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REVIEW

Systematic Review and Meta-Analysis of the Association Between C-Reactive Protein and Major Cardiovascular Events in Patients with Peripheral Artery Disease

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WHAT THIS PAPER ADDS

Patients with peripheral artery disease (PAD) are at substantial risk of cardiovascular events. It has previously been suggested that C-reactive protein (CRP) can assist in risk stratifying healthy individuals for medical treatment. The prognostic value of CRP in patients with established atherosclerosis is less clear. No meta-analysis has previously assessed the association between CRP and cardiovascular events in PAD patients. This study suggests that elevated CRP is predictive of cardiovascular events in PAD patients. Further study is required to establish whether targeted inhibition of inflammation reduces cardiovascular events among high risk patients with raised CRP.

Background: Patients with peripheral artery disease (PAD) are at substantial risk of cardiovascular events. There is interest in using blood markers, such as C-reactive protein (CRP), to monitor prognosis and treatment efficacy in PAD patients. The aim of this meta-analysis was to assess the association between CRP and major cardiovascular events in PAD patients.

Method: Studies evaluating the association between CRP and major cardiovascular events (myocardial infarction, stroke, cardiac revascularisation and mortality) were identified using MEDLINE and the Cochrane library. Studies that did not include participants with PAD, measure CRP, or follow-up patients for cardiovascular events were excluded. Meta-analyses of published adjusted hazard ratios (HR) were conducted using an inverse variance-weighted random effects model, and heterogeneity was assessed with the I^2 index.

Results: A total of 16 studies involving 5041 participants met the inclusion criteria for the systematic review. Eight studies were included in the meta-analyses. Summary effect estimates were reported as HR comparing higher and lower quantiles, and HR per unit increase in $\log_e$CRP. PAD patients with higher CRP had a significantly greater risk of major cardiovascular events compared with those with lower CRP (HR 2.26, 95% CI 1.65–3.09, $p < 0.001$). The HR for major cardiovascular events was 1.38 (95% CI 1.16–1.63, $p < 0.001$) per unit increase in $\log_e$CRP.

Conclusions: The present findings suggest that high circulating CRP is predictive of major cardiovascular events in PAD patients.

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INTRODUCTION

Peripheral artery disease (PAD) generally occurs as a result of atherosclerotic narrowing and thrombotic occlusion of the lower limb arteries.[1] Patients with PAD have approximately a three-fold higher risk of cardiovascular and all-cause mortality compared to those without PAD; although predicting outcomes for individual patients remains challenging.[2] There is great interest in identifying markers that can more accurately quantify cardiovascular risk and guide management of PAD patients. Age, gender, smoking, diabetes and hypertension are examples of clinical risk factors that have been associated with increased morbidity and mortality in PAD patients.[3] Other factors that assist in risk stratification include the presence of comorbid

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diseases, clinical staging of PAD and objective measures of PAD severity (such as ankle brachial index [ABI]).[2,4]

C-reactive protein (CRP) is an established marker of systemic inflammation. Results from Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) suggest that in the primary prevention setting, CRP may assist in risk stratifying participants for medical treatment.[5] However, the prognostic value of CRP in patients with established atherosclerosis who have a high risk of major cardiovascular events is less clear. It has previously been reported that patients with PAD have significantly higher levels of circulating CRP in comparison with patients with stable coronary artery disease (independent of anti-inflammatory therapy, metabolic syndrome, and smoking).[6] It has been suggested that an elevated inflammatory state may contribute to the poor prognosis of PAD patients relative to patients with other cardiovascular diseases previously reported.[7] No systematic review or meta-analysis has previously assessed the association between CRP and cardiovascular events in PAD patients. The aim of this systematic review and meta-analysis was to analyse the association between CRP and major cardiovascular events (myocardial infarction [MI], stroke, cardiac revascularisation, and mortality) in patients with PAD.

METHODS

Literature search

This systematic review was conducted following the recommendations of the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines[8] and meta-analysis of observational studies in epidemiology (MOOSE) proposal.[9] The MEDLINE/PubMed (US National Library of Medicine, Bethesda, MD, USA) database and Cochrane library were searched from inception to March 26, 2017. Databases were searched using the terms “peripheral arterial disease” or “peripheral vascular disease” or “intermittent claudication” or “claudicants” or “arterial occlusive disease”; and “C-reactive protein” or “high sensitivity C-reactive protein” or “CRP” or “hsCRP”; and “all-cause mortality” or “total mortality” or “cardiovascular events” or “MACE”, across all fields. Focused searches were also undertaken using a range of terms including “myocardial infarction”, “stroke”, “coronary heart disease” and “cardiovascular death” to identify additional studies of relevance. Lastly, manual searches were performed using the related articles function in PubMed, and through hand searching the reference lists of included studies.

Eligibility criteria

For inclusion, studies had to be observational cohort studies, and report findings for patients with established PAD as confirmed by either an ABI <0.9, diagnostic imaging such as duplex ultrasound or angiography, or previous lower limb endovascular or open surgical revascularisation. Included studies had to report baseline CRP levels in the population concerned, and report rates of cardiovascular events during follow-up. Publications were limited to those in the English language. Interventional studies, case reports, reviews, editorials, and letters were excluded.

Data extraction

Data extraction and quality assessment were conducted by two independent readers (TPS and SS). Data were extracted from the included studies and transcribed into an Excel spreadsheet using a predefined table. A consensus meeting was held to resolve any discrepancies in data. The data collected comprised participant characteristics, including age, gender, lower limb symptoms, and cardiovascular risk factors; use of statin therapy; study inclusion and exclusion criteria; sample size; method of CRP measurement (including assay sensitivity and inter/intra-assay reproducibility); duration of follow-up; and endpoint definitions. The method of statistical analysis, results, and variables adjusted for were also recorded.

Quality assessment

A quality assessment tool was devised using components of the Standard Quality Assessment Criteria for Evaluating Primary Research papers[10] and the Newcastle Ottawa scale (Appendix I).[11] The following were evaluated: (1) whether studies had a clearly defined objective; (2) whether data were collected prospectively or retrospectively; (3) the description of selection criteria; (4) the sample size [<100, 100—1000, or >1000 participants]; (5) whether participant characteristics were sufficiently described; (6) whether the CRP assay type, sensitivity, and reproducibility were described; (7) whether the primary outcome was clearly defined; (8) whether restricted analyses or statistical adjustment was performed for potential confounding variables (including inflammatory states [cancer, infection, metabolic syndrome, and recent MI/stroke]); and (9) the length of follow-up [≤ 1 year, 1—2 years, or ≥ 2 years]. No studies were excluded based on the results of the quality assessment. The criteria used to guide quality assessment are reported in further detail in Appendix I.

Statistical analysis

Meta-analyses were performed pooling studies that reported hazard ratio (HR) estimates for major cardiovascular events (as defined in the Introduction) according to baseline CRP concentration. Adjusted HRs were chosen for inclusion in the meta-analyses. Published HRs were reported both in terms of risk across quantiles, and risk per increase in CRP. Two separate analyses were conducted pooling these different effect estimates. For quantiles, the HR representing the risk in the highest CRP quantile was compared with the lowest (reference) CRP quantile. The association between CRP and cardiovascular events has previously been shown to be log-linear in large epidemiological studies (comprising individuals without pre-existing vascular disease), therefore continuous HRs were pooled that were reported on a natural logarithm scale (per unit increase in

$\log_e$CRP).[12] Where HRs were not reported in the required format, then transformations were applied, with unpublished data requested from corresponding authors. In addition, if data were not reported on a scale compatible with the meta-analysis, compatible effect estimates were requested from corresponding authors. Effect estimates were pooled using inverse variance weighting according to a random effects model. The choice of a random effects meta-analysis was based on methodological heterogeneity, in particular use of different CRP assays across studies, different CRP cut-offs for categorical HRs, and non-uniform outcome definitions. The I^2 index was used to assess the degree of heterogeneity across studies.[13] To determine sources of heterogeneity, sensitivity analyses were performed using the leave-one-out method. Assessment of publication bias using funnel plots was planned if there were a sufficient number of studies ($N \geq 10$).[14] All analyses were conducted using STATA version 14.2 (StataCorp, College Station, TX, 2009).

RESULTS

Study identification

Initial database searches yielded 668 articles after removal of duplicates (Fig. 1). Six hundred and forty nine studies were excluded based on screening their titles and abstracts. Common reasons for exclusion included that the reported cohorts were not restricted to patients with PAD and the lack of reporting of cardiovascular events.[15] Nineteen studies were evaluated for eligibility by assessment of full text publications. Three of these were excluded for specific reasons; 1) evaluation of a panel[16] of biomarkers rather than CRP alone; and 2) assessment of inflammatory biomarkers in a group of PAD patients who were included in an interventional study.[17,18] No additional studies were identified from manually searching the reference lists of the included studies. Overall, 16 studies were included in this systematic review, of which eight were suitable for inclusion in the meta-analysis.

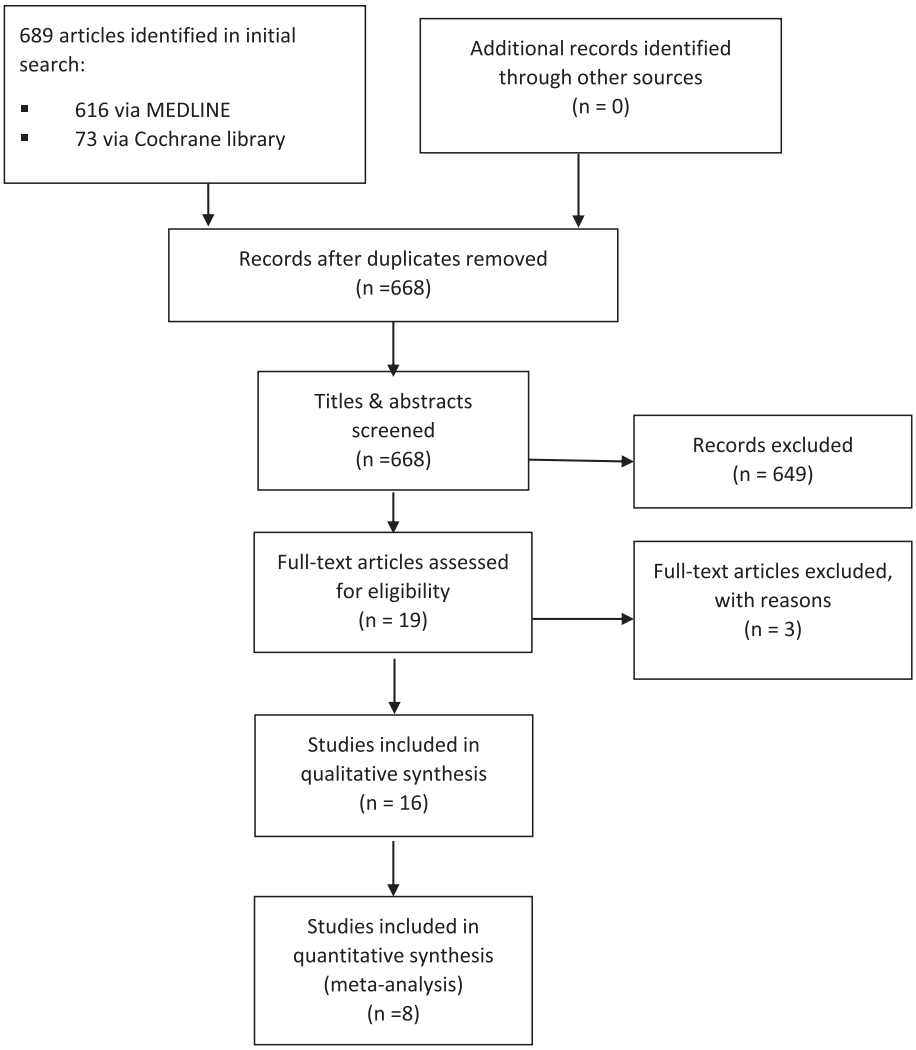

Figure 1. Outline of the systematic review and meta-analysis. A total of 689 published studies evaluating the association between CRP and major cardiovascular events were identified by searching the MEDLINE and Cochrane Library. Appraisal of the titles and abstracts identified 19 studies eligible for full text assessment. Of these, three articles were excluded and the remaining 16 studies were included for review. From these, eight studies were included in the meta-analysis.

Table 1. Study inclusion and exclusion criteria, and follow-up of outcome events.

Study	Country	Sample size	Inclusion criteria	Exclusion criteria	Endpoints assessed	Follow-up, months
Beckman *et al.* (2005)[32]	USA	110	Age ≥18 for ABI and segmental Doppler measurement	Non-skin cancer, hepatic disease, renal disease (creatinine >1.4 mg/dL), infectious disease, planned revascularisation or CLI, or MI, stroke or gangrene within 3 months of presentation	MI, stroke, revascularisation, and death	26.9[a]
Brevetti *et al.* (2008)[22]	Italy	156	ABI<0.9, IC	ABI>1.40, CLI, recent surgical intervention for CAD or PAD (<6 months); recent unstable angina, MI, stroke, heart failure, malignant neoplasia, significant hepatic, renal, or inflammatory disease (<3 months)	Fatal and non-fatal AMI, stroke	17.5[b]
Criqui *et al.* (2010)[34]	USA	397	PAD diagnosed by non-invasive lower extremity arterial testing	Deceased, could not be located, no consent	All-cause mortality, CVD mortality, and non-CVD mortality	79.2[a]
Hogh *et al.* (2008)[21]	Denmark	452	Symptomatic PAD	NR	Primary: any-cause mortality, lower limb amputation or peripheral revascularisation Secondary: thrombosis in lower limbs, MI, stroke or TIA	25.2[a]
Owens *et al.* (2007)[29]	USA	91	Patients scheduled to undergo lower extremity bypass using autogenous vein	Presence of systemic infection, use of non-autogenous conduit for infrainguinal reconstruction, unlikely to comply with follow-up, unable to provide informed consent, immunosuppressive medication, MI or stroke or major surgery ≤30 days	Graft related events Contralateral limb events Non-graft related: MACE (MI, stroke, cardiac revascularisation, any-cause death)	11.4[a]
Pros *et al.* (2013)[25]	France	1157[c]	Age >18, IC, ABI<0.90 or >1.30, positive treadmill test (in the case of normal ABI) and/or arterial stenosis >50% on Duplex ultrasound and/or angiography, or ischaemic rest pain, or ulceration and gangrene or acute lower limb ischaemia related to PAD, acute ischaemia post open bypass or endovascular procedures	Unlikely to return for follow-up, arterial occlusive disease not related to atherosclerosis, acute ischaemia without lower limb atherosclerosis	All-cause mortality or non-fatal stroke or non-fatal MI	12[d]
Rossi *et al.* (2002)[23]	Italy	51	PAD Fontaine-Leriche stages II-IV undergoing lower limb revascularisation	Severe rest ventricular dysfunction/ischaemia, high baseline cardiac risk, systemic inflammatory or infectious disease, neoplasia, peripheral revascularisation or major surgery (<6 months)	Hard: all-cause mortality, cardiac mortality, MI; Soft: new onset angina, PAD restenosis, leg amputation	24[d]
Schlager *et al.* (2009)[24]	Austria	447	Patients undergoing peripheral angioplasty for symptomatic PAD by a retrograde transfemoral approach	Missing hs-CRP levels	Primary: MACE (AMI, PCI/CABG, stroke, any-cause death, amputation, acute renal failure requiring renal replacement therapy) Secondary: MI, stroke, and amputation)	15.6[b]

Continued

Table 1-*continued*

Study	Country	Sample size	Inclusion criteria	Exclusion criteria	Endpoints assessed	Follow-up, months
Skoglund *et al.* (2014)[19]	Sweden	188	Male sex, age>45, ABI<0.90	Rest pain, previous amputation, reduced walking performance attributed to other causes, DM type I, AF	MACE (CV mortality or AMI, stroke, PCI/CABG)	71[b]
Stone *et al.* (2014)[30]	USA	118	Patients who underwent elective EVT including angioplasty or stent in lower extremities, at least one post-operative ABI, contrast angiography, or duplex imaging of the treated limb	Age<18, emergency lower limb revascularisation, lack of pre-procedural hs-CRP and BNP, lack of post-operative follow-up, patients with concomitant arterial aneurysm treatment	MACE (AMI, stroke, any-cause death) MALE (TVR, limb amputation, disease progression by 12 months after the procedure)	30[a] 15[a]
Stone *et al.* (2015)[31]	USA	82	Patients who underwent non-emergency lower extremity surgical reconstructions for PAD, pre-surgery hs-CRP and BNP testing within 30 days, at least one post-operative follow-up (duplex ultrasound examination, conventional contrast angiography, or ankle brachial index [ABI] measurements)	Age<18, emergency lower limb revascularisation, lack of pre-procedural hs-CRP and BNP, lack of post-operative follow-up, patients with concomitant arterial aneurysm treatment	MACE (AMI, stroke, any-cause death) MALE (TVR, limb amputation, disease progression by 12 months after the procedure)	26[a] 23[a]
Urbonaviciene *et al.* (2012)[20]	Denmark	463	IC and CLI	Acute lower limb ischaemia, missing α-defensin and hs-CRP	Cardiovascular or all-cause mortality	73.2[b]
Vainas *et al.* (2005)[26]	The Netherlands	387	Patients with symptomatic PAD	Recent (<6 months) vascular events or interventions, recent (<3 months) antibiotic use, renal or liver failure, inflammatory comorbidity, malignancy, suspected acute phase reaction (CRP>10 mg/L)	All-cause mortality and/or any cardiovascular event	24[b]
Vidula *et al.* (2008)[27]	Croatia	377	PAD with ABI<0.90	Dementia, nursing home residents, wheelchair bound, foot or leg amputees, recent major surgery, non-English speaking patients	Cardiovascular mortality and all-cause mortality	40.8[a]
Vrsalović *et al.* (2015)[33]	USA	319	Symptomatic PAD Fontaine IIB-IV, left ventricular ejection fraction >50%	Concomitant malignancy and autoimmune disorders	MACE (AMI, urgent PCI/CABG, stroke, and any-cause death)	24[b]
Otaki *et al.* (2017)[28]	Japan	246	PAD diagnosed by ABI or angiography, underwent endovascular intervention	Acute coronary syndrome within 3 months preceding admission, haemodialysis, and malignant disease	MACE (all-cause death and rehospitalisation because of cardiovascular disease such as cardio-embolic stroke, ischaemic heart disease, heart failure, CLI, and amputation)	30[b]

CLI = critical limb ischaemia; IC = intermittent claudication; PAD = peripheral artery disease; MACE = major adverse cardiovascular events; MALE = major adverse limb events; MI = myocardial infarction; CAD = coronary artery disease; CVD = cardiovascular disease; TIA = transient ischaemic attack; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; EVT = endovascular therapy; (hs)-CRP = (high specificity) C-reactive protein; BNP = brain natriuretic peptide; TVR = target vessel revascularisation; AF = atrial fibrillation; DM = diabetes mellitus; NR = not reported.

[a] Indicates mean.

[b] Indicates median.

[c] Derivation cohort = 640; validation cohort = 517.

[d] All participants were followed to a fixed time-point.

Study characteristics

The included studies were published between 2002 and 2017 (Table 1), with sample sizes ranging from 51 to 1157. Six studies were conducted in the USA, and the remaining studies were conducted in Sweden,[19] Denmark,[20,21] Italy,[22,23] Austria,[24] France,[25] Netherlands,[26] Croatia[27] and Japan.[28] All studies included patients who had documented PAD. Six studies included patients who underwent, or were scheduled to undergo surgical intervention for PAD.[23,24,28–31] Baseline mean ABI ranged from 0.51 to 0.69 for the nine studies reporting this information. Average follow-up duration ranged from 11.4 to 79.2 months. Endpoint definitions were not uniform throughout the studies. Five studies reported major adverse cardiovascular events (MACE), which included MI, non-fatal stroke, coronary revascularisation, and mortality.[19,24,29,32,33] Of these, only one study defined mortality as death from cardiovascular causes;[19] and two other studies included amputation[28] and acute renal failure in their definition of MACE.[24] Four studies looked at cardiovascular mortality outcomes.[20,23,27,34] The remaining studies reported a composite endpoint consisting of MI and stroke[21,22,25,30,31] or all-cause mortality and/or any coronary event (MI, coronary revascularisation, de novo unstable angina pectoris).[26] With regards to the eight studies specifically included in the meta-analysis; six included at least two of the major cardiovascular events under investigation, and the other two studies reported cardiovascular and/or all-cause mortality.[20,27]

Participant characteristics

A total of 5041 patients were investigated in the 16 included studies, with the average age of participants ranging from 61 to 75 years (Table 2). The proportion of male participants ranged from 37% to 100%. One study did not report age or patient sex.[23] The number of patients with a history of smoking (including current and past) varied (26–81%). Furthermore, the definition for smoking was not uniform across studies. Some used pack year history;[27,34] while others either included current and previous smokers in the same group[26,32] or separated them in different groups.[19,23,24] Statin use on admission ranged from 20% to 83%; 10 studies reported statin use of $\geq$50%. Participant comorbidities varied across studies. The prevalence of diabetes ranged from 19% to 54%; hypertension from 21% to 94%; and renal impairment from 6% to 24%. Only 12 studies reported details regarding previous MI or coronary artery disease; which ranged from 11% to 61%.[19–25,27–31]

Quality assessment

The quality of the included studies is reported in Table 3. Of the 16 studies, 13 were performed prospectively and three were conducted retrospectively.[30,31,34] Generally, authors provided detailed selection criteria. Twelve studies had sample sizes ranging from 100 to 1000 patients; three studies had sample sizes less than 100 and one study included greater than 1000 participants. Nine studies corrected results for age, gender, and at least two vascular risk factors, although variables included in the regression analyses were not uniform. Two studies[30,31] did not specify which variables were adjusted for, and one study[21] did not make any adjustments.

The CRP assay used was only reported in 14 studies (Table S1). Of these, 13 studies used high sensitivity CRP assays. Assay sensitivity was reported in six studies and the lower detection limit ranged from 0.02 mg/dL to 0.15 mg/L. No studies reported intra- or inter-assay reproducibility. Overall, based on the pre-specified quality assessment method, one study was considered to be of low quality; three studies of high quality, and the remaining 12 of medium quality.

Association between CRP and major cardiovascular events

The 16 included studies presented their results in different formats. Receiver operating characteristic (ROC) curve analysis and C-statistics were employed in five studies to assess the validity of high sensitivity CRP (hs-CRP) as a predictive marker for the reported endpoints.[20–22,25,34] Two studies used odds ratios (OR)[23,25] and nine studies reported HRs (Table 4).

HRs indicated the relative risk for cardiovascular events corresponding to the CRP measure used. Summary effect estimates were reported in terms of HR per unit increase of CRP, HR per unit increase in log CRP, HR per standard deviation in log CRP, and higher vs. lower quantiles. There was variation in the upper and lower CRP limits used for comparison across the studies. For example, Stone *et al.* (2014) used a cutoff of CRP $\geq$0.80 mg/dL vs. CRP $<$0.80 mg/dL,[30] while Vrsalović *et al.* (2015) and Owens *et al.* (2007) used CRP $>$5 mg/L vs. CRP$<$5 mg/L.[29,33] A significant association between elevated CRP and major cardiovascular events was noted in six studies (determined by multivariate Cox proportional hazards analysis), while there was no significant association reported in three studies.[20,22,28] In two studies, the association between CRP and major cardiovascular events was not significant in the longer term, compared with short-term follow-up ($>$2 years).[27,34] Studies that conducted ROC curve analysis and C-statistic reported conflicting results.[20–22,25,34] For example, Hogh *et al.* (2008) reported that the optimal predictive cutoff for secondary events (MI, stroke, transient ischaemic attack, and lower limb thrombosis) was 10 mg/mL hs-CRP, with a sensitivity of 63% and specificity of 54%; C-statistic of 0.62 (95% CI 0.50–0.73; $p < .05$), at a mean follow-up of 2.1 $\pm$ 1.4 years.[21] On the other hand, Brevetti *et al.* (2008) reported that there was no significant predictive value of CRP with regards to major cardiovascular events, with a C-statistic of 0.53 (95% CI 0.41–0.65; $p = .670$) at a median of 17.5 months.[22]

Data synthesis

Four studies reported HRs across categories of CRP concentration, and four studies reported the overall HR per increase in $\log_e$CRP concentration. Meta-analysis of

Table 2. Participant characteristics.

Study	*n*	Age	Male	Smoking	HTN	Cholesterol	Statin	DM	CAD	ABI	CLI	Renal impairment
Beckman *et al.* (2005)[a 32]	60	67 ± 9[b]	39 (65%)	16 (27%)	39 (65%)	NR	42 (70%)	28 (47%)	NR	0.68 ± 0.13[d]	NR	NR
Brevetti *et al.* (2008)[22]	156	67 (8)[b]	120 (77%)	126 (81%)	126 (81%)	123 (79%)	101 (65%)	75 (48%)	77 (49%)	0.69 (0.15)[b]	NR	NR
Criqui *et al.* (2010)[c 34]	259	70[b]	92%	55 (0.08)[n]	84%	54%	NR	43%	NR	NR	NR	NR
Hogh *et al.* (2008)[21]	452	66 (10)[b]	260 (76%)	265 (59%)	230 (51%)	NR	90 (20%)	61 (14%)	63 (14%)	NR	NR	NR
Owens *et al.* (2007)[29]	91	63 ± 12[b]	63 (69%)	73 (81%)	74 (81%)	NR	65 (72%)	48 (53%)	44 (49%)	0.51[b]	50 (55%)	5 (6%)
Pros *et al.* (2013)[e 25]	640	70 ± 13[b]	438 (68%)	26%	448 (70%)	336 (53%)	499 (78%)	42%	135 (21%)	[f]	NR	[g]
Rossi *et al.* (2002)[h 23]	51	NR	NR	12%/8%[i]	11 (21%)	7 (13%)	NR	14 (27%)	6 (11%)	NR	NR	NR
Schlager *et al.* (2009)[24]	447	71 (63–79)[j]	262 (59%)	30%/39%[i]	411 (92%)	385 (86%)	343 (77%)	132 (30%)	82 (18%)	NR	NR	108 (24%)
Skoglund *et al.* (2014)[k 19]	36	70 ± 6[b]	100%	25%/67%/8%[i]	26 (72%)	NR	NR	8 (22%)	13 (36%)	0.64 ± 0.18[d]	NR	[g]
Stone *et al.* (2014)[h 30]	32	65 (45–83)[j]	37%	53%	94%	72%	50%	44%	59%	NR	NR	16%
Stone *et al.* (2015)[h 31]	59	61 ± 12[b]	38 (64%)	31 (53%)	49 (83%)	48 (81%)	30 (51%)	31 (52%)	36 (61%)	NR	NR	11 (19%)
Urbonaviciene *et al.* (2012)[c 20]	126	70 ± 8[b]	60%	55%	53%	5 ± 1[l]	21%[h]	19%	25%	0.59 ± 0.18[d]	55 (44%)	NR
Vainas *et al.* (2005)[26]	387	65 (10)[b]	68%	297 (77%)	221 (57%)	321 (83%)	321 (83%)	105 (27%)	NR	NR	36 (9%)	NR
Vidula *et al.* (2008)[m 27]	76	74 (9)[b]	68%	40 ± 4[n]	87%	5 [l]	39%	38%	35%	0.65 ± 0.02[d]	NR	NR
Vrsalović *et al.* (2015)[33]	319	71 (63–78)[j]	212 (67%)	173 (54%)	277 (87%)	242 (76%)	194 (61%)	172 (54%)	NR	0.58 ± 0.14[d]	134 (42%)	[g]
Otaki *et al.* (2017)[28]	246	75 ± 9[b]	81%	NR	81%	NR	54%	44%	31%	0.60 ± 0.16[d]	NR	NR

The number of decimal places reported in the included studies varied. Where possible, data have been reported consistently in the table by rounding up of numbers where appropriate. For studies that did not report baseline characteristics of the entire sample size; stratified characteristics based on highest CRP quantile or cardiovascular events have been reported.
HTN = hypertension; DM = diabetes mellitus; CAD = coronary artery disease; ABI = ankle brachial pressure index; CLI = critical limb ischaemia; NR = not reported.

[a] PAD group.
[b] Indicates mean (standard deviation).
[c] Deceased PAD patients.
[d] Mean ABI (± SE).
[e] Derivation cohort.
[f] Reported as ABI group frequency: ≥1.3, 12.1%; 0.9–1.29, 3.6%; 0.7–0.89, 11.2%; 0.5–0.69, 25.2%, 0.3–0.49, 24.5%; <0.3, 23.3%.
[g] Reported as estimated glomerular filtration rate (eGFR) group frequency or mean eGFR.
[h] Characteristics as a function of abnormal/high/highest (quantile).
[i] Smoking history reported as percentages across groups: current (%)/former (%)/never (%)[19] or current (%)/ex-smoker (%).[23,24]
[j] Indicates interquartile range.
[k] PAD with events.
[l] Mean total cholesterol mmol/L (± SE).
[m] Age and sex-adjusted characteristics of descendants.
[n] Cigarette smoking, pack years.

Table 3. Quality of included studies.

Study	Clearly defined objective	Prospective study design	Description of selection criteria	Sample size	Participant characteristics described	CRP measurement described	Outcome well defined	Confounding variable adjustment	Follow-up, years	Overall score
Owens *et al.* (2007)[29]	Y	Y	Y	<100	Y	P	Y	P	≤1	Medium
Brevetti *et al.* (2008)[22]	Y	Y	Y	100–1000	Y	P	Y	Y	1–2	Medium
Vidula *et al.* (2008)[27]	Y	Y	Y	100–1000	Y	P	P	Y	≥2	Medium
Schlager *et al.* (2009)[24]	Y	Y	Y	100–1000	Y	P	Y	Y	1–2	Medium
Urbonaviciene *et al.* (2012)[20]	Y	Y	P	100–1000	Y	P	Y	Y	≥2	Medium
Skoglund *et al.* (2014)[19]	Y	Y	Y	100–1000	Y	P	Y	P	≥2	Medium
Stone *et al.* (2014)[30]	Y	N	Y	100–1000	Y	P	Y	P	≥2	Medium
Stone *et al.* (2015)[31]	Y	N	Y	<100	Y	N	Y	P	≥2	Medium
Vrsalović *et al.* (2015)[33]	Y	Y	Y	100–1000	Y	P	Y	P	≥2	Medium
Criqui *et al.* (2010)[34]	P	N	P	100–1000	Y	P	P	Y	≥2	Low
Vainas *et al.* (2005)[26]	Y	Y	P	100–1000	Y	P	Y	Y	≥2	Medium
Rossi *et al.* (2002)[23]	Y	Y	Y	<100	Y	P	Y	Y	≥2	High
Hogh *et al.* (2008)[21]	Y	Y	P	100–1000	Y	P	Y	N	≥2	Medium
Pros *et al.* (2013)[25]	Y	Y	P	>1000	Y	N	Y	Y	≤1	Medium
Beckman *et al.* (2005)[32]	Y	Y	Y	100–1000	Y	P	Y	Y	≥2	High
Otaki *et al.* (2017)[28]	Y	Y	Y	100–1000	Y	P	Y	Y	≥2	High

CRP = C-reactive protein; Y = yes; N = no; P = partially.

categorical data demonstrated that PAD patients with elevated CRP had a higher risk of cardiovascular events than those with a lower CRP (HR 2.26, 95% CI 1.65—3.09, $p < .001$), although follow-up of these studies was limited to ≤2 years (Fig. 2). Meta-analysis of continuous data demonstrated that the risk of major cardiovascular events increased with higher concentrations of CRP (HR 1.38 per unit increase in $\log_e$CRP, 95% CI 1.16—1.63, $p < .001$) (Fig. 3). The statistical heterogeneity across studies was low (I^2 0.00% and I^2 12.7%, respectively). Both comparisons demonstrated a strong association between CRP and major cardiovascular events, and removal of any one study in the sensitivity analysis did not alter the overall findings (Table S2). As the number of studies included was small (i.e. $N < 10$), the potential influence of publication bias could not be assessed reliably.

DISCUSSION

A number of circulating biomarkers have been studied with regards to their value in predicting adverse events in PAD.[35] Of these, CRP has been one of the most widely studied. To the authors' knowledge, this is the first meta-analysis evaluating the association between CRP and major cardiovascular events in PAD patients. The only other biomarker which has been systematically evaluated (with meta-analysis) in PAD patients is D-dimer.[36] Interestingly, the results of this other study suggested that elevated circulating D-dimer levels may be a useful predictor of arterial thrombotic events (comprising MI, ischaemic stroke, and vascular death) in the short term. The findings of the present analysis suggested that elevated CRP levels in PAD patients predicted major cardiovascular events, although it was not possible to perform sensitivity analyses based on study quality as nearly all studies included in the meta-analyses were of medium quality. PAD patients in the highest grouping of CRP concentrations had approximately double the risk of major cardiovascular events compared with those in the lowest grouping. For every unit increase in $\log_e$CRP concentration, the risk of major cardiovascular events increased by approximately 40%. It is important to note that the present results occur in the context of patients with pre-existing atherosclerosis. The association between CRP and cardiovascular events in patients without established cardiovascular disease has previously been reported in a large meta-analysis comprising 160,309 individuals.[12] The age and sex adjusted results of that study suggested that CRP had a log-linear association with coronary events, ischaemic stroke, and deaths from vascular and non-vascular disease. Interestingly, the risk ratios for cardiovascular events were attenuated after adjusting for cardiovascular risk factors and plasma fibrinogen. This suggested that the observed association between CRP and cardiovascular events may be, at least in part, secondary to traditional risk factors and other inflammatory markers. The present analyses demonstrated comparable effect estimates to this previous meta-analysis, suggesting that the prognostic value of CRP remains in individuals with

Table 4. Association between CRP and major cardiovascular events in patients with PAD.

Study	Population	Effect estimate of CRP reported in terms of	Endpoint	Follow-up, months	Effect estimate	95% CI	*p* value	Statistical adjustment
Brevetti *et al.* (2008)[22]	$n = 156$ PAD patients with ABI<0.9	Per mg/L increase	MI and stroke	17.5[a]	HR 0.88	0.60—1.29	.514	ABI, BMI, CAD, cerebrovascular diseases, and MPOx levels
Owens *et al.* (2007)[b 29]	$n = 91$ patients to undergo lower extremity bypass	CRP>5 mg/L vs. CRP<5 mg/L	Adverse graft related or CVD events (MI, stroke, cardiac revascularisation, any-cause death)	11.4[c]	HR 2.28	1.15—4.51	.018	Age, non-white race, CAD, and CLI as the reason for having lower extremity revascularisation
Schlager *et al.* (2009)[b 24]	$n = 447$ patients with PAD admitted for angioplasty[d]	Quartile 4 vs. Quartile 1	MACE (AMI, PCI/CABG, stroke, any-cause death, amputation, ARFRR)	15.6[a]	HR 2.79	1.47—5.28	<.001	Age, sex, smoking, HTN, creatinine, LDL, DM, CAD, history of MI, heart failure, AF, PAD, history of stroke, renal artery stenosis, and statin
Stone *et al.* (2014)[b 30]	$n = 118$ with lower extremity endovascular revascularisation	Elevated hsCRP>0.80 mg/dL vs. hsCRP<0.80 mg/dL	CV events (stroke, MI, CV death)	24[c]	HR 2.9	1.1—7.6	.034	NR
Vrsalović *et al.* (2015)[b 33]	$n = 319$ with symptomatic PAD and left ventricular ejection fraction >50%	CRP>5 mg/L vs. CRP<5 mg/L	MACE (AMI, PCI/CABG, stroke, death)	24[a]	HR 1.89	1.18—3.02	.008	Age, gender, traditional CVD risk factors, anaemia, polyvascular disease, CLI, statin treatment, and impaired renal function (GFR<60 mL/min)
Skoglund *et al.* (2014)[b 19]	$n = 98$ with IC and ABI < 0.9	Log (hsCRP) per SD increase	CV events (CV mortality or AMI, stroke, PCI/CABG)	71[a]	HR 1.54[f]	1.10—2.15	<.05	Age, previous AMI, BP-lowering drugs, ambulatory blood pressures
Urbonaviciene *et al.* (2012)[b 20]	$n = 118$ with IC and $n = 275$ CLI	log(e) increase in CRP	CV or all-cause mortality	73.2[a]	HR 1.22 (IC) HR 1.17 (CLI)	0.89—1.67 (IC) 0.85—1.62 (CLI)	.078	Age, gender, BMI, smoking status, DM, ABI, previous MI, total cholesterol, serum cystatin C, and statin therapy on admission
Vidula *et al.* (2008)[b 27]	$n = 377$ with ABI <0.90	log (1.5) increase in CRP	All-cause mortality	40.8[c]	HR 1.14[e]	1.05—1.24[e]	.003	Age, sex, race, DM, cigarette smoking, ABI, and number of CVD
Rossi *et al.* (2002)[23]	$n = 51$ with PAD at Fontaine II-IV	Per increase in CRP tertile	All-cause mortality, cardiac mortality, MI	24[g]	OR 2.7	1.2—6.3	.015	Age, sex, smoking, DM, HTN, cholesterol >200 mg/L, fibrinogen >400 mg/dL, Fontaine-Leriche stage, previous CAD, Eagle score index and CRP

Pros *et al.* (2013)[25]	$n = 640$ with PAD ABI <0.90 or >1.30	CRP us 70 UI vs. <6.4 UI	All-cause mortality or non-fatal stroke or non-fatal MI	12[g]	OR 2.35	1.17—4.7	.02	Age, Rutherford stage, MI, heart failure, hypercholesterolaemia, DM, ABI, GFR, previous angioplasty, anti-platelet agents, and statins
Otaki *et al.* (2017)[b,28]	$n = 246$ PAD patients who underwent endovascular intervention	Log (hs-CRP) per SD increase	MACE (all-cause mortality, cardio-embolic stroke, ischaemic heart disease, heart failure, CLI, and amputation.	30[a]	HR 1.20[f]	0.89—1.63	.23	Age, ischaemic heart disease, log BNP, 1- carboxy-terminal telopeptide

SD = standard deviation; AF = atrial fibrillation; BNP = brain natriuretic peptide; MPOx = myeloperoxidase; CLI = critical limb ischaemia; PAD = peripheral artery disease; IC = intermittent claudication; CAD = coronary artery disease; LDL = low density lipoprotein; MACE = major adverse cardiovascular events; ABI = ankle brachial index; MI = myocardial infarction; CV = cardiovascular; CVD = cardiovascular disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; (hs)-CRP = (high sensitivity) C-reactive protein; BMI = body mass index; DM = diabetes mellitus; CABG = coronary artery bypass grafting; PP = pulse pressure; BP = blood pressure; GFR = glomerular filtration rate; HTN = hypertension; ARFRR = acute renal failure requiring renal replacement therapy; NR = not reported.

[a] Indicates median.

[b] Indicates included in meta-analysis.

[c] Indicates mean.

[d] Only 224 patients included as meta-analysis, as HR comparing upper quartile with lower (reference) quartile used.

[e] Transformed to natural logarithm scale for meta-analysis using change of base formula (transformed HR 1.47, 95% CI 1.13—1.98).

[f] Transformed to HR per unit-increase in $\log_e$CRP by dividing β by SD of logCRP (Skoglund *et al.* — HR 2.05, 95% CI 1.29—3.27; Otaki *et al.* — HR 1.36, 95% CI 0.82—2.29).

[g] All participants were followed to a fixed time-point.

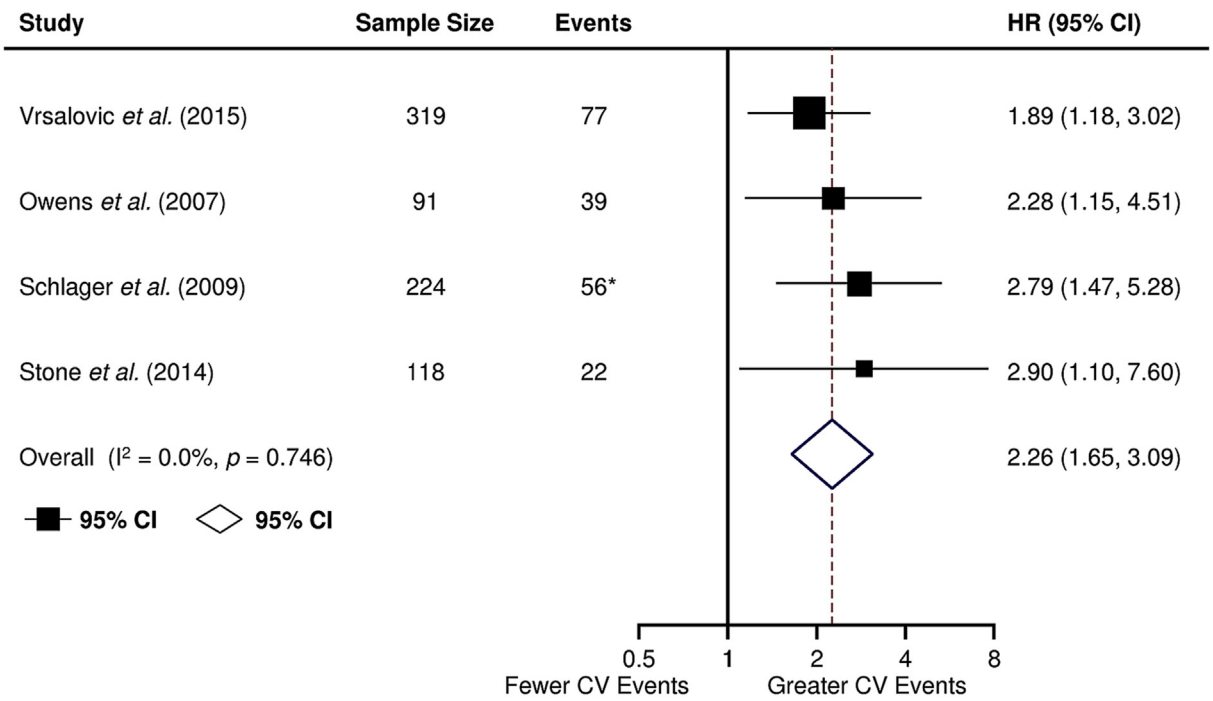

Figure 2. Forest plot illustrating hazard ratios for major cardiovascular events in PAD patients with high vs. low C-reactive protein concentrations. HR = hazard ratio; CV = cardiovascular. Square boxes indicate hazard ratios from the primary studies, for the risk of major cardiovascular events among PAD patients in upper C-reactive protein quantiles compared with patients in lower C-reactive protein quantiles. The size of the box reflects the statistical weight of the study. Horizontal lines indicate the 95% CI. The diamond represents the overall hazard ratio and 95% CI (HR 2.26, 95% CI 1.65—3.09, $p<.001$), calculated with random effects meta-analysis. *Represents number of events in upper and lower quartiles, estimated from Kaplan-Meier curves.

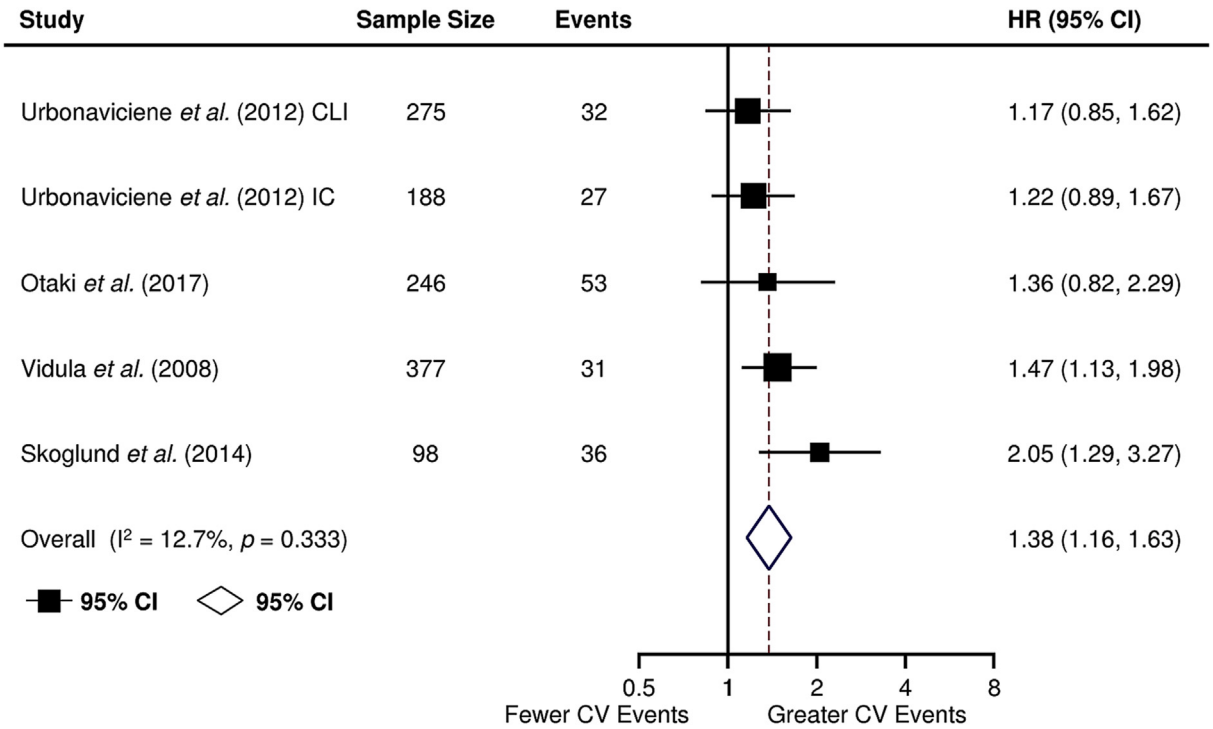

Figure 3. Forest plot illustrating hazard ratios for major cardiovascular events per increase in $\log_e$C-reactive protein among PAD patients. HR = hazard ratio; IC = intermittent claudication; CLI = critical limb ischaemia; CV = cardiovascular. Square boxes indicate hazard ratios from the primary studies, for the risk of major cardiovascular events per 1-unit increase in $\log_e$ C-reactive protein. The size of the box reflects the statistical weight of the study. Horizontal lines indicate the 95% CI. The diamond represents the overall hazard ratio and 95% CI (HR 1.38, 95% CI 1.16—1.63, $p < .001$), calculated using random effects meta-analysis.

established vascular disease. However, it is unclear whether treatments which selectively reduce CRP confer cardiovascular benefits.

Previously published Mendelian randomisation studies suggest that genetically raised concentrations of CRP are not associated with the development of conventional cardiovascular risk factors and risk of coronary events, suggesting that it is unlikely CRP plays a causal role in atherosclerosis.[37,38] However, evidence from this systematic review suggests that high levels of CRP may help identify those with existing atherosclerosis, who are at increased risk of cardiovascular events. Given the high absolute cardiovascular risk of all PAD patients, it is unlikely that CRP can be used to direct current medical treatment of atherosclerosis, as intensive cardiovascular risk control is currently recommended for all PAD patients. However, elevated CRP may assist in identifying patients who are at higher risk of cardiovascular events after surgical interventions and may benefit from closer follow-up, as reported by Owens *et al.* (2007) and Stone *et al.* (2014).[29,30] In addition, inflammatory markers such as CRP may be useful in identifying vascular patients with residual risk, in whom novel anti-inflammatory drugs can be trialled. Results from the Improved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) trial suggested that the addition of ezetimibe to statin therapy significantly reduced vascular events compared with statin therapy alone. Of note, the statin and ezetimibe group had greater reductions in hs-CRP in comparison with the statin only group.[39] However, the underlying question this study and previous studies pose,[5] is whether selective suppression of inflammation results in improved cardiovascular outcomes. The Canakinumab Anti-inflammatory Thrombosis Outcomes trial (CANTOS) is testing whether the interleukin-1β (IL-1β) inhibitor canakinumab reduces cardiovascular events in patients with stable coronary artery disease, who have higher vascular risk based on elevated hs-CRP ($>$2 mg/L).

It is possible that use of a single biomarker may be inadequate to estimate prognosis in PAD patients. A multimarker approach may be more appropriate. Urbonaviciene *et al.* (2012) reported that PAD patients with both high α-defensin and high hs-CRP concentration were approximately five times more likely to develop cardiovascular events than those with either elevated α-defensin or high hs-CRP alone.[20] A range of other inflammatory markers including interleukin-6, d-dimer, fibrinogen, and intercellular adhesion molecule-1 have been linked with poorer lower extremity performance and adverse lower limb bypass graft related events.[35] Further studies are required to identify their usefulness in risk stratification for cardiovascular events in PAD patients. If biomarkers do become more commonly used in clinical practice, it is likely they will still need to be combined with established clinical risk factors. For example, Beckman *et al.* (2005) reported that CRP is likely to be more predictive of cardiovascular events (MI, stroke, and death) when combined with other risk factors, such as ABI.[32] Larger multi-centre studies are warranted to further validate the use of a multi-marker approach to predict adverse events.

This study has a number of limitations. Firstly, a limited number of studies were identified. Two studies reported ORs and could not be included in the meta-analysis which further restricted the sample size. Some authors have suggested that CRP may have a greater predictive value during shorter follow-up durations, or when combined with other established risk factors such as ABI, diabetes, and metabolic syndrome.[6] It was not possible to stratify this meta-analyses based on such factors. However, previous studies including patients with PAD report that CRP is predictive of cardiovascular events in patients with and without diabetes.[12] Variables such as ABI were not uniformly adjusted for in multivariate analyses and it was not possible to identify which variables were adjusted for in two studies.[30,31] It is also important to note that CRP is a non-specific biochemical marker of inflammation and elevated levels could possibly be attributed to existing comorbidities in some participants. Factors that were not uniformly adjusted for which could have influenced CRP levels include cancer, obesity, presence of infection, smoking, and recent MI.[40] Only 11 of the 16 studies excluded participants with underlying inflammatory conditions suspected to elevate CRP levels. Furthermore, there was variation in the method of CRP measurement across studies. Although 13 of the 14 studies that reported measurement methods used high sensitivity assays, only six studies published detection limits. No studies reported intra- and inter-assay reproducibility. Identification of optimal risk stratification CRP cutoff points was outside the scope of this study. Previous studies have suggested that the very low ($<$0.5 mg/L) and very high ($>$10 mg/L) levels of hsCRP provide the most useful prognostic information for atherosclerotic risk assessment.[41] Given the log-linear association between CRP and cardiovascular events, most of the risk occurs with small changes in the low-normal CRP concentrations.[12] Statins reduce the risk of cardiovascular events in patients with PAD, and have also been shown to lower circulating CRP concentrations. It was not possible to adjust for statin use on admission, although statin use in reporting studies was generally high. Thus, it is likely that the level of inflammation in the present study population is not a true reflection of inflammation in general for PAD patients.[6] As alluded to earlier, the definition of endpoints were heterogenous across individual studies. Composite endpoints such as MACE have been inconsistently defined in cardiovascular research.[42] The use of different MACE definitions across studies may have potentially influenced the magnitude of associations reported, but is unlikely to have altered the direction of the associations. We can not exclude the possibility that the reported summary estimates are an underestimate or overestimate of the true association.

Conclusion

This meta-analysis suggests that PAD patients with elevated CRP have a higher risk of major cardiovascular events.

Large, randomised studies are awaited to clarify whether targeted inhibition of inflammation reduces cardiovascular events among high risk patients with raised CRP.

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CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2017.05.009.

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