Emerging biomarkers for cardiovascular risk prediction and personalized treatment options in patients with polyvascular atherosclerotic disease

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1. Synopsis

1.1. Introduction

1.1.1 Atherosclerosis and polyvascular disease

Atherosclerotic cardiovascular disease (ASCVD) and its different forms of manifestation leading to coronary artery disease (CAD), lower-leg peripheral arterial disease (PAD), and cerebrovascular disease (CeVD) is among the primary causes of death worldwide.[1,2] The treatment of ASCVD has improved substantially in recent decades, driven by advances in pharmacologic secondary prevention and surgical or interventional techniques, leading to improved clinical outcomes for patients.[3] Nonetheless, despite adherence to guideline-directed medical therapy, individuals with atherosclerotic disease display a residual annual risk of approximately 5% for major adverse cardiovascular events (MACE), underscoring the need for enhanced risk stratification to identify those individuals at increased risk and subsequent tailored treatment strategies.[4-6]

In a substantial proportion of patients with ASCVD, atherosclerotic changes are present across two or more arterial vascular beds from the coronary, cerebrovascular and lower-leg peripheral arterial tree. This more extensive form of atherosclerosis, involving multiple arterial territories, is referred to as polyvascular atherosclerotic disease (PolyVD).[7] The prevalence of PolyVD among patients with ASCVD has been reported to range between 15-25%, based on data from large-scale registries and clinical trials.[8-11] With regard to clinical outcomes, PolyVD represents an unfavorable atherothrombotic phenotype, as individuals with extensive atherosclerotic disease experience a more than 2-fold increased risk for recurrent MACE in contrast to patients with monovascular disease (MVD).[9,10,12-14] Importantly, patients with PolyVD also frequently exhibit the greatest absolute and relative risk reduction from secondary preventive treatment strategies, showcasing the importance of stringent

adherence to guideline directed therapy in these individuals.[12,15-18] Thus, enhanced risk assessment strategies that incorporate individual patient characteristics are needed to more accurately evaluate the risk of adverse events and to potentially guide clinical management in this high-risk population.

1.1.2 Cardiovascular risk assessment and circulating biomarkers

The anticipated benefit of implementing a preventive strategy, both in the context of primary or secondary prevention, depends on the cardiovascular risk profile of the affected individual.[19] In the primary prevention setting, several validated risk prediction models are available to facilitate this estimation. Amongst them are the Pooled Cohort Equation, developed in the United States, and the Systematic COronary Risk Evaluation 2 model, established in Europe.[20,21] For patients with established ASCVD, risk assessment is mostly being carried out on the basis of demographic features, the burden of cardiovascular risk factors, presence of comorbidities, as well as selected imaging characteristics.[22] However, both the models used in the primary prevention as well as the secondary prevention setting are limited by their heavy reliance on classical risk factors, including age, sex, blood pressure, cholesterol levels, smoking status, and diabetes. These factors, while predictive at a population level, may lack the granularity needed for accurate individual-level risk stratification, especially in patients at very high risk such as individuals with PolyVD.

In this context, circulating biomarkers may play a valuable role in improving individualized risk prediction, as they reflect underlying biological processes such as inflammation and myocardial injury, which are not fully captured by traditional risk scores. Moreover, specific biomarker concentrations have been demonstrated to correlate with adverse clinical outcomes. For example, recent studies have shown

that increased concentrations of high-sensitivity troponin T and I (hsTnT/I), a marker of myocardial damage, are linked to incident adverse events both in the general population and in individuals with ASCVD.[23-25] In addition, the essential role of chronic low-grade inflammation as driver of the development and progression of ASCVD has been established.[26-29] A commonly used and broadly available biomarker reflecting inflammatory activity is high-sensitivity C-reactive protein (hsCRP), which has been linked with adverse outcomes in patients with and without ASCVD.[30-32]

Notably, emerging evidence suggests that incorporating selected biomarkers can refine risk categorization.[32-34] Integrating biomarkers into risk assessment frameworks may therefore improve the prognostic accuracy of outcome prediction and enable personalized preventive strategies. However, in patients with most extensive atherosclerotic disease, i.e. PolyVD, data on the prognostic utility of circulating cardiovascular biomarkers including hsTnT/I and hsCRP remain limited.

1.1.3. Interventional treatment of coronary disease and impact of polyvascular disease

Recent advances in interventional cardiology have significantly expanded the therapeutic armamentarium for patients with complex cardiovascular disease. Percutaneous coronary intervention (PCI) has emerged as a viable alternative to coronary artery bypass grafting in selected patients with stenotic coronary disease also involving the left main coronary artery.[35] Refinements with regard to the interventional aspects of PCI, including new generation drug-eluting stents, intravascular imaging, and physiologic lesion assessment has enhanced the safety and efficacy of PCI procedures, which is supported by data from randomized trials and registry analyses.[36-38]

The presence of PolyVD is recognized as a risk enhancer for incident thrombotic events in patients undergoing PCI, according to the most recent European Society of Cardiology guidelines on acute coronary syndromes.[39] In addition to presenting with extra-coronary atherosclerosis, patients with PolyVD are typically older and present with a higher burden of comorbidities.[7,12] As such, the negative impact of PolyVD on both procedural and long-term outcomes following PCI has been consistently demonstrated.[40,41]

Patients undergoing left-main PCI represent a high-risk subset, as revascularization of the left main coronary artery is considered a complex interventional procedure.[35] Many patients with stenotic left-main disease are deferred from coronary artery bypass grafting (CABG, i.e. a surgical approach to coronary revascularization), as they are predominantly elderly and exhibit a higher burden of comorbidities, such as kidney disease and cardiovascular risk factors, thus representing the typical profile of patients with PolyVD. However, despite the clinical significance of more extensive ASCVD, contemporary data on the prognostic implications of PolyVD in patients undergoing left-main PCI remain limited.

1.2. Research Question

Within this context, this PhD thesis aims to investigate the predictive value of biomarkers across varying severities of atherosclerotic disease. Additionally, it explores how the presence of extensive atherosclerosis - specifically PolyVD - influences clinical outcomes following interventional left-main revascularization.

The following key aspects are examined:

1. The prognostic utility of high-sensitivity Troponins as emerging cardiac biomarker for the outcome prediction throughout the extent of atherosclerotic disease.
2. The impact of residual inflammatory burden measured by hsCRP as prognostic marker according to the presence of absence of PolyVD.
3. The interplay between lifestyle risk factors, inflammatory burden and severity of atherosclerotic disease.
4. The prognosis of patients with and without PolyVD undergoing left-main PCI.

1.3. Materials/Methods and Results - Original works

1.3.1. Outcome prediction using high-sensitivity troponins across the extent of atherosclerotic disease

Rohde J*, Brunner FJ*, Goßling A, Graap H, Arnold N, Blaum C, Kellner C, Pieper L, Köster L, Lorenz T, Zeller T, Blankenberg S, Waldeyer C, **Bay B**.

Prognostic utility of high-sensitivity troponins according to atherosclerotic vascular disease severity.

Atherosclerosis. 2025 Mar 20;403:119167. doi:

10.1016/j.atherosclerosis.2025.119167.

*shared first authorship

Background and aim: Circulating biomarkers are increasingly being used as tool in the assessment of risk for patients with and without atherosclerotic disease.[42] A broadly available cardiac biomarker are troponins T and I, most often quantified via high-sensitivity assays.[43] Next to their utilization in the diagnosis of acute coronary syndromes, increased concentrations of hsTnT/I have been shown to associate with adverse outcomes both in the population, as well as in patients with ASCVD.[23-25,39] However, whether the extent of ASCVD affects circulating levels of hsTnT/I as well as the prognostic capabilities of cardiac troponins is unknown, which we therefore investigated in a contemporary cohort.

Methods: We utilized data from the single center cohort INTERCATH (NCT04936438), where patients admitted for coronary angiography at the University Heart and Vascular Center Hamburg, Germany were included from 2015-2021. For current analysis, patients with a chronic coronary syndrome and available hsTnT/I concentrations were included. Subgroups according to ASCVD extent were created –

no ASCVD, MVD (i.e. CAD detected on angiography) and PolyVD (CAD and in addition PAD and/or CeVD at baseline, which was quantified via patient history). HsTnT/I concentrations were measured at inclusion using commercially available assays.

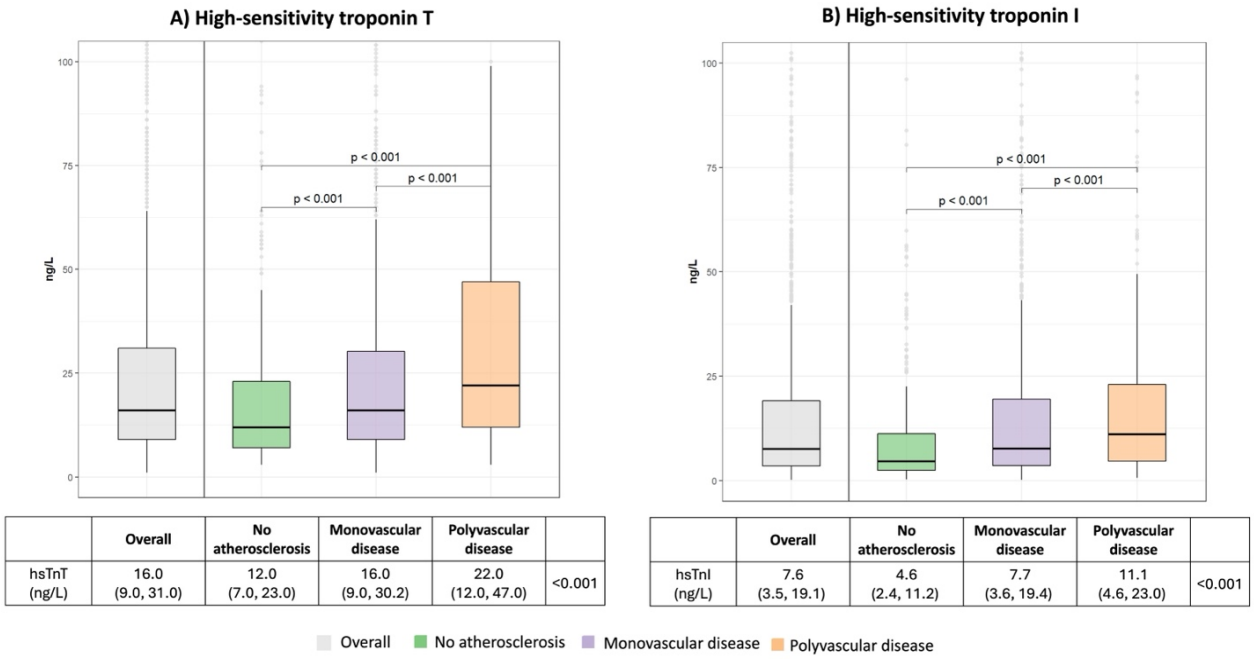
A linear regression analysis was conducted to assess the relationship between hsTnT and hsTnI (log-transformed) and the extent of atherosclerotic disease. Also, to investigate the association of log-transformed hsTnT and hsTnI per change of standard deviation (SD) with all-cause mortality and MACE, which included cardiovascular mortality, unplanned coronary revascularization procedures (interventional and surgical), myocardial infarction, or stroke, a Cox regression analysis was performed. Both regression analyses were adjusted, correcting for age, female sex, arterial hypertension, body mass index (BMI), hyperlipoproteinemia, active smoking, diabetes, estimated glomerular filtration rate (eGFR) and Gensini score.

Main results: In a total of n=2,273 patients (median age 70.2 years [Interquartile range [IQR]: 60.9, 76.8], 28.7% female) 21.5% had no ASCVD, 61.2% patients had MVD and 17.3% displayed PolyVD. A step-wise increase of hsTnT as well as hsTnI according to ASCVD extent was noted (also see *Figure 1*). However, on linear regression analysis neither MVD (hsTnT – Beta: 0.00 [95%-Confidence Interval [95%-CI]: -0.14, 0.14]; p=0.99 and hsTnI – Beta: 0.04 [95%-CI: -0.15, 0.23]; p=0.66) nor PolyVD (hsTnT – Beta: 0.13 [95%-CI: -0.05, 0.32]; p=0.16 and hsTnI – Beta: 0.09 [95%-CI: -0.17, 0.35]; p=0.48) was independently associated with hsTn concentrations. Median follow-up was 4.24 years (IQR: 4.19, 4.27). All-cause mortality was highest in the PolyVD group (42.9%), followed by MVD (24.5%) and no atherosclerosis (18.3%). MACE rates were similar in individuals with PolyVD (46.9%)

and MVD (42.8%), while significantly lower in patients without atherosclerosis (8.5%). With regard to outcomes an SD increase of $_{log}$hsTnT (MVD – Hazard ratio [HR] per SD: 1.32 [95%-CI: 1.15, 1.51]; p<0.001 and PolyVD - 1.42 [1.16, 1.73]; p<0.001) and and $_{log}$hsTnI (MVD - 1.35 [1.17, 1.56]; p<0.001 and PolyVD - 1.38 [1.14, 1.68]; p=0.0013) both associated with all-cause mortality during follow-up in patients with ASCVD, whereas this was not the case for patients without atherosclerotic disease. No association of $_{log}$hsTnT/I with MACE was noted in any subgroup (*Table 1*).

Conclusion: Patients with a more extensive ASCVD exhibited higher hsTnT/I concentrations and a greater occurrence of all-cause mortality and MACE. The strong association between hsTnT/I levels and all-cause mortality in ASCVD patients highlights the significance of these biomarkers in risk assessment. These data underscore the predictive capabilities of troponins as prognostic marker with regard to all-cause mortality in patients across the spectrum of atherosclerotic disease.

Figure 1: Blood levels of high-sensitivity troponin T and high-sensitivity troponin I for the entire cohort and in relation to the severity of atherosclerotic vascular disease.



	Overall	No atherosclerosis	Monovascular disease	Polyvascular disease	
hsTnT (ng/L)	16.0 (9.0, 31.0)	12.0 (7.0, 23.0)	16.0 (9.0, 30.2)	22.0 (12.0, 47.0)	<0.001

	Overall	No atherosclerosis	Monovascular disease	Polyvascular disease	
hsTnI (ng/L)	7.6 (3.5, 19.1)	4.6 (2.4, 11.2)	7.7 (3.6, 19.4)	11.1 (4.6, 23.0)	<0.001

HsTnI: high-sensitivity troponin I; hsTnT: high-sensitivity troponin T.

Table 1: Multivariable Cox regression analysis of high-sensitivity troponin T and high-sensitivity troponin I with outcomes across the extent of atherosclerotic vascular disease.

All-cause mortality				
	No atherosclerosis	**Monovascular disease**	**Polyvascular disease**	**p-interaction**
hsTnT, HR per change of SD (95% CI)	1.26 (0.95, 1.68); p=0.11	1.32 (1.15, 1.51); p<0.001	1.42 (1.16, 1.73); p<0.001	0.75
hsTnI, HR per change of SD (95% CI)	1.13 (0.83, 1.53); p=0.44	1.35 (1.17, 1.56); p<0.001	1.38 (1.14, 1.68); p=0.0013	0.51
Major adverse cardiovascular events				
	No atherosclerosis	**Monovascular disease**	**Polyvascular disease**	**p-interaction**
hsTnT, HR per change of SD (95% CI)	0.95 (0.60, 1.51); p=0.84	0.99 (0.87, 1.13); p=0.86	1.01 (0.79, 1.30); p=0.91	0.97
hsTnI, HR per change of SD (95% CI)	1.08 (0.66, 1.75); p=0.77	1.12 (0.99, 1.28); p=0.075	0.88 (0.67, 1.16); p=0.38	0.27

CI: Confidence interval; CABG: Coronary artery bypass graft; HR: Hazard ratio; hsTnI: High-sensitivity troponin I; hsTnT: High-sensitivity troponin T; PCI: Percutaneous coronary intervention; SD: Standard deviation.

1.3.2. Inflammation in patients undergoing percutaneous coronary intervention according to the presence of polyvascular disease

Bay B, Vogel B, Sharma R, Sartori S, Leone PP, Nathani M, Oliva A, Smith KF, Hooda A, Sweeny J, Dangas G, Kini A, Krishnan P, Sharma SK, Mehran R.

Inflammatory risk and clinical outcomes according to polyvascular atherosclerotic disease status in patients undergoing PCI.

Clin Res Cardiol. 2024 Jun 20. doi: 10.1007/s00392-024-02471-w.

Background and aim: Over the last years, for patients with atherosclerotic disease, low-grade inflammation has been recognized as a residual risk factor, even after adherence to guideline directed pharmacological treatment.[26] Most commonly, inflammation is quantified though the use of a hsCRP assay.[30] More recently, hsCRP has been proven to be a more potent predictor of outcome than low density lipoprotein cholesterol (LDL-C) levels in statin-treated patients, both in the population as well as after PCI.[31,32] However, data on the association of hsCRP and clinical outcomes according to the severity of ASCVD are scare, which we aimed to investigate in a contemporary cohort of PCI patients.

Methods: We implemented an analysis including patients undergoing PCI which were included in the Mount Sinai PCI database (Mount Sinai Hospital, New York, USA) between 2012-2020. Patients with a chronic coronary syndrome and available hsCRP concentrations at baseline were included. In contrast, individuals with a history of cancer, hsCRP values >10 mg/l, and acute coronary syndromes were excluded.

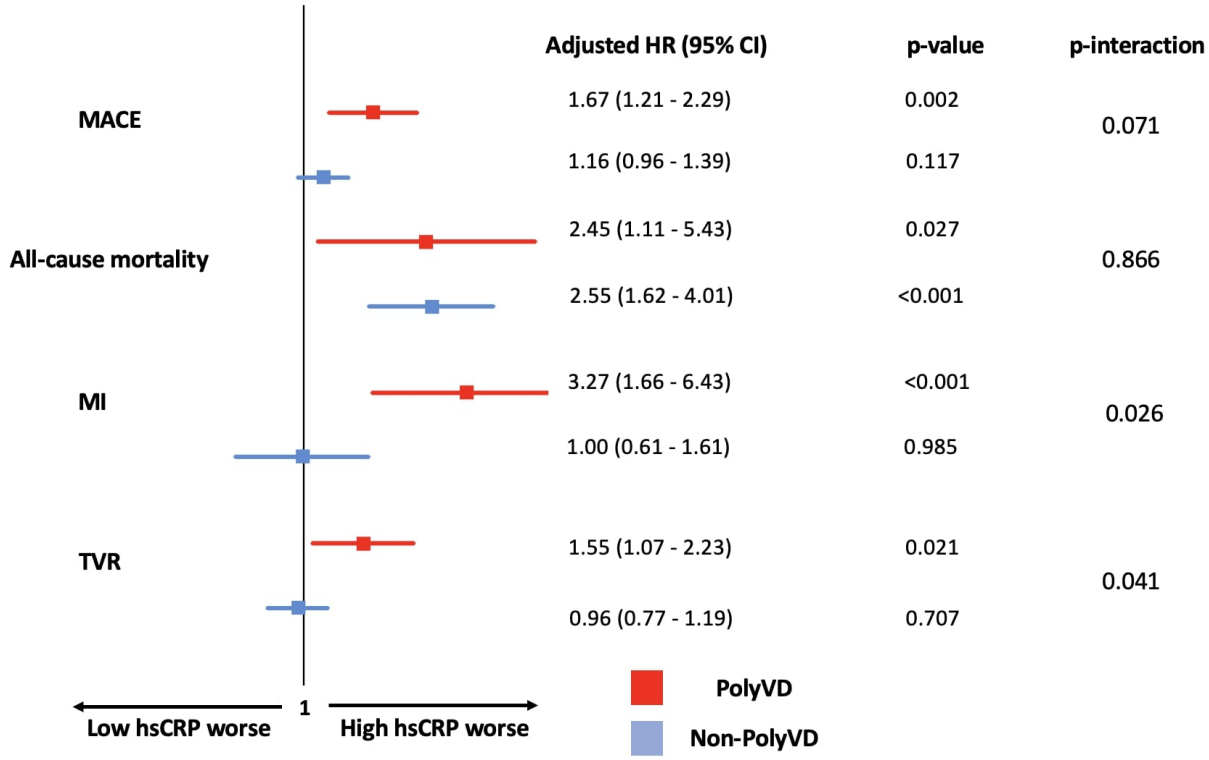
Patients were stratified according to the presence of PolyVD and hsCRP levels (>3 mg/l and ≤3 mg/l) before the baseline PCI. PolyVD was deemed prevalent if either a

history of PAD and/or CevD (quantified via patient history) was present at baseline in addition to CAD. The primary MACE endpoint comprised all-cause mortality, spontaneous myocardial infarction (MI), or target vessel revascularization (TVR) after 1 year follow-up. A Cox regression model adjusting for age, sex, ethnicity (Caucasian as reference group), BMI, current smoking, diabetes, LDL-C concentrations, hypertension, chronic kidney disease (CKD), anemia, atrial fibrillation, lung disease, previous CABG, and intake of statins was calculated.

Main results: From the overall cohort of n=10,359 participants, a total of 17.4% patients had PolyVD at baseline. Individuals with PolyVD were older (68.9±10.0 vs. 65.3±10.9 years; $p<0.001$), and had a higher burden of comorbidities. Amongst individuals who had PolyVD, a greater proportion displayed elevated hsCRP levels (33.6%) than in the non-PolyVD subgroup (24.7%). After 12 months of follow-up, the highest MACE rates were seen in patients with PolyVD who had elevated hsCRP levels (PolyVD+hsCRP >3 mg/l: 16.0%). In contrast, similar MACE incidences were recorded in patients with PolyVD and hsCRP ≤3 mg/l (10.1%) and in non-PolyVD patients with hsCRP >3 mg/l (10.6%). Lastly individuals without PolyVD and an hsCRP ≤3 mg/l had the overall lowest event rates (8.7%). Notably, on fully adjusted Cox regression analysis, increased hsCRP concentrations remained an independent predictor for adverse outcomes in patients with PolyVD. This was however not the case for patients without PolyVD (*Figure 2*).

Conclusion: In patients with PolyVD, hsCRP was an independent predictor of MACE, which was not observed in individuals without PolyVD. These results emphasize the synergistic relationship between atherosclerotic disease extent and inflammation on clinical outcomes.

Figure 2: Adjusted Cox regression analysis investigating the association of high-sensitivity C-reactive protein with clinical outcomes according to the presence of absence of polyvascular disease after 12 months follow-up



CI: Confidence interval; hsCRP: high-sensitivity C-reactive protein; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; PolyVD: Polyvascular atherosclerotic disease; TVR: Target vessel revascularization.

1.3.3. Inflammatory burden according to lifestyle risks factors and atherosclerotic disease extent

Bay B*, Blaum C*, Kellner C, Bei der Kellen R, Ojeda F, Waibel J, Arnold N, Behrendt CA, Rimmele DL, Thomalla G, Twerenbold R, Blankenberg S, Zyriax B, Brunner FJ*, Waldeyer C*.

Inflammatory burden, lifestyle and atherosclerotic cardiovascular disease: insights from a population based cohort study.

Sci Rep. 2023 Dec 8;13(1):21761. doi: 10.1038/s41598-023-48602-7.

*shared first/last authorship

Background and aim: As described, inflammation plays a pivotal role in the development and progression of atherosclerotic disease.[26] Recent seminal trials have also been able to showcase that targeting the inflammatory cascade via pharmacological compounds can improve outcomes in patients with ASCVD.[27-29] However, concentrations of inflammatory biomarkers such as hsCRP can be influenced by a multitude of patient characteristics.[44-47] Previously, data investigating the impact of so-called lifestyle risk factors (LRF), i.e. lack of physical activity (PA), poor diet, smoking and elevated BMI have demonstrated that these factors can influence hsCRP concentrations.[48] However, investigations exploring the interplay between ASCVD extent, LRF and inflammatory biomarkers are lacking, which we sought to evaluate in a large population-based study.

Methods: Data from the population-based cohort study Hamburg City Health Study (HCHS; Hamburg, Germany) was used. Participants with available hsCRP concentrations at baseline were included for analysis, whereas individuals with an

hsCRP >10 mg/l, chronic inflammatory disorders, prevalent neoplastic disease, intake of immunosuppressants, or antineoplastic medication were excluded.

The overall population was stratified according to ASCVD extent (0, 1 or ≥2 affected vascular systems from the coronary, cerebrovascular and lower leg peripheral arterial beds). CAD was deemed prevalent via medical history. CeVD was diagnosed via the combination of patient history (prior stroke), or by an intima-media thickness of ≥1 mm, vascular plaque, or stenoses on carotid ultrasound at baseline. PAD was diagnosed via medical history, or an ankle-brachial-index (ABI) ≤0.9. LRF (lack of PA [<1.5 hours/week of exercise], overweight [BMI ≥25 kg/m^2] current smoking, and poor adherence to a Mediterranean diet [simple Mediterranean diet score ≤2 points]) were assessed using a standardized questionnaire. A linear regression model was used to investigate the association of LRF with logarithmic hsCRP concentrations in the overall population, as well as the different ASCVD subgroups. Adjustment was carried out for age, sex, diabetes, arterial hypertension, intake of statins and CKD.

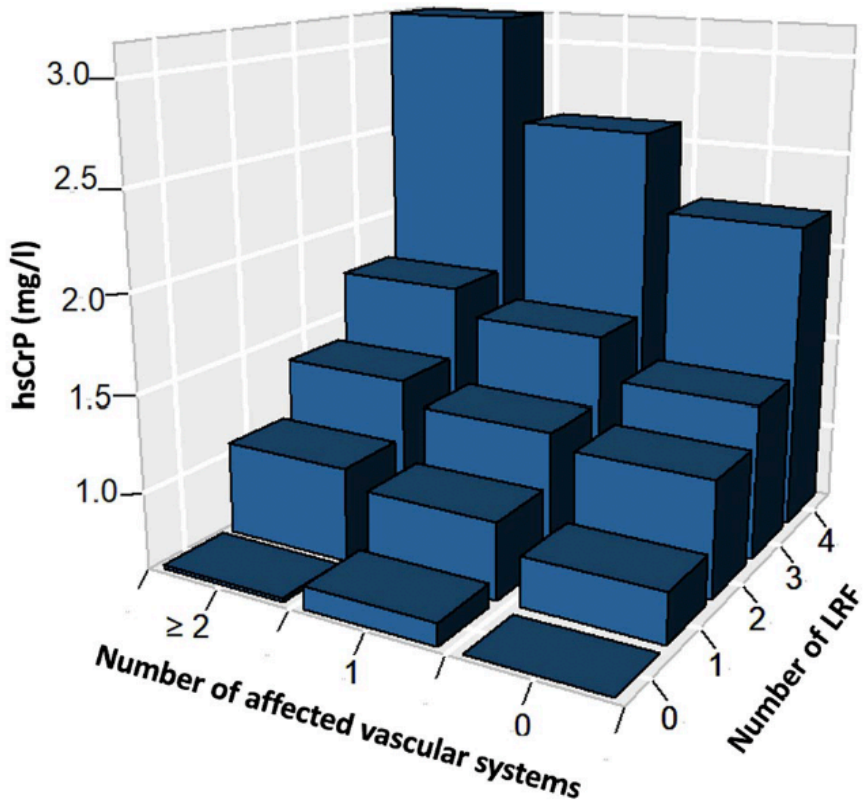
Main results: From the overall included n=6,765 (median age 61.0 [54.0, 68.0], 51.1% female sex) participants, 51.4% individuals had no ASCVD, 35.7% and 12.8% participants had atherosclerosis in 1 or ≥2 (i.e. PolyVD) arterial vascular beds, respectively. Individuals with ≥2 vascular beds affected had a substantially higher prevalence of 3 and more LRF than those with no ASCVD or 1 affected vascular bed. In the overall cohort, a median hsCRP of 1.1 (IQR: 0.6, 2.3) mg/l was noted. Also, we found an incremental increase of hsCRP concentrations according to ASCVD severity (no ASCVD: 1.0 [0.5, 2.1] mg/l; ASCVD in 1 vascular bed: 1.2 [0.6, 2.4] mg/l; ASCVD in ≥2 vascular beds: 1.3 [0.7, 2.9] mg/l; p <0.001). This was also documented with an increasing number of LRF (hsCRP for 0 LRF: 0.7 [0.4, 1.2] mg/l;

1 LRF: 0.9 [0.5, 1.9] mg/l; 2 LRF: 1.2 [0.7, 2.6] mg/l; 3 LRF: 1.5 [0.8, 3.1] mg/l; 4 LRF: 2.5 [1.2, 4.4] mg/l; p <0.001).

Of note, participants with the greatest extent of ASCVD and the highest number of LRF had the highest levels of hsCRP (*Figure 3*). On multivariable linear regression analysis, an independent association of LRF with hsCRP concentrations across the extent of ASCVD was seen (*Table 2*). Interestingly, elevated BMI showed the strongest association with hsCRP across all levels of ASCVD involvement (overall cohort: Beta 0.68 [95% CI: 0.63, 0.73], no ASCVD: 0.69 [0.61, 0.76], ASCVD in 1 vascular system: 0.67 [0.58, 0.77], ASCVD in ≥2 vascular systems: 0.63 [0.47, 0.79]; all p<0.001).

Conclusion: In this large-scale contemporary population, we were able to demonstrate that LRF and ASCVD have synergistic effects on the inflammatory burden measured by hsCRP. These data might help identify patients in whom targeted improvement of LRF, and alternatively anti-inflammatory agents, could be used with the aim to improve outcomes.

Figure 3. Median high-sensitivity C-reactive protein levels according to the number of affected vascular systems and number of lifestyle-related risk factors.



HsCRP: High-sensitivity C-reactive protein; LRF: Lifestyle-related risk factors.

Table 2: Adjusted linear regression analysis investigating the association of lifestyle-related risk with high-sensitivity C-reactive protein according to the number of affected vascular systems.

Overall		
Number of LRF	**Beta (95% CI)**	**p-value**
1	0.32 (0.23, 0.42)	<0.001
2	0.59 (0.50, 0.67)	<0.001
3	0.76 (0.66, 0.85)	<0.001
4	1.17 (1.01, 1.35)	<0.001
No atherosclerosis		
Number of LRF	**Beta (95% CI)**	**p-value**
1	0.30 (0.18, 0.42)	<0.001
2	0.59 (0.48, 0.70)	<0.001
3	0.70 (0.57, 0.83)	<0.001
4	1.05 (0.79, 1.31)	<0.001
1 affected vascular system		
Number of LRF	**Beta (95% CI)**	**p-value**
1	0.33 (0.16, 0.49)	<0.001
2	0.55 (0.40, 0.71)	<0.001
3	0.78 (0.60, 0.95)	<0.001
4	1.19 (0.90, 1.47)	<0.001
≥2 affected vascular systems		
Number of LRF	**Beta (95% CI)**	**p-value**
1	0.45 (0.13, 0.77)	0.007
2	0.66 (0.36, 0.97)	<0.001
3	0.87 (0.56, 1.18)	<0.001
4	1.29 (0.85, 1.74)	<0.001

hsCRP: high-sensitivity C-reactive protein; LRF: lifestyle-related risk factors.

1.3.4. Impact of polyvascular disease on outcome after left-main PCI

Bay B, Sharma R, Roumeliotis A, Power D, Sartori S, Murphy J, Vogel B, Smith KF, Oliva A, Hooda A, Sweeny J, Dangas G, Kini A, Krishnan P, Sharma SK, Mehran R. *Impact of Polyvascular Disease in Patients undergoing unprotected Left Main Percutaneous Coronary Intervention.*

Am J Cardiol. 2024 May 1;222:113-120. doi: 10.1016/j.amjcard.2024.04.037.

Background and aim: For patients with stenotic CAD, PCI has become the mainstay of revascularization.[35] Patients with left main coronary disease are at especially high-risk for adverse events if left untreated.[36] Over the last years, a percutaneous treatment approach for left-main CAD has proven its safety and efficacy, and is thus recommended by current guidelines as viable alternative to CABG for left-main revascularization.[35,37] However, there is a lack of data on the impact of extensive atherosclerotic disease, i.e. PolyVD, in patients treated by left-main PCI. This is especially important, since patients with PolyVD typically represent an older and more comorbid population.[7,12] In this population, a percutaneous approach is often favored for the treatment of left main coronary artery disease in clinical practice.[49] We therefore aimed to investigate the impact of PolyVD on outcomes after left-main PCI in a single-center analysis.

Methods: The current analysis was implemented in patients undergoing unprotected left-main coronary intervention with and without PolyVD which were included in the Mount Sinai left-main PCI database (Mount Sinai Hospital, New York, USA) from 2014-2019. PolyVD was defined as the presence of either PAD and/or CeVD (based on patient history) in addition to CAD at baseline. The main outcome of interest was MACE as a composite of all-cause mortality and spontaneous MI within 1 year after

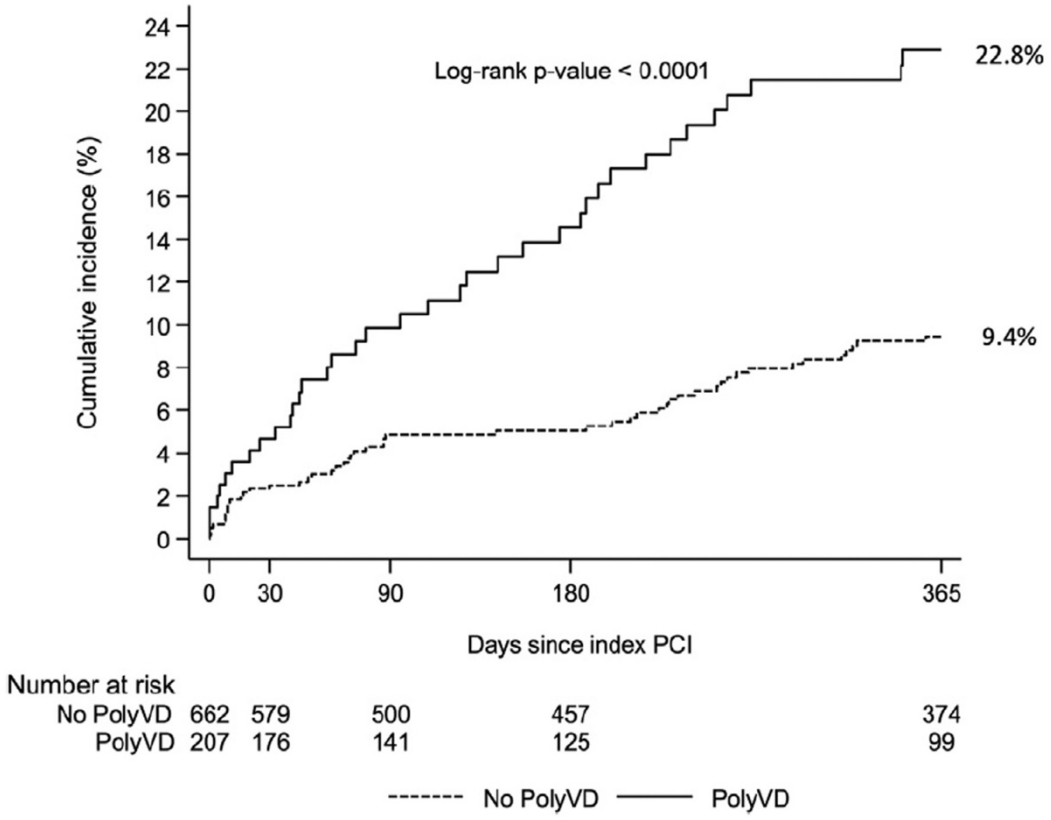
the PCI at baseline. Secondary outcomes included target lesion revascularization (TLR) and TVR. An adjusted Cox regression model was calculated, with adjustment for age, sex, hypertension, diabetes mellitus, CKD, lung disease, anemia, non–ST-segment elevation myocardial infarction, left ventricular ejection fraction, and Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score.

Main results: Overall, 869 patients (mean age 70.9±12.2 years, 33.3% female) were included. A total of n=207 (23.8%) had PolyVD, whereas n=662 (76.2%) were included in the non-PolyVD subgroup. Patients with PolyVD were older and more comorbid (i.e. with higher rates of cardiovascular risk factors, diabetes and CKD). Also, with regard to lesion characteristics, a higher rate of calcified lesions was noted in PolyVD patients, whereas SYNTAX scores were similar between groups. At 1-year follow-up, patients with PolyVD were noted to have over twice as many events of the primary MACE endpoint (PolyVD: 22.8% vs. non-PolyVD: 9.4%, also see *Figure 4*), which was mainly due to higher rates of all-cause mortality (PolyVD: 18.3% vs. non-PolyVD: 7.1%). On adjusted Cox regression analysis (*Table 3*), the presence of PolyVD remained an independent predictor of MACE (HR: 1.87; 95%-CI: 1.15-3.05; p=0.012) as well as all-cause mortality (HR: 2.24; 95%-CI: 1.27-3.92; p=0.005). No significant association of PolyVD with incident MI was documented. Also, no between group differences were noted for TLR (HR: 0.82; 95%-CI: 0.42 - 1.59; p=0.557) as well as TVR (HR: 0.86; 95%-CI: 0.48 - 1.54; p=0.607) on adjusted analysis.

Conclusion: In a contemporary population of patients undergoing left-main PCI, nearly one quarter had PolyVD. The presence of extensive ASCVD was associated with increased rates of MACE, an association which remained statistically significant

after multivariable adjustment. In summary, our findings emphasize the presence of extra-coronary vascular disease a risk modifier in patients undergoing left-main PCI.

Figure 4: Cumulative incidence curves of major adverse cardiovascular events for the polyvascular disease and non-polyvascular disease population 1 year after the baseline left-main PCI.



MACE: Major adverse cardiovascular events; PolyVD: Polyvascular disease; PCI: Percutaneous coronary intervention.

Table 3: Adjusted Cox regression analysis investigating the impact of polyvascular disease on clinical outcomes in patients undergoing left-main PCI after 1-year follow-up.

	PolyVD N=207 (23.8%)	Non PolyVD N=662 (76.2%)	Adjusted Hazard ratio (95% CI)	p-value
	No. of events (%)			
Primary outcome				
MACE	37 (22.8%)	50 (9.4%)	1.87 (1.15 - 3.05)	0.012
Components of the primary outcome				
All-cause mortality	30 (18.3%)	38 (7.1%)	2.24 (1.27 - 3.92)	0.005
Spontaneous MI	11 (8.4%)	16 (3.3%)	1.29 (0.55 - 3.06)	0.557
Secondary outcomes				
TLR	12 (8.5%)	49 (10.4%)	0.82 (0.42 - 1.59)	0.557
TVR	15 (11.0%)	64 (13.5%)	0.86 (0.48 - 1.54)	0.607

CI: confidence interval; MACE: Major adverse cardiovascular events; MI: myocardial infarction; PolyVD: Polyvascular disease; TLR: target lesion revascularization; TVR: target vessel revascularization.

1.4. Discussion

In this PhD thesis, the following key findings were made:

1. Elevated concentrations of hsTnT/I were significantly associated with increased all-cause mortality, but not MACE, across the spectrum of ASCVD severity.
2. In patients with PolyVD undergoing PCI, hsCRP was identified as a predictor of MACE, whereas this association was not observed in those without PolyVD.
3. Lifestyle factors demonstrated a strong association with hsCRP concentrations, irrespective of the number of vascular beds affected by atherosclerotic disease.
4. The presence of PolyVD was independently associated with an increased risk of adverse cardiovascular events among individuals undergoing left-main PCI, primarily driven by a higher rate of all-cause mortality.

The use of hsTn assays has become central to diagnosing patients with suspected acute coronary syndromes.[39] Elevated concentrations of hsTnT/I in stable patients have been shown to predict adverse clinical outcomes, irrespective of their diagnostic utility in the ACS setting.[23,24,50-53] One key aspect of this PhD thesis was to investigate the prognostic utility of hsTn concentrations across the spectrum of ASCVD extent, which was implemented in the contemporary INTERCATH cohort. We demonstrated that hsTnT/I had a similar and independent relationship with all-cause mortality in patients with MVD and PolyVD. This confirms previous findings in the general population and for patients with CAD only, where hsTnT/I was shown to associate with all-cause mortality, underscoring the role of troponins in outcome prediction.[23,24,50-53] Whether the integration of hsTn concentrations can enable tailored and potentially intensified secondary preventive strategies in PolyVD patients

remains to be determined in future prospective studies. Notably, in our analysis, no association of neither hsTnT nor hsTnI with MACE was observed in any subgroup. Previous studies have documented an association between both hsTnT and hsTnI levels with adverse cardiovascular events.[23,24,53] Whilst the current study may be limited in statistical power to detect an association between hsTnT/I and MACE, it provides novel insights in the clinical utility of the emerging cardiovascular biomarker hsTn across the spectrum of ASCVD.

As further cardiovascular biomarker reflecting low-grade chronic inflammation, we investigated the association of hsCRP with adverse cardiovascular events in patients with and without PolyVD undergoing PCI. We documented that patients with PolyVD had the highest concentrations of hsCRP, showcasing the interplay between ASCVD extent and hsCRP levels, a finding which confirms previous data from the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial.[54] Moreover, with regard to outcomes, a strong and independent association of hsCRP levels with MACE was noted for patients with PolyVD, whilst this was not the case for individuals without PolyVD. This observation is novel and, to our knowledge, has not been previously described in the literature, emphasizing the key role of inflammation for incident adverse events, especially in patients with extensive ASCVD.

Recently, the pharmacological targeting of essential steps within the inflammatory cascade has been shown to improve cardiovascular outcomes in patients with CAD.[27-29,55] Colchicine is currently the only available anti-inflammatory therapy recommended by clinical guidelines for the treatment of inflammation in patients with ASCVD, and two recent meta-analyses have underscored the efficacy of this treatment strategy on outcomes.[22,56,57] However, the ideal target population for both

currently available and emerging anti-inflammatory agents, including treatments such as interleukin-6 inhibitors, has yet to be clearly defined.[55] Since we were able to demonstrate a strong association of hsCRP with adverse outcomes in patients with PolyVD, this very high-risk subgroup may derive substantial benefit from pharmacological strategies addressing residual inflammatory risk. However, this will have to be confirmed in dedicated outcome trials.

In addition to pharmacological treatment of the inflammatory burden, LRF which encompass physical inactivity, smoking, poor diet, and overweight have previously been associated with elevated hsCRP concentrations.[48] However, the concomitant influence on circulating markers of inflammation of ASCVD affecting several arterial beds in addition to LRF was unknown. Within this PhD, we demonstrated that the number of affected arterial beds and the burden of LRF had a synergistic effect on hsCRP concentrations, with the highest levels of hsCRP documented in individuals with the greatest extent of ASCVD and most LRF. Also, a consistent association of LRF with hsCRP concentrations was noted on regression analysis across the number of arterial beds affected by atherosclerosis. Our findings suggest that patients with PolyVD, who exhibit both the highest hsCRP concentrations and the highest incidence of adverse events, may particularly benefit from comprehensive LRF optimization. Previously, in a modeling study for patients with CAD, 38% of the overall population achieved hsCRP levels <2 mg/L through lifestyle modifications alone.[48] By addressing modifiable lifestyle factors, the high-risk PolyVD population PolyVD could hypothetically improve their outcome independent of pharmacological anti-inflammatory therapies and potentially avoid medication associated side effects such as gastrointestinal hospitalizations.[58] Specifically, BMI reduction in overweight individuals poses to be a potentially effective strategy for lowering hsCRP

concentrations, as excess body weight demonstrated the strongest independent association with chronic systemic inflammation in our analysis.

With regard to interventional treatment of CAD, and specifically left-main CAD, PCI has emerged as a feasible and safe alternative to CABG.[36-38] PolyVD patients face an increased risk of both peri-procedural complications and long-term adverse outcomes after undergoing PCI.[40,41] Especially since PolyVD patients are often of advanced age and have a substantial burden of comorbidities, frequently rendering them as unsuitable for CABG, there is a need for data assessing the impact of more extensive ASCVD on outcomes following left-main PCI. In our analysis using a large single center registry, we found that nearly one fourth of patients undergoing unprotected left-main PCI had PolyVD, a population which displayed a high burden of comorbidities. This is also comparable to previous data in other real-world registries such as the National Cardiovascular Data CathPCI Registry, where 21.8% and 21.6% of individuals who underwent left-main PCI had PAD or CeVD, respectively.[59]

Moreover, in our study PolyVD patients undergoing left-main PCI had significantly higher rates of the composite MACE outcome at 1-year, largely attributable to an increased incidence of all-cause mortality. This confirms findings for patients with extensive atherosclerotic disease who underwent PCI for non left-main lesions, e.g. from the e-Ultimaster study, where a higher event rate in patients with PolyVD for the investigated cardiovascular endpoint was noted.[40] The increase in mortality in our study during follow-up are likely attributable to additional patient-related factors, e.g. frailty resulting from the cumulative burden of comorbidities. Given that the elevated mortality was not driven by the recorded ischemic events, it is essential to implement both secondary preventative strategies such as optimal management of

cardiovascular risk factors, but also non-cardiovascular comorbidities including kidney disease to improve outcomes in this patient population. From an interventional perspective, rates of MI and TVR during follow-up were comparable. This finding supports the notion that a percutaneous approach for the treatment of left-main CAD is procedurally effective and represents a viable therapeutic option, even in patients with non-coronary atherosclerotic disease.

In summary, this PhD thesis contributes to the advancement of research in patients with PolyVD by exploring biomarkers with potential clinical utility in guiding therapeutic decision-making, and by evaluating the impact of extensive ASCVD on clinical outcomes following interventional procedures, specifically left-main PCI.

2. List of abbreviations

ABI	Ankle-brachial-index
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CeVD	Cerebrovascular disease
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
HCHS	Hamburg City Health Study
HR	Hazard ratio
hsCRP	High-sensitivity C-reactive protein
hsTnI	High-sensitivity troponin I
hsTnT	High-sensitivity troponin T
IQR	Interquartile range
LDL-C	Low density lipoprotein cholesterol
LRF	Lifestyle risk factors
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MVD	Monovascular disease
PA	Physical activity
PAD	Lower-leg peripheral arterial disease
PCI	Percutaneous coronary intervention
PolyVD	Polyvascular atherosclerotic disease
SD	Standard deviation
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
TLR	Target lesion revascularization;
TVR	Target vessel revascularization

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4. Research articles

4.1. Prognostic utility of high-sensitivity troponins according to atherosclerotic vascular disease severity.

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Prognostic utility of high-sensitivity troponins according to atherosclerotic vascular disease severity☆

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ABSTRACT

Background and aims: Patients with atherosclerotic vascular disease (ASVD) affecting two or more different vascular beds, so called Polyvascular disease (PolyVD), are at an increased risk for adverse outcomes. In those patients, the prognostic utility of high-sensitivity troponin T and I (hsTnT/I) is under-investigated. We therefore aimed to explore the association between hsTnT/I with the extent of ASVD and outcomes in a contemporary cohort.

Methods: Patients undergoing coronary angiography with available hsTnT/I concentrations from the cohort study INTERCATH were included. Subgroups of patients without ASVD, monovascular disease (MVD), and PolyVD were created. Cox regression analyses were computed to investigate the associations of hsTnT/I with the extent of ASVD and clinical outcomes (all-cause mortality and major adverse cardiovascular events; MACE).

Results: In 2273 included patients, a stepwise increase of both hsTnT and hsTnI was observed according to the extent of ASVD. However, this association was statistically not significant after adjustment. hsTnT and hsTnI were independently associated with all-cause mortality for PolyVD (adjusted hazard ratio per standard deviation for hsTnT: 1.42 [95 %-CI: 1.16, 1.73]; $p < 0.001$ and hsTnI: 1.38 [1.14, 1.68]; $p = 0.0013$) and MVD (hsTnT: 1.32 [1.15, 1.51]; $p < 0.001$ and hsTnI: 1.35 [1.17, 1.56]; $p < 0.001$), whereas no association of hsTn with MACE was seen across the burden of ASVD.

Conclusions: Patients with a greater extent of ASVD had higher concentrations of hsTnT/I and an increased incidence of all-cause mortality as well as MACE. hsTnT/I concentrations were reliably linked to all-cause mortality in patients with ASVD, underscoring the role of biomarkers in risk prediction.

1. Introduction

Polyvascular disease (PolyVD) represents a malignant athero-thrombotic phenotype for which a substantially increased risk for incident cardiovascular events has previously been described [1]. This subtype of atherosclerotic vascular disease (ASVD) is defined via the presence of atherosclerosis in two or more arterial vascular beds [2]. In contrast to patients with no atherosclerosis or monovascular disease (MVD), i.e. atherosclerosis in a single vessel bed, a stepwise increase for the risk of adverse outcomes is described [2–4]. Hence, it is imperative to implement risk stratification to address the elevated residual likelihood for adverse events in this high-risk population.

Cardiac troponins are a component of the myofibrillar structure of the cardiomyocyte, which are released into the bloodstream following myocardial injury [5]. High-sensitivity troponin (hsTn) assays have become the mainstay in the diagnosis of patients with suspected acute coronary syndromes [6]. Over the last years, elevated concentrations of hsTnT and hsTnI have been shown to associate with adverse outcomes in

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the general population as well as in patients affected by chronic coronary disease, i.e. outside of scope of acute coronary syndromes [7–12]. HsTn assays have also been proposed as a tool to identify patients at elevated risk of adverse events and to determine the necessity for intensified secondary preventive interventions [13–15].

However, whether the presence of and extent of ASVD affects concentrations of hsTnT or hsTnI is unknown. In addition, data about the prognostic capability of hsTnT and hsTnI according to the presence and extent of ASVD is sparse, which we therefore sought to investigate in a contemporary cohort.

2. Patients and methods

2.1. Cohort description

Data from the all-comer single-center prospective cohort study INTERCATH (NCT04936438) undergoing coronary angiography at the University Heart and Vascular Center Hamburg, Germany were used. The study rationale have been described previously [16]. In summary, screening of all patients aged 18 years and older with adequate knowledge of the German language undergoing coronary angiography was carried out. In case of life threatening arrhythmias, cardiogenic shock, or other states of hemodynamic compromise, patients were not evaluated for inclusion. From 2015 to 2021, a total of 3012 patients were recruited into the cohort. For current analysis, patients after cardiac transplantation, presentation with myocardial infarction (MI, classified according to current guidelines at the time of admission, i.e. the 3rd and 4th Universal Definition, and adjudicated by physicians), missings in variables needed for the determination of ASVD extent, missings for both hsTnT and hsTnI and hsTn values equaling zero were excluded [17, 18]. An approval was obtained from the local ethics committee (PV4303, Hamburg, Germany) and all patients provided written and informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.2. Ascertainment of baseline characteristics

Medication and past medical history were collected through medical records and a standardized questionnaire. Cardiovascular risk factors were defined as follows: age, male gender, diabetes mellitus (self-reported or documented diabetes, self-reported use of antidiabetic medications, or an HbA1c level greater than 6.5 % at baseline), hyperlipoproteinemia (self-reported or documented hyperlipoproteinemia or self-reported use of lipid-lowering medication), current smoking, body mass index (BMI), and arterial hypertension (self-reported or documented hypertension or self-reported use of antihypertensive drugs).

2.3. Laboratory and biomarker measurements

Blood samples were collected at baseline, immediately after obtaining written informed consent and prior to coronary angiography. Standard laboratory parameters such as total cholesterol, triglycerides, high density lipoprotein-cholesterol (HDL-C), high-sensitivity C-reactive protein (hsCRP), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR) were determined within clinical routine. Using the Friedewald formula, low-density lipoprotein-cholesterol (LDL-C) concentrations were calculated. HsTnT (Roche Diagnostics Elecsys) was measured using standard laboratory measures within the clinical routine. HsTnI concentrations were measured in a batch-wise fashion using stored samples in our biomarker laboratory using a commercially available immunoassay (Abbott Diagnostics, ARCHITECT STAT).

2.4. Evaluation of atherosclerotic vascular disease extent

Coronary artery disease (CAD) was defined as the presence of coronary atherosclerosis on coronary angiography at baseline. CAD was categorized using different scoring methods aiming to quantify the anatomical complexity of coronary disease - the residual SYNTAX Score was calculated using the online available tool [19]. Gensini segments were identified and scored according to the published recommendations [20]. Lower extremity peripheral arterial disease (PAD) was deemed prevalent if a history of PAD was reported. Correspondingly, Cerebrovascular disease (CeVD) was judged to be prevalent if a previous history of stroke was documented.

Patients were stratified into subgroups according to the presence and extent of ASVD as follows: individuals with ASVD in any vascular system (from the peripheral and cerebral arterial vascular tree) in addition to CAD were included in the PolyVD subgroup, whilst patients with CAD only were included in the MVD subgroup. Lastly, if no atherosclerosis was present, patients were included in the no ASVD group.

2.5. Follow-up

Census follow-up was implemented via telephone- and/or mail-interview using a standardized questionnaire. Outcome measures of interest included all-cause mortality and major adverse cardiovascular events (MACE). The composite MACE endpoint included cardiovascular death, unplanned coronary revascularization procedures (i.e. Percutaneous coronary interventions [PCI] or Coronary artery bypass grafting [CABG]), non-fatal myocardial infarction, or non-fatal stroke. Moreover, all-cause mortality was ascertained from the death registry. Physicians adjudicated all incident endpoints using obtained medical records.

2.6. Statistical analyses

Categorical variables are presented as numbers and percentages. Continuous variables are depicted as median along with the 25th and 75th percentiles. Between-group comparisons were conducted using the chi-square test or the Kruskal-Wallis test, respectively. HsTnT and hsTnI concentrations across the extent of ASVD were visualized using boxplots. The association of log-transformed hsTnT and hsTnI with ASVD extent was evaluated using a linear regression analysis (unadjusted and adjusted for age, female sex, arterial hypertension, BMI, hyperlipoproteinemia, active smoking, diabetes, eGFR and Gensini score). The median duration of follow-up was calculated using the Kaplan-Meier follow-up estimator. Kaplan-Meier curves for all-cause mortality and the composite MACE endpoint according to the extent of ASVD were computed. Survival curve differences were compared using the log-rank test. Cox regression analysis was performed to explore the association of hsTnT and hsTnI (as hazard ratio [HR] per change of standard deviation [SD]) with the named outcomes both unadjusted as well as adjusted for the following potential confounders: age, female sex, arterial hypertension, BMI, hyperlipoproteinemia, active smoking, diabetes, eGFR and Gensini score. We added an interaction term for the interaction of hsTn with the extent of ASVD. Additional sensitivity analyses adjusting for the presence of PAD and/or stroke in patients with PolyVD were implemented. Statistical analyses were carried out utilizing R statistical software, version 4.2.1 (R Foundation for Statistical Computing).

3. Results

3.1. Baseline characteristics

A total of 2273 patients met eligibility criteria for analyses after implementing in- and exclusion criteria. Among the excluded patients, n = 237 individuals with an MI at baseline were omitted from the current analysis. (see Supplementary Fig. S1 for study flowchart). Baseline characteristics including cardiovascular risk factors, comorbidities,

ASVD extent and standard laboratory values for the overall cohort and the study subgroups are illustrated in Table 1. Median age was 70.2 years (60.9, 76.8) and n = 653 (28.7 %) included patients were female. Concerning ASVD extent, the following distribution was noted: n = 489 patients (21.5 %) had no atherosclerosis, n = 1390 (61.2 %) patients had MVD and n = 394 (17.3 %) displayed PolyVD (CAD: n = 394 (100 %); PAD: n = 237 [60.2 %]; CeVD: n = 203 [51.5 %]). All three vascular beds were affected in n = 46 (11.7 %) patients of the PolyVD cohort.

Patients with a greater burden of atherosclerotic disease were older (no atherosclerosis: 62.2 years [54.3, 73.1] vs. MVD: 71 years [62.0, 77.0] vs. PolyVD: 74.0 years [66.3, 78.7]; p < 0.001) and less likely to be female (no atherosclerosis: 42.5 % vs. MVD: 25.2 % vs. PolyVD: 24.1 %; p < 0.001). Moreover, a greater burden of cardiovascular risk factors such as diabetes, hyperlipoproteinemia and active smoking was prevalent in individuals with PolyVD. An incremental increase of baseline hsCRP (no atherosclerosis: 2.6 [1.0, 6.8] mg/L vs. MVD: 2.7 [1.0, 7.5] mg/L vs. PolyVD: 4.1 [1.3, 11.4] mg/L; p < 0.001) and NT-proBNP concentrations (no atherosclerosis: 396.0 [125.0, 1277.5] ng/L vs. MVD: 460.0 [153.0, 1696.0] ng/L vs. PolyVD: 957.0 [287.2, 2985.0] ng/L; p < 0.001) was noted according to the extent of ASVD. Notably, in persons with PolyVD a significantly higher SYNTAX (MVD: 7.0 [0, 14.0] vs. PolyVD: 11.0 [3.0, 20.0]; p < 0.001) and Gensini score (MVD: 13.0 [4.5, 35.0] vs. PolyVD: 21.0 [7.5, 45.8]; p < 0.001) was noted on coronary angiography.

3.2. Biomarkers and association with atherosclerotic vascular disease extent

Biomarker concentrations across the ASVD extent are displayed in Fig. 1. A stepwise increase in hsTnT blood concentrations was noted with increasing extent of ASVD (no atherosclerosis: 12.0 [7.0, 23.0] ng/L, MVD: 16.0 [9.0, 30.2] ng/L and PolyVD: 22.0 [12.0, 47.0] ng/L; p < 0.001). A similar distribution of hsTn concentrations was noted for hsTnI, as patients with PolyVD had the highest hsTnI levels (no atherosclerosis: 4.6 [2.4, 11.2] ng/L, MVD: 7.7 [3.6, 19.4] ng/L and PolyVD: 11.1 [4.6, 23.0] ng/L; p < 0.001).

After adjustment for possible confounders no independent association of PolyVD (0.13 [−0.05, 0.32]; p = 0.16) and MVD (Beta 0.00 [95 %-CI: −0.14, 0.14]; p = 0.99) with hsTnT was documented. A similar finding was seen for the association of PolyVD (0.09 [−0.17, 0.35]; p = 0.48) and MVD (0.04 [−0.15, 0.23]; p = 0.66) with hsTnI (Fig. 2). Unadjusted results of the linear regression analysis are included in Supplementary Table S1.

3.3. Clinical outcomes

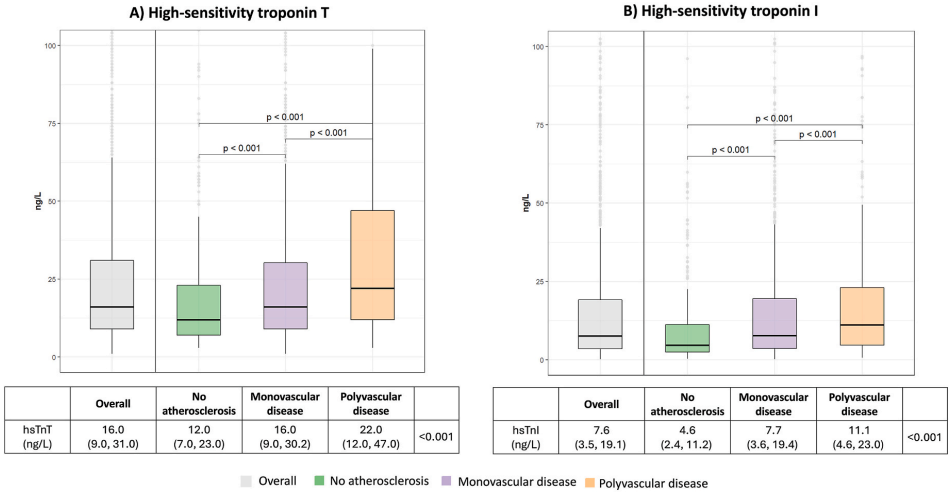
During the median follow-up time of 4.24 years (4.19, 4.27) a total of n = 468 patients died (99.03 % availability of all-cause mortality data) and n = 494 MACEs (98.50 % availability for MACE data) were noted. Kaplan-Meier curves for the endpoints all-cause mortality and MACE according to the extent of ASVD are included in Fig. 3. The highest rate of all-cause mortality after 5 years of follow-up was documented in the PolyVD population, where 42.9 % of patients died. Substantially lower rates of all-cause mortality were found in the MVD (24.5 %) and no atherosclerosis (18.3 %) subgroups. Concerning MACE, a similar incidence of cardiovascular events was noted in patients with MVD and PolyVD. Here, individuals with PolyVD had the highest MACE rate with 46.9 % after 5 years, whereas in the MVD population event rates of 42.8 % were seen. In contrast, low rates of MACE (8.5 % during the follow-up) were noted in patients without atherosclerosis. Kaplan-Meier curves for the individual components of the composite MACE endpoint are included in Supplementary Fig. S2.

Results of the fully adjusted Cox regression analysis investigating the association of hsTnT and hsTnI with the outcomes all-cause mortality and MACE are displayed in Table 2. After multivariable adjustment, a strong and independent association of $_{log}$hsTnT with all-cause mortality was noted for the PolyVD (adjusted HR per SD: 1.42 [95 %-CI: 1.16, 1.73]; p < 0.001) and MVD (1.32 [1.15, 1.51]; p < 0.001) subgroup, whereas this was not the case for patients without atherosclerosis (1.26 [0.95, 1.68]; p = 0.11). No interaction was documented for the utility of

Table 1
Baseline characteristics.

	Overall (n = 2273)	No atherosclerosis (n = 489)	Monovascular disease (n = 1390)	Polyvascular disease (n = 394)	p-value
Age (years)	70.2 (60.9, 76.8)	62.2 (54.3, 73.1)	71.0 (62.0, 77.0)	74.0 (66.3, 78.7)	<0.001
Female sex No. (%)	653 (28.7)	208 (42.5)	350 (25.2)	95 (24.1)	<0.001
Cardiovascular risk factors and medical history					
Arterial hypertension No. (%)	2003 (88.3)	364 (74.4)	1263 (91.0)	377 (95.9)	<0.001
BMI (kg/m^2)	26.8 (24.1, 30.4)	26.5 (23.4, 29.5)	26.9 (24.4, 30.5)	26.7 (24.1, 30.1)	0.038
Hyperlipoproteinemia No. (%)	1207 (53.7)	129 (26.4)	806 (57.9)	272 (69.0)	<0.001
Diabetes No. (%)	508 (22.4)	61 (12.5)	318 (22.9)	129 (32.7)	<0.001
Active smoking No. (%)	349 (15.4)	70 (14.3)	194 (14.0)	85 (21.6)	0.0012
Family history of CAD No. (%)	830 (36.4)	156 (32.5)	554 (39.9)	120 (30.5)	<0.001
History of MI No. (%)	500 (21.9)	–	369 (26.5)	131 (33.3)	<0.001
History of CAD No. (%)	1129 (49.7)	–	845 (60.8)	284 (72.1)	<0.001
History of PAD No. (%)	237 (10.4)	–	–	237 (60.2)	<0.001
History of Stroke No. (%)	203 (8.9)	–	–	203 (51.5)	<0.001
Laboratory values					
eGFR (mL/min)	73.3 (54.8, 88.0)	80.0 (63.3, 92.0)	73.6 (55.2, 87.8)	63.0 (44.6, 82.2)	<0.001
Total cholesterol (mg/dL)	163.0 (136.0, 196.0)	181.0 (148.0, 206.0)	161.0 (135.0, 195.0)	153.0 (132.0, 177.0)	<0.001
Triglycerides (mg/dL)	113.0 (84.0, 158.0)	104.0 (78.0, 143.0)	112.0 (84.0, 157.8)	127.0 (95.8, 176.0)	<0.001
HDL-C (mg/dL)	46.0 (38.0, 57.0)	49.0 (40.0, 62.8)	46.0 (38.0, 56.0)	43.0 (35.2, 53.0)	<0.001
LDL-C (mg/dL)	88.5 (66.0, 117.0)	103.0 (77.0, 126.0)	87.0 (65.0, 116.0)	78.0 (61.2, 99.8)	<0.001
hsCRP (mg/L)	2.9 (1.1, 8.0)	2.6 (1.0, 6.8)	2.7 (1.0, 7.5)	4.1 (1.3, 11.4)	<0.001
NT-proBNP (ng/L)	508.0 (159.2, 1774.5)	396.0 (125.0, 1277.5)	460.0 (153.0, 1696.0)	957.0 (287.2, 2985.0)	<0.001
Extent of atherosclerotic vascular disease					
PAD No. (%)	237 (10.4)	–	–	237 (60.2)	–
CeVD No. (%)	203 (8.9)	–	–	203 (51.5)	–
CAD No. (%)	1783 (78.4)	–	1389 (100)	394 (100)	<0.001
SYNTAX score (points)	5.0 (0, 13.0)	–	7.0 (0, 14.0)	11.0 (3.0, 20.0)	<0.001
Gensini score (points)	9.0 (1.0, 32.0)	–	13.0 (4.5, 35.0)	21.0 (7.5, 45.8)	<0.001

BMI Body mass index; *CAD* Coronary artery disease; *PAD* Peripheral artery disease; *CeVD* Cerebrovascular disease; *eGFR* Estimated glomerular filtration rate; *HDL-C* High density lipoprotein cholesterol; *hsCRP* High sensitivity C-reactive protein; *LDL-C* Low-density lipoprotein cholesterol; *NT-proBNP* N-terminal prohormone of brain natriuretic peptide; *SYNTAX* SYNergy between PCI with TAXUS™ and Cardiac Surgery.



	Overall	No atherosclerosis	Monovascular disease	Polyvascular disease	
hsTnT (ng/L)	16.0 (9.0, 31.0)	12.0 (7.0, 23.0)	16.0 (9.0, 30.2)	22.0 (12.0, 47.0)	<0.001

	Overall	No atherosclerosis	Monovascular disease	Polyvascular disease	
hsTnI (ng/L)	7.6 (3.5, 19.1)	4.6 (2.4, 11.2)	7.7 (3.6, 19.4)	11.1 (4.6, 23.0)	<0.001

Fig. 1. Blood concentrations of high-sensitivity troponin T and high-sensitivity troponin I for the overall cohort and across the extent of atherosclerotic vascular disease. Median high-sensitivity troponin T and high-sensitivity troponin I values and the interquartile range is provided. *HsTnI* high-sensitivity troponin I; *hsTnT* high-sensitivity troponin T.

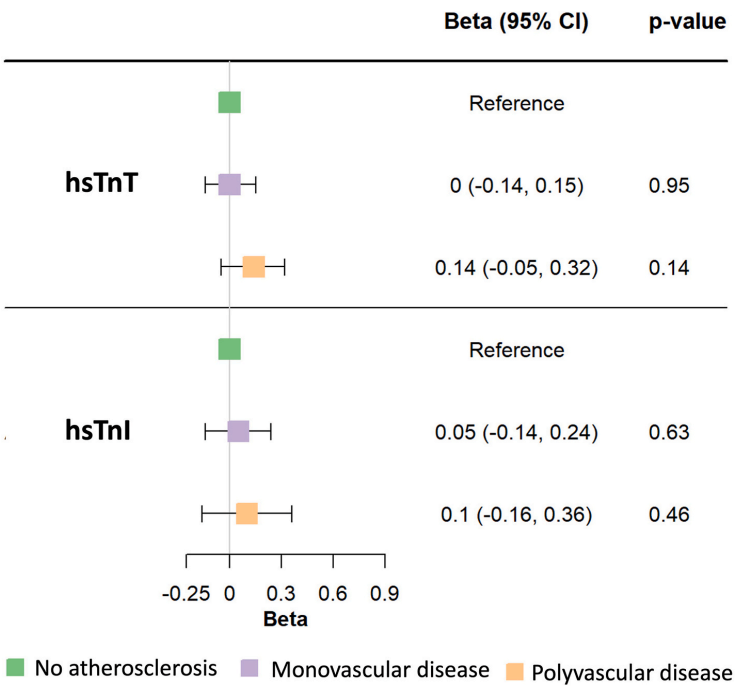


Fig. 2. Adjusted association of atherosclerotic disease extent with high-sensitivity troponin T and high-sensitivity troponin I concentrations. The beta and the 95 %-confidence interval is provided. Troponin concentrations were log-transformed. The final model was adjusted for age, female sex, arterial hypertension, body mass index, hyperlipoproteinemia, active smoking, diabetes, estimated glomerular filtration rate and Gensini score. *95 %-CI* 95 %-confidence interval; *HsTnI* High-sensitivity troponin I; *hsTnT* High-sensitivity troponin T.

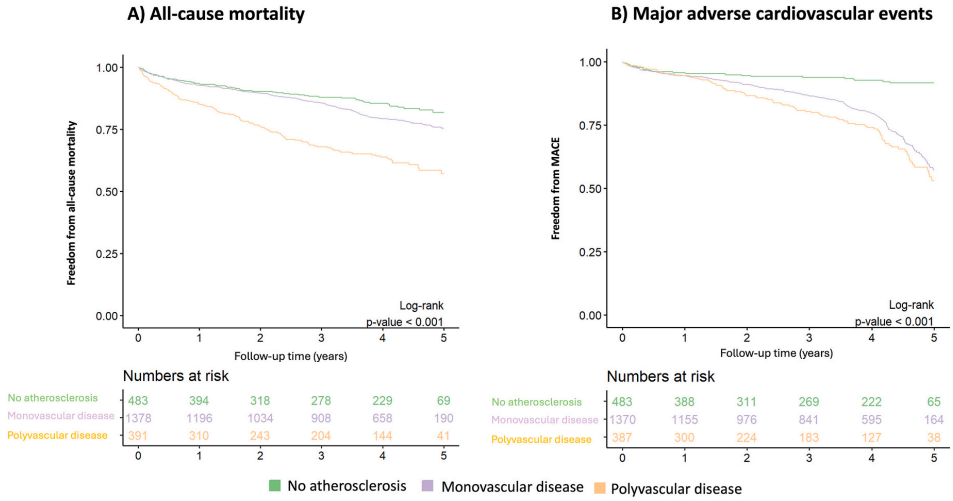


Fig. 3. Kaplan-Meier curves for incident endpoints according to atherosclerotic disease extent. Kaplan-Meier curves for all-cause mortality and major adverse cardiovascular events are included in Panel (A) and (B), respectively. Major adverse cardiovascular events are defined as the composite of cardiovascular death, unplanned coronary revascularization procedures (i.e. PCI or CABG), non-fatal myocardial infarction, or non-fatal stroke. The log-rank test was used to detected differences between the survival curves. *CABG* Coronary artery bypass graft; *PCI* Percutaneous coronary intervention.

$_{log}$hsTnT across the ASVD extent (p-interaction = 0.75). Of note, no association of $_{log}$hsTnT with MACE was seen in all subgroups (p-interaction = 0.97).

Concerning the association of $_{log}$hsTnI with clinical outcomes, we were able to document an independent correlation with all-cause mortality in patients with atherosclerosis (PolyVD: 1.38 [1.14, 1.68]; p = 0.0013 and MVD: 1.35 [1.17, 1.56]; p < 0.001) whilst this was not noted for patients without atherosclerotic disease (1.13 [0.83, 1.53]; p = 0.44; p-interaction p = 0.51). Lastly, after multivariable adjustment no independent association of $_{log}$hsTnI with MACE was present in any subgroup, although a statistically borderline non-significant trend in the MVD cohort (1.12 [0.99, 1.28]; p = 0.075) was documented (p-interaction = 0.27). Unadjusted results of the Cox regression analysis are included in Supplementary Table S2. Full results of the additional regression analysis also adjusting for history of stroke and/or PAD are displayed in Supplementary Table S3.

4. Discussion

In the current study exploring the association of ASVD extent with concentrations of hsTnT and hsTnI, as well as the prognostic utility of these cardiac biomarkers in a prospective cohort study (also see Fig. 4), we describe the following main findings.

i. Patients with a greater extent of ASVD, i.e. individuals with PolyVD, had a distinct baseline risk profile which included higher age, greater burden of comorbidities and higher SYNTAX and Gensini scores.
ii. We documented an incremental increase of both hsTnT as well as hsTnI according to ASVD extent, albeit this association was not significant after multivariable adjustment
iii. A stepwise increase of the event rate of incident adverse events (both all-cause mortality and MACE) was noted according to the severity of ASVD. Also, patients with PolyVD had the highest event rates of both all-cause mortality and MACE, underscoring the prognostic impact of atherosclerosis extent.
iv. hsTnT and hsTnI displayed a comparable and independent association with all-cause mortality in patients with ASVD. No association of cardiac troponins with MACE was seen in any subgroup after adjustment for various confounders including anatomical CAD complexity.

Our current findings have direct clinical implications for clinicians treating patients with ASVD. In the current investigation, a study implemented in a contemporary cohort of patients undergoing coronary angiography, we describe PolyVD in nearly one out of five patients. This is in concurrence with other cohorts which have investigated the prevalence of PolyVD in patients with CAD, such as the REduction of Atherothrombosis for Continued Health (REACH) Registry and Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative, as well as with more contemporary studies [2,21]. Moreover, we currently describe patients with a greater extent of ASVD as being older, less likely to be female, having a greater burden of comorbidities, and exhibiting higher CAD complexity as measured by the SYNTAX and Gensini scores.

Of note, a higher concentration of hsTnT and also hsTnI was documented according to the extent of ASVD, and patients with PolyVD had the highest concentrations of both hsTn subtypes. Importantly, whilst the measured values of hsTnT were above the 99th percentile (14 ng/L) for the MVD and PolyVD population, this was not the case for hsTnI, as all subgroups were below the previously documented 99th percentile for the utilized hsTnI assay (27 ng/L) [22,23]. However, on linear regression analysis we found that ASVD extent did not associate with hsTnT/I concentrations after adjusting for potential confounders, i.e. age, female sex, hypertension, BMI, hyperlipoproteinemia, active smoking, diabetes, eGFR and anatomical complexity of CAD as measured by the Gensini score. We, as well as others, have previously shown the association of CAD severity (measured by the SYNTAX and Gensini Score) with levels of hsTnT and hsTnI [9–11,24]. This has been hypothesized to be due to subclinical impaired myocardial perfusion and micro embolisms caused by the presence of CAD [5]. In addition, elevation of troponins in individuals with different atherosclerotic disease manifestations aside from CAD, i.e. patients with PAD and/or CeVD, have also been noted [25–28]. In these patients Troponin release is not caused by acute cardiomyocyte necrosis, i.e. an MI, but rather due several pathways/disease

Table 2
Adjusted association of log-transformed high-sensitivity troponin T and high-sensitivity troponin I with all-cause mortality and major adverse cardiovascular events across the extent of atherosclerotic vascular disease.

All-cause mortality				
	No atherosclerosis	Monovascular disease	Polyvascular disease	p-interaction
hsTnT, HR per change of SD (95 % CI)	1.26 (0.95, 1.68); p = 0.11	1.32 (1.15, 1.51); p < 0.001	1.42 (1.16, 1.73); p < 0.001	0.75
hsTnI, HR per change of SD (95 % CI)	1.13 (0.83, 1.53); p = 0.44	1.35 (1.17, 1.56); p < 0.001	1.38 (1.14, 1.68); p = 0.0013	0.51
Major adverse cardiovascular events				
	No atherosclerosis	Monovascular disease	Polyvascular disease	p-interaction
hsTnT, HR per change of SD (95 % CI)	0.95 (0.60, 1.51); p = 0.84	0.99 (0.87, 1.13); p = 0.86	1.01 (0.79, 1.30); p = 0.91	0.97
hsTnI, HR per change of SD (95 % CI)	1.08 (0.66, 1.75); p = 0.77	1.12 (0.99, 1.28); p = 0.075	0.88 (0.67, 1.16); p = 0.38	0.27

Adjusted hazard ratios per change of standard deviation for high-sensitivity troponin T/high-sensitivity troponin I and their 95 %-Confidence interval are provided. In the final multivariable model adjustment for age, female sex, arterial hypertension, body mass index, hyperlipoproteinemia, active smoking, diabetes, estimated glomerular filtration rate and Gensini score was carried out. The composite major adverse cardiovascular events endpoint included cardiovascular death, unplanned coronary revascularization procedures (i.e. PCI or CABG), non-fatal myocardial infarction, or non-fatal stroke. An interaction term for high-sensitivity troponin T/high-sensitivity troponin I with the extent of atherosclerotic disease was used. *95 %-CI* 95 %-Confidence interval; *CABG* Coronary artery bypass graft; *HR* Hazard ratio; *HsTnI* High-sensitivity troponin I; *hsTnT* High-sensitivity troponin T; *PCI* Percutaneous coronary intervention; *SD* Standard deviation.

entities including subclinical myocardial ischemia such as coronary stenosis, left ventricular hypertrophy, heart failure and valvular heart disease. Moreover, in some non-cardiac disease entities such as critical illness such as sepsis, acute respiratory distress syndrome and stroke, elevated hsTn levels have been documented [5]. Also, a non-cardiac expression of troponins, which has been described for skeletal muscle, or further comorbidities in these patients has been hypothesized to lead to elevated hsTn concentrations in these individuals [29,30]. However, a multifactorial elevation of hsTn concentrations in patients with a greater extent of ASVD seems likely.

Next to cross-sectional analysis concerning the association of ASVD extent with hsTnT and hsTnI levels, we demonstrate a strong and comparable association of both utilized troponin assays with incident all-cause mortality in patients with ASVD (i.e. in patients with either MVD or PolyVD), which was underscored by a non-significant interaction term. Of note, patients with PolyVD had very high rates of all-cause mortality (42.9 %) during a median follow-up of 4.24 years, whereas patients with MVD (24.5 %) and no atherosclerosis (18.3 %) had substantially lower rates of all-cause death. Intriguingly, in our current investigation no association of hsTnT and hsTnI with the composite MACE outcome was noted, a finding which was regardless of atherosclerotic disease extent. Previously, for both hsTnT and hsTnI a correlation with adverse cardiovascular events in the general population and also in cohorts with prevalent atherosclerotic disease was documented [7,8,12]. In contrast to those large scale analyses, the present study might however be underpowered for hard endpoints, both due to the overall available sample size and also the mid-term follow-up of 4 years. Of note, a trend with a borderline non-significant association of hsTnI with the composite MACE endpoint was documented in patients with MVD in our analysis. In addition, we have previously shown that only hsTnI, but not hsTnT correlated with MACE in stable patients undergoing coronary angiography after adjusting for confounders which also included the anatomical CAD complexity quantified via the Gensini score [9]. Similar findings were made in a recent publication investigating the prognostic value of biomarkers in a population-based analysis [12]. Here, the association of the investigated cardiovascular biomarkers, which included hsTnT and hsTnI, was stronger with all-cause mortality, compared to fatal and non-fatal atherosclerotic cardiovascular disease events. Therefore, these data as well as our results emphasize the utility of troponins in the evaluation of overall mortality risk, a finding that was not influenced by the number of arterial beds affected by atherosclerosis in the current analysis. However, no definite conclusion with regard to the superiority of either used troponin assay can be made from the current results. With regard to the prediction of all-cause mortality seems to be superior, whereas hsTnI has a more consistent association with MACE. Further studies will be needed to define the ideal assay in the prediction of adverse events.

Concerning the translation of our findings to clinical practice, we hypothesize that the integration of troponins into the clinical routine to enable risk stratification of patients with atherosclerotic disease might have merit. This could be of particular importance for patients with the most extensive ASVD, i.e. individuals with PolyVD. Although the PolyVD population is already known to represent a very high-risk patient cohort, the current data underscore that even in these patients, hsTn can serve as a useful risk marker to identify those at an increased risk for all-cause mortality during follow-up. While all patients with established ASVD should receive secondary preventive treatments, such as a platelet inhibitor and lipid-lowering therapy, several studies have examined the use of cardiovascular biomarkers, and particularly cardiac troponins, to identify those at especially high risk for adverse events [13,14,31]. The integration of cardiac troponins into prediction models could potentially enhance risk stratification of patients, even in those with the greatest extent of atherosclerosis, potentially guiding intensified secondary preventive treatment strategies. Importantly, with the current study we were able to demonstrate that troponins can be used as continuous parameter in risk prediction. However, further prospective studies are needed to demonstrate the potential of the integration of hsTn into clinical decision making, especially taking into account the extent of ASVD.

5. Limitations

Whilst the current study includes well-characterized patients from a prospective single-center cohort, some limitations have to be considered: All patients underwent an invasive quantification of the coronary artery tree, however no prospective diagnostic tests were implemented to detected PAD and CeVD. Thus, it is possible that atherosclerotic disease occurring outside of the coronary arteries may be underreported. Also, the presence of CAD was obligatory for the definition of both MVD and PolyVD. The reported association can therefore not be generalized to patients with different composition of MVD or PolyVD, respectively. Moreover, even though we report on all-cause mortality and several physician adjudicated adverse cardiovascular endpoints, events associated with the peripheral arterial system, e.g. lower extremity revascularization or amputation as well as hospitalizations for heart failure were not available. Moreover, due to the limited sample size no final conclusions with regard to association of hsTnT/I with MACE can be made.

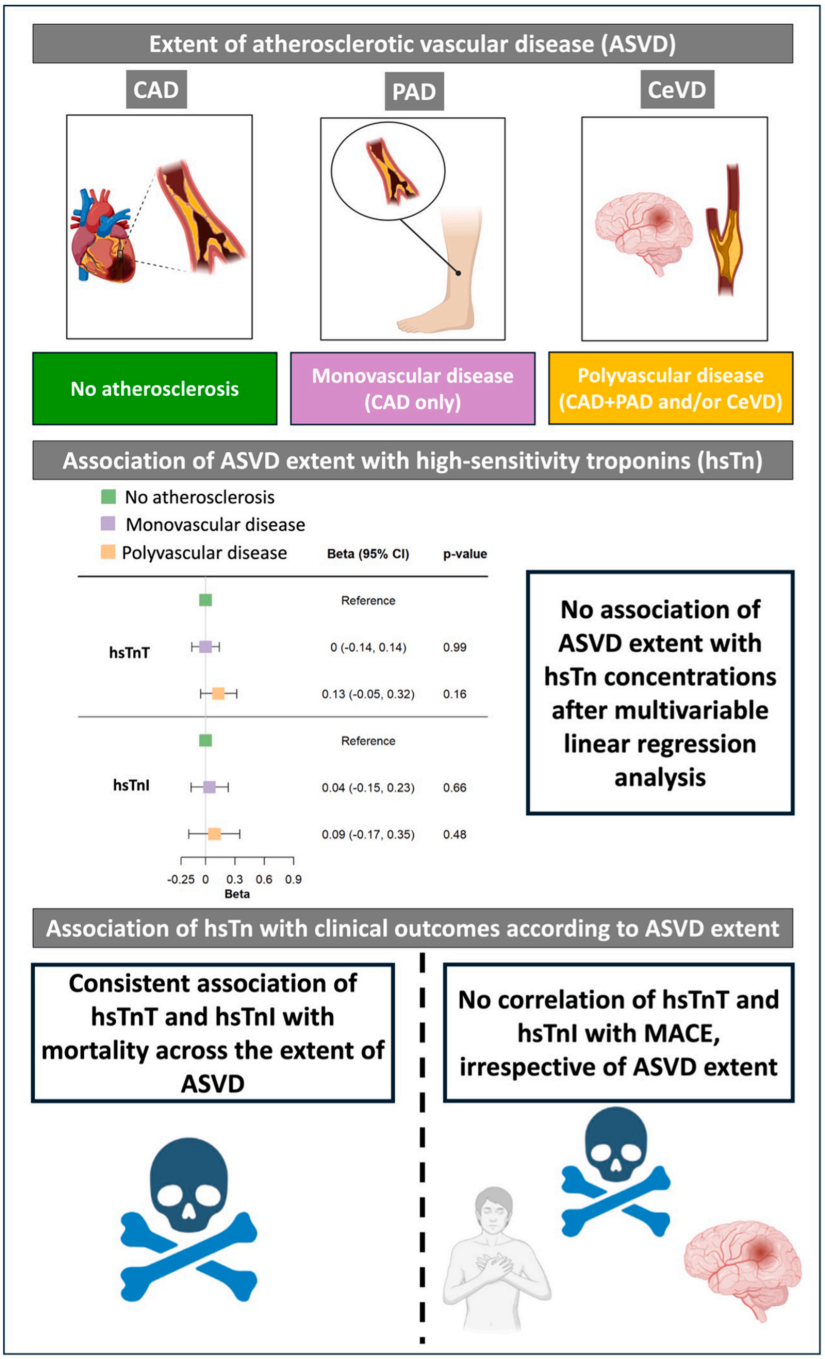

Extent of atherosclerotic vascular disease (ASVD)
CAD
PAD
CeVD
No atherosclerosis
Monovascular disease (CAD only)
Polyvascular disease (CAD+PAD and/or CeVD)
Association of ASVD extent with high-sensitivity troponins (hsTn)
No atherosclerosis
Monovascular disease
Polyvascular disease
Beta (95% CI)
p-value
hsTnT
Reference
0 (-0.14, 0.14) 0.99
0.13 (-0.05, 0.32) 0.16
hsTnI
Reference
0.04 (-0.15, 0.23) 0.66
0.09 (-0.17, 0.35) 0.48
-0.25 0 0.3 0.6 0.9
Beta
No association of ASVD extent with hsTn concentrations after multivariable linear regression analysis
Association of hsTn with clinical outcomes according to ASVD extent
Consistent association of hsTnT and hsTnI with mortality across the extent of ASVD
No correlation of hsTnT and hsTnI with MACE, irrespective of ASVD extent

Fig. 4.

No mechanistic data is available for the current analysis; therefore, no definitive inferences can be drawn regarding the causal relationship between hsTnT/I and the observed associations. In addition, data on the prevalence and potential of frailty in our cohort was not available. Lastly, as a single-center cohort from a Western European metropolitan area, limitations with regard to the generalizability of our results apply.

6. Conclusion

In conclusion, in a contemporary cohort of patients undergoing coronary angiography, an incremental increase in hsTnT and hsTnI levels with ASVD extent was noted. However, this association was no longer significant after adjusting for confounders. Although both hsTnT and hsTnI showed a similar association with all-cause mortality in patients with ASVD, no association with MACE was observed in any subgroup after adjusting for confounders, including anatomical CAD complexity.

Author contribution

JR: Formal analysis, Methodology, Data curation, Investigation, Visualization, Writing – original draft, preparation, Writing – review & editing. FJB: Conceptualization, Formal analysis, Visualization, Writing – original draft, preparation, Writing – review & editing, Supervision, Project administration, Funding acquisition. AG: Formal analysis, Investigation, Writing – review & editing. HG: Data curation, Investigation, Visualization. NA: Data curation, Investigation, Writing – review & editing. CB: Data curation, Investigation, Writing – review & editing. CK: Formal analysis, Investigation, Writing – review & editing. LP: Data curation, Investigation, Writing – review & editing. LK: Data curation, Investigation, Writing – review & editing. TL: Data curation, Investigation, Writing – review & editing. CW: Conceptualization, Writing – review & editing, Supervision, Project administration. TZ: Supervision, Project administration, Funding acquisition. SB: Supervision, Project administration, Funding acquisition. BB: Formal analysis, Methodology, Data curation, Investigation, Visualization, Writing – original draft, preparation, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Ethics approval

This study was approved by the local ethics committee (PV4303, Hamburg, Germany), all patients provided written and informed consent and research was carried out in accordance with appropriate ethical guidelines.

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Conflicts of interest

JR reports research funding from the Gertaud and Heinz Rose-Stiftung outside of the submitted work. FJB reports grants from Daiichi Sankyo, Pfizer, and Sanofi, non-financial support from Abbott, ASAHI INTECC, and Inari Medical, personal fees from Amgen, Daiichi Sankyo, Inari, and Novartis outside of the submitted work. NA reports consulting fees and grant support from Novartis, all outside of the submitted work. CW reports lecture and consulting fees from AMGEN, Novartis, Daiichi Sankyo, Sanofi and AstraZeneca, all outside of the submitted work. TZ reports having a patent pending on the use of a computing device to estimate the probability of myocardial infarction and being a cofounder and shareholder of ARTEMIS Hamburg GmbH. SB has received research funding from Abbott Diagnostics, Bayer, SIEMENS, Singulex and Thermo Fisher. SB received honoraria for lectures from Abbott, Abbott Diagnostics, AstraZeneca, Bayer, AMGEN, Medtronic, Pfizer, Roche, SIEMENS Diagnostics, SIEMENS, Thermo Fisher and as member of Advisory Boards and for consulting for Bayer, Novartis and Thermo Fisher, all outside of the submitted work. BB reports research funding from the Gertaud and Heinz Rose-Stiftung outside of the submitted work. All other authors have no conflicts of interest.

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The graphical abstract was created with BioRender.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2025.119167.

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4.2. Inflammatory risk and clinical outcomes according to polyvascular atherosclerotic disease status in patients undergoing PCI.

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ORIGINAL PAPER

Inflammatory risk and clinical outcomes according to polyvascular atherosclerotic disease status in patients undergoing PCI

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Abstract

Background Individuals suffering from polyvascular atherosclerotic disease (PolyVD) face a higher likelihood of adverse cardiovascular events. Additionally, inflammation, assessed by high-sensitivity C-reactive protein (hsCRP), affects residual risk following percutaneous coronary intervention (PCI). We aimed to explore the interplay between PolyVD and hsCRP in terms of clinical outcomes after PCI.

Methods Patients undergoing PCI for chronic coronary disease at a tertiary center between January 2012 and February 2020 were included for the current analysis. PolyVD was defined by additional history of cerebrovascular and/or peripheral artery disease. HsCRP levels were defined as elevated when the measured baseline concentration was > 3 mg/L. The primary outcome of interest was major adverse cardiovascular events (MACE), a composite of all-cause mortality, spontaneous MI, or target vessel revascularization.

Results Overall, 10,359 participants were included in the current study, with 17.4% affected by PolyVD and 82.6% included in the non-PolyVD subgroup. Patients with PolyVD had higher hsCRP levels than those without. Among the PolyVD group, a larger proportion (33.6%) exhibited elevated hsCRP compared to the non-PolyVD group (24.7%). Patients with both PolyVD and elevated hsCRP levels had significantly higher adverse event rates than all other subgroups at 1-year follow-up. Furthermore, an independent association between elevated hsCRP and MACE was observed within the PolyVD population, while this was not the case for individuals without PolyVD.

Conclusion A residual risk of adverse outcomes after PCI linked to inflammation appears to be present among individuals with PolyVD. This could help define further target populations for anti-inflammatory treatment options.

Part of this work has been presented at the EuroPCR Congress 2024.

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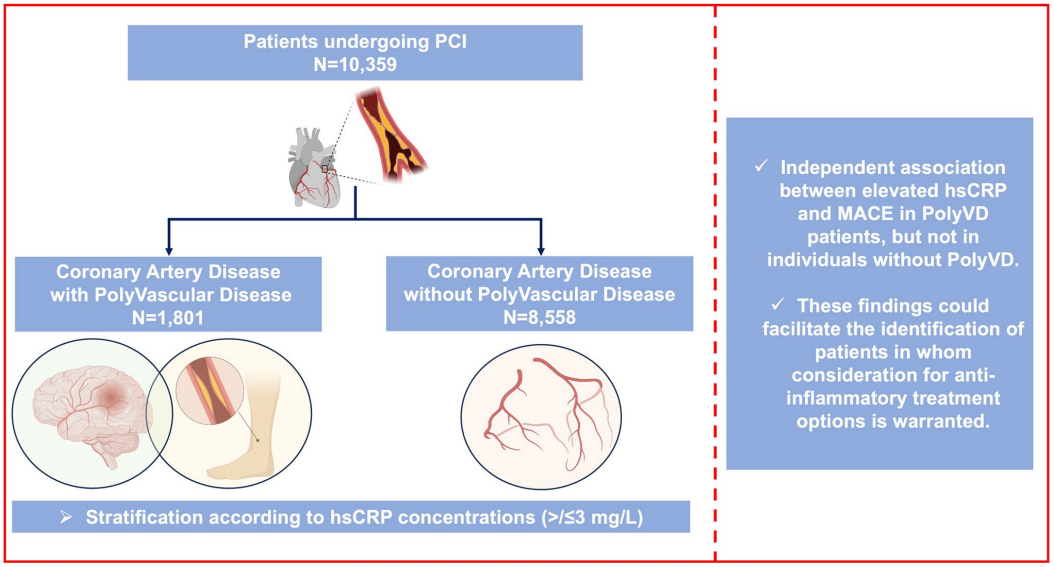
Graphical Abstract



Keywords Inflammation · Outcomes · Polyvascular atherosclerotic disease · Percutaneous coronary intervention

Introduction

Atherosclerotic cardiovascular disease (ASCVD), and its manifestation within the coronary wall leading to coronary artery disease (CAD), is one of the leading causes of death globally [1, 2]. Treatment of CAD has evolved over the last decades through advancements in surgical as well as interventional techniques and pharmacologic secondary prevention therapies, resulting in improved clinical outcomes of affected patients. However, a high residual risk for major adverse cardiovascular events (MACE) of 5% per year has been reported in contemporary studies even after adherence to guideline directed medical therapy [3–5]. Polyvascular atherosclerotic disease (PolyVD) is defined as the existence of atherosclerosis across two or more arterial vascular beds, representing an unfavorable atherothrombotic phenotype with a greater extent of atherosclerotic disease. Individuals with PolyVD experience up to fivefold increased risk for recurrent MACE [6].

At the same time, a robust relationship between markers of inflammation and adverse outcomes has been demonstrated in patients with established ASCVD [7, 8]. In this setting, pharmacological targeting of key steps within the inflammatory cascade was proven to yield improved cardiovascular outcomes, ushering in a new era in the treatment of CAD [9–12]. High-sensitivity C-reactive protein (hsCRP) concentrations have been commonly used to assess inflammatory burden and related inflammatory risk.

Research efforts analyzing the inflammatory burden, quantified using hsCRP, in the high-risk PolyVD population are scarce. We therefore sought to investigate the interplay between PolyVD status and hsCRP concentrations in a contemporary unselected cohort of patients undergoing percutaneous coronary intervention (PCI) for chronic coronary disease.

Materials and methods

Ethics declaration

This study was conducted in adherence to the regulations set forth by the Declaration of Helsinki and approved by the local institutional review board at Mount Sinai Hospital, New York, USA. Written and informed consent was obtained from all participants.

Study population

All patients hospitalized for PCI at a large tertiary referral center between January 2012 and February 2020 were included in the study cohort. An institutional review board sanctioned the study. The study design and rationale have previously been described [13]. Briefly, baseline characteristics including individual patient factors, medical history, procedural data, medications at discharge, and laboratory values were prospectively collected for each patient. The technical aspects of the PCI at baseline and further treatment were at the discretion of the treating physician. For current analysis, the overall cohort was divided according to the presence or absence of PolyVD, defined by a prior history of peripheral artery disease (PAD) and/or cerebrovascular disease (CeVD) at enrolment. In these subgroups, patients were stratified according to hsCRP levels (> 3 mg/L and ≤ 3 mg/L), aiming to identify patients with the highest inflammatory risk as defined by the Centers for Disease Control and Prevention and the American Heart Association [14]. Participants with neoplastic disease, hsCRP values > 10 mg/L compatible with an active infection, and acute coronary syndromes were excluded from the current analysis.

Outcome and endpoint definition

Follow-up data 1 year after the index PCI was collected prospectively by research coordinators via telephone interviews and assessment of electronic health records. The primary endpoint of this study was the rate of MACE, a composite of all-cause mortality, myocardial infarction (MI), or target vessel revascularization (TVR) at 1 year. MI was classified using the third universal definition [15]. TVR was defined as any instance of recurrent revascularization within the primary coronary vessel which was treated during the index PCI. Secondary outcomes were the rate of individual MACE components, target lesion revascularization (TLR), definite/probable stent-thrombosis, and bleeding events at 1 year.

Statistical analysis

Variables were presented as mean values with standard deviations for continuous variables and as frequencies for categorical variables. To compare continuous variables with a normal distribution, the independent samples Student's *t*-test was employed, while the Mann–Whitney *U* test was utilized for variables which displayed non-normal distribution. Categorical variables were assessed using the χ^2 test. The Kaplan–Meier method was employed to evaluate cumulative incidences of primary and secondary endpoints at 1 year. Between-group comparisons were made using the log-rank test to determine the time to the initial event. Multivariate Cox regression models were applied to account for differences in baseline risk between patients with and without PolyVD, and formal interaction testing was conducted to investigate potential risk modifications by hsCRP concentrations. Adjustment was carried out for age, sex, ethnicity (Caucasian as reference group), body mass index (BMI), current smoking, diabetes, low-density lipoprotein cholesterol (LDL-c) concentrations, hypertension, chronic kidney disease, anemia, atrial fibrillation, lung disease, previous coronary artery bypass grafting, and intake of statins. Hazard ratios (HR) and their corresponding 95% confidence intervals (CI) were reported. A two-sided p-value < 0.05 was deemed statistically significant.

Results

Baseline characteristics

After implementing exclusion criteria, a total of 10,359 patients (median age 65.9 ± 10.8 years, female sex in 25.6%) met the criteria for the current analysis. Among them, 1801 patients (17.4%) were included in the PolyVD group, and 8558 patients (82.6%) were part of the non-PolyVD cohort. Baseline characteristics of the overall study cohort and by PolyVD status are displayed in Supplementary Table 1. Individuals with PolyVD were significantly older (68.9 ± 10.0 vs. 65.3 ± 10.9 years; $p < 0.001$) and were more likely to be female (30.5% vs. 24.6%; $p < 0.001$). Moreover, a higher burden of cardiovascular risk factors such as current smoking, diabetes mellitus, hypertension, and hyperlipidemia was noted in the PolyVD group. Also, non-cardiovascular comorbidities like chronic kidney disease, lung disease, and anemia were more prevalent in individuals with PolyVD. Notably, in PolyVD patients, a significantly higher hsCRP concentration was documented (2.7 ± 2.3 vs. 2.2 ± 2.2 mg/L; $p < 0.001$). In addition, an incremental increase of circulating hsCRP concentrations was noted according to the number of vascular beds affected by ASCVD (also see Table 1).

Table 1 High-sensitivity C-reactive protein concentrations in the overall cohort, according to the number of vascular beds affected by atherosclerotic disease

	Overall, $N = 10,359$	Non-PolyVD, $N = 8558$ (82.6%)	2-part PolyVD, $N = 1611$ (15.6%)	3-part PolyVD, $N = 190$ (1.8%)	p-value
hsCRP, mg/L	2.3 ± 2.2	2.2 ± 2.2	2.7 ± 2.4	3.0 ± 2.3	< .001

Values are mean ± SD. *hsCRP* high-sensitivity C-reactive protein, *PolyVD* polyvascular atherosclerotic disease

Baseline characteristics according to the presence or absence of PolyVD and hsCRP concentrations are shown in Table 2. Among patients with PolyVD, a larger proportion had elevated hsCRP levels (33.6%) than in the non-PolyVD subgroup (24.7%). Consistent for both individuals with and without PolyVD, patients with elevated hsCRP had a higher BMI and were more likely to be female. Moreover, in patients with an elevated inflammatory load, a greater burden of comorbidities like diabetes and chronic kidney disease was noted (further details with

Table 2 Baseline characteristics of the PolyVD and non-PolyVD population stratified according to the inflammatory burden

	PolyVD ($N=1801$)			Non-PolyVD ($N=8558$)		
	hsCRP > 3, $N=605$ (33.6%)	hsCRP ≤ 3, $N=1196$ (66.4%)	*p*-value	hsCRP > 3, $N=2116$ (24.7%)	hsCRP ≤ 3, $N=6442$ (75.3%)	*p*-value
Patient demographics						
Age, years	68.0 ± 9.8	69.3 ± 10.1	0.008	65.1 ± 11.1	65.4 ± 10.8	0.254
BMI, kg/m^2	29.9 ± 6.0	28.1 ± 5.2	< .001	30.5 ± 5.9	28.1 ± 4.9	< .001
Female sex	218 (36.0%)	331 (27.7%)	< .001	687 (32.5%)	1419 (22.0%)	< .001
Race/ethnicity			0.044			< .001
Caucasian	234 (40.1%)	510 (44.5%)		852 (42.4%)	2786 (45.8%)	
African American	83 (14.2%)	129 (11.3%)		226 (11.2%)	458 (7.5%)	
Asian	61 (10.4%)	150 (13.1%)		368 (18.3%)	1431 (23.5%)	
Hispanic	177 (30.3%)	317 (27.7%)		441 (22.0%)	1067 (17.5%)	
Others	29 (5.0%)	40 (3.5%)		122 (6.1%)	344 (5.7%)	
Medical history						
Current smoker	99 (16.4%)	165 (13.8%)	0.146	271 (12.8%)	625 (9.7%)	< .001
Anemia	327 (54.9%)	536 (45.8%)	< .001	855 (41.4%)	2072 (33.0%)	< .001
Diabetes mellitus	391 (64.6%)	683 (57.1%)	0.002	1091 (51.6%)	2946 (45.7%)	< .001
Insulin dependent	188 (48.1%)	235 (34.4%)	< .001	393 (36.0%)	828 (28.1%)	< .001
Hypertension	591 (97.7%)	1155 (96.6%)	0.194	2011 (95.1%)	5993 (93.0%)	< .001
Hyperlipidemia	579 (95.7%)	1151 (96.2%)	0.582	1962 (92.7%)	6073 (94.3%)	0.010
Lung disease	75 (12.4%)	93 (7.8%)	0.001	142 (6.7%)	265 (4.1%)	< .001
Atrial fibrillation	68 (11.2%)	118 (9.9%)	0.366	169 (8.0%)	365 (5.7%)	< .001
Chronic kidney disease	251 (41.5%)	369 (30.9%)	< .001	639 (30.2%)	1420 (22.0%)	< .001
Dialysis	51 (8.4%)	36 (3.0%)	< .001	109 (5.2%)	105 (1.6%)	< .001
Prior PCI	350 (57.9%)	658 (55.0%)	0.252	1044 (49.3%)	3246 (50.4%)	0.402
Prior MI	191 (31.6%)	293 (24.5%)	0.001	513 (24.2%)	1504 (23.3%)	0.399
Prior CABG	151 (25.0%)	309 (25.8%)	0.687	302 (14.3%)	1019 (15.8%)	0.088
LVEF, %	54.0 ± 10.9	55.0 ± 10.2	0.058	55.3 ± 10.2	55.8 ± 9.6	0.082
Laboratory						
hsCRP, mg/L	5.5 ± 1.9	1.3 ± 0.8	< .001	5.4 ± 1.9	1.2 ± 0.8	< .001
HbA1c, %	7.7 ± 1.7	7.3 ± 1.5	< .001	7.6 ± 1.7	7.3 ± 1.5	< .001
LDL-c, mg/dL	81.3 ± 33.0	74.2 ± 27.8	< .001	83.3 ± 33.1	74.9 ± 28.2	< .001
Discharge medication						
DAPT	559 (92.5%)	1129 (94.4%)	0.125	2000 (94.6%)	6200 (96.3%)	< .001
Aspirin	562 (93.0%)	1134 (94.8%)	0.129	2009 (95.0%)	6254 (97.1%)	< .001
Statin	558 (92.4%)	1139 (95.2%)	0.014	1967 (93.0%)	6187 (96.1%)	< .001
Insurance						
Private	247 (42.2%)	498 (43.4%)	0.645	1073 (53.6%)	3532 (57.8%)	0.001
Medicaid	91 (15.6%)	145 (12.6%)	0.093	249 (12.4%)	506 (8.3%)	< .001
Medicare	242 (41.4%)	493 (42.9%)	0.530	646 (32.3%)	1893 (31.0%)	0.270
Military	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	4 (0.1%)	0.578

Values are *n* (%) or mean ± SD. *BMI* body mass index, *CABG* coronary artery bypass graft, *CAD* coronary artery disease, *DAPT* dual antiplatelet therapy, *hsCRP* high-sensitivity C-reactive protein, *LDL-c* low-density lipoprotein cholesterol, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PolyVD* polyvascular disease

regard to the presence of risk factors in the PolyVD and non-PolyVD cohort with hsCRP concentrations > 3 mg/L can be found in Supplementary Table 2). In addition, details with regard to CAD severity, procedural characteristics, and complications are included in Supplementary Table 3.

Outcome according to the extent of atherosclerotic cardiovascular disease and hsCRP concentrations

The unadjusted clinical outcomes in patients with and without PolyVD stratified by hsCRP concentrations are displayed in Table 3. After a follow-up of 12 months, substantially increased rates of MACE were observed when elevated hsCRP levels were present both among patients in the PolyVD group (16.0% vs. 10.1%) and in the non-PolyVD cohort, though less pronounced in the latter (10.6% vs. 8.7%, see Fig. 1). Similarly, rates of each individual MACE component in the PolyVD cohort were increased in individuals with hsCRP > 3 mg/L.

The results of the fully adjusted regression analysis can be found in Fig. 2. Elevated hsCRP concentrations remained an independent predictor of the primary endpoint even after adjustment for multiple confounders in the PolyVD cohort ($_{adj}$HR: 1.67, 95% CI (1.21–2.29); $p = 0.002$), while no association was seen in the non-PolyVD group ($_{adj}$HR: 1.16, 95% CI (0.96–1.39); $p = 0.117$, $p_{interaction} = 0.071$). Higher hazards for all-cause mortality were seen in patients with hsCRP > 3 mg/L within both PolyVD and non-PolyVD subgroups. However, elevated hsCRP was only independently associated with incident MI and TVR in the PolyVD group, while this was not the case for the non-PolyVD group. Lastly, a significant interaction according to PolyVD status was noted for the association of hsCRP with MI ($p = 0.026$) and TVR ($p = 0.041$). Further, between-group differences for secondary outcomes are detailed in Supplementary Table 4, and Kaplan–Meier event rates according to the presence of risk factors are included in Supplementary Table 5.

Discussion

The objective of the study was to investigate the interplay between PolyVD status and hsCRP concentrations in a contemporary unselected cohort of patients undergoing PCI for chronic coronary disease. The main findings of our study are the following: (i) PolyVD was present in over 17% of patients undergoing PCI for chronic coronary disease; (ii) the proportion of patients displaying elevated hsCRP concentrations was higher among patients with than without PolyVD; (iii) an elevated inflammatory burden was associated with worse ischemic outcomes in patients with PolyVD, while this did not hold true for individuals without PolyVD.

Extensive ASCVD affecting vascular beds in addition to the coronary arteries (i.e., PolyVD) was initially identified as an independent risk factor in patients with acute coronary syndromes in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE)

Table 3 Unadjusted hazard ratios for the investigated primary outcome in the PolyVD and non-PolyVD cohort stratified according to the inflammatory burden after 12 months of follow-up

Outcomes	PolyVD ($N = 1801$)				Non-PolyVD ($N = 8558$)			
	hsCRP > 3 ($N = 605$)	hsCRP ≤ 3 ($N = 1196$)	Hazard ratio (95% CI)	*p*-value	hsCRP > 3 ($N = 2116$)	hsCRP ≤ 3 ($N = 6442$)	Hazard ratio (95% CI)	*p*-value
	No. of events (%)				No. of events (%)			
MACE								
Mortality, MI, or TVR	85 (16.0%)	101 (10.1%)	1.67 (1.25–2.23)	< .001	192 (10.6%)	482 (8.7%)	1.23 (1.04–1.45)	0.015
MACE components								
All-cause mortality	19 (3.6%)	13 (1.3%)	2.86 (1.41–5.79)	0.003	44 (2.4%)	48 (0.9%)	2.82 (1.88–4.25)	< .001
MI	25 (4.9%)	18 (1.8%)	2.72 (1.49–4.99)	0.001	29 (1.6%)	65 (1.2%)	1.37 (0.89–2.13)	0.155
TVR	59 (11.4%)	79 (8.0%)	1.48 (1.06–2.07)	0.023	130 (7.3%)	409 (7.4%)	0.98 (0.80–1.19)	0.831

MACE was defined as the composite of all-cause mortality, spontaneous myocardial infarction, and target vessel revascularization. The percentages displayed above represent Kaplan–Meier rates at 12 months after index procedure. *CI* confidence interval, *hsCRP* high-sensitivity C-reactive protein, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *PolyVD* polyvascular disease, *TLR* target lesion revascularization, *TVR* target vessel revascularization

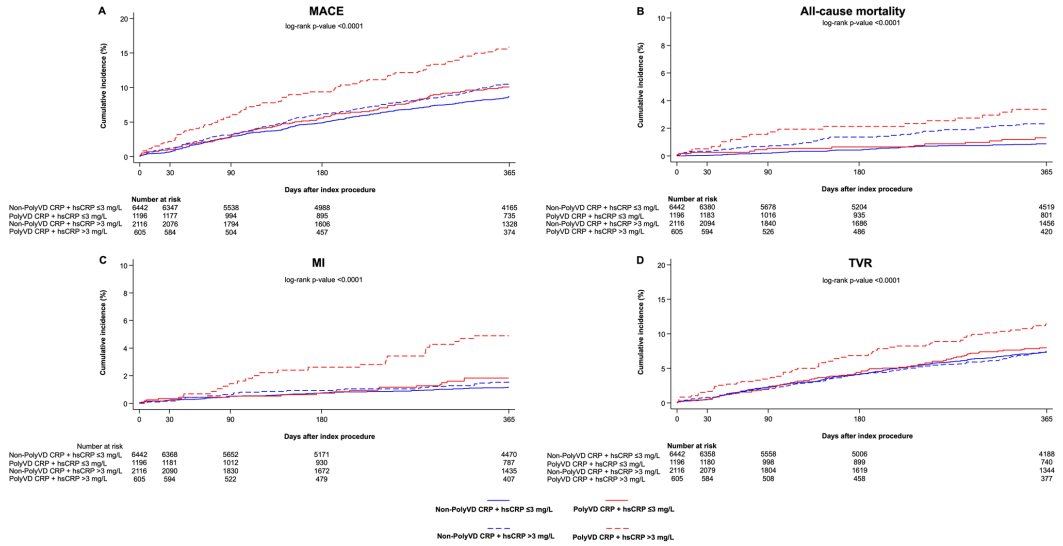


Fig. 1 Cumulative incidence curves of major adverse cardiovascular events (MACE) and its individual components for the PolyVD and non-PolyVD cohort stratified according to the inflammatory burden 12 months after the index procedure. MACE was defined as the composite of all-cause mortality, spontaneous myocardial infarction, and target vessel revascularization. MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PolyVD, polyvascular disease; TVR, target vessel revascularization

quality improvement initiative [16]. Among a total of 95,749 patients, PolyVD was present in 12.7% of the study population. In the literature, varying proportions (from 5.1 to 25.3%) of PolyVD have been reported in contemporary

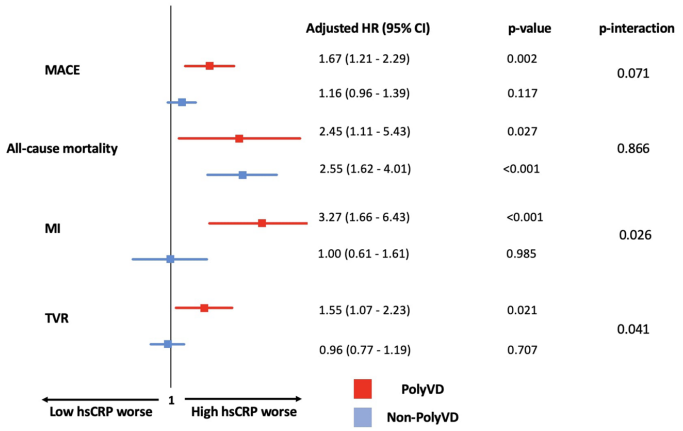


Fig. 2 Adjusted hazard ratios for the investigated primary outcome in the PolyVD and non-PolyVD cohort stratified according to the inflammatory burden after 12 months of follow-up. MACE was defined as the composite of all-cause mortality, spontaneous myocardial infarction, and target vessel revascularization. Model adjusted for age, sex, ethnicity (Caucasian as reference group), body mass index (BMI), current smoking, diabetes, low-density lipoprotein cholesterol (LDL-c) concentrations, hypertension, chronic kidney disease, anemia, atrial fibrillation, lung disease, previous coronary artery bypass grafting, and intake of statins. CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PolyVD, polyvascular atherosclerotic disease; TLR, target lesion revascularization; TVR, target vessel revascularization

cohorts with CAD, mostly including individuals undergoing PCI [17–19]. In our cohort, nearly one patient out of five was affected by PolyVD. Akin to other registries, patients with PolyVD in our cohort were of advanced age and exhibited a greater prevalence of cardiovascular risk factors and additional comorbidities compared to patients with CAD alone.

Interestingly, patients with PolyVD were more likely to have elevated hsCRP blood concentrations than patients within the non-PolyVD group. In addition, the incremental number of vascular beds affected by ASCVD was associated with a gradual increase of hsCRP concentrations in our cohort. It has previously been reported that patients with more extensive ASCVD, i.e., atherosclerosis affecting multiple vascular beds, display a higher concentration of inflammatory biomarkers [20–23]. Also, in a sub-analysis from the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) Trial, PolyVD was an independent predictor for elevated hsCRP concentrations [24].

High event rates of composite and individual ischemic events were reported among PolyVD patients in multiple previous studies, even in the early in-hospital phase after PCI [16–19, 25, 26]. The utility of hsCRP in the prediction of adverse events has been reported before. For example, in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial per SD change of $_{log}$hsCRP, a significantly elevated incidence of cardiac death, MI, or unplanned coronary revascularization was noted [27]. This data is corroborated by other reports from registry-based cohorts, where hsCRP predicted intermediate- and long-term cardiovascular outcomes after PCI [28, 29]. However, for patients with PolyVD undergoing PCI, a scarcity of data exists with regard to the predictive utility of hsCRP concentrations. In the present study, we demonstrate that patients with elevated hsCRP levels > 3 mg/L in the PolyVD group had remarkably high rates of MACE, which was evident in 16% of our population after 12 months. Moreover, an independent association of elevated hsCRP concentrations with our composite ischemic outcome and each of its individual components was documented in the PolyVD cohort. On the other hand, this was not the case for individuals without PolyVD. Therefore, not only has PolyVD been recognized as a particularly aggressive atherothrombotic phenotype, but also its combination with an elevated inflammatory burden seems to further exacerbate the malignancy of this ASCVD subtype. Hence, risk assessment of this patient population should also include the quantification of hsCRP concentrations, aiming to identify individuals with the highest probability for adverse events. Additionally, in the analysis for individual components of the primary endpoint, elevated hsCRP concentrations were independently associated with incident MI as well as TVR in the PolyVD group. Akin to the composite primary endpoint, this association was not observed for individuals in the non-PolyVD group, and a significant interaction was documented. Hence, hsCRP concentrations could be more useful to predict incident MI as well as TVR in PolyVD patients than in those without.

The finding that hsCRP seems to be a strong and independent risk modifier in patients with PolyVD has clinical implications. Groundbreaking trials highlighting the efficacy and safety of anti-inflammatory therapies in individuals with established ASCVD have been conducted [9–11]. Of note, in our cohort, both in the PolyVD and non-PolyVD cohort, a significantly higher rate of all-cause mortality was seen according to the inflammatory status. However, the large outcome trials in the field of anti-inflammatory therapies failed to document an impact of the investigated compounds (i.e., colchicine and canakinumab) on all-cause mortality. Therefore, the impact of these agents on outcomes including all-cause mortality in PolyVD patients can only be speculated [9–11]. In addition, the specification of the precise target population for existing pharmacological interventions (e.g., colchicine) has yet to be definitively established [12]. Our results support systematic assessment of hsCRP levels and evaluation of potential add-on anti-inflammatory treatment in high-risk individuals with the greatest extent of ASCVD. However, in the PolyVD population, a significantly higher rate of chronic kidney disease is noted, potentially limiting the widespread use of agents such as colchicine in these patients, as advanced kidney disease represents a contraindication for colchicine use. In these patients, newer pharmacological treatment modalities such as the IL-6 ligand monoclonal antibody treatment might pose an alternate treatment strategy. Large-scale randomized controlled trials are currently underway for this agent [30].

Limitations

While this analysis represents an analysis in a contemporary all-comers cohort of patients undergoing PCI, some limitations warrant contemplation. The diagnosis of CAD is inherent to the definition of the cohort, and an invasive diagnostic procedure and treatment was carried out for coronary atherosclerosis. However, no specific diagnostic tests were applied for the detection of PAD and CeVD, and the diagnosis was based on patient history. Therefore, a reporting bias is possible with regard to the two latter disease entities, potentially affecting classification of patients into subgroups. Also, residual confounding bias due to the nature of the study cannot be excluded. To account for the potential presence of an active infection, patients with high hsCRP concentrations > 10 mg/L were from current analysis. However, we cannot rule out that in some individuals an active infection or other disease entities associated with high inflammatory burden such as cancer or autoimmune diseases might have confounded the presented results. Moreover, because of a significant amount of missing data in the HbA1C measurement, we refrained from conducting an adjusted regression

analysis involving this variable. Instead, we utilized a history of diabetes to address this comorbidity. Lastly, this study was implemented using data from a large tertiary hospital in a US metropolitan area. Hence, the generalizability of our findings to other cohorts and geographical locations is limited.

Conclusion

In a contemporary PCI cohort of patients undergoing PCI for chronic coronary disease, a relevant proportion of patients present with PolyVD. Among individuals with PolyVD, one-third had elevated hsCRP concentrations. Patients with both PolyVD and elevated hsCRP experienced the highest event rates within the overall population, showcasing the synergistic adverse effects of the extent of ASCVD and low-grade vascular inflammation. Moreover, hsCRP remained an independent predictor for adverse ischemic outcomes among PolyVD patients, while this was not observed for the non-PolyVD cohort. Our findings could help define patients with PolyVD and elevated hsCRP as an appropriate target population for anti-inflammatory therapies and related clinical investigations.

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Data availability The data underlying this article will be shared on reasonable request by the corresponding author.

Declarations

Competing interests BB is supported by a grant from the German Heart Foundation (grant number S/06/23). GD received research grants to institution and support for attending meetings from Daiichi Sankyo. RM reports institutional research payments from: Abbott, Abiomed, Affluent Medical, Alleviant Medical, Amgen, AM-Pharma, Arena, AstraZeneca, AtriCure Inc., Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CeloNova, CERC, Chiesi, Concept Medical, Cytosorbents, Daiichi Sankyo, Duke, Element Science, Essential Medical, Faraday, Idorsia Pharmaceuticals, Janssen, MedAlliance, Mediasphere, Medtelligence, Medtronic, MJH Healthcare, Novartis, OrbusNeich, Penumbra, PhaseBio, Philips, Pi-Cardia, PLx Pharma, Population Health Research Institute, Protembis, RecCor Medical Inc., RenalPro, RM Global, Sanofi, Shockwave, Vivasure, Zoll; Personal fees from: Affluent Medical, Cardiovascular Research Foundation (CRF), Cordis, Daiichi Sankyo Brasil, E.R. Squibb & Sons, Esperion Science/Innovative Biopharma, Europa Group/Boston Scientific, Gaffney Events, Educational Trust, Henry Ford Health Cardiology, Ionis Pharmaceuticals, MedCon International, Novartis, NovoNordisk, PeerView Institute for Medical Education, TERUMO Europe N.V., Vectura, VoxMedia, WebMD, IQVIA, Radcliffe, TARSUS Cardiology; No Fees from: AMA (Scientific Advisory Board), SCAI (Women in Innovations Committee Member); Faculty CRF; Honorarium: JAMA Cardiology (Associate Editor), ACC (BOT Member, SC Member CTR Program); Equity < 1% in: Applied Therapeutics, Elixir Medical, Stel, ControlRad (spouse). All other authors declare no conflicts of interest.

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4.3. Inflammatory burden, lifestyle and atherosclerotic cardiovascular disease: insights from a population based cohort study.

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Inflammatory burden, lifestyle and atherosclerotic cardiovascular disease: insights from a population based cohort study

Benjamin Bay[1,2,3,6]✉, Christopher Blaum[1,6], Caroline Kellner[1,3], Ramona Bei der Kellen[1], Francisco Ojeda[1,3], Julia Waibel[1,2,3], Natalie Arnold[1,2,3], Christian-A. Behrendt[3], David L. Rimmele[4], Goetz Thomalla[4], Raphael Twerenbold[1,2,3], Stefan Blankenberg[1,2,3], Birgit Zyriax[5], Fabian J. Brunner[1,2,3,6] & Christoph Waldeyer[1,2,6]

The inflammatory burden as measured by high-sensitivity C-reactive Protein (hsCRP) is recognized as a cardiovascular risk factor, which can however be affected by lifestyle-related risk factors (LRF). Up-to-date the interplay between hsCRP, LRF and presence and extent of atherosclerotic disease is still largely unknown, which we therefore sought to investigate in a contemporary population-based cohort. We included participants from the cross-sectional population-based Hamburg City Health Study. Affected vascular beds were defined as coronary, peripheral, and cerebrovascular arteries. LRF considered were lack of physical activity, overweight, active smoking and poor adherence to a Mediterranean diet. We computed multivariable analyses with hsCRP as the dependent variable and LRF as covariates according to the number of vascular beds affected. In the 6765 individuals available for analysis, we found a stepwise increase of hsCRP concentration both according to the number of LRF present as well as the number of vascular beds affected. Adjusted regression analyses showed an independent association between increasing numbers of LRF with hsCRP levels across the extent of atherosclerosis. We demonstrate increasing hsCRP concentrations according to both the number of LRF as well as the extent of atherosclerosis, emphasizing the necessity of lifestyle-related risk factor optimization.

Inflammation is considered to be a residual cardiovascular risk factor in patients with cardiovascular disease, even after optimization of other risk factors such as lipid levels[1]. Recently, the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS), the Colchicine Cardiovascular Outcomes Trial (COLCOT) and the Low-Dose Colchicine 2 (LoDoCo2) trials have significantly advanced our understanding of the causal relationship between inflammation and the development and progression of atherosclerosis. Here, an improved outcome in patients with known atherosclerotic cardiovascular disease (ASCVD) was documented after therapeutic targeting of essential steps within the inflammatory cascade[2–4].

High-sensitivity C-reactive Protein (hsCRP) has become the mainstay in the quantification of the inflammatory burden and has been shown to associate with cardiovascular outcome both in the general population and patients with ASCVD[5–7]. Within the broad spectrum of atherosclerosis, manifestations include coronary artery disease (CAD), cerebrovascular disease (CeVD) and lower extremity peripheral artery disease (PAD).

Interestingly, levels of markers of systemic inflammation correlate with the number of vascular beds affected by atherosclerosis[8]. Moreover, atherosclerosis itself can influence further inflammatory processes[9]. In addition,

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hsCRP is influenced by numerous factors such as lack of physical activity, poor diet, smoking and elevated body-mass-index (BMI)[10–13]. These factors have been termed lifestyle-related risk factors (LRF). Optimization of LRF via lifestyle changes is associated with a lower inflammatory burden in patients with CAD[14]. Previous studies have considered only a small spectrum of factors influencing hsCRP and, to the best of our knowledge, no previous studies have investigated the impact of these confounders on hsCRP according to the presence and extent of ASCVD.

In the current study, we aim to delineate the association of the inflammatory burden with LRF stratified by the presence and extent of atherosclerosis in a well-defined contemporary population-based cohort.

Results

Baseline characteristics

Of the 6765 individuals at baseline 3454 (51.1%) were female and the median age was 61 (Quartile [Q] 1/3: 54, 68) years. Overall, 3480 (51.4%) individuals had no ASCVD, whilst 2418 (35.7%) and 867 (12.8%) participants displayed atherosclerosis in 1 or ≥ 2 vascular beds, respectively. Concerning the individual affected vascular beds, CAD was present in 456 (6.7%) individuals at baseline, whilst CeVD or PAD was documented in 2425 (35.8%) and 1386 (20.5%) of the total study population, respectively. In general, participants with ASCVD and with more extensive ASCVD (i.e. ≥ 2 vascular beds affected) were older and more often male. In addition, co-morbidities such as arterial hypertension, diabetes mellitus and CKD were more likely to be present in individuals with, than those without ASCVD. LDL-c concentrations were comparable in persons without ASCVD (LDL-c: 122.0 [Q1/3: 99.6, 146.1] mg/dl) and those with 1 affected vascular system (LDL-c: 121.3 [Q1/3: 97.2, 145.8] mg/dl), whilst individuals with ≥ 2 vascular beds affected had the lowest registered LDL-c (LDL-c: 106.8 [Q1/3: 79.0, 136.8] mg/dl). Use of statins was higher in participants with 1 (n = 458 [19.0%]) and ≥ 2 (n = 401 [46.2%]) vascular beds compared to those without (n = 269 [7.7%]) ASCVD. Further baseline characteristics are displayed in Table 1, whilst baseline data without multiple imputations are shown in the supplement (Table S4).

Concerning LRF, a total of 4078 (60.3%) persons from the overall cohort were defined as overweight, and 2475 (36.6%) participants had low levels of PA. Poor adherence to a Mediterranean diet was present in 3471 (51.3%) participants, and 1399 (20.7%) were current smokers. Individuals with ≥ 2 vascular beds affected exhibited a higher prevalence of 3 (21.4%) or 4 (5.0%) LRF compared to participants with 1 affected vascular system (3 LRF:

	Overall (n = 6765)	No atherosclerosis (n = 3480)	1 affected vascular system (n = 2418)	≥ 2 affected vascular systems (n = 867)	*p* value
Age (years)	61.0 (54.0, 68.0)	58.0 (52.0, 64.9)	64.0 (57.0, 70.0)	68.3 (62.6, 72.9)	< 0.0001
Female sex no. (%)	3454 (51.1)	1991 (57.2)	1135 (47.0)	328 (37.8)	< 0.0001
Comorbidities					
Arterial hypertension no. (%)	4095 (63.6)	1735 (53.1)	1632 (70.1)	728 (86.2)	< 0.0001
Diabetes mellitus no. (%)	506 (7.5)	145 (4.2)	208 (8.6)	153 (17.7)	< 0.0001
History of stroke no. (%)	186 (2.8)	0 (0)	96 (4.0)	90 (10.4)	< 0.0001
Chronic kidney disease no. (%)	129 (2.1)	31 (1.0)	55 (2.4)	44 (5.4)	< 0.0001
Medication					
Statins no. (%)	1128 (16.7)	269 (7.7)	458 (19.0)	401 (46.2)	< 0.0001
Antihypertensive medication no. (%)	2323 (36.0)	816 (24.8)	954 (41.2)	553 (65.7)	< 0.0001
Laboratory values					
hsCRP (mg/l)	1.1 (0.6, 2.3)	1.0 (0.5, 2.1)	1.2 (0.6, 2.4)	1.3 (0.7, 2.9)	< 0.0001
Total cholesterol (mg/dl)	208.0 (182.0, 236.0)	210.0 (186.0, 237.6)	208.2 (182.1, 237.1)	192.2 (159.5, 227.6)	< 0.0001
Triglycerides (mg/dl)	98.0 (73.0, 140.0)	93.8 (69.9, 131.3)	101.0 (75.3, 145.4)	113.2 (81.5, 156.5)	< 0.0001
HDL-C (mg/dl)	62.0 (50.0, 76.0)	64.0 (52.1, 78.0)	61.1 (49.7, 75.8)	55.8 (45.4, 69.6)	< 0.0001
LDL-C (mg/dl)	120.0 (96.0, 145.0)	122.0 (99.6, 146.1)	121.3 (97.2, 145.8)	106.8 (79.0, 136.8)	< 0.0001
HbA1C (%)	5.5 (5.3, 5.8)	5.5 (5.3, 5.7)	5.6 (5.3, 5.8)	5.7 (5.4, 6.0)	< 0.0001
Affected vascular systems					
CAD no. (%)	456 (6.7)	-	109 (4.5)	347 (40.1)	< 0.0001
CeVD no. (%)	2425 (35.8)	-	1600 (66.2)	826 (95.3)	< 0.0001
PAD no. (%)	1386 (20.5)	-	710 (29.4)	676 (78.0)	< 0.0001

Table 1. Baseline characteristics of the total study population and according to the number of affected vascular systems. Missing data of the variables needed for regression analysis and for the classification of subgroups were handled through multivariate imputation by chained equations (MICE). Categorical variables are shown as absolute numbers and percentages, comparison between subgroups was made using the Chi-squared test. Continuous variables are described by median and the 1st/3rd quartile, comparison between subgroups was made using the Kruskall-Wallis test. *CAD* coronary artery disease; *CeVD* Cerebrovascular disease; *HbA1C* Glycated haemoglobin; *HDL-C* high-density lipoprotein cholesterol; *hsCRP* high-sensitivity C-reactive protein; *LDL-C* low-density lipoprotein cholesterol; *PAD* Peripheral artery disease.

17.3% and 4 LRF: 3.4%) or no atherosclerosis (3 LRF: 14.5% and 4 LRF: 2.4%). Further information concerning LRF is shown in Table 2 and in the supplement (Table S5, without multiple imputations).

Distribution of hsCRP according to LRF and number of vascular beds affected

In the overall cohort, a median hsCRP of 1.1 (Q1/3: 0.6, 2.3) mg/l was documented (*see* Table S2 *for sex-specific hsCRP concentrations in the overall cohort)*. We found a stepwise increase of hsCRP levels according to the number of vascular beds affected (hsCRP for no vascular beds affected: 1.0 [0.5, 2.1] mg/l; 1 vascular bed affected: 1.2 [Q1/3: 0.6, 2.4] mg/l; ≥ 2 vascular beds affected: 1.3 [Q1/3: 0.7, 2.9] mg/l; $p < 0.001$) and also with each incremental increase of LRF (hsCRP for 0 LRF: 0.7 [Q1/3: 0.4, 1.2] mg/l; 1 LRF: 0.9 [Q1/3: 0.5, 1.9] mg/l; 2 LRF: 1.2 [Q1/3: 0.7, 2.6] mg/l; 3 LRF: 1.5 [Q1/3: 0.8, 3.1] mg/l; 4 LRF: 2.5 [Q1/3: 1.2, 4.4] mg/l; $p < 0.001$). When stratifying by number of affected vascular systems and number of LRF, individuals with ≥ 2 vascular beds affected and 4 LRF had the highest concentrations of hsCRP (hsCRP: 3.22 [Q1/3: 1.57, 5.35] mg/l) in comparison to those without ASCVD and no LRF (hsCRP: 0.6 [Q1/3: 0.38, 1.2] mg/l; *see* Fig. 1 *and* Table S6 + Figure S1 *without multiple imputations*) .

Association of hsCRP with LRF

In unadjusted analysis, the number of LRF showed a strong association with hsCRP both in the total cohort as well as according to the number of affected vascular beds (*see* Table S7). After adjusting for confounders, the association of LRF with hsCRP proved to be consistent in the overall cohort (1 LRF: Beta 0.32 [95% CI 0.23, 0.42], $p < 0.001$; 2 LRF: Beta 0.59 [95% CI 0.50, 0.67], $p < 0.001$; 3 LRF: Beta 0.76 [95% CI 0.66, 0.85], $p < 0.001$; 4 LRF: Beta 1.17 [95% CI 1.01, 1.35], $p < 0.001$), and across all groups of ASCVD extent (*see* Table 3, *and furthermore* Table S8 *for analyses without multiple imputations*).

Regarding the relation of hsCRP with each individual LRF, overweight consistently displayed the strongest association with hsCRP across the extent of ASCVD (total cohort: Beta 0.68 [95% CI 0.63, 0.73], participants without atherosclerosis: Beta 0.69 [95% CI 0.61, 0.76], participants with 1 affected vascular system: Beta 0.67 [95% CI 0.58, 0.77], participants with ≥ 2 affected vascular systems: Beta 0.63 [95% CI 0.47, 0.79]; all $p < 0.001$) after multivariable adjustment. Other LRF such as smoking showed a consistent and significant association with hsCRP across the extent of ASCVD, whilst the association of PA, and sMDS with hsCRP varied (*see* Table S9, *and furthermore* Table S10 *for analyses without multiple imputations*).

Discussion

The current study investigating the association of hsCRP with LRF stratified by the presence and extent of ASCVD in this large-scale contemporary population-based cohort yielded the following main findings:

1. An increase in hsCRP concentrations was found with both an increasing number of LRF and with a greater extent of ASCVD.

	Overall (n = 6765)	No atherosclerosis (n = 3480)	1 affected vascular system (n = 2418)	≥ 2 affected vascular systems (n = 867)	*p* value
LRF					
BMI (kg/m²)	26.0 (23.5, 29.0)	25.4 (23.1, 28.4)	26.3 (23.8, 29.3)	27.3 (24.7, 30.3)	< 0.0001
Overweight (BMI ≥ 25 [kg/m²])	4078 (60.3)	1913 (55.0)	1535 (63.5)	630 (72.7)	< 0.0001
Obesity (BMI ≥ 30 [kg/m²])	1292 (19.1)	549 (15.8)	509 (21.0)	234 (27.0)	< 0.0001
Weekly physical activity (h/week)	2.0 (0, 4.0)	2.0 (0.5, 4.0)	2.0 (0, 4.0)	2.0 (0, 4.0)	0.078
Physical activity (< 1,5 h/week)	2475 (36.6)	1191 (34.2)	916 (37.9)	368 (42.5)	0.0005
sMDS	2.0 (2.0, 3.0)	2.3 (2.0, 3.0)	2.0 (1.9, 3.0)	2.0 (1.2, 3.0)	0.088
sMDS ≤ 2	3471 (51.3)	1755 (50.4)	1248 (51.6)	467 (53.9)	0.21
Current smoking no. (%)	1399 (20.7)	658 (18.9)	524 (21.7)	218 (25.1)	0.0003
Number of LRF					
0 no. (%)	905 (13.4)	552 (15.9)	283 (11.7)	69 (8.0)	< 0.0001
1 no. (%)	2255 (33.3)	1198 (34.4)	802 (33.2)	256 (29.5)	0.085
2 no. (%)	2290 (33.8)	1143 (32.8)	833 (34.5)	313 (36.1)	0.29
3 no. (%)	1108 (16.4)	505 (14.5)	417 (17.3)	186 (21.4)	< 0.0001
4 no. (%)	208 (3.1)	82 (2.4)	82 (3.4)	43 (5.0)	0.0019

Table 2. Lifestyle-related risk factors of the total study population and according to the number of affected vascular systems. Missing data of the variables needed for regression analysis and for the classification of subgroups were handled through multivariate imputation by chained equations (MICE). Categorical variables are shown as absolute numbers and percentages, comparison between subgroups was made using the Chi-squared test. Continuous variables are described by median and the 1st/3rd quartile, comparison between subgroups was made using the Kruskall-Wallis test. BMI body mass index; LRF lifestyle-related risk factors; sMDS simple Mediterranean diet score.

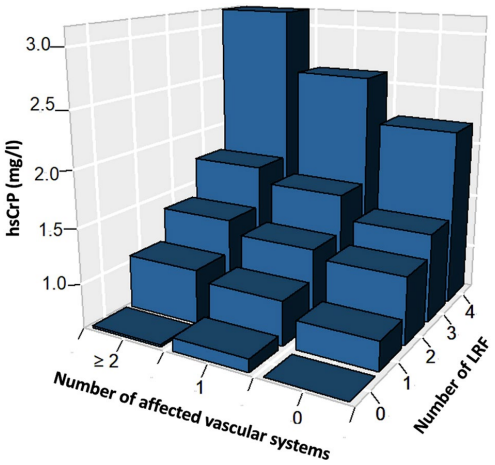

Figure 1. Median high-sensitivity C-reactive protein levels according to the number of affected vascular systems and number of lifestyle-related risk factors. *HsCRP* High-sensitivity C-reactive protein; *LRF* Lifestyle-related risk factors.

Overall		
Number of LRF	**Beta (95% CI)**	***p* value**
1	0.32 (0.23, 0.42)	< 0.001
2	0.59 (0.50, 0.67)	< 0.001
3	0.76 (0.66, 0.85)	< 0.001
4	1.17 (1.01, 1.35)	< 0.001
No atherosclerosis		
Number of LRF	**Beta (95% CI)**	***p* value**
1	0.30 (0.18, 0.42)	< 0.001
2	0.59 (0.48, 0.70)	< 0.001
3	0.70 (0.57, 0.83)	< 0.001
4	1.05 (0.79, 1.31)	< 0.001
1 affected vascular system		
Number of LRF	**Beta (95% CI)**	***p* value**
1	0.33 (0.16, 0.49)	< 0.001
2	0.55 (0.40, 0.71)	< 0.001
3	0.78 (0.60, 0.95)	< 0.001
4	1.19 (0.90, 1.47)	< 0.001
≥ 2 affected vascular systems		
Number of LRF	**Beta (95% CI)**	***p* value**
1	0.45 (0.13, 0.77)	0.007
2	0.66 (0.36, 0.97)	< 0.001
3	0.87 (0.56, 1.18)	< 0.001
4	1.29 (0.85, 1.74)	< 0.001

Table 3. Fully adjusted linear regression analysis for the association of LRF with hsCRP according to the extent of ASCVD. Missing data of the variables needed for regression analysis and for the classification of subgroups were handled through multivariate imputation by chained equations (MICE). The regression coefficient (Beta) and the 95% confidence interval (95% CI) are given. HsCRP was log-transformed. Adjustment was made for age, sex, diabetes, arterial hypertension, intake of statins and chronic kidney disease. The category with no LRF served as reference. *ASCVD* atherosclerotic cardiovascular disease; *hsCRP* high-sensitivity C-reactive protein; *LRF* lifestyle-related risk factors.

2. The highest concentration of hsCRP was found in individuals with the greatest atherosclerotic burden and most LRF, whilst the lowest concentrations were documented in patients without ASCVD and LRF.
3. Even after controlling for major confounders a significant and independent relationship between number of LRF and hsCRP levels was noted, with increasing trend across the extent of ASCVD.

Overall, this underscores the strong association between LRF, low-grade inflammation quantified by hsCRP, and the presence and extent of ASCVD.

Our study represents a contemporary central European population-based cohort with a high rate of ASCVD, since approximately half of the total sample studied presented with atherosclerosis in either the coronary, peripheral or cerebral arteries. With 6.7% the prevalence of CAD in our cohort is comparable to other Western European large scale studies, such as the UK Biobank, where 4.6% of all participants reported atherosclerotic coronary changes[15]. However, a strikingly high rate of PAD with 20.5% and CeVD in 35.8% of the cohort was determined. This is in concurrence with a previously published investigation of the overall HCHS cohort (n = 10,000 participants), where PAD and CeVD were diagnosed in a similar frequency (23.6% and 30.2%, respectively)[16]. In our study, CeVD was defined either by medical history or through imaging findings on carotid ultrasound incorporating intima media thickness (IMT), plaques and carotid stenosis. This in contrast to other population-based cohorts such as the Study of Health in Pomerania, where prevalent ASCVD was registered by participant history only (20% of the overall cohort at baseline)[17]. A recent meta-analysis investigating the prevalence of CeVD (investigating IMT and hemodynamically relevant stenosis of the carotid arteries, respectively) among individuals from 30 to 79 years of age is in line with our findings. Here, a carotid stenosis was diagnosed in 1.5% of the study population, whilst in 24.4% of all investigated individuals either a carotid plaque or increased IMT was registered[18].

With regard to lower extremity PAD prevalence our findings are in agreement with other studies, albeit a varying prevalence has been reported on a population-based level in the literature (e.g. 21% pathological ABI in the German Epidemiological Trial on Ankle Brachial Index study and 17.8% in the Prevalence of Peripheral Arterial Disease in Subjects with a Moderate Risk of Cardiovascular Disease in Primary Prevention population)[19,20]. In our study both imaging and non-invasive tests such as ABI measurement were used to diagnose PAD. Hence the relatively increased proportions of CeVD and lower extremity PAD are most likely due to the use of non-invasive tests, which identified subclinical atherosclerosis. In summary our study paints a realistic picture of prevalent ASCVD in a European middle-aged population-based sample, underpinning the essential role of screening methods for the early identification of atherosclerotic changes within the arterial vascular tree.

Concerning the overall inflammatory burden in our study, we report low concentrations of hsCRP with a median of 1.1 mg/l in the total study cohort. Our findings are corroborated by reports from other population-based cohorts. Steppuhn and colleagues reported a median hsCRP level of 1.15 mg/l from the German Health Interview and Examination Survey for Adults investigating 7006 adults aged 18 to 79 years[21]. Slightly higher hsCRP concentrations of 1.5 mg/l were present in the European prospective investigation into cancer in Norfolk population study (EPIC)[22]. Moreover, in diseased cohorts such as the INTERCATH study a median hsCRP of 1.8 mg/l was noted in a cohort of 1014 CAD patients[14]. Whilst the inflammatory burden in our overall cohort was low, we were able to demonstrate that both a higher burden of LRF and a greater extent of ASCVD is associated with rising hsCRP concentrations. This independent association of the number of LRF with hsCRP concentrations was seen across the strata of ASCVD. Our findings have both clinical and scientific implications. Recently, Ridker and colleagues were able to demonstrate that in patients already treated with statins the inflammatory burden as measured by hsCRP was the strongest predictor for major adverse cardiovascular events, and both cardiovascular as well as all-cause mortality[7]. In a study from Blaum and colleagues, the investigators were able to demonstrate that the number of LRF was strongly associated with hsCRP concentrations. Furthermore, and similar to our results, the authors demonstrated in their CAD cohort that overweight had the strongest association with the inflammatory burden[14]. This finding has been validated in multiple studies where adiposity was shown to correlate with an inflammatory state, potentially through secretion of pro-inflammatory cytokines such as IL-6 or TNF-a by adipose tissue[13,23]. Accordingly, a positive effect on the inflammatory load after weight loss has been demonstrated in overweight patients[24,25]. The anti-inflammatory potential inherent in risk factor optimization is underlined in the study by Blaum and colleagues, where 37.9% of the study cohort would achieve hsCRP levels < 2 mg/l after a hypothesized optimization of risk factors (i.e. weight loss, smoking cessation, adherence to a mediterranean diet, regular PA), and therefore to levels below the threshold used in the enrolment of seminal trials investigating anti-inflammatory treatment (i.e. CANTOS and COLCOT)[3,4,14]. Thus, solely by the optimization of their LRF burden, a relevant health benefit could be unlocked by the patients themselves ahead of the initiation of a specific anti-inflammatory therapy and the potentially associated side-effects of these medications. Our findings therefore underline the necessity of lifestyle optimization as recommended in the guidelines on cardiovascular disease prevention in clinical practice from the European Society of Cardiology[26].

In our cohort individuals with the greatest atherosclerotic burden (i.e. ≥ 2 vascular systems affected) and most LRF had the highest concentrations of hsCRP, displaying the synergistic effect of atherosclerosis itself and LRF on the overall inflammatory burden. Patients with atherosclerosis in two or more vascular beds are a sub-population in whom a particularly high risk for recurrent events has been described[27]. An intensified approach to secondary prevention has therefore been proposed to reduce the incidence of adverse cardiovascular events and mortality in this patient population[28]. Accordingly, optimization of LRF should particularly be prioritized in this cohort.

On the other end of the spectrum, we were also able to show that in participants without ASCVD, the number of LRF was significantly and independently associated with hsCRP concentrations. Besides the use of CRP as biomarker to assess the residual inflammatory risk, the causal role of this acute-phase protein in the development of ASCVD has also been investigated[9]. A contribution of CRP to endothelial dysfunction and hypertension by

the inhibition of nitric oxide, impaired endothelial-associated vascular relaxation, and association with plaque instability by activating NF-κB has been demonstrated[29]. Therefore, it can be hypothesized that the optimization of LRF might be associated with a delayed development of atherosclerotic precursors. However, further studies are needed to ascertain these findings in primary prevention.

Limitations

Whilst the studied population represents a large contemporary cohort, some limitations merit consideration. Since random recruitment took place from a statistical sample of a middle-aged population of the German city of Hamburg, a translation of our findings to other ethnicities, age groups, or geographical regions can only be carried out with caution. Moreover, whilst the selection of participants was carried out randomly, a recruitment bias is possible since healthier individuals are more likely to accept taking part in a study. Also, a relevant proportion of participants (32%) of the overall cohort of 10,000 individuals had to be excluded due to missing hsCRP samples, and comorbidities such as prevalent neoplastic diseases or inflammatory disorders. Lastly, whilst CeVD and PAD were deemed present either by medical history or imaging studies, for CAD solely self-reported information from the individual participants' medical history was available. However, the CAD prevalence reported in our study is comparable to other large-scale population-based cohorts such as the UK Biobank.

Conclusion

In this contemporary population-based cohort, a significant association of lifestyle-related risk factors such as diet, physical activity, smoking, and overweight with the inflammatory burden as measured by hsCRP across the extent of atherosclerotic disease was determined. We demonstrate that both the presence and extent of ACSVD and the burden of LRF have additive effects on the inflammatory load. These findings emphasize the important role of subclinical inflammation in individuals with and without ASCVD and might be helpful for the definition of target populations for anti-inflammatory compounds across the extent of atherosclerotic disease.

Methods

Study cohort

The Hamburg City Health Study (HCHS) is a prospective population-based cohort study that aims to gather extensive data on risk factors for chronic diseases, with a focus on organ system function and structure through a wide range of assessments. It involves 45,000 randomly selected participants from Hamburg, Germany, aged 45 to 74, and includes a detailed examination of lifestyle, environment, genetics, and health outcomes. This large-scale, long-term assessment, conducted in a European metropolitan population, seeks to explore the interplay between biological and psychosocial factors in the context of health and disease. Hereby, the HCHS aims to identify risk factors for major chronic diseases and survivorship, with the goal of accurately determining the prevalence and incidence of common diseases, and the development of complex models for predicting health outcomes. More details on the study are described elsewhere[30].

The current cross-sectional analysis incorporates data from the first 10,000 individuals. Baseline examinations, which included the completion of validated patient questionnaires to self-report lifestyle, blood draws, and non-invasive tests, were conducted during a single-day visit at the HCHS Epidemiological Study Center of the University Medical Center Hamburg-Eppendorf between 2016 and 2018. An ethics approval was obtained from the ethics committee of the Medical Association of Hamburg (PV5131) and the study is registered at ClinicalTrials.gov (NCT03934957). Written informed consent was obtained from all participants. Moreover, the study and all applied methods were performed in accordance with the relevant guidelines and regulations.

In- and exclusion criteria

Participants with valid measurements of hsCRP (i.e. within the limit of detection of the used assay) concentration at baseline were included in the current study. Individuals with chronic inflammatory disorders (defined as rheumatoid arthritis, multiple sclerosis, psoriasis, inflammatory bowel disease), prevalent cancer, intake of immunosuppressive or antineoplastic medication, or missing information of more than 3 values of the previously mentioned criteria were excluded. Also, participants with missing hsCRP concentrations or hsCRP concentrations > 10 mg/l compatible with an acute infection were excluded. After applying the in- and exclusion criteria 6675 datasets were left for the presented analyses (see Fig. 2 for further details). The reporting of the current study was in accordance with the Strengthening the reporting of observational studies in epidemiology (STROBE) statement[31].

Assessment of cardiovascular risk factors, co-morbidities and further variables

Intake of medications was validated via Anatomical Therapeutic Chemical Classification System Codes (ATC-Code) for anti-hypertensive, anti-diabetic medications and statins. Diabetes mellitus was defined as taking medication of the ATC group A10, a fasting glucose > 126 mg/dL, a non-fasting glucose > 200 mg/dL, an HbA1C > 6.5%, or self-reported diabetes. Arterial hypertension was considered to be prevalent when taking medication in ATC group C09A, C09C, C07A, C03C, C03A, C03D, C08C, C02D, C02A, C09X, C01D, a measured resting systolic blood pressure > 140 mmHg/resting diastolic blood pressure > 90 mmHg at inclusion, or self-reported hypertension. Prevalent chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) below 60 ml/min as estimated by the CKD-EPI formula or by medical history[32].

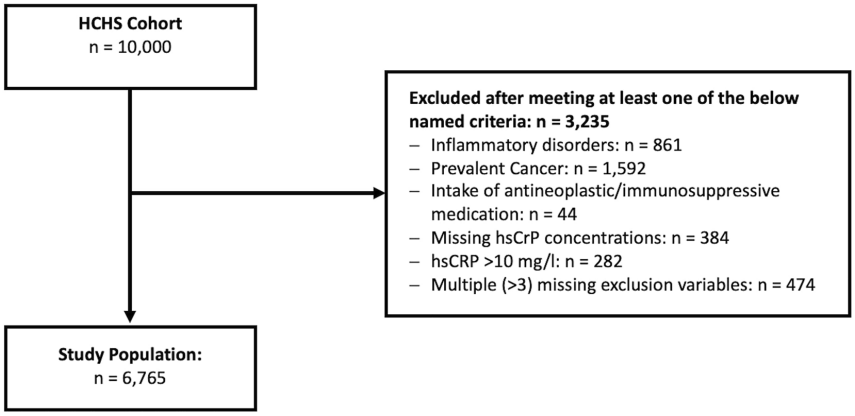

Figure 2. Study flowchart. *HCHS* Hamburg city health study; *hsCRP* High-sensitivity C-reactive protein.

Laboratory measurements

Laboratory measurements (including quantification of glycated hemoglobin (HbA1C), cholesterol levels and hsCRP) were carried out at the HCHS laboratories on the same day as the baseline examination. HsCRP was quantified using a commonly available assay (SIEMENS Healthineers, Atellica High Sensitivity C-reactive protein; Range: 0.16–10.00 mg/l, limit of detection ≤ 0.16 mg/l). Calibration was carried out within the clinical routine.

Assessment of atherosclerotic burden

Prevalent CAD was assessed via self-reported medical history. CeVD was diagnosed by medical history including previous stroke, or by IMT of ≥ 1 mm, vascular plaque (defined as localized IMT thickening of ≥ 1.5 mm), or stenoses (defined as systolic flow velocity > 200 m/s in the common, internal and external carotid artery) on carotid ultrasound at inclusion[33]. PAD was diagnosed via medical history, or pathological ankle-brachial-index (ABI, ≤ 0.9)[34]. Proportions of patients with history of ASCVD and atherosclerosis detected at baseline (for CeVD and PAD) are shown in Table S1.

Assessment of lifestyle-related risk factors

LRF that were taken into consideration were lack of physical activity (PA), defined as < 1.5 h/week of exercise, overweight, defined as BMI ≥ 25 kg/m^2, current smoking, defined as active smoking or recently quitted smoking within the last 6 months, and poor adherence to a Mediterranean diet. A simple Mediterranean diet score (sMDS) as used in the Stabilisation of atherosclerotic plaque by initiation of darapladib therapy (STABILITY) trial was calculated to investigate dietary habits[35]. Briefly, participants answered a food questionnaire in which 4 food groups (consumption of fruit, vegetables, fish, and alcohol) were queried, and points according to the frequency of consumption (maximum 2 points, minimum 0 points) were distributed (see supplementary Table S3). A score ranging from 0 to 8 points was then calculated. Poor adherence to Mediterranean diet was defined as an sMDS ≤ 2 points.

Statistical analyses

Categorical variables are shown as absolute numbers and percentages, compared using Chi-squared test. Continuous variables are reported as median and 1st/3rd quartile (Q1/3) and were compared using Kruskall-Wallis test. To analyse the burden of ASCVD, the population was divided into subgroups according to the number of vascular beds affected (no ASCVD, 1 affected vascular system, ≥ 2 affected vascular systems). Uni- and multivariable linear regression models in the overall cohort and each subgroup with logarithmic hsCRP as dependent variable and LRF (both number of LRF as a categorical variable and each individual LRF) as covariate were calculated and adjusted for age, sex, diabetes, arterial hypertension, intake of statins and chronic kidney disease. Missing data of the variables needed for regression analysis and for the classification of subgroups (overweight, PA, sMDS, smoking, diabetes, CAD, PAD and CeVD) were handled by Multivariate Imputation by Chained Equations (MICE), as proposed by Buuren and Groothuis-Oudshoorn (20 imputed data sets, R Package MICE)[36]. Results were considered as statistically significant at a significance level of a two-sided alpha < 0.05. All statistical tests were carried out using R version 4.1.2.

Previous Presentation

Part of this work has been presented as an abstract presentation at the Congress of the European Society of Cardiology 2023.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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B.B. C.B., F.J.B. and C.W. contributed to conceptualization, data analysis and writing. C. K., R.B.K and F. O. contributed to data analysis and writing. J.W., N.A., C.A.B, D.L., G.T. and B.Z. contributed to data curation, validation and review & editing. R.T. and S.B. contributed to supervision, methodology, writing and review & editing. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Competing interests
GT reports honoraria as consultant or lecturer from Acandis, Alexion, Amarin, Bayer, Boehringer Ingelheim, BristolMyersSquibb/Pfizer, Daiichi Sankyo and Stryker, all outside of the submitted work. RT reports research support from the German Center for Cardiovascular Research (DZHK), the Kühne Foundation, the Joachim Herz Foundation as well as speaker honoraria/consulting honoraria from Abbott, Amgen, Astra Zeneca, Psyros, Roche, Siemens, Singulex and Thermo Scientific BRAHMS. RT is co-founder and shareholder of the ART-EMIS Hamburg GmbH, which holds an international patent application on the use of a computing device to estimate the probability of myocardial infarction (International Publication Numbers WO2022043229A1, TW202219980A). SB has received research funding from Abbott Diagnostics, Bayer, SIEMENS, Singulex and Thermo Fisher. SB received honoraria for lectures from Abbott, Abbott Diagnostics, AstraZeneca, Bayer, AMGEN, Medtronic, Pfizer, Roche, SIEMENS Diagnostics, SIEMENS, Thermo Fisher and as member of Advisory Boards and for consulting for Bayer, Novartis and Thermo Fisher, all outside of the submitted work. FJB reports grants from Daiichi Sankyo, Pfizer, and Sanofi, non-financial support from Abbott, ASAHI INTECC, and Inari Medical, personal fees from Amgen and Novartis outside of the submitted work. CW reports lecture and consulting fees from AMGEN, Novartis, Daiichi Sankyo, Sanofi and AstraZeneca, all outside of the submitted work. All other authors declare no competing interests.

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4.4. Impact of polyvascular disease in patients undergoing unprotected left main percutaneous coronary intervention.

Impact of Polyvascular Disease in Patients Undergoing Unprotected Left Main Percutaneous Coronary Intervention

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Percutaneous coronary intervention (PCI) has demonstrated its safety and efficacy in treating left main (LM) coronary artery disease (CAD) in select patients. Polyvascular disease (PolyVD) is associated with adverse events in all-comers with CAD. However, there is little data examining the interplay between PolyVD and LM-PCI, which we sought to investigate in a retrospective single-center study. We included patients who underwent unprotected LM-PCI at a tertiary center from 2012 to 2019. The study population was stratified based on the presence or absence of PolyVD (i.e., medical history of cerebrovascular and/or peripheral artery disease in addition to LM-CAD). The primary outcome was major adverse cardiovascular events (MACE) combining all-cause mortality and spontaneous myocardial infarction within 1 year after index PCI. Overall, 869 patients were included, and 23.8% of the population had PolyVD. Subjects with PolyVD were older and had a greater burden of co-morbidities. After 1-year follow-up, PolyVD patients exhibited significantly higher rates of both MACE (22.8% vs 9.4%, p <0.001) and bleeding events compared with those without PolyVD. MACE was primarily driven by an increase in all-cause mortality (18.3% vs 7.1%, p <0.001). Results persisted after adjusting for confounders. In conclusion, in patients who underwent LM-PCI, the presence of PolyVD is linked to an increased risk of MACE and bleeding after 1 year of follow-up, which highlights the vulnerability of this population. **© 2024 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2024;222:113−120)**

Keywords: bleeding, cerebrovascular disease, coronary artery disease, mortality, myocardial infarction, peripheral artery disease

Percutaneous coronary intervention (PCI) has emerged as a viable alternative to surgical coronary artery bypass grafting for unprotected left main (LM) coronary artery disease (CAD). The involvement of the LM coronary artery is associated with both a high risk of morbidity and mortality if left untreated. Although coronary artery bypass grafting (CABG) has traditionally been regarded as the gold standard for the treatment of LM-CAD, PCI has proved to be a safe and efficacious treatment approach in selected patients, with comparable outcomes to CABG.[1−3] Patients with polyvascular disease (PolyVD) are at elevated risk for adverse peri-procedural and long-term outcomes after PCI.[4,5] PolyVD is defined as atherosclerotic changes present in ≥2 vascular beds encompassing either coronary, peripheral, or cerebral arterial systems. Subjects with PolyVD typically are older and display a greater burden of co-morbidities such as kidney disease and cardiovascular risk factors, and thus represent a typical LM-PCI patient population.[6] A proportionally elevated adverse event rate has been noted according to the number of vascular beds affected.[4,7−9] However, data regarding clinical characteristics and prognosis of patients with PolyVD who underwent coronary intervention for CAD involving the LM in clinical practice are scarce. We, therefore, sought to investigate the prevalence and outcomes of patients hospitalized for unprotected LM-PCI with and without PolyVD in a retrospective real-world cohort study.

Methods

All patients from 2014 to 2019 who underwent PCI for unprotected LM-CAD at a large tertiary hospital were included retrospectively. Patients who underwent PCI with bare-metal stents, previous CABG surgery, and cardiac arrest at presentation were excluded from current analysis (see Supplementary Figure 1 for the study flow chart). The coronary intervention (including choice of access, stent used, and interventional technique) was carried out using standard techniques at the discretion of the interventionalist. Post-PCI pharmacotherapies, such as dual-antiplatelet

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See page 118 for Declaration of Competing Interest.

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therapy regimens, were chosen according to patient characteristics, clinical presentation acuity, and the preferences of the treating medical team. The study was conducted in compliance with the Declaration of Helsinki and approval from local ethics committees and institutional review board was obtained ahead of study implementation.

Data collection was carried out using the catheterization laboratory database of the Mount Sinai Hospital. Baseline characteristics were ascertained using digitalized medical records or through a standardized patient survey ahead of the index PCI.

Patients were classified into the PolyVD group when they presented with both CAD and a documented medical history of peripheral artery disease (PAD) and/or cerebrovascular disease (CeVD) at baseline. PAD and CeVD diagnosis was based on a combination of patient history and electronic medical records. Patients without a history of PAD and/or CeVD were included in the non-PolyVD group. Although all included patients underwent coronary angiography and LM-PCI as part of the inclusion criteria of the present study, no specific diagnostic tests (neither noninvasive nor invasive) were carried out to detect PAD and/or CeVD.

One-year follow-up was carried out through telephone evaluation, mail correspondence, and reviews of electronic health records after the index hospitalization. All in-hospital events and end points which occured after discharge which led to readmission to the Mount Sinai Hospital were judged by a clinical event committee.[10] Incident end points outside of the Mount Sinai Hospital were obtained through telephone interviews and verified through obtained medical records from external practitioners. The primary composite outcome of major adverse cardiovascular events (MACE) end point was defined as all-cause mortality and spontaneous myocardial infarction (MI) (defined using the third universal definition of MI) within 1 year after the index PCI.[11] Secondary outcomes of interest after 1-year follow-up were the following: target lesion revascularization (TLR) (specified as the need for recurrent revascularization within 5 mm to the index stent placement), target vessel revascularization (TVR) (any instance of recurrent revascularization within the entirety of the primary coronary vessel which was treated during the index PCI). A secondary bleeding outcome was defined as overall bleeding, which was a composite of major in-hospital bleeding (characterized as any bleeding that occurred during the index hospitalization of the patient, associated with a reduction in hemoglobin levels greater than 3 g/100 ml, necessitating a blood transfusion or procedural/surgical intervention at the bleeding site) and major postdischarge bleeding (specified as any episode of bleeding that required either hospitalization or a blood transfusion).

Continuous variables were presented as either mean ± SD or median with the interquartile range, and their comparison was implemented using the Student's *t* test, Mann-Whitney *U* test, or Wilcoxon test, depending on the normality of the data (assessed using the Kolmogorov-Smirnov goodness-of-fit test). Categorical variables were expressed as the number and percentage. Comparisons were carried out through the use of the chi-square test (using Yates's correction for continuity), or Fisher's exact test. Incident end points were documented by the observed number of events and the estimated rates using Kaplan-Meier analysis. The cumulative incidence of the outcome of interest and all individual end points at 1 year was evaluated using the Kaplan-Meier method and compared between groups using the log-rank test to determine the time to the first event. Estimated risks are presented as unadjusted and adjusted hazard ratios (HR/adjHR) along with their corresponding 95% confidence intervals (95% CIs). AdjHRs were computed using a multivariable Cox regression model adjusting for age, gender, hypertension, diabetes mellitus, chronic kidney disease (CKD), lung disease, anemia, non-ST-segment elevation MI, left ventricular ejection fraction, and Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score. A two-sided p value <0.05 was considered statistically significant. All statistical analyses were conducted using Stata version 16.0, developed by Stata Corp.

Results

After applying exclusion criteria, a total of 869 patients were included for analysis, of whom 207 (23.8%) were included in the PolyVD group and 662 (76.2%) in the non-PolyVD cohort. In the PolyVD subgroup, atherosclerotic disease in 2 vascular beds was present in 177 cases (85.5%), whereas 30 cases (14.5%) of 3-bed PolyVD was noted. When categorized based on various combinations of PolyVD, the most common combination was the presence of CAD and CeVD with 93 cases (44.9%). This was followed by the combination of CAD and PAD with 84 cases (40.6%, see Figure 1 for further information).

Overall, patients with PolyVD were significantly older and had a higher burden of classical cardiovascular risk factors such as diabetes mellitus and arterial hypertension, as well as co-morbidities like CKD, anemia, previous gastrointestinal bleed and lung disease. Medications at discharge were similar, aside from a higher rate of warfarin and prasugrel prescribed for the PolyVD cohort. Full baseline characteristics including clinical presentation for PCI are listed in Table 1.

Features of the baseline PCI including LM-specific procedural and angiographic criteria are listed in Table 2 and Supplementary Table 1, respectively. A higher prevalence of calcified lesions was noted in the PolyVD cohort. SYNTAX scores were similar between the 2 subgroups, albeit a

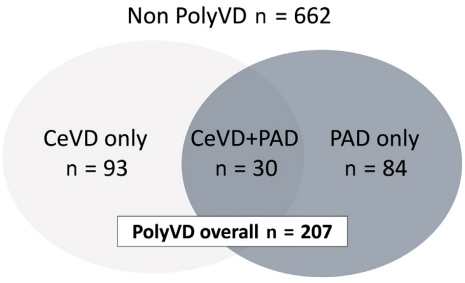

Figure 1. Proportions of patients with and without PolyVD and also stratified according to the affected vascular beds.

Table 1
Baseline characteristics of the overall, polyvascular disease and non-polyvascular disease population

	Overall N=869 (100%)	PolyVD N=207 (23.8%)	Non-PolyVD N=662 (76.2%)	p-value
Clinical Parameters				
Age, years	70.9±12.2	72.9±10.4	70.3±12.6	0.003
Female sex	289 (33.3%)	76 (36.7%)	213 (32.2%)	0.226
Race/ethnicity				0.203
Caucasian	481 (58.0%)	110 (56.4%)	371 (58.5%)	
African American	62 (7.5%)	17 (8.7%)	45 (7.1%)	
Asian	98 (11.8%)	16 (8.2%)	82 (12.9%)	
Hispanic	133 (16.0%)	39 (20.0%)	94 (14.8%)	
Others	55 (6.6%)	13 (6.7%)	42 (6.6%)	
BMI, kg/m^2	28.0±5.6	27.7±5.2	28.1±5.7	0.366
Diabetes Mellitus	359 (41.3%)	106 (51.2%)	253 (38.2%)	<0.001
Insulin-dependent	134 (37.3%)	58 (54.7%)	76 (30.0%)	<0.001
Hypertension	798 (91.8%)	199 (96.1%)	599 (90.5%)	0.010
Hyperlipidemia	799 (91.9%)	197 (95.2%)	602 (90.9%)	0.051
Chronic kidney disease	273 (31.4%)	87 (42.0%)	186 (28.1%)	<0.001
Dialysis	35 (4.0%)	17 (8.2%)	18 (2.7%)	<0.001
Anemia	436 (50.9%)	136 (66.3%)	300 (46.1%)	<0.001
Current smoker	91 (10.5%)	29 (14.0%)	62 (9.4%)	0.057
CHF on presentation	257 (29.6%)	68 (32.9%)	189 (28.5%)	0.237
LVEF, %	51.7±13.6	50.3±14.0	52.1±13.4	0.111
Atrial fibrillation	99 (11.4%)	29 (14.0%)	70 (10.6%)	0.174
Ischemic history				
Previous MI	233 (26.8%)	79 (38.2%)	154 (23.3%)	<0.001
Prior GI Bleed	16 (1.8%)	9 (4.3%)	7 (1.1%)	0.005
Family history of CAD	182 (20.9%)	41 (19.8%)	141 (21.3%)	0.645
Peripheral arterial disease	114 (13.1%)	114 (55.1%)	0 (0.0%)	<0.001
Cerebrovascular disease	123 (14.2%)	123 (59.4%)	0 (0.0%)	<0.001
Lung disease	111 (12.8%)	49 (23.7%)	62 (9.4%)	<0.001
Medications at discharge				
Aspirin	813 (94.2%)	194 (94.6%)	619 (94.1%)	0.764
Statin	801 (92.8%)	191 (93.2%)	610 (92.7%)	0.822
Clopidogrel	535 (62.0%)	137 (66.8%)	398 (60.5%)	0.102
Prasugrel	158 (18.3%)	27 (13.2%)	131 (19.9%)	0.029
Ticagrelor	164 (19.0%)	38 (18.5%)	126 (19.1%)	0.845
DAPT	811 (94.0%)	193 (94.1%)	618 (93.9%)	0.906
Rivaroxaban	16 (1.9%)	3 (1.5%)	13 (2.0%)	0.774
Dabigatran	3 (0.4%)	0 (0.0%)	3 (0.5%)	1.000
Apixaban	23 (2.7%)	5 (2.5%)	18 (2.8%)	0.829
Warfarin	38 (5.5%)	15 (9.2%)	23 (4.4%)	0.019
Clinical presentation for PCI				
Asymptomatic	49 (5.7%)	11 (5.4%)	38 (5.8%)	0.852
Stable angina	404 (46.9%)	78 (38.4%)	326 (49.5%)	0.006
Unstable angina	268 (31.1%)	66 (32.5%)	202 (30.7%)	0.617
NSTEMI	130 (15.1%)	44 (21.7%)	86 (13.1%)	0.003
STEMI	11 (1.3%)	4 (2.0%)	7 (1.1%)	0.298

Values are n (%) or mean ± SD.

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = chronic heart failure; DAPT = dual-antiplatelet therapy; GI = gastro-intestinal; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PolyVD = polyvascular disease; STEMI = ST-segment elevation myocardial infarction.

higher SYNTAX score after exclusion of points because of the LM lesion in patients with PolyVD than non-PolyVD patients was documented. Other procedural and angiographic parameters were comparable between the groups.

Outcomes after 1-year follow-up are documented in Figure 2. MACE occurred in 22.8% of the PolyVD and 9.7% of the non-PolyVD patients (HR 2.62, 95% CI 1.71 to 4.01, p <0.001). This finding was driven mainly by a higher incidence of all-cause mortality (18.3% vs 7.1%, HR 2.75, 95% CI 1.70 to 4.43, p <0.001). Spontaneous MI during follow-up occurred in 8.4% versus 3.3% (see Supplementary Figure 2). Overall stroke rates were low, with an incidence of 0.6% both in the PolyVD as well as non-PolyVD cohort. Other registered ischemic end points such as TVR and TLR did not differ between the groups. Overall bleeding rates were significantly increased in the PolyVD population, whereas postdischarge bleeding rates were equal between groups. These results were consistent after multivariable Cox regression for MACE (adjHR 1.87, 95% CI 1.15 to 3.05, p = 0.012) and driven by all-cause mortality when analyzed individually (adjHR 2.24, 95% CI 1.27 to 3.92, p = 0.005, see Figure 3). In contrast, the adjHR

Table 2
Procedural characteristics of the overall, polyvascular disease, and non-polyvascular disease population

	Overall N=869 (100%)	PolyVD N=207 (23.8%)	Non-PolyVD N=662 (76.2%)	p-value
Procedural parameters				
Staged PCI	88 (10.1%)	23 (11.1%)	65 (9.8%)	0.591
CTO	22 (2.5%)	5 (2.4%)	17 (2.6%)	0.903
Bifurcation	460 (52.9%)	107 (51.7%)	353 (53.3%)	0.681
B2C lesion	721 (83.0%)	174 (84.1%)	547 (82.6%)	0.633
Thrombotic	15 (2.2%)	4 (2.4%)	11 (2.1%)	0.764
Calcification				0.019
None/Mild	423 (49.2%)	84 (41.4%)	339 (51.6%)	
Moderate	201 (23.4%)	60 (29.6%)	141 (21.5%)	
Severe	236 (27.4%)	59 (29.1%)	177 (26.9%)	
PCI with stent	865 (99.5%)	206 (99.5%)	659 (99.5%)	1.000
Stent length, mm	55.3±51.2	56.4±54.7	54.9±50.2	0.710
Maximum Stent diameter, mm	3.7±0.4	3.7±0.4	3.7±0.4	0.414
Number of stents, n	2.0±1.0	2.0±0.9	2.0±1.0	0.720
Number of lesions, n	2.4±1.5	2.4±1.5	2.4±1.5	0.687
Contrast volume, ml	153.1±63.1	148.6±68.5	154.5±61.3	0.270
Procedure duration, min	80.9±45.1	78.9±42.8	81.6±45.8	0.504
Use of MCS devices				
IABP	74 (8.5%)	26 (12.6%)	48 (7.3%)	0.017
Transvalvular Microaxial Flow Pump	110 (12.7%)	23 (11.1%)	87 (13.1%)	0.443
Devices used				
Guideliner	34 (3.9%)	8 (3.9%)	26 (3.9%)	0.968
Orbital atherectomy	16 (1.8%)	1 (0.5%)	15 (2.3%)	0.137
Rotational atherectomy	359 (41.3%)	92 (44.4%)	267 (40.3%)	0.294
Access site				
Radial	92 (10.6%)	23 (11.1%)	69 (10.4%)	0.779
Femoral	750 (86.3%)	174 (84.1%)	576 (87.0%)	0.281
Other	4 (0.5%)	1 (0.5%)	3 (0.5%)	1.000

Values are n (%) or mean ± SD.

CTO = chronic total occlusion; IABP = intra-aortic balloon pump; LVEF = left ventricular ejection fraction; MCS = Mechanical Circulatory Support; PCI = percutaneous coronary intervention; PolyVD = polyvascular disease.

for incident spontaneous MI was no longer significant after adjusting for most likely confounders. A consistent, albeit attenuated association of all bleeding was noted with PolyVD status (full results of regression analysis are listed in Table 3). In an exploratory analysis of the different combinations of affected vascular beds patients with PolyVD, the concomitant presence of CAD and CeVD had the highest event rates of the primary outcome. Subgroup analysis stratified according to the affected vascular beds in the PolyVD group are listed in Supplementary Table 2.

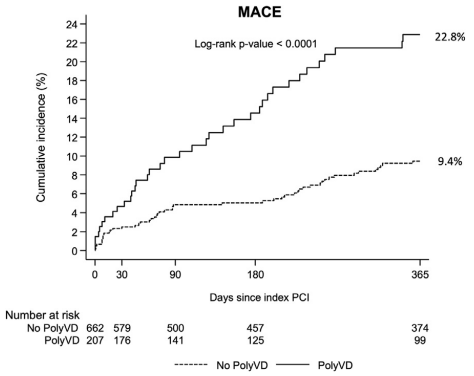

Figure 2. Cumulative incidence curves of major adverse cardiovascular events as a composite of all-cause mortality and spontaneous myocardial infarction for the PolyVD and non-PolyVD population 1 year after the index procedure.

Discussion

In the current analysis, examining the impact of PolyVD on outcomes after PCI for unprotected LM-CAD, a subgroup not extensively studied in existing literature, we report the following key findings: (1) Nearly a quarter of all patients who underwent LM-PCI present with PolyVD, and in this patient cohort an elevated burden of co-morbidities is present; (2) Patients with PolyVD had significantly elevated rates of the composite MACE outcome at 1-year,

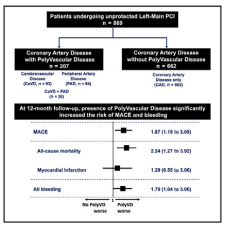

Figure 3. Central illustration.

Table 3
Clinical outcomes of the polyvascular disease and non-polyvascular disease population after 1-year follow-up

	PolyVD N=207 (23.8%)	Non-PolyVD N=662 (76.2%)	Unadjusted Hazard ratio (95% CI)	p-value	Adjusted Hazard ratio (95% CI)	p-value
			No. of events (%)			
Primary outcome						
MACE	37 (22.8%)	50 (9.4%)	2.62 (1.71 - 4.01)	**<0.001**	1.87 (1.15 - 3.05)	**0.012**
Components of the primary outcome						
All-cause mortality	30 (18.3%)	38 (7.1%)	2.75 (1.70 - 4.43)	**<0.001**	2.24 (1.27 - 3.92)	**0.005**
Spontaneous MI	11 (8.4%)	16 (3.3%)	2.53 (1.17 - 5.46)	**0.018**	1.29 (0.55 - 3.06)	0.557
Secondary outcomes						
Stroke	1 (0.6%)	3 (0.6%)	1.20 (0.12 - 11.5)	0.874	1.50 (0.11 - 20.7)	0.762
TVR	15 (11.0%)	64 (13.5%)	0.84 (0.48 - 1.48)	0.554	0.86 (0.48 - 1.54)	0.607
TLR	12 (8.5%)	49 (10.4%)	0.88 (0.47 - 1.65)	0.686	0.82 (0.42 - 1.59)	0.557
All bleeding (key bleeding outcome)	26 (13.0%)	41 (6.4%)	2.06 (1.26 - 3.37)	**0.004**	1.79 (1.04 - 3.06)	**0.035**
Postdischarge bleeding	4 (2.5%)	8 (1.5%)	1.71 (0.52 - 5.69)	0.379	1.92 (0.52 - 7.11)	0.330

The percentages described previously represent Kaplan-Meier rates at 1 year after the index procedure. MACE was defined as the composite of all-cause mortality and MI. Model adjusted for age, gender, hypertension, diabetes mellitus, LVEF, CKD, NSTEMI, SYNTAX score, lung disease, and anemia.

CI = confidence interval; CKD = chronic kidney disease; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PolyVD = polyvascular disease; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery score; TLR = target lesion revascularization; TVR = target vessel revascularization.

primarily driven by a higher incidence of all-cause mortality; (3) The subgroup of patients with PolyVD had increased rates of bleeding after 1-year follow-up.

These findings emphasize the heightened susceptibility for adverse events of PolyVD patients, particularly in the context of LM-PCI. Our study offers novel insights into the specific risk profile and outcomes of this vulnerable patient population, potentially informing future research and clinical practice.

In most of the seminal trials of CABG versus PCI for LM-CAD, no data regarding the prevalence of PolyVD has been reported.[2,12–15] In the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial, 9.6% of patients were registered to have prevalent PAD, whereas in 6.25% of the study population a history of stroke (and thus CeVD) was noted.[15] Furthermore, the investigators of the SYNTAX study implemented a subanalysis, exploring the impact of established cardiovascular disease (present in 46.7%) defined as ≥1 previous MI, previous CeVD, or established PAD, and therefore differing from the definition used in our work.[4] In real-world registry-based populations of patients who underwent LM-PCI, the proportion of subjects with either PAD or CeVD is notably higher compared with the mentioned randomized trials investigating the mode of LM revascularization. For example, a recent report from the National Cardiovascular Data Registry CathPCI Registry was able to document that from the totality of patients who underwent unprotected LM-PCI, 21.8% and 21.6% had PAD or CeVD, respectively. This difference in the rates of CeVD and PAD for registry-based investigations versus clinical trial data could partially be explained because patients were found to be older and more co-morbid than the population included in the mentioned clinical trials.[16] In our single-center cohort, PolyVD was noted in nearly a quarter of all patients who underwent LM-PCI, thus representing a major co-morbidity of LM-CAD patients. Underscoring previous data regarding the PolyVD population, these subjects were older and had a higher burden of cardiovascular risk factors and other disease entities than patients with CAD only. This frail cohort, which is enriched for co-morbidities, represents the typical patient population who is selected for LM-PCI in clinical practice, as these subjects are often deemed unsuitable for surgical revascularization.[17]

Regarding outcomes, we found that patients with PolyVD who underwent unprotected LM-PCI display significantly elevated rates of the composite primary MACE outcome of all-cause death and spontaneous MI than patients with CAD only (i.e., non-PolyVD patients). This is mainly driven by elevated rates of all-cause mortality, where a significant and independent association with the presence of PolyVD was documented. Our findings agree with reports from other PCI populations that investigated the effect of PolyVD on event rates during follow-up. For example, a recent study of patients who underwent PCI from the e-Ultimaster registry reported a significantly higher event rate in patients with PolyVD for all investigated end points, that is, cardiac death, target vessel-related MI, and TLR which was clinically driven (both for the composite end point and all individual end points alike).[5] Interestingly, regarding secondary outcomes in our study, cerebral ischemic outcomes did not differ between the investigated subgroups, albeit only 4 strokes were noted in the follow-up timeframe. This is divergent from reports from the EXCEL substudy exploring the effect of CeVD on outcomes after LM-revascularization. Here, the investigators reported that patients with a history of CeVD had significantly higher rates of both incident stroke and survival 3 years after revascularization in comparison to those without a history of CeVD.[18] With low follow-up event rates of stroke, our study is most likely underpowered to draw meaningful conclusions from the reported incident adverse cerebrovascular events. Reassuringly, whereas there was a proportionally higher rate of spontaneous MI in the PolyVD subgroup after 12 months of follow-up in our study, this

association was no longer significant after adjusting for most likely confounders. Also, incident TVR and TLR were not different between the 2 groups, asserting the procedural efficacy of the initial LM-revascularization for PolyVD patients.

Hence, the excess rate of MACE and mortality documented in our study is possibly because of further patient-related factors potentially including frailty because of the cumulative burden of co-morbidities. Although the elevated rate of mortality is not being caused by the captured ischemic end points, a maximization of established secondary preventive measures including treatment of concomitant diabetes, CKD, and lipid goal attainment is imperative with the aim to improve outcomes in this vulnerable patient population.[19–21]

We also demonstrated a borderline significant increase of bleeding events in patients with than those without PolyVD. Because postdischarge bleeding rates did not differ between the groups, this difference is likely attributable to in-hospital and thus early bleeding. Previously, differing results regarding the association between the extent of atherosclerotic cardiovascular disease and bleeding events have been reported. In a secondary analysis from the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial, the presence of PolyVD was not correlated with an elevated risk of major bleeding compared with patients with PAD alone.[22] Comparable findings were reported from a subanalysis of the GLOBAL-LEADERS study.[23] However, in 1.4 million patients who underwent PCI in the United States, patients with extracardiac vascular disease were at increased risk for major bleeding events during hospitalization, a finding that was corroborated by other studies.[5,24,25] However, all mentioned studies used varying definitions for PolyVD, thus limiting the comparability to our cohort. Of note, none of the mentioned studies exclusively included patients who underwent LM-PCI, which was the case for our cohort. In this patient population a heightened risk for adverse bleeding events has been previously described because over half of the patients were at high bleeding risk using the classification of the High Bleeding Risk Academic Research Consortium in a previous single-center investigation.[17] Moreover, in the PolyVD population, more patients were prescribed warfarin, and in addition a higher rate of previous gastrointestinal bleeds was noted, potentially contributing to the elevated rates of bleeding in our dataset.

This study has some limitations. Although we present data from a well-characterized cohort of patients who underwent LM-PCI, several limitations merit consideration. First, this is a single-center registry limiting external validity. However, as a tertiary referral hospital, a patient population with a high complexity and many co-morbidities are included. Second, this analysis was implemented in a retrospective registry where potential unmeasured confounding cannot be accounted for. However, multivariable adjustment for a multitude of confounders was carried out, aiming to limit the bias of our reported results. Also, the current analysis represents an exploratory analysis and delivers hypothesis-generating data only. Third, specific causes of death and other end points such as vascular complications were not available for adjudication. Fourth, whereas all patients underwent invasive coronary angiography and subsequent LM-PCI, no standardized invasive or noninvasive assessment of the further arterial vascular beds, that is, peripheral or cerebral arteries, was carried out. Therefore, the diagnosis of PAD and CeVD, and consequently PolyVD, was established based on the medical history of the patient, likely leading to an underestimation of the true prevalence of PolyVD. Also, no subtypes of PAD and or CeVD were available. Of note, in the present study, only patients who underwent PCI for LM-revascularization were included.

In conclusion, in the present study, we highlight the significance of PolyVD in patients who underwent unprotected LM-PCI, as we observed PolyVD status in nearly one-quarter of patients. Subjects with PolyVD had higher rates of MACE, which was driven by increased rates of all-cause death. Reassuringly, after multivariable adjustment no increased likelihood of MI was noted during follow-up in the PolyVD cohort. However, bleeding complications were increased in this high-risk population compared. Overall, our findings underscore that patients with extensive atherosclerotic disease represent a particularly frail and vulnerable patient group, also when undergoing LM-revascularization by PCI, and meticulous planning of revascularization and peri-interventional treatment approaches is imperative for these patients.

Declaration of competing interest

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CRediT authorship contribution statement

Benjamin Bay: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Raman Sharma:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Anastasios Roumeliotis:** Writing – review & editing, Investigation, Data curation, Conceptualization. **David Power:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Samantha Sartori:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jonathan Murphy:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Birgit Vogel:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation. **Kenneth F. Smith:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Angelo Oliva:** Writing – review & editing, Visualization, Methodology, Investigation, Data curation. **Amit Hooda:** Writing – review & editing, Methodology, Investigation, Data curation. **Joseph Sweeny:** Writing – review & editing, Methodology, Investigation, Data curation. **George Dangas:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Conceptualization. **Annapoorna Kini:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Prakash Krishnan:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Samin K. Sharma:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Roxana Mehran:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.04.037.

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5. Zusammenfassung

Atherosklerotische kardiovaskuläre Erkrankungen (ASCVD) stellen die weltweit führende Todesursache dar. Patient:innen mit polyvaskulärer Atherosklerose (PolyVD), d.h. ASCVD in ≥2 arteriellen Gefäßgebieten, weisen ein besonders hohes Risiko für adverse Ereignisse auf. Ziel dieser PhD-Dissertation war es, die Relevanz von Biomarkern sowie den Einfluss von PolyVD auf klinische Endpunkte bei interventionell behandelten Patient:innen zu untersuchen.

In der vorliegenden Dissertation konnte gezeigt werden, dass hochsensitives Troponin T/I in Patient:innen mit mono- und polyvaskulärer Atherosklerose unabhängig mit der Gesamtmortalität assoziiert war, jedoch nicht mit dem Auftreten von kardiovaskulären Ereignissen (MACE). Hochsensitives C-reaktives Protein (hsCRP) zeigte eine signifikante Assoziation mit MACE bei PolyVD-Patient:innen nach perkutaner Koronarintervention (PCI), nicht jedoch bei Patient:innen ohne PolyVD. Des Weiteren wurde die Beziehung zwischen Lebensstil-assoziierter Risikofaktoren (LRF), dem Ausmaß der Atherosklerose und hsCRP untersucht. LRF zeigten eine unabhängige Assoziation mit hsCRP, ungeachtet der ASCVD-Ausprägung, was das Zusammenspiel zwischen Lebensstilfaktoren, Atherosklerose Ausmaß und Inflammation unterstreicht. Zudem war PolyVD mit einer erhöhten MACE-Rate 12 Monate nach Hauptstamm-Intervention assoziiert, was den prognostischen Einfluss nicht-koronarer Atherosklerose bei komplexen Revaskularisationen verdeutlicht.

Zusammenfassend liefert diese Dissertation neue Erkenntnisse zur prognostischen Bedeutung von Biomarkern je nach ASCVD Ausmaß und betont den Einfluss des PolyVD auf klinische Ergebnisse nach perkutaner Hauptstamm-Intervention.

6. Summary

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of mortality globally. Patients with polyvascular disease (PolyVD), defined as ASCVD affecting ≥2 arterial beds, are at high-risk for adverse events. This PhD thesis aimed to investigate the prognostic role of cardiovascular biomarkers and the impact of PolyVD in patients undergoing interventional procedures on clinical outcomes.

Data from national and international cohorts were analyzed. High-sensitivity troponin T/I was found to be independently associated with all-cause mortality in both mono- and polyvascular ASCVD, but not with major adverse cardiovascular events (MACE). High-sensitivity C-reactive protein (hsCRP), a marker of chronic low-grade inflammation, was significantly associated with MACE in PolyVD patients undergoing percutaneous coronary intervention (PCI), whilst this was not observed in those without PolyVD. The interaction between lifestyle risk factors (LRF) - i.e. smoking, overweight, physical inactivity, and poor diet - atherosclerosis extent, and hsCRP levels was evaluated in a population-based cohort. LRF were independently associated with hsCRP concentrations regardless of ASCVD severity, showcasing the interplay between LRF, atherosclerosis and inflammatory burden. The analysis further demonstrated that PolyVD was associated with increased MACE rates 12 months after left-main PCI, underscoring the adverse prognostic implications of non-coronary ASCVD in complex revascularization procedures.

In conclusion, this thesis provides novel insights into the prognostic relevance of biomarkers in patients with PolyVD and highlights the clinical impact of atherosclerotic disease extent on outcomes following left-main PCI.

7. Declaration of personal contribution to publications

I, Benjamin Tilman Bay, hereby certify that I have independently worked on the following parts of the research articles:

Research article 1 (Atherosclerosis 2025): This manuscript was published with the doctoral student as senior author. The data used for the analysis are from the INTERCATH cohort, for which the doctoral student is a Co-Principial investigator and was involved in patient recruitment as well as being the lead of the implemented census follow-up. The planning, conception and literature research was done by the doctoral student. The statistical analysis plan (SAP) was written by the doctoral student. The statistical analyses were implemented by Alina Goßling, MSc according to the SAP written by the doctoral student. The interpretation of the results was carried out by the doctoral student in collaboration with the first authors Julia Rohde and Priv.-Doz. Dr. Fabian J. Brunner. The writing of the manuscript as well as the revision after peer-review was carried out by the doctoral student in collaboration with the first-authors Dr. Julia Rohde and Priv.-Doz. Dr. Fabian J. Brunner.

Research article 2 (Clinical Research in Cardiology 2024): This manuscript was published with the doctoral student as first-author. The planning, conception and literature research was done by the doctoral student. The SAP was written by the doctoral student. The statistical analyses were implemented by Dr. Samantha Sartori according to the SAP written by the doctoral student. The interpretation of the results was carried out by the doctoral student. The writing of the manuscript as well as the revision after peer-review was carried out by the doctoral student. The overall project was supervised by Prof. Dr. Roxana Mehran.

Research article 3 (Scientific Reports 2024): This manuscript was published with the doctoral student as shared first-author together with Dr. Christopher Blaum. The planning, conception and literature research was done by the doctoral student. The SAP was written by the doctoral student. The statistical analyses were implemented by Caroline Kellner, MSc according to the SAP written by the doctoral student. The interpretation of the results was carried out by the doctoral student in collaboration with the shared first-author Dr. Christopher Blaum. The writing of the manuscript as well as the revision after peer-review was carried out by the doctoral student in collaboration with the shared first-author Dr. Christopher Blaum. The overall project was supervised by Priv.-Doz. Dr. Fabian J. Brunner and Priv.-Doz. Dr. Christoph Waldeyer.

Research article 4 (American Journal of Cardiology 2024): This manuscript was published with the doctoral student as first-author. The planning, conception and literature research was done by the doctoral student. The SAP was written by the doctoral student. The statistical analyses were implemented by Dr. Samantha Sartori according to the SAP written by the doctoral student. The interpretation of the results was carried out by the doctoral student. The writing of the manuscript as well as the revision after peer-review was carried out by the doctoral student. The overall project was supervised by Prof. Dr. med. Roxana Mehran.

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9. Curriculum vitae

Der Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt.

10. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe, insbesondere ohne entgeltliche Hilfe von Vermittlungs- und Beratungsdiensten, verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe. Das gilt insbesondere auch für alle Informationen aus Internetquellen.

Soweit beim Verfassen der Dissertation KI-basierte Tools („Chatbots“) verwendet wurden, versichere ich ausdrücklich, den daraus generierten Anteil deutlich kenntlich gemacht zu haben. Die „Stellungnahme des Präsidiums der Deutschen Forschungsgemeinschaft (DFG) zum Einfluss generativer Modelle für die Text- und Bilderstellung auf die Wissenschaften und das Förderhandeln der DFG“ aus September 2023 wurde dabei beachtet.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

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