Optimal Duration of Dual Antiplatelet Therapy After Two-Stent Treatment in Coronary Bifurcation Lesions

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In complex true coronary bifurcation lesions with severe or diffuse stenosis in both the main and side branches, drug-eluting stent (DES) deployment in both branches (2-stenting) is required. A systematic approach has been recently reported to provide less target lesion failure (TLF) than with the provisional approach.¹ However, patients with high bleeding risk (HBR) are included in >30% of this cohort of progressed atherosclerosis. The optimal period for continuation of dual antiplatelet therapy (DAPT) after 2-stenting has not yet been established.

In this issue of the Journal, Kang et al² investigate 454 patients in the COBIS III registry who finally underwent 2-stenting for bifurcation lesions and report no difference in TLF according to stenting sequence (provisional or systematic) or technique. They also found that left main disease and short-term DAPT were associated with TLF, and the time period of the interaction of TLF and DAPT was as long as 2.5 years (Table).² The efficacy of long-term DAPT is consistent with a previous pooled analysis of 6 randomized trials that demonstrated the efficacy of long-term DAPT on cardiac ischemic events (cardiac death, myocardial infarction [MI], and stent thrombosis [ST]) in complex percutaneous coronary intervention (PCI), including 2-stenting in bifurcation lesions (complex PCI, adjusted hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.35–0.89; noncomplex PCI, 1.01 [0.75–1.35], $P_{\text{interaction}}=0.01$).³ However, a pooled analysis of 8 trials,⁴ 5 of which were the same as in the previous study,³ was performed according to lesion complexity stratification and HBR (Table). The findings demonstrated that long-term DAPT significantly increased the bleeding risk in noncomplex PCI in HBR patients (absolute difference +2.61%, $P=0.003$), and a significant benefit on ischemic events was found only in non-HBR patients (complex PCI, –3.86%, $P=0.04$; noncomplex PCI, –1.14%, $P=0.05$), which indicated the inefficacy of long-term DAPT in complex PCI in HBR patients.⁴ A post-hoc analysis of EXCEL, one of the pivotal trials of unprotected left main disease including 2-stenting in 43%, was performed according to the presence of DAPT continuation after 1 year, which presented a non-significant increase of primary endpoint risk (all-cause death, MI, stroke [HR, 1.59; 95% CI, 0.69–3.48]) and death (2.69 [0.82–8.849]), which suggested the inefficacy of long-term DAPT.⁵

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The effectiveness of 1-month DAPT after implantation of 2nd-generation DES with durable polymer (Pt-Cr everolimus-eluting stent, Co-Cr zotarolimus-eluting stent, and Co-Cr everolimus-eluting stent) has been recently reported in all-comers' trials in HBR patients.^{6–8} In these studies, bifurcation lesions were enrolled in 15–25% of cases. However, the 2-stenting ratio was either not described^{6,7} or extremely low.⁸ Hence, the safety of ultra-short-term DAPT after 2-stenting using these DES has not been confirmed. In a pooled analysis of 2 registries for left main and bifurcation lesions, CHANCE, using polymer-free biolimus-eluting stent (PF-BES) and in RAIN using 2nd-generation DES with a strut thickness of approximately 80 μm (ultra-thin DES) (Table), 1-month DAPT after PCI using the ultra-thin DES resulted in more frequent ischemic events than when using PF-BES (22% vs. 12%, $P=0.04$).⁹ A substudy of bifurcation lesions was conducted in the GLOBAL LEADERS using PF-BES with a randomized comparison between 1-month DAPT plus 23-month monotherapy of ticagrelor and 12-month conventional DAPT plus 12-month monotherapy of aspirin (Table). The substudy included a large number of 2-stenting cases (489 patients), which led to a higher composite endpoint of death and new-onset Q-MI than with the 1-stent treatment (7.2% vs. 4.0%, $P=0.008$), and treatment with 1-month DAPT followed by monotherapy with ticagrelor resulted in less ST compared with conventional DAPT treatment (HR 0.46, 95% CI 0.22–0.97).¹⁰ These findings indicate that using PF-BES will likely result in rapid intimal coverage, and subsequent monotherapy with a potent antiplatelet agent is effective even in short-term DAPT after complex PCI in patients with HBR.

In the present study,² probable and definite ST frequency was acceptably low (1.3%) even after 2-stenting. However, short-term DAPT was identified as an independent risk factor for TLF, which suggested that TLF was related to subclinical thrombus attachment on the overlapped stent struts with delayed healing, malapposed struts, more floating struts at the branch ostium, and dissection at the stent edge of the gap between the 2 stents. There remains room for improvement in TLF before

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received May 13, 2021; accepted May 13, 2021; J-STAGE Advance Publication released online June 17, 2021

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ISSN-1346-9843

Table. Previous Studies of the Effect of the Duration of DAPT After Complex Coronary Intervention, Including Bifurcation Lesions

Study	Type	Date	Objective	Stent	Bifurcation, n (% to whole PCI)	2-stent, n (% to whole PCI)
Giustino et al ³	Pooled 6 RCTs analysis*	2016	All comers	1 st-generation DES 12–15%, 2nd-generation DES 85–88%	ND	661 (6.9)
EXCEL ⁵	Post-hoc analysis in RCT	2018	UPLM	DP-EES	633 (100)	272 (43)
SENIOR ⁶	RCT	2018	HBR (elderly, >75 years)	DP-EES vs. BMS	263 (14.9)	ND
Costa et al ⁴	Pooled 8 RCTs analysis [#]	2019	All comers	BMS 8–20%, 1 st-generation DES 6–10%, 2nd-generation DES 71–83%	ND	1,197 (8.0)
STOP-DAPT 2 ⁷	RCT	2019	HBR	DP-EES	769 (25.6)	16 (0.5)
CHANCE and RAIN ⁹	Pooled 2 registries analysis	2020	UPLM and bifurcation (CHANCE, HBR 77.7%)	CHANCE: PF-BES, RAIN: Ultra-thin DES	843 (100)	ND
GLOBAL LEADERS Bifurcation ¹⁰	RCT	2020	All comers	PF-BES	2,498 (100)	489 (19.8)
ONYX-ONE ⁷	RCT	2020	HBR	DP-ZES vs. PF-BES	453 (16.0)	ND
COBIS III: 2-stent ²	Registry	2021	UPLM and bifurcation	2nd-generation DES	454 (100)	454 (100)

Study	DAPT	Clinical results
Giustino et al ³	Short DAPT (3–6 months) vs. Long DAPT (≥12 months)	Long vs. short DAPT on primary endpoint (cardiac death, MI, ST), adjusted HR (95% CI): Complex PCI, 0.56 (0.35–0.89); Noncomplex PCI, 1.01 (0.75–1.35); $P_{\text{interaction}}=0.01$. Major bleeding risk: complex PCI, 1.81 (0.67–4.91); noncomplex PCI, 1.75 (0.98–3.12), $P_{\text{interaction}}=0.96$
EXCEL ⁵	DAPT <1 year vs. DAPT ≥1 year	Long vs. short DAPT on primary endpoint (MI, death, stroke), HR 1.59 (95% CI 0.69–3.48; $P=0.28$), all-cause death 2.69 (0.82–8.84, $P=0.10$)
SENIOR ⁶	DAPT 1 month for stable AP, 6 months for ACS	DP-EES vs. BMS on the primary endpoint (all-cause death, MI, stroke, TLR), relative risk 0.71 (95% CI 0.52–0.94, $P=0.02$)
Costa et al ⁴	Short DAPT (3–6 months) vs. long DAPT (≥12 months)	Long vs. short DAPT, absolute difference: Ischemic events in non-HBR patients: Complex PCI, –3.86%, $P=0.04$; Noncomplex PCI, –1.14%, $P=0.05$. In HBR patients, Complex PCI, +1.30%, $P=0.76$; Noncomplex PCI, +1.45%, $P=0.39$. Bleeding risk in non-HBR patients: Complex PCI, +0.28%, $P=0.57$; Noncomplex PCI, +0.12%, $P=0.53$. In HBR patients, Complex PCI, +3.04%, $P=0.30$; Noncomplex PCI, +2.61%, $P=0.003$.
STOP-DAPT 2 ⁷	1-month DAPT vs. 12-month DAPT	Short vs. long DAPT in primary endpoint (cardiovascular death, MI, ST, stroke, major bleeding), absolute difference, –1.34% (–2.57% to –0.11%); HR, 0.64 (0.42–0.98), noninferiority ($P<0.001$), superiority ($P=0.04$)
CHANCE and RAIN ⁹	CHANCE: DAPT <1-month 40%, <12-months 99.9%. RAIN: Operator's discretion	Ultra-thin DES vs. PF-BES: primary endpoint (cardiac death, MI, TLR, ST) after 1-year, 9% vs. 8%, $P=0.56$; 2-stent group, TLR 8.7% vs. 4.5%, $P=0.75$, ST 4.3% vs. 3.2%, $P=0.91$. 1-month DAPT group, primary endpoint 22% vs. 12%, $P=0.04$
GLOBAL LEADERS Bifurcation ¹⁰	1-month DAPT+23-month ticagrelor vs. 12-month DAPT+12-month aspirin	Primary endpoint (all-cause death, new Q-MI), 1-stent 4.2% vs. 2-stent 7.0%, $P=0.008$. Short vs. long DAPT on ST, HR 0.46, 95% CI 0.22–0.97
ONYX-ONE ⁷	1-month DAPT	DP-ZES vs. PF-BES, primary endpoint (cardiac death, MI, ST), risk difference, 0.2%, $P=0.01$ for noninferiority; secondary endpoint (cardiac death, MI, TLR), risk difference 0.2%, $P=0.007$ for noninferiority
COBIS III: 2-stent ²	Operator's discretion	Risk of TLF: LM bifurcation, HR 3.192 (95% CI 1.568–6.500, $P=0.001$); Short DAPT, 0.988/1-month increase (0.980–0.995, $P=0.002$)

*Pooled analysis of 6 RCTs (EXCELLENT, OPTIMIZE, PRODIGY, RESET, SECURITY, ITALIC). #Pooled analysis of 8 RCTs (EXCELLENT, OPTIMIZE, PRODIGY, RESET, SECURITY, BIOSCIENCE, COMFORTABLE, ZEUS). ACS, acute coronary syndrome; AP, angina pectoris; BES, biolimus-eluting stent; BMS, bare metal stent; CI, confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DP, durable polymer; EES, everolimus-eluting stent; HBR, high bleeding risk; HR, hazard ratio; PCI, percutaneous coronary intervention; PF, polymer-free; MI, myocardial infarction; ND, not described; RCT, randomized control trial; ST, stent thrombosis; TLF, target lesion failure; TLR, target lesion revascularization; UPLM, unprotected left main; ZES, zotarolimus-eluting stent.

encouragement of prolonged DAPT. (1) There is a dominance of systematic 2-stenting over provisional 2-stenting (65.2% vs. 25.8%). In particular, a higher frequency of TLF after systematic 2-stenting (crush stenting used most frequently) in the non-left main bifurcation compared with provisional 2-stenting suggests priority of the provisional approach in this lesion. (2) Significant efficacy of intravascular ultrasound (IVUS) was not observed in this study. Although stent under-expansion in 2-stenting is a critical risk factor for TLF, and is documented well with IVUS, more detailed intravascular observation may be required. Optical coherence tomography with higher resolution and 3D reconstruction may be another option to improve clinical outcomes.¹¹ (3) Efficacy of final kissing balloon inflation (FKB) after 2-stenting was not demonstrated. FKB is generally recommended to reduce TLF because of the wide stent expansion of both the main and side branches and the decrease in stent malapposition.¹² Simultaneously, FKB includes risks of non-uniform dilation, stent deformation,¹² and remaining incomplete strut apposition after suboptimal guidewire recrossing.¹¹ Performing assessments before and after FKB using intravascular imaging is appropriate.

The results of the present study of 2-stenting in bifurcation lesions raise the following clinical issues. First, a more detailed survey of thrombus-related failure during and after the procedure is necessary. Second, stricter selection of 2-stenting for HBR patients should be considered. If 2-stenting is inevitable, short-term DAPT followed by a potent antiplatelet agent is a potential alternative to long-term DAPT. Third, the priority of systematic 2-stenting over the provisional approach is limited in complex true bifurcation lesions, which is more evident in the non-left main bifurcation.

Disclosure

The author does not have any conflicts of interest.

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