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Pre-existing treatment with aspirin or statins influences clinical presentation, infarct size and inflammation in patients with de novo acute coronary syndromes

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ABSTRACT

Background: Influence of pre-existing treatment with aspirin and/or statins prior to a first acute coronary syndrome (ACS) on clinical presentation, infarct size and inflammation markers. We analyzed patients from the *Swiss Program University Medicine ACS*-cohort (SPUM-ACS; *ClinicalTrials.gov number: NCT01075867*).
Methods: 1639 patients were categorized into 4 groups: (1) patients without either drug (n = 1181); (2) patients only on aspirin (n = 157); (3) patients only on statins (n = 133) and (4) patients on both drugs (n = 168). Clinical features, electrocardiogram (ECG), creatinine kinase (CK, U/l), high-sensitivity troponin T (hsTNT, μg/l), N-terminal brain natriuretic peptide (NT-proBNP, ng/l), leucocytes (Lc, G/l), neutrophils (Nc, G/l), C-reactive protein (CRP, mg/l) and angiographic features were documented at baseline.
Results: Incidences of ST-elevation myocardial infarction (STEMI) were 64% in group 1, 45% in group 2, 52% in group 3 and 40% in group 4 ($p < 0.0001$). Those with both drugs had significantly lower CK (median 145 U/l, interquartile range (IQR) 89–297), hsTNT (median 0.13 μg/l, IQR 0.03–0.52) and higher left ventricular ejection fraction values (LVEF) (mean 55 ± 12%) compared to untreated patients (median CK 273 U/l, IQR 128–638; median hsTNT 0.26 μg/l, IQR 0.08–0.85; mean LVEF 51 ± 11%) ($p < 0.0001$, $p = 0.001$, $p = 0.028$, respectively). Co-medicated groups matched for high risk factors presented less frequently as STEMIs ($p < 0.0001$), had significantly smaller infarcts determined by CK and hsTNT (both $p < 0.0001$) and lower CRP levels ($p = 0.01$) compared to patients without pre-existing treatment with either drug.
Conclusion: Pre-existing treatment with aspirin and/or statins and particularly with their combination changes the clinical presentation, infarct size, inflammation markers and LVEF in patients suffering their first ACS.

1. Introduction

The burden of cardiovascular (CV) diseases remains high in the Western world and is increasing in less industrialized countries. In 2016, almost every second death was due to a cardiovascular problem such as coronary artery disease (CAD), stroke or other cardiovascular diseases with increasing numbers, especially in women [1,2]. Aspirin and statins used alone or in combination are well-established preventive medications in individuals at risk for future major cardiovascular events (MACE) as they reduce adverse clinical events [3,4]. Furthermore, their importance in secondary prevention after acute myocardial infarction (MI) or stroke is certified. Indeed, the recommended target values for LDL-cholesterol after acute coronary syndrome (ACS) has been lowered in the ESC guidelines over the years and is currently set at 1.8 mmol/l or less [5–8]. Besides, the use of statins and aspirin has also recently been recommended for the primary prevention of cardiovascular events in individuals with well-controlled risk factors, such as hypertension [9]. Finally, elevated inflammatory markers such as C-reactive protein (CRP) have been implicated in the progression of atherosclerosis and in changes in plaque composition and biology, which are known contributions to MACE after an ACS [10,11]. There is strong evidence that both LDL-

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cholesterol and inflammation are involved in the development of ACS [12–14]. Indeed, the recent CANTOS trial showed that inhibition of the interleukin-CRP pathway is associated with reduced MACE in patients after ACS [15].

Here, we investigated whether patients taking aspirin and/or statins prior to their first ACS had a more favorable clinical presentation (assessed by ECG), smaller infarct size (assessed by myocardial necrosis markers) and degree of inflammation (assessed by leucocytes, neutrophils and CRP) compared to the collective not taking those medications prior to their first ACS.

2. Methods

2.1. Study population

We analyzed 1639 patients with a first acute coronary syndrome (ACS) enrolled in the *Swiss Program University Medicine ACS* (SPUM-ACS study), which is a prospective multicenter cohort with participation of the University Hospitals of Bern, Lausanne, Geneva and Zurich (see www.spum-acs.ch). All patients underwent urgent coronary angiography for an ACS, which was the time point of inclusion into the SPUM program (within hours after hospital admission). Inclusion criteria were: (1) patients older than 18 years being admitted within 5 days (preferably within 72 h) after pain onset with the main diagnosis of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) or unstable angina pectoris (unstable AP); (2) ACS diagnostic criteria in clinical presentation, electrocardiogram (ECG) and/or laboratory evidence of myocardial necrosis (positive hsTNT levels) and (3) record of first ACS in patients history. Exclusion criteria were: (1) severe physical disability or inability to comprehend the study; (2) less than one year of life expectancy due to non-cardiac illnesses; (3) pre-existing treatment with antiplatelet drugs other than aspirin such as clopidogrel, prasugrel, ticagrelor or others; and (4) history of a previous ACS. Written informed consent was obtained from all patients and the local institutional review boards approved this study.

2.2. Patient history, blood samples and follow-up

During inclusion (hospitalization and coronary angiography), baseline clinical data including demographics, medical history, baseline medication (in this study: intake of either aspirin, statins or both), pain onset and additional information were recorded using a standardized questionnaire and reports (e.g. assignments). Blood samples were collected at the time of angiography, when the radial or femoral sheet had been introduced (t1) and 12–24 h later (t2). The hsTNT- and NT-proBNP samples then were analyzed in the central core lab of clinical chemistry (university hospital of Zurich) or in the clinical chemistry labs of the participating university hospitals. Follow-up was obtained during the hospitalization, after 30 days (phone call) and after one year including another blood sampling (clinical visit).

2.3. Categorization

The 1639 eligible subjects were categorized into 4 groups according to treatment prior to the event: (1) those who had not been treated with either aspirin or statins (control group, n = 1181); (2) those on aspirin (acetylsalicylic acid, mostly 100 mg/d), but not on statins (n = 157); (3) those on statins only (n = 133) and (4) those on co-medication (n = 168). Patients treated with other antiplatelets (i.e. clopidogrel, prasugrel, ticagrelor or others) were excluded from this study.

2.4. Clinical presentation

The assessment of the different ACS-types was performed at hospital entry based on clinical symptoms, ECG features and levels of hsTNT. The distribution of STEMI, NSTEMI and unstable AP was compared between the 4 groups.

2.5. Infarct size, inflammation and left ventricular ejection fraction

Infarct size was estimated using serum CK levels (n = 1428) and hsTNT levels (n = 1425) at t1 and the increase of CK 12 to 24 h after t1 (CK diff) in a smaller subgroup. CRP levels (n = 1418), leucocytes (Lc, n = 1560) and neutrophils (Nc, n = 1301) were also measured at t1. LVEF (n = 1136) was measured using left ventricular (LV) angiography during the catheterization process and NT-proBNP (n = 1342) was utilized to estimate the degree of heart failure (also t1).

2.6. Statistical analysis and matched analysis

To examine differences between the groups one-way analysis of variance (ANOVA) or the Kruskal-Wallis test was used for continuous variables, as appropriate. Chi-square test (χ^2) was used for categorical variables. All probability values and confidence intervals were two-sided. Matched analysis included propensity score matching for high risk factors as age, sex, LDL-cholesterol, diabetes mellitus, hypertension and intake of ACE-inhibitors and beta blockers (*Framingham risk score*). 3:1 matching was performed comparing the control group to the aspirin only and statins only group, 1:1 matching was performed comparing the control group to the co-medicated group. Probability values (p values) of <0.05 were considered significant. All statistical analysis was performed using SPSS version 23.0 software (SPSS Inc., Chicago, IL). Figures were made with Microsoft® Excel® 2011 (© 2010 Microsoft Corporation. All rights reservEd.).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the study population and matched cohorts comparing the control group to the co-medicated group are listed in Table 1. The control group (mean age 60.42 ± 12.05 years) was significantly younger than the groups with pre-existing treatment (mean age only aspirin group 70.16 ± 11.79 years, only statin group 64.43 ± 11.37 years, co-medicated group 69.26 ± 11.31 years; $p < 0.0001$). Sex, ethnic status and blood pressure profiles were distributed equally throughout the groups. Total cholesterol and especially LDL-cholesterol plasma levels were higher in the control group (mean 5.32 ± 1.13 mmol/l for total cholesterol and 3.53 ± 1.01 mmol/l for LDL-cholesterol levels) and lower in those receiving only statins (mean 4.53 ± 1.03 mmol/l for total cholesterol and 2.74 ± 0.93 mmol/l for LDL-cholesterol) or especially both aspirin and statins (mean 4.17 ± 1.12 mmol/l for total cholesterol and 2.40 ± 0.98 mmol/l for LDL-cholesterol) ($p < 0.0001$). Major cardiovascular risk factors as hypertension, hypercholesterolemia or diabetes mellitus were more frequent in the groups with either aspirin, statins or both than in the control group ($p < 0.0001$), while a history of smoking (n = 1617) was distributed almost equally throughout the groups ($p = 0.049$) with the largest number of smokers in the control group (70%) and the lowest number in the group with aspirin only (59.9%). Interestingly the history of known coronary artery disease (CAD) was almost 25% in the control group, receiving neither of the two medications, with no significant differences compared to the other groups receiving either aspirin or statins alone or both ($p = 0.961$). It was unknown, whether there has not been a prescription or patients decided on their own, not to take the medication, which was suggested. Co-medication with ACE-inhibitors, angiotensin II receptor blockers (antagonists), beta blockers or diuretics was the highest in the aspirin and statins group (all $p < 0.0001$). The intake of oral anticoagulants was distributed equally between the groups ($p = 0.13$). Using propensity score analysis the previously significant differences between the groups regarding age, sex, LDL-cholesterol, diabetes mellitus, hypertension and intake of ACE-inhibitors and beta blockers disappeared or converged as also visible in Table 1 and the supplementary material.

3.2. Clinical presentation

STEMI, NSTEMI and unstable AP rates of the study population and matched cohorts are shown in Fig. 1. There were significantly lower numbers of STEMIs in the aspirin only group (45.2%) and the aspirin and statins group (39.9%) compared to the control group (64%) ($p < 0.0001$). The rates of unstable AP (considered the most favorable presentation) were 1.5% in the control group, 6.4% in the only aspirin group, 1.5% in the only statin group and 13.1% (highest) in the co-medicated group ($p < 0.0001$). Matching for high risk factors showed an independent effect of pre-existing treatment with aspirin and statins on the type of ACS at admission with a 60.9% STEMI rate in the control group and only 39.5% of STEMI in the aspirin and statins group ($p < 0.0001$). In the matched cohorts only 2.4% presented with unstable AP in the control group, but 13.2% in the aspirin and statins group ($p < 0.0001$).

3.3. Infarct size and left ventricular ejection fraction

The infarct size, LVEF and NT-proBNP levels at baseline are shown in Table 2 for the study population and the matched cohorts comparing

Table 1
Baseline characteristics of the study population and the matched cohort (Control group: aspirin and statin).

Variables	Categories, units	Study population (n = 1639)					Matched cohort (1:1)		
							Control group: aspirin and statin (n = 336)		
		Control group	Only aspirin	Only statin	Aspirin and statin	*p* value	Control group	Aspirin and statin	*p* value
		n = 1181	n = 157	n = 133	n = 168		n = 169	n = 167	
Age	Years	60.42 ± 12.05	70.16 ± 11.79	64.43 ± 11.37	69.26 ± 11.31	<0.0001	67.62 ± 12.07	69.21 ± 11.33	0.214
Sex	Female	232 (19.6)	45 (28.7)	26 (19.5)	38 (22.6)	0.062	37 (21.9)	37 (22.2)	1
	Male	949 (80.4)	112 (71.3)	107 (80.5)	130 (77.4)		132 (78.1)	130 (77.8)	
Ethnic status	Asian	13 (1.1)	1 (0.6)	1 (0.8)	0 (0.0)	0.492	1 (0.6)	0 (0.0)	0.118
	Black	5 (0.4)	0 (0.0)	1 (0.8)	0 (0.0)		1 (0.6)	0 (0.0)	
	Caucasian	1135 (96.1)	152 (96.8)	126 (94.7)	166 (98.8)		160 (94.7)	165 (98.8)	
	Other	18 (1.5)	4 (2.5)	4 (3.0)	0 (0.0)		3 (1.8)	0 (0.0)	
	Unknown	10 (0.8)	0 (0.0)	1 (0.8)	2 (1.2)		4 (2.4)	2 (1.2)	
SBP	mm Hg	129.87 ± 23.35	133.51 ± 24.85	128.27 ± 21.74	132.24 ± 22.38	0.137	129.76 ± 23.35	132.37 ± 22.39	0.298
	n	1175	156	133	167		168	166	
DBP	mm Hg	77.02 ± 14.33	75.17 ± 14.85	75.36 ± 14.44	74.41 ± 13.79	0.065	75.21 ± 14.29	74.43 ± 13.83	0.612
	n	1173	156	133	167		168	166	
Total cholesterol	mmol/l	5.32 ± 1.13	4.83 ± 1.14	4.53 ± 1.03	4.17 ± 1.12	<0.0001	4.66 ± 1.00	4.17 ± 1.12	<0.0001
LDL-cholesterol	mmol/l	3.53 ± 1.01	3.04 ± 0.96	2.74 ± 0.93	2.40 ± 0.98	<0.0001	2.87 ± 0.95	2.40 ± 0.99	<0.0001
HDL-cholesterol	mmol/l	1.19 ± 0.34	1.17 ± 0.35	1.20 ± 0.41	1.18 ± 0.35	0.87	1.17 ± 0.34	1.19 ± 0.35	0.6
Serum creatinine	μmol/l	79.44 ± 28.89	95.73 ± 65.43	81.58 ± 23.96	94.01 ± 85.13	<0.0001	87.68 ± 42.46	94.15 ± 85.37	0.378
	n	1181	157	132	168		169	167	
History of									
Diabetes mellitus	Yes	120 (10.2)	48 (30.6)	33 (24.8)	55 (32.7)	<0.0001	40 (23.7)	54 (32.3)	0.089
	No	1061 (89.8)	109 (69.4)	100 (75.2)	113 (67.3)		129 (76.3)	113 (67.7)	
Smoking	Yes	827 (70.0)	94 (59.9)	89 (66.9)	108 (64.3)	0.049	107 (63.3)	108 (64.7)	0.908
	No	339 (28.7)	60 (38.2)	42 (31.6)	58 (34.5)		59 (34.9)	57 (34.1)	
	Unknown	15 (1.3)	3 (1.9)	2 (1.5)	2 (1.2)		3 (1.8)	2 (1.2)	
Hypertension	Yes	521 (44.1)	123 (78.3)	93 (69.9)	135 (80.4)	<0.0001	123 (72.8)	134 (80.2)	0.123
	No	660 (55.9)	34 (21.7)	40 (30.1)	33 (19.6)		46 (27.2)	33 (19.8)	
Hypercholesterolemia	Yes	592 (50.1)	80 (51.0)	131 (98.5)	145 (86.3)	<0.0001	60 (35.5)	145 (86.8)	<0.0001
	No	589 (49.9)	77 (49.0)	2 (1.5)	23 (13.7)		109 (64.5)	22 (13.2)	
Stroke	Yes	5 (0.4)	9 (5.7)	2 (1.5)	9 (5.4)	<0.0001	1 (0.6)	9 (5.4)	0.01
	No	1176 (99.6)	148 (94.3)	131 (98.5)	159 (94.6)		168 (99.4)	158 (94.6)	
CAD	Yes	288 (24.4)	37 (23.6)	32 (24.1)	43 (25.6)	0.961	42 (24.9)	43 (25.7)	0.9
	No	872 (73.8)	119 (75.8)	100 (75.2)	121 (72.0)		124 (73.4)	120 (71.9)	
	Unknown	21 (1.8)	1 (0.6)	1 (0.8)	4 (2.4)		3 (1.8)	4 (2.4)	
Angiography with or without PCI	Yes	4 (0.3)	25 (15.9)	1 (0.8)	50 (29.8)	<0.0001	1 (0.6)	50 (29.9)	<0.0001
	No	1177 (99.7)	132 (84.1)	132 (99.2)	118 (70.2)		168 (99.4)	117 (70.1)	
CABG	Yes	1 (0.1)	6 (3.8)	1 (0.8)	18 (10.7)	<0.0001	0 (0.0)	18 (10.8)	<0.0001
	No	1180 (99.9)	151 (96.2)	132 (99.2)	150 (89.3)		169 (100)	149 (89.2)	
PVD	Yes	17 (1.4)	17 (10.8)	3 (2.3)	20 (11.9)	<0.0001	2 (1.2)	20 (12.0)	<0.0001
	No	1164 (98.6)	140 (89.2)	130 (97.7)	148 (88.1)		167 (98.8)	147 (88.0)	
ACE-inhibitors	Yes	95 (8.0)	30 (19.1)	20 (15.0)	47 (28.0)	<0.0001	30 (17.8)	47 (28.1)	0.027
	No	1084 (91.8)	127 (80.9)	111 (83.5)	120 (71.4)		139 (82.2)	120 (71.9)	
	Unknown	2 (0.2)	0 (0.0)	2 (1.5)	1 (0.6)		0 (0.0)	0 (0.0)	
ATII receptor antagonists	Yes	143 (12.1)	45 (28.7)	32 (24.1)	51 (30.4)	<0.0001	38 (22.5)	51 (30.5)	0.108
	No	1036 (87.7)	112 (71.3)	99 (74.4)	116 (69.0)		131 (77.5)	116 (69.5)	
	Unknown	2 (0.2)	0 (0.0)	2 (1.5)	1 (0.6)		0 (0.0)	0 (0.0)	
Calcium channel blockers	Yes	65 (5.5)	34 (21.7)	26 (19.5)	34 (20.2)	<0.0001	22 (13.0)	34 (20.4)	0.08
	No	1114 (94.3)	123 (78.3)	105 (79.0)	134 (79.8)		147 (87.0)	133 (79.6)	
	Unknown	2 (0.2)	0 (0.0)	2 (1.5)	0 (0.0)		0 (0.0)	0 (0.0)	
Beta blockers	Yes	118 (10.0)	47 (29.9)	23 (17.3)	81 (48.2)	<0.0001	61 (36.1)	80 (47.9)	0.036
	No	1061 (89.8)	110 (70.1)	108 (81.2)	87 (51.8)		108 (63.9)	87 (52.1)	
	Unknown	2 (0.2)	0 (0.0)	2 (1.5)	0 (0.0)		0 (0.0)	0 (0.0)	
Diuretics	Yes	108 (9.1)	40 (25.5)	27 (20.3)	52 (31.0)	<0.0001	31 (18.3)	52 (31.1)	0.008
	No	1072 (90.8)	117 (74.5)	104 (78.2)	116 (69.0)		138 (81.7)	115 (68.9)	
	Unknown	1 (0.1)	0 (0.0)	2 (1.5)	0 (0.0)		0 (0.0)	0 (0.0)	
Oral anticoagulants	Yes	27 (2.3)	3 (1.9)	6 (4.5)	8 (4.8)	0.13	9 (5.3)	8 (4.8)	1
	No	1154 (97.7)	154 (98.1)	127 (95.5)	160 (95.2)		160 (94.7)	159 (95.2)	

All data are described as a percentage (%) or mean ± standard deviation (SD), as appropriate. SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; PVD, peripheral vascular disease; ACE, angiotensin converting enzyme; ATII, angiotensin II.

the control group and the co-medicated group. CK values (t1) are also visible in Fig. 2 for the whole study population and all the matched groups. Median CK levels were the highest in the control group (median 273 U/l, IQR 128–638) and lower in the aspirin only group (median 178 U/l, IQR 89–454) and co-medication group and 144.50 U/l, IQR 89–297) ($p < 0.0001$). Likewise the median increase of CK (CK diff) was the highest in the control group (median 560 U/l, IQR 57–1838), little lower in the statin group (median 248 U/l, IQR 28–1800), significantly lower in the aspirin group (median 66 U/l, IQR 12–1195) and the lowest in the co-medicated group (median 44 U/l, IQR 11.5–756.5) ($p < 0.0001$). Similarly, median hsTNT levels at baseline were lower in the co-medicated group than in the other groups (median 0.13 μg/l, IQR 0.03–0.53; $p = 0.001$ vs. other groups). The hsTNT values are shown in Fig. 2 for the study population and matched cohorts. In line with necrosis biomarker levels, higher LVEF (assessed by ventriculography) was documented in the aspirin and statins group (mean 54.8 ±

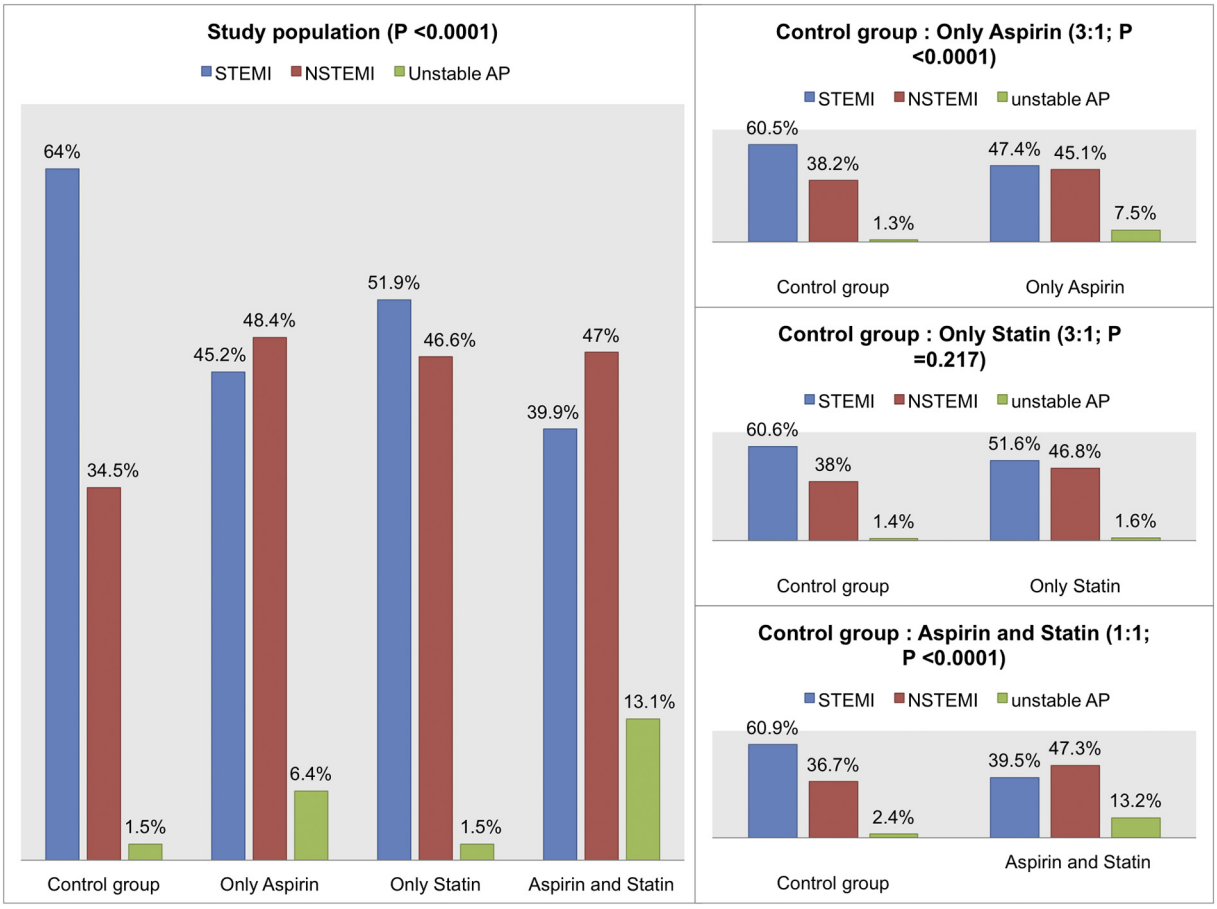

Fig. 1. ECG presentation of the study population and matched cohorts. The control group had higher percentage of STEMIs (64%) compared to those receiving aspirin (45.2%), statins (51.9%) or both (39.9%) ($p < 0.0001$). The highest incidence of unstable AP was documented in the aspirin and statins group (13.1%). 1:1 matching between the control group and the co-medicated group (with aspirin and a statin) showed a significant difference in the incidence of STEMI (60.9% vs. 39.5%), NSTEMI (36.7% vs. 47.3%) and especially unstable AP (2.4% vs 13.2%) ($p < 0.0001$).

Table 2
Infarct size, left ventricular ejection fraction and inflammation markers of the study population and the matched cohort (Control group: aspirin and statin).

Variables	Units	Study population (n = 1639)					Matched cohort (1:1)		
							Control group: aspirin and statin (n = 336)		
		Control group	Only aspirin	Only statin	Aspirin and statin	*p*-Value	Control group	Aspirin and statin	*p* value
		n = 1′181	n = 157	n = 133	n = 168		n = 169	n = 167	
CK	U/l	273 (128–638)	178 (89–454)	266 (120–538)	144.50 (89–297)	<0.0001	277 (135–629)	147 (91–299)	<0.0001
	n	1039	146	111	132		147	131	
CK diff	U/l	560 (57–1838)	66 (12–1195)	248 (28–1800)	44 (11.5–756.5)	<0.0001			
	n	311	51	27	36				
hs troponin T	μg/l, ng/ml	0.26 (0.08–0.85)	0.22 (0.06–0.94)	0.29 (0.07–0.76)	0.13 (0.03–0.53)	0.001	0.43 (0.12–1.33)	0.13 (0.04–0.53)	<0.0001
	n	1026	131	120	148		150	147	
NT-proBNP	ng/l, pg/ml	201.50 (71–670)	573 (156–2230)	301 (112−1002)	346.50 (111–1438)	<0.0001	380 (126–1545)	353 (111–1451)	0.624
	n	978	125	99	140		139	139	
LVEF	%	51.37 ± 10.83	51.91 ± 12.74	52.48 ± 11.53	54.82 ± 11.54	0.028	50.74 ± 10.41	54.82 ± 11.54	0.006
	n	844	102	87	103		124	103	
Leucocytes	G/l (10,9), K/μl (10,3)	10.73 ± 3.83	9.85 ± 3.71	9.59 ± 3.30	9.43 ± 4.09	<0.0001	10.20 ± 3.79	9.44 ± 4.10	0.088
	n	1124	151	126	159		157	158	
Neutrophils	G/l (10,9), K/μl (10,3)	7.96 (5.67–10.47)	7.31 (5.03–9.60)	6.56 (4.97–8.50)	6.22 (4.24–8.86)	<0.0001	7.46 (4.94–9.92)	6.23 (4.24–8.88)	0.02
	n	948	123	98	132		132	131	
CRP	mg/l	2.60 (1.10–6.60)	4.50 (1.80–11.30)	3.05 (1.43–8.05)	2.25 (0.90–8.03)	0.001	3.70 (1.40–15.40)	2.20 (0.90–8.10)	0.01
	n	1019	131	120	148		149	147	

All data are given as mean ± SD or median (interquartile range, IQR), as appropriate. CK, creatine kinase; diff, difference; hs, high-sensitivity; NT-proBNP, N-terminal brain natriuretic peptide; LVEF, left ventricular ejection fraction; CRP, C-reactive protein.

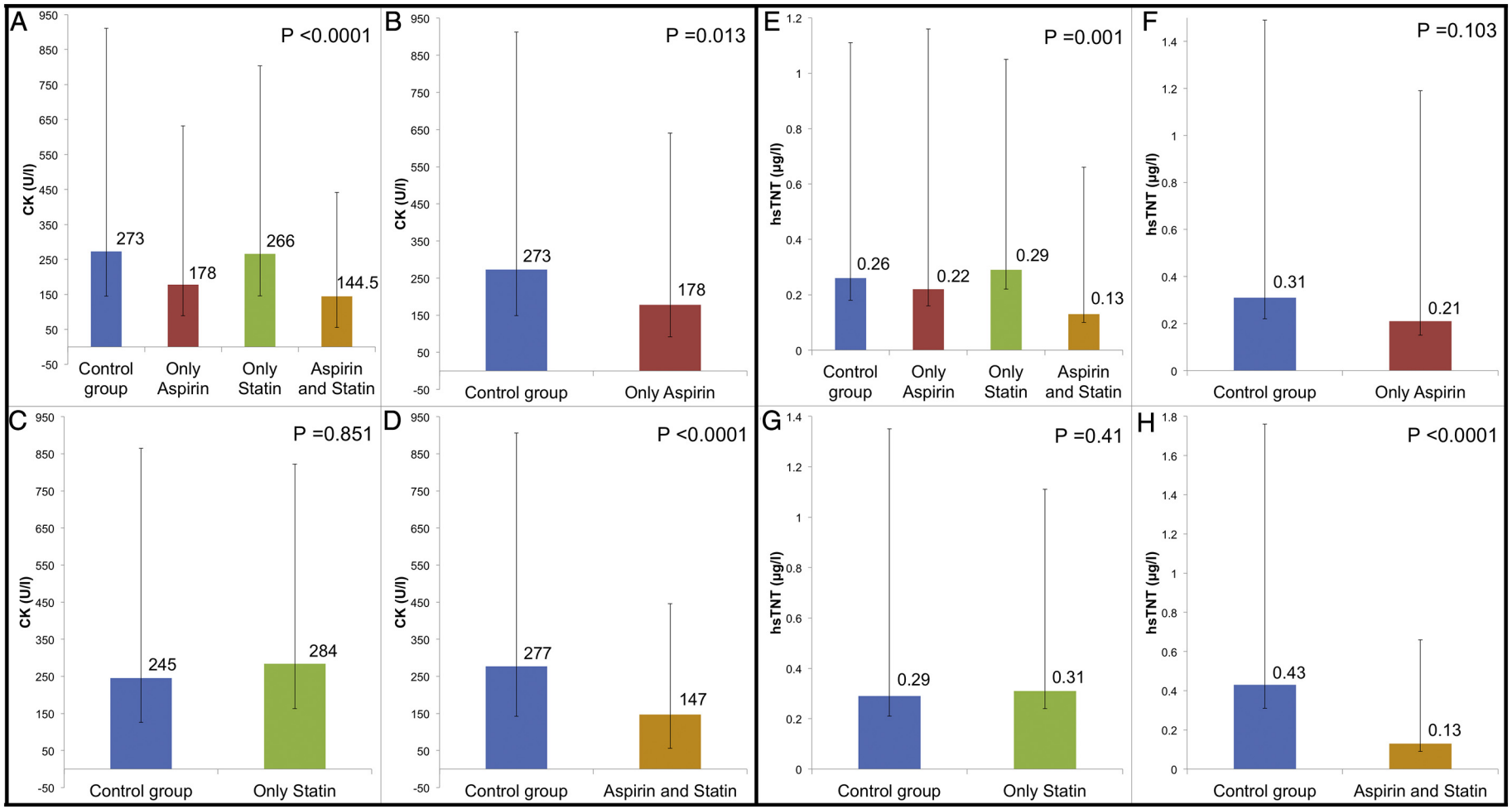

Fig. 2. CK and hsTNT levels at baseline of the study population and matched cohorts. The CK values (median, IQR) of the entire study population (A) and the matched cohorts (B–D) are shown. Also the hsTNT values for the entire study population (E) and the matched cohorts (F–H) are shown. B/F = Control group: only aspirin (3:1 matching); C/G = Control group: only statin (3:1 matching); D/H = Control group: aspirin and statin (1:1 matching). Higher CK median levels were observed in the control group (median 273 U/l, IQR 128–638) and lower values in the co-medicated group (median 144.50 U/l, IQR 89–297) ($p < 0.0001$). Matched analysis showed there were significantly lower median CK levels in the group receiving aspirin and statins comparing to the control group (D) (median 147 U/l, IQR 91–299 vs. 277 U/l, IQR 135–629, respectively; $p < 0.0001$). Lower hsTNT median values were observed in the co-medicated group (median 0.13 µg/l, IQR 0.03–0.53) than in the control group (median 0.26 µg/l, IQR 0.08–0.85) ($p = 0.001$). The highest hsTNT levels were documented in the group receiving only statins (median 0.29 µg/l, IQR 0.07–0.76). Matched cohort analysis showed significantly lower levels of hsTNT in the co-medicated group vs. the control group (D) (median 0.13 µg/l, IQR 0.04–0.53 vs. 0.43 µg/l, IQR 0.12–1.33, respectively; $p < 0.0001$).

11.5%; $p < 0.0001$ vs. other groups). Matched cohorts showed similar results with significantly higher levels of CK and hsTNT (both $p < 0.0001$) as well as significantly lower LVEF ($p = 0.006$) in the control group compared to the combined aspirin/statins group. NT-proBNP levels were the lowest in the control group (median 201.50 ng/l, IQR 71–670) and the highest in the group taking aspirin prior to the first ACS (median 573 ng/l, IQR 156–2230) ($p < 0.0001$), which was also the oldest group with the highest creatinine levels.

3.4. Markers of inflammation

Cellular and biochemical markers of inflammation at baseline are shown in Table 2 for the entire study population and the matched cohort comparing the control group to the co-medicated group. Higher counts for leucocytes and neutrophils were measured in the control group (mean 10.73 ± 3.83 G/l and median 7.96 G/l, IQR 5.67–10.47, respectively) and lower counts in the statins only group (mean 9.59 ± 3.30 G/l and median 6.56 G/l, IQR 4.97–8.50, respectively) and the aspirin and statins group (mean 9.43 ± 4.09 G/l and median 6.22 G/l, IQR 4.24–8.86, respectively) (both $p < 0.0001$). The highest CRP plasma levels were detected in the only aspirin group (median 4.50 mg/l, IQR 1.80–11.30). In the matched cohorts, the co-medicated group showed significantly lower inflammatory markers assessed by neutrophil counts and CRP values than the control group ($p = 0.02$ and $p = 0.01$, respectively).

4. Discussion

In this study we observed that prolonged pre-existing treatment with aspirin or statins, and particularly with their combination markedly and favorably affected the clinical presentation, infarct size and degree of inflammation in patients with a de novo ACS selected from a large and well-documented prospective real world cohort. Interestingly we observed that the clinical presentation (ECG presentation) and infarct size, as assessed by biomarkers, were especially favorable in the groups with pre-existing treatment with aspirin, while there was lower inflammation (particularly cellular) in the groups with statins. The highest CRP values were observed in the aspirin group which was the oldest group and the one with the most co-morbidities without an additional statin therapy.

Epidemiological evidence has suggested that the incidence of STEMI has been declining in recent years, particularly in countries with a well-developed health care system and implementation of current guideline-based cardiovascular management [16,17]. Here we provide evidence suggesting that the increased use of aspirin and statins in primary prevention regarding ACS may have significantly altered the clinical presentation of patients with a first event. Indeed, the prevalence of STEMIs was significantly lower in the combined aspirin/statins group than in the untreated group. Previous studies suggested that pre-existing aspirin or statin intake independently would reduce the incidence of STEMI [18–20]. In the present large cohort we could substantiate those observations, but additionally we show that the combination of aspirin with a statin was particularly effective in this context on a first time ACS. Of note, there is strong experimental and clinical evidence that statins stabilize coronary plaques by reducing the lipid core and increasing the thickness of the fibrous cap, thereby reducing the risk of plaque rupture, which is the main mechanism leading to coronary occlusion and STEMI [21,22]. In addition, aspirin inhibits platelet aggregation and therefore reduces the probability of an occluding clot on top of a ruptured plaque and conversely the occurrence of a STEMI [18]. This observation reflects the results of several ESC [23] and National registries [24] documenting an increased use of aspirin and statins in primary prevention as recommended in high-risk patients by European and U.S. guidelines [25,26].

Obviously, even patients with pre-existing treatment with either aspirin or statins or both may still experience an ACS, as documented in this study. However, we demonstrate that they are much more likely to present as a NSTEMI or unstable AP, which are much more favorable clinical presentations in the acute setting. Indeed, the in-hospital mortality of NSTEMI and unstable AP is far lower than that of STEMI [27].

There are multiple reasons that may explain the lack of full protection from ACS even with the combination of aspirin and statins: First, the dose of the statin may not have been high enough and the value of optimal LDL-cholesterol levels may not have been reached. Indeed, in this registry the mean plasma LDL-Cholesterol of those taking statin and aspirin averaged 2.4 mmol/l. Several trials have shown dose-dependent protection by statins [28]. Furthermore, the recent GLAGOV trial, which investigated the lipid-lowering monoclonal antibody evolocumab, a PCSK9 inhibitor, in combination with statins, documented that the plaque regression can only be achieved by LDL-cholesterol levels that are far below those attainable by statins alone [29,30]. Under such conditions it has been shown that the incidence of MACE can be further reduced [28]. Aside from that, additional risk factors, which were not focus of this study, may not have been optimally controlled and/or adherence with prescribed therapy may have been inadequate. Finally, not all pathogenetic aspects of atherosclerosis and thrombosis have been fully clarified and/or are addressed by aspirin and statins.

An acute myocardial infarction is associated with inflammation both in the systemic and the coronary circulation — thus elevated CRP levels are a strong predictor of cardiovascular events [31,32]. Interestingly, both cellular inflammation, as assessed by leucocyte and neutrophil counts, as well as humoral inflammation, reflected by CRP plasma levels, were reduced in patients with pre-existing treatment with statins compared to those untreated. The anti-inflammatory effects of statins have been well described both experimentally and in clinical trials, nevertheless currently considered being secondary to the main impact of lowering LDL-cholesterol levels [33–37]. Here we expand these observations to the clinical presentation of patients with an ACS suggesting that those taking a statin and particularly in combination with aspirin are markedly protected from inflammatory bursts which are considered major contributors to the destabilization of the fibrous cap and platelet activation.

The fact that either aspirin or statins alone, and particularly used in combination markedly reduced the occurrence of coronary artery occlusion, a hallmark of STEMI, may explain why left ventricular ejection fraction was highest in the aspirin and statins group. As shown before for aspirin and statins individually, pretreatment with either drug alone decreases in-hospital mortality and lowers the mortality incidence after one month [38,39]. However outcomes after de novo ACS with a prolonged combination therapy with aspirin and statins in advance have not been sufficiently investigated. This may be particularly important for the long-term outcome of complicated and multimorbid patients and the rate of MACE, in particular the incidence of heart failure after the acute event.

4.1. Limitations

Although the present study is based on data from a well-documented prospective registry, the analysis presented here was not prespecified. The exact duration of pre-existing treatment of the drugs was not known, as assessment was based on a binominal questionnaire (yes/no). Further it is possible that also angiographies without PCI were counted as PCI. Also, there were significant differences in baseline characteristic between the patient groups that could only be partially circumvented by the matched subgroup analysis. Nevertheless, the main results of the initial analysis in the entire cohort were consistent with those of the matched subgroups. Furthermore, the statistical power was not strong enough in the matched subgroups to perform a meaningful analysis of short- and/or long-term outcomes, which should be confirmed in larger cohorts.

5. Conclusion

In summary, we were able to demonstrate for the first time that in a large prospective real world cohort, pre-existing treatment with either aspirin or statins, or even more so their combination markedly and favorably influenced the clinical presentation of patients with a de novo ACS. In particular, pre-existing treatment with aspirin and statins was associated with a lower degree of inflammation and most likely as a consequence a reduction of STEMI vs. NSTEMI and unstable AP, smaller infarcts as reflected by CK and hsTNT, and a preservation of LVEF. The current patient population did not allow for long-term outcome analysis, which would need to be confirmed by further clinical trials.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.050.

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