Polymer-free sirolimus-eluting stents in a large-scale all-comers population

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ABSTRACT

Objective The objective of this study was to assess the safety and efficacy of a polymer-free sirolimus coated, ultrathin strut drug-eluting stent (PF-SES) in an unselected patient population with a focus on acute coronary syndrome (ACS). Furthermore, stable coronary artery disease (CAD) with short (<6 months) versus long (>6 months) dual antiplatelet therapy (DAPT) were also studied.

Methods Patients who received PF-SES were investigated in an unselected large-scale international, single-armed, multicenter, ‘all comers’ observational study. The primary endpoint was the 9-month target lesion revascularisation (TLR) rate, whereas secondary endpoints included the 9-month major adverse cardiac events (MACE) and procedural success rates. A priori defined subgroups such as patients with ACS, diabetes, lesion subsets and procedural characteristics relative to DAPT were investigated.

Results A total of 2877 patients of whom 1084 had ACS were treated with PF-SES (1.31±0.75 stents per patient). At 9 months, the accumulated overall TLR rate was 2.3% (58/2513). There was no significant difference between ACS and stable CAD (2.6% vs 2.1%, p=0.389). However, the overall MACE rate was 4.3% (108/2513) with a higher rate in patients with ACS when compared with the stable CAD subgroup (6.1% vs 3.2%, 50/1566, p<0.001).

Conclusions PF-SES angioplasty is safe and effective in the daily clinical routine with low rates of TLR and MACE in an unselected patient population. Our data are in agreement with prior clinical findings that extended DAPT duration beyond 6 months do not improve clinical outcomes in patients with stable CAD (ClinicalTrials.gov Identifier NCT02629575).

Trial registration number NCT02629575.

INTRODUCTION

Drug-eluting stents (DES) have greatly reduced the need for repeat revascularisation despite studies revealing that first-generation DES were associated with stent thrombosis (ST) rates that were less favourable when compared with bare-metal stents.1

The theoretical advantage of new coating technologies such as bioabsorbable polymers or non-polymer coating and the potential patient benefit of a shortened dual-antiplatelet therapy (DAPT) may herald a new milestone in DES development. This, in turn, may enable patients to undergo other non-coronary treatments with a reduced risk of bleeding.

Currently, there are polarised opinions regarding the length of DAPT which range from an extended DAPT duration beyond 12 months with more favourable long-term...
clinical outcomes³ to a greatly shortened DAPT duration.³
The polymer-free matrix of the investigational device in
this large-scale study consists of sirolimus and its matrix
builder probucol which was initially studied in the ISAR-
TEST 5 trial comparing a polymer-free sirolimus-eluting
stent (PF-SES) to a zotarolimus-eluting stent (ZES)⁴ with
similar safety and efficacy. The objective of the study was to assess the safety
and efficacy of PF-SES for the treatment of ‘real-world’
de novo and restenotic lesions in native coronary arteries
and coronary bypass grafts.

METHODS
End points and definitions
The international ISAR 2000 all-comers registry (ClinicalTrials.gov Identifier NCT02629575) prospectively
enrolled patients in Europe and Asia. The study protocol
was approved by all relevant ethics committees prior to
patient recruitment. The primary endpoint was the 9-month target lesion revascularisation (TLR) rate,
whereas secondary endpoints were the 9-month major
adverse cardiac events (MACE) rate, the in-hospital
MACE rate and the corresponding rates of myocardial
infarction (MI) and TLR (coronary artery bypass grafting
and re-PCI (percutaneous coronary intervention). Cardiac death was only defined inhospital, whereas the
all-cause death rate was used to define MACE at 9 months
(MI, TLR, inhospital cardiac death and all deaths post
discharge). The Academic Research Consortium (ARC)
criteria⁵ were used to define acute/subacute stent thrombosis.
Renal insufficiency was defined with a glomerular filtra-
tion rate (GFR) of <90mL/min/1.73m² with a cut-off
GFR rate for mandatory dialysis of <15mL/min/1.73m². Severe
tortuosity had to meet the angulation criterion of >45°.

Centres
Patients were prospectively enrolled in 26 Asian (South
Korea and Malaysia) and 36 European (Czech Republic,
France, Germany, Slovakia and Spain) cardiac centres
(see online supplementary appendix I).

MATERIALS
PF-SES (Coroflex ISAR, B. Braun Melsungen,
Melsungen,%20AG,%20Germany) were implanted
according to each institution’s guidelines and in
accordance with proper indications for national reim-
bursement. Briefly, the bare-metal backbone of the
PF-SES has been investigated previously by Leschke et
al,⁶ whereas the sirolimus matrix coating was extensively
studied in the ISAR-TEST 5 trial⁴ with very favourable
clinical outcomes up to 5years² and in various subgroups
such as patients with STElevation myocardial infarction⁴ and
diabetics.³ The polymer-free stent platform consists of
a premounted, thin strut (50/60 µm) cobalt–chrom-
imium stent whose abluminal surface only is sandblasted
to permit a microporous surface for the polymer-free
matrix consisting of sirolimus and probucol. The concen-
tration of sirolimus is 1.2 µg/mm² on the abluminal stent
surface only. Sirolimus is the active antiproliferative drug,
and probucol is an excipient controlling the release of
the drug. Probucol mimics the function of a polymer by
retarding the release of sirolimus. Non-clinical testing
showed that traces of sirolimus or probucol can be
detected beyond 8 weeks. Different from drug-coated
polymer-free stents without an excipient, the release of
sirolimus over time is comparable to polymer-coated DES.
This matrix coating concept has been evaluated in the
aforementioned clinical trials on a different stent plat-
form (Yukon stent, Translumina, Hechingen, Germany). Non-inferiority of the polymer-free sirolimus–probucol
coated stent has been demonstrated in comparison to the
ZES.⁴⁶⁻⁹ The device is available in lengths of 8–32 mm
and has a crossing profile (0.79–0.93 mm).

Inclusion and exclusion criteria
Patients ≥18 years of age with stable angina or objec-
tive proof of ischaemia or patients with acute coronary
syndrome (ACS) had to meet the requirements forPCI.¹⁰
Single or multiple vessel stenting was allowed in de novo
or restenotic lesions with reference diameters from 2.0
to 4.0 mm.

Procedural approach
Femoral or radial vascular access was permitted with
recommended introducer sheaths of at least 5 Fr in diam-
er. Moreover, operators could predilate with a balloon
catheter of their preference or chose direct stenting at
their discretion. Intravenous heparin (70 IU/kg) was
given to all patients and supplemented when required. If
possible platelet aggregation inhibitor loading was
recommended prior to the procedure according to the
institutional preferences of the cardiac centre.

Postprocedural medication
Due to the international characteristic of this study, it was
permissible to use various antiplatelet inhibition agents
(≥6 months) such as clopidogrel 75 mg/day, prasugrel
10 mg/day or ticagrelor 2×90 mg/day as recommended
by the treating physician while acetylsalicylic acid
100–325 mg/day was prescribed life long.

Data collection
A dedicated and established electronic data capture
system was used, which immediately informed the inves-
tigator of data quality issues. This database was used in
prior large-scale unselected patient cohorts.⁶¹¹ The accu-
ricacy of the data sets on a national level was verified by the
national principal investigators in each country when the
routinely performed web-based plausibility checks indi-
cated discrepancies.

Statistical analysis
For all tests, the significance level α was 0.05. The two-sided
Fisher’s exact test or the χ² statistic was used whenever

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Table 1 Patient demographics

| Variable                        | All patients | Stable CAD | ACS       | p Value Stable CAD vs ACS |
|--------------------------------|--------------|------------|-----------|---------------------------|
| No of patients                 | 2877         | 1793       | 1084      | –                         |
| No of lesions                  | 3254         | 2031       | 1223      | –                         |
| No of DES used                 | 3858         | 2453       | 1405      | –                         |
| Age (years)                    | 66.9±11.2    | 67.9±10.2  | 65.2±12.5 | <0.001                    |
| Male gender, n (%)             | 2126 (73.9)  | 1311 (73.1)| 815 (75.2)| 0.221                     |
| Diabetes, n (%)                | 1090 (37.9)  | 708 (39.5) | 382 (35.2)| 0.023                     |
| Hypertension, n (%)            | 2107 (73.2)  | 1362 (76.0)| 745 (68.7)| <0.001                    |
| Renal insufficiency, n (%)     | 161 (5.6)    | 108 (6.0)  | 53 (4.9)  | 0.200                     |
| Dialysis dependence, n (%)     | 48 (1.7)     | 35 (2.0)   | 13 (1.2)  | 0.127                     |
| Haemodialysis, n (%)           | 31 (1.1)     | 23 (1.3)   | 8 (0.7)   | 0.302                     |
| Percutaneous dialysis, n (%)   | 17 (0.6)     | 12 (0.7)   | 5 (0.5)   |                           |
| STEMI, n (%)                   | 472 (16.4)   | 0 (0.0)    | 472 (43.5)| –                         |
| NSTEMI, n (%)                  | 612 (21.3)   | 0 (0.0)    | 612 (56.5)| –                         |
| Region, n (%)                  | 2025 (70.4)  | 1256 (70.1)| 769 (70.9)| 0.612                     |
|                               | 852 (29.6)   | 537 (29.9)| 315 (29.1)|                           |

Bold values are statistically significant.

ACS, acute coronary syndrome; CAD, coronary artery disease; DES, drug-eluting stents; NSTEMI, non-ST segment elevation myocardial infarction; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction.

RESULTS

Between November 2014 and December 2015, a total of 2877 patients were recruited to receive PF-SES. Patient demographics are detailed in table 1. The rate of diabetes mellitus (DM) was 37.9% (1090/2877) in the overall population, whereas 1084 patients or 37.6% were treated for ACS. Dialysis-dependent patients amounted to 1.7% (48/2877) in the overall cohort. Most patients were recruited in Europe (70.4%, 2025/2877) while the frequency of ACS between regions was not significantly different (p=0.612).

Lesion morphologies

Overall, 3254 lesions were treated with 3858 PF-SES (table 2) primarily for de novo lesions (96.7%, 3146/3254). Significant differences in lesion characteristics between patients with stable coronary artery disease (CAD) and those with ACS were observed in the rates of thrombotic occlusions (3.6% vs 24.5%, p<0.001), thrombus burden (7.6% vs 25.2%, p<0.001), in-stent restenosis (ISR, 4.1% vs 2.0%, p=0.002) and the degree of stenosis (85.0%±10.7% vs 89.9%±11.0%, p<0.001). The average use of PF-SES was significantly higher in the non-ACS group (1.36±0.79 vs 1.29±0.67, p=0.031). The technical success rate to implant the PF-SES was not different between groups (98.4% vs 98.0%, p=0.411).

Comedication

In terms of the preprocedural drug therapy (table 3), the new antiplatelet inhibitors prasugrel and ticagrelor were more frequently used in patients with ACS (p<0.001). Patients without preloading amounted to 10.5% (302/2877) in the overall cohort. Postprocedural DAPT use was different between patient groups. Patients with stable CAD received more frequently clopidogrel (80.9% vs 51.7%, pgroup<0.001) and less often prasugrel (5.0% vs 19.4%) and ticagrelor (11.8% vs 26.7%) when compared with patients with ACS.
The recommended duration DAPT (Table 4) was significantly longer in patients with ACS ($p_{\text{group}} < 0.001$), for example, the percentage of patients who underwent 12 months of DAPT was 70.4% (763/1084) versus 42.4% (761/1793). The number of patients with unknown length of DAPT was considerable (17.1%, 493/2877) in the total study population.

### Clinical results

#### Inhospital events

Inhospital clinical MACE (Table 5) was significantly higher in patients with ACS when compared with those with non-ACS (2.8% vs 0.6%, $p<0.001$), which were driven by MI (1.8% vs 0.3%, $p<0.001$), cardiac death (1.2% vs 0.2%, $p<0.001$) and TLR (0.8% vs 0.3%, $p=0.039$).

#### Nine-month events

The follow-up rate for the entire cohort was 87.3% (2513/2877). $\chi^2$ statistics and t-tests revealed that the risk profile (demographic and lesion morphological) was not different between those patients with and without 9-month follow-up (see online supplementary appendix II). At 9 months, the primary endpoint TLR was not significantly different between both groups (ACS: 2.6% vs stable CAD: 2.1%, $p=0.389$). However, the 9-month MACE rate was almost twice as high as in patients with ACS when compared...
Table 3  Periprocedural drug therapy

| Drug type | Drug | All patients (%) | Stable CAD (%) | ACS (%) | p-Value Stable CAD vs ACS |
|-----------|------|------------------|----------------|---------|--------------------------|
| Pre-PCI   | APT  | Clopidogrel      | 1529 (53.1)    | 1061 (59.2) | 468 (43.2) | <0.001                   |
|           |      | Prasugrel        | 328 (11.4)     | 162 (9.0)   | 166 (15.3)  |
|           |      | Ticagrelor       | 383 (13.3)     | 156 (8.7)   | 227 (20.9)  |
|           |      | Ticlopidine      | 19 (0.7)       | 9 (0.5)     | 10 (0.9)    |
|           |      | Aspirin only     | 316 (11.0)     | 205 (11.4)  | 111 (10.2)  |
|           |      | No preloading    | 302 (10.5)     | 200 (11.2)  | 102 (9.4)   |
|           | OAC  | All OAC          | 54 (1.9)       | 40 (2.2)    | 14 (1.3)    | 0.072                    |
|           |      | VKA              | 33 (1.1)       | 25 (1.4)    | 8 (0.7)     | 0.188                    |
|           |      | NOAC, eg,        | 21 (0.7)       | 15 (0.8)    | 6 (0.5)     |
|           |      | rivaroxaban      |                |            |             |                          |
| Post-PCI  | APT  | Clopidogrel      | 2010 (69.9)    | 1450 (80.9) | 560 (51.7)  | <0.001                   |
|           |      | Prasugrel        | 300 (10.4)     | 90 (5.0)    | 210 (19.4)  |
|           |      | Ticagrelor       | 501 (17.4)     | 212 (11.8)  | 289 (26.7)  |
|           |      | Aspirin only     | 28 (1.0)       | 16 (0.9)    | 12 (1.1)    |
|           |      | Unknown          | 38 (1.3)       | 25 (1.4)    | 13 (1.2)    |

ACS, acute coronary syndrome; APT, antiplatelet therapy; CAD, coronary artery disease; NOAC, new oral anticoagulative; OAC, oral anticoagulatives; PCI, percutaneous coronary intervention; VKA, vitamin k antagonist.

with the stable CAD group (6.1% vs 3.2%, p<0.001) due to MI and overall mortality.

The Kaplan-Meier (K-M) analysis for the primary endpoint (figure 1) did not indicate a significant difference between ACS and non-ACS patients (log-rank p=0.141). In contrast, the K-M curves (figure 2) for freedom of MACE in the ACS and non-ACS patient subgroups were different (log-rank p<0.001), that is, patients with ACS have significantly higher MACE rates, which manifests itself in an early divergence of the K-M curves.

Nine-month MACE subgroup analyses

Additional χ² analyses were conducted for 9-month MACE in a number of subgroups (figure 3), which did not reveal differences in terms of preloading (p=0.878), diabetes (p=0.995), dialysis (p=0.429) and region (Europe vs Asia, p=0.317). However, the presence of ISR in bare-metal stent (BMS) or DES at baseline led to numerically higher 9-month MACE rates (8.3% vs 4.2%, p=0.064) when compared with patients with de novo lesions. Finally, in the patient with stable CAD subgroup, the clinical event rates at 9 months were not different between patients who received 6 months of DAPT and those who had more than 6 months of DAPT (table 6). In these patients with stable CAD, there were no significant differences in terms of cardiovascular and lesion morphological risk factors at baseline between the short and long DAPT subgroups with the exception of

Table 4  Recommended duration of dual antiplatelet therapy during follow-up

| Variable                  | All patients | Stable CAD | ACS | p Value Stable CAD vs ACS |
|---------------------------|--------------|------------|-----|---------------------------|
| No of patients            | 2877         | 1793       | 1084| –                         |
| DAPT duration in months   | 10.0±2.8     | 9.4±2.9    | 11.0±2.2 | <0.001                   |
| 1 month, n (%)            | 24 (0.9)     | 17 (0.9)   | 7 (0.7)     | <0.001                   |
| 1–3 months, n (%)         | 34 (1.2)     | 24 (1.3)   | 10 (0.9)     |
| 3–6 months, n (%)         | 12 (0.4)     | 8 (0.4)    | 4 (0.4)     |
| 6 months, n (%)           | 503 (17.5)   | 416 (23.2) | 87 (8.0)     |
| >6–12 months, n (%)       | 282 (9.8)    | 210 (11.7) | 72 (6.6)     |
| 12 months, n (%)          | 1524 (53.0)  | 761 (42.4) | 763 (70.4)   |
| >12 months, n (%)         | 5 (0.2)      | 3 (0.2)    | 2 (0.2)     |
| Unknown status, n (%)     | 493 (17.1)   | 354 (19.7) | 139 (12.8)   |

ACS, acute coronary syndrome; CAD, coronary artery disease; DAPT, dual-antiplatelet therapy.
### Table 5 Clinical outcomes

| Variable                                      | All patients | Stable CAD | ACS   | p Value Stable CAD vs ACS |
|-----------------------------------------------|--------------|------------|-------|---------------------------|
| No of patients                                | 2877         | 1793       | 1084  | –                         |
| Patients with clinical follow-up at 9 months or early event, n (%) | 2513 (87.3)  | 1566 (87.3)| 947 (87.4) | 0.986                     |
| Follow-up time (months)                       | 8.7±1.8      | 8.6±1.9    | 9.0±1.7 | <0.001                    |
| Time to discharge, median (IQR) (days)        | 2.0 (2.0)    | 1.0 (1.0)  | 3.0 (4.0) | 0.021                    |
| Inhospital MACE, n (%)                        | 41 (1.4)     | 11 (0.6)   | 30 (2.8) | <0.001                    |
| Inhospital TLR, n (%)                         | 14 (0.5)     | 5 (0.3)    | 9 (0.8) | 0.039                     |
| Inhospital MI, n (%)                          | 25 (0.9)     | 6 (0.3)    | 19 (1.8) | <0.001                    |
| Inhospital cardiac death, n (%)               | 17 (0.7)     | 4 (0.2)    | 13 (1.2) | 0.001                     |
| 9-month MACE, n (%)                           | 108 (4.3)    | 50 (3.2)   | 58 (6.1) | <0.001                    |
| 9-month TLR (re-PCI, CABG), n (%)             | 58 (2.3)     | 33 (2.1)   | 25 (2.6) | 0.389                     |
| 9-month MI, n (%)                             | 58 (2.3)     | 17 (1.1)   | 41 (4.3) | <0.001                    |
| 9-month all-cause death, n (%)                | 38 (1.5)     | 14 (0.9)   | 24 (2.5) | <0.001                    |
| 9-month accumulated definite/probable stent thrombosis, n (%) | 17 (0.7)   | 9 (0.6)    | 8 (0.8) | 0.424                     |
| Acute stent thrombosis, ≤24 hours, n (%)      | 9 (0.4)      | 4 (0.3)    | 5 (0.5) | 0.372                     |
| Subacute stent thrombosis, 1–30 days, n (%)   | 1 (0.0)      | 0 (0.0)    | 1 (0.1) |                          |
| Late stent thrombosis, ≥30 days, n (%)        | 7 (0.3)      | 5 (0.3)    | 2 (0.2) |                          |

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MACE, major adverse cardiac events; MI, myocardial infarction; re-PCI, re-percutaneous coronary intervention; TLR, target lesion revascularisation.

**Figure 1** Kaplan-Meier curve for freedom from TLR of patients with stable CAD and those with ACS. ACS, acute coronary syndrome; CAD, coronary artery disease; TLR, target lesion revascularisation.
renal insufficiency, which was higher in the short DAPT subgroup (10.9% vs 4.9%, p<0.001).

For comparison purposes, a subgroup of patients with a follow-up closer to 12 months (11.8±1.3 months) was also investigated. Their event rates were equally low with a stent thrombosis rate of 1.7% (2/115), MACE 4.3% (5/115), TLR 1.7% (2/115), MI 2.6% (3/115) and all-cause death rate of 0.9% (1/115).

Bleeding complications
The accumulated rate of bleeding complications (Bleeding Academic Research Consortium (BARC) 1–5) was 1.8% (33/1793) in the stable CAD group and 2.4% (26/1084) in the ACS group (p=0.306). There were no differences in bleeding frequency among patients who received different antithrombotic agents.

Figure 2 Kaplan-Meier curve for freedom from MACE of patients with stable CAD and those with ACS. ACS, acute coronary syndrome; CAD, coronary artery disease; MACE, major adverse cardiac events.

Figure 3 MACE rates in subgroups of the overall cohort. ACS, acute coronary syndrome; CAD, coronary artery disease; ISR, in-stent restenosis; MACE, major adverse cardiac events.
in either group. However, patients who were on triple therapy in the stable CAD group had significantly more bleeding events when compared with those with DAPT only (15.0%, 6/40 vs 1.5%, 27/1753, p<0.001). In the ACS group, triple therapy was also associated with a higher rate of bleeding events (14.3%, 2/14 vs 2.2%, 24/1070; p=0.003).

DISCUSSION

The analogue BMS backbone and the PF-SES had similar procedural/technical success rates. This can be rationalised with similar lesion crossing profiles of the cramped stents with identical stent architectures and identical delivery catheters. In terms of clinical outcomes, however, there is a pronounced clinical benefit of the sirolimus–probucol coating used in this study since the 9-month MACE and TLR rates were significantly lower for the PF-SES (BMS analogue MACE 10.2%, TLR 4.4% vs PF-SES MACE 4.3% and TLR 2.3%). A propensity score matching with the BMS database seems the only ethically feasible avenue to determine the exact added value of the sirolimus–probucol coating. This comparison of uncoated versus coated stents of identical design does not have the lustre of a clinical game changer but may certainly confirm the finding of the Norwegian Coronary Stent Trial (NORSTENT), that is, a significant difference in TLR rates.

Basically, the LEADERS-FREE trial with the availability of the 2-year data could not demonstrate non-inferiority for BMS to DES as the default treatment strategy in recognised indication niches such as patients with increased bleeding risks.

In reference to the ISAR-TEST 5 trial, the TLR rates in this registry were quite different, that is, 2.3% at 9 months versus 10.3% at 12 months in the ISAR trial despite a comparable all-comers population in both studies. One explanation for this finding is the angiographic follow-up of ischaemia measurements, for example, fraction flow reserve. This, in turn, may have contributed to higher TLR rates in the ISAR-5 trial. However, this single-armed study included patients with long lesions and ISR, which were excluded in the ISAR-5 trial. Given that the lesion subsets in this registry appear to be more challenging to treat, our 2.3% TLR rate at 9 months fares well with previous findings considering the framework of a registry with potential under-reporting.

Iqbal et al reported MACE rates in an all-comers population treated with either ZES or everolimus-eluting stents (EES). At 9 months, the MACE rates were in the 6%–8% range without significant differences between EES and ZES. Because interstudy comparison is always plagued by methodological challenges, we can merely state that MACE rates in this study are comparable.

Colombo et al conducted a single-armed study in an Italian all-comers population which demonstrated similar efficacy of a polymer-free sirolimus-eluting stent by using organic acids to modulate the drug release. They found target vessel failure rates of 10.1% (62/615) in the overall population. Despite the fact that the clinical event rates in this study are numerically lower, it allows the critical question whether diabetes can be considered as a true cardiovascular risk factor for increased MACE and TLR rates in modern DES. In this regard, our registry data did not reveal a significant difference in terms of MACE between diabetics and non-diabetics (4.3% vs 4.3%, p=0.995) which is in agreement with the ISAR-TEST 5 diabetic subgroup study and the findings of Colombo et al.

A more relevant question which seems to drive the current opinion is the debate whether DAPT can be discontinued if the need should arise, for example, an unplanned surgery. As pointed out by Stefanini et al, there is no class effect of modern DES, that is, different coating and release characteristics hinder the bridging of clinical benefits between devices of different design and coating technology.

Out of the myriad of potential explanatory variables in our χ² analyses, only the ACS status (p<0.001) seems to have an impact on our 9-month MACE (figure 3).

| Variable | All patients | Less or equal to 6 months of DAPT | Longer than 6 months of DAPT | p Value long vs short DAPT |
|----------|--------------|----------------------------------|-----------------------------|----------------------------|
| No of patients | 1566 | 384 | 1182 | – |
| 9-month MACE, n (%) | 50 (3.2) | 12 (3.1) | 38 (3.2) | 0.931 |
| 9-month TLR (re-PCI, CABG), n (%) | 33 (2.1) | 8 (2.1) | 25 (2.1) | 0.970 |
| 9-month MI, n (%) | 17 (1.1) | 4 (1.0) | 13 (1.1) | 0.924 |
| 9-month death all causes, n (%) | 14 (0.9) | 4 (1.0) | 10 (0.8) | 0.723 |
| 9-month accumulated definite/probable stent thrombosis, n (%) | 9 (0.6) | 3 (0.8) | 6 (0.5) | 0.538 |

CABG, coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual-antiplatelet therapy; MACE, major adverse cardiac events; MI, myocardial infarction; re-PCI, re-percutaneous coronary intervention; TLR, target lesion revascularisation.
Established risk factors such as diabetes, stent length or multivessel disease do not seem to increase MACE in patients with ACS and those with stable CAD. Because of the non-polymer matrix, the PF-SES used in this assessment is transformed into a BMS once the sirolimus-probucol matrix is fully released. Recently published meta-analyses by D’Ascenzo et al. and Savarese et al. investigated the effect of DAPT duration in first-generation and second-generation DES. D’Ascenzo et al. concluded that DAPT for up to 6 months can be justified in patients receiving EES and ZES. However, the observed decreased risk of major bleeding must be balanced at a higher risk of MI if the shorter DAPT is chosen. Savarese et al. reported that prolonged DAPT did not reduce mortality rates. Our results, nevertheless, indicate that a shorter DAPT duration up to 6 months did not show higher event rates in the elective patient cohort. Elective patients who received up to 6 months of DAPT had comparable rates for MACE (3.1% vs 3.2%, p=0.931) and TLR (2.1% vs 2.1%, p=0.970). We also investigated the 9-month MACE rates of patients with stable CAD in subgroups of 0–3, 3–6s, 6–12 months and beyond 12 months which yielded 5.4%, 2.9%, 3.3% and 0.0%, respectively, whereas patients with unknown DAPT duration had a 9-month MACE rate of 3.1%. In this analysis we could not detect a difference among these subgroups (p=0.937). Despite the fact that this analysis was not powered to detect differences, this finding warrants further investigations. Mauri et al. who concluded that longer DAPT had clinical benefits for patients with stable CAD and those with ACS could not be demonstrated in our study since our follow-up horizon was substantially shorter than the one reported in the DAPT study.

The recently published results of the NORTENT study revealed that DES implantations had no benefit over BMS in terms of the combined rate of all-cause mortality and non-fatal MI (16.6% vs 17.1%, p=0.66) within a follow-up period of 6 years. In contrast, the 6-year TLR rates were clearly in favour of DES angioplasty (16.5% vs 19.8%, p=0.001) which is in agreement with our results and the findings of the uncoated analogue BMS backbone. Finally, a careful ramification based on our findings can be made relative to balancing the bleeding risks and DAPT duration. As proposed by Yeh et al., a benefit-risk ratio for extended DAPT could be quantified on a ‘penalty’ point system. In future subgroup analyses of this large-scale study, the application of this proposed rating system is highly desirable.

Limitations

Intrinsic to an observational study of this size, the less stringent control in terms of data collection and study monitoring may have introduced event under-reporting. Furthermore, the follow-up rate of 87.3% is not ideal; however, the 2513 patients with a clinical follow-up provided a wealth of data for meaningful subgroup analyses. Moreover, patients with 9-month follow-up did not have an ‘easier’ cardiovascular risk profile when compared with those lost to follow-up, which would have skewed the clinical results. We suspect that this large patient base may compensate for some of the inaccuracies that were introduced by the aforementioned lack of 100% on-site monitoring. Another shortcoming of our work is the fact that reliable dyslipidemia data could not be obtained and the smoking status was not determined at baseline. This established risk factor would have been very desirable for our exploratory logistic regression analyses. Although we could not detect increased rates of MACE in the absence of preloading or shorter DAPT in our data set, our findings are hypothesis generating and do, therefore, not replace a properly designed non-inferiority trial with primary endpoint ST rate as described by Waliszewski and Rittger, with patient numbers in the 2000–8000 patient range per treatment group.

CONCLUSION

PF-SES angioplasty was safe and effective in ACS patients with low rates of TLR and MACE which are comparable to reports of other polymer-free DES technologies. Patients who were not able to receive antiplatelet preloading do not have higher rates of TLR or MACE at 9 months. Established risk factors such as diabetes, lesion length, vessel diameter or presence of B2/C lesions do not seem to increase TLR in patients with ACS and those with stable CAD. The impact of shortened DAPT remains to be speculative; however, stable CAD patients with a DAPT duration of up to 6 months did not have higher TLR rates when compared with those with DAPT durations longer than 6 months.

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