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Editorial

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The Newer-Generation DES, Really Nothing to Special?

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▸ See the article "Efficacy and Safety of Sirolimus-Eluting Stent With Biodegradable Polymer Ultimaster™ in Unselected Korean Population: A Multicenter, Prospective, Observational Study From Korean Multicenter Ultimaster Registry" in volume 54 on page 339.

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In recent years, newer-generation of drug-eluting stents (DESs) have been developed and widely used for contemporary coronary revascularization. In the history of stent development, in-stent restenosis from neointimal hyperplasia and neoatherosclerosis has been identified as a one of main mechanisms of stent failure. In this regard, first-generation DES was designed to contain mTOR inhibitors on their surface for anti-proliferative effect and the polymer, coated on the metallic stent strut, was used for the controlled release of these drugs. Since the hypersensitivity reactions to polymer has been known as the possible cause of late or very late stent thrombosis (VLST),[1] initial types of second-generation DES used biocompatible durable polymer and showed excellent safety and efficacy in daily practice.[2] Conversely, newer-generation DES used biodegradable polymer, instead of durable polymer, which is fully resorbed over months to years. In addition, several stents had abluminal distribution of biodegradable polymer to minimize luminal immunologic reaction or even had direct drug reservoir on metallic stent surface without polymer. Furthermore, strut thickness became thinner, mostly less than 81 μm, for the purpose of reducing the restenosis rate.[3] **Table 1** presented the characteristics of currently available representative newer-generation DESs in Korea.

Contrary to expectations, previous studies reported not-outstanding efficacy of newer-generation DESs compared with second generation DESs. In terms of target lesion failure (TLF), most all-comer trials demonstrated non-inferiority, not superiority of biodegradable polymer-DESs compared with durable polymer-DESs. Similarly, long-term risks of TLF were comparable among second and newer-generation DESs in multiple network meta-analyses, despite short-term results seemed favorable to ultrathin-strut biodegradable polymer-DES.[4][5] Only BIOSTEMI trial showed ultrathin-strut biodegradable polymer sirolimus-coated stent (Orsiro™; Biotronik, Bülach, Switzerland) was superior to the durable polymer everolimus-coated stent (Xience Prime/Xpedition; Abbott Vascular, Santa Clara, CA, USA) in patients with STEMI at 5 years.[6] Ultimaster™ (Terumo, Tokyo, Japan) is one of the newer-generation DESs with a thin strut (80 μm) cobalt-chromium, sirolimus-eluting stent platform coated with abluminal biodegradable polymer which are fully resorbed within 3 to 4 months. Park et al.[7] presented one-year result of Ultimaster™ from a multicenter, prospective, observational registry of Korean all-comer patients. Due to the single-arm study design, authors summarized the results of previous landmark studies of Ultimaster™ as a comparator to demonstrate the clinical performance of the Ultimaster™ in Korean patients with diverse

Table 1. Representative newer-generation drug-eluting stents in Korea

Stent platform	Orsiro™	Biomime	Synergy™	Ultimaster™	Biofreedom Ultra	Cre8 EVO
Manufacturer	Biotronik (Germany)	Meril Life Science (India)	Boston Scientific (USA)	Terumo (Japan)	Biosensors (Singapore)	Alvimedica (Italy)
Platform alloy	Cobalt-chromium	Cobalt-chromium	Platinum-chromium	Cobalt-chromium	Cobalt-chromium	Cobalt-chromium
Anti-proliferative drug	Sirolimus	Sirolimus	Everolimus	Sirolimus	Biolimus A9	Sirolimus + Fatty acid
Strut thickness (μm)	61	65	74	80	84–88	80
Polymer (degradation time)	PLLA (12–15 months)	PLLA & PLGA (2 months)	PLGA (3–4 months)	PLCL (3–4 months)	None	None
Polymer distribution	Conformal	Conformal	Abluminal	Abluminal	Abluminal	Abluminal
Outcomes of largest all-comer registry	SCAAR registry; 4,561 patients; 2-year TLR: 1.5%, definite ST: 0.67%	The merit-3 registry; 1,161 patients; 1-year TLR: 0.52%, definite ST: 0.09%	SCAAR registry; 4,247 patients; 1-year clinically driven restenosis: 1.1%, definite ST: 0.4%	e-Ultimaster registry; 37,198 patients; 5-year TLF: 3.2%, definite ST: 1.7%	Trial is ongoing	Trial is ongoing

PLCL = poly-DL-lactide-co-caprolactone; PLGA = poly-L-lactide-co-glycolide; PLLA = poly-L-lactide; ST = stent thrombosis; TLF = target lesion failure; TLR = target lesion revascularization.

Data Sharing Statement

The data required to reproduce these findings cannot be shared as this is an editorial.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

risk profile. They included 576 patients, 40% of whom had diabetic mellitus (DM) and 68% of whom presented with acute coronary syndrome (ACS). The 1-year cumulative incidence of TLF was 4.1% and incidence of definite or probable ST was 0.6%. Despite the larger proportion of patients with DM or ACS in Korean registry, the 1-year risk of TLF was comparable and risk of ST was numerically lower compared with those of other global data. This can give us confirmatory information regarding the efficacy and safety of Ultimaster™ on the real-world practice in Korea.

However, the result of current study has several limitations and the results should be interpreted with caution. As mentioned in limitation section of the study, the study sample size was relatively small and not powered for subgroup analyses based on the reported cumulative incidence of adverse clinical events. In addition, due to the lack of direct comparator with another stent platform, robust statistical analyses were not possible to detect insightful differences between Ultimaster™ and other stent platforms according to lesion complexity, patient's ischemic or bleeding risk. Furthermore, follow-up duration was short and detailed angiographic and procedural data were not available. Since the development of the second-generation durable polymer-DESs with excellent safety and efficacy, accumulated evidences have indicated that patient comorbidities, lesion complexity/characteristics, and procedural optimization drive the clinical outcome, rather than DESs itself. Nevertheless, regarding stent thrombosis (ST), there may be light for newer-generation DESs, especially thin- or ultrathin-strut biodegradable polymer-DESs.[8] The occurrence of ST was known to have multifactorial pathophysiology, includes patient-, lesion-, procedural- and stent-related factors. Confined to VLST, risk factors remain poorly understood unlike early or late ST.[9] Because, uncovered struts and delayed reendothelialization have been suggested as a one of most important possible causes for VLST, the stent platforms itself, especially strut thickness, may have a role in the occurrence of VLST.[10] Considering the very low cumulative incidence of ST, larger study population with longer follow-up period are needed to take sufficient power for discrimination. In network meta-analysis with 19,437 patients and median follow-up period of 50 months, ultrathin-strut biodegradable polymer-DESs had significant low risk of ST compared with durable polymer zotarolimus-eluting stent.[5] Also in patient level pooled data from DES trials with 9,700 patients and median follow-up period of 10 years, the rate of definite ST was significantly lower in biodegradable polymer-DESs than in early durable polymer-DESs (1.0% vs. 3.5%).[11] Upcoming 10-year, large-scale pooled data of newer-generation DESs will finally answer this question: the newer-generation DES, really nothing to special?

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