



Plasma Biomarkers to Predict Cardiovascular Outcome in Patients With Peripheral Artery Disease

A Systematic Review and Meta-Analysis

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OBJECTIVE: Patients with lower extremity peripheral artery disease (PAD) are at increased risk of major adverse cardiovascular events. Numerous plasma biomarkers have been investigated in lower extremity PAD, but none are used for clinical risk assessment. We aimed to provide a comprehensive overview of biomarker testing in PAD as a first step to improve risk stratification.

APPROACH AND RESULTS: A systematic literature review in MEDLINE/PubMed, Cochrane, and Embase was performed, identifying all studies investigating plasma biomarkers in association with cardiovascular events and mortality in lower extremity PAD. Forty-seven studies comprising 21 473 PAD patients met our criteria and were included. Effect estimates were provided by the studies based on a minimum follow-up of 1 year. Meta-analyses were performed by pooling studies per biomarker for each end point. Patients with increased high-sensitivity CRP (C-reactive protein) levels had a relative risk of 1.86 (1.48–2.33) for major adverse cardiovascular events and a relative risk of 3.49 (2.35–5.19) for mortality. Increased fibrinogen and D-dimer levels were associated with an increased relative risk of mortality of 2.08 (1.46–2.97) and 2.22 (1.24–3.98), respectively. Additionally, patients with increased NT-proBNP (N-terminal pro-B-type natriuretic peptide) and high-sensitivity cTnT (cardiac troponin T) levels were at an even higher risk of mortality with relative risks of 4.50 (2.98–6.81) and 3.33 (2.70–4.10), respectively.

CONCLUSIONS: This systematic review identifies promising biomarkers representing different pathophysiological processes implicated in lower extremity PAD, including high-sensitivity CRP, neutrophil-lymphocyte ratio, fibrinogen, D-dimer, NT-proBNP, and high-sensitivity cTnT. Clinical implementation should be preceded by a management study to test the utility of a combination of these markers for individual risk stratification. Ultimately, this may contribute to tailored treatment and increased effectiveness of current treatment strategies in PAD.

GRAPHIC ABSTRACT: A [graphic abstract](#) is available for this article.

Key Words: lower extremity ■ meta-analysis ■ peptide fragments ■ peripheral artery disease ■ risk assessment

Peripheral artery disease (PAD) is a manifestation of systemic atherosclerosis resulting in progressive blood flow restriction in peripheral arteries, ultimately leading to atherothrombosis. Although PAD can occur in multiple arterial beds, the focus in this systematic review will be on lower extremity PAD. Like any atherosclerotic disease, the prevalence of lower extremity PAD

continues to increase worldwide, now affecting 5% of the population aged 45 to 49 years up to 18% at the age of 85 to 89 years in high-income countries.¹ Risk factors contributing to this high prevalence include hypertension, obesity, hyperlipidemia, diabetes mellitus, and smoking.² Lower extremity PAD patients have increased mortality rates compared with non-PAD populations, mainly

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Nonstandard Abbreviations and Acronyms

ADMA	asymmetrical dimethylarginine
CRP	C-reactive protein
cTnT	cardiac troponin T
GDF-15	growth differentiation factor 15
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
hs-cTnT	high-sensitivity cardiac troponin T
IL	interleukin
MACE	major adverse cardiovascular event
MPO	myeloperoxidase
NLR	neutrophil-lymphocyte ratio
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAD	peripheral artery disease
RR	relative risk
SAA	serum amyloid A

due to higher incidences of myocardial infarction and stroke.^{3–6} These patients typically have more extensive coronary artery disease and increased progression of atherosclerosis.⁷

While on average the risk of cardiovascular complications including death is increased, there is marked heterogeneity among patients. Individual risk estimation in PAD patients is based on the Fontaine or Rutherford classification in combination with the ankle-brachial index, which is the current gold standard for vascular severity classification. These classifications divide lower extremity PAD into 2 major groups: namely patients with claudication (Fontaine I and II) and patients with chronic limb threatening ischemia (Fontaine III and IV). Patients with claudication tend to be the mild PAD group, whereas patients with chronic limb-threatening ischemia are the more severe PAD patients. To improve the risk estimation in lower extremity PAD as a whole, many plasma biomarkers have been investigated. Since systemic atherosclerosis is characterized by chronic inflammation, most of the investigated biomarkers are inflammation related. A recent systematic review specifically focused on CRP (C-reactive protein) and showed an association with major cardiovascular events in lower extremity PAD populations.⁸

Coagulation markers, such as D-dimer and fibrinogen, have also been extensively studied. A systematic review conducted in 2013 found a 2-fold increased risk of arterial thrombotic events and cardiovascular mortality in subjects with lower extremity PAD and increased levels of D-dimer. Short-term prediction of cardiovascular events was found to be more successful compared with long-term prediction (>4 years).⁹ The third group of biomarkers are cardiac markers including NT-proBNP (N-terminal pro-B-type natriuretic peptide)^{10,11} and

Highlights

- Biomarkers are needed to identify high-risk lower extremity peripheral artery disease patients who could benefit from personalized medical treatment strategies targeting coagulation, lipid metabolism, and inflammation.
- Plasma biomarker high-sensitivity CRP (C-reactive protein) may be used to increase effectiveness of major adverse cardiovascular event risk stratification in lower extremity peripheral artery disease.
- Neutrophil-lymphocyte ratio, fibrinogen, D-dimer, NT-proBNP (N-terminal pro-B-type natriuretic peptide), high-sensitivity cardiac troponin T, and adiponectin are promising biomarker candidates for mortality prediction in lower extremity peripheral artery disease.
- Clinical implementation should be preceded by a management study to test the utility of a combination of these markers for individual risk stratification.

high-sensitivity cTnT (cardiac troponin T; hs-cTnT),¹⁰ but these biomarkers have not been reviewed systematically in lower extremity PAD thus far. Apart from these 3 major groups of plasma biomarkers, there are >30 proteins that were found to be associated with cardiovascular risk and increased mortality.

In this systematic review and meta-analysis, we provide a comprehensive overview of state of the art biomarker testing in PAD, as a first step to improved risk assessment.

METHODS

We conducted and reported this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.¹² The protocol was published on PROSPERO (International Prospective Registry of Systematic Reviews; submitted November 4, 2019; awaiting number; <https://www.crd.york.ac.uk>).

Literature Search

This systematic review used MEDLINE/PubMed, Cochrane, and Embase to identify all cohort studies and case-control studies on plasma biomarkers in populations with PAD. All databases were searched systematically up to April 2019 by 2 independent researchers using identical search terms. Used terms were “peripheral artery disease,” “peripheral vascular disease,” or “intermittent claudication” or “critical limb ischemia” or “critical limb-threatening ischemia” and “plasma biomarker” and “cardiovascular outcome” or “cardiovascular mortality” or “mortality” or “cardiovascular event” or “myocardial infarction” or “stroke” or “limb loss” or “amputation.” When available, we also included the attached MeSH term to the search and also applied the following filters: publication date from January 2000 and later, studies conducted on humans, and English language. To prevent missing studies that did not have “plasma

biomarker” as a key word, we added the specific names of biomarkers to the search and also performed hand searching. Although the focus of this review is on lower extremity PAD, we used the search term PAD as this term was more commonly used in the past. Both researchers performed eligibility assessment. Eligible studies were screened on title and abstract first using the inclusion and exclusion criteria.

Study Eligibility

In this systematic review, case-control studies and cohort studies, both prospective and retrospective analyzing patients with lower extremity PAD, were included. Lower extremity PAD had to be confirmed with an ankle-brachial index below 0.90 or by the use of medical records showing that patients had undergone an intervention for lower extremity PAD. Furthermore, only studies that investigated a plasma biomarker and had defined a cardiovascular end point after at least 1 year of follow-up were included. Biomarkers that were reported in multiple studies (>2) were included in this review. Investigation of a non-plasmatic or calculation-based biomarker and studies on a population other than a PAD population and the absence of a cardiovascular outcome were reasons for exclusion.

Data Extraction

Two authors independently performed the search, selection of studies, data extraction, and assessment of quality (B.K. and L.W.). Disagreements were resolved in a consensus discussion. A third author (A.t.C.-H) checked for accuracy and made the final decision. Data were systematically extracted from the full-text articles and were categorized per biomarker. Duplicate publications of the same study were checked for additional data. Categorized data consisted of author's name and publication year, period, and location of investigation, study design and study population (total number of patients and distribution of intermittent claudication and chronic limb-threatening ischemia), setting and follow-up duration, outcome, results (adjusted), and conclusion.

Quality Assessment

Risk of bias of the included studies through assessment of the methodological quality was performed using the Newcastle Ottawa Assessment Scale.¹³ Cohort studies were scored on the following topics: representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at the start of study, comparability of cohorts on the basis of the design or analysis, assessment of outcome, follow-up length, and adequacy of follow-up. Case-control studies were scored on other topics: adequacy of case definition, representativeness of the cases, selection of controls, definition of controls, comparability of cases and controls on the basis of the design or analysis, ascertainment of exposure, method of ascertainment between cases and controls, and nonresponse rate. Based on these topics, studies were allocated stars, ranging from 0 (worst possible) to 9 (best possible).

Analysis

The total number of events and the total population within a study were collected, and risk ratios were calculated across

different thresholds. Dichotomous outcomes were expressed as relative risks (RRs) with their 95% CIs. All results in the meta-analyses were unadjusted and may, therefore, differ with the adjusted hazard ratios (HRs) as presented in some of the underlying studies. If a study did only report time-to-event curves without exact numbers of events within a group, the event rate was estimated by using the reported Kaplan-Meier curves. Meta-analyses were performed by pooling studies per biomarker for each outcome using the Mantel-Haenszel method in a random effects meta-analysis model. Heterogeneity among included studies was explored qualitatively and quantitatively by using the χ^2 test of heterogeneity and I^2 statistics. In cases with $>50\%$ heterogeneity, sensitivity analyses were performed. All meta-analyses were performed using Review Manager (computer program, version 5.3; Copenhagen, Nordic Cochrane Centre, Cochrane Collaboration, 2014). $P<0.05$ is significant.

RESULTS

Study Identification

The full search was performed in 3 databases and resulted in 1688 hits, of which 1608 were excluded after title and abstract inspection. The remaining 80 articles were screened by full-text inspection, leading to exclusion of another 15 articles. The remaining 65 articles were then clustered by specific type of biomarker. Of the 65 remaining articles, 18 were on biomarkers that were only studied once; these specific biomarkers did not occur in any of the other studies. We, therefore, chose to just refer to these studies and not to include them in our qualitative or quantitative assessments (Figure 1).

Study Characteristics

The 47 studies selected were performed all over the world but were mostly conducted in Western countries. The period in which these studies were performed ranged from 1990 to 2015. Most studies ($n=41$) had a cohort study design, of which 10 were retrospectively analyzed. The remaining 6 studies had a case-control study design. Study setting could be divided into 4 categories: random (outpatients and inpatients), inpatients only, pre-intervention, and post-intervention. The mean/median follow-up was at least 12 months (Tables I through IV in the [Data Supplement](#)).

The 47 included studies were sorted per biomarker; several studies appeared in different groups as they investigated multiple biomarkers. The following biomarkers were studied: 13 studies investigated high-sensitivity CRP (hs-CRP),^{11,14–26} 2 reported on GDF-15 (growth differentiation factor 15),^{14,27} 2 on MPO (myeloperoxidase),^{24,28} 6 on the neutrophil-lymphocyte ratio (NLR),^{29–34} 2 assessed SAA (serum amyloid A),^{22,35} 6 reported on fibrinogen,^{19,35–39} another 7 assessed D-dimer,^{22,25,38,40–43} 7 investigated NT-proBNP,^{11,15,17,44–47} 5 hs-cTnT,^{10,44,45,48,49} 4 asymmetrical dimethylarginine (ADMA),^{50–53} 4 assessed

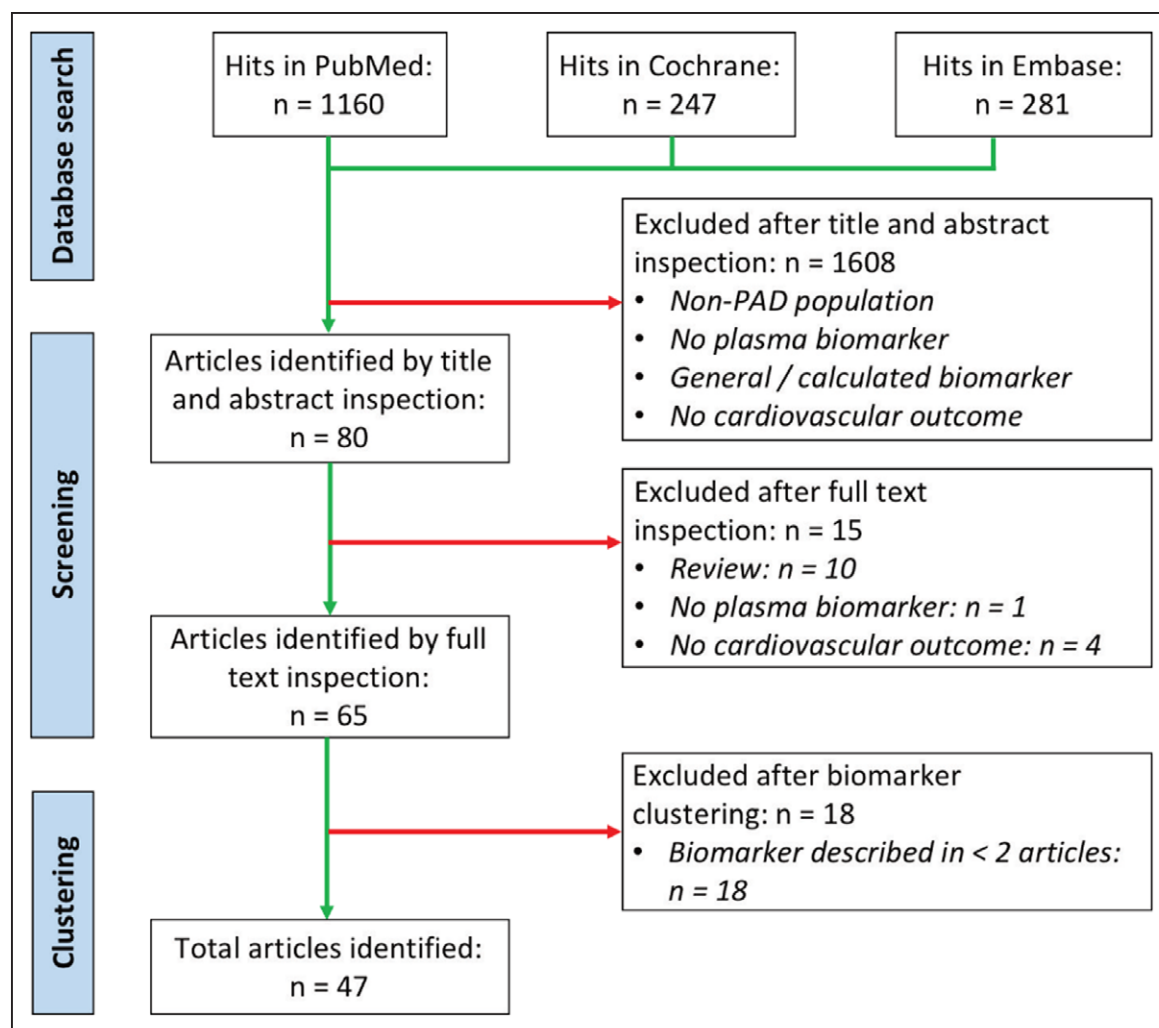


Figure 1. Search and study selection.

PAD indicates peripheral artery disease.

adiponectin,^{54–57} and 3 homocysteine.^{18,22,58} Investigated outcomes were heterogenous across studies but mainly included all-cause mortality, cardiovascular mortality, cardiovascular events, major adverse cardiovascular events (MACE), major adverse limb events, coronary events, amputation-free survival, amputation, reintervention for lower extremity PAD, and graft patency. Studies investigating hs-CRP, fibrinogen, D-dimer, NT-proBNP, hs-cTnT, and adiponectin provided sufficient data to perform meta-analyses. The remaining biomarkers did not have sufficient data to create forest plots and are, therefore, not visualized.

The 18 articles that were not selected studied α -defensin,²¹ matrix metalloproteinase 10,⁵⁹ galectin-3,⁶⁰ soluble tumor necrosis-like weak inducer of apoptosis,⁶¹ ferritin,⁶² activated protein C–protein C inhibitor complex,⁶³ angiotensin-related growth factor,⁶⁴ fatty acid-binding protein 4,⁶⁵ alkyl-phosphatidylcholine and alkenylphosphatidylcholine lipids,⁶⁶ high-density lipoprotein cholesterol,⁶⁶ malondialdehyde-modified low-density lipoprotein,⁶⁷ lipoprotein-associated

phospholipase A2,⁶⁸ cardiac troponin I,⁶⁹ phosphate,⁷⁰ carboxy-terminal telopeptide of type I collagen,¹⁵ cholinesterase,⁷¹ eicosapentaenoic acid/arachidonic acid ratio,⁷² or endothelin-1.⁷³

Patient Characteristics

A total number of 21 473 lower extremity PAD patients were investigated in the studies, with an average age between 56 and 75 years. Eight thousand three hundred seventy-eight patients were classified as claudicants, 5313 patients had chronic limb-threatening ischemia, and for another 7782, lower extremity PAD severity was not documented. The classifications for each biomarker are shown in Table 1.

Quality Assessment

The results of quality assessment are shown in Table 2 for the cohort studies and in Table 3 for the case-control studies. In general, the cohort studies scored higher

Table 1. Peripheral Artery Disease Severity and Average Age of the Patient Populations for Each Biomarker

Biomarker	No. of Studies	Patients, n	IC, n	CLTI, n	Unknown, n	Age, y
hs-CRP	13	3866	1873	879	1114	64–75
GDF-15	2	632	260	362	10	67–70
MPO	2	562	451	90	21	67
NLR	6	3108	798	1754	556	64–74
SAA	2	488	41	50	397	63–69
Fibrinogen	6	2879	1592	412	875	62–72
D-dimer	7	2493	114	9	2370	56–72
NT-proBNP	7	1312	969	182	161	64–75
hs-cTnT	5	1676	1019	657	0	58–72
ADMA	4	2119	132	106	1881	69–74
Adiponectin	4	1229	736	493	0	66–71
Homocysteine	3	1109	393	319	397	69–76

ADMA indicates asymmetrical dimethylarginine; CLTI, chronic limb-threatening ischemia; GDF-15, growth differentiation factor-15; hs-cTnT, high-sensitivity cardiac troponin T; hs-CRP, high-sensitivity C-reactive protein; IC, intermittent claudication; MPO, myeloperoxidase; NLR, neutrophil-lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SAA, serum amyloid A.

compared with the case-control studies due to the lack of representativeness of the patients. In most cases, the exposed cohort was representative for the general lower extremity PAD population. Studies that did not score a star on this topic had either a population of only male patients or had a specific patient population such as patients undergoing a lower extremity bypass intervention.^{25,26,33,37,45,48,49,54,57} All studies performed well in the selection of the nonexposed cohort, ascertainment of exposure, and demonstration of the absence of outcome at the start of the study. Also, only studies with a follow-up >1 year were selected, and loss to follow-up was minimal in all studies. Only 1 study did not correct for risk factors,²⁴ and 10 studies did not elaborate on the assessment of outcome (mortality).^{20,23,26,27,29,33,47,54,57,58} For the case-control studies, almost all studies provided a clear description of the cases and controls. The selection of controls was imperfect as some of these populations were considered hospital controls instead of community controls. Furthermore, the ascertainment of exposure was not noted in 2 studies,^{14,51} and neither was the method of ascertainment for cases and controls. Lastly, the nonresponse rate was not shared in 3 studies.^{10,14,18}

Inflammatory Markers and Cardiovascular Outcomes in Lower Extremity PAD Patients

An overview of all outcomes for the biomarkers is shown in Table 4.

High-Sensitivity CRP

A total of 13 studies investigated hs-CRP levels and cardiovascular outcome in patients with lower extremity PAD. Twelve studies were of good methodological quality, and only 1 was of poor quality. Hazard ratios or RRs were provided in most studies, and, when possible,

a multivariate analysis was performed to control for bias. The overall population in which hs-CRP was measured consisted of mostly claudicants (1873 patients) but also more severe PAD (879 patients). Both newly diagnosed PAD patients and patients who already underwent revascularization of the lower limbs were included. All-cause mortality was most widely used as outcome, the results of which are shown in a forest plot (Figure 2A). Overall, the risk ratio for all-cause mortality in patients with elevated hs-CRP levels was 3.49 (2.35–5.19) without heterogeneity between studies. Cardiovascular mortality specifically was reported in 3 studies^{21,22,25} but did not show a significant increase in patients with higher hs-CRP levels. As shown in Figure 2B, Patients with high hs-CRP levels also had a higher risk ratio for MACE compared with patients with low hs-CRP levels (RR, 1.86 [1.48–2.33]).

GDF-15

The stress-responsive cytokine GDF-15 is produced among others by macrophages, vascular smooth muscle cells, and adipocytes.⁷⁴ Only 2 studies investigated GDF-15 as a biomarker to predict outcome in lower extremity PAD populations.^{14,27} Both studies were qualitatively assessed as good and had a combined population of 632 patients (260 claudication patients, 362 chronic limb-threatening ischemia patients, and 10 patients missing). Included patients either were undergoing an iliofemoral endarterectomy or were not eligible for conventional revascularization. One study showed a decreased risk of amputation-free survival in patients with elevated GDF-15 levels, with HRs ranging from 1.57 (1.02–2.41) to 1.78 (1.18–2.69).²⁷ The second study used all-cause mortality as outcome and showed higher levels of GDF-15 in patients who died, compared with patients who survived during the follow-up period (5749.6 versus 2849.4 pg/mL; $P=0.028$).¹⁴

Table 2. Quality Assessment of Cohort Studies by the Use of the Newcastle Ottawa Assessment Scale

	1. Representativeness of the Exposed Cohort	2. Selection of the Nonexposed Cohort	3. Ascertainment of Exposure	4. Demonstration That Outcome of Interest Was Absent at Start	5. Comparability of Cohorts on the Basis of the Design/Analysis	6. Assessment of Outcome	7. Was Follow-Up Long Enough for Outcomes to Occur	8. Adequacy of Follow-Up of Cohorts	9. Total Number of Stars
Otaki et al ¹⁵	●	●	●	●	●	●	●	●	9
Vrsalović et al ¹⁶	●	●	●	●	●	●	●	●	9
Stone et al ¹⁷	●	●	●	●	●	●	●	●	9
Bleda et al ¹⁹	●	●	●	●	●	●	●	●	9
Owens et al ²⁰	●	●	●	●	●	●	●	●	8
Urbonaviciene ²¹	●	●	●	●	●	●	●	●	9
Criqui et al ²²	●	●	●	●	●	●	●	●	9
Vainas et al ²⁶	●	●	●	●	●	●	●	●	7
Brevetti et al ²⁴	●	●	●	●	●	●	●	●	7
Mueller et al ⁴⁶	●	●	●	●	●	●	●	●	9
Shadman et al ⁴⁷	●	●	●	●	●	●	●	●	9
Clemens et al ⁴⁴	●	●	●	●	●	●	●	●	8
Bosevski et al ³⁸	●	●	●	●	●	●	●	●	7
Komarov et al ⁴³	●	●	●	●	●	●	●	●	9
Vidula et al ⁴²	●	●	●	●	●	●	●	●	9
Vidula et al ⁴¹	●	●	●	●	●	●	●	●	9
Schlager et al ²³	●	●	●	●	●	●	●	●	8
Musicant et al ²⁵	●	●	●	●	●	●	●	●	8
De Haan et al ²⁷	●	●	●	●	●	●	●	●	8
Owens et al ³⁵	●	●	●	●	●	●	●	●	9
Amrock and Weitzman ³⁰	●	●	●	●	●	●	●	●	9
Erturk et al ³²	●	●	●	●	●	●	●	●	9
Pourafkari et al ²⁹	●	●	●	●	●	●	●	●	8
Luo et al ³¹	●	●	●	●	●	●	●	●	9
Chan et al ³³	●	●	●	●	●	●	●	●	8
Gonzalez-Fajardo ³⁴	●	●	●	●	●	●	●	●	9
Haslacher et al ²⁸	●	●	●	●	●	●	●	●	9
Altes et al ³⁶	●	●	●	●	●	●	●	●	9
Bartlett et al ³⁷	●	●	●	●	●	●	●	●	8
Doweik et al ³⁹	●	●	●	●	●	●	●	●	9
Heneghan and Sultan ⁵⁸	●	●	●	●	●	●	●	●	8
Owens et al ⁵⁴	●	●	●	●	●	●	●	●	7
Urbonaviciene ⁵⁵	●	●	●	●	●	●	●	●	9
Dieplinger et al ⁵⁶	●	●	●	●	●	●	●	●	9
Komai and Juri et al ⁵⁷	●	●	●	●	●	●	●	●	7
Falkensammer ⁴⁵	●	●	●	●	●	●	●	●	8
Szczeklik et al ⁴⁸	●	●	●	●	●	●	●	●	8
Linnemann et al ⁴⁹	●	●	●	●	●	●	●	●	8
Staniszewska ⁵⁰	●	●	●	●	●	●	●	●	9
Wilson et al ⁵²	●	●	●	●	●	●	●	●	9
Mittermayer et al ⁵³	●	●	●	●	●	●	●	●	9

●, present; ●, partially present; ●, absent.

Myeloperoxidase

This white blood cell-derived inflammatory enzyme is classified as belonging to the peroxidases. MPO generates

reactive oxidants and radical species that initiate oxidative degradation of lipids. MPO is mostly expressed in neutrophils⁷⁵ but can also be found in monocytes and

Table 3. Quality Assessment of Case-Control Studies by the Use of the Newcastle Ottawa Assessment Scale

	1. Is the Case Definition Adequate	2. Representativeness of the Cases	3. Selection of Controls	4. Definition of Controls	5. Comparability of Cases and Controls on the Basis of This Design	6. Ascertainment of Exposure	7. Same Method of Ascertainment for Cases and Controls	8. Nonresponse Rate	9. Total Number of Stars
Hsu et al ¹⁴	●	●	●	●	●	●	●	2	
Mueller et al ¹⁸	●	●	●	●	●	●	●	7	
Skoglund et al ¹¹	●	●	●	●	●	●	●	8	
McDermott et al ⁴⁰	●	●	●	●	●	●	●	8	
Pohlhammer et al ¹⁰	●	●	●	●	●	●	●	8	
Böger et al ⁵¹	●	●	●	●	●	●	●	4	

●, present; ●, partially present; ●, absent.

macrophages.⁷⁶ Levels of MPO in regard to cardiovascular outcome were reported in 2 studies, one of which was conducted as a prospective cohort study while the other was a retrospective cohort study. Both studies mainly investigated patients with chronic limb-threatening ischemia, both newly diagnosed patients and patients undergoing endovascular therapy. The first study reports an HR of 6.80 (1.20–38.69; $P=0.031$) for cardiovascular events,²⁴ while the other study reports an HR of 1.68 (1.09–2.60; $P<0.05$) for MACE.²⁸

Neutrophil-Lymphocyte Ratio

The NLR⁷⁷ was reported in 6 studies. All of these were cohort studies; only one of which was performed prospectively. Nonetheless, all studies were assessed as qualitatively good studies with at least 7 of 9 stars. Chronic limb-threatening ischemia was present in most

patients (n=1754), while patients experiencing claudication were underrepresented (n=798). All-cause mortality was used most often as outcome and showed an association with increased NLR (HR, 1.20, $P=0.012$ ³⁰; HR, 1.10, $P<0.001$ ²⁹; HR, 1.97, $P=0.03$).³³ Comparable results were seen for cardiovascular mortality (HR, 2.04; $P=0.004$),³² major adverse limb events (HR, 1.09; $P<0.001$),²⁹ amputation (HR, 1.14; $P<0.001$),³¹ and amputation-free survival (HR, 2.38; $P=0.000$).³⁴

Serum Amyloid A

This group of apolipoproteins is upregulated during the acute phase of inflammation. Two studies reported results for SAA, both of which were cohort studies of good quality. Although the follow-up period differed substantially between the studies, their results show comparable outcomes. None of both showed significant associations

Table 4. Associations Between Plasma Biomarkers and Different Outcomes

	All-Cause Mortality		Cardiovascular Mortality		MACE/MALE/AFS	
hs-CRP	+++	RR, 3.49	–		+++	RR, 1.86
GDF-15	+		0		+	HR, 1.57–1.70
MPO	0		0		+	HR, 1.68–6.80
NLR	+++	HR, 1.10–1.97	+	HR, 2.04	+++	HR, 1.09–2.33
SAA	–		–		–	
Fibrinogen	+++	RR, 2.08	+	HR, 2.68	+	
D-dimer	++	HR, 1.17	+	RR, 2.15	–	
NT-proBNP	+++	RR, 4.60	–		++	HR, 1.55–1.60
hs-cTnT	+++	RR, 3.14	0		+++	HR, 2.20–3.71
ADMA	++	HR, 1.31–2.23	0		++	HR, 1.70–5.20
Adiponectin	+++	RR, 1.99	0		–	
Homocysteine	–		0		+	OR, 3.4

+++ , association found in ≥3 studies; ++ , association found in 2 studies; + , association found in 1 study; 0 , association not investigated; – , no association found in any study. ADMA indicates asymmetrical dimethylarginine; AFS, amputation-free survival; GDF-15, growth differentiation factor-15; HR, hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; hs-CRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular event; MALE, major adverse limb event; MPO, myeloperoxidase; NLR, neutrophil-lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; RR, relative risk; and SAA, serum amyloid A.

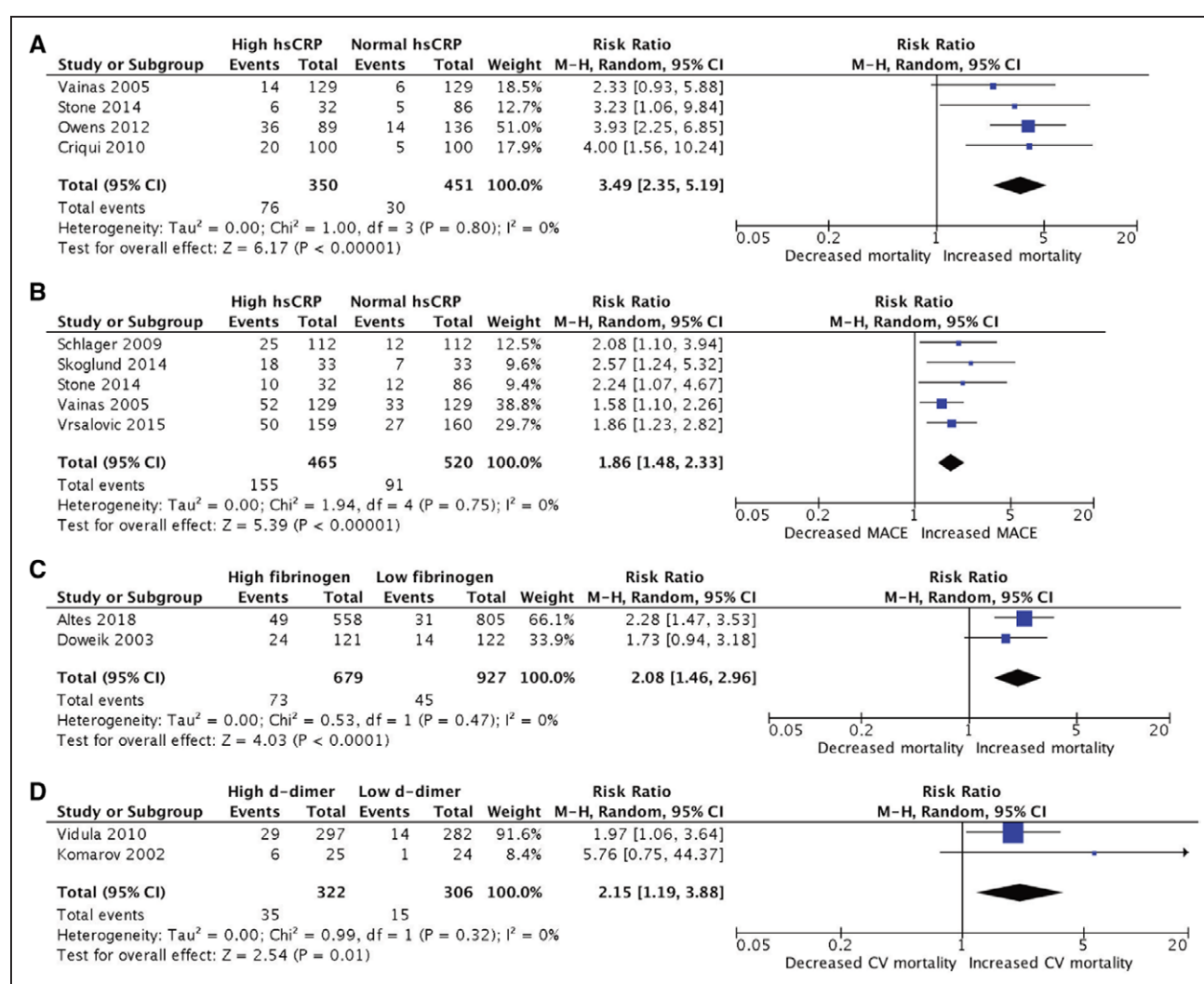


Figure 2. Forest plots for inflammatory and coagulation markers.

A, High-sensitivity CRP (C-reactive protein; hs-CRP) levels and the risk of mortality. **B**, hs-CRP levels and the risk of major adverse cardiovascular events (MACE). **C**, Fibrinogen levels and the risk of mortality. **D**, D-dimer levels and the risk of mortality (all-cause and cardiovascular [CV] mortality). The diamond and its width indicate the pooled risk ratio and the corresponding 95% CI. M-H indicates Mantel-Haenszel.

with cardiovascular outcome. One study reported no association between SAA and MACE (HR, unknown),³⁵ while the other study found no association between SAA and all-cause mortality (HR, unknown; $P=0.12$) and cardiovascular mortality (HR, unknown; $P=0.19$).²²

Coagulation-Inflammation Cross Talk Markers and Cardiovascular Outcome in Lower Extremity PAD Patients

Fibrinogen

Levels of fibrinogen were measured in 6 studies, all prospective cohort studies, which all scored as qualitatively good (7–9 stars). Patient samples were randomly taken, including outpatients and inpatients with PAD. In 3 of 5 studies, all-cause mortality was significantly increased (odds ratio, 1.44 [1.02–1.94]³⁷; HR, 1.90 [1.11–3.41; $P=0.02$]),³⁹ with higher fibrinogen levels (446.35 mg/L)

in patients who died versus 349.8 mg/L in patients who survived ($P=0.013$ ¹⁹; Figure 2C). Cardiovascular mortality was increased in patients with higher fibrinogen levels (HR, 2.68 [1.39–5.16; $P=0.003$]).³⁹ MACE, however, did not show an association with levels of fibrinogen.³⁵

D-Dimer

There were 7 studies that investigated D-dimer levels in relation to cardiovascular outcome in PAD patients. The distribution of intermittent claudication and chronic limb-threatening ischemia patients was only indicated in 1 study. Nonetheless, all studies were qualitatively assessed as good. The severity of the lower extremity PAD was not described in most studies, but overall, most patients were newly diagnosed with lower extremity PAD. All-cause mortality was significantly increased in patients with high D-dimer levels in 2 studies (HR, 2.55 and 1.17 [1.04–1.32; $P=0.007$]).^{38,42} Cardiovascular mortality was increased in one (RR, 1.97 [1.06–3.65]),⁴¹ with an overall

RR for all studies of 2.15 (1.19–3.88; Figure 2D). Specifically, coronary events were more abundant in patients with elevated D-dimer levels ($P=0.028$).⁴⁰

Cardiac Markers and Cardiovascular Outcome in Lower Extremity PAD Patients

NT-proBNP

Seven studies reported NT-proBNP as biomarker. All 7 studies were of good quality, and HRs were present for all studies. Overall, most included patients were diagnosed with intermittent claudication ($n=969$), and only

a small group had chronic limb-threatening ischemia ($n=182$). All-cause mortality was the most investigated outcome, and increased HRs were seen in patients with elevated NT-proBNP levels. Three studies provided data for meta-analysis and are presented in a forest plot (Figure 3A and 3B). It is shown that patients with increased NT-proBNP levels are at increased risk of mortality compared with PAD patients with normal NT-proBNP levels with a risk ratio of 4.60 (2.09–10.10). MACE only appeared to be associated with higher levels of NT-proBNP in 1 of 3 studies, with an HR of 1.60 (1.16–2.22; $P<0.01$).¹⁵

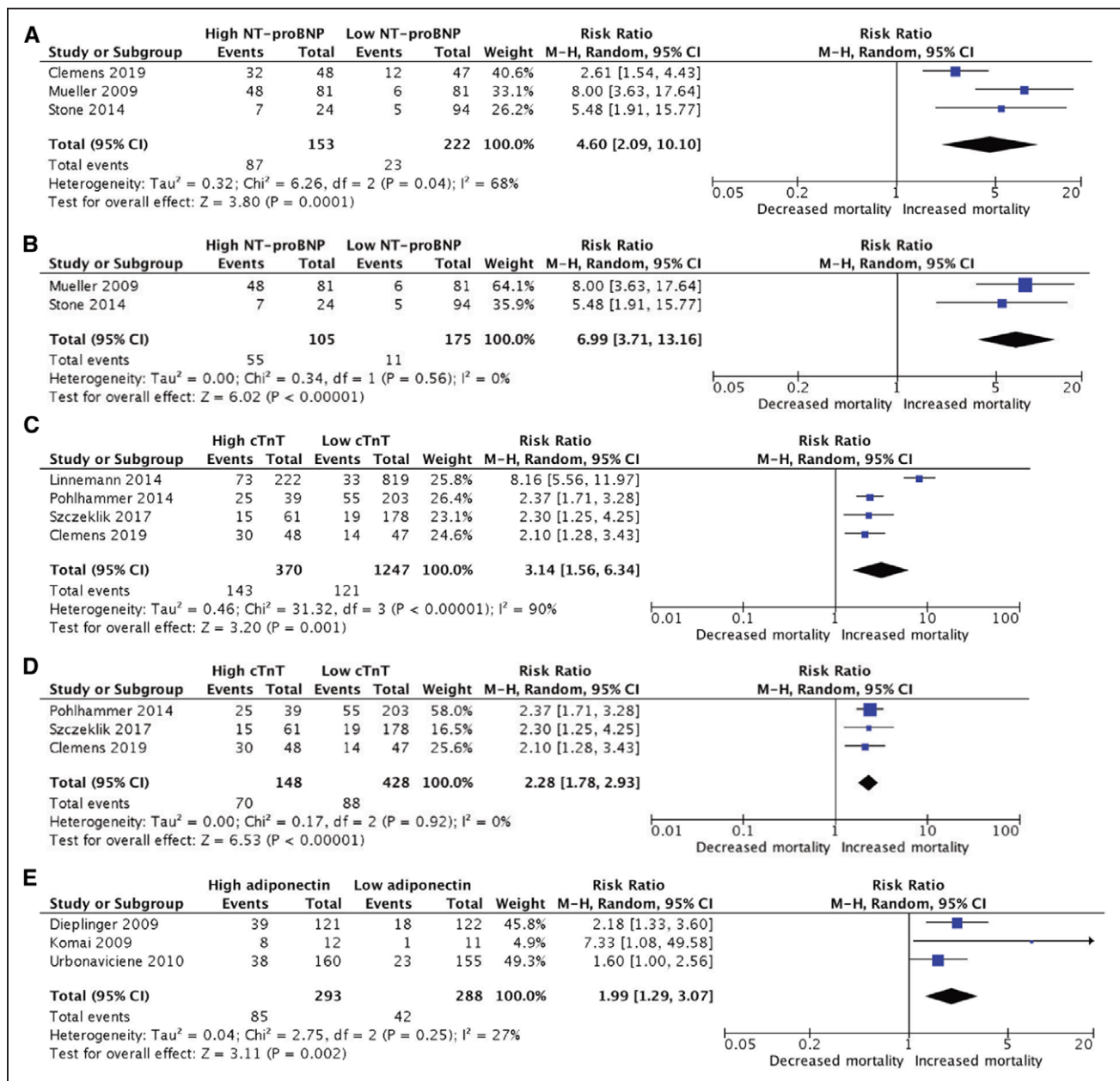


Figure 3. Forest plots for cardiac markers and markers for arterial vessel wall damage.

A, NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels and the risk of mortality. **B**, Sensitivity analysis of **A**. **C**, hs-cTnT (high-sensitivity cardiac troponin T) levels and the risk of mortality. **D**, Sensitivity analysis of **C**. **E**, Adiponectin and the risk of mortality. The diamond and its width indicate the pooled risk ratio and the corresponding 95% CI. M-H indicates Mantel-Haenszel.

High-Sensitivity cTnT

This cardiac marker was investigated in 5 studies, 4 of which were cohort studies and 1 was a case-control study. All studies were of good quality (7–9 stars) and contained both inpatient and outpatient PAD populations. Within the total investigated population of 1676 patients, 1019 had intermittent claudication and 657 had chronic limb-threatening ischemia. All-cause mortality was increased in patients with elevated hs-cTnT levels with an RR of 3.14 (1.56–6.34), and 2.28 (1.78–2.93), after performing the sensitivity analysis (Figure 3C and 3D). MACE was also increased in 2 of 3 studies, with HRs of 2.89 ($P=0.004$),⁴⁸ 3.25 ($P=0.01$),¹⁰ and 1.04 ($P=0.562$),⁴⁵ respectively.

Biomarkers of Arterial Vessel Wall Damage and Cardiovascular Outcome in Lower Extremity PAD Patients

Asymmetrical Dimethylarginine

Asymmetrical dimethylarginine is a known risk marker in vascular disease, inhibiting the NO synthase and causing endothelial dysfunction, vasoconstriction, elevation of blood pressure, and aggravation of atherosclerosis. ADMA was investigated in 4 studies, all of methodological good quality. A total of 2119 patients were investigated comprising both inpatients and outpatients with lower extremity PAD. All-cause mortality was increased with high ADMA levels (HR, 2.23; $P=0.024$)⁵⁰ and HR, 1.31; $P=0.037$).⁵¹ MACE was also increased in patients with higher levels of ADMA (HR, 5.2; $P<0.001$)⁵² and HR, 1.70; $P=0.043$).⁵³

Adiponectin

The adipocyte-specific adiponectin was investigated in 4 prospective cohort studies, which were all published in 2009 or 2010. These studies yielded a total of 1129 patients who were mostly claudicants ($n=736$). All-cause mortality was increased in lower extremity PAD patients with higher adiponectin levels (RR, 1.99 [1.29–3.07]; Figure 3E) in contrast to studies investigating specifically cardiovascular events, which showed less cardiovascular events in patients with higher levels of adiponectin (HR, 0.73 [0.54–0.98]).⁵⁵

Homocysteine

In 3 studies, levels of homocysteine were investigated: 2 cohort studies and 1 case-control study. The PAD population was a mixed population of claudicants and patients with chronic limb-threatening ischemia; most of them were included during hospital admission. All-cause mortality was not associated with homocysteine levels (RR, 1.17; $P=0.444$),¹⁸ but graft occlusion was more abundant in patients with higher homocysteine levels (odds ratio, 7.97; $P<0.0001$).⁵⁸

DISCUSSION

This systematic review aimed to provide a comprehensive overview of biomarker testing in lower extremity PAD as a first step to improve risk stratification. We categorized the biomarkers studied based on the underlying pathophysiological processes, into markers of inflammation, coagulation, cardiac damage, or vessel wall damage (Figure 4). Several biomarkers that could potentially be used for risk stratification in PAD patients were identified. The inflammatory markers hs-CRP and NLR were found to be associated with a 2- to 3-fold increased risk of all-cause mortality and MACE. Coagulation markers D-dimer and fibrinogen were associated with a >2-fold increase in both all-cause and cardiovascular mortality. The cardiac markers NT-proBNP and hs-cTnT were associated with a 2- to 4-fold risk of all-cause mortality and MACE, while the markers of vessel wall damage ADMA and adiponectin were only weakly associated with all-cause mortality. In spite of the identification of these potentially useful plasma biomarkers, surprisingly, to date, none are used for clinical risk stratification in lower extremity PAD.

Recently, new treatment strategies to prevent atherothrombotic complications were developed and introduced into clinical practice. These new treatment strategies target coagulation,⁷⁸ inflammation,⁷⁹ and lipid metabolism⁸⁰ and are all associated with comparable and substantial reductions in overall mortality varying from 14% to 32%.

The COMPASS trial (Cardiovascular Outcomes in People using Anticoagulation Strategies)⁷⁸ showed that in a population with stable chronic arterial disease, including lower extremity PAD, dual pathway inhibition based on a low-dose anticoagulant combined with an antiplatelet drug further improved cardiovascular outcomes and reduced mortality when compared with treatment with antiplatelet therapy alone. This indicates that hypercoagulability presents a cardiovascular risk in lower extremity PAD patients. A recent cost-effectiveness analysis identified subgroups of patients with varying benefit of dual pathway inhibition, indicating that there could be added value in better selection of patients.⁸¹ It could be expected that markers of coagulation such as D-dimer, and possibly fibrinogen, might be useful to identify hypercoagulable patients who could benefit most from this intensified antithrombotic therapy. Fibrinogen is, apart from its role in coagulation, also an inflammatory marker associated with atherosclerotic plaque formation.⁸² It is thought that fibrinogen is important in early atherogenesis, preceding or facilitating low-density lipoprotein accumulation,⁸³ indicating that fibrinogen could be a high potential marker to predict long-term all-cause and cardiovascular mortality in lower extremity PAD. Specific anti-inflammatory treatment strategies targeting IL (interleukin)-1 β —the key mediator of the inflammatory response—have been shown to be effective in reducing cardiovascular events.⁷⁹ In the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis

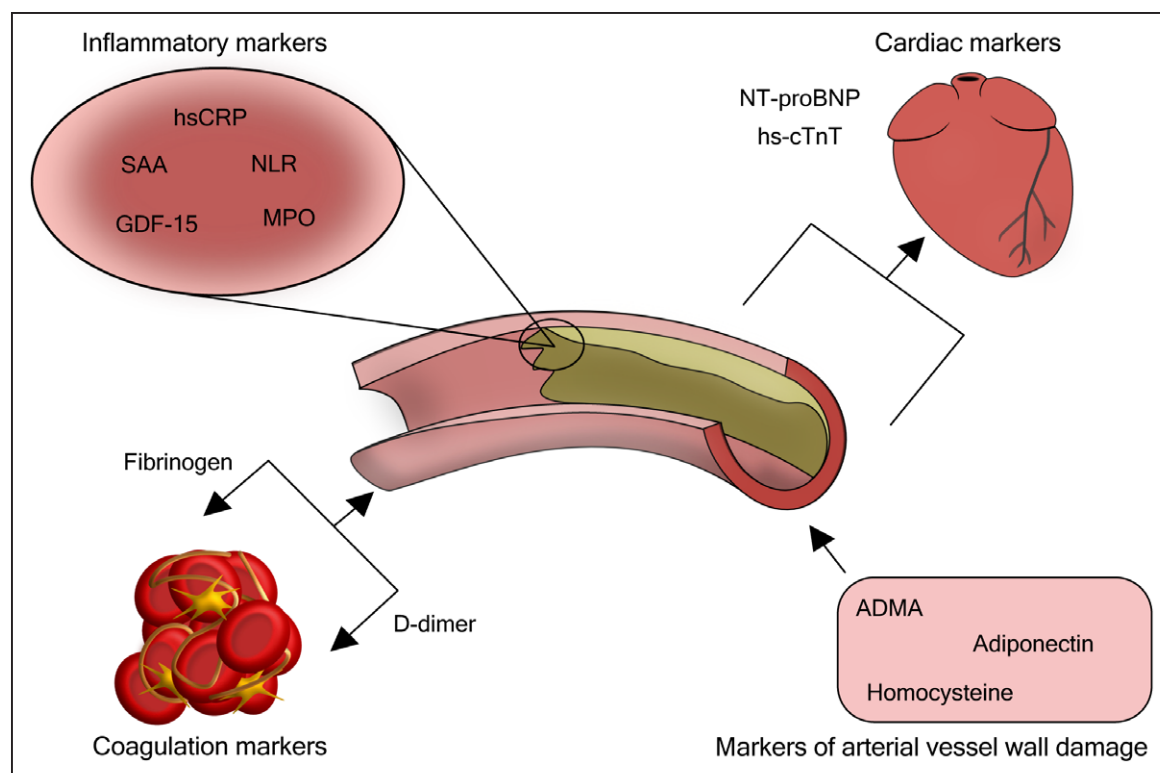


Figure 4. Plasma biomarkers included in this review.

High-sensitivity CRP (C-reactive protein; hs-CRP) indicates a state of chronic inflammation with increased numbers of neutrophils (neutrophil-lymphocyte ratio [NLR]) expressing proatherogenic markers such as MPO (myeloperoxidase). Fibrinogen plays an important role in early atherogenesis, apart from its role in coagulation, whereas D-dimer marks a hypercoagulable state. Cytokines such as GDF-15 (growth differentiation factor-15) and acute-phase proteins like SAA (serum amyloid A) are implicated in further progression of atherosclerotic lesions. Within these lesions, adiponectin, asymmetrical dimethylarginine (ADMA), and homocysteine cause further damage and disruption of the arterial vessel wall. Progression of atherosclerosis leads to ischemia in organs, including the heart. Cardiac markers NT-proBNP (N-terminal pro-B-type natriuretic peptide) and hs-cTnT (high-sensitivity cardiac troponin T) reflect myocardial ischemia, which can be primarily due to coronary artery disease but can also be a sign of systemic microvascular disease and inflammation.

Outcomes Study), patients treated with an IL-1 β -lowering drug showed a dose-dependent reduction in plasma CRP levels, and administration of the drug in higher doses showed a significant reduction in cardiovascular events and death.⁸⁴ Thus, the use of inflammatory markers could potentially improve patient stratification and management in that respect. NLR—an intensively investigated inflammatory marker and an indicator of relative inflammatory cellular activities—is easy to measure and interpret. Although several studies show an association between NLR and all-cause mortality, this association is weaker compared with hs-CRP. NLR could, however, be a potential biomarker to predict short-term (<2 years) cardiovascular mortality in lower extremity PAD, but to date, only 1 study has observed this particular association. NT-proBNP and hs-cTnT are already embedded in the ABC (age, biomarkers, clinical history) score for the prediction of stroke in patients with atrial fibrillation.⁸⁵ Both are cardiac markers, NT-proBNP is clinically used as a marker for heart failure, and troponins are used to diagnose cardiac ischemia.^{86,87} High levels of NT-proBNP are associated with vulnerable plaque components⁸⁸ and have been shown to predict outcome in patients with coronary heart disease and patients who experienced

an ischemic stroke.^{89,90} In PAD patients, similar results have been published with a strong association between all-cause mortality and increased NT-proBNP levels. The association with MACE and NT-proBNP is less frequently studied but also showed a moderately increased risk. The contribution to risk stratification in patients with PAD could be in identifying patients who also have evidence of heart failure (with preserved ejection fraction), a combination of entities with a particularly poor outcome.^{91,92} hs-cTnT also appears to be a good predictor for all-cause mortality and MACE in lower extremity PAD patients. In comparison to NT-proBNP, the studies investigating hs-cTnT had more patients with chronic limb-threatening ischemia and were, therefore, more prone to MACE. The increased hs-cTnT levels in high-risk PAD patients may reflect microvascular organ damage of the heart as >1 in 2 PAD patients experience concomitant coronary artery disease.^{2,49} However, hs-cTnT does not only reflect myocardial ischemia due to coronary artery disease, but it can also indicate systemic vascular (including microvascular) disease, associated with heart and kidney failure.^{49,93,94} Comparing the risk ratios of both markers, NT-proBNP does seem to be a stronger predictor for all-cause mortality and especially for long-term

mortality. Finally, markers of arterial vessel wall damage are weak predictors of cardiovascular outcome in lower extremity PAD. Adiponectin has been thoroughly investigated in patients with coronary heart disease, with ambiguous outcomes being positively or negatively associated with mortality and cardiovascular risk.^{95,96} Similar results were found in this review, as high adiponectin levels were associated with increased all-cause mortality but not with amputation-free survival.^{54,56,57} Although studies investigating ADMA show promising results, more studies need to be performed to confirm the predictive potential of this biomarker. Homocysteine is not recommended to be used as a predictive marker for cardiovascular outcome.

How can these data be translated to practice? One way forward may be to design management studies addressing the value of a panel of biomarkers as discussed, including hs-CRP, NLR, fibrinogen, D-dimer, NT-proBNP, and hs-cTnT. Tailoring based on biomarker results as compared with standard care without such biomarkers could reveal the utility of such approach for early identification of specific contributing risks, including inflammation, hypercoagulability, and heart failure. Now that more potent pharmacological interventions are becoming available to target specific mechanisms, a biomarker-supported strategy may help identify those patients with lower extremity PAD, who may benefit most from intensified treatment. The financial consequences of using biomarkers may be limited as one may assume that most of these markers may be tested on one or only few occasions per patient. In fact, we previously explored the cost-effectiveness of D-dimer and the societal value (headroom) of a hypothetical perfect biomarker for risk assessment and subsequent tailored treatment allocation in lower extremity PAD patients. We concluded that further risk assessment and treatment stratification based on the use of D-dimer could be a cost-effective health intervention. Identification of high-risk patients and prescription of intensified antithrombotic therapy could potentially save substantial costs and improve chances of survival.⁹⁷ It can be expected that this will also be the case for other biomarkers in lower extremity PAD with similar risk associations.

By investigating which of the biomarkers are increased in an individual patient, the treatment strategy may be adapted to provide optimal personalized vascular protection. For instance, in a patient with increased levels of inflammatory markers but normal levels of coagulation markers, intensifying anti-inflammatory treatment would better suit the preventive strategy than escalating anticoagulant therapy. By individualizing treatment to the needs for each specific patient, the risk of adverse cardiovascular events, bleeding, or other complications can be expected to be limited.

This study has several limitations, mainly due to the heterogeneity of the underlying evidence. Although a total number of 50 studies were included in this

systematic review, the number of studies per biomarker was limited. We were only able to include studies that provided sufficient data for meta-analysis. For each biomarker, the primary end point differed between studies, and, therefore, only studies with the same end point could be included in the meta-analyses. Within each meta-analysis, we included studies with a different but minimal follow-up of 1 year. Lastly, we used unadjusted results in the meta-analyses, which could differ from reported adjusted results in each study. Several studies did not report baseline data on PAD severity, such as the Fontaine classification, which makes it difficult to interpret results for subgroups within PAD. Notwithstanding these limitations, this systematic review was able to provide a comprehensive overview of biomarker testing in lower extremity PAD, which can be used as a first step to improve risk stratification.

CONCLUSIONS

The clinical application of biomarkers to stratify patients at increased risk for adverse cardiovascular events in lower extremity PAD is urgently needed. This systematic review identifies promising candidate biomarkers representing different pathophysiological processes implicated in lower extremity PAD, including hs-CRP, NLR, fibrinogen, D-dimer, NT-proBNP, and hs-cTnT. Combining these markers for individual risk stratification might result in improved treatment choices and increased effectiveness of current treatment strategies in lower extremity PAD patients and is expected to be societally cost-effective. This strategy needs testing in management studies.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340. doi: 10.1016/S0140-6736(13)61249-0
2. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liao CS, Richard AJ, Röther J, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors

- in outpatients with atherothrombosis. *JAMA*. 2006;295:180–189. doi: 10.1001/jama.295.2.180
3. Diehm C, Allenberg JR, Haberl R, Darius H, Mahn M, Tepohl G, Holland-Letz T, Pittrow D, Trampisch HJ. High all-cause mortality in patients with peripheral arterial disease in primary care: five-years results of the getabi study. *Circulation*. 2007;116:833–841.
 4. Cea Soriano L, Fowkes FGR, Johansson S, Allum AM, García Rodríguez LA. Cardiovascular outcomes for patients with symptomatic peripheral artery disease: A cohort study in The Health Improvement Network (THIN) in the UK. *Eur J Prev Cardiol*. 2017;24:1927–1937. doi: 10.1177/2047487317736824
 5. Inglis SC, Bebchuk J, Al-Suhaim SA, Case J, Pfeffer MA, Solomon SD, Hou YR, Pitt B, Dargie HJ, Ford I, et al. Peripheral artery disease and outcomes after myocardial infarction: an individual-patient meta-analysis of 28,771 patients in CAPRICORN, EPEHESUS, OPTIMAAL and VALIANT. *Int J Cardiol*. 2013;168:1094–1101. doi: 10.1016/j.ijcard.2012.11.033
 6. Spencer FA, Lessard D, Doubeni C, Yarzebski J, Gore JM, Goldberg RJ. Treatment practices and outcomes of patients with established peripheral arterial disease hospitalized with acute myocardial infarction in a community setting. *Am Heart J*. 2007;153:140–146. doi: 10.1016/j.ahj.2006.09.009
 7. Moussa ID, Jaff MR, Mehran R, Gray W, Dangas G, Lazić Z, Moses JW. Prevalence and prediction of previously unrecognized peripheral arterial disease in patients with coronary artery disease: the Peripheral Arterial Disease in Interventional Patients Study. *Catheter Cardiovasc Interv*. 2009;73:719–724. doi: 10.1002/ccd.21969
 8. Singh TP, Morris DR, Smith S, Moxon JV, Golledge J. Systematic review and meta-analysis of the association between C-reactive protein and major cardiovascular events in patients with peripheral artery disease. *Eur J Vasc Endovasc Surg*. 2017;54:220–233. doi: 10.1016/j.ejvs.2017.05.009
 9. Kleingriss MC, ten Cate H, ten Cate-Hoek AJ. D-dimer as a marker for cardiovascular and arterial thrombotic events in patients with peripheral arterial disease. A systematic review. *Thromb Haemost*. 2013;110:233–243. doi: 10.1160/TH13-01-0032
 10. Pohlhammer J, Kronenberg F, Rantner B, Stadler M, Peric S, Hammerer-Lercher A, Klein-Weigel P, Fraedrich G, Kollerits B. High-sensitivity cardiac troponin T in patients with intermittent claudication and its relation with cardiovascular events and all-cause mortality—the CAVASIC Study. *Atherosclerosis*. 2014;237:711–717. doi: 10.1016/j.atherosclerosis.2014.10.097
 11. Skoglund PH, Arpegård J, Ostergren J, Svensson P. Amino-terminal pro-B-type natriuretic peptide and high-sensitivity C-reactive protein but not statin C predict cardiovascular events in male patients with peripheral artery disease independently of ambulatory pulse pressure. *Am J Hypertens*. 2014;27:363–371. doi: 10.1093/ajh/hpt278
 12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi: 10.1136/bmj.b2535
 13. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (Nos) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. 2000.
 14. Hsu LA, Wu S, Juang JJ, Chiang FT, Teng MS, Lin JF, Huang HL, Ko YL. Growth differentiation factor 15 may predict mortality of peripheral and coronary artery diseases and correlate with their risk factors. *Mediators Inflamm*. 2017;2017:9398401. doi: 10.1155/2017/9398401
 15. Otaki Y, Watanabe T, Takahashi H, Yamaura Y, Nishiyama S, Arimoto T, Shishido T, Miyamoto T, Kubota I. Serum carboxy-terminal telopeptide of type I collagen (I-CTP) is predictive of clinical outcome in peripheral artery disease patients following endovascular therapy. *Heart Vessels*. 2017;32:149–156. doi: 10.1007/s00380-016-0858-2
 16. Vrsalović M, Vučur K, Car B, Krčmar T, Vrsalović Presečki A. C-reactive protein, renal function, and cardiovascular outcome in patients with symptomatic peripheral artery disease and preserved left ventricular systolic function. *Croat Med J*. 2015;56:351–356. doi: 10.3325/cmj.2015.56.351
 17. Stone PA, Schlarb H, Campbell JE, Williams D, Thompson SN, John M, Campbell JR, AbuRahma AF. C-reactive protein and brain natriuretic peptide as predictors of adverse events after lower extremity endovascular revascularization. *J Vasc Surg*. 2014;60:652–660. doi: 10.1016/j.jvs.2014.03.254
 18. Mueller T, Hinterreiter F, Luft C, Poelz W, Haltmayer M, Dieplinger B. Mortality rates and mortality predictors in patients with symptomatic peripheral artery disease stratified according to age and diabetes. *J Vasc Surg*. 2014;59:1291–1299. doi: 10.1016/j.jvs.2013.11.063
 19. Bleda S, De Haro J, Acin F, Varela C, Esparza L, López de Maturana I. Inflammatory burden predicts long-term outcomes in endovascular therapy in peripheral arterial disease. *Ann Vasc Surg*. 2013;27:459–466. doi: 10.1016/j.avsg.2012.02.027
 20. Owens CD, Kim JM, Hevelone ND, Gasper WJ, Belkin M, Creager MA, Conte MS. An integrated biochemical prediction model of all-cause mortality in patients undergoing lower extremity bypass surgery for advanced peripheral artery disease. *J Vasc Surg*. 2012;56:686–695. doi: 10.1016/j.jvs.2012.02.034
 21. Urbonaviciene G, Frystyk J, Flyvbjerg A, Urbonavicius S, Henneberg EW, Lindholt JS. Markers of inflammation in relation to long-term cardiovascular mortality in patients with lower-extremity peripheral arterial disease. *Int J Cardiol*. 2012;160:89–94. doi: 10.1016/j.ijcard.2011.03.030
 22. Criqui MH, Ho LA, Denenberg JO, Ridker PM, Wassel CL, McDermott MM. Biomarkers in peripheral arterial disease patients and near- and longer-term mortality. *J Vasc Surg*. 2010;52:85–90. doi: 10.1016/j.jvs.2010.02.004
 23. Schlager O, Amighi J, Haumer M, Sabeti S, Dick P, Mlekusch W, Loewe C, Koppenssteiner R, Minar E, Schillinger M. Inflammation and adverse cardiovascular outcome in patients with renal artery stenosis and peripheral artery disease. *Atherosclerosis*. 2009;205:314–318. doi: 10.1016/j.atherosclerosis.2008.12.022
 24. Brevetti G, Schiano V, Laurenzano E, Giugliano G, Petretta M, Scopacasa F, Chiariello M. Myeloperoxidase, but not C-reactive protein, predicts cardiovascular risk in peripheral arterial disease. *Eur Heart J*. 2008;29:224–230. doi: 10.1093/eurheartj/ehm587
 25. Musicant SE, Taylor LM Jr, Peters D, Schuff RA, Urankar R, Landry GJ, Moneta GL. Prospective evaluation of the relationship between C-reactive protein, D-dimer and progression of peripheral arterial disease. *J Vasc Surg*. 2006;43:772–780; discussion 780. doi: 10.1016/j.jvs.2005.12.051
 26. Vainas T, Stassen FR, de Graaf R, Twiss EL, Hergreen SB, Welten RJ, van den Akker LH, van Diejen-Visser MP, Bruggeman CA, Kitslaar PJ. C-reactive protein in peripheral arterial disease: relation to severity of the disease and to future cardiovascular events. *J Vasc Surg*. 2005;42:243–251. doi: 10.1016/j.jvs.2005.03.060
 27. De Haan JJ, Haitjema S, den Ruijter HM, Pasterkamp G, de Borst GJ, Teraa M, Verhaar MC, Gremmels H, de Jager SCA. Growth differentiation factor 15 is associated with major amputation and mortality in patients with peripheral artery disease. *J Am Heart Assoc*. 2017;6:e006225.
 28. Haslacher H, Perkmann T, Gruenewald J, Exner M, Endler G, Scheichenberger V, Wagner O, Schillinger M. Plasma myeloperoxidase level and peripheral arterial disease. *Eur J Clin Invest*. 2012;42:463–469. doi: 10.1111/j.1365-2362.2011.02601.x
 29. Pourafkari L, Choi C, Garajehdaghi R, Tajili A, Dostluoglu HH, Nader ND. Neutrophil-lymphocyte ratio is a marker of survival and cardiac complications rather than patency following revascularization of lower extremities. *Vasc Med*. 2018;23:437–444. doi: 10.1177/1358863X18774623
 30. Amrock SM, Weitzman M. Multiple biomarkers for mortality prediction in peripheral arterial disease. *Vasc Med*. 2016;21:105–112. doi: 10.1177/1358863X15621797
 31. Luo H, Yuan D, Yang H, Yukui M, Huang B, Yang Y, Xiong F, Zeng G, Wu Z, Chen X, et al. Post-treatment neutrophil-lymphocyte ratio independently predicts amputation in critical limb ischemia without operation. *Clinics (Sao Paulo)*. 2015;70:273–277. doi: 10.6061/clinics/2015(04)09
 32. Erturk M, Cakmak HA, Surgit O, Celik O, Aksu HU, Akgul O, Gurdogan M, Bulut U, Ozalp B, Akbay E, et al. Predictive value of elevated neutrophil to lymphocyte ratio for long-term cardiovascular mortality in peripheral arterial occlusive disease. *J Cardiol*. 2014;64:371–376. doi: 10.1016/j.jjcc.2014.02.019
 33. Chan C, Puckridge P, Ullah S, Delaney C, Spark JI. Neutrophil-lymphocyte ratio as a prognostic marker of outcome in infrapopliteal percutaneous interventions for critical limb ischemia. *J Vasc Surg*. 2014;60:661–668. doi: 10.1016/j.jvs.2014.03.277
 34. González-Fajardo JA, Brizuela-Sanz JA, Aguirre-Gervás B, Merino-Díaz B, Del Río-Solá L, Martín-Pedrosa M, Vaquero-Puerta C. Prognostic significance of an elevated neutrophil-lymphocyte ratio in the amputation-free survival of patients with chronic critical limb ischemia. *Ann Vasc Surg*. 2014;28:999–1004. doi: 10.1016/j.avsg.2013.06.037
 35. Owens CD, Ridker PM, Belkin M, Hamdan AD, Pomposelli F, Logerfo F, Creager MA, Conte MS. Elevated c-reactive protein levels are associated with postoperative events in patients undergoing lower extremity vein bypass surgery. *J Vasc Surg*. 2007;45:2–9; discussion 9.
 36. Altes P, Perez P, Esteban C, Sánchez Muñoz-Torrero JF, Aguilar E, García-Díaz AM, Álvarez LR, Jiménez PE, Sahuquillo JC, Monreal M; FRENA Investigators. Raised fibrinogen levels and outcome in outpatients with peripheral artery disease. *Angiology*. 2018;69:507–512. doi: 10.1177/0003319717739720
 37. Bartlett JW, De Stavola BL, Meade TW. Assessing the contribution of fibrinogen in predicting risk of death in men with peripheral arterial disease. *J Thromb Haemost*. 2009;7:270–276. doi: 10.1111/j.1538-7836.2008.03236.x

38. Bosevski M, Kostoska S, Tosev S, Borozanov V. Usefulness of D-dimers and fibrinogen plasma determination in patients with polyvascular disease. *Angiol Sosud Khir.* 2006;12:9–15.
39. Doweik L, Maca T, Schillinger M, Budinsky A, Sabeti S, Minar E. Fibrinogen predicts mortality in high risk patients with peripheral artery disease. *Eur J Vasc Endovasc Surg.* 2003;26:381–386. doi: 10.1016/s1078-5884(03)00340-x
40. McDermott MM, Liu K, Green D, Greenland P, Tian L, Kibbe M, Tracy R, Shah S, Wilkins JT, Huffman M, et al. Changes in D-dimer and inflammatory biomarkers before ischemic events in patients with peripheral artery disease: The BRAVO Study. *Vasc Med.* 2016;21:12–20. doi: 10.1177/1358863X15617541
41. Vidula H, Tian L, Liu K, Criqui MH, Ferrucci L, Guralnik JM, Green D, Ridker P, McDermott MM. Comparison of effects of statin use on mortality in patients with peripheral arterial disease with versus without elevated C-reactive protein and D-dimer levels. *Am J Cardiol.* 2010;105:1348–1352. doi: 10.1016/j.amjcard.2009.12.054
42. Vidula H, Tian L, Liu K, Criqui MH, Ferrucci L, Pearce WH, Greenland P, Green D, Tan J, Garside DB, et al. Biomarkers of inflammation and thrombosis as predictors of near-term mortality in patients with peripheral arterial disease: a cohort study. *Ann Intern Med.* 2008;148:85–93. doi: 10.7326/0003-4819-148-2-200801150-00003
43. Komarov A, Panchenko E, Dobrovolsky A, Karpov Y, Deev A, Titaeva E, Davletov K, Eshkeeva A, Markova L. D-dimer and platelet aggregability are related to thrombotic events in patients with peripheral arterial occlusive disease. *Eur Heart J.* 2002;23:1309–1316. doi: 10.1053/euhj.2001.3116
44. Clemens RK, Annema W, Baumann F, Roth-Zetsche S, Seifert B, von Eckardstein A, Amann-Vesti BR. Cardiac biomarkers but not measures of vascular atherosclerosis predict mortality in patients with peripheral artery disease. *Clin Chim Acta.* 2019;495:215–220. doi: 10.1016/j.cca.2019.04.061
45. Falkensammer J, Frech A, Duschek N, Gasteiger S, Stojakovic T, Scharnagl H, Huber K, Fraedrich G, Greiner A. Prognostic relevance of ischemia-modified albumin and NT-proBNP in patients with peripheral arterial occlusive disease. *Clin Chim Acta.* 2015;438:255–260. doi: 10.1016/j.cca.2014.08.031
46. Mueller T, Dieplinger B, Poelz W, Endler G, Wagner OF, Haltmayer M. Amino-terminal pro-B-type natriuretic peptide as predictor of mortality in patients with symptomatic peripheral arterial disease: 5-year follow-up data from the Linz Peripheral Arterial Disease Study. *Clin Chem.* 2009;55:68–77. doi: 10.1373/clinchem.2008.108753
47. Shadman R, Allison MA, Criqui MH. Glomerular filtration rate and N-terminal pro-brain natriuretic peptide as predictors of cardiovascular mortality in vascular patients. *J Am Coll Cardiol.* 2007;49:2172–2181. doi: 10.1016/j.jacc.2007.02.047
48. Szczeklik W, Krzanowski M, Maga P, Partyka Ł, Kościelniak J, Kaczmarczyk P, Maga M, Pieczka P, Suska A, Wachsmann A, et al. Myocardial injury after endovascular revascularization in critical limb ischemia predicts 1-year mortality: a prospective observational cohort study. *Clin Res Cardiol.* 2018;107:319–328. doi: 10.1007/s00392-017-1185-z
49. Linnemann B, Sutter T, Herrmann E, Sixt S, Rastan A, Schwarzwaelder U, Noory E, Buergelin K, Beschoner U, Zeller T. Elevated cardiac troponin t is associated with higher mortality and amputation rates in patients with peripheral arterial disease. *J Am College Cardiol.* 2014;63:1529–1538.
50. Staniszevska A, Rajagopalan S, Al-Shaheen A, Thies F, Brittenden J. Increased levels of symmetric dimethyl-arginine are associated with all-cause mortality in patients with symptomatic peripheral arterial disease. *J Vasc Surg.* 2015;61:1292–1298. doi: 10.1016/j.jvs.2015.01.002
51. Böger RH, Endres HG, Schwedhelm E, Darius H, Atzler D, Lüneburg N, von Stritzky B, Maas R, Thiem U, Benndorf RA, et al. Asymmetric dimethyl-arginine as an independent risk marker for mortality in ambulatory patients with peripheral arterial disease. *J Intern Med.* 2011;269:349–361. doi: 10.1111/j.1365-2796.2010.02322.x
52. Wilson AM, Shin DS, Weatherby C, Harada RK, Ng MK, Nair N, Kielstein J, Cooke JP. Asymmetric dimethylarginine correlates with measures of disease severity, major adverse cardiovascular events and all-cause mortality in patients with peripheral arterial disease. *Vasc Med.* 2010;15:267–274. doi: 10.1177/1358863X10364552
53. Mittermayer F, Krzyzanowska K, Exner M, Mlekusch W, Amighi J, Sabeti S, Minar E, Müller M, Wolzt M, Schillinger M. Asymmetric dimethylarginine predicts major adverse cardiovascular events in patients with advanced peripheral artery disease. *Arterioscler Thromb Vasc Biol.* 2006;26:2536–2540. doi: 10.1161/01.ATV.0000242801.38419.48
54. Owens CD, Kim JM, Hevelone ND, Hamdan A, Raffetto JD, Creager MA, Conte MS. Novel adipokines, high molecular weight adiponectin and resistin, are associated with outcomes following lower extremity revascularization with autogenous vein. *J Vasc Surg.* 2010;51:1152–1159. doi: 10.1016/j.jvs.2009.12.051
55. Urbonaviciene G, Frystyk J, Flyvbjerg A, Henneberg EW, Lindholt JS. Association of serum adiponectin with risk for cardiovascular events in patients with peripheral arterial disease. *Atherosclerosis.* 2010;210:619–624. doi: 10.1016/j.atherosclerosis.2009.12.030
56. Dieplinger B, Haltmayer M, Poelz W, Mueller T. Value of adiponectin as predictor of 5-year all-cause mortality in patients with symptomatic peripheral arterial disease: results from the Linz Peripheral Arterial Disease (LIPAD) study. *Clin Chim Acta.* 2009;408:87–91. doi: 10.1016/j.cca.2009.07.014
57. Komai H, Juri M. Impact of reduced endogenous anti-coagulation protein activity on vascular events of peripheral arterial disease. *Int Angiol.* 2009;28:138–143.
58. Heneghan HM, Sultan S. Homocysteine, the cholesterol of the 21st century. Impact of hyperhomocysteinemia on patency and amputation-free survival after intervention for critical limb ischemia. *J Endovasc Ther.* 2008;15:399–407. doi: 10.1583/08-2385.1
59. Martinez-Aguilar E, Gomez-Rodriguez V, Orbe J, Rodriguez JA, Fernández-Alonso L, Roncal C, Páramo JA. Matrix metalloproteinase 10 is associated with disease severity and mortality in patients with peripheral arterial disease. *J Vasc Surg.* 2015;61:428–435. doi: 10.1016/j.jvs.2014.09.002
60. Madrigal-Matute J, Lindholt J, Jes S, Fernandez-Garcia Carlos E, Benito-Martin A, Burillo E, Zalba G, Belouqui O, Llamas-Granda P, Ortiz A, Egido J, et al. Galectin-3, a biomarker linking oxidative stress and inflammation with the clinical outcomes of patients with atherothrombosis. *J Am Heart Assoc.* 2014;3:e000785.
61. Urbonaviciene G, Martin-Ventura JL, Lindholt JS, Urbonavicius S, Moreno JA, Egido J, Blanco-Colio LM. Impact of soluble TWEAK and CD163/TWEAK ratio on long-term cardiovascular mortality in patients with peripheral arterial disease. *Atherosclerosis.* 2011;219:892–899. doi: 10.1016/j.atherosclerosis.2011.09.016
62. Depalma RG, Hayes VW, Chow BK, Shamayeva G, May PE, Zacharski LR. Ferritin levels, inflammatory biomarkers, and mortality in peripheral arterial disease: a substudy of the Iron (Fe) and Atherosclerosis Study (FeAST) Trial. *J Vasc Surg.* 2010;51:1498–1503. doi: 10.1016/j.jvs.2009.12.068
63. Blomstrand D, Kölbl T, Lindblad B, Gottsäter A. Activated protein C-protein S inhibitor complex in peripheral arterial disease. *Ann Vasc Surg.* 2010;24:588–595. doi: 10.1016/j.avsg.2010.02.006
64. Nie H, Liang Y, Wang HX, Ren HL, Wang YW, Li FD, Zheng YH. Angiopoietin-related growth factor is independently associated with lower extremity peripheral arterial disease. *J Diabetes Complications.* 2017;31:433–438. doi: 10.1016/j.jdiacomp.2016.10.019
65. Höbaus C, Herz CT, Pesau G, Wrba T, Koppensteiner R, Scherthaner GH. FABP4 and cardiovascular events in peripheral arterial disease. *Angiology.* 2018;69:424–430. doi: 10.1177/0003319717728226
66. Moxon JV, Jones RE, Wong G, Weir JM, Mellett NA, Kingwell BA, Meikle PJ, Golledge J. Baseline serum phosphatidylcholine plasmalogen concentrations are inversely associated with incident myocardial infarction in patients with mixed peripheral artery disease presentations. *Atherosclerosis.* 2017;263:301–308. doi: 10.1016/j.atherosclerosis.2017.06.925
67. Takamura TA, Tsuchiya T, Oda M, Watanabe M, Saito R, Sato-Ishida R, Akao H, Kawai Y, Kitayama M, Kajinami K. Circulating malondialdehyde-modified low-density lipoprotein (MDA-LDL) as a novel predictor of clinical outcome after endovascular therapy in patients with peripheral artery disease (PAD). *Atherosclerosis.* 2017;263:192–197. doi: 10.1016/j.atherosclerosis.2017.06.029
68. Fatemi S, Gottsäter A, Zarrouk M, Engström G, Melander O, Persson M, Acosta S. Lp-PLA2 activity and mass and CRP are associated with incident symptomatic peripheral arterial disease. *Sci Rep.* 2019;9:5609. doi: 10.1038/s41598-019-42154-5
69. Eisen A, Bonaca MP, Jarolim P, Scirica BM, White HD, Tendera M, Dellborg M, Nicolau JC, Morais J, Fox KA, et al. High-sensitivity troponin I in stable patients with atherosclerotic disease in the TRA 2°P - TIMI 50 Trial. *Clin Chem.* 2017;63:307–315. doi: 10.1373/clinchem.2016.264788
70. Zettervall SL, Soden PA, Ultee KH, Seldon C, Oh J, McGann K, Schermerhorn ML, Guzman RJ. Elevated serum phosphate levels are associated with decreased amputation-free survival after interventions for critical limb ischemia. *J Vasc Surg.* 2017;65:431–437. doi: 10.1016/j.jvs.2016.06.097
71. Gremmel T, Wadowski PP, Mueller M, Kopp CW, Koppensteiner R, Panzer S. Serum cholinesterase levels are associated with 2-year ischemic outcomes after angioplasty and stenting for peripheral artery disease. *J Endovasc Ther.* 2016;23:738–743. doi: 10.1177/1526602816655521
72. Hishikari K, Kimura S, Yamakami Y, Kojima K, Sagawa Y, Otani H, Sugiyama T, Kuwahara T, Hikita H, Takahashi A, et al. The prognostic value

- of the serum eicosapentaenoic acid to arachidonic acid ratio in relation to clinical outcomes after endovascular therapy in patients with peripheral artery disease caused by femoropopliteal artery lesions. *Atherosclerosis*. 2015;239:583–588. doi: 10.1016/j.atherosclerosis.2015.02.035
73. Chen N, Chen L, Jiang S, Wang Z, Liu T. Predictive value of P-selectin and endothelin-1 for vascular restenosis after interventional procedures for peripheral artery disease. *Exp Ther Med*. 2019;17:3907–3912. doi: 10.3892/etm.2019.7407
 74. Milks MW, Nambi V. Chapter 8 - Cardiac injury, maladaptation, and heart failure incidence. In: Nambi V, ed. *Biomarkers in Cardiovascular Disease*. Amsterdam, the Netherlands: Elsevier; 2019:81–96.
 75. Schultz J, Kaminker K. Myeloperoxidase of the leucocyte of normal human blood. I. Content and localization. *Arch Biochem Biophys*. 1962;96:465–467. doi: 10.1016/0003-9861(62)90321-1
 76. Bos A, Wever R, Roos D. Characterization and quantification of the peroxidase in human monocytes. *Biochim Biophys Acta*. 1978;525:37–44. doi: 10.1016/0005-2744(78)90197-3
 77. Aykan AÇ, Hatem E, Kalaycıoğlu E, Karabay CY, Zehir R, Gökdeniz T, Altıntaş Aykan D, Çelik Ş. Neutrophil-to-lymphocyte ratio may be a marker of peripheral artery disease complexity. *Anatol J Cardiol*. 2016;16:497–503. doi: 10.5152/AnatolJCardiol.2015.6240
 78. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377:1319–1330. doi: 10.1056/NEJMoa1709118
 79. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914
 80. Karatasakis A, Danek BA, Karacsonyi J, Rangan BV, Roesle MK, Knickelbine T, Miedema MD, Khalili H, Ahmad Z, Abdullah S, et al. Effect of pcsk9 inhibitors on clinical outcomes in patients with hypercholesterolemia: A meta-analysis of 35 randomized controlled trials. *J Am Heart Assoc*. 2017;6:e006910.
 81. Petersohn S, Pouwels X, Ramaekers B, Ten Cate-Hoek A, Joore M. Rivaroxaban plus aspirin for the prevention of ischaemic events in patients with cardiovascular disease: a cost-effectiveness study [published online March 29, 2020]. *Eur J Prev Cardiol*. <https://journals.sagepub.com/doi/full/10.1177/2047487320913380>.
 82. Lowe GD, Rumley A. Fibrinogen and its degradation products as thrombotic risk factors. *Ann NY Acad Sci*. 2001;936:560–565. doi: 10.1111/j.1749-6632.2001.tb03544.x
 83. Spronk HM, van der Voort D, Ten Cate H. Blood coagulation and the risk of atherothrombosis: a complex relationship. *Thromb J*. 2004;2:12. doi: 10.1186/1477-9560-2-12
 84. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ; CANTOS Trial Group. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet*. 2018;391:319–328. doi: 10.1016/S0140-6736(17)32814-3
 85. Berg David D, Ruff Christian T, Jarolim P, Giugliano Robert P, Nordio F, Lanz Hans J, Mercuri Michele F, Antman Elliott M, Braunwald E, Morrow David A. Performance of the abc scores for assessing the risk of stroke or systemic embolism and bleeding in patients with atrial fibrillation in engage af-timi 48. *Circulation*. 2019;139:760–771.
 86. Iwanaga Y, Nishi I, Furuichi S, Noguchi T, Sase K, Kihara Y, Goto Y, Nonogi H. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. *J Am Coll Cardiol*. 2006;47:742–748. doi: 10.1016/j.jacc.2005.11.030
 87. Shah MR, Hasselblad V, Tasissa G, Christenson RH, Binanay C, O'Connor CM, Ohman EM, Stevenson LW, Califf RM. Rapid assay brain natriuretic peptide and troponin I in patients hospitalized with decompensated heart failure (from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness Trial). *Am J Cardiol*. 2007;100:1427–1433. doi: 10.1016/j.amjcard.2007.06.035
 88. Hong YJ, Ahn Y, Sim DS, Yoon NS, Yoon HJ, Kim KH, Park HW, Kim JH, Jeong MH, Cho JG, et al. Relation between N-terminal pro-B-type natriuretic peptide and coronary plaque components in patients with acute coronary syndrome: virtual histology-intravascular ultrasound analysis. *Coron Artery Dis*. 2009;20:518–524. doi: 10.1097/MCA.0b013e32832a196e
 89. Yang J, Zhong C, Wang A, Xu T, Bu X, Peng Y, Wang J, Peng H, Li Q, Ju Z, et al; on behalf of the CATIS Investigation Groups. Association between increased N-terminal pro-brain natriuretic peptide level and poor clinical outcomes after acute ischemic stroke. *J Neurol Sci*. 2017;383:5–10. doi: 10.1016/j.jns.2017.10.014
 90. Mishra RK, Judson G, Christenson RH, DeFilippi C, Wu AHB, Whooley MA. The association of five-year changes in the levels of N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) with subsequent heart failure and death in patients with stable coronary artery disease: the heart and soul study. *Cardiology*. 2017;137:201–206. doi: 10.1159/000466682
 91. Sandesara PB, Hammadah M, Samman-Tahhan A, Kelli HM, O'Neal WT. Peripheral artery disease and risk of adverse outcomes in heart failure with preserved ejection fraction. *Clin Cardiol*. 2017;40:692–696. doi: 10.1002/clc.22716
 92. Smith SL, Matthews EO, Moxon JV, Golledge J. A systematic review and meta-analysis of risk factors for and incidence of 30-day readmission after revascularization for peripheral artery disease. *J Vasc Surg*. 2019;70:996–1006.e7. doi: 10.1016/j.jvs.2019.01.079
 93. Matsushita K, Kwak L, Yang C, Pang Y, Ballew SH, Sang Y, Hoogeveen RC, Jaar BG, Selvin E, Ballantyne CM, et al. High-sensitivity cardiac troponin and natriuretic peptide with risk of lower-extremity peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) study. *Eur Heart J*. 2018;39:2412–2419. doi: 10.1093/eurheartj/ehy106
 94. Tanindi A, Cemri M. Troponin elevation in conditions other than acute coronary syndromes. *Vasc Health Risk Manag*. 2011;7:597–603. doi: 10.2147/VHRM.S24509
 95. Zhang H, Mo X, Hao Y, Huang J, Lu X, Cao J, Gu D. Adiponectin levels and risk of coronary heart disease: a meta-analysis of prospective studies. *Am J Med Sci*. 2013;345:455–461. doi: 10.1097/MAJ.0b013e318262dbef
 96. Sook Lee E, Park SS, Kim E, Sook Yoon Y, Ahn HY, Park CY, Ho Yun Y, Woo Oh S. Association between adiponectin levels and coronary heart disease and mortality: a systematic review and meta-analysis. *Int J Epidemiol*. 2013;42:1029–1039. doi: 10.1093/ije/dyt087
 97. Vaidya A, Joore MA, ten Cate-Hoek AJ, ten Cate H, Severens JL. Cost-effectiveness of risk assessment and tailored treatment for peripheral arterial disease patients. *Biomark Med*. 2014;8:989–999. doi: 10.2217/bmm.14.45