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Impact of the number of modifiable risk factors on clinical outcomes after percutaneous coronary intervention: An analysis from the e-Ultimaster registry

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ABSTRACT

Aims: A substantial proportion of the patients undergoing percutaneous coronary intervention (PCI) have none of the of standard modifiable cardiovascular risk factors (SMuRFs): hypertension, diabetes, hypercholesterolaemia and smoking. The aim of this analysis was to compare clinical outcomes after PCI according to the number of SMuRFs.

Methods: Patients with an indication for a PCI were stratified based upon the number of SMuRFs: 0, 1, 2 or 3–4. The primary outcome was target lesion failure (TLF), a composite of cardiac death, target vessel-related myocardial infarction or clinically driven target lesion revascularization at 1-year. Inverse weighted propensity score (IWPS) adjustment was performed to adjust for differences in baseline characteristics.

Results: The prevalence of SMuRFs was: 0 SMuRF 16.4 %; 1 SMuRF 27.8 %; 2 SMuRFs 34.7 % and 3–4 SMuRFs 21.1 %. Patients without SMuRFs were younger, more likely to be male and had less complex coronary artery disease. The incidence of TLF increased with the number of SMuRFs: 2.65 %, 2.75 %, 3.23 %, and 4.24 %, $P_{trend} < 0.001$. The relative risk (RR) for a TLF was 60 % higher (95 % confidence interval 1.32–1.93, $p < 0.01$) for patients with 3–4 SMuRFs compared to patients without SMuRFs. The trend remained ($P_{trend} < 0.01$) after IWPS with TLF rates of 2.88 %, 2.64 %, 2.88 % and 3.65 %. The RR for a TLF was 27 % higher (95 % CI 1.05–1.53, $p < 0.01$).

Conclusion: The incidence of clinical events at 1-year increased with the number of SMuRFs. While patients without SMuRFs have a relatively favourable risk profile, more research is needed to optimize therapeutic management in the majority of patients.

Abbreviations: ACS, Acute coronary syndrome; CCS, Chronic coronary syndrome; CD, Clinically driven; CI, Confidence interval; DES, Drug-eluting stent; IPSW, Inverse propensity score weighted; MACE, Major adverse cardiovascular events; MI, Myocardial infarction; POCE, Patient-oriented composite endpoint; PCI, Percutaneous coronary intervention; RR, Relative risk; SMuRF, Standard modifiable cardiovascular risk factors; TLF, Target lesion failure; TVF, Target vessel failure; TVMI, Target vessel MI.

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1. Background

It is well known that interventions that aim to reduce the burden of standard modifiable cardiovascular risk factors (SMuRFs: hypertension, diabetes, hypercholesterolaemia and smoking) are essential to reduce the risk of ischemic heart disease and potentially improve outcomes following revascularization [1,2]. Nonetheless, individuals who present with acute coronary syndrome (ACS) without SMuRFs (SMuRF-less) represent a growing and relevant (25 %) proportion of the ACS population [3]. Recent evidence suggests that SMuRF-less patients may be at increased risk of adverse event following ACS [4–7]. The primary explanation underpinning the emerging prevalence of SMuRF-less patients is likely to be that our community success in reducing traditional risk factors has unmasked the challenging issue of how to advise those without known modifiable risk factors.

Most published data on outcomes of patients with versus without SMuRF is focused on patients with ACS in general and STEMI in particular. It is unknown whether among those with SMuRFs, the number of SMuRFs impacts the outcomes of patients, and if that impact extends beyond patients with STEMI or differs according to the clinical presentation of the patient (ACS versus chronic coronary syndrome (CCS)).

We aimed to compare the clinical outcomes of patients undergoing percutaneous coronary intervention (PCI) according to number of known SMuRF in a large cohort of patients enrolled in the prospective, multinational, observational e-Ultimaster stent study as well as evaluate the clinical outcomes according to the clinical presentation.

2. Methods

2.1. Study design

The e-Ultimaster registry is a large, prospective, multicenter, observational study [8–10]. This study was conducted worldwide to evaluate the safety and performance of the Ultimaster drug eluting stent (DES) system (Terumo Corporation, Tokyo, Japan) in an all-comer clinical setting. Patients with coronary artery disease, with reference vessel diameters between 2.5 and 3.5 mm, eligible for PCI using DES according to local hospital practice and who were treated with the Ultimaster stent were included.

The present study analyzed the clinical outcomes of patients according to the presence of SMuRFs: hypertension, diabetes, hypercholesterolaemia, and smoking. The assessment of the presence of SMuRFs was made by the hospital staff based upon review of hospital charts and referral letters. Patients were stratified into those (1) without SMuRFs (SMuRF-less), (2) with one SMuRF, (3) with two SMuRFs, and (4) with three or four SMuRFs. Secondly, an analysis according to the clinical presentation including solely ACS or CCS patients was performed. Local institutional review board approval was obtained at each institution and all subjects provided written informed consent. The ClinicalTrials.gov study identifier is NCT02188355.

2.2. Study device

The Ultimaster coronary stent system is a new-generation, open cell, cobalt-chromium, thin-strut (80-μm) sirolimus eluting stent with an abluminal bioresorbable polymer coating (poly-D, L-lactic acid polycaprolactone). Sirolimus is released over a 3–4-month period after which the polymer coating is fully degraded [11].

2.3. Outcomes and definitions

The primary outcome was target lesion failure (TLF), defined as a composite of cardiac death, target vessel-related myocardial infarction (TV-MI) or clinically driven target lesion revascularization (CD-TLR) at 1-year. Secondary outcomes included any death, cardiac death, any MI, TV-MI, CD-TLR, definite/probable stent thrombosis, and a patient oriented composite endpoint (POCE), defined as the composite of any death, any MI, and any coronary revascularization

All endpoint related serious adverse events were reviewed and adjudicated by an independent clinical event committee according to the Academic Research Consortium (ARC) definitions [12]. For MI, the extended historical myocardial definition was applied that primarily uses creatine kinase myocardial band (MB) as a cardiac biomarker criterion but, if not measured, troponin values for the determination of a *peri*-procedural (48 h post-PCI) were used.

2.4. Statistical analysis

Baseline characteristics were reported as percentages and numbers for categorical variables and as mean and standard deviation for continuous variables. Statistical differences between baseline characteristics were reported using a Kruskal-Wallis for continuous variables, a $\chi 2$ test for binary variables and a Cochran–Mantel–Haenszel (CMH) test for categorical variables with 3 or more categories. Ordinal logistic regression with the group as outcome and the variable as predictor using no SMuRF as reference was performed to test for a trend with an increased number of SMuRFs. The clinical outcomes were reported at 1-year of follow-up with the number of patients available for follow-up including those with a reported clinical event as denominator. An inverse propensity score weighted (IPSW) analysis was performed to address differences in baseline patient and lesion characteristics, including the following variables selected based upon their prognostic relevance: male, family history of CAD, clinical presentation, balloon post-dilatation, bifurcation, intracoronary imaging, ostial lesion, left main, current smoker, thrombus aspiration, radial access, left anterior descendants, severe/moderate calcification, balloon pre-dilatation, number of lesions identified, diameter of the smallest implanted stent, renal impairment, in-stent restenosis, and age. Therefore, a multinomial logistic regression model was performed to calculate the propensity score, predicting the probability of a subject being attributed to one of the four groups studied (no SMuRFs, 1 SMuRF, 2 SMuRFs, and 3–4 SMurFs) using the baseline patient and lesion characteristics listed above. The inverse of this propensity score (probability of belonging to the arm the subject was attributed to) was subsequently used as weight in the weighted analyses and was calculated as 1/(propensity score). Standardized differences of variables were used to generate the propensity score before and after inverse weighted propensity score adjustment. After adjustment, all covariates in the planned propensity score had standardized differences < 0.10 and were not significantly different between the 4 studied groups. Interaction between the number of SMuRFs and clinical presentation (CCS or ACS) was tested for key clinical endpoints. No correction was made for multiple testing. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 37,198 patients were included in the study, of which 6,092 (16.4 %) were SMuRF-less, 10,345 (27.8 %) had 1 SMuRF, 12,908 (34.7 %) had 2 SMuRFs, and 7,853 (21.1 %) had 3–4 SMuRFs (Fig. 1).

3.1. Demographics and comorbidities

Compared to patients with $\geq$ 2 SMuRF, SMuRF-less patients and those with 1 SMuRF were younger (mean age 63.7 $\pm$ 11.5 and 63.2 $\pm$ 11.8 years old vs 65.1 $\pm$ 11.0 and 64.2 $\pm$ 10.6 years old; $p < 0.0001$), more likely to be male (77.6 %, 78.1 % vs 74.1 %, 75.0 %; $p < 0.0001$) and had lower mean BMI (26.6 $\pm$ 4.1, 27.1 $\pm$ 4.3 vs 28.0 $\pm$ 4.6, 29.1 $\pm$ 5.0; $p < 0.0001$). The incidence of PAD, renal impairment, and known ischemic heart disease increased with the number of SMurRFs. Among patients with SMuRF, hypertension was the most common SMuRF,

followed by hyperlipidemia (Table 1).

4. Clinical presentation and procedural data

The groups differed in the clinical syndrome at presentation (Table 1). ST segment elevation myocardial infarction (STEMI) was more common among SMuRF-less patients or those with one SMuRF, compared to those with multiple SMuRF (24.0 %, 24.5 % vs 17.3 %, 16.2 %; $p < 0.0001$); the rate of unstable angina increased with the numbers of SMuRFs.

Differences were also observed in the pattern of coronary disease according to the number of SMuRFs. The rate of left main PCI increased with the number of SMuRFs (2.4 % vs. 2.7 %, and 3.5 % for patients with no, single, and multiple SMuRFs, respectively $p < 0.0001$), with similar incremental patterns observed for calcified lesions (15.1 %, 17.6 %, 20.3 %, and 21.8 $p < 0.0001$ %). Bifurcation lesions were more common in patients with at least one SMuRF compared to SMuRF-less patients (12.1–12.6 % vs 8.7 % $p < 0.0001$); similarly, the number of lesion treated was smaller in SMuRF-less patients (1.23 vs 1.31–1.34 in patients with at least one SMuRF; $p < 0.0001$). Radial access rates decreased with the increase in number of SMuRFs (from 84.4 % in SMuRF-less patiets to 77.9 % in those with 3 or 4 SMuRFs, $p < 0.0001$.

4.1. Clinical outcomes

Table 2 presents the crude clinical outcome data 1-year after the index PCI procedure. For most clinical outcomes, the rate of events incrementally increased with the number of SMuRFs. This is true for the primary endpoint of TLF (2.65 %, 2.75 %, 3.23 % and 4.24 % for 0, 1, 2, and 3–4 SMuRFs, respectively, $P_{trend} < 0.0001$), where patients with 3–4 SMuRFs had a 60 % higher risk for a TLF compared to patients without a SMuRF (RR 1.60, 95 % CI 1.32;1.93, $p < 0.01$). Similarly, for the other predefined clinical endpoints, including POCE ($P_{trend} < 0.0001$), all-cause mortality ($P_{trend} < 0.0001$), cardiac mortality ($P_{trend} < 0.0001$), MI ($P_{trend} < 0.0001$), TV-MI ($P_{trend} < 0.001$) and CD-TLR ($P_{trend} < 0.0001$. The incremental risk these endpoints for patients with 3–4 SMuRFs compared to SMuRF-less patients was 59–104 %. There was no significant trend in the incidence of stent thrombosis ($P_{trend} = 0.06$) along the groups. See figure S1.

In order to account for the differences in baseline patient and lesion characteristics between the different groups, an IPSW analysis was performed. The adjusted event rates are presented in Table 3 and Fig. 2, Fig. 3. and S2. The incidence of TLF was 2.88 %, 2.64 %, 2.88 % and 3.65 % for patients with 0, 1, 2 and 3–4 SMuRFs, respectively, $P_{trend} < 0.01$). Presence of 3–4 SMuRFs represented a 27 % higher risk for TLF. Similarly, a positive trend was observed for POCE ($P_{trend} < 0.001$), cardiac death ($P_{trend} = 0.02$), any MI ($P_{trend} < 0.01$), TV-MI ($P_{trend} = 0.03$) and CD-TLR ($P_{trend} = 0.05$). The incremental risk these endpoints for patients with 3–4 SMuRFs compared to SMuRF-less patients was 21–58 %. No trend was observed for stent thrombosis.

4.2. Outcomes for chronic and acute coronary syndrome patients

Results for patients presenting with a chronic or acute coronary syndrome are presented in the supplementary tables S1-S6 and figures S3-S6. A positive trend was observed for a higher event rate both before and after IWPS for most of the clinical endpoints for chronic coronary syndrome patients with higher event rates for 3–4 SMuRFs compared to no SMuRF. Similarly for ACS patients, there was a positive trend for a higher event rate along with an increase in SMuRFs before IWPS. However, after IWPS in ACS patients, the trend only remained present for TLF ($P_{trend} = 0.04$) and any MI ($P_{trend} = 0.04$). No interaction was demonstrated between the number of SMuRFs and clinical presentation on the main clinical endpoints before and after IWPS, except for TV-MI after IWPS ($p = 0.03$). See figure S5 and S6.

5. Discussion

Our study analyzed real-world data from a multicenter, prospective, observational study of > 37 000 patients who underwent PCI with contemporary new-generation thin strut DES and estimated the effect of standard modifiable risk factors on 1-year clinical outcomes. To the best of our knowledge, this is the largest analysis of the impact of SMuRF on clinical outcomes in CCS and ACS patients undergoing PCI with a new-generation DES. Main finding is that the clinical event rate at 1-year increased along with the number of SMuRFs. Secondly, this was observed in both CCS and ACS patients albeit the trend for a higher event rate with the number of SMuRFs largely disappeared after IWPS adjustment in the ACS group.

Our study highlights the importance of an often overlooked subgroup of patients, who despite having no traditional cardiovascular risk factors, undergo coronary interventions for a variety of reasons. Over 16 % of the patients did not have any SMuRF in our cohort. We observed that SMuRF-less patients were younger, more likely to be male and had a lower BMI with less complex coronary artery disease. This high rate of patients with significant coronary artery disease requiring PCI but without 'traditional' risk factor should encourage further research to identify other risk factor, such as (but not limited to) inflammatory diseases [13,14]. As out results are based on a cohort, we could not assess the prevalence of inflammatory disease in the SMuRFless population of to look at other factors as CRP. After IWPS adjustment, this favourable risk profile for SMuRF-less patients did translate in a 17–40 % [1-(1/RR)] reduced risk for a cardiovascular event at one year follow up, depending on the event type, compared to patients with 3–4

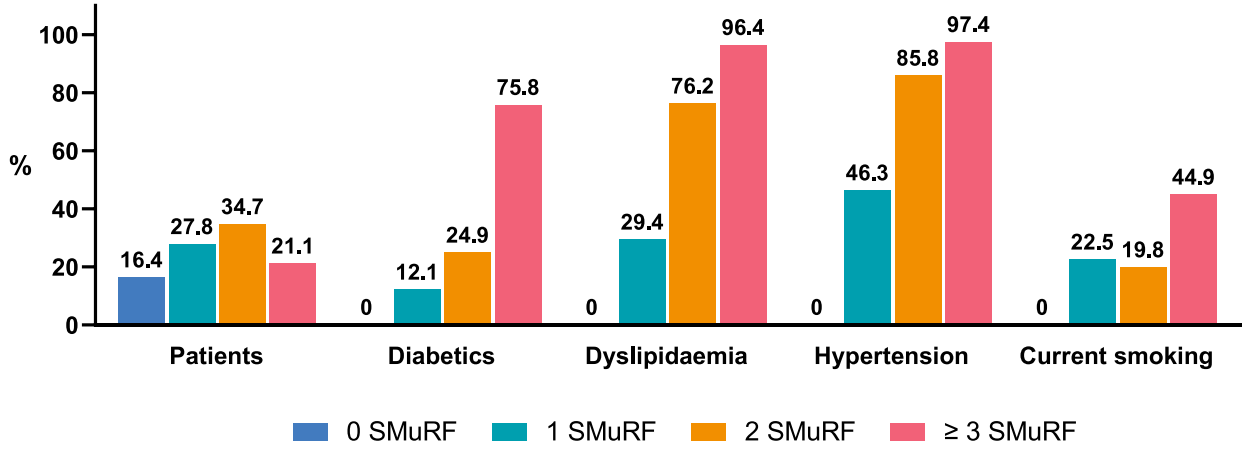

Fig. 1. Distribution of number of standard modifiable cardiovascular risk factors (SMuRF).

Table 1
Baseline patient and procedural characteristics stratified by the number of standard modifiable cardiovascular risk factors.

Variable	No SMuRF	1 SMuRF	2 SMuRFs	3–4 SMuRFs	P-value for trend	P-values (1 vs No)	P-values (2 vs No)	P-values (3–4 vs No)
Number of patients	6092	10,345	12,908	7853				
Male sex	77.56 (4725/6092)	78.05 (8074/10345)	74.12 (9568/12908)	75.00 (5890/7853)	<0.0001	0.47	<0.0001	<0.001
Age	63.66 ± 11.50 (6092)	63.20 ± 11.77 (10345)	65.14 ± 11.04 (12908)	64.17 ± 10.61 (7853)	<0.0001	<0.01	<0.0001	0.02
Baseline BMI (kg/m^2)	26.63 ± 4.13 (3862)	27.13 ± 4.31 (8577)	27.96 ± 4.63 (10834)	29.05 ± 5.04 (6673)	<0.0001	<0.0001	<0.0001	<0.0001
Diabetes mellitus	0.00 (0/5636)	12.11 (1242/10260)	24.86 (3191/12835)	75.83 (5946/7841)	<0.0001	<0.0001	<0.0001	<0.0001
Diabetes mellitus type					0.30			
Insulin dependent diabetes mellitus	–	23.61 (293/1241)	19.39 (618/3187)	20.36 (1210/5942)				
Non-insulin dependent diabetes mellitus	–	76.39 (948/1241)	80.61 (2569/3187)	79.64 (4732/5942)				
Smoking Status					<0.0001	<0.0001	<0.0001	<0.0001
Current		22.52 (2166/9618)	19.83 (2426/12231)	44.94 (3305/7355)				
Never	47.71 (2040/4276)	38.26 (3680/9618)	38.53 (4713/12231)	26.47 (1947/7355)				
Previous	35.52 (1519/4276)	28.43 (2734/9618)	31.19 (3815/12231)	22.34 (1643/7355)				
Unknown	16.77 (717/4276)	10.79 (1038/9618)	10.44 (1277/12231)	6.25 (460/7355)				
Hypercholesterolemia	0.00 (0/3605)	29.39 (2588/8806)	76.24 (9351/12266)	96.42 (7523/7802)	<0.0001	<0.0001	<0.0001	<0.0001
Hypertension	0.00 (0/3809)	46.34 (4349/9385)	85.78 (10848/12646)	97.44 (7643/7844)	<0.0001	<0.0001	<0.0001	<0.0001
Peripheral vascular disease	2.42 (107/4417)	4.29 (415/9680)	7.10 (871/12273)	11.48 (862/7510)	<0.0001	<0.0001	<0.0001	<0.0001
Previous myocardial infarction	15.93 (718/4508)	18.15 (1783/9823)	24.94 (3108/12462)	29.40 (2243/7630)	<0.0001	<0.01	<0.0001	<0.0001
Previous PCI	16.70 (759/4544)	20.71 (2040/9848)	29.23 (3683/12602)	33.07 (2544/7693)	<0.0001	<0.0001	<0.0001	<0.0001
Previous CABG	3.85 (174/4514)	3.58 (352/9821)	6.57 (823/12534)	7.66 (589/7693)	<0.0001	0.42	<0.0001	<0.0001
Renal impairment	2.74 (154/5611)	4.74 (483/10200)	7.75 (992/12798)	11.79 (919/7798)	<0.0001	<0.0001	<0.0001	<0.0001
Chronic coronary syndrome	44.55 (2714/6092)	40.32 (4171/10345)	47.36 (6113/12908)	46.78 (3674/7853)	<0.0001	<0.0001	<0.001	<0.01
Silent ischemia	10.31 (628/6092)	7.94 (821/10345)	8.61 (1111/12908)	10.23 (803/7853)	0.17	<0.0001	0.0001	0.87
Stable angina	34.24 (2086/6092)	32.38 (3350/10345)	38.75 (5002/12908)	36.56 (2871/7853)	<0.0001	<0.01	<0.0001	<0.01
Acute coronary syndrome	55.43 (3377/6092)	59.58 (6164/10345)	52.54 (6782/12908)	53.18 (4176/7853)	<0.0001	<0.0001	<0.001	<0.01
Unstable angina	9.08 (553/6092)	11.20 (1159/10345)	12.85 (1659/12908)	13.29 (1044/7853)	<0.0001	<0.0001	<0.0001	<0.0001
NSTEMI	22.34 (1361/6092)	23.86 (2468/10345)	22.37 (2887/12908)	23.70 (1861/7853)	0.61	0.034	0.97	0.06
STEMI	24.02 (1463/6092)	24.52 (2537/10345)	17.32 (2236/12908)	16.18 (1271/7853)	<0.0001	0.46	<0.0001	<0.0001
Radial arterial access	84.41 (5142/6092)	81.42 (8423/10345)	79.89 (10312/12908)	77.92 (6119/7853)	<0.0001	<0.0001	<0.0001	<0.0001
Target Vessels								
Left main	2.40 (146/6092)	2.69 (278/10345)	3.53 (456/12908)	3.54 (278/7853)	<0.0001	0.26	<0.0001	<0.0001
Right coronary artery	32.04 (1952/6092)	33.66 (3482/10345)	34.96 (4512/12908)	35.90 (2819/7853)	<0.0001	0.03	<0.0001	<0.0001
left anterior descending artery	53.53 (3261/6092)	53.49 (5534/10345)	50.86 (6565/12908)	48.61 (3817/7853)	<0.0001	0.97	<0.001	<0.0001
Circumflex artery	25.05 (1526/6092)	26.93 (2786/10345)	28.64 (3697/12908)	29.72 (2334/7853)	<0.0001	<0.01	<0.0001	<0.0001
Arterial or venous graft	0.69 (42/6092)	0.66 (68/10345)	1.49 (192/12908)	1.81 (142/7853)	<0.0001	0.81	<0.0001	<0.0001
Number of lesions treated	1.23 ± 0.53 (6088)	1.31 ± 0.61 (10337)	1.33 ± 0.63 (12893)	1.34 ± 0.63 (7840)	<0.0001	<0.0001	<0.0001	<0.0001
Number of successfully implanted stents	1.44 ± 0.79 (6086)	1.55 ± 0.85 (10326)	1.59 ± 0.89 (12863)	1.60 ± 0.90 (7823)	<0.0001	<0.0001	<0.0001	<0.0001
Total length successfully implanted stent	29.85 ± 18.35 (6079)	30.78 ± 18.95 (10307)	31.61 ± 20.39 (12837)	31.61 ± 20.27 (7809)		<0.01	<0.0001	<0.0001
Chronic total occlusion	5.15 (314/6092)	4.73 (489/10345)	5.17 (667/12908)	5.27 (414/7853)	0.28	0.226	0.97	0.76

(*continued on next page*)

Table 1 (*continued*)

Variable	No SMuRF	1 SMuRF	2 SMuRFs	3–4 SMuRFs	P-value for trend	P-values (1 vs No)	P-values (2 vs No)	P-values (3–4 vs No)
Bifurcation	8.73 (532/6092)	12.56 (1299/10345)	12.48 (1611/12908)	12.14 (953/7853)	<0.0001	<0.0001	<0.0001	<0.0001
Severe or moderate calcification	15.13 (922/6092)	17.58 (1819/10345)	20.31 (2622/12908)	21.79 (1711/7853)	<0.0001	<0.0001	<0.0001	<0.0001

Table 2
Clinical events at 1 year before inverse weighted propensity score adjustment stratified by the number of standard modifiable cardiovascular risk factors.

Variable	No SMuRF	1 SMuRF	2 SMuRFs	3–4 SMuRFs	P-value for trend	Relative Risk [95 % CI] p-value (1 vs No)	Relative Risk [95 % CI] p-value (2 vs No)	Relative Risk [95 % CI] p-value (3–4 vs No)
Number of patients	5878	9904	12,268	7339				
Target lesion failure	2.65 (156/5878)	2.75 (272/9904)	3.23 (396/12268)	4.24 (311/7339)	<0.0001	1.03 [0.85;1.26] p = 0.73	1.22 [1.01;1.46] p = 0.04	1.60 [1.32;1.93] p < 0.01
Patient oriented composite endpoint	5.14 (302/5878)	5.93 (587/9904)	6.65 (816/12268)	8.19 (601/7339)	<0.0001	1.15 [1.01;1.32] p = 0.04	1.29 [1.14;1.47] p < 0.01	1.59 [1.39;1.82] p < 0.01
Any death	1.75 (103/5878)	1.91 (189/9904)	2.04 (250/12268)	2.78 (204/7339)	<0.0001	1.09 [0.86;1.38] p = 0.48	1.16 [0.93;1.46] p = 0.19	1.59 [1.25;2.01] p < 0.01
Cardiac death	1.07 (63/5878)	1.09 (108/9904)	1.24 (152/12268)	1.80 (132/7339)	<0.0001	1.02 [0.75;1.39] p = 0.91	1.16 [0.86;1.55] p = 0.33	1.68 [1.25;2.26] p < 0.01
Any myocardial infarction	0.83 (49/5878)	1.05 (104/9904)	1.18 (145/12268)	1.70 (125/7339)	<0.0001	1.26 [0.90;1.77] p = 0.18	1.42 [1.03;1.96] p = 0.03	2.04 [1.47;2.84] p < 0.01
Target vessel myocardial infarction	0.66 (39/5878)	0.79 (78/9904)	0.91 (112/12268)	1.19 (87/7339)	<0.001	1.19 [0.81;1.74] p = 0.38	1.38 [0.96;1.98] p = 0.08	1.79 [1.23;2.60] p < 0.01
Any clinically driven target lesion revascularization	1.41 (83/5878)	1.49 (148/9904)	1.59 (195/12268)	2.25 (165/7339)	<0.0001	1.06 [0.81;1.38] p = 0.68	1.13 [0.87;1.45] p = 0.36	1.59 [1.23;2.07] p < 0.01
Stent thrombosis, definite/probable	0.68 (40/5878)	0.54 (53/9904)	0.67 (82/12268)	0.86 (63/7339)	0.06	0.79 [0.52;1.18] p = 0.25	0.98 [0.67;1.43] p = 0.93	1.26 [0.85;1.87] p = 0.25

Table 3
Clinical events at 1 year after inverse weighted propensity score adjustment stratified by the number of standard modifiable cardiovascular risk factors.

Variable	No SMuRF	1 SMuRF	2 SMuRFs	3–4 SMuRFs	P-value for trend	Relative Risk [95 % CI] p-value (1 vs No)	Relative Risk [95 % CI] p-value (2 vs No)	Relative Risk [95 % CI] p-value (3–4 vs No)
Number of patients	5878	9904	12,268	7339				
Target lesion failure	2.88 (169/5878)	2.64 (262/9904)	2.88 (353/12268)	3.65 (268/7339)	<0.01	0.92 [0.76;1.11] p = 0.38	1.00 [0.84;1.20] p = 0.99	1.27 [1.05;1.53] p < 0.01
Patient oriented composite endpoint	5.85 (344/5878)	5.73 (567/9904)	5.96 (732/12268)	7.08 (520/7339)	<0.001	0.98 [0.86;1.11] p = 0.74	1.02 [0.90;1.15] p = 0.77	1.21 [1.06;1.38] p < 0.01
Any death	1.87 (110/5878)	1.84 (182/9904)	1.73 (212/12268)	2.34 (172/7339)	0.07	0.98 [0.78;1.24] p = 0.89	0.93 [0.74;1.16] p = 0.52	1.25 [0.99;1.59] p = 0.06
Cardiac death	1.11 (65/5878)	1.02 (101/9904)	1.05 (128/12268)	1.51 (111/7339)	0.02	0.92 [0.68;1.25] p = 0.60	0.94 [0.70;1.26] p = 0.68	1.36 [1.00;1.84] p = 0.05
Any myocardial infarction	0.92 (54/5878)	0.99 (98/9904)	1.07 (132/12268)	1.46 (107/7339)	<0.01	1.08 [0.77;1.50] p = 0.66	1.17 [0.85;1.60] p = 0.34	1.58 [1.14;2.19] p < 0.01
Target vessel myocardial infarction	0.72 (42/5878)	0.74 (73/9904)	0.82 (101/12268)	1.01 (74/7339)	0.03	1.03 [0.71;1.50] p = 0.88	1.15 [0.80;1.64] p = 0.45	1.42 [0.97;2.06] p = 0.07
Any clinically driven target lesion revascularization	1.59 (94/5878)	1.44 (143/9904)	1.48 (182/12268)	1.97 (145/7339)	0.05	0.90 [0.70;1.17] p = 0.45	0.93 [0.73;1.19] p = 0.57	1.24 [0.96;1.60] p = 0.10
Stent thrombosis, definite/probable	0.75 (44/5878)	0.49 (48/9904)	0.62 (76/12268)	0.84 (61/7339)	0.15	0.65 [0.43;0.98] p = 0.04	0.83 [0.57;1.20] p = 0.32	1.12 [0.76;1.65] p = 0.56

SMuRFs. No difference in event rates were observed between SMuRF-less patients and patients with 1 SMuRF or 2 SMuRFs, but this should be appreciated in the context of the low event rates attributable to multiple factors such as a guideline-directed medical therapy and the use of a contemporary stent [9]. Moreover, the cumulative event curves will probably further diverge with a longer follow-up. Nevertheless, an incremental number of SMuRFs was associated with a trend for a higher event rate.

The overall incidence of SMuRF-less patients in our cohort was 16.4 %. Previous studies reported wide prevalence of SMuRF-less ranging

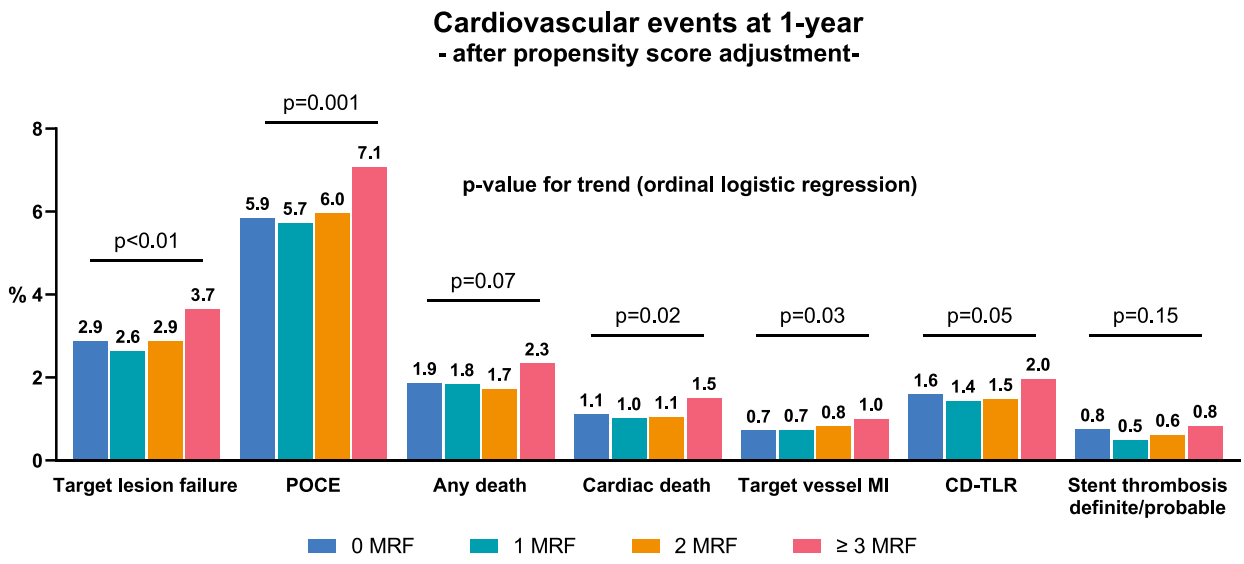

Fig. 2. Cardiovascular events at 1-year after inverse weighted propensity score adjustment.

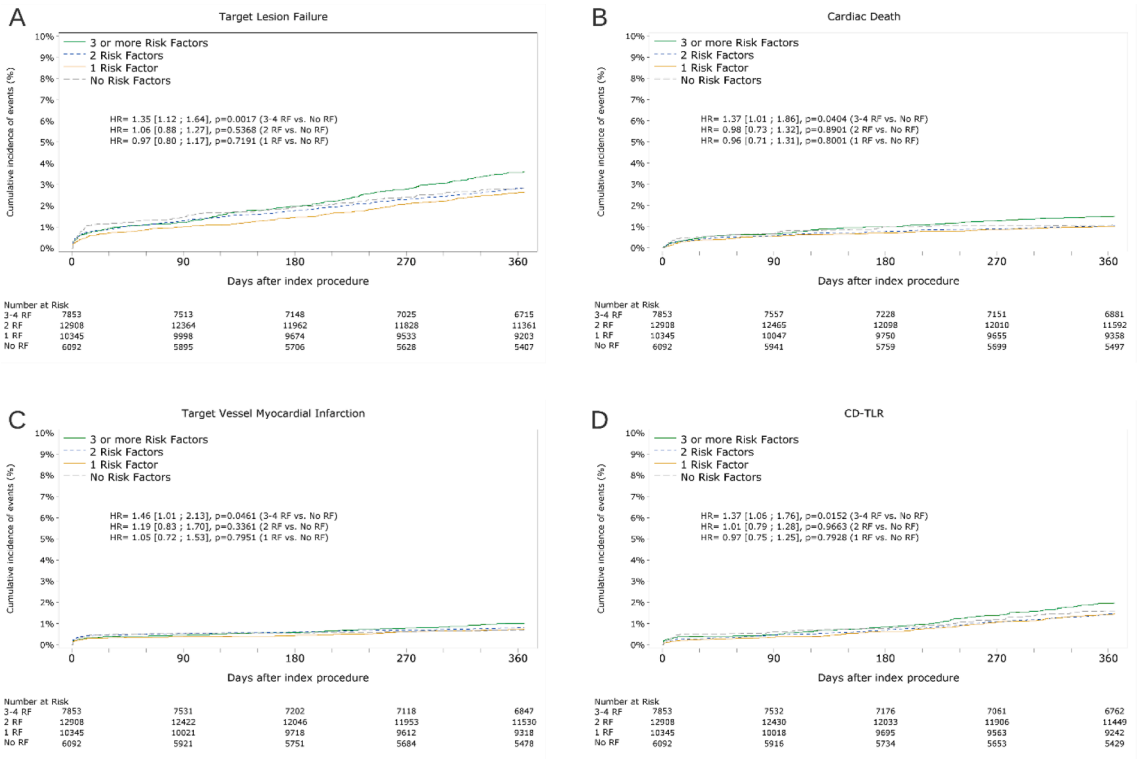

Fig. 3. Kaplan-Meir cumulative event curves after after inverse weighted propensity score adjustment. A: target lesion failure; B: cardiac death; C: target vessel myocardial infarction; D: clinically driven target lesion revascularization.

between 8 % and 25 % and is increasing over the years [3,5,15,16]. A recent global *meta*-analysis estimated prevalence of SMuRF-less patient as 12 % of ACS patients [17]. However, it should be noted that our cohort included patients undergoing PCI for ACS as well as CCS, the relative high prevalence of SMuRF-less patients in our cohort may also be partly related to the fact that even when presenting with STEMI, SMuRF-less patients are less likely to undergo PCI, potentially due to higher prevalence of MINOCA in this group [16,18,19].

Some previous studies reported that SMuRF-less patients tend to be younger, and more likely to be men [16]. Our findings support these previous studies. We also report lower prevalence of peripheral vascular disease, renal impairment and previous MI in the SMuRF-less group, in accordance with previous studies [17]. From the procedural point of view, SMuRF-less patients were less likely to undergo left main or bifurcation PCI and were less likely to undergo PCI for calcified lesion, facts that can be explained by the lower prevalence of diabetes mellitus, peripheral vascular disease, and renal failure. The lower number of lesions treated in the SMuRF-less group also hints on less extensive coronary disease in this group.

In accordance with the younger age of the patients, the lower burden of co-morbidities and the lower prevalence of complex PCI, we report lower crude rate of adverse clinical outcomes in the SMuRF-less group.

Most of the previous studies reported worse clinical outcomes among SMuRF-less patients [15,17–19]. In our cohort which included only patients treated with contemporary DES, even after adjustment to baseline demographics, co-morbidities and procedural characteristics, we did not find worse clinical outcome in the SMuRF-less group. Furthermore, compared to the SMuRF-less group, patients with 3 or more SMuRF had significantly worse outcome. It should be noted, that most of the previous trials included only ACS patients. However, even in the ACS subgroup, we did not observe worse clinical outcomes in the SMuRF-less group. In fact, there was a positive trend for a higher clinical event rate along the number of SMuRFs before IWPS adjustment, which largely became non-significant after IWPS adjustment. Moreover, no interaction was observed between the number of SMuRFs and clinical presentation on the clinical event incidence suggesting absence of a modifying effect of clinical presentation on the impact of the number of SMuRFs on the clinical event rate.

The contradiction between previous reports and our study about the event rate in SMuRF-less patients presenting with ACS may be explained by the fact that in our cohort all patients underwent invasive treatment. In an analysis from the UK using the Myocardial Ischaemia National Audit Project (MINAP) registry, Weight et al. reported higher in hospital mortality among SMuRF-less patients admitting with STEMI [15]. However, following adjustment for invasive coronary angiography (ICA) and revascularization, results for in-hospital mortality were no longer significant. Another important aspect in the long-term clinical outcomes in the secondary prevention. There is numerous data that in real life SMuRF-less patients, even after STEMI, are less likely to receive appropriate secondary prevention measures [1,17,19]. In some of the previous reports, the worse clinical outcomes of SMuRF-less patients did not persist following adjustment to secondary prevention treatment prescribed [1].

We hypotheses that the fact that all patients in our cohort were treated invasively and the participation in a registered clinical trial may have led to higher likelihood of secondary prevention treatment prescribed to the patients, this may also contributed to attenuate the trend toward worse clinical outcomes in this subgroup. Our finding emphasize the need to tailor personalized care and to ensure appropriate secondary prevention measure even for patients without known SMuRFs.

6. Strengths and limitations

As mentioned, our study is one of the largest contemporary prospective study, which examines clinical outcomes of patients undergoing PCI with new-generation, thin struts DES. Our study included over 37,000 patients with our 16 % of the patients without know SMuRFs, with pre-specified clinical outcomes and very low rate of patients lost to follow-up.

Nevertheless, this study has some limitations. First, although we adjusted for numerous demographics, comorbidities, and other baseline and procedural characteristics, we cannot exclude the presence of other potential confounders. For example, we do not have data on prevalence of inflammatory diseases. Second, this is an observational study, and the procedural techniques, as well as adjunct medical therapy, were based on operator choice, rather than randomized, as per in randomized controlled trials, or pre-defined. Third, only one type of new generation stent was used [20], and our finding may not be applicable to older stents or to other new-generation DES. Fourth, the follow-up was only 1-year, and a longer follow-up might have shown a divergence between SMuRF-less patients and patients with one or more SMuRFs. Finally, we assessed the number of SMuRFs, as defined by the patient's medical records. The protocol did not include specific investigations such as blood pressure monitoring, compulsory HbA1C test, lipid profile etc. There is a possibility of misclassification of patients with subclinical or unknown risk factors as 'SMuRF-less patients'.

7. Conclusion

In this real-world analysis, about one out of six patients undergoing PCI has no SMuRF, while over 50 % have two or more. Following treatment with new generation thin struts DES, SMuRF-less patients did not experience worse clinical outcomes, and a greater number of SMuRFs correlated with more cardiovascular events in both the clinical history as well as in the first year after the PCI. Further research is still needed in order to optimize therapeutic management in the majority of patients undergoing PCI.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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