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Unrestricted use of polymer-free sirolimus eluting stents in routine clinical practice

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Abstract

Stent designs with ultrathin struts may further increase the procedural success of challenging lesion subsets. The objective of this study was to assess the safety and efficacy of ultrathin strut, polymer-free sirolimus eluting stent (PF-SES) implantations in a large scale, unselected patient population.

Adult patients underwent percutaneous coronary interventions (PCI) with a thin-strut PF-SES. Data from two all-comers observational studies having the same protocol (ClinicalTrials.gov Identifiers: NCT02629575 and NCT02905214) were pooled. The accumulated target lesion revascularization (TLR) rate at 9-12 months was the primary endpoint. All dual antiplatelet therapy strategies according to the applicable guidelines were permissible.

In total, 7243 patients were prospectively enrolled for PCI with PF-SES in stable coronary artery disease or acute coronary syndrome (ACS). Major risk factors in the overall cohort were diabetes (37.3%), ST elevation myocardial infarction (18.1%) and non-ST myocardial infarction (24.6%). The follow-up rate was 88.6% in the overall population. The TLR rate in the overall cohort was 2.2% whereas definite/probable stent thrombosis (ST) occurred in 0.7%. In patients with in-stent restenosis lesions, the major adverse cardiac events rate was 6.4% whereas the corresponding rate for isolated left main coronary artery (LMCA) disease was highest with 6.7% followed by patients with culprit lesions in vein bypasses (VB, 7.1%). The mortality rate in patients treated in VB lesions was highest with 5.4%, followed by the isolated LMCA subgroup (3.4%) and ACS (2.6%).

PCI with PF-SES in an unselected patient population, is associated with low clinical event and ST rates. Furthermore, PF-SES angioplasty in niche indications demonstrated favorable safety and efficacy outcomes with high procedural success rates.

Abbreviations: ACS = acute coronary syndrome, BARC = bleeding academic research consortium, BP-BES = biodegradable biolimus stent, CABG = coronary artery bypass graft, CAD = coronary artery disease, cTr = cardiac troponin, DAPT = dual antiplatelet therapy, DCB = drug coated balloon, DES = drug eluting stent, DP-EES = durable polymer everolimus-eluting stent, GFR = glomerular filtration rate, ISR = in-stent restenosis, LMCA = left main coronary artery, MACE = major adverse cardiac events, MI = myocardial infarction, NSTEMI = non-ST elevation myocardial infarction, PCI = percutaneous coronary intervention, PF-SES = polymer-free sirolimus eluting stent, PS = propensity score, RCT = randomized controlled trial, ST = stent thrombosis, STEMI = ST elevation myocardial infarction, TLR = target lesion revascularization, VB = venous bypass.

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1. Introduction

Clinical safety and efficacy studies in all-comers or unselected patient populations are becoming a corner stone of evidence for latest generation drug eluting stents (DES). In a recent report by Yamaji et al[1] 2 groups of DES were compared using propensity score (PS) matching to reduce the bias originating from the clinical indications for biodegradable polymer sirolimus-eluting stents and durable polymer everolimus-eluting stents (DP-EES). In their PS matched cohorts, Yamaji and coworkers[1] did not find any difference in the composite primary endpoint (6.9% vs 8.0%, $P = .24$), which consisted of cardiac death, target vessel myocardial infarction (MI) and target lesion revascularization (TLR).

In the randomized SORT OUT VIII trial,[2] a biodegradable polymer everolimus-eluting stent (BP-EES) and a biodegradable biolimus stent (BP-BES) were studied. The primary endpoint was target lesion failure (TLF) consisting of cardiac death, all-cause MI and TLR at 12 months. Their study did also not reveal a difference in the primary endpoint between these two DES technologies (BP-EES: 4.0% vs. BP-BES 4.4%, $P_{\text{non-inferiority}} < .001$).

A polymer-free strut sirolimus-eluting stent (PF-SES)[3,4] with postulated rapid strut coverage[5] was investigated in an unselected patient population. To study the clinical performance of PF-SES in an unselected cohort, we pooled clinical data from 2 large all-comers populations (ClinicalTrials.gov Identifiers: NCT02629575 and NCT02905214) to increase statistical power for meaningful statistical analyses also required for smaller patient subgroups. "All-comers" was defined as the routine use of the device within its approved indications in setting of clinical routine.

Besides the assessment of the overall safety and efficacy in an unselected patient population, a secondary purpose of this report was also to determine the clinical results in in niche indications. These include PF-SES stenting in isolated left main coronary artery disease (LMCA), in-stent restenosis (ISR) and in VB.

2. Materials and methods

2.1. Study design

Patients in 82 European and Asian centers were prospectively enrolled in the international ISAR 2000 all-comers registry (ClinicalTrials.gov Identifier NCT02629575)[3,4] and the ISAR 2000 all-comers extended registry (ClinicalTrials.gov Identifier NCT02905214). Due to national reimbursement issues for percutaneous coronary interventions (PCI), a follow-up window with a timeframe of 9 to 12 months was permissible to accommodate for differences between their national health care systems. All relevant ethics committees approved the study protocol prior to patient recruitment.

2.2. End points and definitions

The primary end point was the accumulated TLR rate (TLR, coronary artery bypass grafting and Re-PCI). The rates of MI, all-cause death and major adverse cardiac events (MACE) consisting of TLR, MI and all-cause death were part of the secondary endpoints. The all-cause death rate was used to define MACE at 9 to 12 months while cardiac death was only defined during hospitalization. The definition of acute/subacute stent thromboses (ST) was based on the academic research consortium criteria[6] while bleeding events were defined according to the bleeding academic research consortium (BARC) classification.[7] Major bleeding episodes were collectively defined as BARC 3a-5. The criteria for renal insufficiency and mandatory dialysis were glomerular filtration rate (GFR) < 90 mL/min/1.73m^2 and a cut-off GFR rate < 15 mL/min/1.73 m^2 respectively. Severe tortuous vessels were defined by the angulation criterion of $>45°$. Criteria for MI were

(1) the 2-fold increase of the upper normal value with significant proportion of CK-MB,
(2) the rise or fall in cardiac troponin (cTr) concentration with at least one value above the 99th percentile upper reference limit or
(3) $>20\%$ rise in cTr.[8] For statistical analyses, events 'as reported by the site' were used and not adjudicated.

2.3. Centers and ethics approvals

Cardiac centers in 39 Asia (South Korea, Malaysia) and 43 Europe (Croatia, Czech Republic, France, Germany, Slovakia, Spain) took part in this study to prospectively enroll patients. Ethics approvals were obtained from relevant national and/or local ethics committees. For the French arm of this study, these non-interventional studies were approved by the Comité Consultative sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS dossier no. 14.613) and the Commission Nationale de l'informatique et des Libertés (CNIL, demande d'autorisation n°915019).

2.4. Materials

An ultrathin strut polymer-free sirolimus-eluting stent technology (PF-SES, Coroflex ISAR or Coroflex ISAR NEO, B.Braun Melsungen AG, Germany) was used in this pooled analysis. The PF-SES has a probucol-sirolimus coating on the abluminal stent side to mimic a polymer-based drug elution as previously described by Krackhardt et al.[3] PF-SES were implanted following each institution's guidelines and preferences.

2.5. Inclusion and exclusion criteria

Adult patients with both stable angina and objective proof of ischemia or patients with acute coronary syndrome (ACS) had to meet the requirements for PCI at the time the study was being conducted.[9] Stenting was allowed in de novo or restenotic lesions of single or multiple vessels with reference diameters from 2.0 to 4.0 mm.

2.6. Procedural approach

Radial or femoral vascular access were permitted with a recommended introducer sheath of at least 5 French in diameter. Pre-dilatation with a balloon catheter of the operators' preference

or the direct stenting approach could be chosen. Intravenous heparin (70 IU/kg) was given in all patients and supplemented as needed. According to the institutional preferences of the cardiac centers, platelet aggregation inhibitor loading was recommended but not mandatory.

2.7. Post-procedural medication

Various anti-platelet therapy regimens such as clopidogrel 75 mg/d, prasugrel 10 mg/d or ticagrelor 2 x 90 mg/d were permissible. Acetylsalicylic acid 100 to 325 mg/d was prescribed life long.

2.8. Data collection

An electronic data capture system[10,11] was employed with integrated plausibility checks during each stage of the data entry. These electronic captures included patient demographics, lesion morphological and procedural data, in-hospital clinical events as well as accumulated clinical event rates at the 9 to 12-month follow-up (clinical visit, phone interview). Each participating country had a national principal investigator who verified the accuracy of the dataset on a national level whenever routinely performed web based plausibility checks indicated discrepancies. Completeness of data was checked centrally at the inclusion and follow-up stages and dedicated study nurses were informed to complete missing data.

2.9. Statistical analysis

Dichotomous and categorical variables are described in counts and percentages and evaluated with the 2-sided Fisher exact test or the Chi^2 statistic whenever applicable. Means and standard deviations were used to describe continuous variables. They were compared with the unpaired *t* test or the Mann-Whitney *U* test in case the Shapiro-Wilk test revealed a strong deviation from a normal distribution. For more than 2 groups, one-way analysis of variance was used. The significance level α was 0.05 for all tests.

Despite the observational character of this pooled analysis, a pro-forma biometric estimate was conducted based on the pertinent literature with the predecessor PF-SES.[3] A non-inferiority design with assumed TLR rates of 3% in the control group, 2.5% in the treatment group, a non-inferiority margin of 1% with α=5% and a power of 80% requires 1866 analyzable patients. Given follow-up rate of 85%, a minimum of 2195 patients would have to be recruited. Category variables were defined based on continuous variables either according to the established definitions (section 2.2) or according to age decades (eg, octogenarians >80 years, ≤90 years).To study predictors for accumulated clinical events, Cox-regression analysis was conducted for the accumulated MACE rate for the entire cohort.

SPSS version 24.0 (IBM, Munich, Germany) was used for all statistical analyses and nQuery/nTerim V.2.0 (Statistical Solutions Ltd., Cork, Ireland) for biometric estimates.

3. Results

3.1. Baseline characteristics

Patients (n = 7243) were treated with PF-SES between November 2014 and December 2017. A flow chart of patient recruitment and follow-up adherence in CAD and ACS patients is provided in appendix 1. Cardiovascular risk factors (Table 1) were diabetes (37.3%), male gender (74.1%), ST elevation myocardial infarction (STEMI) (18.1%) and NSTEMI (24.6%).

Lesion morphologies and procedural details are provided in Table 1. Overall, there were 3.7% of patients treated for isolated LMCA, 3.2% for ISR, and 0.7% of patients had culprit lesions in VB.

Distributions of demographic factors across age decades are shown in Figure 1. As age progresses, the proportions of male gender decreases whereas those for diabetes and hypertension increase. Moreover, patients with STEMI are generally younger with about one third in the ≤40-year age group while in the octogenarian comparator group the STEMI rate is less than 13.7% (Fig. 1). Likewise, the rates for NSTEMI increase with age from 21.7% (>60, ≤70 years) to 41.7% (>90 years). The technical success rate to cross the culprit lesion was 98.5% (8969/9103 stents) with comparable outcomes for LMCA stenting (98.7%), ISR (98.7%) and VB (97.5%).

3.2. Co-medication

Peri-procedural drug therapy for all patients, stable coronary artery disease (CAD) and ACS patients are described in Table 2. There was also a considerable number of patients who received second generation P2Y12 receptor inhibitors (ticagrelor, prasugrel) for stable CAD (18.6%, 772/7243) whereas in case of ACS; ticagrelor was prescribed in 33.0%, and prasugrel in 14% in this patient group. The recommended duration of dual antiplatelet therapy (DAPT) was longer in ACS patients as compared to elective patients (9.9 ± 2.9 months vs 11.2 ± 2.4 months, $P < .001$, Table 3).

3.3. Clinical results

3.3.1. Overall cohort. There were 6420 patients (88.6%) available for follow-up (Table 4 and Appendix 1). Overall, the accumulated MACE rate was 4.4% and the TLR rate was 2.2% (Fig. 2, Table 4). The acute ST rate was 0.3% and 0.3% for late ST. Kaplan-Meier survival analysis revealed that the freedom from MACE curves were significantly different between elective and ACS patients (log-rank $P < .001$, Fig. 3).

3.3.2. Subgroups. The TLR rate was significantly higher in ACS patients as compared to elective patients (2.8% vs 1.7%, $P = .003$). Likewise, MACE, MI, and all-cause mortality rates were all significantly higher in ACS patients (Table 4). However, ST rates in both groups were not different (0.6% vs 0.8%, $P = .213$). There was also no difference in bleeding complications ($P = .065$) in spite of the numerically higher rates for major (0.6% vs 0.2%, $P = .347$) and significantly different rates of minor bleeding episodes (3.2% vs 2.3%, $P = .033$) in ACS patients.

A priori defined subgroups of patients with ISR, isolated LMCA and vein VB were also investigated. Figure 2 illustrates the clinical event rates in these subgroups. In patients with ISR lesions, the MACE rate was 6.4% (13/202) whereas the corresponding rate for LMCA was 6.7% (14/208). In patients with VB culprit lesions, the MACE rate was 7.1% (4/56). The mortality rate in patients treated in VB lesions was highest with 5.4% (3/56), followed by the LMCA subgroup (3.4%, 7/208) and ACS patients (2.6%, 71/2685). For LMCA disease the other individual MACE components (Fig. 2) were 5.3% (TLR), 1.0% (MI) and 1.4% (ST).

3.3.3. Extended follow-up. Due to local reimbursement requirements, a follow-up window of 9 to 12 months was requested by several European countries. Follow-up data with a

Table 1

Patient demographics, lesion characteristics, and procedural data.

Variable	All patients	Stable CAD	ACS	*P*-value stable CAD vs ACS
Number of patients	7243	4148	3095	-
Number of lesions	8305	4829	3476	-
Number of DES used	9103	5373	3730	-
Age, yr	66.4 ± 11.3	67.2 ± 10.5	65.2 ± 12.2	<.001
Male gender	5365 (74.1%)	3045 (73.4%)	2320 (75.0%)	.136
Diabetes	2700 (37.3%)	1646 (39.7%)	1054 (34.1%)	<.001
Hypertension	5027 (69.4%)	3030 (73.0%)	1997 (64.5%)	<.001
Renal insufficiency	455 (6.3%)	273 (6.6%)	182 (5.9%)	.224
Dialysis dependence	87 (1.2%)	68 (1.6%)	19 (0.6%)	<.001
STEMI	1311 (18.1%)	0 (0.0%)	1311 (42.4%)	-
NSTEMI	1784 (24.6%)	0 (0.0%)	1784 (57.6%)	-
Region				
Europe	5600 (77.3%)	3078 (74.2%)	2522 (81.5%)	<.001
Asia	1643 (22.7%)	1071 (25.8%)	572 (18.5%)	
Target vessel				
LAD	3571 (43.0%)	2037 (42.2%)	1534 (44.1%)	.007
CX	2134 (25.7%)	1307 (27.1%)	827 (23.8%)	
RCA	2539 (30.6%)	1447 (30.0%)	1092 (31.4%)	
graft	61 (0.7%)	38 (0.8%)	23 (0.7%)	
Thrombotic occlusion	1099 (13.2%)	301 (6.2%)	798 (23.0%)	<.001
Chronic total occlusion	248 (3.0%)	182 (3.8%)	66 (1.9%)	<.001
Thrombus burden	1017 (12.2%)	150 (3.1%)	867 (24.9%)	<.001
Diffuse vessel disease	3270 (39.4%)	1921 (39.8%)	1349 (38.8%)	.371
Calcification	2358 (28.4%)	1375 (28.5%)	983 (28.3%)	.846
Ostial lesion	667 (8.0%)	399 (8.3%)	268 (7.7%)	.361
Bifurcations	1188 (14.3%)	672 (13.9%)	516 (14.8%)	.233
Severe tortuosity	800 (9.6%)	463 (9.6%)	337 (9.7%)	.870
Left main coronary arteries	271 (3.7%)	146 (3.5%)	125 (4.0%)	.250
In-stent restenosis	253 (3.0%)	170 (3.5%)	83 (2.4%)	.003
Saphenous vein graft	61 (0.7%)	38 (0.8%)	23 (0.7%)	.992
AHA/ACC type B2/C lesion	4415 (53.2%)	2484 (51.4%)	1931 (55.6%)	<.001
Reference diameter (mm)	2.86 ± 0.50	2.85 ± 0.48	2.88 ± 0.53	.010
Lesion length	18.5 ± 9.2	18.5 ± 9.7	18.5 ± 8.6	.932
Degree of stenosis (%)	86.3 ± 11.6	84.8 ± 11.1	89.5 ± 11.5	<.001
Predilation	5609 (67.5%)	3203 (66.3%)	2406 (69.2%)	.006
DESs used	9103	5373	3730	-
Multi-vessel PCI				
1-vessel	6761 (93.3%)	3881 (93.5%)	2880 (93.1%)	.742
2-vessel	448 (6.2%)	250 (6.0%)	198 (6.4%)	
3-vessel	37 (0.5%)	20 (0.5%)	17 (0.5%)	
DES per patient	1.26 ± 0.64	1.27 ± 0.66	1.24 ± 0.61	.125
DES diameter (mm)	2.86 ± 0.50	2.84 ± 0.47	2.86 ± 0.53	.027
DES length (mm)	20.9 ± 8.2	20.9 ± 8.5	20.8 ± 7.6	.976
DES inflation pressure (atm)	14.4 ± 2.9	14.3 ± 2.9	14.6 ± 2.8	<.001
Final result % stenosis	1.5 ± 6.1	1.5 ± 5.8	1.4 ± 6.4	.644
Overall technical success per stent	8969 (98.5%)	5301 (98.7%)	3668 (98.3%)	.209

ACS = acute coronary syndrome, CAD = coronary artery disease, CX = circumflex, DES = drug-eluting stent, LAD = left anterior descending, NSTEMI = Non-ST-elevation myocardial infarction, RCA = right coronary artery, STEMI = ST-elevation myocardial infarction.

duration ≥12 months were analyzed to better respond to the documentation needs for selected countries. There was a total of 555 patients with a follow-up duration (≥12 months) of 13.3 ± 2.1 months. The corresponding TLR rate in the longer follow-up group was 1.6% (9/555) vs 2.3% (132/5865) in the patient group with the shorter follow-up ($P = .334$). Further analyses revealed that the accumulated MACE (4.0% vs 4.4%, $P = .619$) and MI rates (2.2% vs 1.4%, $P = .172$) were not different. In the longer follow-up cohort, the accumulated mortality rate was lower (0.5% vs 1.7%, $P = .039$), however, there was no difference in the accumulated rates for definite/probably stent thrombosis (0.7% vs 0.7%, $P = .878$).

3.3.4. Predictors for accumulated MACE. To study predictors for accumulated MACE events, we conducted a Cox regression analysis for various cardiovascular risk factors, lesion and device related attributes as well as the DAPT duration (Fig. 4). Age ($P < .001$), diabetes ($P_{Cox} = .009$), ACS ($P < .001$), ISR ($P = .024$) and vessel diameter ($P = .007$) were predictors for MACE. In contrast, MACE was not predicted by gender ($P = .246$), hypertension ($P = .166$), B2/C lesion type ($P = .156$), presence of left main CAD ($P = .083$), stenting in vein grafts ($P = .296$) or by long lesions ($P = .102$). In addition, large stent diameters (4.0 mm) or long stents (>30 mm) are no predictors for accumulated MACE.

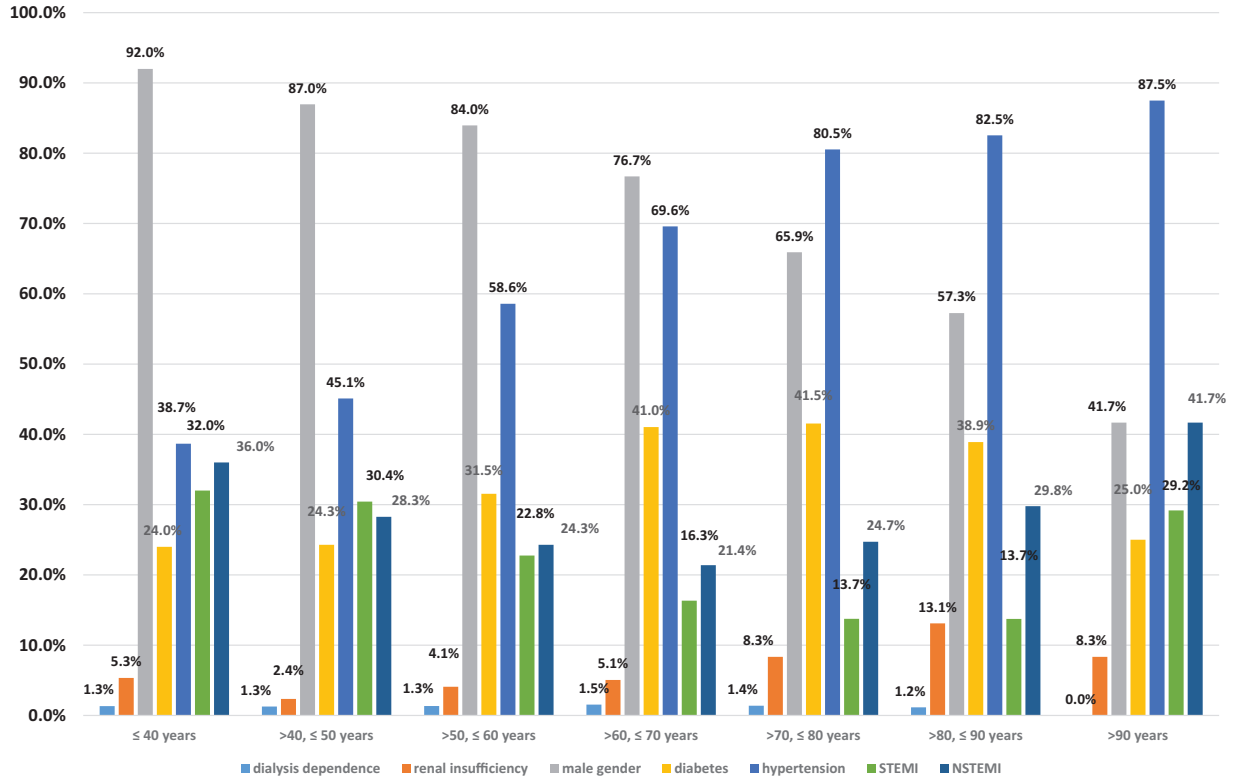

Figure 1. Study group demographics across age decades.

4. Discussion

Within the framework of observational statistics, we observed MACE rates ranging from 3.0% in elective patients to 6.7% in patients with isolated LMCA. Moreover, our analyses revealed that in the studied niche indications, the clinical event rates are acceptably low as compared to those reported in the relevant literature. In the entire cohort, we report a MACE rate of 4.4% mostly driven by TLR (2.2%). Other studies conducted under

Table 2

Peri-procedural drug therapy.

Drug type		Drug	all patients	stable CAD	ACS	*P*-value stable CAD vs ACS
Pre PCI	antiplatelet therapy	clopidogrel	3730 (51.5%)	2361 (56.9%)	1371 (44.3%)	<.001
		ticagrelor	1095 (15.1%)	367 (8.8%)	728 (23.5%)	
		prasugrel	524 (7.2%)	199 (4.8%)	325 (10.5%)	
		aspirin only	603 (8.3%)	363 (8.7%)	240 (7.8%)	
		Other (ticlopidine, GP IIb/IIIa)	30 (0.4%)	14 (0.3%)	16 (0.5%)	
		no preloading	1262 (17.4%)	847 (20.4%)	415 (13.4%)	
Post PCI	antiplatelet therapy	clopidogrel	4776 (65.9%)	3227 (77.7%)	1549 (50.0%)	<.001
		ticagrelor	1624 (22.4%)	604 (14.6%)	1020 (33.0%)	
		prasugrel	600 (8.3%)	168 (4.0%)	432 (14.0%)	
		aspirin only	41 (0.6%)	25 (0.6%)	16 (0.5%)	
		other	8 (0.1%)	2 (0.1%)	6 (0.2%)	
		unknown*	197 (2.7%)	125 (3.0%)	72 (2.3%)	
DAPT		DAPT interruption	645 (10.0%)	305 (8.2%)	340 (12.7%)	<.001
		No DAPT interruption	5414 (84.3%)	3171 (84.8%)	2243 (83.5%)	
		unknown	364 (5.7%	262 (7.0%)	102 (3.8%)	
		DAPT interruption ≤6 months	175 (27.1%)	121 (39.7%)	54 (15.9%)	<.001
		DAPT interruption >6 months	470 (72.9%)	184 (60.3%)	286 (84.1%)	
Triple therapy		DAPT + vitamin K antagonist or NOAC	103 (1.4%)	66 (1.6%)	37 (1.2%)	.157

ACS = acute coronary syndrome, CAD = coronary artery disease, DAPT = dual antiplatelet therapy.
* the DAPT length in these patients could not be confirmed at the time of the follow-up, NOAC = novel oral anticoagulant.

Table 3

Recommended duration of dual antiplatelet therapy during follow-up.

Variable	all patients	stable CAD	ACS	*P*-value stable CAD vs ACS
Number of patients	7243	4148	3095	-
DAPT duration in mo	10.5±2.7	9.9±2.9	11.2±2.4	<.001
1 mo	57 (0.8%)	28 (0.7%)	29 (1.0%)	<.001
1-3 mo	73 (1.1%)	54 (1.4%)	19 (0.7%)	
3 mo - 6 mo	20 (0.3%)	15 (0.4%)	5 (0.2%)	
6 mo	893 (13.9%)	727 (19.4%)	166 (6.2%)	
>6 mo-12 mo	602 (9.4%)	417 (11.2%)	185 (6.9%)	
12 mo	3818 (59.4%)	1865 (49.9%)	1953 (72.7%)	
Unknown status*	964 (15.0%)	633 (16.9%)	331 (12.3%)	

ACS = acute coronary syndrome, CAD = coronary artery disease, DAPT = dual antiplatelet therapy.
* the DAPT length in these patients could not be confirmed at the time of the follow-up.

clinical routine revealed similar rates. Tadano et al[12] investigated bioresorbable polymer sirolimus-eluting stent in a "real-world" cohort comprising of 1,727 patients with similar cardiovascular risk factors. Their MACE and TLR rates of 5.2% and 2.4% respectively agree well with our outcomes.

4.1. Clinical routine vs. selected patient trials

In spite of the commonly known challenge of clinical event underreporting in so called all-"comers populations", it seems important to briefly discuss a potential source of bias as pointed out by Hicks and Temple.[13] In their editorial, they discussed that MI, as part of most composite endpoints, might not always be well defined. Our definition of MI was based on the relevant European Society of Cardiology (ESC) recommendations.[8] We did not detect differences in the rates of peri-procedural MI in any particular region. This enables the conduct of global observational studies, especially in light of increased scrutiny of regulatory agencies. Furthermore, the introduction of the European Medical Device Regulation (MDR) in May 2020 do require these all-comers data to document the safety, efficacy and usability of DES in real-world clinical use.

4.2. LMCA in clinical routine

PCI in patients with isolated LMCA is a high-risk procedure due to a large volume of the myocardium at risk.[14,15] Tanaka et al[16] conducted a retrospective study in all-comers patients who were treated with coronary artery bypass graft (CABG) or DES. They found that fewer patients reached the composite endpoint comprising of death, MI and stroke in the DES group less frequently as those treated with bypass surgery (6.9% vs

Table 4

Clinical outcomes.

Variable	all patients	stable CAD	ACS	*P*-value stable CAD vs ACS
Number of patients	7243	4148	3095	-
Patients with clinical long term follow-up or early event	6420 (88.6%)	3738 (90.1%)	2685 (86.8%)	<.001
Follow-up time, mo	9.4±2.1	9.3±2.1	9.4±2.1	<.001
Time to discharge, d	4.6±21.5	3.6±18.9	5.9±24.6	<.001
In-hospital MACE	103 (1.6%)	26 (0.7%)	77 (2.9%)	<.001
In-hospital TLR	60 (0.9%)	15 (0.4%)	45 (1.7%)	<.001
Re-PCI	46 (0.7%)	10 (0.3%)	36 (1.3%)	<.001
CABG	14 (0.2%)	5 (0.1%)	9 (0.3%)	.088
In-hospital MI	44 (0.7%)	10 (0.3%)	34 (1.3%)	<.001
In-hospital cardiac death	47 (0.7%)	10 (0.3%)	37 (1.4%)	<.001
Accumulated MACE	**280 (4.4%)**	**111 (3.0%)**	**169 (6.3%)**	**<.001**
Accumulated TLR	141 (2.2%)	65 (1.7%)	76 (2.8%)	.003
Re-PCI	128 (2.0%)	57 (1.5%)	71 (2.6%)	.002
CABG	26 (0.4%)	10 (0.3%)	16 (0.6%)	.041
Accumulated MI	95 (1.5%)	27 (0.7%)	68 (2.5%)	<.001
Accumulated death all causes	102 (1.6%)	31 (0.8%)	71 (2.6%)	<.001
Accumulated definite/probable stent thrombosis	43 (0.7%)	21 (0.6%)	22 (0.8%)	.213
Acute stent thrombosis, ≤24	19 (0.3%)	8 (0.2%)	11 (0.4%)	.097
Subacute stent thrombosis,1–30 d	3 (>0.1%)	0 (0.0%)	3 (0.1%)	
Late stent thrombosis, ≥30 d	21 (0.3%)	13 (0.3%)	8 (0.3%)	
Bleeding complications				
Minor*	173 (1.6%)	87 (2.3%)	86 (3.2%)	.065
Major†	32 (0.5%)	16 (0.2%)	16 (0.6%)	

ACS = acute coronary syndrome, CABG = coronary artery bypass grafting, CAD = coronary artery disease, MACE = major adverse cardiac events, Re-PCI = repeated percutaneous coronary intervention, TLR = target lesion revascularization.
* minor bleeding episodes 2.3% vs 3.2% (P = .033).
† major bleeding episodes 0.4% vs 0.6% (P = .347).

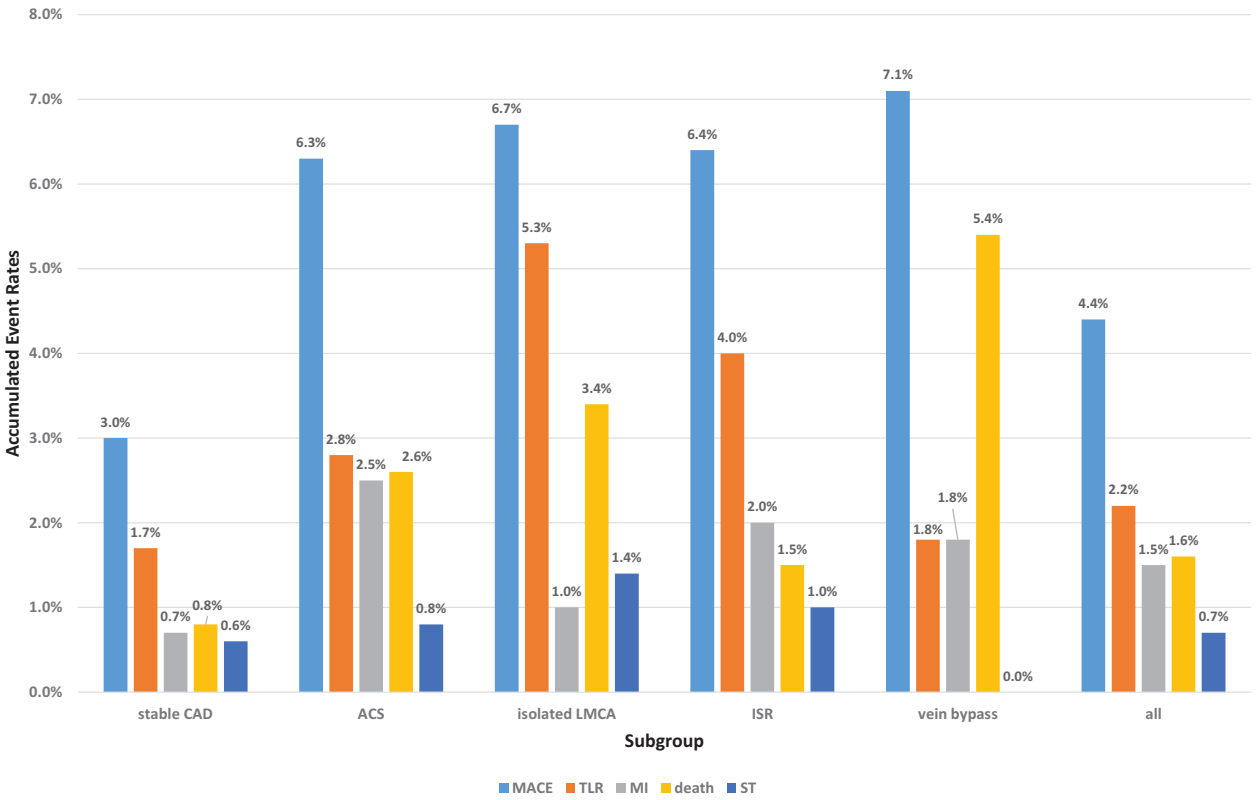

Figure 2. Accumulated clinical event rates in stable CAD, ACS, isolated left main coronary artery (LMCA), in-stent restenosis (ISR) and vein bypasses (VB).

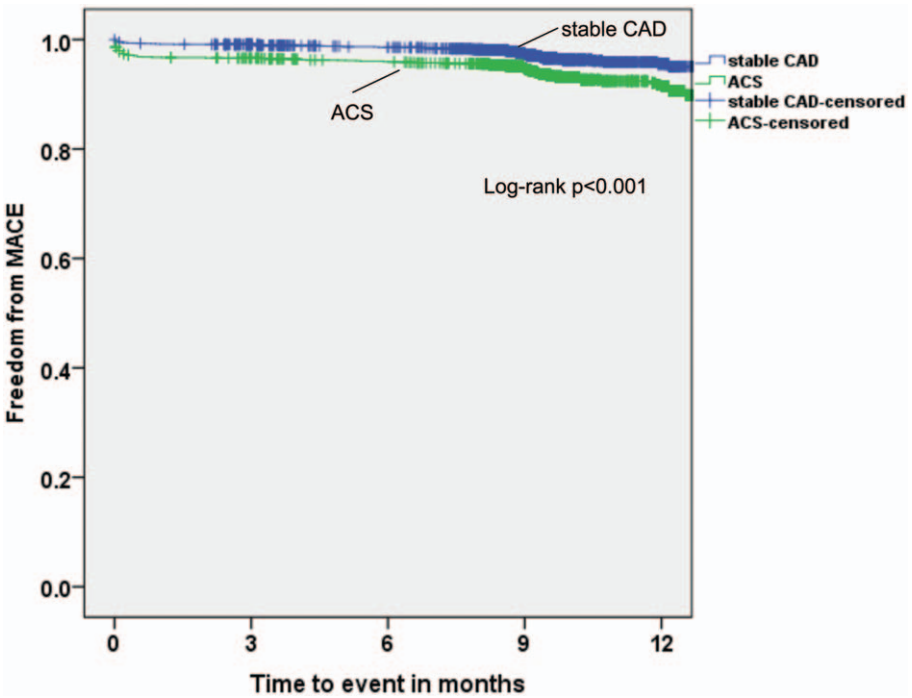

Figure 3. Kaplan-Meier curves for freedom from accumulated MACE in stable CAD and ACS patients. ACS = acute coronary syndrome, CAD = coronary artery disease, MACE = major adverse cardiac events.

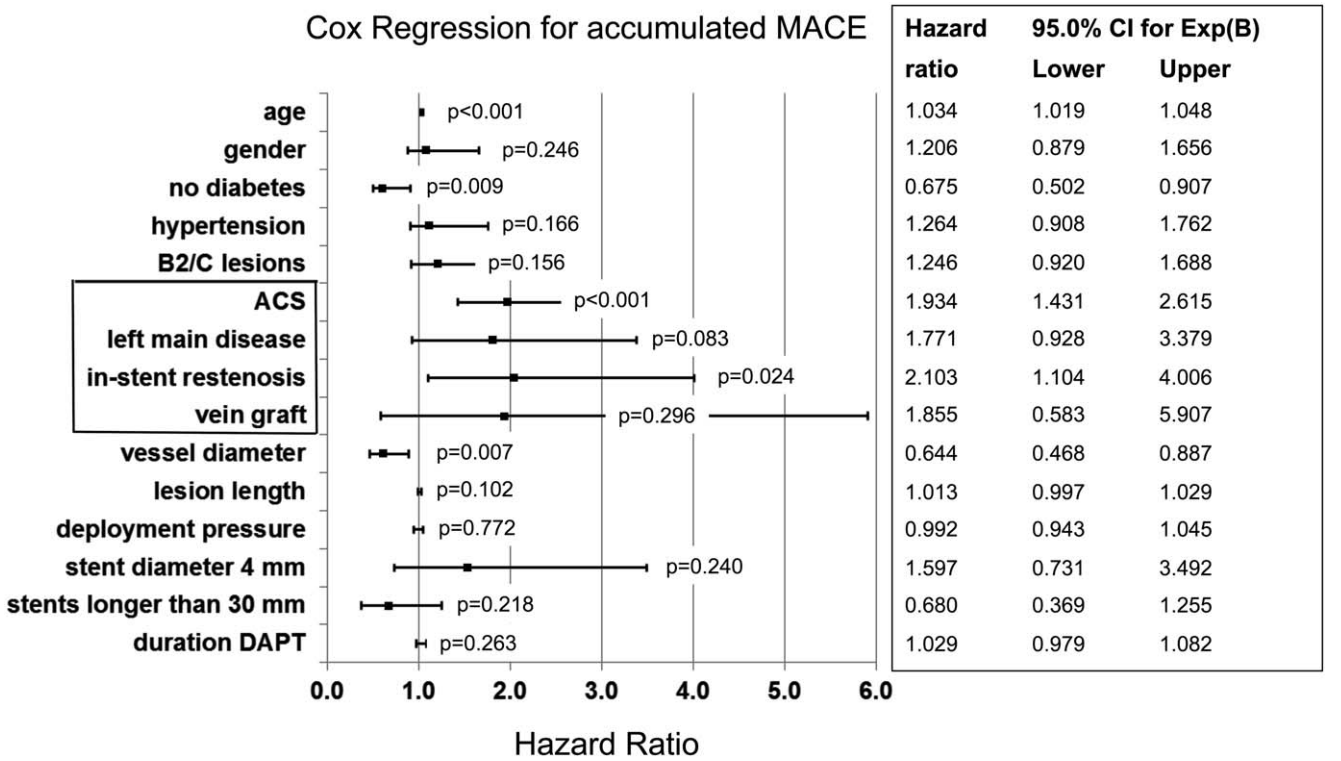

Figure 4. Cox-regression for accumulated MACE. MACE = major adverse cardiac events.

10.7%). A comparison of their 6.9% composite endpoint rate (not including TLR) is difficult since in our series we observed a 6.7% MACE rate, without the inclusion of stroke.

In the recently published Interventional Cardiology Research Incorporation Society-Drug-Eluting-Stents-Left MAIN Revascularisation study, Yoon et al. and coworkers[17] retrospectively compared the clinical outcomes of patients with LMCA, who were either treated with CABG or PCI in terms of major adverse cardiac and cardiovascular events (MACE and stroke). They concluded that PCI with improved stent technologies in the observed treatment periods (1995–2002, 2003–2006 and 2007–2014) have narrowed the gap to the gold standard CABG for this lesion subset. Of course, this statement has 2 ramifications, that is, these improvements hinged on progressing procedural learning curves and/or safer/more effective devices to treat this high-risk patient group. Patients treated with PF-SES had a mortality rate of 3.4% in our series which appears reasonably low and agree with the findings by Andrade et al[18] who reported a 12-month mortality of 3.0 to 3.7%. However, there are also reports on real-world patients with multivessel CAD including LMCA which fared better with CABG in terms of all-cause mortality.[19] One drawback of our subgroup analysis is the limitation to isolated LMCA; a completely documented SYNTAX score would also have been highly desirable for an enhanced patient selection.

De Rosa et al[20] conducted a meta-analysis to investigate composite clinical endpoint (MACE + stroke) on the long-term outcomes of CABG and stenting in unprotected LMCA which did not reveal any differences between these 2 treatment modalities. Moreover, they found that CABG performed better than stenting in diabetics and in females while PCI fared better in older patients. In our series, increased MACE rates in patients with LMCA could not be explained by gender or diabetes. Only older age was a predictor for MACE in our subgroup. However, due to the small subgroup for this type of analysis, we could not explain sufficient variability in our data (Nagekerke R Squared < 10%). Hence, our finding must be judged with caution.

4.3. ISR

The primary focus of recently conducted clinical research for the treatment of ISR has been the head-to-head comparison of drug coated balloon (DCB) angioplasty and DP-EES. If we consider the latest randomized controlled trials (RCTs) for this lesion subset, the Drug eluting Balloon for In-Stent Restenosis (DARE)[21] and Restenosis Intra-Stent of Drug Eluting Stents: Drug Eluting Balloon versus Everolimus-Eluting Stent (RIBS) IV[22] trials represent the current cornerstones of debate. While both studies use almost identical in- and exclusion criteria, their choice in different primary endpoints and lesion preparation may serve as a potential explanation why the DARE trial revealed superiority for DCB angioplasty and why the RIBS IV trial showed better outcomes for DP-EES. The convincing argument of not adding another stent layer to the ISR, operators' preference to use a DES in a double or multilayer stent implantation procedure appears very reasonable. However, the real-word use of DES in ISR may not be underestimated and, unfortunately for the DCB advocates, both strategies were given a class I recommendation by the ESC in its most recent version. Our clinical event rates for patients with ISR were 6.4% (MACE) and 4.0% (TLR) which are quite reasonable. These low rates may have been favored by the fact that a substantial number of patients were treated for ISR in BMS, which can be judged as a more benign form of ISR compared to ISR in DES.[10]

4.4. Vein grafts

There is considerable debate whether the use of DES in this niche indication carries any benefit. Garg et al[23] concluded from their meta-analysis that the evidence to use DES instead of BMS is not convincing enough since the corresponding rates for death, MI and TLR were not significantly lower as compared to stenting with BMS. The argument introduced by Hall and Brilakis[24] that DES may not even be as cost-effective as BMS due to higher device costs does not hold true in most European countries since DES pricing for example, in Germany is on a much lower level as compared to the US. DES price differences as compared to BMS are quite low as compared to the US scenario. Shah and coworkers[25] reported that in their meta-analysis there were lower rates for MACE and TLR in patients treated with DES as compared to those receiving BMS whereas there were no differences in terms of mortality and MI. In the randomized DIVA trial,[26] DES were compared to BMS to treat lesions in saphenous vein grafts. They reported no differences in their primary endpoint target vessel failure (DES: 17% vs BMS: 19%, $P=.70$) or all-cause mortality (DES: 6% vs BMS: 5%, $P=.63$). Compared to our results, we reported a MACE rate of 7.1%, which is on a lower level to their corresponding target vessel failure rate of 17%. However, their 12-month all-cause mortality rates of 5% (BMS) and 6% (DES) agree well with our accumulated mortality rate of 5.4%. However, these comparisons of clinical event rates between RCT's and observational are associated with considerable bias and must be done with caution.

4.5. DAPT interruption, bleeding events and procedural success rates

We report a DAPT interruption rate of 2.5% at 6 months for patients with stable CAD (Table 3), which is in the in the same range as those rates reported at 30 days in the PARIS registry.[26] A comparison between our study and the PARIS registry for ACS patients seems more straightforward. Our DAPT discontinuation (<12 months) amounted to 15.0% which is about twice as high as the corresponding rate reported by Moalem et al of 6.5%.[27] The documented bleeding episodes (Table 4) in our study were 3.8% in ACS and 2.5% in stable CAD patients. These seem low, however, they should be judged with caution due to potential event underreporting in observational studies.

The use of the device in this study is associated with high procedural success rates ranging from 98.5% to 98.7% range for stenting in difficult to treat lesions. In VB, the rate is slightly lower (97.5%) which may also be explained with the more challenging guiding catheter backup in this lesion subset.

4.6. Limitations

There is always data granularity in terms of patient demographics, lesion morphologies, event underreporting and real-world DAPT modifications during follow-up. In addition, the follow-up duration was despite the defined time window of 9 to 12 months quite heterogeneous with 9.4 ± 2.1 months in the overall cohort. Moreover, there was a considerable number of patients (Tables 2 and 3) with unconfirmed use of P2Y12 receptor inhibitors (clopidogrel, ticagrelor, prasugrel) and their corresponding DAPT duration. Hence, the clinical benefit of 1 particular DAPT regimen could not be assessed in this cohort. The overall follow-up rate was >88% and one could reasonably suspect that underreporting occurred equally in all patient subgroups. Since this assessment is descriptive in nature, potential confounders and bias introducing factors were not studied in detail.

A limitation of this study is that overlap between niche indications occurred. Patients who had for example, an IST in a vein graft were reported in both groups.

5. Conclusions

The use of PF-SES based on a latest generation thin-strut CoCr backbone was safe and effective in an unselected patient population with low rates of MACE and TLR in European and Asian health care settings. Despite MACE rates being higher in patients with ACS and isolated LMCA, ISR, and VB as compared to elective patients, PF-SES angioplasty remains an acceptable option for these niche indications.

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Appendix 1: Study flow chart with follow-up adherence in stable coronary artery disease (CAD) and acute coronary syndrome (ACS) patients.

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