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Adjustment of the SMART risk score by bioactive adrenomedullin enables a more accurate prediction of mortality in patients with ASCVD

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ABSTRACT

Background and aims: Bioactive adrenomedullin 1-52 (bio-ADM) is a novel biomarker for the assessment of endothelial function and prediction of adverse outcomes in patients with acute heart failure and cardiogenic shock. The SMART (Second Manifestations of Arterial Disease) risk score is a validated tool for risk assessment in patients with established atherosclerotic cardiovascular disease (ASCVD). Here we assessed whether bio-ADM adds incremental prognostic value to the SMART risk score in stable patients with ASCVD.

Methods: Circulating bio-ADM levels were measured in 452 stable patients with ASCVD. Endpoints evaluated were all-cause and cardiovascular mortality; follow up was 3 years.

Results: Bio-ADM was higher in non-survivors (n = 45; median 36.8 pg/mL) compared to survivors (n = 407; median 18.3 pg/mL; $p < 0.0001$). Bio-ADM was found to be a strong predictor for all-cause mortality (Chi^2: 44.58; C-index: 0.79) as well as cardiovascular death (Chi^2: 33.29; C-index: 0.85) and proved to be superior to other markers including hs-Troponin T (Chi^2: 7.77; C-index: 0.73) and $eGFR_{CKD\text{-}EPI\ 2021}$ (Chi^2: 25.10; C-index: 0.70). In multivariable analyses adjusting for age, sex, diabetes mellitus, hypertension, smoking, NT-proBNP, and $eGFR_{CKD\text{-}EPI\ 2021}$, bio-ADM remained independently associated with all-cause mortality (HR: 1.6; 95 % CI: 1.2–2.1; Chi^2: 96.17; $p < 0.00001$; C-index: 0.89) and cardiovascular death (HR: 1.7; 95 % CI: 1.1–2.5; Chi^2: 57.71; $p < 0.00001$; C-index: 0.88). Addition of bio-ADM to the SMART risk score meaningfully improved model performance in predicting mortality (SMART risk score: Chi^2: 19.91; $p = 0.0001$; C-index: 0.69; SMART risk score + bio-ADM: Chi^2: 54.51; $p < 0.00001$; C-index: 0.81).

Conclusions: Bio-ADM levels are independently associated with mortality and provide incremental added value on top of the SMART risk score in stable patients with ASCVD.

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1. Introduction

Risk assessment in cardiovascular disease (CVD) has become essential for personalized management in primary and secondary prevention. The growing and increasingly complex spectrum of innovative diagnostic and therapeutic tools calls for guideline-based personalized medicine [1,2]. Clinical tools and calculators for risk stratification in patients with and without CVD, based on demographic parameters, laboratory biomarkers and medical data are important parts of novel guideline recommendations for daily clinical practice [3]. The SMART (Second Manifestations of Arterial Disease) risk score is a validated tool for risk assessment in patients with established atherosclerotic cardiovascular disease (ASCVD) [4,5]. It incorporates demographics (sex, age), clinical data (history of smoking, diabetes mellitus, antithrombotic treatment, systolic blood pressure) and basic laboratory parameters (creatinine, high-sensitivity C-reactive protein (hsCRP), total cholesterol, high-density lipoprotein cholesterol) as well as patient history of ASCVD (i.e. years since first cardiovascular event, coronary artery disease, cerebrovascular disease, aortic aneurysm, peripheral artery disease) and estimates individual risk for myocardial infarction, stroke and cardiovascular death in individual patients with clinically manifest ASCVD in the next 10 years.

Bioactive adrenomedullin 1-52 (bio-ADM) is a 52 amino acid peptide belonging to the adrenomedullin (ADM) family and a novel biomarker for vascular integrity. The ADM-axis was first described in 1993 when ADM was isolated from human pheochromocytoma and found to be a potent vasodilator with marked hypotensive effects via induction of nitric oxide [6–8]. Furthermore, ADM is essential for maintaining the integrity and stability of endothelial barrier function [6,9–12]. Various pleiotropic functions of ADM have been identified, such as anti-inflammatory effects and inhibition of adverse cardiac remodeling [6,11,12]. The main sources of ADM are vascular smooth muscle cells, endothelial cells, leukocytes, and cardiomyocytes. Initial translation of the precursor protein pre-pro-ADM is followed by proteolytic procession to pro-ADM and further cleavage to four circulating fragments: proadrenomedullin N-terminal 20 peptide-glycine, mid-regional-proADM, C-terminal-proADM and ADM-Gly. ADM-Gly, through C-terminal amidation by peptidyl-glycine alpha-amidating monooxygenase (PAM), is converted into its biologically active and stable form, bio-ADM [10,13].

Bio-ADM has been identified as a relevant biomarker for risk stratification in patients with sepsis or septic shock. Elevated bio-ADM plasma levels are associated with higher rates of the *Sequential Organ Failure Assessment* score (SOFA score) and of the severity of disease [14–19]. Furthermore, in patients with acute heart failure elevated bio-ADM levels are associated with adverse prognosis and mortality [20–24]. However, the predictive value of bio-ADM levels in stable patients with ASCVD is unknown. This prompted us to investigate the role of bio-ADM as a potential novel risk marker for cardiovascular outcomes in stable patients with ASCVD.

2. Methods

2.1. Study population and follow-up

In the present study, circulating bio-ADM levels were assessed in 452 hemodynamically stable individuals with established ASCVD admitted to the Department of Cardiology at University Hospital Aachen for various cardiological reasons. Patients were recruited between February 2012 and June 2016. Exclusion criteria were age <18 years, myocardial infarction within the last 30 days, hemodynamically unstable conditions or failure to provide written informed consent. Written informed consent was obtained from all participants in the study. Baseline information, including personal medical history, CVD, comorbidities, cardiovascular risk factors, and medication, was obtained from all participants at inclusion. ASCVD was defined as the presence of coronary artery disease (CAD), history of coronary revascularization, presence of cerebrovascular disease, history of stroke or presence of peripheral artery disease (PAD). The evaluated endpoints of the study were all-cause mortality and cardiovascular (CV) death. Follow-up was 3 years and conducted via medical and hospital records, structured questionnaires, and phone calls. Human biological samples were processed and stored by the RWTH centralized Biomaterial Bank (RWTH cBMB, Aachen, Germany), and their provision adhered to the regulations of the RWTH cBMB. Ethical approval for centralized biobanking was obtained from the Ethics Committee of the Medical Faculty Aachen (EK 206/09). The study protocol received approval from the local ethics committee (EK 206/09) and adhered to the ethical guidelines outlined in the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (European guidelines).

2.2. Laboratory parameters

At baseline, laboratory measurements including serum chemistry with hematology, lipid profile, glucose metabolism, estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration 2021 ($eGFR_{CKD\text{-}EPI\ 2021}$), high-sensitivity (hs) Troponin T and N-terminal pro-B-natriuretic peptide (NT-proBNP) were obtained by venipuncture by all participants upon their study inclusion. Plasma bio-ADM was measured in EDTA plasma samples using the immuno-luminometric sphingotest® assay (SphingoTec GmbH, Hennigsdorf, Germany) as described previously [13,21]. The laboratory staff performing the biomarker measurement was blinded to clinical and demographic data of the patients. The upper normal range (UNR) in healthy adult subjects is 29 pg/mL (90 % CI 27 pg/mL – 38 pg/mL). According to the instructions for use, the assay is highly specific for the amidated C-terminus of ADM and has a limit of detection of 6.3 pg/mL with bio-ADM concentrations being above the limit of detection in healthy subjects.

2.3. Statistical analysis

Data were presented as medians and interquartile ranges (IQR) or counts and percentages as appropriate. Continuous variables were compared using the Kruskal-Wallis test, and categorical data were assessed with Pearson's Chi-squared (Chi^2) test for count data. Biomarker data underwent log transformation. Cox proportional-hazards regression was used to analyze the effect of biomarkers or risk factors on survival in uni- and multivariable analyses. Model predictive values were evaluated using the model likelihood ratio Chi^2 statistic, and the concordance index (C-index) served as an effect measure. Hazard ratios (HR) for bio-ADM were standardized to describe the HR for a bio-ADM change of one interquartile range (IQR). Nested regression models were used to assess the added value of bio-ADM on top of clinical variables or risk scores. For SMART risk score calculation, individual missing values have been imputed with population means, including hsCRP levels. Kaplan-Meier survival curves were plotted for illustrative purposes, with log-rank p-values calculated at pre-specified cut points. Baseline characteristics and Kaplan–Meier curves are presented based on dichotomization at the UNR of 29 pg/mL for bio-ADM and empirical quartiles derived from this cohort (Q1: bio-ADM <14.1 pg/mL, Q2: bio-ADM between 14.1 and 19.3 pg/mL, Q3: bio-ADM between 19.3 and 30.5 pg/mL, and Q4: bio-ADM >30.5 pg/mL). All statistical analyses were performed using R version 4.2.2 (http://www.r-project.org, library rms, Hmisc, ROCR) and the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Baseline characteristics

Baseline characteristics including demographic, clinical and laboratory data are shown in Table 1. Median bio-ADM levels were 19.3 (IQR 14.2–30.5) pg/mL. Median age was 69 years and cardiovascular risk

factors such as hypertension (80.7 %), active smoking (22.0 %), type 2 diabetes mellitus (35.0 %) were common. ASCVD subtypes comprised CAD (94.4 %), history of coronary revascularization (64.4 %), presence of cerebrovascular disease (14.6 %), history of stroke (13.2 %) or PAD (15.5 %). Higher bio-ADM levels were associated with body mass index, type 2 diabetes mellitus, glycated hemoglobin, laboratory markers of cardiac congestion (NT-proBNP) and kidney dysfunction (creatinine and $eGFR_{CKD\text{-}EPI\ 2021}$).

3.2. Bio-ADM is associated with all-cause mortality and cardiovascular death and provides incremental added value on top of the SMART risk score in patients with ASCVD

Higher bio-ADM levels were associated with higher mortality (all-cause death: n = 45, median 36.8 pg/mL) compared to survivors (n = 407; median 18.3 pg/mL; p < 0.0001). Kaplan-Meier plots (Figs. 1–4) and univariable Cox regression analyses found higher bio-ADM levels to be associated with all-cause mortality (HR: 2.4; 95 % CI: 2.0–3.0; p < 0.00001; Table 2) and cardiovascular death (HR: 2.6; 95 % CI: 2.0–3.4; p < 0.00001; Table 3).

Predictive values of biomarkers are indicated by the model likelihood ratio (LR) Chi^2 statistics and the C-index (Tables 2 and 3). Bio-ADM was found to be associated with all-cause mortality (Chi^2: 44.58; C-index: 0.79) as well as cardiovascular death (Chi^2: 33.29; C-index: 0.85) and proved to be superior to other markers including high-sensitivity Troponin T (all-cause mortality: Chi^2: 7.77; C-index: 0.73; CV-death: Chi^2: 9.10; C-index: 0.79) and $eGFR_{CKD\text{-}EPI\ 2021}$ (all-cause mortality: Chi^2: 25.10; C-index: 0.70; CV-death: Chi^2: 19.42; C-index: 0.74). The significant association of bio-ADM with all-cause mortality and cardiovascular death remained significant in multivariable models and addition of bio-ADM on top of multivariable models improved risk prediction (Tables 2 and 3).

In Model 1, adjusted for age and sex, bio-ADM showed a significant association with all-cause mortality (HR: 2.3; 95 % CI: 1.9–2.9; Chi^2: 52.66; p < 0.00001; C-index: 0.809) and cardiovascular death (HR: 2.6; 95 % CI: 2.0–3.4; Chi^2: 36.71; p < 0.00001; C-index: 0.848). This

Table 1
Baseline characteristics
Continuous variables are expressed as medians and interquartile ranges (IQR). Categorical variables are shown as absolute and relative frequencies. Continuous variables were compared using the Kruskal-Wallis test, and categorical data were assessed with Pearson's Chi-squared (Chi^2) Test for Count Data. Abbreviations: bio-ADM: Bioactive Adrenomedullin 1-52; BMI: body mass index; CAD: coronary artery disease; PAD: peripheral artery disease; CHF: congestive heart failure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; $eGFR_{CKD\text{-}EPI\ 2021}$: estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration 2021; hs-Troponin T: high-sensitivity Troponin T; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; RAAS: Renin-angiotensin-aldosterone system; SMART: Second Manifestations of Arterial Disease.

Characteristics	*n*	All	bio-ADM ≤14.1 pg/mL	bio-ADM 14.1–19.3 pg/mL	bio-ADM 19.3–30.5 pg/mL	bio-ADM >30.5 pg/mL	*p-value*
Age – years	452	69 [60–76]	66 [58–74]	66 [56–73]	71 [63.5–76]	73 [63–77]	0.0019
Female – no. (%)	452	93 (20.6)	14 (12.4)	21 (18.6)	28 (24.3)	30 (27)	0.033
BMI – kg/m^2	449	27.7 [25.1–30.5]	25.85 [23.85–28.4]	26.8 [24.3–29.7]	28.4 [26.25–30.75]	29.8 [27.6–33.8]	<0.0001
Risk factors							
Hypertension – no. (%)	450	363 (80.7)	91 (81.2)	88 (77.9)	92 (80)	92 (83.6)	0.7426
Smoking, current – no. (%)	450	99 (22)	25 (22.3)	25 (22.1)	24 (20.9)	25 (22.7)	0.8833
Type 2 diabetes – no. (%)	452	158 (35)	26 (23)	25 (22.1)	42 (36.5)	65 (58.6)	<0.0001
CVD							
CAD – no. (%)	447	422 (94.4)	108 (96.4)	105 (94.6)	105 (92.9)	104 (93.7)	0.6929
Coronary revascularization – no. (%)	452	291 (64.4)	77 (68.1)	70 (61.9)	74 (64.3)	70 (63.1)	0.7836
Cerebrovascular disease – no. (%)	425	62 (14.6)	9 (8.8)	17 (15.9)	17 (15.7)	19 (17.6)	0.2882
Stroke – no. (%)	425	56 (13.2)	12 (11.8)	17 (15.9)	14 (13)	13 (12)	0.8031
PAD – no. (%)	425	66 (15.5)	9 (8.8)	14 (13.1)	16 (14.8)	27 (25)	0.0097
History of CHF – no. (%)	412	264 (64.1)	53 (53)	61 (57.5)	68 (66)	82 (79.6)	0.0004
Laboratory							
Total cholesterol – mg/dL	306	169 [143–195]	179 [150–198]	167 [151.5–189]	169 [142–195.25]	159 [132.25–192.75]	0.1477
LDL-C – mg/dL	296	74 [48–109.25]	75 [50–110]	75.5 [47.25–101.5]	77 [61–118]	65 [43.25–107.75]	0.2795
HDL-C – mg/dL	292	56.5 [43–90.25]	65 [50–98.5]	64 [44–97.5]	51.5 [42–74.25]	48 [37–82.25]	0.0033
Triglycerides – mg/dL	272	122.5 [92–182.25]	99 [83–168.5]	125 [92–176]	130 [103–205]	139 [97–178]	0.0211
Glycated hemoglobin – %	320	5.8 [5.5–6.6]	5.7 [5.4–6.1]	5.7 [5.4–6.35]	5.85 [5.4–6.57]	6.45 [5.77–7.5]	<0.0001
Leukocytes –/nL	419	7.4 [6–9]	7.5 [5.7–9.15]	7.1 [6–8.7]	7.05 [5.9–8.38]	7.8 [6.55–9.25]	0.1696
Creatinine – mg/dL	389	1 [0.9–1.2]	0.92 [0.8–1.1]	1 [0.9–1.11]	1 [0.9–1.12]	1.11 [1–1.46]	<0.0001
$eGFR_{CKD\text{-}EPI\ 2021}$ – mL/min/$1.73m^2$	452	79.58 [68.79–91.31]	85.8 [74.42–99.62]	81.27 [70.8–91.63]	79.97 [70.24–90.95]	73.95 [55.31–82.86]	<0.0001
hs-Troponin T – pg/mL	211	17 [10–35.5]	13 [8–26]	15 [7.75–22.25]	17 [12–28.75]	33 [15–67]	0.0001
NT-proBNP – pg/mL	335	421 [143.5–1462]	242 [82–691]	323 [122.75–890.25]	538.5 [159–1278.5]	1459.5 [420–4225.75]	<0.0001
Medication							
Antithrombotic agents – no. (%)	425	393 (92.5)	101 (99)	99 (92.5)	101 (93.5)	92 (85.2)	0.0021
Oral anticoagulant therapy – no. (%)	425	149 (35.1)	26 (25.5)	36 (33.6)	33 (30.6)	54 (50)	0.0013
Diuretics – no. (%)	425	267 (62.8)	52 (51)	62 (57.9)	67 (62)	86 (79.6)	0.0001
Statins – no. (%)	425	382 (89.9)	95 (93.1)	96 (89.7)	100 (92.6)	91 (84.3)	0.1208
Calcium channel blockers – no. (%)	425	97 (22.8)	20 (19.6)	20 (18.7)	32 (29.6)	25 (23.1)	0.2138
Beta blockers – no. (%)	425	364 (85.6)	89 (87.3)	92 (86)	93 (86.1)	90 (83.3)	0.87
RAAS inhibitors – no. (%)	425	372 (87.5)	90 (88.2)	94 (87.9)	96 (88.9)	92 (85.2)	0.8535
Insulin therapy – no. (%)	425	45 (10.6)	6 (5.9)	7 (6.5)	7 (6.5)	25 (23.1)	<0.0001
Metformin – no. (%)	425	71 (16.7)	10 (9.8)	14 (13.1)	20 (18.5)	27 (25)	0.0178
SMART risk score	452	19.21 [11.81–30.97]	14.86 [11.1–24.14]	16.56 [10.48–27.2]	20.74 [13.8–33.11]	25.15 [15.81–42.04]	<0.0001

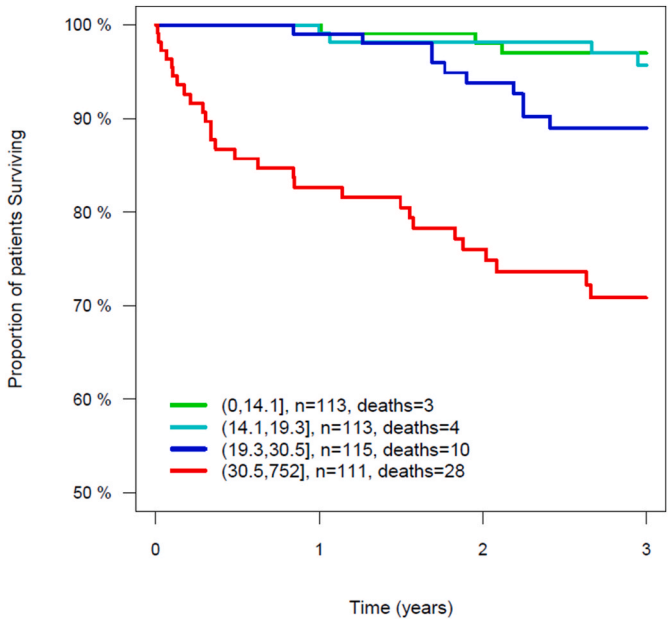

Fig. 1. Kaplan–Meier cumulative event curves for all-cause mortality
Kaplan–Meier cumulative event curves for all-cause mortality with patients separated by bio-ADM quartiles: Q1: bio-ADM <14.1 pg/mL, Q2: bio-ADM between 14.1 and 19.3 pg/mL, Q3: bio-ADM between 19.3 and 30.5 pg/mL, and Q4: bio-ADM >30.5 pg/mL. Abbreviations: bio-ADM: Bioactive Adrenomedullin 1-52.

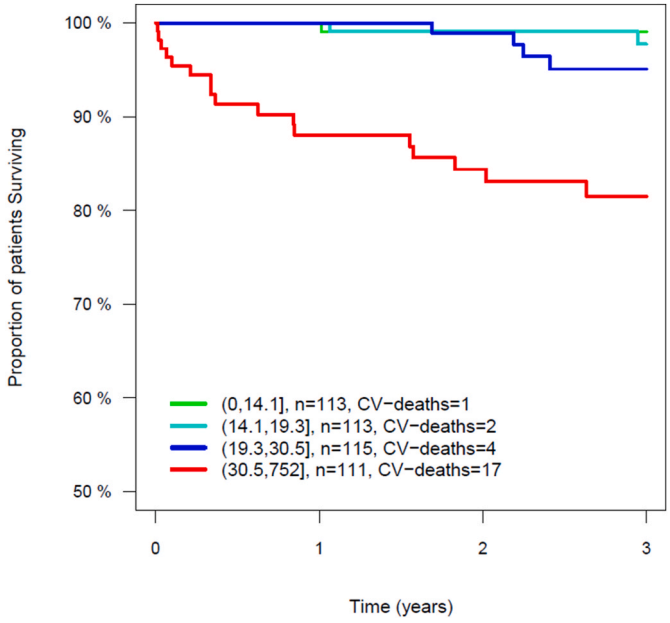

Fig. 2. Kaplan–Meier cumulative event curves for cardiovascular death
Kaplan–Meier cumulative event curves for cardiovascular death with patients separated by bio-ADM quartiles: Q1: bio-ADM <14.1 pg/mL, Q2: bio-ADM between 14.1 and 19.3 pg/mL, Q3: bio-ADM between 19.3 and 30.5 pg/mL, and Q4: bio-ADM >30.5 pg/mL. Abbreviations: bio-ADM: Bioactive Adrenomedullin 1-52; CV: cardiovascular.

association remained stable in Model 2, which additionally was adjusted for diabetes mellitus, hypertension, and smoking (all-cause mortality: HR: 2.3; 95 % CI: 1.8–3.0; Chi^2: 65.72; $p < 0.00001$; C-index: 0.799; cardiovascular death: HR: 2.7; 95 % CI: 1.9–3.9; Chi^2: 48.77; $p < 0.00001$; C-index: 0.837). Further adjustment in Model 3, incorporating NT-proBNP and $eGFR_{CKD\text{-}EPI\ 2021}$, showed a stable association with all-

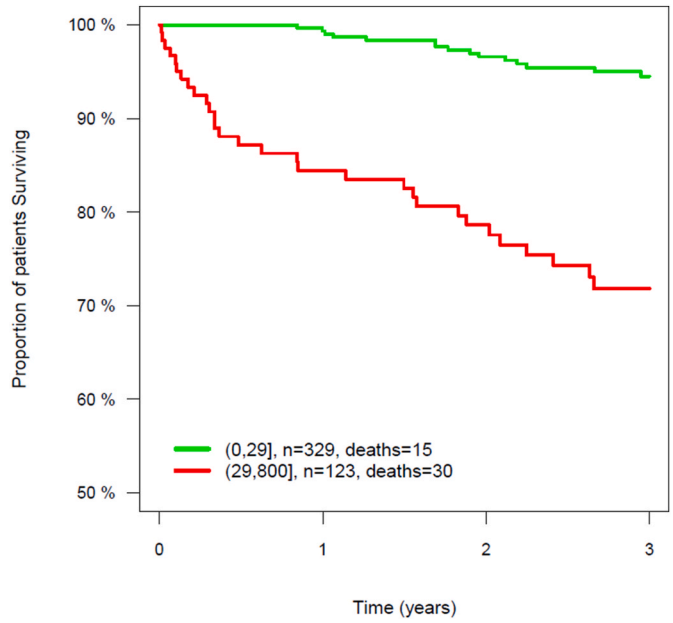

Fig. 3. Kaplan–Meier cumulative event curves for all-cause mortality
Kaplan–Meier cumulative event curves for all-cause mortality with patients separated by bio-ADM upper normal range (UNR) of 29 pg/mL. Abbreviations: bio-ADM: Bioactive Adrenomedullin 1-52.

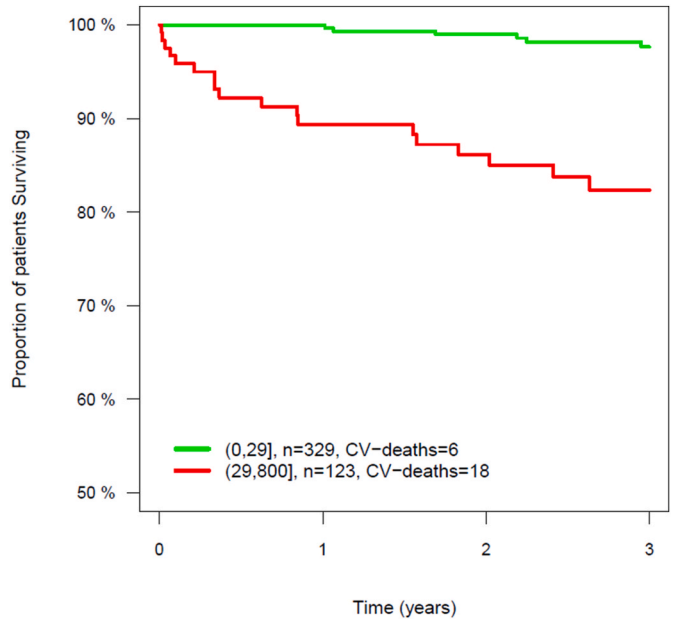

Fig. 4. Kaplan–Meier cumulative event curves for cardiovascular death
Kaplan–Meier cumulative event curves for cardiovascular death with patients separated by bio-ADM upper normal range (UNR) of 29 pg/mL. Abbreviations: bio-ADM: Bioactive Adrenomedullin 1-52; CV: cardiovascular.

cause mortality (HR: 1.6; 95 % CI: 1.2–2.1; Chi^2: 96.17; $p < 0.00001$; C-index: 0.893) and cardiovascular death (HR: 1.7; 95 % CI: 1.1–2.5; Chi^2: 57.71; $p < 0.00001$; C-index: 0.879). Similarly, in Model 4, which additionally included body mass index and high-sensitivity troponin T, bio-ADM remained significantly associated with all-cause mortality (HR: 2.8; 95 % CI: 1.9–4.2; Chi^2: 37.69; $p = 0.00002$; C-index: 0.778) and cardiovascular death (HR: 3.2; 95 % CI: 1.7–5.8; Chi^2: 37.25; $p = 0.00002$; C-index: 0.844).

Furthermore, the addition of bio-ADM to the SMART risk score

Table 2
Uni- and multivariable Cox regression analyses for all-cause mortality
Predictive values of biomarkers are indicated by the model likelihood ratio (LR) Chi^2 statistics and the C-index. Hazard ratios (HR) for bio-ADM were standardized to describe the HR for a bio-ADM change of one interquartile range (IQR). Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, diabetes mellitus, hypertension and smoking. Model 3 was adjusted for age, sex, diabetes mellitus, hypertension, smoking, NT-proBNP and $eGFR_{CKD\text{-}EPI\ 2021}$. Model 4 was adjusted for age, sex, diabetes mellitus, hypertension, smoking, body mass index and high-sensitivity troponin T. *adjusted HR for bio-ADM
Abbreviations: bio-ADM: Bioactive Adrenomedullin 1-52; CI: Confidence interval; hs-Troponin T: high-sensitivity Troponin T; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; $eGFR_{CKD\text{-}EPI\ 2021}$: estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration 2021; HR: Hazard ratio.

	n	HR [95 % CI]	Chi^2	*p-value*	C-index [95 % CI]
bio-ADM	452	2.4 [2.0–3.0]	44.58	<0.00001	0.794 [0.724, 0.864]
hs-Troponin T	211	1.9 [1.3–2.8]	7.77	0.0053	0.726 [0.612, 0.841]
NT-proBNP	335	12.7 [6.9–23.3]	83.14	<0.00001	0.889 [0.846, 0.932]
$eGFR_{CKD\text{-}EPI\text{-}21}$	452	0.5 [0.3–0.6]	25.10	<0.00001	0.696 [0.621, 0.772]
model 1	452		13.83	0.001	0.645
model 1, bio-ADM	452	2.3 [1.9–2.9]*	52.66	<0.00001	0.809
model 2	450		34.67	0.00001	0.702
model 2, bio-ADM	450	2.3 [1.8–3.0]*	65.72	<0.00001	0.799
model 3	333		88.94	<0.00001	0.885
model 3, bio-ADM	333	1.6 [1.2–2.1]*	96.17	<0.00001	0.893
model 4	209		16.37	0.03737	0.682
model 4, bio-ADM	209	2.8 [1.9–4.2]*	37.69	0.00002	0.778

Table 3
Uni- and multivariable Cox regression analyses for cardiovascular death
Predictive values of biomarkers are indicated by the model likelihood ratio (LR) Chi^2 statistics and the C-index. Hazard ratios (HR) for bio-ADM were standardized to describe the HR for a bio-ADM change of one interquartile range (IQR). Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, diabetes mellitus, hypertension and smoking. Model 3 was adjusted for age, sex, diabetes mellitus, hypertension, smoking, NT-proBNP and $eGFR_{CKD\text{-}EPI\ 2021}$. Model 4 was adjusted for age, sex, diabetes mellitus, hypertension, smoking, body mass index and high-sensitivity troponin T. *adjusted HR for bio-ADM
Abbreviations: bio-ADM: Bioactive Adrenomedullin 1-52; CI: Confidence interval; hs-Troponin T: high-sensitivity Troponin T; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; $eGFR_{CKD\text{-}EPI\ 21}$: estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration 2021; HR: Hazard ratio.

	n	HR [95 % CI]	Chi^2	*p-value*	C-index [95 % CI]
bio-ADM	452	2.6 [2.0–3.4]	33.29	<0.00001	0.849 [0.772, 0.926]
hs-Troponin T	211	2.2 [1.4–3.5]	9.10	0.00255	0.785 [0.682, 0.889]
NT-proBNP	335	12.7 [5.7–28.4]	47.70	<0.00001	0.892 [0.835, 0.950]
$eGFR_{CKD\text{-}EPI\text{-}21}$	452	0.4 [0.3–0.6]	19.42	0.00001	0.736 [0.643, 0.829]
model 1	452		5.95	0.005108	0.615
model 1, bio-ADM	452	2.6 [2.0–3.4]*	36.71	<0.00001	0.848
model 2	450		23.07	0.00166	0.719
model 2, bio-ADM	450	2.7 [1.9–3.9]*	48.77	<0.00001	0.837
model 3	333		51.91	<0.00001	0.866
model 3, bio-ADM	333	1.7 [1.1–2.5]*	57.71	<0.00001	0.879
model 4	209		22.81	0.00361	0.756
model 4, bio-ADM	209	3.2 [1.7–5.8]*	37.25	0.00002	0.844

enhanced model performance and provided incremental added value for the prediction of all-cause mortality (SMART risk score: Chi^2: 19.91; $p = 0.00001$; C-index: 0.69; SMART risk score + bio-ADM: Chi^2: 54.51; $p < 0.00001$; c-index: 0.81; Delta Chi^2: 34.6; Delta C-index: 0.12; Table 4) and cardiovascular death (SMART risk score: Chi^2: 10.10; $p = 0.00148$; C-index: 0.70; SMART risk score + bio-ADM: Chi^2: 38.06; $p < 0.00001$; C-index: 0.86; Delta Chi^2: 27.96; Delta C-index: 0.16; Table 5).

Table 4
Cox regression analyses for all-cause mortality for the SMART risk score and bio-ADM
Predictive values of biomarkers are indicated by the model likelihood ratio (LR) Chi^2 statistics and the C-index. Abbreviations: bio-ADM: Bioactive Adrenomedullin 1-52; CI: Confidence interval; SMART: Second Manifestations of Arterial Disease risk score.

	n	Chi^2	*p-value*	C-index [95 % CI]
SMART	452	19.91	0.00001	0.694 [0.612, 0.776]
SMART, bio-ADM	452	54.51	<0.00001	0.813

Table 5
Cox regression analyses for cardiovascular death for the SMART risk score and bio-ADM
Predictive values of biomarkers are indicated by the model likelihood ratio (LR) Chi^2 statistics and the C-index. Abbreviations: bio-ADM: Bioactive Adrenomedullin 1-52; CI: Confidence interval; SMART: Second Manifestations of Arterial Disease risk score.

	n	Chi^2	*p-value*	C-index [95 % CI]
SMART	452	10.10	0.00148	0.698 [0.581, 0.814]
SMART, bio-ADM	452	38.06	<0.00001	0.857

4. Discussion

This study demonstrates for the first time that bio-ADM is a powerful and independent predictor for all-cause mortality and cardiovascular death in stable patients with established ASCVD. Moreover, bio-ADM proved to be superior by providing significant incremental prediction of all-cause mortality and cardiovascular death on top of other established cardiovascular risk markers such as high-sensitivity Troponin T and $eGFR_{CKD\text{-}EPI\ 2021}$. Multivariable adjustment for age, sex, cardiovascular risk factors (i.e. diabetes mellitus, hypertension, smoking, body mass index) and laboratory risk markers (i.e. hs-Troponin T, $eGFR_{CKD\text{-}EPI\ 2021}$ and NT-proBNP) did not affect the significant association of bio-ADM levels with all-cause mortality and cardiovascular death. Finally, addition of bio-ADM to the SMART risk score provided incremental added value (improved discrimination and calibration) for risk prediction in patients with ASCVD. Using state-of-the-art statistical approaches, we systematically assessed the added prognostic value of bio-ADM beyond conventional risk factors through discrimination (C-statistics), model fit and calibration (likelihood ratio Chi^2), which has been previously described as the most statistically efficient approach for evaluating biomarker utility in nested comparisons [25–27]. The association of bio-ADM with mortality remained significant after extensive multivariable adjustment, including demographic, clinical, and laboratory risk markers. The methodology applied in this study aligns with established approaches for biomarker-based risk stratification and biomarker-guided therapies that have been previously used to demonstrate the incremental prognostic value of hsCRP [28–35], BNP and NT-proBNP [36–42] and high-sensitivity troponin [43,44] in major cardiovascular risk and outcome studies. This comparative approach highlights bio-ADM as a promising candidate for further integration into

ASCVD risk models. Importantly, the incorporation of bio-ADM into the established and well-calibrated SMART risk score led to a significant enhancement in risk prediction, underscoring its potential clinical utility. In 2007, Omland et al. demonstrated similar changes in C-index after addition of BNP or NT-proBNP to multivariable risk models predicting cardiovascular mortality [39]. Moreover, a large systemic review published in 2018 assessing the added value of the ankle-brachial index (ABI), hsCRP levels, and coronary artery calcium (CAC) score in primary prevention showed similar improvement of cardiovascular risk prediction as indicated by the change in C-index [28] when compared to the incremental value of bio-ADM in addition to the SMART risk score in our study. Given that a biomarker's clinical performance, as outlined by the FDA and the BEST glossary [45,46], depends on its ability to enhance established risk models, our findings highlight bio-ADM as a novel biomarker with added value for long-term cardiovascular risk assessment.

The SMART risk score addresses the unmet need of 10-year risk estimation for recurrent vascular events in patients with manifest ASCVD. When applied in clinical practice the SMART risk score allows optimization of medical treatment strategies, assistance in setting motivational goals in patient care and is recommended by the 2021 *European Society of Cardiology (ESC) Guidelines on Cardiovascular Disease Prevention in Clinical Practice* [3]. Moreover, biomarker-based prognosis and risk stratification for improving clinical risk assessment is increasingly endorsed by major cardiovascular societies, including the American Diabetes Association (ADA), the American College of Cardiology (ACC), and the ESC [51–55]. These organizations discuss the integration of biomarkers such as NT-proBNP, high-sensitivity troponin, and hsCRP to refine prediction models and guide patient management. However, the ideal biomarker combination for clinical routine remains under investigation, as ongoing research aims to identify optimal markers for cardiovascular risk stratification.

In previous studies, bio-ADM was found to be a biomarker reflecting systemic endothelial (dys-)function and improving clinical risk stratification in critically ill patients [16,47]. Alongside patients with sepsis or acute heart failure, the role of circulating bio-ADM levels has been investigated in other highly vulnerable patient cohorts, such as in perioperative settings. A significant association between elevated bio-ADM plasma levels and an increased incidence of adverse events, as well as unfavorable short-term outcomes has been observed in patients after major cardiac surgery [48]. Additionally, in patients who have undergone complex aortic surgery, an association between increased bio-ADM levels and postoperative cardiogenic shock, respiratory instability and mortality has been described [48–50]. However, the predictive value of bio-ADM beyond critically ill, unstable, or patients in a peri-operative setting has not been explored in larger cohorts so far. To the best of our knowledge this is the first study investigating the role of bio-ADM in stable patients with ASCVD.

Here we showed that addition of bio-ADM on top of the SMART risk score provides incremental added value improving discrimination and calibration. With established ASCVD and highly prevalent cardiovascular risk factors such as hypertension, diabetes mellitus and dyslipidemia our cohort represents a high-risk patient population. During the last decades, multiple novel pharmacological interventions have been investigated and established in primary and secondary prevention of ASCVD. However, ASCVD still accounts for approximately one third of all deaths globally and even with optimal medical treatment according to current guidelines a significant and inacceptable high residual cardiovascular risk remains [3,56,57]. Therefore, there is an urgent clinical unmet need to a) early identify vulnerable patients at high cardiovascular risk and b) to identify novel therapeutic targets to improve outcomes of patients with ASCVD. With the novel anti-ADM monoclonal antibody Adrecizumab being currently investigated in critically ill patients with promising outcomes, the results of this study further support a potential role for ADM-targeted therapies in stable patients with ASCVD to improve individualized treatment options and eventually outcomes [17,58]. Future research should focus on whether measuring bio-ADM can influence therapeutic decision-making and improve patient outcomes.

4.1. Limitations

This study has various strengths and limitations. A limitation of the study is its single-center data collection and the absence of a validation cohort restricting the consideration of potential external factors and compromising the generalizability of our findings. Also, the patient cohort and number of outcomes were small in comparison to previous cohort studies. Future studies with prospective multi-center cohorts are necessary to validate our findings and further establish the role of bio-ADM in cardiovascular risk stratification. However, we observed a robust correlation between bio-ADM levels and hard clinical outcomes as well as a clinically relevant added value in risk prediction.

Further limitations of this study include incomplete data documentation and the necessity of imputation of certain variables, especially hsCRP levels, as well as certain sub-specifications of ASCVD, such as aortic aneurysms, which are subsumed under ASCVD in some definitions. Nevertheless, imputation was performed using study population mean values that have been validated in the primary cohort and development studies of the SMART risk score [4,5,59]. Previous studies have demonstrated robust model performance of the SMART risk score with imputed hsCRP values [5,59,60]. Despite imputation, we were able to observe similar sufficient model performance in our cohort study, suggesting strong predictive capacity of the SMART risk score even with missing values. However, it is essential to validate these findings in larger cohorts with hsCRP measurements to ensure the accuracy and reliability of the model. Direct comparison of bio-ADM and hsCRP within derivation and validation cohorts would provide further insights into their roles in cardiovascular risk stratification. Future studies incorporating both biomarkers are necessary to assess their relative and combined prognostic value in ASCVD populations.

Another limitation is the lack of data on non-fatal cardiovascular events, as the study design focused on fatal outcomes. While non-fatal events are clinically relevant, biomarkers predictive of mortality often show similar associations with major non-fatal events. Future prospective studies incorporating both fatal and non-fatal outcomes are needed to further assess the clinical utility of bio-ADM in secondary prevention.

It is important to highlight that the association observed in our study does not allow for causal interpretation, given the observational, cross-sectional study design and the limited number of events.

5. Conclusions

In summary, in patients with established ASCVD, bio-ADM levels are independently associated with cardiovascular death and all-cause mortality. Bio-ADM provided significant added value to established cardiovascular risk factors and biomarkers and incrementally improved risk prediction of the SMART risk score. These findings need to be validated in external cohorts. Future large prospective studies are warranted to evaluate clinical applicability of bio-ADM as a novel biomarker and potential therapeutical target for patients with CVD.

CRediT authorship contribution statement

Berkan Kurt: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Matthias Rau:** Conceptualization, Formal analysis, Investigation, Supervision, Visualization, Writing – review & editing. **Oliver Hartmann:** Formal analysis, Visualization, Writing – review & editing. **Andreas Bergmann:** Formal analysis, Resources, Funding acquisition, Methodology, Writing – review & editing. **Martin Reugels:** Conceptualization, Formal analysis, Visualization, Writing – review & editing. **Susanne Just:** Investigation, Methodology, Writing – review & editing.

Florian A. Wenzl: Conceptualization, Writing – review & editing. **Julia Moellmann:** Investigation, Methodology, Writing – review & editing. **Jens Spießhöfer:** Conceptualization, Writing – review & editing. **Andrea Milzi:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Kinan Kneizeh:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Kirsten Thiele:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Mathias Hohl:** Conceptualization, Writing – review & editing. **Simina-Ramona Selejan:** Conceptualization, Writing – review & editing. **Emiel P.C. van der Vorst:** Conceptualization, Writing – review & editing. **Edgar Dahl:** Investigation, Resources, Writing – review & editing. **Jörg Schröder:** Supervision, Investigation, Writing – review & editing. **Thomas F. Lüscher:** Conceptualization, Writing – review & editing. **Nikolaus Marx:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Michael Lehrke:** Conceptualization, Investigation, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Florian Kahles:** Conceptualization, Formal analysis, Funding acquisition, Resources, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Data availability statement

The data file used and analyzed during the current study, and the summary statistics are available from the corresponding author on reasonable request.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: B. K. has served as a speaker for SphingoTec/4TEEN4 Pharmaceuticals and received travel reimbursement from 4TEEN4 Pharmaceuticals, Novo Nordisk, the German Society of Lipidology, the German Cardiac Society, Boehringer Ingelheim and Lilly. F.K. has served as a speaker for Novo Nordisk, Amgen, Lilly, AstraZeneca, C.T.I., Cogitando, DGK-Akademie, consulted Novo Nordisk, Lilly, Bayer, PricewaterhouseCoopers/Strategy&, and received travel support from Amgen, Novo Nordisk, Boehringer Ingelheim, Bayer, SphingoTec/4TEEN4 Pharmaceuticals, C.T.I., Cogitando, and Lilly. F.A.W. has no conflicts of interest related to this manuscript but reports support from the Fund for Fostering Young Scientists of the University of Zurich, Research Funding for excellent research by the University of Zurich, the Theodor und Ida Herzog-Egli Foundation, the Kurt und Senta Herrmann Foundation, the Foundation for Cardiovascular Research – Zurich Heart House, the European Society of Cardiology, the Swiss Society of Cardiology, the Swiss Heart Foundation, the Medical University of Graz, Amgen Switzerland, Roche Diagnostics, the Critical Care Clinical Trialists Consortium, the Sphingotec GmbH, the 4TEEN4 Pharmaceuticals GmbH, and the PAM Theragnostics GmbH outside this work. M.L. received grants and personal fees from Boehringer Ingelheim, grants and personal fees from MSD, grants and personal fees from Novo Nordisk, personal fees from Amgen, Sanofi, Astra Zeneca, Bayer, Lilly, Abiomed, Daiichi Sankyo. N.M. has served as speaker for Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly, Novo Nordisk. N.M. declines all personal compensation from pharma or device companies. O.H., F.D.L.S. and A.B. are employed by SphingoTec GmbH, the company providing the assay for bio-ADM measurements. SphingoTec GmbH had no influence on the design of the study. TFL does not accept honoraria from industry partners, but received educational and research grants from Abbott, Amgen, AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Daichi-Sankyo, Eli Lilly, Novartis, Novo Nordisk, Sanofi and Vifor. All other authors have no conflict of interest to declare.

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