Clinical Research in Cardiology (2022) 111:795–805
https://doi.org/10.1007/s00392-022-01994-4

ORIGINAL PAPER

Complex vs. non-complex percutaneous coronary intervention with newer-generation drug-eluting stents: an analysis from the randomized BIOFLOW trials

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Received: 10 December 2021 / Accepted: 15 February 2022 / Published online: 25 February 2022

Abstract

Background Patients undergoing complex percutaneous coronary intervention (PCI) are at higher risk of adverse outcomes, but data are scarce in the era of newer-generation coronary stents.

Aim We sought to compare the clinical outcomes after complex PCI with a bioresorbable-polymer sirolimus-eluting stent (BP-SES) versus a durable-polymer everolimus-eluting stent (DP-EES).

Methods Patients ($n=2350$) from BIOFLOW-II, -IV, and -V randomized trials were categorized into non-complex PCI vs. complex PCI. Complex PCI had at least one of the following criteria: multi-vessel PCI, ≥ 3 lesions treated, ≥ 3 stents implanted, total stent length ≥ 60 mm. Endpoints were target lesion failure (TLF: cardiac death, target-vessel myocardial infarction [TV-MI], or target lesion revascularization [TLR]) and probable/definite stent thrombosis (ST) at three years.

Results Patients with complex PCI ($n=348$) were older and presented more often with acute coronary syndrome than non-complex PCI patients ($n=2002$). Complex PCI lesions were more often type B2/C and bifurcation lesions and required more pre- and post-dilatation. Complex PCI patients had higher rates of TLF (14.6% vs. 8.1%; aHR 1.89, 95% CI [1.31–2.73],

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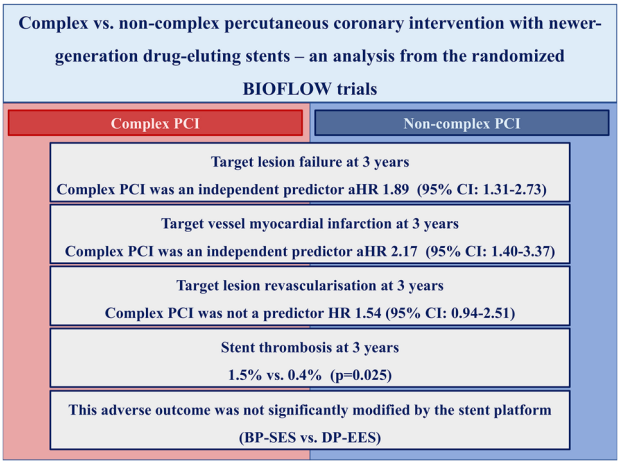
$p=0.001$), TV-MI (10.2% vs. 4.4%, aHR 2.17, 95% CI [1.40–3.37], $p=0.001$), and ST (1.5% vs. 0.4%, $p=0.025$) as compared with non-complex PCI. TLF was not lower with BP-SES as compared to DP-EES in complex PCI (12.6% vs 18.2%, $p=0.16$).

Conclusion Patients undergoing complex PCI with the newer-generation DES still sustain a higher risk of TLF, TV-MI and stent thrombosis as compared with non-complex PCI. This adverse outcome was not significantly modified by the stent platform (BP-SES vs. DP-EES).

Clinical trial registration Clinicaltrial.gov NCT01356888, NCT01939249, NCT02389946, https://clinicaltrials.gov/show/NCT01356888; https://clinicaltrials.gov/show/NCT01939249; https://clinicaltrials.gov/show/NCT02389946.

Graphical abstract



Keywords BIOFLOW · Newer-generation drug-eluting stent · Orsiro · Xience · Complex percutaneous coronary intervention

Abbreviations

BP-SES	Bioresorbable-polymer sirolimus-eluting stent
DES	Drug-eluting stent
DP-EES	Durable-polymer everolimus-eluting stent
PCI	Percutaneous coronary intervention
ST	Stent thrombosis
TLF	Target lesion failure
TLR	Target lesion revascularization
TV-MI	Target-vessel myocardial infarction

Introduction

Percutaneous coronary intervention (PCI) has rapidly evolved in the past decades. The drug-eluting stent technology has progressed into thinner struts, bio-compatible or bio-resorbable polymers, and more effective anti-proliferative drugs, resulting in lower early and late adverse event rates [1, 2]. As a consequence, PCI is now often performed in patients with challenging coronary artery morphologies which may result in a "complex PCI". Patients requiring complex PCI are at a higher risk of ischemic and bleeding events [3, 4]. As complex PCI represents a large proportion of contemporary PCIs [3, 5], there is growing interest in improving the clinical outcomes after these complex interventions.

Recently, the BIOFLOW-V trial [6] demonstrated a lower rate of target lesion failure (TLF) and stent thrombosis (ST) with the ultra-thin-strut bio-resorbable-polymer sirolimus-eluting stent (BP-SES) as compared with a thin-strut durable-polymer everolimus-eluting stent (DP-EES).

The majority of studies on complex PCI focused on the optimal antiplatelet therapy and duration of the antiplatelet regimen [7–10], with only few studies on head-to-head comparison of different stent platforms [5, 11]. In the present study, we sought to investigate the long-term clinical outcomes of patients undergoing complex PCI with a BP-SES versus DP-EES in a pooled dataset of the randomized BIOFLOW-II [12], BIOLFOW-IV [13], and BIOFLOW-V [6] trials.

Methods

Study population and design

This is a post hoc analysis of patient-level data pooled from the multicenter, randomized BIOFLOW-II, BIOFLOW-IV,

and BIOFLOW-V trials. The study designs are available on ClinicalTrials.gov (NCT01356888, NCT01939249, NCT02389946). The trials compared PCI with BP-SES (Orsiro, Biotronik, Bülach, Switzerland) versus DP-EES (Xience, Abbott, Santa Clara, CA) in de novo native coronary artery lesions. Patient inclusion and exclusion criteria are summarized in Online Table 1.

The trials complied with the provisions of the Declaration of Helsinki and were approved by the institutional review board or ethics committee at each enrolling site. Eligible patients signed written informed consent. An independent clinical events committee adjudicated all clinical endpoints. An independent core laboratory (MedStar Cardiovascular Research Network, Angiographic Core Laboratory, Washington DC, USA) analyzed all angiographic data. The trials were funded by Biotronik. The authors (R.H., R.T., G.R.) had unrestricted access to the data and are responsible for the analyses and drafting of the manuscript.

For this analysis, we divided the study population into patients who underwent complex PCI vs. non-complex PCI. Complex PCI was defined according Coughlan et al. [14] as PCI with at least one of the following four characteristics: multi-vessel PCI, ≥ 3 lesions treated, ≥ 3 stents implanted, or total stent length ≥ 60 mm implanted.

Study endpoints

The main endpoints were target lesion failure (TLF) at 3 years (a composite of cardiac death, target-vessel myocardial infarction [TV-MI], or ischemia-driven target lesion revascularization [TLR]) and definite or probable stent thrombosis (ST; according to the Academic Research Consortium criteria [ARC]) [15].

Peri-procedural MI was defined according to the modified ARC criteria as a troponin, or creatine kinase myocardial band (CK-MB) measured within 48 h of the interventional procedure elevated > 3 times above the upper normal limit of normal. Spontaneous MI was defined as any troponin or CK-MB elevation above the upper limit of normal with associated ischemic symptoms, new electrocardiographic abnormalities suggestive of ischemia, or new development of imaging evidence of infarction. Ischemia-driven re-vascularization was defined as any repeat revascularization of the target lesion or vessel due to either ischemic symptoms or abnormal coronary physiologic study and ≥ 50% coronary stenosis by quantitative angiography, or any revascularization of a ≥ 70% diameter stenosis. Cardiac death was any death due to any proximate cardiac cause, unwitnessed death, or death of unknown cause.

Table 1 Clinical characteristics at baseline

	Complex PCI $n = 348$ pts	Non-complex PCI $n = 2002$ pts	p value
Age, years	65.3 ± 9.9	64.4 ± 10.2	< 0.0001
BMI	25.1 ± 13.0	25.3 ± 12.8	< 0.0001
Female	29.0 (101/348)	24.8 (496/2002)	0.093
Hypertension	81.2 (281/346)	77.8 (1543/1983)	0.156
Hyperlipidemia	75.2 (261/347)	75.6 (1511/1998)	0.870
Diabetes mellitus	32.6 (113/347)	32.6 (653/2001)	0.980
Smoker	62.6 (218/348)	60.5 (1210/2001)	0.443
Prior myocardial infarction	27.8 (96/345)	27.8 (552/1984)	0.999
Prior PCI/CABG	32.4 (112/346)	42.6 (848/1992)	< 0.0001
Prior stroke or TIA	5.2 (18/348)	6.8 (135/2000)	0.271
Renal disease	8.1 (28/347)	7.6 (152/2002)	0.758
Cancer	10.4 (36/347)	8.9 (178/2000)	0.378
Clinical presentation			
Stable angina	53.4 (186/348)	53.8 (1007/2001)	0.032
Documented silent ischemia	11.2 (39/348)	15.9 (319/2001)	
Acute coronary syndrome[a]	35.3 (123/348)	30.2 (605/2001)	0.057
Multi-vessel treatment	82.5 (287/348)	0 (0/2002)	< 0.0001
≥ 3 lesions treated per pt	7.8 (27/348)	0 (0/2002)	< 0.0001
≥ 3 stents per patient	35.6 (124/348)	0 (0/2002)	< 0.0001
Total stent length ≥ 60 mm	25.9 (90/348)	0 (0/2002)	< 0.0001
Total stent length	49.6 ± 18.2	22.1 ± 9.4	< 0.0001

Data are mean ± SD or percent % (n/N)

[a]NSTEMI and unstable angina

Statistical methods

Patient-level data were combined in one dataset. Continuous variables were summarized as mean ± SD or as medians with lower and upper quartile and compared using two-sided *t* test or the non-parametric Wilcoxon rank-sum test. Categorical variables were summarized as frequencies and percentages and were compared using the chi-square or Fischer's exact test. The clinical endpoints were compared using the time-to-event Kaplan–Meier estimates and Cox regression and presented as hazard ratio (HR) and 95% confidence interval (95% CI). For calculation of predictors of TLF, TV-MI and clinical indicated TLR, a Cox regression analysis was performed using the following co-variables: age, BMI, gender, prior PCI/CABG, presentation with acute coronary syndrome, type B2/C lesion, bifurcation as target lesion, reference vessel diameter ≤ 2.75 mm. Additionally, the stent (DP-ESS vs BP-SES) and complex PCI were forced into the analysis. To avoid multi-collinearity, the components of type B2/C lesion were not included in the model. The treatment effect associated with BP-SES or DP-EES with complex PCI or non-complex PCI was calculated from the Cox regression analysis with a *p* value for interaction. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). A *p* value of less than 0.05 was established as the level of statistical significance.

Results

Out of 2360 patients, ten had no core-laboratory data and were excluded from this analysis; 348 (14.8%) underwent a complex PCI and 2002 (85.2%) underwent a non-complex PCI. Three years of follow-up was complete in 93.7% of complex PCI and in 93.5% of non-complex PCI patients. Patients with a complex PCI were older and presented more often with an acute coronary syndrome. The comorbidities were well balanced among the groups (Table 1). Complex PCI lesions were more often type B2/C and bifurcation lesions and required more pre- and post-dilatations (Table 2).

Clinical outcomes at three years are presented in Fig. 1 and Table 3. TLF at three years occurred more frequently in complex PCI patients as compared with non-complex PCI patients (14.6% vs. 8.1%, Log-Rank $p < 0.0001$; HR: 1.90, 95% CI [1.38–2.61], $p < 0.0001$). The difference was mainly driven by TV-MI (10.2% vs. 4.4%, Log-Rank $p < 0.0001$; HR: 2.35, 95% CI [1.59–3.48], $p < 0.0001$). The rate of clinically driven TLR differed between the groups without reaching statistical significance (5.9% vs. 4.0%, Log-Rank $p = 0.085$; HR: 1.54, 95% CI [0.94–2.51], $p = 0.088$). Cardiac death occurred more frequently after complex PCI (2.1% vs 0.9%, Log-Rank $p = 0.047$; HR: 2.37, 95% CI [0.98–5.72]). Definite or probable stent thrombosis occurred in five cases (1.5%) after complex PCI and in eight cases (0.4%) after non-complex PCI, significantly higher in the former group yet with a wide confidence interval of hazard (Log-Rank $p = 0.016$; HR: 3.60, 95% CI [1.18–11.00], $p = 0.025$) (Fig. 2). After accounting for confounders, complex PCI was significantly associated with TLF (adjusted HR 1.89, 95% CI [1.31–2.73], $p = 0.001$) and TV-MI (aHR 2.17, 95% CI [1.40–3.37], $p = 0.001$) (Supplemental Table 2). The difference in TLF was significant in the first year (Log-Rank $p < 0.0001$), but waned thereafter (Log-Rank $p = 0.712$) (Supplemental Fig. 1). Conversely, landmark analysis showed that the difference observed for TV-MI in the first month (Log-Rank $p < 0.0001$), remained significant over the second and third years (Log-Rank $p = 0.049$) (Supplemental Fig. 1).

The rates of TLF were improved with BP-SES as compared to DP-EES in both, non-complex PCI (7.0% vs. 10.2%; HR 0.68, 95% CI [0.50–0.93], $p = 0.017$) and in complex PCI (12.6% vs. 18.2%; HR 0.68, 95% CI [0.39–1.18], $p = 0.171$), but statistical significance was not reached in complex PCI. For TV-MI, the differences between BP-SES and DP-EES did not meet significance either for non-complex PCI (3.9% vs. 5.5%; HR 0.70, 95% CI [0.46–1.08], $p = 0.107$) or for complex PCI (8.0% vs. 14.1%; HR 0.57, 95% CI [0.29–1.10], $p = 0.092$) (Fig. 3 and Table 4). No interaction for the clinical outcomes over three years was observed between the stent platform and the complexity of PCI ($p_{interaction} = 0.976$ for TLF, $p_{interaction} = 0.583$ for TV-MI, $p_{interaction} = 0.571$ for cTLR, $p_{interaction} = 0.509$ for cardiac death, $p_{interaction} = 0.475$ for def./prob. ST). On landmark analysis of the clinical outcomes between one and three years, no significant interaction between PCI complexity and the stent platform was observed (Suppl. Fig. 2).

Discussion

In this patient-level pooled analysis from the randomized BIOFLOW trials, we found that in spite of the advancements in stent technology reached with newer-generation DESs complex, PCI is still associated with worse clinical outcomes at three years, especially with an increased risk for TLF, TV-MI and stent thrombosis. The observation of a trend toward improved outcomes in patients with complex PCI treated with BP-SES as compared with DP-EES is hypothesis-generating and should be explored in future studies.

Patients who undergo complex PCI are described to be at high risk of ischemic events [3, 7–9]. This association is multifactorial. Patients requiring complex interventions have more likely an advanced coronary artery disease, which per se is linked with concomitant comorbidities [16]. In our study population, patients who underwent complex PCI were

Table 2 Lesion characteristics and procedural parameters (core lab)

	Complex PCI $n=687$ lesions	Non-complex PCI $n=2083$ lesions	p value
Complex lesion (B2/C)	60.6 (413/682)	54.7 (1131/2066)	0.008
AHA/ACC lesion type			
Type A lesion	11.6 (79/682)	12.4 (256/2066)	0.003
Type B1 lesion	27.9 (190/682)	32.9 (679/2066)	
Type B2 lesion	26.0 (177/682)	27.3 (565/2066)	
Type C lesion	34.6 (236/682)	27.4 (566/2066)	
Bifurcation lesion	13.1 (90/687)	10.5 (219/2083)	0.062
Thrombus	0.7 (5/687)	1.1 (23/2083)	0.392
Vessel tortuosity			
None	61.9 (425/687)	63.9 (1330/2083)	0.461
Moderate	21.4 (147/687)	21.3 (444/2083)	
Severe	16.7 (115/687)	14.8 (309/2083)	
Calcification			
None/mild	80.5 (553/687)	83.7 (1743/2083)	0.080
Moderate	15.6 (107/687)	12.2 (255/2083)	
Severe	3.9 (27/687)	4.1 (85/2083)	
Long lesion > 20 mm	19.7 (135/684)	14.7 (304/2083)	0.002
RVD, mm	2.57 (2.23. 2.90)	2.66 (2.32. 3.03)	< 0.0001
RVD ≤ 2.75 mm	64.9 (446/687)	57.5 (1198/2083)	0.001
Procedural characteristics			
Stent[a]			
BP-SES	64.9 (226/348)	66.7 (1335/2002)	0.526
DP-EES	35.1 (122/348)	33.3 (667/2002)	
Stent diameter ≤ 3 mm	92.7 (637/687)	68.9 (1416/2056)	< 0.0001
Max. stent impl. pressure atm	14.00 (14.0. 16.0)	14.00 (12.0–16.0)	< 0.0001
Pre-dilatation	93.1 (638/685)	87.5 (1792/2048)	< 0.0001
Post-dilatation	58.6 (377/643)	46.7 (912/1952)	< 0.0001
Diam. stenosis at baseline	59.45 (49.40. 69.45)	60.60 (50.6. 70.45)	0.050
Diam. stenosis post-procedure	7.60 (2.70–13.20)	7.40 (1.90–12.60)	0.072

[a]Patient level

older. However, comorbidities like diabetes, hypertension, dyslipidemia, or renal disease were well balanced among the groups. Of note, disease progression in patients with advanced coronary artery disease is common [16]. Thus, our data show that in the long term, patients with complex PCI remain at higher risk for TV-MI, which may reflect the disease progression. Another aspect likely to influence the higher rate of ischemic risk in patients requiring complex PCI is that a considerable amount of those patients may have incomplete myocardial re-vascularization, which in turn is linked with a higher rate of mortality [16]. Besides the underlying comorbidities, the procedural aspect plays a major role. The likelihood of stent malapposition or delayed endothelialization with longer stents or multiple stenting with overlap is high [16, 17]. Moreover, PCI in complex lesions may result in lesser stent expansion and malapposition [18]. All together those factors are associated with worse acute and long-term stent outcomes [19].

The higher rate of TLF in our analysis was mainly driven by the higher rate of TV-MI. In the landmark analysis, the difference in TLF was significant in the first year, thereafter the TLF-rates were comparable. TV-MI however was significantly higher after complex PCI in the first 30 days, and thereafter the rates remained higher till the third year. The higher rates in the first 30 days can be considered as peri-procedural MI and can be explained that complex PCI required more often pre- and post-dilatation leading to longer vessel occlusion times. Further side-branch compromise in the setting of a complex PCI is an anticipated complication. The ongoing higher rate of TV-MI beyond the first 30 days might be a reflection of an ongoing progression of the atherosclerotic disease over the three years of follow-up, as explained above.

When using a BP-SES, the TLF and TV-MI rates were numerically lower as compared with DP-EES without reaching statistical significance. In the formal interaction testing,

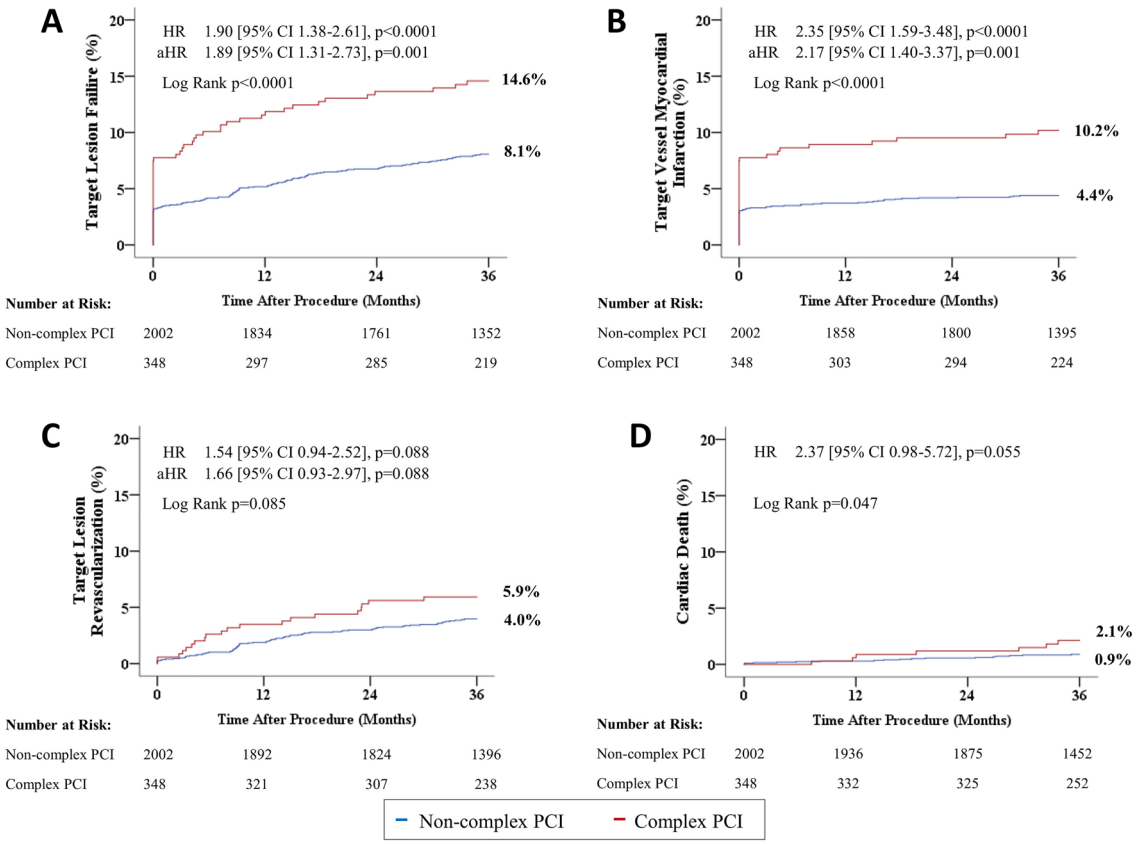


Fig. 1 Clinical outcomes after three years in patients undergoing complex PCI and non-complex PCI. Kaplan–Meier estimates for target lesion failure (**A**) and their components target-vessel myocardial infarction (**B**), clinical indicated target lesion re-vascularization (**C**), and cardiac death (**D**)

Table 3 Clinical outcomes at three years in patients undergoing complex or non-complex PCI

	Complex PCI ($n=348$)	Non-complex PCI ($n=2002$)	p value Log-rank	HR (95% CI)	p value	aHR (95% CI)	p value
Target lesion failure	14.6% (50)	8.1% (157)	<0.0001	1.898 (1.381–2.610)	<0.0001	1.887 (1.307–2.727)	0.001
TV-MI	10.2% (35)	4.4% (87)	<0.0001	2.353 (1.589–3.483)	<0.0001	2.172 (1.399–3.372)	0.001
Spont. TV-MI	2.4% (8)	1.4% (26)	0.150	1.774 (0.803–3.919)	0.156	–	
cTLR	5.9% (20)	4.0% (76)	0.085	1.536 (0.939–2.513)	0.088	1.661 (0.928–2.973)	0.088
Cardiac death	2.1% (7)	0.9% (17)	0.047	2.371 (0.983–5.717)	0.055	–	
All-cause death	4.6% (15)	3.5% (67)	0.373	1.289 (0.736–2.256)	0.374	–	
Def/pro stent thrombosis	1.5% (5)	0.4% (8)	0.016	3.597 (1.177–10.996)	0.025	–	

Kaplan–Meier estimates (no of events)

TV-MI target-vessel myocardial infarction, *Spont. TV-MI* spontaneous target-vessel myocardial infarction, *cTLR* clinically driven target lesion revascularization

P = Log-Rank. * = Log-Rank over all 4 groups

the safety of BP-SES and DP-EES was consistent in the complex PCI and the non-complex PCI group. However, the crude event rates of TLF, TV-MI, and clinically driven TLR were consistently numerically lower in patients treated with BP-SES as compared with those treated with DP-EES. Thinner struts are described to cause less side branch coverage which might result in a lower rate of peri-procedural MI [20] with BP-SES. Moreover, endothelialization is faster in stents with thinner struts as compared with thicker struts [17]. Especially this attribute might be more important in a

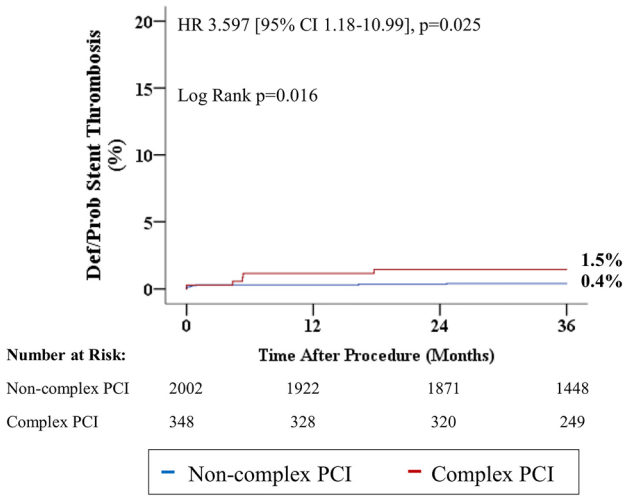


Fig. 2 Kaplan–Meier estimates for definite or probable stent thrombosis after three years in patients undergoing complex PCI and non-complex PCI

complex PCI with more overlapping stents a higher likelihood of malapposition. Taken together, these explanations might rationalize the favorable ischemic outcomes after PCI with BP-SES as compared with DP-ESS, particularly in terms of lower long-term TLR rates with BP-SES. Of note, the risk profile of BIOFLOW-trial patients is different of those included in other analyses on complex PCI from randomized trials. The subgroup analysis from the TWILIGHT trial [8] included per-protocol patients with high risk, and the post hoc analysis of the ISAR REACT 5 trial [14] was conducted on acute coronary syndrome patients. Such differences lead to lower proportion of patients undergoing complex PCI in the BIOFLOW trials as compared with those studies. This may explain why the lower TLR rates with BP-SES did not meet statistical significance, despite the presence of multi-lesion and multi-vessel PCI in this group. This analysis is underpowered to draw a solid conclusion and the statistical significance was not met for all the endpoints. Nevertheless, those data are in line with the overall safety of BP-SES previously demonstrated in the BIOFLOW trials [6, 12, 13, 20] and a large-scale meta-analysis of ten randomized trials [21].

The rate of ST was significantly higher after complex PCI with an increase of the three and half-fold risk. BP-SES had numerically lower rates than DP-EES, without statistical significance, most likely due to the low event numbers. However, the overall log-rank *p* value for the stent platform and the complexity of PCI was significant, without a significant interaction test.

The term complex deserves further discussion in the context of this analysis. There is a difference between a complex PCI, a complex lesion, or a complex patient. While complex lesion and complex patient can be categorized as generic entities with some overlap, complex PCI is difficult to quantify as a generic entity as it usually stems from complexity of the patient and/or the lesion. The outcome of a complex patient may be more sensitive to the anti-platelet or anti-coagulant regimen, the necessity for a mechanical support device during the intervention, the access site management, and the restriction of contrast media in case of renal impairment. For the approach in a complex lesion, the use of intracoronary imaging, fluoroscopic stent enhancement, dedicated lesion preparation techniques, stent implantation technique, and the stent type may be more important. A complex PCI is most likely linked with a complex lesion or a complex patient as discussed above which may explain the inconsistency of the definitions in literature [5, 7, 9, 10, 14, 22]. In our analysis, we restricted the term complex PCI to the probably most frequently performed complex PCIs in clinical practice which is long and multiple stenting.

Limitations

The analysis has limitations which need to be addressed. First, this is a post hoc analysis of a patient-level pooled dataset from randomized trials comparing two different stent platforms. Patients were not randomized to complex or non-complex PCI and unmeasured confounders cannot be excluded. Second, while the allocation to the stent platforms allows us to compare the stents with complexity of PCI, the modest number of patients in the complex PCI group prevents us from reaching significant data on interaction between the stent platforms and the complexity of PCI on the clinical outcomes. Therefore, this analysis should be considered as hypothesis generation rather than conclusive. Third, our definition of complex PCI did not include chronic total occlusion nor intervention of a bifurcation using a two-stent technique, which were excluded or not documented in all patients. As previously mentioned, however, no standardized definition for complex PCI exists, leading to different criteria for complex PCI in previously published analyses in this field [5, 7, 9, 10, 22]. Therefore, the findings of the present analysis cannot be extrapolated to all complex PCI subsets, e.g., CTO and bifurcation PCI with two-stent technique. Fourth, data on antiplatelet therapy were not available.

Conclusion

In this post hoc analysis of the randomized BIOFLOW trials, patients undergoing complex PCI with newer-generation DES still are at a higher risk for TLF, TV-MI and stent thrombosis as compared with patients undergoing non-complex PCI, with no interaction between stent platform (BP-SES vs. DP-EES) and the complexity of PCI.

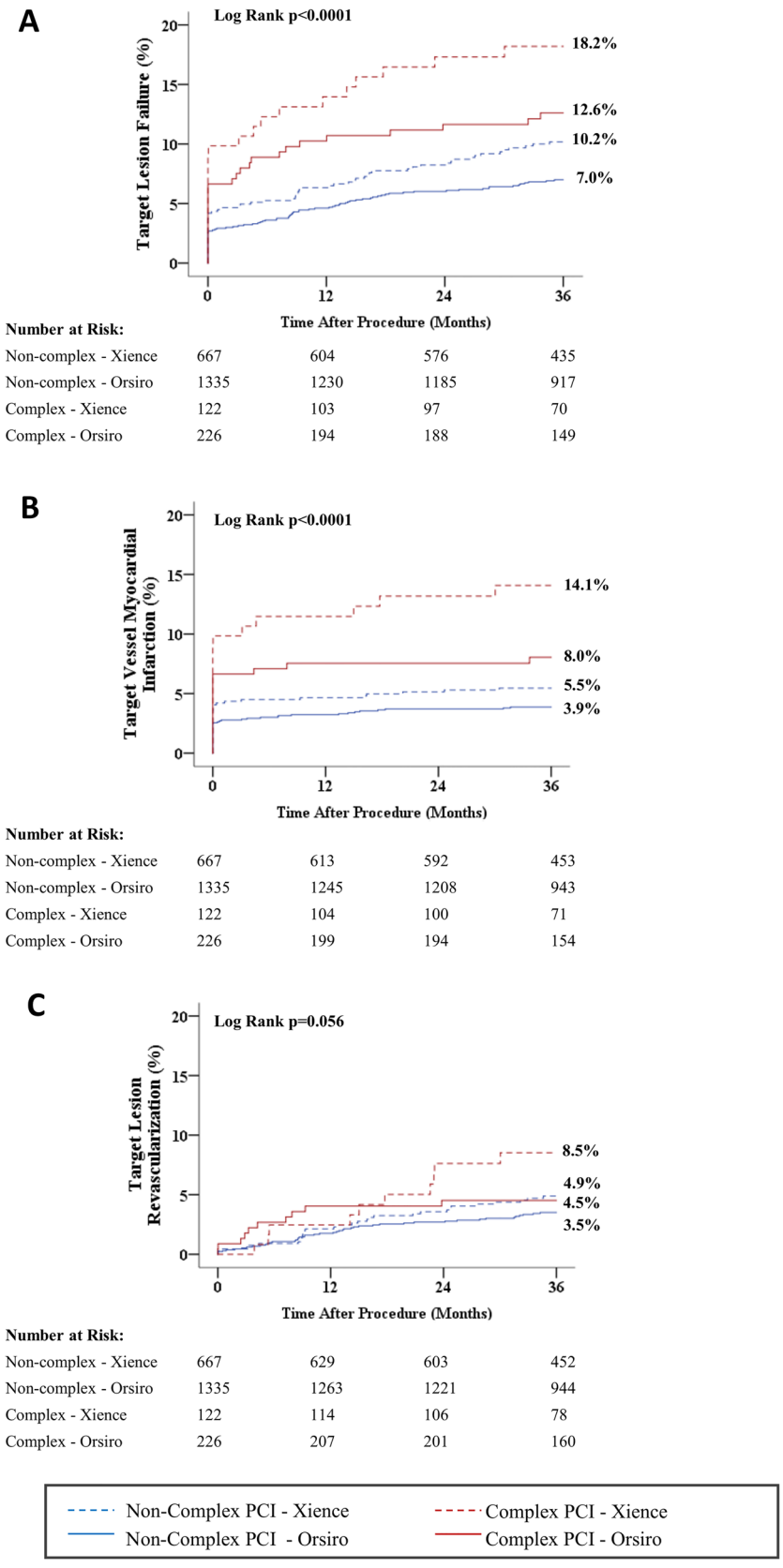


Fig. 3 Clinical outcomes after three years in patients undergoing complex PCI and non-complex PCI with bio-resorbable-polymer sirolimus-eluting stents or durable-polymer everolimus-eluting stents. Kaplan–Meier estimates for target lesion failure (**A**), target-vessel myocardial infarction (**B**), and clinical indicated target lesion revascularization (**C**)

Table 4 Clinical outcomes at three years in patients undergoing complex or non-complex PCI with Orsiro or Xience

	Complex PCI					Non-complex PCI					p^*	$p_{interaction}$
	Orsiro ($n=226$)	Xience ($n=122$)	p	HR (95% CI)	p	Orsiro ($n=1335$)	Xience ($n=667$)	p	HR (95% CI)	p		
TLF	12.6% (28)	18.2% (22)	0.160	0.677 (0.387–1.183)	0.171	7.0% (91)	10.2% (66)	0.016	0.680 (0.495–0.933)	0.017	<0.0001	0.976
TV-MI	8.0% (18)	14.1% (17)	0.079	0.565 (0.291–1.097)	0.092	3.9% (51)	5.5% (36)	0.102	0.704 (0.459–1.079)	0.107	<0.0001	0.583
Spont. TV-MI	1.4% (3)	4.3% (5)	0.101	0.321 (0.077–1.343)	0.120	1.3% (17)	1.4% (9)	0.887	0.943 (0.420–2.116)	0.887	0.096	0.201
cTLR	4.5% (10)	8.5% (10)	0.168	0.545 (0.227–1.308)	0.174	3.5% (45)	4.9% (31)	0.159	0.721 (0.456–1.139)	0.161	0.056	0.571
Cardiac death	2.4% (5)	1.7% (2)	0.718	1.351 (0.262–6.962)	0.719	0.8% (10)	1.1% (7)	0.491	0.713 (0.272–1.874)	0.493	0.205	0.509
All-cause death	3.3% (7)	6.9% (8)	0.138	0.473 (0.171–1.303)	0.147	3.2% (41)	4.1% (26)	0.341	0.788 (0.482–1.288)	0.342	0.224	0.374
Def/pro ST	0.9% (2)	2.5% (3)	0.248	0.364 (0.061–2.179)	0.268	0.4% (5)	0.5% (3)	0.804	0.834 (0.199–3.491)	0.804	0.025	0.475

Kaplan–Meier estimates (No of events). P = Log-Rank. * = Log-Rank over all 4 groups

TLF target lesion failure, *TV-MI* target-vessel myocardial infarction, *Spont. TV-MI* spontaneous target-vessel myocardial infarction, *cTLR* clinically driven target lesion re-vascularization

Funding The BIOFLOW trials were funded by BIOTRONIK.

Declarations

Conflict of interest Dr. Hemetsberger has received speakers' honoraria from Boston Scientific. Dr. Abdelghani has nothing to declare. Dr. Toelg has received speakers' honoraria from Biotronik. Dr. Garcia-Garcia has received institutional research/grant support from Biotronik. Dr. Farhan, Dr. Mankerious, Dr. Elbasha, Dr. Allali have nothing to declare. Dr. Windecker reports research and educational grants to the institution from Abbott, Amgen, Astra Zeneca, BMS, Bayer, Biotronik, Boston Scientific, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Johnson & Johnson, Medicure, Medtronic, Novartis, Polares, OrPha Suisse, Pfizer, Regeneron, Sanofi-Aventis, Sinomed, Terumo, V-Wave. SW serves as unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, V-Wave and Xeltis, but has not received personal payments by pharmaceutical companies or device manufacturers. He is also member of the steering/excecutive committee group of several investigated-initiated trials that receive funding by industry without impact on his personal remuneration. Stephan Windecker is an unpaid member of the Pfizer Research Award selection committee in Switzerland. Dr Lefèvre has received consultant fees from Biotronik and Abbott and Honoraria from Abbott, Terumo, Boston and Edwards. Dr. Saito has nothing to declare. Dr. Kandzari has received institutional research/grant support from Biotronik, Boston Scientific, Medinol, Medtronic, and Orbus Neich, and personal consulting honoraria from Boston Scientific, Cardiovascular Systems, Inc., and Medtronic. Dr Waksman reports consultant fees from Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Corindus, Lifetech Medical, Medtronic, and Philips Volcano; advisory board for Abbott Vascular, Amgen, Boston Scientific, Medtronic, and Philips Volcano; grant support from Abbott Vascular, Biosensors, Biotronik, Boston Scientific, and Edwards Lifesciences; and speakers bureau from AstraZeneca. Dr. Richardt has received institutional research grants from St. Jude Medical, Biotronik, and Medtonic.

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