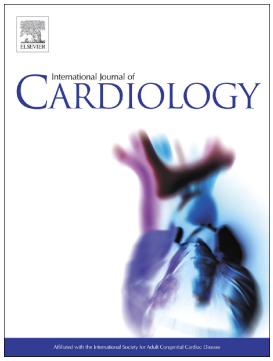


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# History of peripheral artery disease and cardiovascular risk of real-word patients with acute coronary syndrome: Role of inflammation and comorbidities.

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**List of Abbreviations**:

ACS = Acute coronary syndromes

BARC = Bleeding Academic Research Consortium

CAD = Coronary artery disease

CRP = C-reactive protein

CI = Confidence interval

CV = Cardiovascular

HR = Hazard ratio

Hs-CRP = High-sensitivity C-reactive protein

LEAD = Lower extremity arterial disease

MACE = Major cardiovascular events

N/L = Neutrophil to lymphocyte

Non-STEMI = non ST elevation myocardial infarction

PAD = Peripheral artery disease

sFlt-1 = Soluble fms-like tyrosine kinase-1

SPUM = Special Program University Medicine

STEMI = ST elevation myocardial infarction

TIMI = Thrombolysis in Myocardial Infarction

TRS-2P = Risk Score for Secondary Prevention

UA = unstable angina

VHR = Very high risk

## ABSTRACT

**Background:** Patients with acute coronary syndromes (ACS) remain at risk of cardiovascular disease (CVD) recurrences. Peripheral artery disease (PAD) may identify a very high risk (VHR) group who may derive greater benefit from intensified secondary prevention.

**Methods:** Among ACS-patients enrolled in the prospective multi-center *Special Program University Medicine* (SPUM), we assessed the impact of PAD on major cardiovascular events (MACE: composite of myocardial infarction, stroke and all-cause death) and major bleeding. Multivariate analysis tested the relation of each significant variable with MACE, as well as biomarkers of inflammation and novel markers of atherogenesis.

**Results:** Out of 4,787 ACS patients, 6.0% (n=285) had PAD. PAD-patients were older (p<0.001), with established CVD and signs of increased persistent inflammation (hs-CRP; 23.6±46.5 vs 10.4±27.2mg/l, p<0.001 and sFlt-1; 1399.5 ± 1501.3 vs 1047.2 ± 1378.6ng/l, p=0.018). In-hospital-death (3.2% vs 1.4%, p=0.022) and -MACE (5.6% vs 3.0%, p=0.017) were higher in PAD-patients. MACE at 1 year (13.6% vs 7.9%,p<0.001) remained increased even after adjustment for confounders (Adj. HR 1.53, 95% CI: 1.14-2.08, p=0.005). Major bleeding did not differ between groups (Adj. HR 1.18; 95% CI 0.71-1.97, p=0.512). Although PAD predicted MACE, PAD-patients were prescribed less frequently for secondary prevention at discharge.

**Conclusions:** In this real-world ACS patient cohort, concomitant PAD is a marker of VHR and is associated with increased and persistent inflammation, higher risk for MACE without an increased risk of major bleeding. Therefore, a history of PAD may be useful to identify those ACS patients at VHR who require more aggressive secondary prevention.

## INTRODUCTION

Despite effective evidence-based therapies, patients presenting with acute coronary syndromes (ACS) are at high residual risk of death and major cardiovascular events (MACE). [1-3] A wide range of drugs targeting different pathways activated through the life cycle of the atherosclerotic plaque have been developed. [4] Notwithstanding, patients at very-high risk (VHR) are often undertreated, although they are more likely to derive a greater benefit from more intensified treatment strategies. [5-6] In this context, an established diagnosis of peripheral artery disease (PAD) is progressively considered as an important comorbidity for the identification of patients with accentuated plaque burden and thus at very high risk (VHR) [7, 8].

Indeed, a previous diagnosis of PAD informs the *Thrombolysis in Myocardial Infarction* (TIMI) *Risk Score for Secondary Prevention* (TRS-2P), an easy-to-use risk stratification tool in patients with stable coronary artery disease and previous myocardial infarction for the prediction of recurrent MACE [9] whose application has been broadened to the ACS spectrum more recently [10]. Here, we tested the potential of TRS-2P score variables, in particular concomitant PAD, to identify ACS patients at high ischaemic or bleeding risk, as such patients may derive greater clinical benefit from intensified secondary prevention strategies.

## METHODS

*Study population*

The prospective multi-center Special Program University Medicine (SPUM-ACS) cohort (ClinicalTrials.gov number, NCT01000701) recruited patients with a diagnosis of ACS, who were referred for coronary angiography to one of the four participating Swiss University Hospitals (Zurich, Bern, Lausanne, and Geneva) between December 2009 and December 2017. Female and male patients, aged >18 years, admitted for cardiac catheterization within 5 days after chest pain onset, with the main diagnosis of ST-elevation myocardial infarction (STEMI), non-STEMI or unstable angina (UA) were included. Exclusion criteria were severe physical disability, inability to provide informed consent or life expectancy of less than 1 year (for non-cardiac reasons). Further details of this registry have been previously reported [11, 12].

Patient data were collected using a centralized standardized, international electronic case report form (eCRF). The local ethics committee approved the study and all patients gave informed consent. For the present study the population was stratified according to the presence of PAD. History of PAD was defined according to international guidelines as either current intermittent claudication or previous revascularization of the lower extremity, with no further instrumental assessment.

*Study endpoints*

The primary endpoint of the study was defined as 1-year MACE, a composite of non-fatal MI (defined as Q-wave MI or non-Q-wave MI) [13], non-fatal stroke and all-cause death. We also investigated in-hospital MACE and the safety endpoint of major bleeding, defined as BARC 3 to 5 [14]. The incidence of recurrent CV events during follow-up was ascertained by a standardized telephone consultation performed by specialized medical personnel 30 days post discharge, and in a clinical visit at 1 year. When patients could not be reached for the 1-year follow-up visit, medical information was obtained from primary care physicians, family members, hospital records or a registry office. All adverse events occurring within 365 days after the index ACS event were adjudicated by an independent clinical event committee consisting of three experienced cardiologists.

*Biomarker analysis*

Serum aliquots were collected at baseline from blood draws at the time of coronary angiography and after 12 months and stored at -80 ◦C until measurement in the Zurich Core

Laboratory. CRP was measured in serum aliquots using a high-sensitivity latex enhanced immunoturbidimetric assay on a Cobas c 501® autoanalyser (Roche Diagnostics, Mannheim, Germany).

*Statistical analysis*

The baseline characteristics of the patients with PAD and those without PAD were summarised and compared. Categorical variables were expressed as absolute numbers and relative frequencies (percentages) and compared using the chi-squared test; continuous variables were expressed as mean values ± standard deviation (SD) and compared using an independent-sample t test. A Cox regression proportional hazards model was used to evaluate the correlation between PAD and the primary and secondary outcomes at one-year after adjustment for different covariates (age, sex, diabetes, hypertension, dyslipidemia, renal impairment and medical treatment).

The most parsimonious model was identified by simplifying the overall logistic regression of long-term outcomes using the stepwise backward selection of independent predictors, and the selected predictors were used in the proportional hazard analysis of long-term outcomes. All of the tests were two-sided at a significance level of 0.05. Furthermore, a multivariate analysis was performed including the nine variables comprised in the TRS-2P score [9] to test the independent relation of the single variables (age≥75 years, diabetes mellitus, hypertension, PAD, previous stroke, previous coronary artery bypass grafting, history of heart failure, active smoking, and renal dysfunction (defined by an estimated glomerular filtration rate <60 mL/min/1.73 $m^2$, using the Modification of Diet in Renal Disease equation) with MACE in the overall population. The statistical analyses were made using SPSS statistical software version 26.0.

## RESULTS

### *Baseline characteristics*

Baseline clinical characteristics of the study cohort by PAD presence are summarized in **Table 1**. Of 4,787 patients presenting with ACS, 6.0% (n=285) had a history of PAD; of these 78.6% were males and 21.4% females. Compared to ACS patients without PAD, those with PAD were older (median age 70.1 vs. 63.3 years; p<0.001) and had a markedly higher prevalence of traditional risk factors such as hypertension (79.3% vs 54.9%, p<0.001), diabetes (35.8% vs 16.4%, p<0.001), hypercholesterolemia (73.0% vs 62.5%, p<0.001) , wer smoking (44.9% vs 37.5%, p=0.008) and had lower glomerular filtration rates (eGFR, 73.4±24.6 vs 84.5±20.7 ml/min, p=0.002).

*Atherosclerotic cardiovascular disease burden*

Patients with PAD presented with significantly more established atherosclerotic CV disease burden at baseline, with more frequently a previous history of ACS, stroke and/or congestive heart failure and had more commonly undergone prior percutaneous coronary interventions (PCI) or surgical revascularization (all p< 0.001). Patients with PAD presented more frequently as NSTEMI or UA, whereas STEMI presentation at hospital admission was more common in patients without PAD (p< 0.001). Moreover, PAD patients presented more frequently with a multivessel disease compared to patients without PAD (44.8% vs 34.8%, p=0.001) and different culprit lesion location (p <0.001), with higher prevalence of left main involvement.

*Signs of inflammation*

At presentation, PAD patients had a higher C-reactive protein (CRP, 23.6±46.5 vs 10.4±27.2 mg/l, p<0.001). Neutrophils (7.6±3.7x$10^9$/l vs 7.7±4.0x$10^9$/l, p=0.897), lymphocytes (5.2±8.5x$10^9$/l vs 5.1±8.7x$10^9$/l, p=0.765) and N/L ratio (5.2±5.8 vs 5.1±5.7, p=0.780) did not differ between the two groups.

*Novel biomarkers*

In a subgroup analysis of 2,168 patients included in the SPUM-ACS Biomarker Cohort 1, 1,209 patients had available hsCRP measurements both at baseline and at 12-month follow-up. PAD patients presented not only with higher baseline CRP (14.0±26.9 mg/l vs 8.9±22.1 mg/l, p=0.013), but also at 12-month follow-up (20.5±33.6 mg/l vs 14.7±31.4 mg/l, p= 0.047) compared to patients without PAD. PAD patients presented more frequently with persistently

high levels of CRP at follow-up (46.3% vs 36.2%, p=0.016). Furthermore, PAD patients presented higher levels of soluble fms-like tyrosine kinase-1 (sFlt-1, 1399.5 ± 1501.3 ng/l vs 1047.2 ± 1378.6 ng/l, p=0.018). In contrast, no difference was detected for Cyr61 (998.5 ± 3725.0 pg/ml vs 798.8 ± 1341.4 pg/ml, p=0.570) and PlGF (25.6 ± 9.7 ng/l vs 27.2 ± 7.3 ng/l, p=0.109) in the two groups **(Table 2).**

***Medication at presentation and discharge***

On admission, PAD patients were more frequently treated with preventive remedies such as aspirin (72.3% vs 41.7%, p<0.001), DAPT (20.7% vs 8.4%, p<0.001), statins (59.5% vs 40.1%, p<0.001) and ACEi (26.8% vs 22.8%, p<0.001), **Table 1.**

On the contrary, PAD patients were less frequently prescribed secondary preventive therapies at discharge, including dual antiplatelet therapy (DAPT, 78.3% vs. 89.7%, p<0.001) and lipid lowering therapies (96.0% vs. 98.1%, p=0.053), **Table 1.**

***Estimated infarct size***

PAD patients presented with higher baseline values of hs-TnI (3115.0 ± 5373.1 vs 1264 ± 3319.1 ng/l, p<0.001). CK (470.2 ± 904.1 vs 2562.5 ± 47244.6 U/l, p=0.471) and NT-proBNP (727.3 ± 1608.3 vs 630.6 ± 1301.5 pg/ml, p=0.255) did not differ between the two groups. These results are resumed in **Table 1**.

***Major adverse cardiovascular events***

In-hospital death (3.2% vs 1.1%, p=0.022) and in-hospital MACE (5.6% vs 3.0%, p=0.017) were significantly higher in PAD-patients. At 1 year, the primary composite endpoint (MACE) occurred in 411 (8.6%) patients of the overall cohort. Subjects with concomitant PAD at baseline had a 2-times increase in the rate of MACE compared to those without PAD (18.6% vs. 8.0%, p< 0.001, **Figure 1**). All-cause death (3.7% vs. 11.9% p<0.001) and cerebrovascular events (1.6% vs 3.5%, p=0.023) were both significantly higher in PAD patients, with a trend in non-fatal MI (3.3% vs. 5.3%, p=0.060). CV death was 3-times higher in PAD patients (7.0% vs. 2.6%; p<0.001). Major adverse limb events (MALE) occurred in 1.4% of patients with PAD, whereas as expected, these events occurred in a very low number (0.1%) of patients without known PAD at baseline.

After adjustment for differences in baseline characteristics, patients with concomitant PAD had a 53% higher risk of MACE relative to patients without PAD (adjusted [adj.] hazard ratio [HR] 1.53; 95% confidence intervals [CI] 1.14-2.08, p=0.005, **Figure 2, Panel A**) and almost 2-times increase in all-cause death (adj. HR 1.94; 95% CI 1.32-2.84, p=0.001).

Further stratifying PAD patients based on hs-CRP levels revealed that those with higher values (i.e. ≥ 2 mg/l) presented the highest risk of MACE (adj. HR 2.16, 95% CI 1.05-4.44, p=0.035), compared to those with normal values **Supplementary Figure 1**)

***Bleeding outcomes***

At 1 year, a bleeding event was experienced by 410 (8.6%) patients in the overall cohort; of these, 218 (4.6%) were major bleedings according to the BARC classification. Subjects with concomitant PAD at baseline had no significant increase in bleeding rate compared to those without PAD (6.0% vs. 4.5%, p=0.151); of these, only 10 patients were treated with a high-intensity anti-thrombotic regimen, including dual pathway inhibition or triple therapy. After adjustment for differences in baseline characteristics, patients with concomitant PAD had a not significant 18% higher risk of major bleeding relative to patients without PAD (adjusted [adj.] hazard ratio [HR] 1.18; 95% CI 0.71-1.97, p=0.512), **Figure 2, Panel B**). Age≥75 years remained the only independent predictor of major bleeding (adj. HR 1.85; 95% CI 1.37-2.51, p<0.001)

***Cardiovascular risk stratification and independent predictors of MACE based on the TRS-2P Score.***

Distribution of patients across 4 risk categories based on the TRS-2P score is provided in **Figure 3**. The 1-year risk of MACE progressively increased with increasing presence of multiple risk indicators (p for trend <0.001). In the multivariate analysis, including variables from the TRS-2P score, concomitant PAD, was independently associated with MACE, as well as age ≥75 years, type 2 diabetes, stroke history and renal impairment (**Figure 4**).

## DISCUSSION

In this prospective, real-world, multi-center study we found that in ACS patients concomitant history of PAD represents a distinct and independent marker of very high cardiovascular risk. The most relevant finding is that such patients presented with signs of elevated humoral, but not cellular inflammation which persisted long-term and was associated with an increased rate of MACE, CV death and limb ischemia, compared to those without it, while major bleeding did not differ. Patients with PAD succumbed to ACS despite more extensive preventive medication at presentation than those without. Surprisingly, despite the enhanced ischemic risk, patients with PAD received less secondary preventive therapy at discharge and follow-up than those without.

In our population, patients with PAD presented a worse CV risk profile than those without. Besides classical CV risk factors such as hypertension, dyslipidemia, diabetes and smoking, PAD patients presented with markedly elevated CRP levels. Indeed, high circulating hs-CRP has been shown to be predictive of MACE in PAD patients [15]. In our study, in addition, we found persistently higher hs-CRP at 1-year follow-up, reflecting residual inflammatory risk, and higher levels of Flt-1, a novel marker of angiogenesis, whose inhibition in animal models suppresses inflammation and inhibits atherosclerotic plaque growth [16,17]. In contrast, neutrophils, lymphocytes and N/L ratio did not differ between groups. Overall, our results suggest that in this population humoral, rather than cellular inflammation plays a particularly important role in atherosclerosis progression, plaque destabilization [4,12] as well as MACE, and built on our previous findings showing that the combination of inflammatory biomarkers with GRACE score enhance risk discrimination in this setting [18, 19].

The presence of PAD was associated with a worse prognosis as reflected by a higher rate of MACE, as well as limb ischemic events and all-cause death. Thus, in ACS patients, PAD is a surrogate of multiple CV risk factors and more severe atherosclerotic disease including coronary artery disease [20].

Of note, PAD is a variable of the TRS-2P score, initially developed for risk stratification in patients with chronic coronary artery syndrome [9] and more recently applied to ACS patients [10]. Similarly, in our study the TRS-2P score correlated with the gradient of risk for recurrent MACE, establishing its utility in the clinical routine. We extended this concept

confirming history of PAD as a predictor of poor outcome independent of other consolidated atherothrombotic risk factors included in the score, such as diabetes and renal dysfunction in the context of an ACS.

Our findings are particularly relevant considering that patients with PAD, by nature of their particularly high ischemic risk and the generalized nature of the atherosclerotic burden, in a number of recent large randomized clinical trials, found a greater absolute risk reduction with a more intense secondary prevention therapy, which translates into a low number needed to treat [21, 22]. Therefore, early identification of PAD may be particularly important to identify patients who require more intense secondary prevention, both in the immediate post-ACS period, and in the transition from the acute to the chronic phase of their CAD [23, 24]. Prolonged dual anti-thrombotic therapy with ticagrelor 60 mg twice daily or rivaroxaban 2.5 mg twice daily on top of aspirin may represent an advantageous choice in terms of MACE sparing in this VHR group of patients [25]. In addition, PAD is easily identifiable at the bedside using ankle brachial index (ABI), and the investigation of its presence should be encouraged in all patients admitted for ACS, in order to promptly select, among all VHR patients, those who may benefit from a tailored intensive secondary prevention approach.

Of note, major bleeding events represent the most fearful complication of long-term anti-thrombotic therapies required after ACS and has been associated with several adverse events including mortality [26]. In our population, PAD patients showed a non-significant increase in major bleeding events, mainly age-driven, suggesting the potential benefit and relative safety of high-intensity anti-thrombotic therapy in this subgroup of patients. Only a very limited number of PAD patients experienced a major bleeding event during treatment with dual pathway inhibition or triple therapy in our cohort. Furthermore, the greater and persistent humoral inflammation we found in patients with concomitant PAD, suggests a different degree of residual risk linked to inflammation among patients with polyvascular disease and may be therefore useful in identifying those patients who may benefit most from new emerging anti-inflammatory therapy [27, 28].

Despite the strong evidence in favor of a more intense secondary prevention, we found that at one year patients with PAD received less frequently preventive CV treatments, compared to those without PAD. This finding may have multiple etiologies such as greater complexity of the patients who were sicker and therefore more prone to experience MACE or MALE,

together with the suboptimal compliance due to a large burden of polypharmacy. Our study highlights therefore the challenges of translating the results of randomized clinical trials into real-word clinical practice, which is represented by a more heterogenous population and quality of care.

**Limitations**

The results of our study have to be interpreted in light of several limitation. First of all the lack of an external validation represents an important limitation of our study. Secondly, it is not possible to exclude a residual confounding role of other variables not included in the final statistical analysis. Moreover, baseline PAD was diagnosed according to international guidelines only by medical history. The lack of vascular objectivation or ankle-brachial index assessment represents another important limitation of the study. Inflammatory biomarkers analyses are limited to survivors with serial laboratory data available; thus, it is unclear if any of these impacted on MACE. Moreover, a not-negligible group of patients (14,3%) presented a history of malignancies or inflammatory disease at baseline, conditions associated with persistent elevated inflammation. Finally, due to the small group size, meaningful statistical analysis with respect to novel biomarkers is not possible.

**Conclusions**

In conclusion, we found that in a real-world cohort of prospectively recruited ACS patients, concomitant PAD is associated with a higher risk of MACE, limb ischemic events, and CV mortality, compared to patients without PAD, without significant excess in major bleeding. Although confirmatory, we found that a potential important contributor to this heightened risk might be the increased and persistent humoral inflammation in those patients contributing to an unfavorable course acutely and during follow-up. Surprisingly, despite the higher CV risk, patients with PAD were less prescribed secondary preventive therapies. PAD being an easily identifiable marker of VHR, independently from other well-established CV risk factors, may therefore assist clinicians in personalizing atherothrombotic risk stratification and identifying those patients requiring more aggressive secondary preventive and possibly anti-inflammatory therapies and a closer follow-up.

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**Conflicts of Interest**

LR received research grants to the institution by Abbott, Biotronik, Heartflow, Sanofi, Regeneron and speaker/consultation fees by Abbott, Amgen, AstraZeneca, Canon, Novo Nordisk, Medtronic, Sanofi, Occlutech, Vifor. TFL received outside this project research and educational grants from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Daichi Sankyo, Novartis, Sanofi, Servier and Vifor and honoraria from Amgen, Daichi-Sankyo, Novartis, Sanofi all Switzerland, DalCor International, Inbeeo-NonoNordisk, India, Pfizer UK, Philipps, Europe. All other authors have no conflicts of interest.

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Manuscript Title: **History of peripheral artery disease and cardiovascular risk of real-word patients with acute coronary syndrome: Role of inflammation and comorbidities.**

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology.*

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: "The authors report no relationships that could be construed as a conflict of interest."

Andrea Denegri, MD, PhD, FESC

**Table 1.** Baseline characteristics in patients with and without peripheral artery disease. Categorical variables are expressed as percentage while continuous variable as mean ± SD.

| **Baseline characteristics % (n)** | **H/o PAD** (N=285) | **No h/o PAD** (N=4502) | **p-value** |
|---|---|---|---|
| *Demographic* | | | |
| Age (mean ± SD) | 70.1 ± 10.6 | 63.3 ± 12.4 | <0.001 |
| BMI (mean ± SD) | 26.7 ± 4.5 | 27.2 ± 4.3 | 0.071 |
| Female sex, % (n) | 21.4 (61) | 20.5 (925) | 0.388 |
| *Clinical, % (n)* | | | |
| Diabetes | 35.8 (102) | 16.4 (737) | < 0.001 |
| Current smoker | 44.9 (123) | 37.5 (1689) | 0.008 |
| Hypertension | 79.3 (226) | 54.9 (2472) | <0.001 |
| Hypercholesterolemia | 73.0 (208) | 62.5 (2813) | <0.001 |
| Previous MI | 24.3 (69) | 11.4 (513) | < 0.001 |
| Previous PCI | 32.3 (92) | 13.8 (620) | < 0.001 |
| Previous CABG | 12.6 (36) | 3.5 (157) | < 0.001 |
| Stroke history | 8.1 (23) | 2.2 (100) | < 0.001 |
| CHF history | 5.6 (16) | 1.0 (44) | < 0.001 |
| Clinical presentation<br>STEMI<br>NSTEMI<br>UA | <br>32.6 (93)<br>62.1 (177)<br>5.3 (15) | <br>54.5 (2455)<br>42.1 (1896)<br>3.4 (151) | <0.001 |
| Multivessel disease | 44.8 (117) | 34.8 (1490) | 0.001 |
| Culprit lesion<br>LM<br>LAD<br>RCA<br>LCX<br>CABG-graft | <br>3.4 (9)<br>34.5 (90)<br>36.8 (96)<br>20.3 (53)<br>5.0 (13) | <br>1.5 (66)<br>44.9 (1923)<br>32.7 (1398)<br>19.9 (852)<br>1.0 (42) | <0.001 |
| LVEF (mean ± SD) | 49.2 ± 12.8 | 51.5 ± 11.2 | 0.012 |
| Systolic BD (mmHg ±SD) | 129.2 ±22.6 | 129.2 ±23.6 | 0.996 |
| Diastolic BD (mmHg ±SD) | 72.6 ± 16.0 | 75.8 ± 14.8 | <0.001 |
| Laboratory parameters | | | |
| eGFR ( Modification of Diet in Renal Disease equation) mL/min | 73.4 ± 24.6 | 84.5 ± 20.7 | <0.001 |
| hs-CRP (mg/L) | 23.6 ± 46.5 | 10.4 ± 27.2 | <0.001 |
| hs-TnT (ng/L) | 3115.0 ± 5373.1 | 1264.0 ± 3319.1 | <0.001 |
| CK (U/L) | 470.2 ± 964.1 | 2562.5 ± 47244.6 | 0.471 |
| NT-proBNP (pg/mL) | 727.3 ± 1608.3 | 630.6 ± 1301.5 | 0.255 |

| Therapy at admission, % (n) | | | |
|---|---|---|---|
| Aspirin | 72.3 (183) | 41.7 (1183) | <0.001 |
| ACEi | 26.8 (67) | 22.8 (642) | <0.001 |
| DAPT | 20.7 (47) | 8.4 (225) | <0.001 |
| Statins | 59.5 (88) | 30.6 (862) | <0.001 |
| *Therapy at discharge, % (n)* | | | |
| Aspirin | 97.1 (268) | 99.2 (4403) | 0.003 |
| ACEi, | 59.1 (163) | 73.6 (3268) | 0.001 |
| DAPT | 49.5 (141) | 55.9 (2518) | 0.020 |
| Statins | 96.0 (265) | 98.1 (4352) | 0.053 |

H/o, history of; PAD, peripheral artery disease; SD, standard deviation; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CHF, congestive heart failure; e-GFR, estimated glomerular filtration rate; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; BD, blood pressure; ACEi, angiotensin converting enzyme inhibitors; DAPT, dual antiplatelet therapy.

**Table 2.** Inflammatory and novel biomarkers tested for the subgroup analysis of the SPUM-ACS Biomarker Cohort 1. Continuous variable are expressed as mean ± SD.

| **Biomarkers** | **H/o PAD** (N=123) | **No h/o PAD** (N=2045) | **p-value** |
|---|---|---|---|
| Baseline hs-CRP (mg/l) | 14.0 ± 26.9 | 8.9 ± 22.1 | 0.013 |
| 12-month hs-CRP (mg/l) | 20.5 ± 33.6 | 14.7 ± 31.4 | 0.047 |
| Cyr61 (pg/ml) | 998.5 ± 3725.0 | 798.8 ± 1341.4 | 0.570 |
| PlGF (ng/l) | 25.6 ± 9.7 | 27.2 ± 7.3 | 0.109 |
| sFlt-1 (ng/l) | 1399.5 ± 1501.3 | 1047.2 ± 1378.6 | 0.018 |

CRP, C-reactive protein; Cyr61, cysteine-rich angiogenic inducer 61; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1

## ABSTRACT

**Background:** Patients with acute coronary syndromes (ACS) remain at risk of cardiovascular disease (CVD) recurrences. Peripheral artery disease (PAD) may identify a very high risk (VHR) group who may derive greater benefit from intensified secondary prevention.

**Methods:** Among ACS-patients enrolled in the prospective multi-center *Special Program University Medicine* (SPUM), we assessed the impact of PAD on major cardiovascular events (MACE: composite of myocardial infarction, stroke and all-cause death) and major bleeding. Multivariate analysis tested the relation of each significant variable with MACE, as well as biomarkers of inflammation and novel markers of atherogenesis.

**Results:** Out of 4,787 ACS patients, 6.0% (n=285) had PAD. PAD-patients were older (p<0.001), with established CVD and signs of increased persistent inflammation (hs-CRP; 23.6±46.5 vs 10.4±27.2mg/l, p<0.001 and sFlt-1; 1399.5 ± 1501.3 vs 1047.2 ± 1378.6ng/l, p=0.018). In-hospital-death (3.2% vs 1.4%, p=0.022) and -MACE (5.6% vs 3.0%, p=0.017) were higher in PAD-patients. MACE at 1 year (13.6% vs 7.9%,p<0.001) remained increased even after adjustment for confounders (Adj. HR 1.53, 95% CI: 1.14-2.08, p=0.005). Major bleeding did not differ between groups (Adj. HR 1.18; 95% CI 0.71-1.97, p=0.512). Although PAD predicted MACE, PAD-patients were prescribed less frequently for secondary prevention at discharge.

**Conclusions:** In this real-world ACS patient cohort, concomitant PAD is a marker of VHR and is associated with increased and persistent inflammation, higher risk for MACE without an increased risk of major bleeding. Therefore, a history of PAD may be useful to identify those ACS patients at VHR who require more aggressive secondary prevention.

**History of peripheral artery disease and cardiovascular risk of real-word patients with acute coronary syndrome: Role of inflammation and comorbidities.**

## Highlights

- PAD is an easy identifiable marker of residual very high risk in ACS
- PAD in ACS is associated with increased risk of MACE but not of major bleeding
- PAD patients presented persistent increased inflammation
- PAD patients are often undertreated despite a higher residual risk

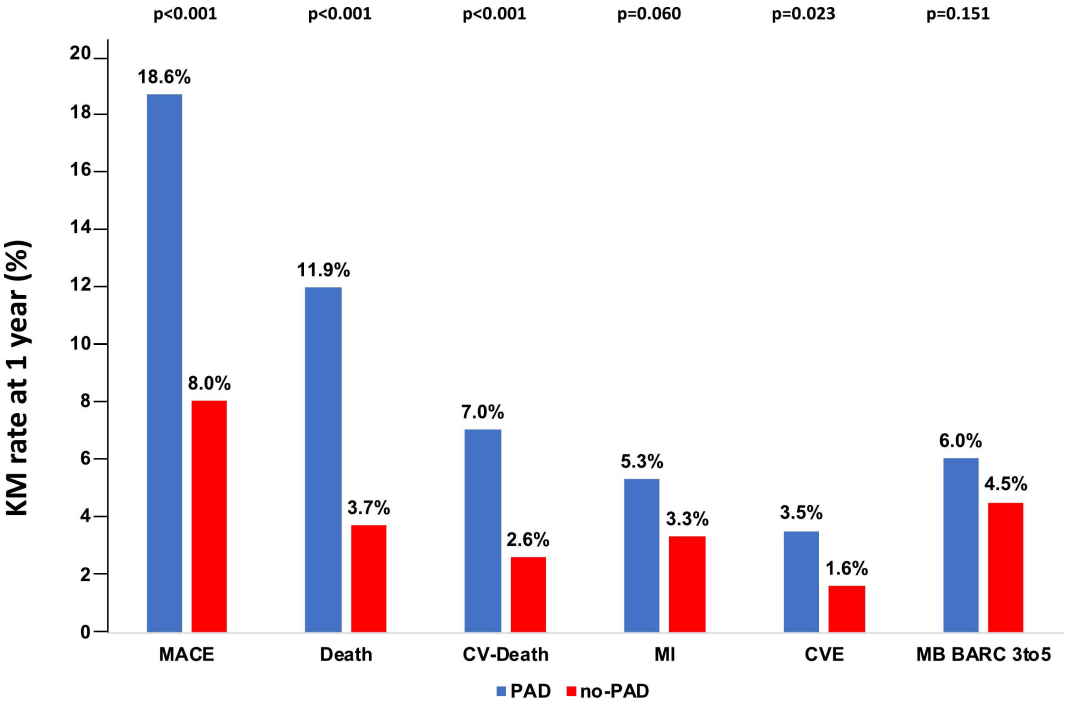
p<0.001
p<0.001
p<0.001
p=0.060
p=0.023
p=0.151
KM rate at 1 year (%)
20
18
16
14
12
10
8
6
4
2
0
18.6%
8.0%
11.9%
3.7%
7.0%
2.6%
5.3%
3.3%
3.5%
1.6%
6.0%
4.5%
MACE
Death
CV-Death
MI
CVE
MB BARC 3to5
PAD
no-PAD

Figure 1

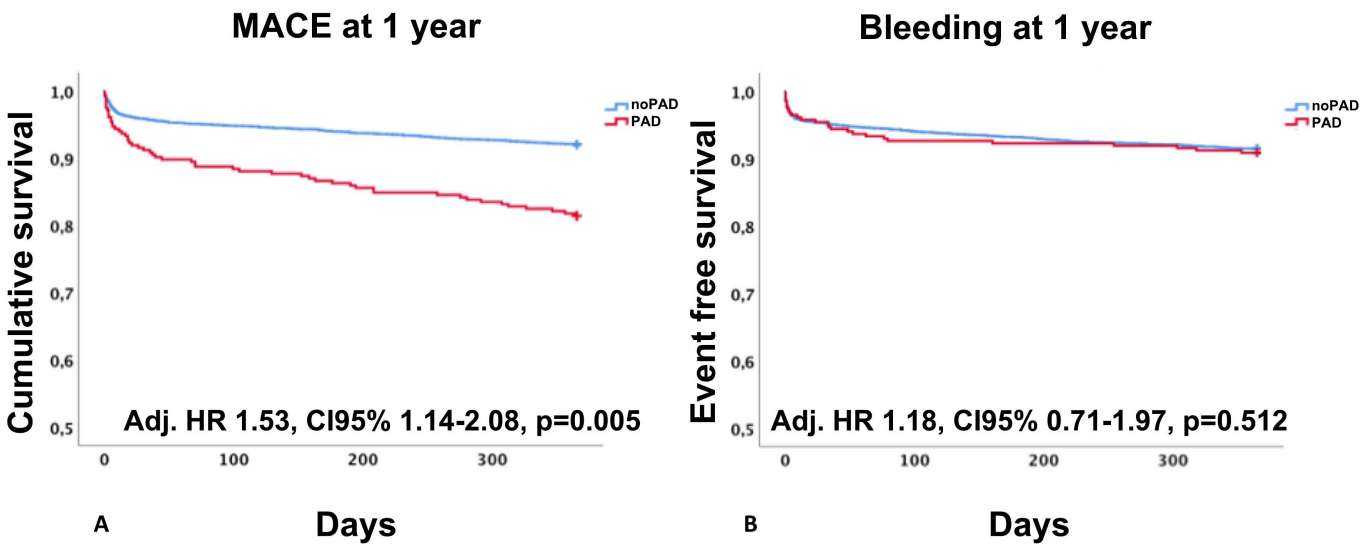
MACE at 1 year
Cumulative survival
1,0
0,9
0,8
0,7
0,6
0,5
noPAD
PAD
Adj. HR 1.53, CI95% 1.14-2.08, p=0.005
0
100
200
300
A
Days
Bleeding at 1 year
Event free survival
1,0
0,9
0,8
0,7
0,6
0,5
noPAD
PAD
Adj. HR 1.18, CI95% 0.71-1.97, p=0.512
0
100
200
300
B
Days

Figure 2

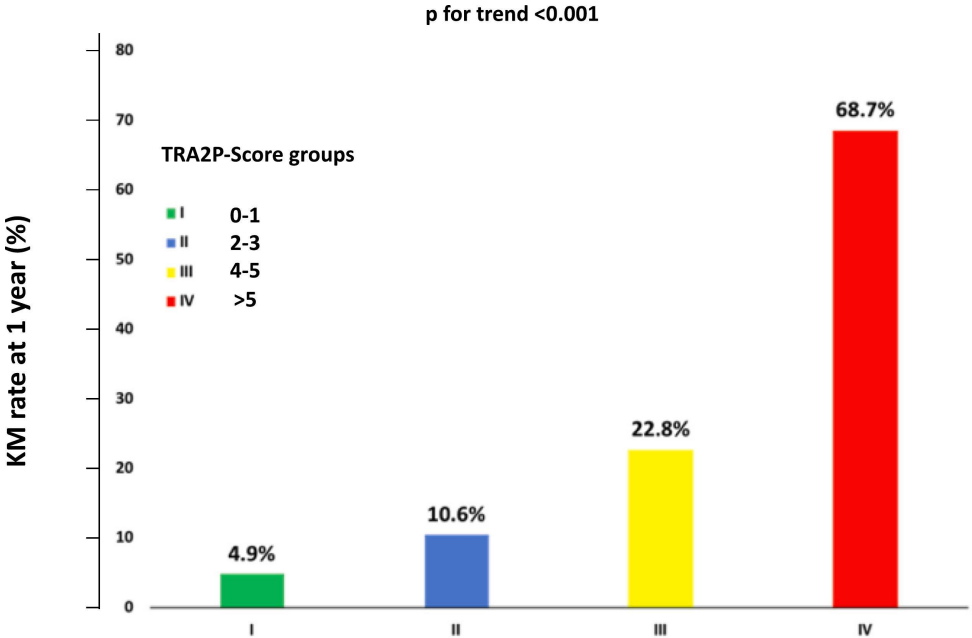
p for trend <0.001
KM rate at 1 year (%)
80
70
60
50
40
30
20
10
0
TRA2P-Score groups
I 0-1
II 2-3
III 4-5
IV >5
4.9%
10.6%
22.8%
68.7%
I
II
III
IV

Figure 3

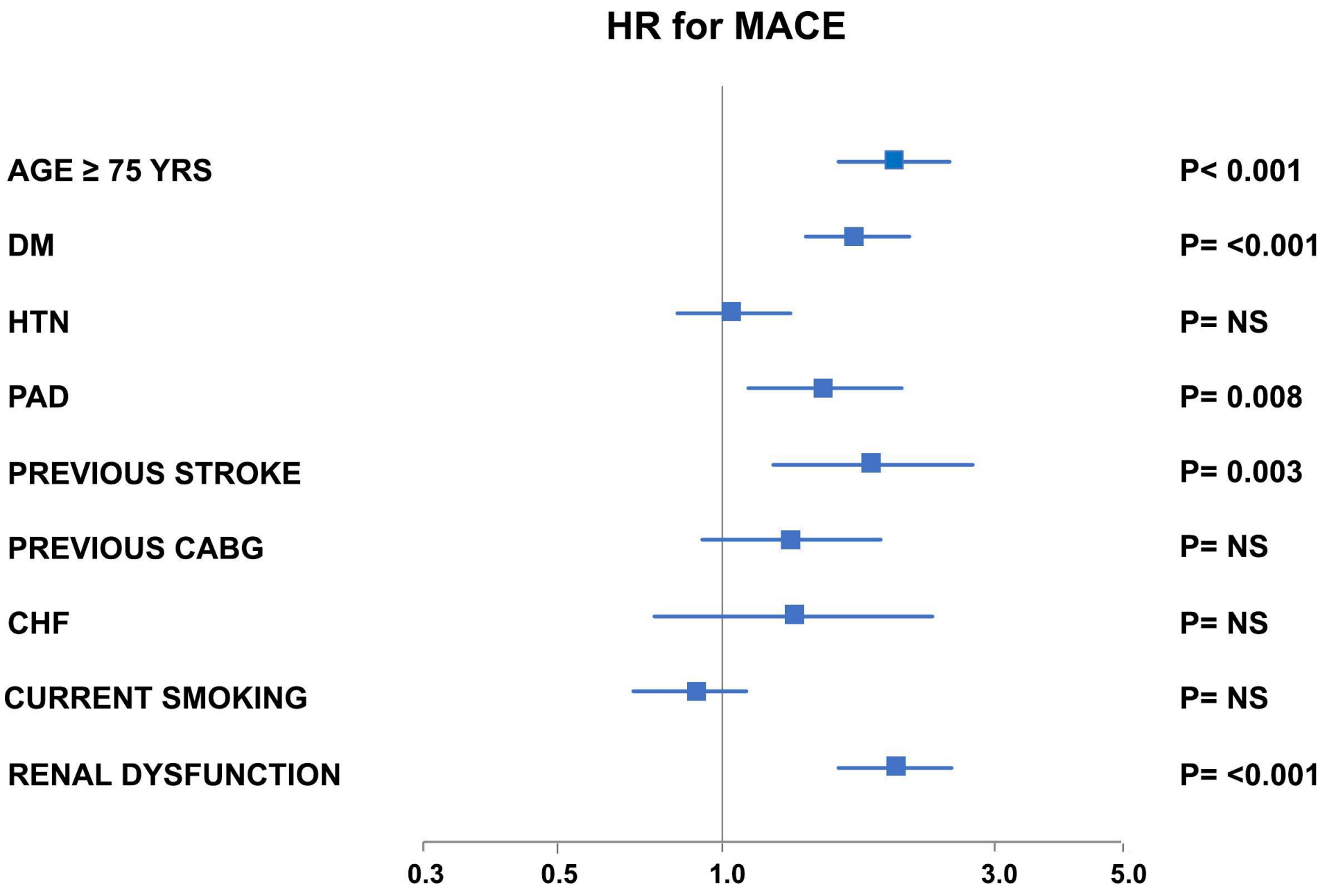
HR for MACE
AGE ≥ 75 YRS
P< 0.001
DM
P= <0.001
HTN
P= NS
PAD
P= 0.008
PREVIOUS STROKE
P= 0.003
PREVIOUS CABG
P= NS
CHF
P= NS
CURRENT SMOKING
P= NS
RENAL DYSFUNCTION
P= <0.001
0.3
0.5
1.0
3.0
5.0

Figure 4