA for women (Hazard ratio (HR), 2.6; 95% CI, 1.3 to 5.4; absolute risk, 3.2%, 95% CI, 2.2 to 4.3) but not in men (HR, 1.3; 95% CI, 0.7 to 2.4; absolute risk, 4.5%; 95% CI, 3.0 to 6.0). Similar results were obtained when the higher 3 aCL SR quartiles were compared with the lowest. |

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| Vaarala O, et al 1995 | PNCC (Nested in Helsinki Heart Study) | Original sample comprised 4,081 participants selected by screening a cohort of 19,000 male employees in private and government owned industries in Helsinki, Finland. | 133 patients with cardiac end points (26 cardiac deaths and 107 non-fatal MI).  133 control subjects matched for treatment (gemfibrozil/placebo) and geographical area. | Middle aged dyslipidaemic men (non-high density lipoprotein cholesterol ≥ 5.2 Millimole per litre (mmol/L).  Patients mean age 49.2 ± 4.4 years.  Controls mean age 47.2 ± 4.8 years. | Primary MI or cardiac death | IgG aCL | 5 years | An increased risk at conventional significance level (p< 0.04) was found only in the highest quartile when compared with the remainder of the population, Relative risk (RR) for MI of 2.0 (95% CI 1.1 – 3.5). Risk was independent of other factors. |

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| Su J, et al 2013 | Prospective study | Population sample. Between 1st July 1997 – 30th June 1998 every third man and woman living in Stockholm, Sweden reaching age of 60 invited to participate. | 211 incident cases of cardiovascular disease (CVD)  633 controls (for each case three controls randomly selected, matched for gender and age (± 60 days). | Cases mean age 60 years; 66.4% males.  Controls mean age 60; 66.4% males. | Incident cases of CVD, new events of coronary heart disease (CHD), defined as fatal and non-fatal MI and ischemic stroke, hospitalization for angina pectoris (AP). | IgG and IgM antibodies to Oxidised cardiolipin (aOxCL);  IgG and IgM aCL | 5 – 7 years | Adjusted ORs.  Increased risk in lowest quartile of IgM aOxCL 1.80  (95% CI: 1.12 – 2.91, p = 0.0159). IgM aOxCL, OR for men in lowest quartile for CVD 2.46 (95% CI: 1.34 – 4.53, p = 0.0037) and for stroke 12.28 (95% CI: 1.48 – 101.77, p = 0.02).  High levels IgM aOxCL (above 86th percentile) and IgG aOxCL (above 95th percentile) associated with decreased risk of CVD: OR 0.485, 95% CI: 0.283 – 0.829, p = 0.0082 / OR 0.23, 95% CI: 0.07 – 0.69, p = 0.0091 respectively.  aCL not associated with CVD (Data not shown). |

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| Wu R, et al 1997 | PNCC | Population sample drawn from (2,322)  Uppsala, Sweden (82% of all 50 year old men living in Uppsala between 1970 and 1972.) | 257 males aged 50 years in Uppsala during 1970 to 1972 | 257 male individuals; 119 patients with MI between 50 to 70 years of age and 138 controls who did not develop MI up to 70 years of age. All study participants were aged 50 years at baseline. | Incident MI and mortality related to MI | IgA, IgM and IgG Anti oxidised low density lipoprotein autoantibodies (Anti OxLDL);  IgG, IgM and IgA aCL | 20 years | Anti OxLDL IgA: OR = 1.30 p=0.08 (95% CI: 0.97-1.73)  IgG: OR = 1.32  p=0.06 (95% CI: 0.99-1.76)  IgM: OR = 1.00  p=0.99 (95% CI: 0.76-1.31)  Anti Cardiolipin-IgA: OR = 1.48 p=0.02  (95% CI: 1.06-2.06)  IgG: OR = 1.49  p=0.01 (95% CI: 1.11-1.99)  IgM: OR = 1.21  p=19 (95% CI: 0.91-1.60) |

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| Greco TP, et al 2007 | Prospective cohort study | Patients with chest pain / acute coronary syndrome (ACS) or documented Coronary artery disease (CAD) admitted to acute care institution (Saint Mary’s Hospital, Waterbury, Connecticut, USA). | 232 study participants | 116 males and 116 females; Mean age 63 years; 86/232 (37%) positive for APAs; 146/232 (63%) negative for APAs. | Cardiac revascularization due to angioplasty failure;  Stent occlusion; New coronary vascular occlusion; Coronary artery bypass;  Secondary MI, cerebrovascular disease (CBV);  Other major cardiovascular event (CVE);  Anti-phospholipid syndrome (aPL) related complications; Death (cardiac and non-cardiac). | IgG, IgM and IgA APAs;  aCL;  β2GP1;  Phosphatidylserine antibodies (aPS);  antiprothrombin antibodies (aPT);  anti oxLDL / β2GP1 (anti atherox) | Mean follow up period 9 months | Requiring procedures (APA positive (+ve) 18.5%, APA negative (–ve) 7.8%, p = 0.115);  Adverse vascular outcomes (APA +ve 29%, APA –ve 11.3%, p = 0.045);  Adverse vascular outcomes + Cardiovascular related death (APA +ve 35.3%, APA –ve 13.6%, p = 0.049);  Stroke / Pulmonary thromboembolism (PTE) (APA +ve 11.8%, APA -ve 0%, p = 0.033). |

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| Tanne D, et al 2002 | Prospective follow up study | Patients admitted to Henry Ford Hospital Department of Neurology, an urban integrated health system that serves as a community resource for stroke. | 300 first ischemic stroke patients. | 48% of study participants are male.  Mean age 64 years. | Death; Recurrent thrombo occlusive events (stroke, TIA, MI, arterial embolism, deep venous thrombosis [DVT] or pulmonary embolism [PE]). | IgG anti cardiolipin autoantibodies | Follow up visits every 6 months for a median of 21 months. | Adjusted RR Death;  Cut off 10 Immunoglobulin G phospholipid units (GPL): 0.85 (95% CI: 0.45 – 1.62) p = 0.62;  Cut off 20 GPL:  1.08 (95% CI: 0.53 – 2.23) p = 0.83;  Cut off 40 GPL: 1.00 (95% CI: 0.37 – 2.71) p = 0.99  Adjusted RR Stroke, MI, Vascular death;  Cut off 10 GPL: 0.86 (95% CI: 0.47 – 1.56) p = 0.60;  Cut off 20 GPL: 1.09 (95% CI: 0.55 – 2.16) p = 0.79;  Cut off 40 GPL: 0.85 (95% CI: 0.30 – 2.36) p = 0.74. |

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| Bili A, et al 2000 | Prospective cohort study | Patients hospitalised for acute MI (AMI) (index MI) as part of thrombo study (USA) | 1150 patients with AMI | Male and female sample. 75 out of 1150 were male. ≥ 21 years of age. 26 out of 1150 were of non-white race. | Recurrent cardiac events:  Rehospitalisation as a result of recurrent non-fatal MI or fatal MI. | aCL IgG and IgM  β2GP1 IgG and IgM | 24.6 months mean follow up period | Elevated IgG aCL Quartile 4 versus Quartile 1 to 3 (Q4: Q1 – 3) HR = 1.63 (95% CI: 1.11 – 2.38) p = 0.01.  Low levels IgM aCL Quartile 1 to 3 versus Quartile 4 (Q1 – 3: Q4) HR = 1.76 (95% CI: 1.10 – 2.82) p = 0.02.  No association between either IgG or IgM β2GP1 with recurrent cardiac events. |
| Heinzlef O, et al 2001 | Prospective cohort study | Patients consecutively hospitalised between September 1991 and October 1993 at 5 centres (Saint Antoine hospital, Paris, CHU Grenoble, Lille and Besancon) for brain infarction. | 242 consecutive patients | Over 60 years of age;  133 out of 242 were female. | Recurrent stroke & AP. Primary vascular events (symptomatic retinal artery occlusions, MI, peripheral embolism, acute leg ischemia treated by amputation, bowel infarction, blue toe syndrome & death from vascular causes). | IgG aCL  Negative group  Less than 10 GPL units  n = 192  Positive group  10 GPL units or more  n = 50  (No patients had more than 80 GPL units) | Mean 2.33 ± 1.25 years  (572 person years of follow up time) | Recurrent stroke  RR = 0.9 (95% CI: 0.5 – 1.2) p = 0.26  New vascular events  RR = 1.0 (95% CI: 0.97 – 1.02) p = 0.73  aCL IgG was not an independent predictor of either recurrent stroke or new vascular events. |

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| Erkkila AT, et al 2005 | Retrospective cohort study | Participants recruited as part of EUROASPIRE study aimed at secondary prevention of Coronary Heart Disease conducted in 1995 – 96 in 9 European countries. | 413 Finnish patients with clinically established CHD, under 71 years at the time of admission. | 284 males and 129 females;  Mean age: 61; range 33 – 74 years | (Secondary events)  CHD death; Non-fatal Acute Myocardial Infarction (AMI); CABG; Percutaneous transluminal coronary angioplasty (PTCA). | OxLDL autoantibodies;  aCL autoantibodies. | 5 year Follow up | CHD Death / AMI:  **Anti oxLDL**  Tertile 1.31 – 2.01 RR=1.04 (95% CI: 0.44 – 2.46);  Tertile >2.01 RR=1.09 (95% CI: 0.47 – 2.56)  **aCL Antibodies**  Tertile 1.31 – 201 RR=2.61 (95% CI: 1.02 – 6.65);  Tertile >2.01 RR=1.06 (95% CI: 0.37 – 3.03)  Revascularisation:  **Anti oxLDL**  Tertile 1.31 – 2.01 RR=0.73 (95% CI: 0.35 – 1.54);  Tertile >2.01 RR= 0.61 (95% CI: 0.27 – 1.34)  **aCL Antibodies**  Tertile 1.31 – 2.01 RR=1.76 (95% CI: 0.77 – 4.00);  Tertile >2.01 RR=1.22 (95% CI: 0.51 – 2.93) |

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| Zielinska J, et al 1999 | Prospective case control study | Over 20 month period ischemic patients consecutively admitted within 48 hours of stroke onset to Department of Neurology, Institute of Psychiatry and Neurology, Warsaw Poland. | 194 consecutive ischaemic stroke patients and 100 controls | Of the 194 cases (93 were women and 101 men; mean age 68.9 ± 13.3 years).  Of 100 controls (54 men and 46 women; mean age 67.8 ± 13.9 years). | Recurrent stroke;  Clinical outcome (mortality;  weakness score; stroke severity scale;  activities daily living scale; cognitive function – mini mental state exam scale) | IgG and IgM aCL | 1 year | aCL +ve group similar to –ve group.  **30 day fatality:**  28.6% (95% CI: 16.6 – 43.3) and 26.2% (95% CI: 19 – 33.4) respectively.  **1 year fatality:**  59.2% (95% CI: 44.2 – 73.0) and 45.5% (95% CI: 37.4 – 53.6) respectively.  **Stroke recurrence at 1 year:**  12.2% (95% CI: 6.8 – 19.7) and 13.2% (95% CI: 3.4 – 28.2) respectively. |

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| Hamsten A, et al 1986 | Prospective cohort study | Patients consecutively admitted to hospitals with intensive care units in Stockholm County between May 1980 and September 1982. | 62 patients (young survivors of MI before age 45) | 56 men and 6 women;  Mean age ± SD 40.7 ± 3.7 years. | Secondary CVE:  - cerebral infarction (CI)  -arterial occlusion (AO) of lower limb  -MI  -PE  -DVT | aCL IgG  (Results related to mean absorption value obtained for sera from 156 volunteer blood donors) | New CVE recorded 36 – 64 months after 1st MI. | 20 / 62 had a major CVE subsequently. 8 / 20 +ve for aCL.  (X² = 4.297, p < 0.05).  [CI (2); AO (2); MI (3); PE (1); DVT (1)]  8 new cases had aCL titres 5 times the mean of volunteer blood donors. |
| Majka DS et al 2013 | Prospective cohort study | Study population drawn from 4 centres in the US (Chicago, Minneapolis, Birmingham, Oakland) as part of the Coronary Artery Risk Development in Young Adults cohort (CARDIA) initiated in 1985. | 2,203 study participants | Healthy participants aged 18 – 30 years. Evenly balanced by gender, black (489 women and 331 men) and white race (495 women and 523 men) and education. | Coronary artery calcification (CAC progression) | β2GP1 IgG, IgA and IgM;  aCL IgG, IgA and IgM. | 5 year follow up | Only anti β2GP1 IgG significantly associated with progression of CAC in all participants OR 3.1 (95% CI 1.1 – 9.1). After stratifying for gender and race, association only significant in Blacks OR 5.8 (95% CI 1.1 – 29.0) and Women OR 4.2 (95% CI 1.0 – 17.0). |

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| Gurlek A, et al 2005 | Prospective follow up study | Patients admitted to coronary care unit (Ankara, Turkey) with a diagnosis of acute coronary syndrome who have undergone percutaneous coronary intervention (PCI) | 80 patients | Male and female sample;  >21 years;  Group I –Mean age 61 ± 10 years;  Group II – Mean age 58 ± 11 years. | Mortality,  Restenosis,  Reinfarction.  (Secondary events) | IgG and IgM aCL;  Positive Group (I)  (n = 30) >40 units IgG aCL;  Negative Group (II) (n = 50) <40 units IgG aCL. | Study sample followed up for 12 months after PCI | Restenosis was observed in 8 of 20 (40%) cardiolipin positive patients and 6 of 43 (14%) cardiolipin negative patients (P < 0.01).  No association is evident between positive aCL and mortality, reinfarction, and intracardiac thrombus. |

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| Asciutto G, et al 2015 | Prospective cohort study | Hospital sample consisting of persons undergoing carotid endarterectomy at a tertiary university Vascular Department  (SWEDEN) | 351 study participants | Sample mean age 70.52 ± 8.57 years.  Males 65.8% (n = 231) | Fatal or non-fatal Acute Myocardial infarction (AMI); Stroke;  Transient ischaemic attack (TIA);  Amaurosis fugax (AF). | -IgM against peptide 210 native (IgM p210 nat);  -IgM against malondialdehyde modified peptide 210  (IgG p210 MDA);  -IgG against native peptide 210  (IgG p210 nat);  -IgG against MDA modified peptide 210  (IgG p210 MDA). | 35.1 ± 16.7 months. | A total of 15 fatal (9 AMI & 6 strokes) and 52 non-fatal events (20 AMI, 15 strokes, 11 TIA, 6 AF) occurred. Patients who suffered fatal CVE had significantly lower plasma levels of IgG p210 nat and IgG p210 MDA. Levels of IgG p210 nat and IgG p210 MDA below median were significantly associated with fatal post-operative CVE, HR = 6.7; 95% CI: 1.5 – 30.6; p = 0.013 and HR = 7.8; 95% CI: 1.7 – 35.5; p = 0.008 respectively. |

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| Bjorkbacka H, et al 2016 | Prospective cohort study | Study sample drawn from Malmo Diet & Cancer Study (A population based cohort study of inhabitants living in Malmo, SWEDEN) | 5,393 study participants | Caucasian sample;  Aged 46 – 58 (Mean 57.64) years;  42% Males (2,269) | Incident fatal and non-fatal MI;  Incident ischaemic heart disease;  Incident fatal and non-fatal stroke (ischaemic, haemorrhagic and unspecified) | IgG and IgM native and MDA modified apolipoprotein B 100 peptide 45 (IgG and IgM-p45MDA) and peptide 210 (IgG and IgM-p210 MDA) autoantibodies | 15 year follow up | A significant association was identified between high levels of  IgM-p45MDA and lower risk of incident coronary events after  adjustment for confounders,  (hazard ratio [95% confidence interval (CI)]: 0.72 [0.55, 0.94],  *P*=0.02. A  significant association also between high levels of IgG-p210native  and decreased risk of coronary events after adjustment  (hazard ratio  [95% CI]: 0.73 [0.56, 0.97], *P*=0.03. All results for highest versus lowest tertile. No significant differences between tertiles for other apoB-100 autoantibodies were detected. |
| Fredrikson GN, et al 2007a | PNCC | Study sample drawn from Malmo Diet & Cancer Study (A population based cohort study of inhabitants living in Malmo, SWEDEN) | 223 study participants; 75 cases and 148 controls | Median Age 61 (range 49 – 67) years;  70% of cases were males;  69% of controls were males. | Fatal and non-fatal MI;  Death due to coronary heart disease. | Anti p45MDA IgG autoantibodies | Median follow up 2.8 years (range 0.1 – 5.9 years) | Low levels of p45MDA IgG were associated with a higher degree of carotid stenosis both among controls (r = −0.19, P< 0.05)  and cases (r = −0.31, P< 0.05), as well as in the study group as a whole (r = −0.23,  P< 0.001), event after adjustment (p = 0.006).  The mean percent  carotid stenosis was almost twice as high among those in the lowest tertile of MDA-p45 IgG as compared to those in the highest tertile (14.6 ± 13.7% versus 7.6 ± 9.6%, P = 0.001). |

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| McLeod O, et al 2014 | Prospective cohort study | Study sample drawn from IMPROVE study (a multi centred longitudinal observational cohort study of high risk individuals involving seven recruiting centres in 5 European countries, i.e. Finland, Sweden, the Netherlands, France and Italy. | 3,338 study participants | Age 64.5 (59.7-67.2) years;  Males n = 1,653 | Change over time in carotid intima media thickness (cIMT) | Circulating IgG-p210 nat and IgM-p210 MDA antibodies (directed against peptide p210 containing amino acids 3136e3155 of apoB- 100). | 30 month follow up period | IgM-p210 MDA autoantibody levels were independently related to several cIMT measures (IMT mean – max β ± 2SE = 0.0132 ± 0.0063; p = 0.037) (ICA – IMT max 0.0343 ± 0.0252; p = 0.007); both in the common carotid artery and in the carotid bulb, including measures of cIMT progression, higher levels being associated with lower cIMT or slower cIMT progression.  The latter was not the case with IgG-p210 nat where there were no associations with rate of cIMT progression besides in certain secondary stratified analyses. |

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| Tsimikas S, et al 2007 | Retrospective study design | Study participants comprised hospital patients undergoing coronary angiography at Mayo Clinic, Rochester, MN. | 504 study participants;  233 had No/MILD angiographically determined CAD whilst 271 had obstructive CAD. | >97% Caucasians;  Male and female sample (193 females), Age 26 – 75 years. | MI, coronary revascularization, percutaneous intervention, coronary artery bypass surgery, stroke and cardiac death.  (Secondary events) | Anti Malondialdehyde low density lipoprotein autoantibodies (Anti MDA LDL) IgG and IgM; Anti  Copper oxidised low density lipoprotein autoantibodies (Anti Cu OxLDL) IgG and IgM | 4 year median follow up period | No Ab associated with CAD. ORs provided for different quartiles.  Anti MDA LDL  IgM Q2: 0.80 (95% CI: 0.68 – 0.91), Q3: 0.64 (95% CI: 0.46-0.87), Q4: 0.51 (95% CI: 0.32-0.82).  IgG Q2: 0.99 (95% CI: 0.84-1.16), Q3: 0.97 (95% CI: 0.71-1.33), Q4: 0.96 (95% CI: 0.60-1.54).  Anti Cu OxLDL  IgM Q2: 0.86 (95% CI: 0.73-1), Q3: 0.73 (95% CI: 0.53-1.01), Q4: 0.63 (95% CI: 0.39-1.01).  IgG AQ2: 1.16 (95% CI: 0.99-1.35), Q3: 1.34 (95% CI: 0.97-1.83), Q4: 1.54 (95% CI: 0.96-2.48). |

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| Tsimikas S, et al 2012 | Prospective study design | Study participants comprise inhabitants of Bruneck, Italy.  [The present study focuses on blood samples from the 1995 examination of the Bruneck Study and the follow-up period for clinical events between 1995 and 2010 (100% follow-up).] | 765 study participants  [Subjects who developed the primary CVD endpoint (n=138) were more likely to be older and male, have higher levels of LDL cholesterol, vascular, coagulation, inflammatory, anthropomorphic and activity risk factors, and to have pre-existent CVD at study entry in 1995.] | Age range 45 – 84 year old men and women from the general community;  Those with a primary composite CVD endpoint -  Mean age 61.4±10.9 years.  Those without a primary composite CVD endpoint - Mean age 68.8±10.5 years. | Incident CVD:  Ischemic stroke, MI, new-onset unstable angina, acute coronary interventions, and vascular death (due to ischemic stroke, MI, sudden cardiac death or aortic aneurysm rupture). Additional endpoints TIA and revascularisation procedures. | Anti MDA LDL IgG and IgM;  Anti Cu OxLDL IgG and IgM | 15 years | Anti Cu-OxLDL IgG- higher risk of CVD (HR: 1.18; 95% CI: 1.02 to 1.37, p<0.028 for 1-SD unit increase) and the individual endpoint of stroke (HR: 1.32; 95%CI: 1.11 - 1.58; p<0.002). IgM HR 0.78 (95% CI: 0.61 to 0.98; p<0.037).  Anti MDA-LDL IgM (HR: 0.79; 95%CI: 0.66 to 0.95; p<0.010) - lower risk CVD, & stroke. IgG not predictive. Data not shown. |
| Wilson PWF, et al 2006 | Prospective study design | Participants included 1192 men and 1492 women who attended examination 4 of the Framingham Offspring Study in 1989 –1993. | 2619 study participants | Sample comprised 1192 males and 1427 females aged 20 – 79 years. | Incident events.  CHD outcome (AP, unstable AP, MI, coronary death);  CVD outcome (CHD, TIA and stroke). | IgG Anti oxLDL autoantibodies | 8 years | Multivariable risk for CVD and CHD  IgG Anti oxLDL (unit effect 1000 units)  Males: RR = 1 (95% CI: 1 – 1)  Females: RR = 1 (95% CI: 1 – 1) |
| Ahmed E, et al 1999 | PNCC | Participants drawn from the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project and the Vasterbotten Intervention Program (VIP) in the 2 northernmost counties of Sweden. | 352 study participants | Men and women aged 25 – 74 years;  119 cases (98 ischemic and 21hemorrhagic, 75 men and 44 women) **and** 233 controls (85 females and 148 males) | Incident Stroke (fatal and non-fatal) | IgG, IgA, and IgM autoantibodies against Cu-OxLDL and MDA-LDL. | 10 years and 8 months | Adjusted risk ratios did not confer a risk for stroke.  Anti Cu-OxLDL IgG RR = 1.1 p=0.592 95%CI 0.700 – 1.869;  IgM RR = 1.1 p=0.541 95%CI 0.742 – 1.766; IgA RR = 1.2 p=0.537 95%CI 0.704 – 1.958.  Anti MDA LDL IgG RR = 1.5 p=0.263 95%CI 0.742 – 2.986; IgM RR = 1.1 p=0.679 95%CI 0.622 – 2.072; IgA RR = 1.2 p=0.648 95%CI 0.593 – 2.319. |

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| Maiolino G, et al 2013 | Prospective cohort study | Participants randomly selected from GENICA study comprising consecutive Caucasian patients referred for coronary angiography to investigate chest pain and/or suspected CAD between 1999 and 2001. | 559 study participants | Caucasian sample;  According to Quartiles of oxLDL Abs  Q1: Mean age 62.3±10.6 years; 147/179 (82% females).  Q2: Mean age 63.1±9.5 years; 144/189 (76% females).  Q3: Mean age 64.4±10.0 years; 136/181 (75% females).  Q4: Mean age 63.2±10.0 years; 148/185 (80% females). | Secondary events.  ACS, Stroke, Cardiovascular death (sudden death or death due to congestive HF, ACS, or stroke). | IgG Anti MDA LDL autoantibodies | Median follow up length 7.2 years | Of the 559 patients 65 (11.6%) had a Cardiovascular death and 153 (27.4%) a Cardiovascular event. The patients in the highest quartile of oxLDL Abs titer had a lower Cardiovascular death-free survival (82.6% vs. 90.5%, respectively, p=0.007 at Kaplan–Meyer analysis) and Cardiovascular event-free survival (66.4% vs. 74.3%, respectively, p=0.036 at Kaplan–Meyer analysis) than those in the low oxLDL Abs group. |

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| Salonen JT, et al 1992 | PNCC | Study participants drawn from Kuopio ischaemic heart disease risk factor study. | 60 study participants.  [An equal number of cases and controls were taken from each of the four age groups:  -2 men aged 42,  -7 men aged 48,  -9 men aged 54,  -12men aged 60 years at baseline.] | Mean age 54.4 years.  30 Eastern Finnish men with accelerated 2yr progression of carotid atherosclerosis and 30 age-matched controls with the least progression. | Progression of carotid AS, i.e. IMT of common carotid artery | IgG, IgM, and IgA Anti MDA LDL, Anti Cu OxLDL and Native LDL autoantibodies | 2 years | 2 year increase in IMT had a strong correlation with titre of antibodies to Anti MDA-LDL (r = 0.41, p = 0.001). Multifactorial log regression coefficient Anti MDA-LDL Ab 1.26 (SE = 0.58) (Wild Chi² = 4.68) (p = 0.031). No relationship observed for other two Abs. Data not shown. |
| Bastenie PA, et al 1977 | Prospective cohort study | Study participants recruited as part of seven counties study (East-West series 1969 - 1974) | 280 and 269 males from rural areas of South-Western Finland (W.F) and  Eastern Finland (E.F) respectively. | Males ages 50 – 69 years at start of study. | Primary event CHD  (non-fatal and fatal) | Thyroid microsomal antibodies;  Thyroglobulin autoantibodies. | 5 years | -ve Thyroid autoimmunity in 1969, 21% (48/234) in West & 24% (46/196) in East acquired CHD. +ve Thyroid antibodies in 1969, 31% (4/13) of W.F. men & 45% (5/11) of E.F. men acquired CHD. The corresponding RR 1.5 & 1.9 respectively. |
| Aho K, et al 1984 | Prospective cohort study comprising 2 population series. | Study participants recruited as part of seven counties study (East-West series 1974 - 1979).  Study participants recruited from a rural district of south western Finland (Sakyla-Koylio series 1973 – 1978). | East-West series:  1105 study participants.  Sakyla-Koylio series:  2268 study participants. | East-West series:  1105 males;  55 – 74 years.  Sakyla-Koylio series:  1045 males and 1223 females;  Middle aged (40 – 60 years) | MI,  Stroke,  CHD (with and without angina),  CHD death. | Thyroid microsomal antibodies;  Thyroglobulin autoantibodies. | 5 years | 18/94 deaths (8 East; 10 West) due to CVD among thyroid +ve and 20/187 deaths (10 East; 10 West) amongst thyroid  -ve (p<0.05). RR = 2.1. Most deaths due to CHD.  Sakyla-Koylio series: 35 male deaths due to CVD and 20 females. 3 males (9%) and 6 females (30%) had thyroglobulin antibodies. |

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| Cambridge G, et al 2013 | Retrospective study | Study participants recruited from nine general medical practices in the UK. | 3052 study participants | Middle aged healthy men aged 50 – 64 years at recruitment.  At F/U nested case control dataset created 288 cases (mean age 56.3 ± 3.5 years) and 144 controls (mean age 56.2 ± 3.5 years). | CHD endpoints recorded after year 5 – acute CHD event, sudden coronary death, fatal AMI, non-fatal AMI, a new major Q wave on the electrocardiograph (ECG) after 5 years of follow-up and surgery for angina pectoris with CHD angiographically demonstrated.  (Primary events) | IgG Anti CCP | 15 year median follow up | 10.4% of cases were Ab positive compared to 3.8% of controls (odds ratio (95%CI) 3.26 (1.36 - 7.80), p = 0.008), remaining significant after adjustment for classical risk factors including smoking and C reactive protein (CRP) (OR 4.23 (95% CI: 1.22 - 14.61) p = 0.02). |

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| Majka DS, et al 2016 | Prospective cohort study | MESA – multicentre based population based cohort | 6814 study participants | Middle aged to elderly multi ethnic female study participants.  Caucasian  n = 1323  African Americans  n = 1000  No clinical symptoms of rheumatoid arthirits (RA) evident. | CHD hard end points: MI, resuscitated cardiac arrest, CHD.  CVD hard end points: MI, cardiac arrest, CHD death, stroke, stroke death.  (Primary events) | Rheumatoid Factor (RF) IgM and IgA;  Anti-Cyclic Citrullinated Protein Autoantibodies (Anti CCP) unspecified | 7.1 year median follow up | HRs (95% CI).  Caucasian women  CHD endpoints  RF IgM 1.2 (0.4 -3.0); RF IgA 1.1 (0.3 – 4.5); Either RF 1.2 (0.5 – 3.0); Both RF 0.8 (0.1 – 6.1); CCP N/A.  CVD endpoints  RF IgM 1.8 (0.9 – 3.4); RF IgA 0.5 (0.1 – 2.2); Either RF 1.6 (0.8 – 3.0); Both RF 0.4 (0.1 – 3.1); CCP N/A.  AA women  CHD endpoints  RF IgM 1.7 (0.7 – 4.5); RF IgA 5.0 (1.9 – 12.7); Either RF 2.5 (1.0 – 6.4); Both RF 4.5 (1.6 – 13.0); CCP 1.1 (0.1 – 8.3).  CVD endpoints  RF IgM 2.1 (1.1 – 4.0); RF IgA 3.4 (1.7 – 6.9); Either RF 2.7 (1.4 – 5.1); Both RF 3.3 (1.5 – 7.3); CCP 2.3 (0.7 – 7.7) |

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| Liang KP, et al 2009 | Population based prospective cohort study | Study participants drawn from all Olmsted County residents who had RF and/or ANA testing between 1/1/1990 and 1/1/2000 and/or CCP testing between 9/1/2003 and 1/1/2005. | 6783 subjects (69.4% females; mean age 49.7±17.04 years) who underwent RF testing, 7852 subjects (23.9% females; mean age 47.5±17.04 years) with ANA testing & 299 subjects (70.9% females; mean age 54.5±15.8 years) with CCP testing. | Sample comprised a mix of male and female individuals with and without rheumatic disease and those with and without history of CVE. | Cardiovascular disease outcomes: MI, HF, PVD and overall mortality | RF;  ANA;  Anti CCP | Follow up period varied for each autoantibody.  All subjects were followed up until 4/1/2007. | Cardiovascular event:  RF HR 1.24 (95% CI: 1.01 – 1.51)  ANA HR 1.26 (95% CI: 1.09 – 1.46) Death:  RF HR 1.43 (95% CI: 1.21 – 1.68) ANA HR 1.18 (95% CI: 1.04 – 1.34). CCP positivity not statistically significantly associated with CVE or death. |
| Mathews JD, et al 1973 | Prospective cohort study | Population sample from rural community of Busselton, Western Australia. | 3407 study participants | 1641 males and 1766 females; Study participants were > 21 years. Study participants described as ‘normal’. | Deaths from vascular causes. | ANA;  RF. | Study participants observed from October 1969 to March 1972.  Follow up ~ 30 months. | 92 deaths. 51 due to vascular causes. Complete data available on 70. 45 deaths comprised males. Data presents Observed (Expected) number with Abs amongst vascular deaths.  ANA detected in 4 males (2.83) and 0 females (2.72).  RF detected in 0 males (1.92) and 0 females (1.00). |

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| Dangas P, et al 2000 | Prospective case control study | Sample drawn from hospital patients. | 55 study participants | 33 consecutive patients with an ACS (85% males; mean age 57± 2 years) and 22 age matched controls (86% males; mean age 57 ± 2 years) followed as outpatients in general medicine clinic without evidence of heart disease. | Recurrent ischaemic events (nonfatal) | Autoantibodies against actin; Autoantibodies against myosin (AMA) IgG | 30 month follow up period | At late F/U 12% (n = 4) suffered MI and 28% (n = 9) required percutaneous (21%. n = 7) or surgical (6%, n = 2) revascularization due to recurrent angina but without evidence of a recurrent acute ischaemic syndrome. All MI patients +ve for both Abs at 1 and 3 months F/U. |
| Pang H, et al 2000 | Prospective case control study | Sample drawn from Institute of Cardiology, Xiehe Hospital, Tongji Medical University, Wuhan, China. | 67 study participants with AMI | Cases: 18 females and 49 males; mean age 61.6 ± 11.03 years. 20 healthy donors served as controls. | Left ventricular structure and end diastolic function, prognosis and mortality. | AMA antibodies unspecified | 6 months | Death occurred in 7 (38.89%) of the AMA-positive group, compared with 5 (10.20%) of the AMA-negative group (p < .05) of patients who had suffered MI in the acute phase. |

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| Sjoberg BG, et al 2009 | PNCC | Study participants recruited from Cardiovascular cohort of Malmo Diet and Cancer Study comprising subjects born between 1926 and 1945 living in Malmo, Sweden. | 1042 study participants | 349 incident CVD cases (200 men – 57%; mean age 60.8 ± 5 years) and 693 age and sex matched controls (395 men – 57%; mean age 60.8 ± 5 years). | Incident Cardiovascular disease event;  Fatal or non-fatal MI, fatal or non-fatal ischaemic stroke or death attributable to underlying CHD. | Anti PC IgM | Average follow up period 10.6 ± 1.7 years (1991 – 2003) | Significant associations were attained with values of Anti- PC below 17 U/ml (corresponding to the lowest 9th percentile) after adjustment (RR: 1.79, 95% CI: 1.09–2.94, p = 0.021). Male only sample: significance was evident at values below 17 U/ml (RR: 2.01, 95% CI: 1.11–3.67, p = 0.022) - not the case among women. Values below 17 U/ml also associated with ischemic stroke (RR = 3.67, 95% CI: 1.34–10.1, p = 0.01), but not with CHD. |

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| De Faire U, et al 2010 | PNCC | Study participants recruited from all 60 year olds living in County of Stockholm, invited to participate in a health screening for CVDs between 1st July 1997 and 30th June 1998. | 4232 study base (2039 men and 2193 women) | 211 incident cases (66.4% males) and 633 controls (66.4% males). | Incident CVD;  New events of CHD, fatal and non-fatal MI, hospitalization for AP, fatal and non-fatal events of ischaemic stroke. | Anti PC IgM | 5 – 7 year follow up | Excess risk for CVD only for those within the lowest quartile of anti-PC values with an RR of 1.37 (CI 0.87–2.16).  For men stronger associations were noted with increasing multivariately adjusted RRs from quartile 4 to quartile 1. Subjects within quartile 1 (values below 29.7 U/ml) had a significantly increased RR of 1.96 (CI 1.09–3.55) |

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| Fiskesund R, et al 2012 | Longitudinal study | Study participants drawn from Swedish component of European Lacidipine Study on Atherosclerosis | 226 study participants | Study participants have established hypertension. Mean age 57.7 ± 7.8 years. 50% were males. | Progression of AS over 4 years (change in cIMT) | Anti PC IgM, IgG1, IgG2 and IgA. | 4 years | No correlation between IgG2 and cIMT changes. IgG1 >75th percentile (OR 0.40, 95% CI: 0.21 -0.76, p=0.005), >90th percentile (OR 0.22, 95% CI: 0.08 – 0.60, p=0.03), >95th percentile (OR 0.24, 95% CI: 0.06 – 0.97, p=0.045) all strongly predictive of no increase in cIMT at F/U. IgA < 25th percentile OR 2.46, 95%CI: 1.22 – 4.999, p=0.012. High IgM - striking negative association with AS progression >90th percentile: OR 0.0119; 95% CI: 0.07 – 0.52, p= 0.001, >95th percentile: OR 0.05; 95% CI: 0.006–0.40, p=0.006). |

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| Caidahl K, et al 2012 | Longitudinal study | Study sample recruited from consecutive patients with ACS admitted to coronary care unit Sahlgrenska University Hospital, Gothenberg, Sweden between September 1995 and March 2001. | 1185 study participants | Median age 66 years; 30% women. | Incident MACE;  MI, acute revascularisation, stroke, cardiovascular death, AND all-cause mortality. | Anti PC IgM  Tertiles:  ≤26.4 (n = 395);  26.5 – 51.6 (n = 396);  >51.6 (n = 394). | Short (6 months), Intermediate (18 months) and long (72 months) follow up periods | Risk of MACE higher in 1st tertile than 2nd and 3rd.  6 months:  Below median HR 1.47 (95% CI: 1.09 – 1.98) p=0.01  Above median HR 1.57 (95% CI: 1.16 – 2.11) p=0.03.  18 months:  Below median HR 1.37 (95% CI: 1.06 – 1.78) p=0.02  Above median HR 1.55 (95% CI: 1.20 – 2.00) p=0.0008  72 months:  Below median HR 1.25 (95% CI: 1.02 – 1.53) p=0.03  Above median HR 1.23 (95% CI: 1.01 – 1.49) p=0.04. |

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| Kervinen H, et al 2003 | PNCC | Study participants drawn from Helsinki heart study (drawn from whole Finland not just Helsinki). | 4081 study base | Dyslipidemic Middle aged men; 233 case-control pairs matched for drug treatment & geographical area. | Incident Non-fatal MI; Coronary heart death | IgA human Heat shock protein 60 (huHSP60)  (Baseline sera) | 8.5 years | The OR for coronary risk associated with high Ab (above median) in this study population was 1.41 (95% CI: 0.96-2.05) after adjustment for age and smoking. Further adjustment for CRP level OR 1.32 (95% CI: 0.87-2.00). |
| Huittinen T, et al 2002 | PNCC | Study participants drawn from Helsinki heart study (drawn from whole Finland not just Helsinki). | 4081 study base | Dyslipidemic Middle aged men; 239 case-control pairs matched for drug treatment & geographical area. | Coronary event; Incident Non-fatal MI; Coronary heart death | IgA and IgG  human specific and Chlamydia pneumoniae (Cpn) specific HSP60;  Cpn IgA and IgG.  (Baseline sera) | 8.5 years | Only huHSP60 IgA was a significant risk factor for coronary events;  3rd quartile OR 2.20 (95% CI: 1.22 – 3.97) and 4th quartile OR 2.01 (95% CI: 1.12 – 3.62). |

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| Huittinen T, et al 2003 | PNCC | Study participants drawn from Helsinki heart study (drawn from whole Finland not just Helsinki). | 4081 study base | Dyslipidemic Middle aged men; 235 case-control pairs matched for drug treatment & geographical area. | Coronary event; Incident Non-fatal MI; Coronary heart death | IgA and IgG huHSP60 and Immuno complex bound and serum Cpn; (Measured at baseline and 3 to 6 months before event.) | 8.5 years | Compared with persistently low levels risk of coronary events 2 fold for persistently elevated (elevated levels at baseline and before coronary event) immune-complex bound and / or serum IgA antibodies to Cpn (OR 1.96; 95%CI: 1.14 – 3.36) and also for serum IgA huHSP60 (OR 2.11; 95% CI: 1.08 – 4.13). |

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| Xu Q, et al 1999 | PNCC | Participants recruited from Bruneck study (age and sex stratified random sample of all inhabitants of Bruneck aged 40 – 79 years such that 125 men and women each from the 5th to 8th decades of age were selected. Survey area located in north of Italy (Bolzano Province). | 750 subjects | Sample aged 45 to 74 years old at recruitment.   * 453 had no AS in 1990. 120 developed AS by 1995 (57.5% males). 333 did not develop AS by 1995 (39.6% males) * 297 had presence of AS in 1990. 82 stenosis in 1995 (63.4% males). 215 no stenosis in 1995 (53.5% males) | Carotid AS and mortality | Anti HSP65 antibodies unspecified | 5 year follow up (1990 to 1995) | ORs:  Small atherosclerotic lesions at 5-year follow-up: 1.00 (95%CI 0.78-1.27)  Large atherosclerotic lesions at 5-year follow-up: 1.42 (95%CI 1.02-1.98)  Survival analysis showed a significant association of baseline antibody levels and mortality after adjustment for age and sex (HR, 1.52 per 1 standard deviation (SD) unit change in HSP65 antibody titers; 95%CI 1.14-2.03. |

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| Mayr M, et al 2000 | PNCC | Participants recruited from Bruneck study (age and sex stratified random sample of all inhabitants of Bruneck aged 40 – 79 years such that 125 men and women each from the 5th to 8th decades of age were selected. Survey area located in north of Italy (Bolzano Province). | 250 study participants | 125 men and 125 women; aged 40 – 79 at recruitment. | Carotid and Femoral AS | Cpn IgA;  Helicobacter pylori (H pylori) IgG;  Cytomegalovirus (CMV) IgG. | 5 year follow up (1990 to 1995) | Immune reactions to Cpn IgA were associated with early and advances stages of AS, emerging as significant risk predictors (OR 1.11; 95%CI: 1.01 – 1.23; p=0.036. Seroprevalence of antibodies to H pylori IgG and CMV IgG were not associated with AS at any stage or significant risk predictors of AS. |

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| Veres A, et al 2002 | PNCC | Study participants drawn from Heart Outcomes Prevention Study, Canada comprising patients at high risk of CVEs. | 3168 study base | 386 cases (mean age 66.5 ± 7.0 years; 16.1% females) and 386 (mean age 66.7 ± 7.0 years; 16.1% females)age and sex matched HOPE study controls; | Cardiovascular death, Incident MI and stroke | IgG huHSP60;  IgG HSP65 | Mean follow up period 4.5 years | Anti HSP60 did not predict any of the CVEs. High levels Anti HSP65 predicted the composite outcome of incident MI, stroke or Cardiovascular death (OR 2.1 95%CI: 1.2 – 3.9, p=0.01).  High Anti HSP65 levels predicted MI (OR 2.3, 95%CI: 1.1 – 4.8, p=0.02). |

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| Kiechl S, et al 2001 | PNCC | Participants recruited from Bruneck study Survey area located in north of Italy (Bolzano Province). | 826 study participants | 415 men and 411 women aged 40 – 79 years.  -Pre-existing carotid plaques in 326 subjects.  -During 5 year F/U new carotid plaques emerged in 332/826.  -500 free of AS at baseline. 125/500 showed a manifestation of first carotid plaque at F/U. | Changes in carotid AS | Cpn IgA;  H pylori IgG;  CMV IgG | 5 year F/U  (1990 – 1995) | Risk of AS development for ALL new plaques markedly elevated among individuals with chronic infection (OR for any infection versus none 2.78, p<0.001.)  Risk of AS development for first carotid plaques markedly elevated for individuals with chronic infection (OR 4.08 95%CI 2.42 – 6.85, p<0.0001).  New carotid plaques: Cpn OR 2 (1.3 – 2.9). H pylori OR 1.5 (0.9 – 2.6). CMV OR 0.8 (0.6 – 1.5). |

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| Birnie DH, et al 2005 | Prospective observational study | Teaching hospital (Canada) | 588 consecutive emergency admission patients with acute chest pain of suspected cardiac origin. | Mean age 62.4 ± 11.9 years; 312/588 (53.2%) Males; 10/588 did not have any anti mhsp65 and 13/588 did not have anti huHsp60.  1 patient lost to F/U | CHD death, non-fatal MI, CABG, PTCA, angiogram or readmission with further cardiac ischaemic chest pain.  (Secondary events) | Anti-huHSP60 and Mycobacterial-HSP65 (mHSP65) | F/U after hospital discharge mean 304 days (range 1 – 788 days) | 277 patients had any study outcome end point: 71 had hard end points (CHD death of non-fatal MI) and 206 had soft end points (PTCA or CABG or angiography or readmission to hospital for chest pain).  Patients with increased titres of Anti-huHSP60 had an adverse prognosis (HR 1.56 (95% confidence interval 1.09 to 2.23) for any adverse event, comparing highest versus lowest quartiles. Anti-mHSP65 titres were not predictive. |

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| Ravandi A, et al 2011 | PNCC | Participants recruited from Age-Sex register of General Practitioners in Norwich, Norfolk, UK.  25,563 healthy men and women enrolled in EPIC Norfolk study between 1993 and 1997. | 748 cases and 1,723 controls | Age range 45 – 79 years.  CASES: mean age 65.7 ± 7.8 years; 62.8% males  CONTROLS: mean age 65.4 ±7.84 years; 61.6% males | Fatal and Non-fatal CAD  (Primary events) | IgG and IgM MDA-LDL;  IgG and IgM immune complexes (ICs) to oxLDL | 6 years | No significant association between tertiles (T) of IgG and IgM MDA-LDL autoantibodies and oxLDL immune complexes and CAD events respectively. Odds Ratios:  IgM Abs T2: 1.01 (0.81 – 1.26). T3: 0.91 (0.72 – 1.15). IgG Abs T2: 0.80 (0.64 – 1.00). T3: 0.94 (0.75 – 1.18). IgG IC T2: 0.89 (0.71 – 1.12). T3: 1.03 (0.82 – 1.29). IgM IC T2: 0.99 (0.79 – 1.24). T3: 0.83 (0.65 – 1.04). |

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| Gigante B, et al 2014 | Prospective cohort multicentre European study | Population based samples  (United States) | 3670 subjects | Age range 57 – 79 years. All study participants had at least 3 established cardiovascular risk factors.  Male and female sample. | cIMT progression and Ischeamic CVE. | IgM anti PC | 30 months | Low anti PC levels increase the risk of ischeamic CVE and cIMT in men. Low levels anti PC associated with highest (>90th) percentile of the fastest cIMT progression over 30 months (OR 1.41; 95% CI 1.02 – 1.9) and with an increased risk of CVE (HR 1.85; 95% CI 1.1 – 3.1). No significant association was found in women. |

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| Fredrikson Gurrilla Nordin PhD, et al 2007. | Randomised control trial (RCT) (Metropolil / Fluvastatin) | Population sample living in Malmo in 1991 (Sweden) | 751 study participants | Age range 49 – 70 years (mean 61.3 ± 5.4 years); Male and Female study population (45.5% males). | cIMT progression | IgG and IgM MDA – p210 autoantibodies | 36 months | High levels IgM associated with a more rapid progression of cIMT at 18 months (r=0.09, P<0.05) and 36 months (r=0.12, P<0.005). At 36 months, the difference in IMT progression rate per year between those with high MDA-p210 IgM levels and those with low was 0.011mm (95% CI: 0.005 – 0.018mm. P<0.0001). |
| Carrero JJ, et al 2009 | Prospective cohort study | Hospital sample (Uppsala and Stockholm) | 203 patients undergoing haemodialysis at 6 dialysis units. | Median age 66 years; 56% males. | CV deaths: MI and Ischeamia, Cardiac arrest, Sudden death, CBV accident, Cerebral haemorrhage, Aortic aneurysm, Other causes of cardiac failure. | IgM anti PC | Mean follow up 41 months (14 – 58 months) | Patients with anti PC values below median (42.1 U/ml) had a higher mortality rate even after adjustment for traditional risk factors HR 1.70 (95% CI 1.19 – 2.68). |
| Puurunen M, et al 1994 | RCT (Gemifibrozil) | Males employees from  -Finnish Railway  - Finnish Post & Telecommunications system  - 5 Industrial companies  (Helsinki Heart Study, Finland) | 135 study participants | Middle aged dyslipidaemic men;  Aged 40 – 55 years. | Cardiac death and Non-fatal MI  (Primary events) | IgG oxLDL | 5 years | Elevated levels of Anti oxLDL predictive of MI after adjustment. A 2.5 fold increased risk (95% CI 1.3 – 4.9) of cardiac end point in highest tertiles of antibody levels versus lowest tertile (p=0.005 for trend). |
| Aho K, et al 1982 | PNCC | Randomly selected population sample from 2 provinces in Eastern Finland. | 11,873 study participants in baseline survey (During F/U there were 102 CVD related deaths amongst the men and 24 CVD related deaths occurred for women. The later were selected as the cases for the PNCC study.) | 102 male cases and 102 male controls;  24 female cases and 24 female controls.  Aged 25 – 69 years. | CVD related deaths:   * Death from ischaemic heart disease (IHD) * Death from other CVD related causes. | RF unspecified  IgG ANA | 5 years | RF & IgG ANA positive in 21 cases (20 in the discordant pairs) & 7 controls (6 in the discordant pairs). RR of CVD death 3.3 (p<0.01). 4 cases positive for ANA; 17 cases positive for RF. 13/91 (14%) of IHD cases positive for ANA and RF. 8/35 (23%) of other CVD cases positive for ANA and RF. |

MONICA, Monitoring and Determinants in Cardiovascular Disease project; VIP, Vasterbotten Intervention Program; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IgA, Immunoglobulin A; aCL, Anti cardiolipin autoantibody; NS, Not significant; 95% CI, 95% Confidence interval; β2GP1, Beta 2 glycoprotein 1 autoantibody; MI, Myocardial infarction; OR, Odds ratio; SR, Screening ration; TIA, Transient ischaemic attack; HR, Hazard ratio; mmol/L, Millimole per litre; RR, Relative risk; IMT, Intima media thickness; cIMT, Carotid intima media thickness; ANA, Anti-nuclear autoantibodies; LAC – Lupus anticoagulant; F/U, Follow up; CVD, Cardiovascular disease; oxCL, Oxidised cardiolipin; aOxCL, autoantibodies to oxidised cardiolipin; CHD, Coronary heart disease; OxLDL, Oxidised low density lipoprotein; APAs, Anti phospholipid autoantibodies; CVE, Cardiovascular event; RA, Rheumatoid arthritis; Δ, Change; aPT/PS, Phosphatidylserine dependent antiprothrombin antibodies; CAD, Coronary artery disease; CBV, Cerebrovascular disease; IQR, Interquartile range; PTE, Pulmonary thromboembolism; GPL, Immunoglobulin G phospholipid units; Q4, 4th quartile; Q3, 3rd quartile; Q2, 2nd quartile; Q1 – 3, 1st to 3rd quartile; CHD, Coronary heart disease; AMI, Acute myocardial infarction; CI, Cerebral infarction; AO, Arterial occlusion of lower limb; PE, Pulmonary emboli; DVT, Deep vein thrombosis; -ve, Negative; +ve, Positive; AP, Angina Pectoris; CAC, Coronary artery calcification; LDL, Low density lipoprotein; Anti MDA-LDL, Anti Malondialdehyde modified low density lipoprotein autoantibodies; Anti Cu OxLDL, Anti Copper oxidised low density lipoprotein autoantibodies; ECG, Electrocardiogram; GENICA study, Gene environment interaction and breast cancer study; Abs, Autoantibodies; Ab, Autoantibody; E.F, Eastern Finland; W.F, Western Finland; Anti CCP, Anti cyclic citrullinated protein autoantibodies; CRP, C reactive protein; RF, Rheumatoid factor; N/A, Not applicable; AA, African American; MESA, Multi ethnic study of atherosclerosis;AF, Amaurosis fugax; IHD, Ischaemic heart disease; M, Male; F, Female; U/ml, Units per millilitre; Anti PC, Anti phosphorylcholine autoantibodies; AMA, Anti cardiac myosin autoantibodies; MACE, Major cardiovascular events; ACS, Acute coronary syndrome; HSP60, Heat shock protein 60; Cpn, Chlamydia pneumoniae; huHSP60, human heat shock protein 60; AS, Atherosclerosis; SD, Standard deviation; T, Tertile; HSP65, Heat shock protein 65; mHSP65, mycobacterial heat shock protein 65; CMV, Cytomegalovirus; H pylori, Helicobacter pylori; PTCA, Percutaneous transluminal coronary angioplasty; CABG, Coronary artery bypass graft; IC, Immune complex; EUROASPIRE, A European Society of Cardiology survey of secondary prevention of coronary heart disease; EPIC Norfolk study, European prospective investigation of cancer Norfolk study; MDA P45, Malondialdehyde peptide 45; MDA P210, Malondialdehyde peptide 210; P210 nat, Peptide 210 native; P45 nat, Peptide 45 native; PNCC, Prospective nested case control study; RCT, Randomised control study.

***Appendix 6:* Summary of data extraction table illustrating the number of positive and negative studies identified by each autoantibody subtype.**

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| **AUTOANTIBODIES**  **(TOTAL NUMBER OF STUDIES)** | **NUMBER OF POSITIVE STUDIES** | **AUTOANTIBODY SUBTYPE** | **POPULATION** | **NUMBER OF NEGATIVE STUDIES** | **AUTOANTIBODY SUBTYPE** | **POPULATION** |
| Anti PC Autoantibodies  (6 studies total:4 cohort studies and 2 PNCCs) | 6 | IgM | 6 samples comprising a mic of males and females. | N/A | N/A | N/A |
| Anti LDL Autoantibodies  (15 studies total: 2 RCTs, 5 PNCCs and 8 cohort studies) | 9 | IgG and IgM Anti MDA LDL;  IgG Anti oxLDL;  IgG and IgM MDA P210;  IgM and IgG MDA P45;  IgG P210 nat. | 2 studies utilised a male only sample whilst 7 others were mixed male and female samples. | 9 | IgA, IgG and IgM Anti oxLDL;  IgG and IgM Anti MDA LDL;  Anti oxLDL unspecified. | All samples comprise a mix of males and females. |
| Anti HSP and Anti infectious agent Autoantibodies  (8 studies total: 7 PNCCs and 1 cohort study) | 8 | IgA Anti huHSP60;  IgA Anti Cpn;  Anti HSP65 unspecified;  IgG Anti HSP65. | 8 Non-clinical samples (3 studies utilised a male only sample whilst 5 others were mixed male and female samples ) | 6 | Anti Cpn specific HSP60; IgG Anti Cpn; IgG Anti huHSP60; IgG Anti H pylori; IgG Anti CMV;  Anti mHSP65 unspecified. | 6 Non-clinical (all samples comprise a mix of males and females). |

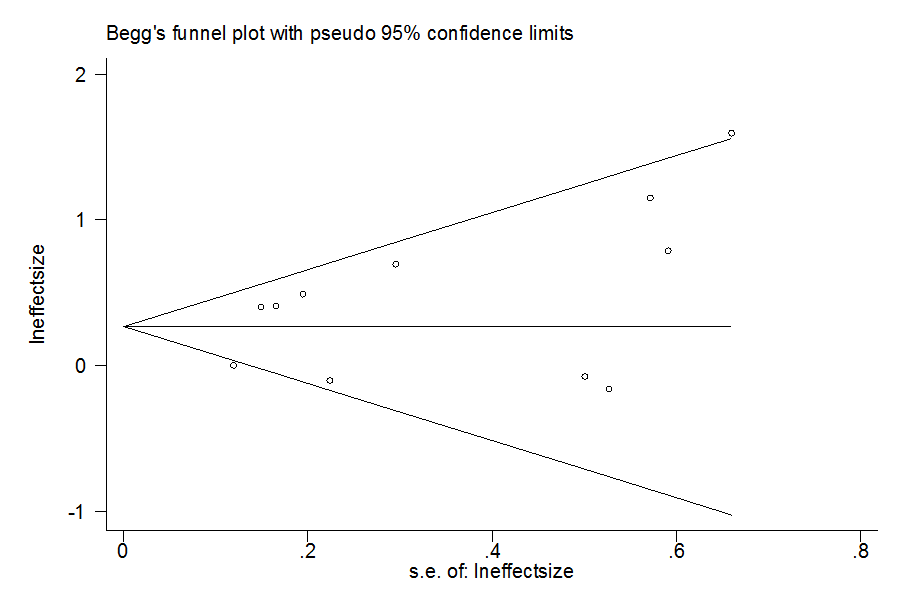
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| Anti CCP Autoantibodies  (3 studies total: 3 cohort studies) | 2 | Anti CCP unspecified;  IgG anti CCP. | 1 female sample and 1 healthy male sample. | 1 | Anti CCP unspecified | Mixed male and female population sample with and without rheumatic disease. |
| Thyroid Autoantibodies  (2 studies total: 2 cohort studies) | 2 | Thyroglobulin and thyroid microsomal autoantibodies Unspecified. | 1 study utilised a male only sample;  1 study utilised 2 samples - 1 male only and another mixed male and female cohort. | N/A | N/A | N/A |
| Anti heart muscle Autoantibodies  (2 studies total: 2 prospective case control studies). | 2 | Anti cardiac myosin autoantibodies unspecified. | 2 Non-clinical samples (all mixed male and female samples). | N/A | N/A | N/A |
| Anti-Nuclear Autoantibodies  (3 studies total: 3 cohort studies) | 2 | ANA unspecified; | 1 sample of mixed individuals with and without rheumatic diseases,  1 Non-clinical sample (both samples comprise a mix of males and females). | 1 | ANA unspecified. | 1 Non-clinical sample; comprising both males and females. |

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| Rheumatoid Factor  (3 studies total: 3 cohort studies) | 2 | IgM RF;  RF Unspecified. | 1 sample of mixed with and without rheumatic disease;  1 Non-clinical sample (both samples comprise a mix of males and females). | 1 | RF Unspecified | 1 Non-clinical sample comprising mixed male and female sample. |
| Anti phospholipid Autoantibodies  (15 studies total: 9 cohort studies, 5 PNCCs and 1 PCC) | 10 | IgG and IgM aCL;  β2GP1. | 2 studies utilised a male only sample and the remaining 8 comprising mixed male and female cohorts. | 10 | IgG, IgA and IgM aCL;  β2GP1. | 5 samples of male and female patients with a history of heart disease;  All studies used mixed male and female samples. |

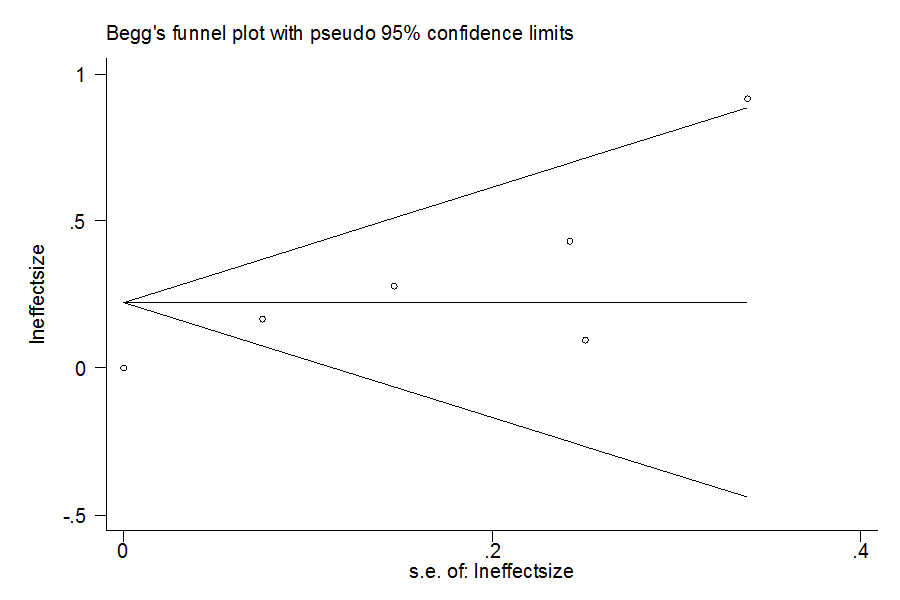
IgG, Immunoglobulin G; IgM, Immunoglobulin M; IgA, Immunoglobulin A; aCL, Anti cardiolipin autoantibody; β2GP1, Beta 2 glycoprotein 1 autoantibody; RF, Rheumatoid factor; ANA, Anti-nuclear autoantibodies; Anti PC, Anti phosphorylcholine autoantibodies; Anti LDL, Anti low density lipoprotein autoantibodies; Anti MDA-LDL, Anti Malondialdehyde modified low density lipoprotein autoantibodies; Anti oxLDL, Anti oxidised low density lipoprotein autoantibodies; Anti HSP, Anti heat shock protein autoantibodies; Anti huHSP60, Anti human heat shock protein 60 autoantibodies; Anti HSP65; Anti Heat shock protein 65 autoantibodies; Anti H pylori, Antibodies against Helicobacter pylori; Anti CMV, Antibodies against Cytomegalovirus; Anti Cpn, Antibodies against chlamydia pneumoniae; Anti Cpn specific HSP60, Antibodies against chlamydia pneumoniae specific heat shock protein 60; Anti mHSP65, Antibodies against mycobacterial heat shock protein 65; Anti CCP, Anti cyclic citrullinated protein autoantibodies; Prospective nested case control studies, PNCCs; Randomised control studies, RCTs; Prospective case control studies, PCCs.

***Appendix 7:* Meta-analysis of studies quantifying the association between a variety of Autoantibodies and Atherosclerotic Related Cardiovascular outcomes.**

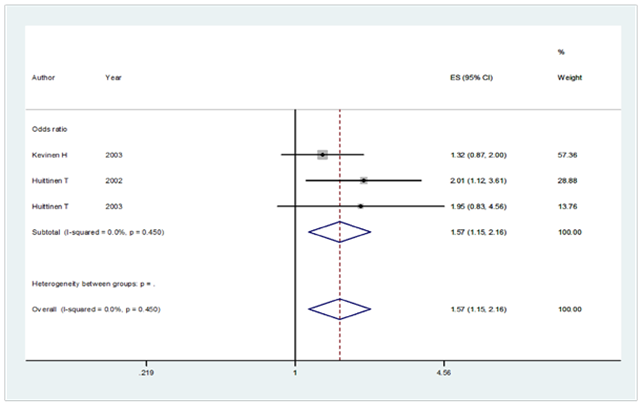
***Figure a:* Egger’s publication bias plot for meta-analysis on association between aCL IgG and AS related CVD outcomes.**



***Figure b:* Egger’s publication bias plot for meta-analysis on association between anti OxLDL IgG and AS related CVD outcomes.**



***Figure c:* A forest plot of studies quantifying association between anti huHSP60 IgA and AS related CVD outcomes.**

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1. The funnel plot appears symmetric, and there is no evidence of bias using the Egger (weighted regression) method (P for bias 0·177).
2. The funnel plot appears symmetric, and there is no evidence of bias using the Egger (weighted regression) method (P for bias 0·172).
3. The analysis included three studies comprising a total of 1,414 individuals. The small squares represent the effect size (ES) signifying the risk associated with high levels of anti huHSP60 IgA autoantibody. The 95% confidence interval (CI) for individual studies is displayed by a horizontal line and a diamond for pooled effects. P-values for heterogeneity for pooled data is shown.

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