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ORIGINAL ARTICLE

Impact of multisite artery disease on clinical outcomes after percutaneous coronary intervention: an analysis from the e-Ultimaster registry

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Background Multisite artery disease is considered a 'malignant' type of atherosclerotic disease associated with an increased cardiovascular risk, but the impact of multisite artery disease on clinical outcomes after percutaneous coronary intervention (PCI) is unknown.

Methods Patients enrolled in the large, prospective e-Ultimaster study were grouped into (1) those without known prior vascular disease, (2) those with known single-territory vascular disease, and (3) those with known two to three territories (i.e coronary, cerebrovascular, or peripheral) vascular disease (multisite artery disease). The primary outcome was coronary target lesion failure (TLF), defined as the composite of cardiac death, target vessel-related myocardial infarction, and clinically driven target lesion revascularization at 1-year. Inverse propensity score weighted (IPSW) analysis was performed to address differences in baseline patient and lesion characteristics.

Results Of the 37 198 patients included in the study, 62.3% had no prior known vascular disease, 32.6% had single-territory vascular disease, and 5.1% had multisite artery disease. Patients with known vascular disease were older and were more likely to be men and to have more co-morbidities. After IPSW, the TLF rate incrementally increased with the number of diseased vascular beds (3.16%, 4.44%, and 6.42% for no, single, and multisite artery disease, respectively, $P < 0.01$ for all comparisons). This was also true for all-cause death (2.22%, 3.28%, and 5.29%, $P < 0.01$ for all comparisons) and cardiac mortality (1.26%, 1.91%, and 3.62%, $P \leq 0.01$ for all comparisons).

Conclusions Patients with previously known vascular disease experienced an increased risk of adverse cardiovascular events and mortality post-PCI. This risk is highest among patients with multisite artery disease.

Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02188355.

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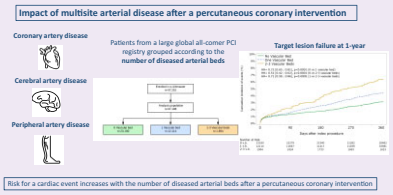
Graphical Abstract Number of diseased arterial beds is a prognostic factor for a cardiac event after a percutaneous coronary intervention.



Keywords Poly-vascular disease • vascular disease • percutaneous coronary intervention • clinical trial • human

Background

Atherosclerosis is a systemic process, and the involvement of one vascular bed is often associated with disorders and dysfunction in other organ systems.[1] Multisite artery disease is defined as the presence of atherosclerosis in two or more vascular beds (i.e. cerebrovascular, coronary, or peripheral) and is considered a 'malignant' type of atherosclerotic disease associated with an increased cardiovascular risk.[2–4]

Ischemic heart disease carries a substantial burden of morbidity and mortality worldwide. Previous studies demonstrated worse short and long-term outcomes in patients with multisite artery disease admitted with myocardial infarction (MI).[5–9] Percutaneous coronary intervention (PCI) is the most common method of revascularization in patients with obstructive coronary artery disease (CAD).[10] Previous studies reported an incremental increase in the risk of morbidity and mortality with the number of diseased vascular beds of patients undergoing PCI.[11–13] However, most of the data on outcomes of patients with ischemic heart disease and known multisite artery disease rely, at least partly, on data from the bare metal stent (BMS) or early-generation drug-eluting stent (DES) era. Newer generation DES and adjunct medical therapy improved post-PCI clinical outcomes in the general population,[14] particularly in patients with multisite artery disease, which is increasingly recognized as a risk factor. It is unknown whether the improved technology, skills, and more contemporary pharmacological preventive therapy have attenuated the increased risk of patients with multisite artery disease undergoing PCI.

We aimed to compare the outcomes of patients with and without previously known vascular disease and multisite artery disease in a large cohort of patients enrolled in the prospective, multinational, and observational e-Ultimaster study.

Methods

Study design

The e-Ultimaster registry is a large, prospective, and multicentre observational study.[15] This study was conducted worldwide to evaluate the safety and performance of the Ultimaster DES system (Terumo Corporation, Tokyo, Japan) in an all-comer clinical setting. Patients with CAD, 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. Local institutional review board approval was obtained at each institution and all subjects provided written informed consent.

The present study analysed the clinical outcomes of patients who were known to have vascular disease prior to the index hospitalization in one or more of the following vascular territories: coronary (defined as a previous MI, PCI, or coronary artery bypass surgery (CABG); cerebrovascular (defined as a previous cerebral vascular accident or transient ischemic attack); and peripheral (defined as previous or current ischaemia in the lower limbs). The assessment of the presence of prior vascular disease was made by the hospital staff based upon review of hospital charts and referral letters.[16] We defined multisite artery disease as the presence of atherosclerosis in two or three vascular beds. Patients were grouped into (1) those without previously known vascular disease, (2) those with known single-territory vascular disease, or (3) those with known two or three diseased vascular territories (multisite artery disease).

Study device

The Ultimaster coronary stent system is a new-generation, open-cell, cobalt-chromium, and 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.[17]

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), and clinically driven target lesion revascularization (CD-TLR) at 1-year. Secondary outcomes included any death, cardiac death, any MI, TV-MI, any CD revascularization, CD-TLR, definite/probable stent thrombosis, and patient oriented composite endpoint (POCE), defined as the composite of any death, any MI, and any coronary revascularization, and target vessel failure (TVF), defined as the composite of cardiac death, TV-MI, clinically driven target vessel revascularization (CD-TVR), and BARC type 3 or 5 bleeding.[18] All endpoint related serious adverse events were reviewed and adjudicated by an independent clinical event committee.

Subcategories of death (cardiac death and non-cardiovascular death), as well as revascularizations and stent thrombosis, were adjudicated according to the Academic Research Consortium (ARC) definitions.[19] 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 periprocedural (<48 h post-PCI), reinfarction (<48 h post-PCI), or spontaneous MI (>48 h post-PCI) were used.

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 *t*-test for continuous variables and a χ^2 test for categorical variables. The clinical outcomes were reported at 1 year of follow-up. 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,

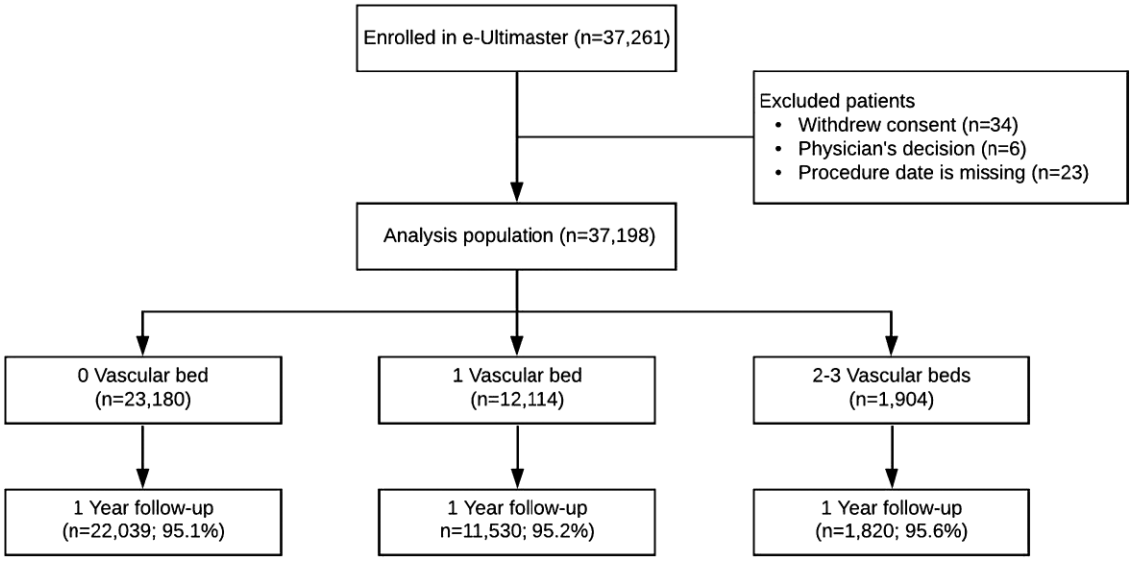


Figure 1 Patient disposition.

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, diabetes mellitus, hypercholesterolaemia, renal impairment, in-stent restenosis, hypertension, 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 three groups studied (no vascular bed, one vascular bed, and two to three vascular beds) 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 then 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 (Supplementary material online, *Figures S1–S3*). After adjustment, all covariates in the planned propensity score had weighted standardized differences <0.1, which indicates an equilibration of these covariates between the groups (the propensity scores logistic regression model beta estimates are presented on Supplementary material online, *Table S2*). The cumulative event rates were estimated by the Kaplan–Meir method, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with Cox hazards regression analysis. *P*-values < 0.05 were considered statistically significant. No correction was made for multiple testing. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

A total of 37 198 patients were included in the study. Of those, 35 389 patients (95.1%) were available for 1-year post-PCI follow-up (*Figure 1*). Of the total population, 23 180 (62.3%) had no prior vascular disease, 12 114 (32.6%) had known vascular disease in a single territory, and 1904 (5.1%) had known multisite artery disease.

Demographics and comorbidities

Patients with known vascular disease were older and were more likely to be male and with more co-morbidities (*Table 1*). The prevalence of diabetes mellitus, hypertension, hyperlipidaemia, and renal impairment correlated with the number of vascular beds involved, while active smoking was less common among patients with previously known single and multisite artery disease, compared with patients without known vascular disease.

Clinical presentation and procedural data

The groups differed in the clinical syndrome at presentation. ST-segment elevation myocardial infarction (STEMI) was most common among patients without previously known vascular disease (27.2%), followed by patients with known single vascular disease (8.8%) and multisite artery disease (6.7%), while patients with known vascular disease were more likely to undergo PCI due to chronic coronary syndrome (36.9% vs. 58.5% vs. 54.3% for patients with no, single, and multisite artery disease, respectively). Differences were observed in the pattern of coronary disease according to the number of diseased vascular beds. Accordingly, the rate of left main PCI increased with the number of diseased vascular beds (2.0% vs. 4.8%, and 6.3% for patients with no, single, and multisite artery disease, respectively), with similar incremental patterns observed for calcified lesions (16.1% vs. 23.2% vs. 27.7%), ostial lesions (5.5% vs. 9.0% vs. 11.3%), and bifurcation lesions (10.6% vs. 13.6% vs. 14.7%). With respect to procedural variables, the use of intracoronary imaging (7.2% vs. 10.2% vs. 11.3%) and femoral access (14.9% vs. 21.1% vs. 23.1%) increased for patients with no, single, and multisite artery disease, respectively. Supplementary material online, *Table S3* presented the patient, vessel, and lesion baseline characteristics for patients with only cerebral, coronary, and peripheral diseased vascular beds.

Clinical outcomes

Table 2 presents crude clinical outcome data at 1 year after the index PCI procedure. For most clinical outcomes, the rate of events incrementally increased with the number of diseased vascular beds. This is true for the primary endpoint of TLF (2.5%, 4.0%, and 7.3%, all *P*-values < 0.01), as well as for other predefined clinical endpoints: TVF (2.8%, 4.7%, and 7.9%, all *P*-values < 0.01), POCE (5.3%, 8.1%, and 12.0%, all *P*-values < 0.01), all-cause mortality (1.6%, 2.5%, and 5.8%, all *P*-values < 0.01), cardiac mortality (0.9%, 1.5%, and 4.1%, all

Table 1 **Patient, vessel, and lesion baseline characteristics (unadjusted) for patients with no, one, and two to three diseased vascular beds**

% (*n*/*N*)	No vascular bed (arm 1) *N* = 23 180	One vascular bed (arm 2) *N* = 12 114	Two to three vascular beds (arm 3) *N* = 1904	*P*-values (arm 1 vs. 2)	*P*-values (arm 1 vs. 3)	*P*-values (arm 2 vs. 3)
Age, mean ± SD (*N*)	62.9 ± 11.3 (23 180)	65.7 ± 10.9 (12 114)	69.7 ± 9.8 (1904)	<0.01	<0.01	<0.01
Gender (male)	74.4 (17 252/23 180)	78.8 (9543/12 114)	76.8 (1462/1904)	<0.01	0.02	0.05
Diabetes mellitus	24.2 (5474/22 648)	33.7 (4056/12 031)	44.8 (849/1893)	<0.01	<0.01	<0.01
Insulin dependent diabetes mellitus	4.3 (980/22 648)	7.5 (897/12 031)	12.9 (244/1893)	<0.01	<0.01	<0.01
Non-insulin dependent diabetes mellitus	82.1 (4487/22 648)	77.9 (3157/12 031)	71.3 (605/1893)	<0.01	<0.01	<0.01
Hypertension	61.4 (12 455/20 290)	76.4 (8829/11 556)	84.7 (1556/1838)	<0.01	<0.01	<0.01
Hypercholesterolaemia	53.4 (10 367/19 428)	68.9 (7754/11 250)	74.5 (1341/1801)	<0.01	<0.01	<0.01
Current smoker	26.7 (5417/20 279)	19.1 (2174/11 417)	17.2 (306/1784)	<0.01	<0.01	0.06
Previous stroke or TIA	0.00 (0/20 859)	7.7 (907/11 827)	51.4 (972/1891)	<0.01	<0.01	<0.01
Peripheral vascular disease	0.00 (0/20 520)	8.7 (1004/11 494)	67.0 (1251/1866)	<0.01	<0.01	<0.01
Renal impairment	4.6 (1038/22 504)	9.6 (1158/12 016)	18.7 (352/1887)	<0.01	<0.01	<0.01
Previous myocardial infarction	0.00 (0/20 791)	56.9 (6696/11 772)	62.1 (1156/1860)	<0.01	<0.01	<0.01
Previous PCI	0.00 (0/20 880)	64.6 (7708/11 928)	70.1 (1318/1879)	<0.01	<0.01	<0.01
Previous CABG	0.00 (0/20 854)	13.3 (1574/11 832)	19.4 (364/1876)	<0.01	<0.01	<0.01
Chronic coronary syndrome	36.9 (8553/23 180)	58.5 (7085/12 114)	54.3 (1034/1904)	<0.01	<0.01	<0.01
Acute coronary syndrome	63.0 (14 613/23 180)	41.4 (5017/12 114)	45.6 (869/1904)	<0.01	<0.01	<0.01
Unstable Angina	10.5 (2441/23 180)	13.9 (1687/12 114)	15.1 (287/1904)	<0.01	<0.01	0.18
NSTEMI	25.3 (5863/23 180)	18.6 (2259/12 114)	23.9 (455/1904)	<0.01	0.18	<0.01
STEMI	27.2 (6309/23 180)	8.8 (1071/12 114)	6.7 (127/1904)	<0.01	<0.01	<0.01
Arterial access						
Femoral	14.9 (3456/23 180)	21.1 (2557/12 114)	23.1 (440/1904)	<0.01	<0.01	0.05
Radial	83.6 (19 381/23 180)	76.2 (9227/12 114)	72.9 (1388/1904)	<0.01	<0.01	<0.01
Femoral and radial	1.2 (283/23 180)	2.1 (258/12 114)	2.5 (47/1904)	<0.01	<0.01	0.35
Vessels treated						
Left main	2.0 (460/23 180)	4.8 (578/12 114)	6.3 (120/1904)	<0.01	<0.01	<0.01
Right coronary artery	33.4 (7749/23 180)	35.7 (4328/12 114)	36.1 (688/1904)	<0.01	0.02	0.73
Left anterior descendants	55.4 (12 849/23 180)	45.6 (5528/12 114)	42.0 (800/1904)	<0.01	<0.01	<0.01
Left circumflex	26.3 (6088/23 180)	30.5 (3692/12 114)	29.6 (563/1904)	<0.01	<0.01	0.42
Arterial or venous bypass graft	0.1 (19/23 180)	2.7 (322/12 114)	5.4 (103/1904)	<0.01	<0.01	<0.01
Number of lesions treated, mean ± SD (*N*)	1.3 ± 0.6 (23 152)	1.3 ± 0.6 (12 102)	1.4 ± 0.6 (1904)	<0.01	<0.01	0.34
Number of successfully implanted stents, mean ± SD (*N*)	1.5 ± 0.8 (23 113)	1.6 ± 0.9 (12 082)	1.7 ± 0.9 (1903)	<0.01	<0.01	0.19
Total length of successfully implanted stent, mean ± SD (*N*)	30.2 ± 18.6 (23 081)	32.6 ± 21.1 (12 053)	32.3 ± 21.5 (1898)	<0.01	<0.01	0.28
Intra-vascular imaging	7.2 (1249/17 242)	10.2 (995/9750)	11.2 (175/1555)	<0.01	<0.01	0.21
Any CTO	4.0 (938/23 180)	6.8 (823/12 114)	6.5 (123/1904)	<0.01	<0.01	0.59
Any bifurcation	10.6 (2463/23 180)	13.6 (1652/12 114)	14.7 (280/1904)	<0.01	<0.01	0.21
Any in stent restenosis	1.7 (385/23 180)	10.8 (1313/12 114)	13.1 (249/1904)	<0.01	<0.01	<0.01
Any ostial lesion	5.5 (1284/23 180)	9.0 (1090/12 114)	11.3 (216/1904)	<0.01	<0.01	<0.01
Any severe or moderate calcification	16.1 (3735/23 180)	23.2 (2812/12 114)	27.7 (527/1904)	<0.01	<0.01	<0.01

Table 2 **Clinical outcomes at 1 year—unadjusted rates and relative risk for patients with no, one, and two to three diseased vascular beds**

% (*n*/*N*)	No vascular bed (arm 1) *N* = 22 039	One vascular bed (arm 2) *N* = 11 530	Two to three vascular beds (arm 3) *N* = 1820	RR (95% CI), *P*-value (arm 1 vs. 2)	RR (95% CI), *P*-value (arm 1 vs. 3)	RR (95% CI), *P*-value (arm 2 vs. 3)
Target lesion failure	2.45 (539/22 039)	4.02 (463/11 530)	7.31 (133/1820)	0.61 (0.54–0.69), $P < 0.01$	0.33 (0.28–0.40), $P < 0.01$	0.55 (0.46–0.66), $P < 0.01$
Target vessel failure	2.83 (623/22 039)	4.69 (541/11 530)	7.91 (144/1820)	0.60 (0.54–0.67), $P < 0.01$	0.36 (0.30–0.43), $P < 0.01$	0.59 (0.50–0.71), $P < 0.01$
POCE	5.25 (1158/22 039)	8.07 (930/11 530)	11.98 (218/1820)	0.65 (0.60–0.71), $P < 0.01$	0.44 (0.38–0.50), $P < 0.01$	0.67 (0.59–0.77), $P < 0.01$
Any death	1.57 (347/22 039)	2.54 (293/11 530)	5.82 (106/1820)	0.62 (0.53–0.72), $P < 0.01$	0.27 (0.22–0.33), $P < 0.01$	0.44 (0.35–0.54), $P < 0.01$
Cardiac death	0.93 (206/22 039)	1.52 (175/11 530)	4.07 (74/1820)	0.62 (0.50–0.75), $P < 0.01$	0.23 (0.18–0.30), $P < 0.01$	0.37 (0.29–0.49), $P < 0.01$
Any myocardial infarction	0.85 (188/22 039)	1.64 (189/11 530)	2.53 (46/1820)	0.52 (0.43–0.64), $P < 0.01$	0.34 (0.25–0.46), $P < 0.01$	0.65 (0.47–0.89), $P < 0.01$
Target vessel myocardial infarction	0.68 (149/22 039)	1.15 (133/11 530)	1.87 (34/1820)	0.59 (0.46–0.74), $P < 0.01$	0.36 (0.25–0.52), $P < 0.01$	0.62 (0.43–0.90), $P = 0.01$
Any CD non-TVR	0.67 (147/22 039)	1.14 (132/11 530)	0.99 (18/1820)	0.58 (0.46–0.74), $P < 0.01$	0.67 (0.41–1.10), $P = 0.11$	1.16 (0.71–1.89), $P = 0.56$
Any CD TVR	1.74 (383/22 039)	2.99 (345/11 530)	3.96 (72/1820)	0.58 (0.50–0.67), $P < 0.01$	0.44 (0.34–0.56), $P < 0.01$	0.76 (0.59–0.97), $P = 0.03$
Any CD TLR	1.30 (287/22 039)	2.16 (249/11 530)	3.02 (55/1820)	0.60 (0.51–0.71), $P < 0.01$	0.43 (0.32–0.57), $P < 0.01$	0.71 (0.54–0.95), $P = 0.02$
Stent thrombosis	0.54 (120/22 039)	0.83 (96/11 530)	1.21 (22/1820)	0.65 (0.50–0.85), $P < 0.01$	0.45 (0.29–0.71), $P < 0.01$	0.69 (0.43–1.09), $P = 0.11$
BARC 3 or 5 bleeding	0.63 (138/22 039)	0.96 (111/11 530)	3.02 (55/1820)	0.65 (0.51–0.83), $P < 0.01$	0.21 (0.15–0.28), $P < 0.01$	0.32 (0.23–0.44), $P < 0.01$
Dual antiplatelet treatment	66.39% (15 390/23 180)	64.81% (7851/12 114)	60.61% (1154/1904	1.02 (1.01–1.04), $P < 0.01$	1.10 (1.06–1.14), $P < 0.01$	1.07 (1.03–1.11), $P < 0.01$

P-values < 0.01), TV-MI (0.7%, 1.2%, and 1.9%, *P* either < 0.01 or 0.01), CD-TLR (1.3%, 2.2%, and 3.0%, *P* < 0.01 for no vs. one and no vs. two to three vascular beds, and *P* = 0.02 for one vs. two to three vascular beds), definite/probable stent thrombosis (0.5%, 0.8%, and 1.2%, *P* < 0.01, <0.01, and 0.11, respectively), and BARC 3 or 5 bleeding (0.6%, 1.0%, and 3.0%, all *P* < 0.01). The number of patients taking DAPT at 1 year decreased with number of diseased vascular beds.

The adjusted event rates are presented in *Table 3*. Patients with known vascular disease were found to have an independently, significantly increased risk of a cardiac event, with incrementally higher event rates along with the number of diseased vascular beds for all cardiac events. Patients with multisite artery disease had an independently increased risk of BARC 3 or 5 bleeding compared with patients without known vascular disease or with single-site vascular disease. For specific *P*-values, see *Table 3*. *Figure 2* and Supplementary material online, *Table S1* present the adjusted cumulative event rate of main clinical outcomes. We compared the clinical outcomes of patients with only cerebral, coronary, and peripheral diseased vascular beds. There were no differences in outcomes between the groups, except for a difference in all-cause death and cardiac death between only coronary bed and only cerebral bed or peripheral bed. After adjustment, we did not observe difference between groups in clinical outcomes (Supplementary material online, *Tables S4 and S5*).

Discussion

Our study analysed real-world data from a multicentre, prospective, observational study of >37 000 patients who underwent PCI with contemporary new-generation thin strut DES and estimated the effect of single and multisite artery disease on 1-year clinical outcomes. To the best of our knowledge, this is the largest analysis of the impact of prior multisite artery disease in patients undergoing PCI with a new-generation DES.

Atherosclerotic vascular and multisite artery diseases were diagnosed in 32.6% and 5.1% of the study population, respectively. In other words, in real-world clinical practice, 1 in every 20 patients has prior diffuse atherosclerosis involving more than one territory at the time of index PCI.

Patients with vascular disease were older with a higher prevalence of male patients and more cardiovascular risk factors. The prevalence of most risk factors (diabetes, hyperlipidaemia, renal failure, and hypertension) was highest in patients with multisite disease. The rate of STEMI, as an indication for PCI, decreased as the number of vascular beds involved increased, while the rate of chronic coronary syndrome correlated with the number of vascular beds. Differences were also observed in the procedural data: rates of femoral access, complex (left main, ostial, calcified, or bifurcation lesion) PCI, and the use of intracoronary imaging increased with the number of diseased vascular beds.

As expected, based on the higher prevalence of risk factors and PCI complexity, patients with single and multisite artery disease experienced a higher crude rate of the primary outcome of TLF as well as other adverse clinical outcomes at 1-year follow-up, including TVF, POCE, cardiac and all-cause mortality, clinically driven revascularization, MI, and stent thrombosis. An incremental increase in the rate of adverse outcomes with the number of vascular beds involved was observed. The higher risk persisted after adjustment for differences in clinical variables, and multisite artery disease was associated with an independent, significantly increased risk of TLF, POCE, cardiac-, and all-cause mortality as well as MI, CD-TLR, and stent thrombosis. Atherosclerosis is a systemic process that tends to involve more than one organ.[20] The prevalence of multisite artery disease in our cohort is lower than previously reported in other registries, such as the CRUSADE registry,[7] where multisite artery disease was diagnosed in 12.8% of the patients. We found a higher prevalence of hypertension and hyperlipidaemia in patients with multisite artery disease. Previous studies found that multisite artery disease is associated with a higher concentration of inflammatory markers, lipoprotein(a), and circulating immune complexes. Long-term exposure and increased levels of very small and small very low-density lipoprotein, intermediate-density lipoprotein, and large low-density lipoprotein particles were also found to be associated with the presence of multisite artery disease, as was increased blood pressure in the literature.[21–23] Interestingly, smoking was less common among patients with single and multisite artery diseases. This was also noted in previous studies,[7,13] and may be related to the cessation of smoking because of previous vascular events in patients with diagnosed vascular disease.

Patients with multisite artery disease were less likely to undergo PCI due to STEMI. Similar findings were previously reported.[6] This may be related to the fact that patients with pre-existent vascular disease are already on antiplatelet agents and statins. Furthermore, as patients with multisite artery disease admitted with MI are less likely to undergo PCI when compared with patients with less extensive atherosclerosis,[6,7] patients with MI and multisite artery disease may be under-represented in our cohort. Patients with multisite artery disease underwent more frequently a PCI to LMCA, ostial, bifurcation, or calcified lesions, compared with patients with single-territory or no vascular disease.

To the best of our knowledge, no previous large-scale study reported the procedural aspects of PCI in patients with multisite artery disease. The more advanced coronary atherosclerosis and subsequent higher complexity of PCI in patients with multisite artery disease may contribute to the worse outcomes of these patients; however, even after adjustment, multisite artery disease was significantly associated with worse clinical outcomes.

Multisite artery disease was found to be independently associated with worse outcomes in patients with peripheral artery disease, diabetes mellitus, or cardiogenic shock.[24–26] In a large registry study of patients admitted with an acute coronary syndrome, multisite artery disease was associated with increased odds of in-hospital adverse events and mortality,[7] as well as increased odds of a recurrent event and long-term mortality.[5] In an analysis of >2 million acute MI admissions, multisite artery disease was also associated with increased odds of major bleeding and cerebrovascular accidents.[6] Earlier data from the BMS era found worse post-PCI outcomes for patients with multisite artery disease.[27] In an analysis of the CREDO-Kyoto Registry Cohort-2, multisite artery disease was associated with increased HR for adverse cardiovascular events, including major adverse cardiac events, all-cause mortality, and stroke during a 3-year follow-up.[13] In a smaller analysis of the SMART study, which included almost 2300 patients with a median follow-up of >7 years, both clinical and subclinical multisite artery disease were also associated with increased HR for MACE and mortality.[11] However, none of the above-mentioned studies included data on contemporary DES.

Our study, which analysed the 1-year clinical outcome following PCI with contemporary new-generation thin strut DES, validates the results of previous studies with BMS and first-generation DES. Even with new-generation, thin strut DES, multisite artery disease independently increased the 1-year risk of several clinical endpoints, such as TLF, TVF, POCE, and even cardiac and all-cause mortality. Furthermore, the risk of a clinical adverse endpoint increases with the number of vascular beds involved. Over the last decades, the clinical outcome of PCI has gradually improved.[14] This can be attributed to better stent platforms, wider use of intracoronary imaging and physiological studies, improved technical skills, and more aggressive adjunct medical treatment. Regardless of the improved overall PCI outcomes, multisite artery disease is still independently associated with an increased risk of adverse clinical outcomes, including mortality. The increased risk reflects the advanced level of systemic atherosclero-

Table 3 **Clinical outcomes at 1 year—adjusted rates and relative risk after inverse-propensity score weighting for patients with no, one, and two to three diseased vascular beds**

(*n*/*N*)	No vascular bed (arm 1) *N* = 22 039	One vascular bed (arm 2) *N* = 11 530	Two to three vascular beds (arm 3) *N* = 1820	RR (95 CI), *P*-value (arm 1 vs. 2)	RR (95 CI), *P*-value (arm 1 vs. 3)	RR (95 CI), *P*-value (arm 2 vs. 3)
Target lesion failure	3.16 (698/22 039)	4.44 (511/11 530)	6.42 (117/1820)	0.71 (0.64–0.80), $P < 0.01$	0.49 (0.41–0.60), $P < 0.01$	0.69 (0.57–0.84), $P < 0.01$
Target vessel failure	3.69 (813/22 039)	5.13 (592/11 530)	7.00 (127/1820)	0.72 (0.65–0.80), $P < 0.01$	0.53 (0.44–0.63), $P < 0.01$	0.73 (0.61–0.88), $P < 0.01$
POCE	6.73 (1484/22 039)	8.95 (1032/11 530)	10.81 (197/1820)	0.75 (0.70–0.81), $P < 0.01$	0.62 (0.54–0.72), $P < 0.01$	0.83 (0.72–0.96), $P = 0.01$
Any death	2.22 (489/22 039)	3.28 (378/11 530)	5.29 (96/1820)	0.68 (0.59–0.77), $P < 0.01$	0.42 (0.34–0.52), $P < 0.01$	0.62 (0.50–0.77), $P < 0.01$
Cardiac death	1.26 (277/22 039)	1.91 (220/11 530)	3.62 (66/1820)	0.66 (0.55–0.78), $P < 0.01$	0.35 (0.27–0.45), $P < 0.01$	0.53 (0.40–0.69), $P < 0.01$
Any myocardial infarction	1.14 (251/22 039)	1.76 (203/11 530)	2.22 (40/1820)	0.65 (0.54–0.78), $P < 0.01$	0.51 (0.37–0.71), $P < 0.01$	0.79 (0.57–1.11), $P = 0.17$
Target vessel myocardial infarction	0.92 (202/22 039)	1.19 (138/11 530)	1.64 (30/1820)	0.77 (0.62–0.95), $P = 0.02$	0.56 (0.38–0.82), $P < 0.01$	0.73 (0.49–1.08), $P = 0.11$
Any CD non-TVR	0.78 (171/22 039)	1.19 (137/11 530)	0.89 (16/1820)	0.65 (0.52–0.82), $P < 0.01$	0.87 (0.52–1.44), $P = 0.58$	1.32 (0.79–2.21), $P = 0.28$
Any CD TVR	2.08 (459/22 039)	3.07 (354/11 530)	3.45 (63/1820)	0.68 (0.59–0.78), $P < 0.01$	0.60 (0.47–0.78), $P < 0.01$	0.89 (0.68–1.16), $P = 0.38$
Any CD TLR	1.52 (336/22 039)	2.24 (258/11 530)	2.61 (47/1820)	0.68 (0.58–0.80), $P < 0.01$	0.58 (0.43–0.79), $P < 0.01$	0.86 (0.63–1.16), $P = 0.32$
Stent thrombosis	0.52 (115/22 039)	0.89 (102/11 530)	1.12 (20/1820)	0.59 (0.45–0.77), $P < 0.01$	0.47 (0.29–0.75), $P < 0.01$	0.80 (0.50–1.28), $P = 0.35$
BARC 3 or 5 bleeding	1.06 (233/22 039)	1.16 (134/11 530)	2.72 (50/1820)	0.91 (0.74–1.12), $P = 0.38$	0.39 (0.29–0.53), $P < 0.01$	0.43 (0.31–0.59), $P < 0.01$

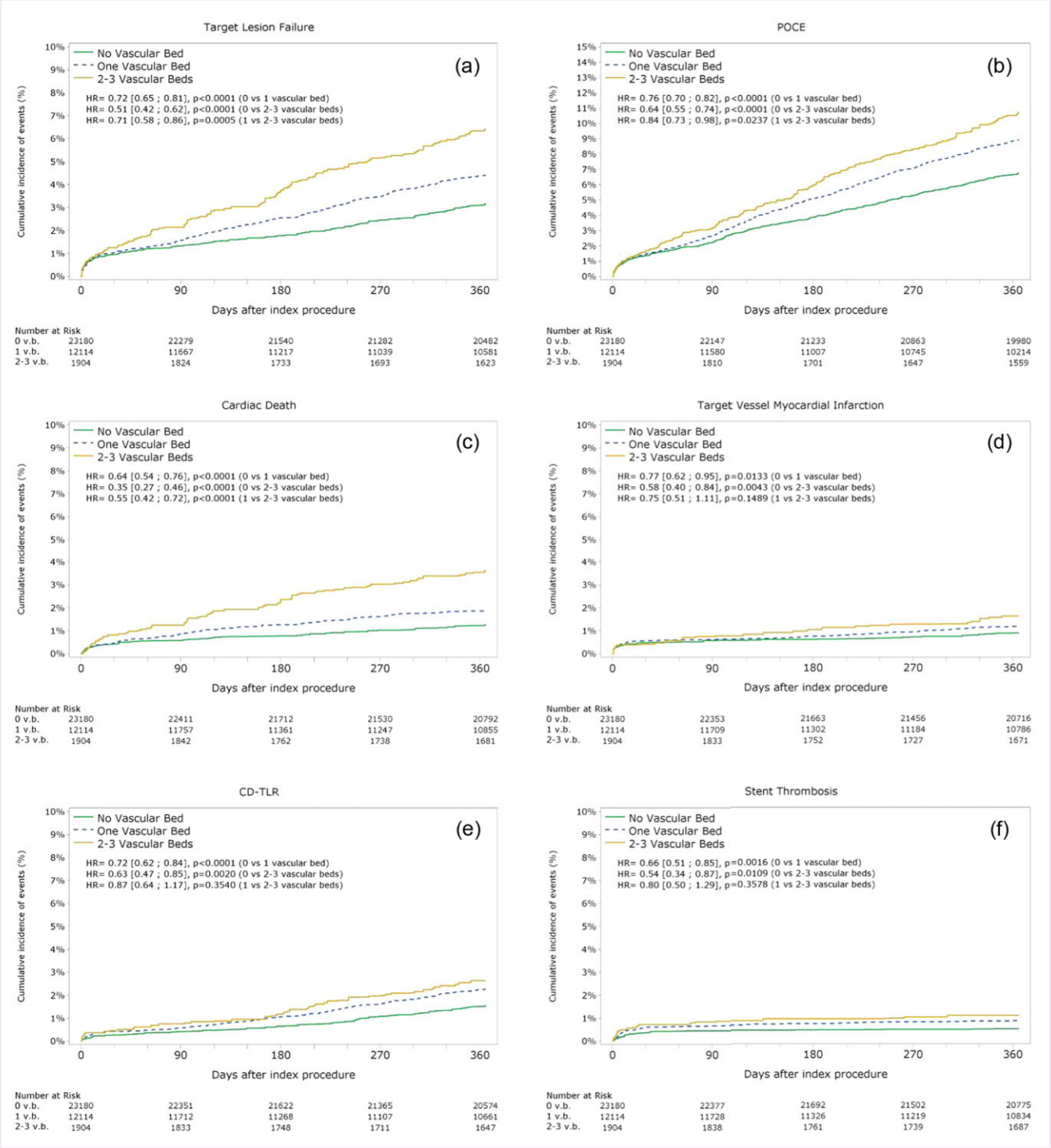


Figure 2 Cumulative event curves after inverse-propensity score weighting. Target lesion failure (a); patient-oriented composite outcome (POCE) (b); cardiac death (c); target vessel myocardial infarction (d); clinically driven target lesion revascularization (CD-TLR) (e); definite/probable stent thrombosis (f).

sis and inflammation that is present in patients with multisite artery disease.

The increased ischemic risk of patients with multisite artery disease led to more aggressive adjunct medical therapy in these patients. In a sub-analysis from the FOURIER trial,[28] PCSK9 inhibition with Evolocumab led to large absolute cardiovascular risk reductions in patients with multisite artery disease. In the COMPASS trial,[29] low-dose Rivaroxaban plus Aspirin led to better cardiovascular outcomes compared with Aspirin alone. The ESC guidelines[30] advocate longer-term dual antithrombotic regimes in patients with high ischemic risk, and multisite artery disease is one of the risk factors. However, in our study, in addition to the increased ischemic risk, we found an increased bleeding risk among patients with multisite artery disease, despite a lower rate of DAPT adherence at 1-year follow-up.

Multisite artery disease is currently not one of the high bleeding risk criteria,[31] but as we report a BARC type 3 or 5 bleeding rate of >3% at 1 year, it should be considered as a minor high-risk criterion. The combination of the increased ischemic and bleeding risks makes patients with multisite artery disease very challenging to manage. The choice of the appropriate post-PCI antithrombotic treatment should be carefully individualized. Furthermore, both clinicians and patients should be aware of this increased risk and incorporate the increased risk into their decision-making process before performing non-urgent procedures.

Strengths and limitations

As mentioned, our study is the largest contemporary prospective series to examine clinical outcomes of patients with single and multisite artery undergoing PCI with new-generation, thin strut DES. Our study included >37 000 patients with >37% prevalence of vascular disease, with pre-specified clinical outcomes and a very low rate of patients lost to follow-up.

Nevertheless, this study has some limitations. First, although we adjusted for demographics, comorbidities, and other baseline and procedural characteristics, we cannot exclude the presence of other potential confounders. Second, this is an observational study, and the procedural techniques as well as adjunct medical therapy were based on operator choice rather than defined per protocol. Third, a single type of DES was used, and our findings may not apply to other new-generation DES. Finally, we assessed the clinical impact of vascular disease, as defined by the patients' medical records. Accordingly, patients with an undiagnosed vascular disease were not classified appropriately, and this may have affected the results. The assessment of the presence of cerebrovascular disease did not take into account whether the origin was cerebral or cardiac, e.g. atrial arrhythmia.

Conclusion

In this real-world analysis, patients with known vascular disease experienced an increased risk for adverse cardiovascular, bleeding events, and mortality post-PCI with the use of new-generation thin strut DES. This risk is highest among patients with multisite artery disease.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Role of the funder/sponsor

The sponsor designed and executed the study, including data collection, management, and statistical analysis.

Conflict of interests:

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Authors' contributions

Drafting of the manuscript: O.K., M.S., and A.R.

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Data availability

Data are available upon reasonable request from the study sponsor.

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