Relationship Between Stent Diameter, Platelet Reactivity, and Thrombotic Events After Percutaneous Coronary Artery Revascularization

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Small vessel diameter and residual platelet reactivity are independent predictors of thrombotic events after percutaneous coronary intervention (PCI). We sought to determine whether an interaction exists between residual platelet reactivity and stent diameter regarding the occurrence of stent thrombosis and other adverse events after PCI. We stratified patients in the prospective ADAPT-DES registry who underwent single-lesion PCI according to if they received a small diameter stent (SDS, defined as a stent with a diameter of 2.25 mm). Patients receiving an SDS were compared with patients receiving a stent ≥2.5 mm using Kaplan-Meier rates and multivariable Cox proportional hazards regression. We defined major adverse cardiac events (MACE) as the composite of cardiac death, myocardial infarction, and stent thrombosis (ST). Among 5,608 patients who underwent single-lesion PCI in ADAPT-DES, 222 (4.0%) patients received an SDS. Patients with an SDS were more likely than patients without an SDS to have 3-vessel disease but received, on average, fewer stents and were less likely to present with a thrombotic lesion. Receiving versus not receiving an SDS was associated with increased risk of ST (adjusted hazard ratio 4.35, 95% confidence interval 1.95 to 9.73, p <0.001) as well as MACE (adjusted hazard ratio 1.75, 95% confidence interval 1.11 to 2.75, p = 0.02). There was no statistical interaction between platelet reactivity and SDS regarding ST (p = 0.12) or MACE (p = 0.51). In conclusion, PCI with small drug-eluting stents is associated with a high risk of thrombotic events, including ST. Further studies should explore whether alternative treatment strategies are appropriate in small vessels. **(Am J Cardiol 2019;124:1363−1371)**

Percutaneous coronary intervention (PCI) of small vessels is associated with a higher risk of adverse thrombotic events,[1−3] but few studies have studied the association between stent diameter and thrombotic risk after PCI.[4] Furthermore, no study has evaluated the association between platelet reactivity, an independent predictor of increased thrombotic risk,[5] stent diameter, and thrombotic risk. Theoretically, residual platelet reactivity could have a greater effect on thrombotic risk in vessels with a small mean effective lumen area, where reduced flow rate and a greater endothelial surface area to blood volume ratio would be expected to facilitate platelet activation. Therefore, we studied the association between the diameter of the implanted stent, platelet reactivity, and the risk of adverse thrombotic events in patients undergoing successful single-lesion PCI with contemporary drug-eluting stents (DES).

Methods

ADAPT-DES was a prospective, multicenter, observational study specifically designed to determine the association between platelet reactivity on clopidogrel and stent thrombosis (ST) after successful DES implantation. The design and primary results of ADAPT-DES have been previously reported.[5] Briefly, a total of 8,582 "all-comers" patients were prospectively enrolled at 11 sites in the United States and Germany. All patients who were successfully treated with 1 or more DES and who were adequately loaded with aspirin and clopidogrel were eligible for enrollment, regardless of clinical presentation or procedural complexity. The only major exclusion criteria were any intraprocedural or periprocedural major complication or if bypass surgery was planned after PCI. Platelet reactivity on aspirin and clopidogrel were assessed using the VerifyNow Aspirin, P2Y12, and IIb/IIIa assays (Accriva Diagnostics,

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San Diego, California) after an adequate loading period to ensure full antiplatelet effect.[5] After PCI, patients were treated with aspirin indefinitely, and clopidogrel was recommended for at least 1 year. All other treatments were as per standard of care. Clinical follow-up was scheduled at 30 days, 1 year, and 2 years. An independent clinical events committee blinded to VerifyNow results adjudicated all death, myocardial infarction (MI), and ST events using original source documents. The institutional review board at each participating center approved the study, and all eligible patients signed written informed consent before enrollment.

The primary objective of this study was to evaluate the unadjusted and adjusted risk of ST after DES PCI using small diameter stents (SDS) versus non-SDS. The primary analysis population consisted of patients undergoing PCI of a single target lesion in a native coronary vessel. The sensitivity analysis population consisted of all patients enrolled in ADAPT-DES.

SDS was defined as a stent with a diameter of 2.25 mm. ST was defined as any target lesion definite or probable ST according to the Academic Research Consortium definition.[6] HPR was defined as on-clopidogrel P2Y12 reaction units >208. Major adverse cardiac events (MACE) was defined as the composite of cardiac death, nonperiprocedural MI (according to the Acute Catheterization and Urgent Intervention Triage Strategy [ACUITY] criteria[5,7]), or ST. Finally, target vessel failure was defined as the composite of death, nonperiprocedural MI, or ischemia-driven target vessel revascularization.

Descriptive statistics are presented as mean ± standard deviation or media (interquartile range) and were compared with the Student *t* test or the Mann-Whitney test; categorical variables are reported as percentages and were compared between groups with the chi-sqaure test. Event rates during follow-up were estimated by the Kaplan-Meier method. Unadjusted and adjusted hazard ratios for 2-year outcomes were estimated using Cox proportional hazards models. Multivariable models were adjusted for the following variables: age, sex, diabetes, current smoker, renal insufficiency, clinical presentation, previous MI, anemia, P2Y12 reaction units, multivessel disease, total stent length,

Table 1
Baseline clinical characteristics

Varible	Stent diameter 2.25 mm (n = 222)	Stent diameter ≥2.5 mm (n = 5,386)	p Value
Age, years	62.9 ± 11.0 (222)	63.0 ± 10.9 (5,386)	0.91
Female	30.6% (68/222)	27.7% (1,492/5,386)	0.34
Body mass index, kg/m^2	29.6 ± 5.5 (222)	29.6 ± 5.8 (5,386)	0.98
Diabetes	34.7% (77/222)	30.8% (1,660/5,386)	0.22
Insulin-treated	14.4% (32/222)	10.9% (585/5,386)	0.10
History of peripheral arterial disease	9.9% (22/222)	9.3% (501/5,386)	0.76
History of congestive heart failure	9.0% (20/222)	7.1% (384/5,386)	0.29
Prior myocardial infarction	29.7% (66/222)	24.2% (1,306/5,386)	0.06
Prior coronary artery bypass grafting	18.5% (41/222)	11.6% (625/5,386)	0.002
Prior percutaneous coronary intervention	54.1% (120/222)	41.6% (2,240/5,386)	0.0002
Arterial hypertension	82.4% (183/222)	78.2% (4,214/5,386)	0.14
Hyperlipidemia	76.6% (170/222)	71.9% (3,871/5,386)	0.13
Active smoker	21.2% (47/222)	24.4% (1,314/5,386)	0.27
Chronic kidney disease	9.0% (20/222)	7.4% (396/5,386)	0.36
History of dialysis	2.7% (6/222)	1.7% (94/5,386)	0.29
Clinical presentation			
Stable coronary artery disease	48.2% (107/222)	46.0% (2,475/5,386)	0.51
Acute coronary syndromes	51.8% (115/222)	54.0% (2,911/5,386)	0.51
Degree of coronary artery disease			
1 Vessel	42.8% (95/222)	48.3% (2,603/5,386)	0.11
2 Vessels	28.4% (63/222)	30.8% (1,657/5,386)	0.45
3 Vessels	28.8% (64/222)	20.9% (1,126/5,386)	0.005
Left main >50% stenosis	0.9% (2/222)	1.6% (86/5,386)	0.25
Left ventricular ejection fraction, %	56.53 ± 11.36 (167)	55.31 ± 12.35 (4,378)	0.21
Laboratory values			
Hemoglobin, g/dl	14.0 ± 1.4 (222)	14.0 ± 1.5 (5,361)	0.89
Creatinine clearance, ml/min[†]	95.8 ± 40.6 (222)	95.5 ± 38.0 (5,357)	0.89
White blood cells, 10^9/L	8.11 ± 3.07 (222)	8.04 ± 3.23 (5,338)	0.74
Platelet count, 10^9/L	229.4 ± 74.9 (222)	229.1 ± 63.4 (5,350)	0.95
VerifyNow P2Y12 testing results			
PRU	175.99 ± 97.13 (218)	188.78 ± 96.58 (5,302)	0.056
HPR (>208 PRU)	39.4% (86/218)	42.8% (2,271/5,302)	0.32
ARU	417.10 ± 57.02 (220)	417.89 ± 53.93 (5,350)	0.83
High ARU (≥550)	7.3% (16/220)	5.1% (271/5,350)	0.15

Values are % (n/N) or mean ± standard deviation (n).
ARU = aspirin reaction units; HPR = high on-clopidogrel platelet reactivity; PRU = P2Y12 reaction units.
[†] Calculated by the Cockcroft-Gault formula.

and DES generation. The consistency of the effect of receiving an SDS according to HPR (no HPR vs HPR) or DES generation (second-generation vs first-generation DES) was evaluated with formal interaction testing. Sensitivity models were conducted using propensity score matching and propensity score adjustment. For the propensity score models, patients who received an SDS were matched 1:10 to patients not receiving an SDS by their estimated propensity to have received an SDS. The propensity for receiving an SDS versus a non-SDS was estimated by using logistic regression, with SDS versus non-SDS as the dependent variable and the following predictor variables: age, sex, diabetes, current smoker, renal insufficiency, clinical presentation, previous MI, previous coronary artery bypass grafting, anemia, P2Y12 reaction units, left anterior descending coronary artery as the culprit vessel, multivessel disease, PCI against a graft vessel, moderate or severe coronary calcification, total stent length, and DES generation. All tests were 2-sided, and p values <0.05 were considered statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Out of 8,582 patients included in the ADAPT-DES study, 5,608 patients (65.3%) had PCI of a single native coronary lesion and were included in the study. In these patients, 222 (4.0%) received an SDS. Patients receiving an SDS were more likely to have 3-vessel disease and to have previously had PCI or coronary artery bypass grafting (Table 1). They were also more likely to have PCI of a smaller target vessel but were less likely to present with an intracoronary thrombus or to have intravascular ultrasound, and they received on average fewer stents (Table 2). The use of antiplatelet drugs was similar for both groups (Supplemental Table 1). The baseline and procedural characteristics of the propensity score matched cohort are shown in Supplemental Tables 2 and 3.

Table 2
Procedural characteristics

Variable	Stent diameter 2.25 mm (n = 222)	Stent diameter ≥2.5 mm (n = 5386)	p Value
Vascular access site			
Femoral	94.6% (210/222)	94.8% (5,105/5,386)	0.90
Radial	5.4% (12/222)	5.0% (269/5,386)	0.78
Total lesion length, mm	14.0 (9.0-20.0)	16.0 (11.0-24.0)	<0.0001
Target vessel diameter, mm	2.3 ± 0.2 (158)	3.0 ± 0.7 (5,455)	<0.0001
Thrombus	9.0% (20/222)	16.8% (903/5,386)	0.002
Calcium	24.8% (55/222)	28.9% (1,554/5,386)	0.19
Ostial	7.7% (17/222)	10.7% (576/5,386)	0.15
Chronic total occlusion	4.1% (9/222)	3.3% (178/5,386)	0.54
Target vessel location			
Left anterior descending coronary artery	45.5% (101/222)	43.7% (2,356/5,386)	0.61
Right coronary artery	19.4% (43/222)	31.6% (1,701/5,386)	0.0001
Left circumflex artery	36.9% (82/222)	23.8% (1,282/5,386)	<0.0001
Left main coronary artery	0.9% (2/222)	2.2% (120/5,386)	0.24
Bypass graft	0.0% (0/222)	0.0% (1/5,386)	>0.99
Number of stents implanted per patient	1.14 ± 0.41 (222)	1.25 ± 0.57 (5,386)	0.0003
Total stent length, mm	19.5 ± 9.0 (222)	23.7 ± 14.2 (5,386)	<0.0001
Maximum inflation pressure	15.83 ± 3.81 (221)	16.33 ± 3.51 (5,386)	0.056
Stent used			
Everolimus-eluting	23.0% (51/222)	66.4% (3,575/5,386)	<0.0001
Zotarolimus-eluting fast-release	0.0% (0/222)	6.9% (373/5,386)	<0.0001
Zotarolimus-eluting slow-release	1.8% (4/222)	1.9% (103/5,386)	>0.99
Paclitaxel-eluting	56.8% (126/222)	13.4% (724/5,386)	<0.0001
Sirolimus-eluting	18.5% (41/222)	11.7% (630/5,386)	0.0023
Other	0.0% (0/222)	0.2% (10/5,386)	>0.99
Intravascular ultrasound used	14.4% (32/222)	42.1% (2,267/5,386)	<0.0001
Document final results	50.0% (16/32)	26.7% (605/2,267)	0.003
Guide and optimize procedure	50.0% (16/32)	73.3% (1,662/2,267)	0.003
Higher stent or postdilation balloon pressure	18.8% (6/32)	16.9% (382/2,267)	0.78
For incomplete expansion	3.1% (1/32)	9.8% (222/2,267)	0.36
For incomplete stent apposition	6.3% (2/32)	4.9% (112/2,267)	0.67
Larger diameter stent or balloon	0.0% (0/32)	29.0% (657/2,267)	0.0003
Longer stents placed	15.6% (5/32)	15.0% (341/2,267)	0.81
Additional stents placed	0.0% (0/32)	3.7% (83/2,267)	0.63
Other	9.4% (3/32)	14.0% (318/2,267)	0.61

Values are % (n/N), median (interquartile range), or mean ± standard deviation (n).

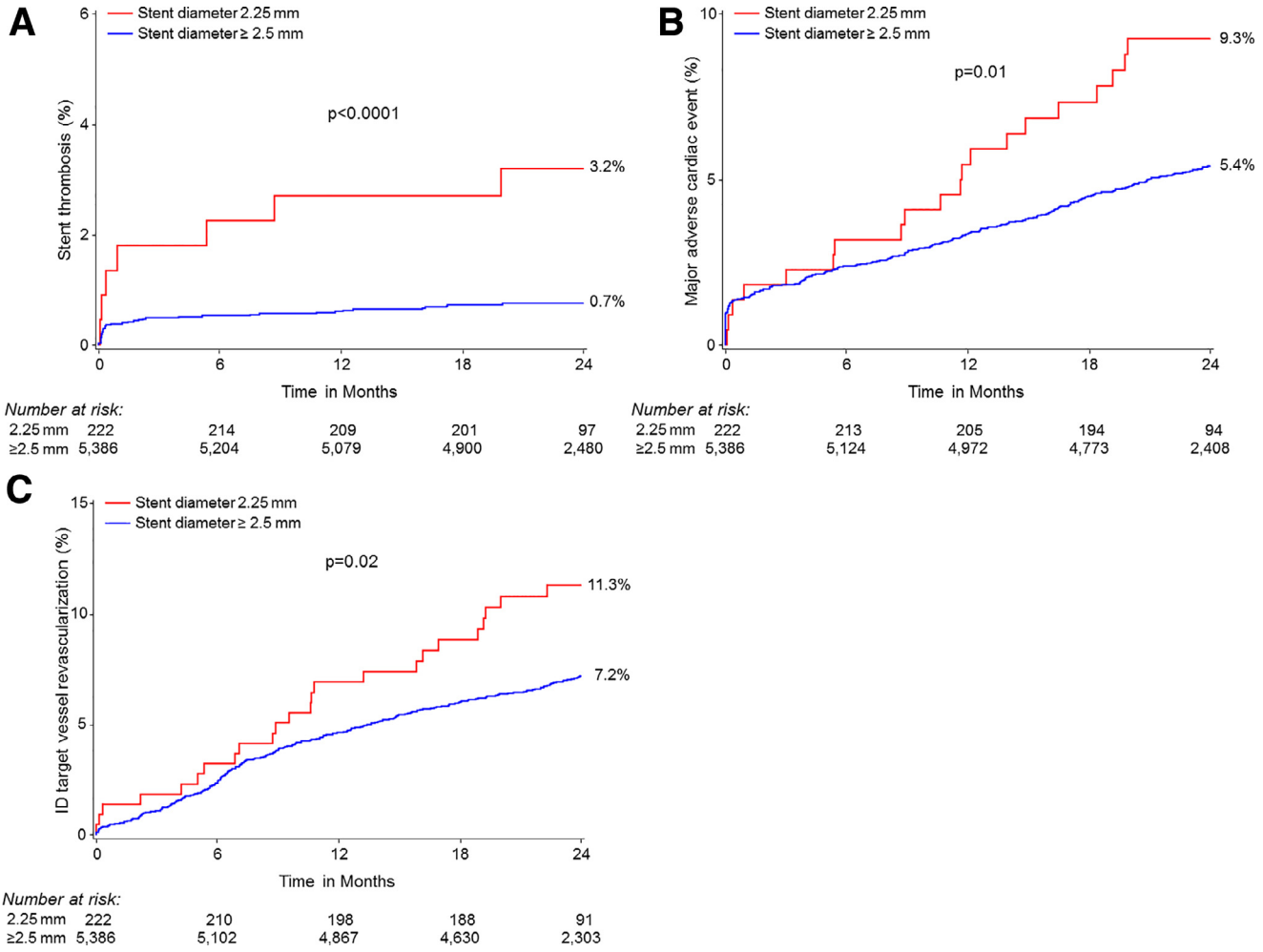

Figure 1. Kaplan-Meier failure rates according to stent diameter 2.25 mm versus ≥2.5 mm. Two-year rates of (*A*) stent thrombosis, (*B*) major adverse cardiac events, and (*C*) ischemia-driven (ID) target vessel revascularization. Major adverse cardiac events was defined as the composite of cardiac death, myocardial infarction, and stent thrombosis. Stent thrombosis was defined as any definite or probable stent thrombosis according to the Academic Research Consortium criteria.

Crude Kaplan-Meier failure rates for ST, MACE, and ischemia-driven target vessel revascularization were higher for patients with SDS versus non-SDS (Figures 1 and 2). The crude rates of other outcomes, including death, were not significantly higher for patients with SDS versus non-SDS (Table 3). After propensity score matching, patients with SDS still had higher rates of ST and MACE but not ischemia-driven target vessel revascularization (Figure 3). SDS versus non-SDS remained significantly associated with ST and MACE after multivariable adjustment for individual risk factors or propensity scores (Figure 4). When patients who received SDS were divided according to whether or not the stent was postdilated to ≥2.5 mm, the thrombotic risk was numerically but not statistically reduced in the nonoverinflated group (3.8% vs 1.6% crude rates of ST, p = 0.39; and 9.7% with vs 8.0% crude MACE rates, p = 0.71, with vs without postdilation with a balloon ≥2.5 mm). There was no statistically significant interaction between receiving an SDS versus a non-SDS and platelet reactivity regarding the risk of ST (p = 0.12) or MACE (p = 0.51). Similarly, there was no significant interaction between receiving an SDS versus non-SDS and DES generation in regard to the risk of ST (adjusted hazard ratio [HR] 4.16, 95% confidence interval [CI] 1.60 to 10.81 with first-generation DES and adjusted HR 4.92, 95% CI 0.45 to 54.29 with second-generation DES, $p_{interaction} = 0.84$) or MACE (adjusted HR 1.50, 95% CI 0.80− to 2.84 with first-generation DES and adjusted HR 2.02, 95% CI 0.84− to 4.86 with second-generation DES, $p_{interaction} = 0.60$).

Discussion

To the best of our knowledge, this analysis performed on 5,608 patients who underwent successful single-lesion PCI with contemporary DES is the largest report exploring the relation between stent diameter and the risk of ST in a prospectively followed patient cohort. It is also the first study to explore how platelet reactivity affects this relation. The main finding is that implantation of drug-eluting SDS is associated with a considerably higher risk of ST and an increased risk of MACE, irrespective of HPR.

Previous studies have shown that stent size is an independent predictor of ST in patients with STEMI who were

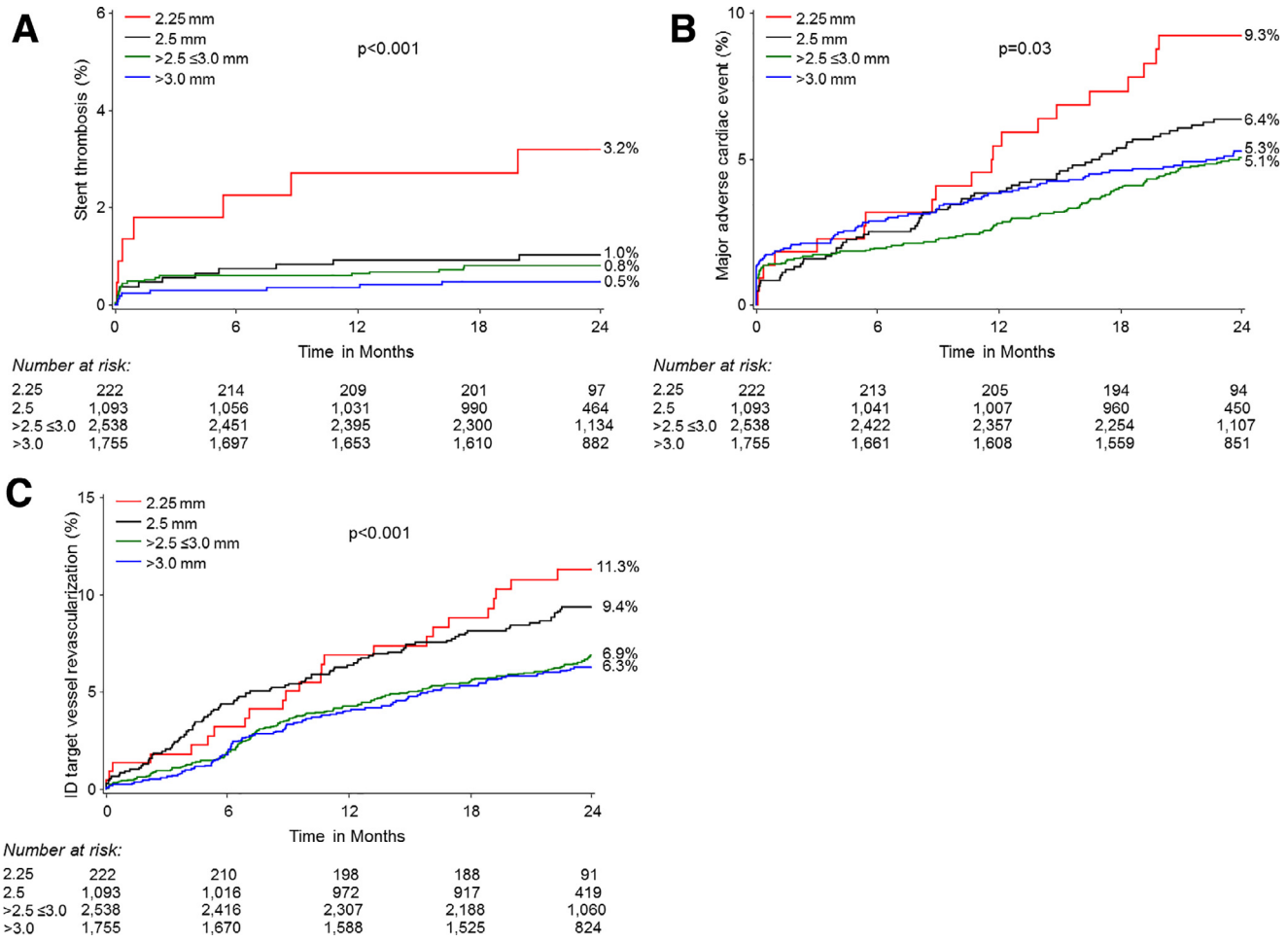

Figure 2. Kaplan-Meier failure rates according to other stent diameters. Two-year rates of (*A*) stent thrombosis, (*B*) major adverse cardiac events, and (*C*) ischemia-driven (ID) target vessel revascularization. Major adverse cardiac event was defined as the composite of cardiac death, myocardial infarction, and stent thrombosis. Stent thrombosis was defined as any definite or probable stent thrombosis according to the Academic Research Consortium criteria.

treated with primary PCI.[4] Our findings are also consistent with the high risk of thrombotic events that has been previously reported for PCI of small vessels.[1–3] Physiologically, our findings are consistent with the fact that flow rate is inversely related to the risk of thrombotic events and decreases with decreasing effective lumen area.[8–10] As mentioned in the introduction, residual platelet reactivity could be expected to have a greater effect on thrombotic risk in vessels with a small mean effective lumen area, where reduced flow rate and a greater endothelial surface area to blood volume ratio would be expected to facilitate platelet activation; however, we found no convincing evidence that platelet reactivity exerts a particularly stronger effect after implantation of SDS.

Further support for the importance of mean lumen area in regard to thrombotic risk after stenting comes from the ABSORB III trial, which compared the Absorb bioresorbable vascular scaffold (Abbott Vascular, Santa Clara, California) to the XIENCE second-generation DES (Abbott Vascular).[3] The Absorb scaffold is a considerably thicker device than the XIENCE stent, and even though Absorb was proven to be noninferior to XIENCE overall, thrombotic event rates were particularly high when Absorb was implanted in small vessels.[3] In light of the ABSORB data, which are likely attributable to the thicker struts of Absorb versus XIENCE, it is somewhat surprising that we found no evidence for an interaction between stent diameter and the use of the thicker first-generation DES versus the thinner second-generation DES in regard to 2-year risk of ST or MACE.[11,12] It should be noted, however, that even in the absence of a disproportionally larger effect of stent diameter on thrombotic risk with first- versus second-generation DES, the effect of stent diameter on thrombotic risk was additive to that of DES generation. Thus, the thrombotic risk is expected to be the highest with first-generation drug-eluting SDS. Furthermore, even if the estimated HR was similar for SDS versus non-SDS regardless of whether first- or second-generation DES were implanted, it should be noted that the interaction tests were statistically underpowered, and we cannot rule out the possibility that a true interaction is present. Of note, there was no statistically significant interaction between treatment arm and vessel size in the ABSORB trial either, even if though the thrombotic events in the Absorb arm were mainly observed after

Table 3
Clinical outcomes

Variable	Stent diameter 2.25 mm (n = 222)	Stent diameter ≥2.5 mm (n = 5,386)	p Value
30 days			
Major adverse cardiac event	1.8% (4)	1.4% (76)	0.64
Target vessel failure*	2.3% (5)	1.7% (93)	0.57
Death	0.9% (2)	0.3% (14)	0.08
Cardiac death	0.9% (2)	0.2% (9)	0.02
Myocardial infarction	0.5% (1)	1.3% (71)	0.26
Ischemia-driven target vessel revascularization	1.4% (3)	0.5% (25)	0.07
Stent thrombosis	1.8% (4)	0.4% (20)	0.001
Bleeding	3.2% (7)	3.2% (171)	0.98
1 year			
Major adverse cardiac event	4.1% (9)	2.0% (103)	0.03
Target vessel failure*	7.8% (17)	6.4% (334)	0.41
Death	1.4% (3)	1.7% (88)	0.73
Cardiac death	0.9% (2)	0.9% (45)	0.93
Myocardial infarction	2.8% (6)	1.3% (67)	0.06
Ischemia-driven target vessel revascularization	6.9% (15)	4.6% (242)	0.12
Stent thrombosis	2.7% (6)	0.6% (32)	0.0002
Bleeding	5.9% (13)	5.9% (314)	>0.99
2 years			
Major adverse cardiac event	9.3% (20)	5.4% (278)	0.01
Target vessel failure*	17.0% (37)	12.6% (650)	0.055
Death	4.6% (10)	3.7% (190)	0.47
Cardiac death	2.8% (6)	1.9% (98)	0.35
Myocardial infarction	5.7% (12)	3.9% (199)	0.20
Ischemia-driven target vessel revascularization	11.3% (24)	7.2% (365)	0.02
Stent thrombosis	3.2% (7)	0.7% (39)	<0.0001
Bleeding	9.3% (20)	8.2% (421)	0.54

Values are n (%).

* Any cardiac death, myocardial infarction, or stent thrombosis.

implantation in smaller vessels.[3] Thus, the exact nature of the relation between external stent diameter, stent strut thickness, and thrombotic risk remains to be established.

Patients who received SDS had higher crude rates of ischemia-driven target vessel revascularization, but this association was weaker than that of stent size and thrombotic events. Although small vessel PCI has been associated with considerably increased risk of restenosis,[13] contemporary DES have reduced this risk.[14–16] Our results are consistent with a recent report the RESOLUTE Global Clinical Trials Program where crude rates of ischemia-driven target vessel revascularization (TVR) were significantly higher in patients undergoing PCI of vessels with reference diameter ≤2.25 mm versus >2.25 mm and ≤2.75 mm, but where this association was no longer statistically significant after multivariable adjustment.[17]

Further data supporting a higher risk of thrombotic and ischemic events with SDS comes from comparative studies of provisional versus routine stenting of the smaller side branch vessel in bifurcation lesions. These studies have not been able to demonstrate any benefit with routine stenting of the side branch.[18–26] Similarly, the dedicated Tryton bifurcation stent (Tryton Medical, Durham, North Carolina) did not reduce adverse events compared with stenting of only the main branch, with balloon angioplasty of the side branch.[27] Interestingly, outcomes with the Tryton stent versus provisional stenting tended to favor the Tryton stent in large side branches.[28] Hence, the lack of improvement in outcomes after routine stenting versus provisional stenting of bifurcation side branches is likely partly explained by the small effective lumen area of the side branch.

Given the fact that SDS are typically implanted in smaller vessels that are less important to maintain patent than vessels supplying large myocardial territories, our results imply that it may be reasonable to consider alternative strategies to stent implantation if the intended stent diameter is small. In other words, it may be worthwhile to avoid implanting stents if the estimated final effective lumen area is small (i.e., <2.5 mm). Given the results observed in recent trials with drug-coated balloons for treatment of small coronary vessels, these devices may be an alternative.[29]

Our investigation has several strengths relative to previous similar studies from other datasets, including a large all-comers population, the prospective nature with blinded ischemic events adjudication, platelet reactivity assessment, and the inclusion of only patients who underwent successful DES PCI, thereby excluding the influence of many intraprocedural complications on outcomes.

Our study also has limitations. First, this is a post-hoc analysis from the ADAPT-DES study; as such, it should be considered hypothesis generating rather than confirmatory. Second, prasugrel only became available late during study enrollment, and ticagrelor was unavailable. Therefore, our

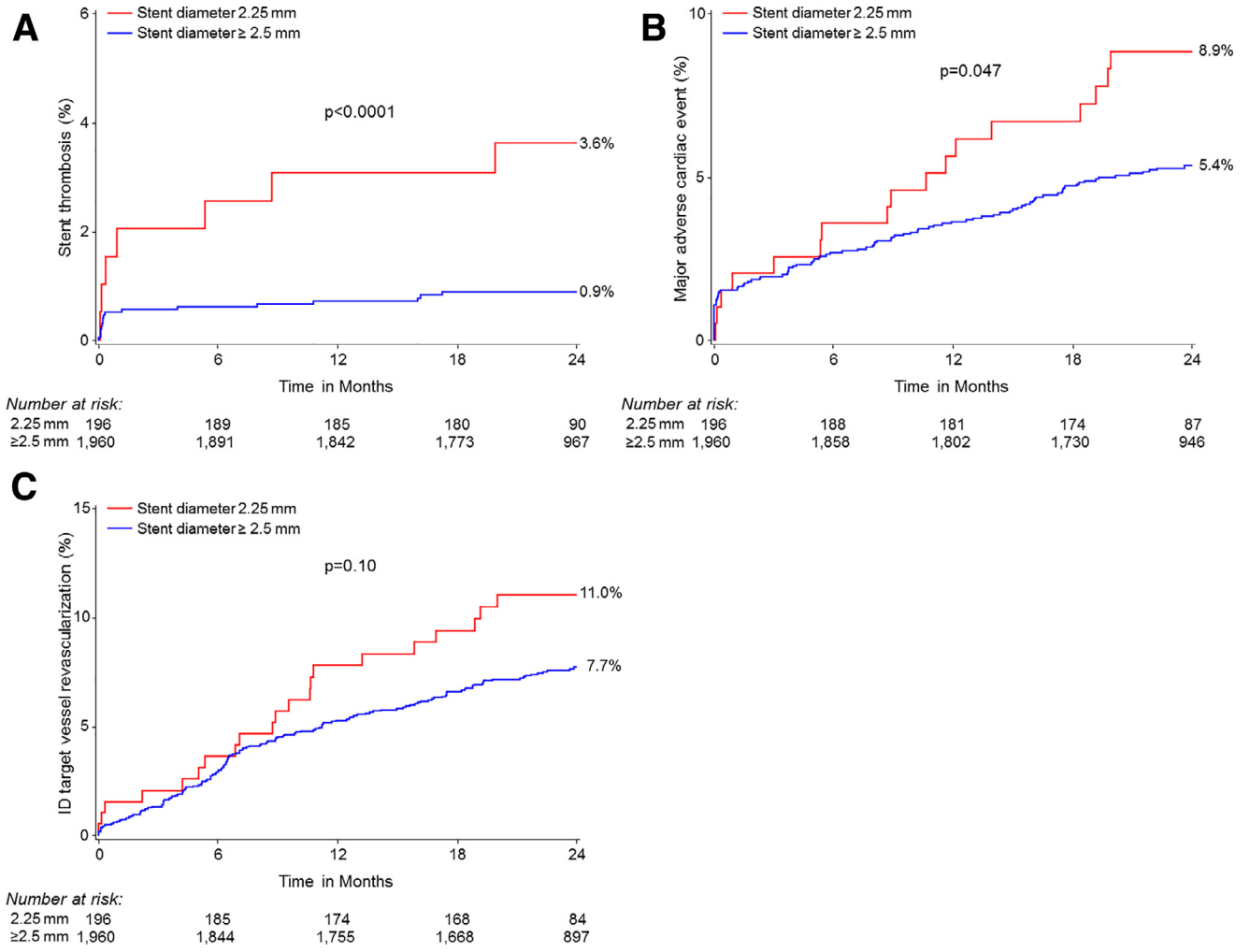

Figure 3. Kaplan-Meier failure rates according to stent diameter after propensity scores matching 1:10 (stent diameter 2.25: ≥2.5 mm). Two-year rates of (*A*) stent thrombosis, (*B*) major adverse cardiac events, and (*C*) ischemia-driven (ID) target vessel revascularization. Major adverse cardiac event was defined as the composite of cardiac death, myocardial infarction, and stent thrombosis. Stent thrombosis was defined as any definite or probable stent thrombosis according to the Academic Research Consortium criteria. The following variables were used to calculate the propensity score: age, sex, current smoker, renal insufficiency, clinical presentation (acute coronary syndrome versus stable coronary artery disease), previous myocardial infarction, previous coronary artery bypass grafting, anemia, left anterior descending coronary artery as the target vessel, multivessel disease, drug-eluting stent generation, platelet reactivity, and total stent length.

findings apply to a clopidogrel-treated PCI population. Third, we cannot rule of *confounding by* indication, that is, the possibility that the effect of small stents on the risk of stent thrombosis is related in part to the possibility that only very tight lesions were treated in smaller vessels, whereas also less severe lesions were treated in larger vessels. Theoretically, the selection of only the tightest lesions in smaller vessels, which are more likely to receive small stents than larger vessels, could impact stent thrombosis risk. Finally, interaction testing could be influenced by low statistical power as well as by the nonlinearity of the interaction.

Disclosures

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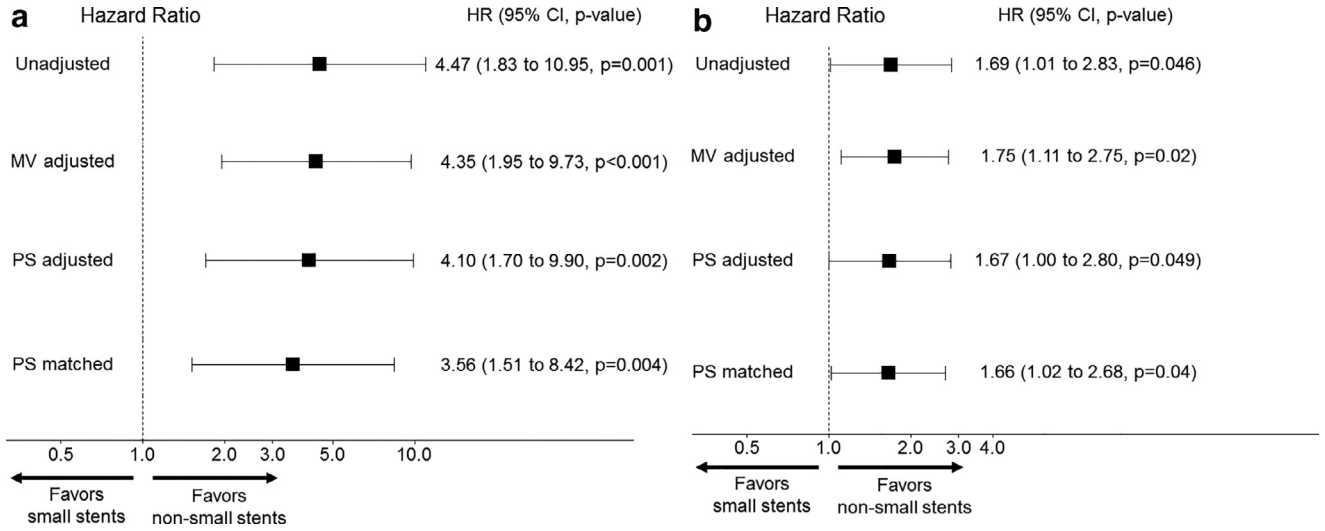

Figure 4. Adjusted risk of stent thrombosis according to stent diameter. Unadjusted and adjusted hazard ratio of (*A*) stent thrombosis and (*B*) major adverse cardiac events associated with small versus nonsmall diameter stents. Major adverse cardiac event was defined as the composite of cardiac death, myocardial infarction, and stent thrombosis. Stent thrombosis was defined as any definite or probable stent thrombosis according to the Academic Research Consortium criteria. The following variables were included in the multivariable model: age, sex, current smoker, diabetes, renal insufficiency, previous myocardial infarction, multivessel disease, clinical presentation, and exclusive use of second-generation drug-eluting stents. The multivariable model for stent thrombosis contains a large number of covariates relative to the number of events; however, it is consistent with the propensity score-based models. The following variables were used to calculate the propensity score: age, sex, current smoker, renal insufficiency, clinical presentation (acute coronary syndrome versus stable coronary artery disease), previous myocardial infarction, previous coronary artery bypass grafting, anemia, left anterior descending coronary artery as the target vessel, multivessel disease, drug-eluting stent generation, platelet reactivity, and total stent length. CI = confidence interval; HR = hazard ratio; MV = multivariable; PS = propensity score.

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Supplementary materials

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1. Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schomig A. Vessel size and long-term outcome after coronary stent placement. *Circulation* 1998;98:1875–1880.
2. Schunkert H, Harrell L, Palacios IF. Implications of small reference vessel diameter in patients undergoing percutaneous coronary revascularization. *J Am Coll Cardiol* 1999;34:40–48.
3. Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, Litt MR, Kini A, Kabour A, Marx SO, Popma JJ, McGreevy R, Zhang Z, Simonton C, Stone GW, ABSORB III Investigators. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. *N Engl J Med* 2015;373:1905–1915.
4. Brodie B, Pokharel Y, Garg A, Kissling G, Hansen C, Milks S, Cooper M, McAlhany C, Stuckey T. Predictors of early, late, and very late stent thrombosis after primary percutaneous coronary intervention with bare-metal and drug-eluting stents for ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 2012;5:1043–1051.
5. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 2013;382:614–623.
6. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–2351.
7. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM, ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203–2216.
8. Reeves RR, Patel M, Armstrong EJ, Sab S, Waldo SW, Yeo KK, Shunk KA, Low RI, Rogers JH, Mahmud E. Angiographic characteristics of definite stent thrombosis: role of thrombus grade, collaterals, epicardial coronary flow, and myocardial perfusion. *Catheter Cardiovasc Interv* 2015;85:13–22.
9. Luscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, Virmani R. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation* 2007;115:1051–1058.
10. van der Giessen AG, Groen HC, Doriot PA, de Feyter PJ, van der Steen AF, van de Vosse FN, Wentzel JJ, Gijsen FJ. The influence of boundary conditions on wall shear stress distribution in patients specific coronary trees. *J Biomech* 2011;44:1089–1095.
11. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 2010;362:1663–1674.
12. Katz G, Harchandani B, Shah B. Drug-eluting stents: the past, present, and future. *Curr Atheroscler Rep* 2015;17:485.
13. Moreno R, Fernandez C, Alfonso F, Hernandez R, Perez-Vizcayno MJ, Escaned J, Sabate M, Banuelos C, Angiolillo DJ, Azcona L, Macaya C. Coronary stenting versus balloon angioplasty in small vessels: a meta-analysis from 11 randomized studies. *J Am Coll Cardiol* 2004;43:1964–1972.

14. Claessen BE, Smits PC, Kereiakes DJ, Parise H, Fahy M, Kedhi E, Serruys PW, Lansky AJ, Cristea E, Sudhir K, Sood P, Simonton CA, Stone GW. Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) Randomized Trials. *JACC Cardiovasc Interv* 2011;4:1209–1215.
15. Ardissino D, Cavallini C, Bramucci E, Indolfi C, Marzocchi A, Manari A, Angeloni G, Carosio G, Bonizzoni E, Colusso S, Repetto M, Merlini PA, SES-SMART Investigators. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. *JAMA* 2004;292:2727–2734.
16. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, Kuntz RE, Popma JJ. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004;43:1110–1115.
17. Parikh MA, Soverow J, Leon MB, Serruys P, Xu B, Yuan Z, Zambahari R, Kirtane A. Outcomes of stenting extra-small (</=2.25 mm) vessels using the Resolute zotarolimus-eluting stent (R-ZES). *EuroIntervention* 2016;12:1215–1221.
18. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR Jr., Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation* 2004;109:1244–1249.
19. Pan M, de Lezo JS, Medina A, Romero M, Segura J, Pavlovic D, Delgado A, Ojeda S, Melian F, Herrador J, Urena I, Burgos L. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. *Am Heart J* 2004;148:857–864.
20. Steigen TK, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbute I, Gunnes P, Mannsverk J, Meyerdierks O, Rotevatn S, Niemela M, Kervinen K, Jensen JS, Galloe A, Nikus K, Vikman S, Ravkilde J, James S, Aaroe J, Ylitalo A, Helqvist S, Sjogren I, Thayssen P, Virtanen K, Puhakka M, Airaksinen J, Lassen JF, Thuesen L. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation* 2006;114:1955–1961.
21. Ferenc M, Gick M, Kienzle RP, Bestehorn HP, Werner KD, Comberg T, Kuebler P, Buttner HJ, Neumann FJ. Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. *Eur Heart J* 2008;29:2859–2867.
22. Colombo A, Bramucci E, Sacca S, Violini R, Lettieri C, Zanini R, Sheiban I, Paloscia L, Grube E, Schofer J, Bolognese L, Orlandi M, Niccoli G, Latib A, Airoldi F. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. *Circulation* 2009;119:71–78.
23. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, Bennett L, Holmberg S, Cotton JM, Glennon PE, Thomas MR, Maccarthy PA, Baumbach A, Mulvihill NT, Henderson RA, Redwood SR, Starkey IR, Stables RH. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation* 2010;121:1235–1243.
24. Chen SL, Santoso T, Zhang JJ, Ye F, Xu YW, Fu Q, Kan J, Paiboon C, Zhou Y, Ding SQ, Kwan TW. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. *J Am Coll Cardiol* 2011;57:914–920.
25. Song YB, Hahn JY, Song PS, Yang JH, Choi JH, Choi SH, Lee SH, Gwon HC. Randomized comparison of conservative versus aggressive strategy for provisional side branch intervention in coronary bifurcation lesions: results from the SMART-STRATEGY (Smart Angioplasty Research Team-Optimal Strategy for Side Branch Intervention in Coronary Bifurcation Lesions) randomized trial. *JACC Cardiovasc Interv* 2012;5:1133–1140.
26. Maeng M, Holm NR, Erglis A, Kumsars I, Niemela M, Kervinen K, Jensen JS, Galloe A, Steigen TK, Wiseth R, Narbute I, Gunnes P, Mannsverk J, Meyerdierks O, Rotevatn S, Nikus K, Vikman S, Ravkilde J, James S, Aaroe J, Ylitalo A, Helqvist S, Sjogren I, Thayssen P, Virtanen K, Puhakka M, Airaksinen J, Christiansen EH, Lassen JF, Thuesen L. Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: Nordic Bifurcation Study 5-year follow-up results. *J Am Coll Cardiol* 2013;62:30–34.
27. Genereux P, Kumsars I, Lesiak M, Kini A, Fontos G, Slagboom T, Ungi I, Metzger DC, Wykrzykowska JJ, Stella PR, Bartorelli AL, Fearon WF, Lefevre T, Feldman RL, LaSalle L, Francese DP, Onuma Y, Grundeken MJ, Garcia-Garcia HM, Laak LL, Cutlip DE, Kaplan AV, Serruys PW, Leon MB. A randomized trial of a dedicated bifurcation stent versus provisional stenting in the treatment of coronary bifurcation lesions. *J Am Coll Cardiol* 2015;65:533–543.
28. Genereux P, Kumsars I, Schneider JE, Lesiak M, Redfors B, Cornelis K, Selmon MR, Dens J, Hoye A, Metzger DC, Muyldermans L, Slagboom T, Francese DP, Ayele GM, Laak LL, Bartorelli AL, Cutlip DE, Kaplan AV, Leon MB. Dedicated bifurcation stent for the treatment of bifurcation lesions involving large side branches: outcomes from the Tryton Confirmatory Study. *JACC Cardiovasc Interv* 2016;9:1338–1346.
29. Jeger RV, Farah A, Ohlow MA, Mangner N, Mobius-Winkler S, Leibundgut G, Weilenmann D, Wohrle J, Richter S, Schreiber M, Mahfoud F, Linke A, Stephan FP, Mueller C, Rickenbacher P, Coslovsky M, Gilgen N, Osswald S, Kaiser C, Scheller B, Investigators B-S. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet* 2018;392:849–856.