Editorial

Exploring alternatives to drug-eluting stents: the potential of combining drug coated balloon with bare-metal stents

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Despite the establishment of optimal pharmacologic therapies for atherosclerotic cardiovascular disease, ST-segment elevation myocardial infarction (STEMI) remains a leading cause of death in developed countries (1). For STEMI cases, coronary stenting with new-generation drug-eluting stents (DES) has demonstrated superior safety and efficacy compared with the use of bare-metal stents (BMS) and first-generation DES, and has gained global consensus as the first-line treatment option (2-4). However, even in the era of new-generation DES, there are the remaining problems of late in-stent restenosis and very late stent thrombosis caused by neoatherosclerosis, which is histologically characterized by accumulation of lipid-laden foamy macrophages within the neointima with or without necrotic core formation and/or calcification (5,6). One potential mechanism of accelerated neoatherosclerosis is the promotion of chronic inflammation derived from the polymers that coat the DES. Dedicated studies are warranted to explore new revascularization methods that reduce events in the chronic phase.

Drug-coated balloons (DCB), first introduced for the treatment of in-stent restenosis, have been gaining attention as an alternative to new-generation DES for *de novo* coronary artery lesions (7). To date, several randomized controlled trials (RCTs) have investigated efficacy of the DCB-only strategy in STEMI (*Table 1*) (8-15). These studies demonstrated that the incidence of adverse cardiovascular events in the early post-revascularization period was similar in the DCB-only group and the DES group (8,10,11). Furthermore, the values of fractional flow reserve and the degree of late lumen loss at 9 months were also comparable between the group (9,12). These results suggested the applicability of DCB-only strategy in STEMI, however, these RCTs had the limitation of small sample sizes and short observation periods. In addition, the DCB-only strategy required bailout stenting in a certain number of cases due to the inability to obtain sufficient luminal gain or the occurrence of coronary artery dissection, a causative factor for late restenosis. Since the majority of coronary dissections are not apparent on angiography, potential vascular injury in the DCB-only strategy may compromise their clinical efficacy (16).

In a recent study published on *Cardiovascular Diagnosis and Therapy*, the authors have explored the potential of the DCB-combined strategy; DCB dilatation following BMS implantation (14). The possible benefits of this strategy are that BMS may provide acute gains, DCB may inhibit endometrial proliferation in the early posttreatment

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Table 1 Randomized control trials evaluating the effects of drug-coated balloon in STEMI

Strategies	DCB *vs.* DES					DCB in BMS (DCB-combined strategy) *vs.* BMS		BMS *vs.* BMS after DCB *vs.* DES
	Gobić (8) [2017]	Vos (9) [2019]	Hao (10) [2021]	Niehe (11) [2022]	Wang (12) [2022]	García-Touchard (13) [2017]	García-Touchard (14) [2023] (current study)	Belkacemi (15) [2012]
Therapies	41:37 for DCB *vs.* DES	60:60 for DCB *vs.* DES	42:42 for DCB *vs.* DES	60:60 for DCB *vs.* DES	92:92 for DCB *vs.* DES	111:112 for DCB in BMS *vs.* BMS	108:111 for DCB in BMS *vs.* BMS	51:50:49 for BMS *vs.* BMS after DCB *vs.* DES
Types of DCB	SeQuent Please (B. Braun, Melsungen, Germany)	Pantera Lux (Biotronik, Berlin, Germany)	Bingo (Yinyi Biotech, Liaoning, China)	Pantera Lux (Biotronik)	Vasoguard (Rientech, Shandong, China)	Pantera Lux in PRO-Kinetic Energy stent (Biotronik)	Pantera Lux in PRO-Kinetic Energy stent (Biotronik)	DIOR (Eurocor, Bonn, Germany)
Comparators	Biomime (Meril Life Sciences, Vapi, India)	Orsiro (Biotronik) or Xience (Abbott, Abbott Park, IL, USA)	Drug-eluting stent (not specified)	Orsiro or Xience	Cordimax (Rientech)	PRO-Kinetic Energy stent	PRO-Kinetic Energy stent	BMS: Genius Magic stent (Eurocor); DES: Taxus (Boston Scientific, Natick, MA, USA)
Bail-out stent implantation in the DCB group	3 cases (7.3%)	1 case (1.6%)	4 cases (9.5%)	11 cases (18%)	None	Not applicable	Not applicable	Not applicable
Primary outcome	Composite of cardiovascular death, reinfarction, target lesion revascularization and stent thrombosis	Fractional flow reserve	Composite of cardiovascular death, re-infarction and revascularization of target lesions	Composite of cardiac death, recurrent myocardial infarction, and ischemia-driven target-lesion revascularization	Late lumen loss	Late lumen loss	Not specified	Late lumen loss
Follow-up period	6 months	9 months	1 year	2 years	9 months	9 months	8 years	6 months
Findings	The primary endpoint was not significantly different between the groups (none *vs.* 5.4%, P=0.29)	The primary endpoint was not significantly different between the groups (0.92 *vs.* 0.91, P=0.27)	The primary endpoint was not significantly different between the groups (11% *vs.* 12%)	The primary endpoint was not significantly different between the groups (5.4% *vs.* 1.9%, P=0.34)	The primary endpoint was not significantly different between the groups (0.24 *vs.* 0.31 mm, P=0.215)	The DCB in BMS group showed significantly smaller late lumen loss that the BMS group (0.31 *vs.* 0.80 mm, P<0.0001)	There was a lower rate of target vessel revascularization (3.7% *vs.* 14.3%, P=0.006) and a trend towards lower target lesion revascularization (2.8% *vs.* 8.9%, P=0.052)	BMS after DCB failed to show angiographic superiority to BMS only. Angiographic results of DES were superior to both BMS and BMS after DCB. (0.74 *vs.* 0.64 *vs.* 0.21 mm, P<0.01)

STEMI, ST-elevation myocardial infarction; DCB, drug-coated balloon; DES, drug-eluting stent; BMS, bare-metal stent.

period, and the absence of polymers may also inhibit neoatherosclerosis formation in the chronic period due to the lack of inflammation. In PEBSI (paclitaxel-eluting balloon after bare metal stent implantation)-1 trial, they have already reported smaller late lumen loss at 9 months and better clinical outcomes at 1 year in the DCB-combined group compared to the BMS group (13). Furthermore, their optical coherence tomography study has also demonstrated that the DCB-combined group exhibited more optimal strut coverage at 3 months compared to the treatment with new-generation sirolimus-eluting stents (17). In the present issue, García-Touchard *et al.* evaluated 8-year clinical follow-up of patients enrolled in the PEBSI-1 trial (14). The main findings of their study are (I) the DCB-combined group showed lower rate of target vessel revascularization (TVR) [3.7% *vs.* 14.3%; hazard ratio: 0.24, 95% confidence interval (CI): 0.08–0.73; P=0.006] and trends towards lower rate of target lesion revascularization (TLR) (2.8% *vs.* 8.9%; hazard ratio: 0.3, 95% CI: 0.083–1.090; P=0.052) compared to the BMS group; (II) there was no significant differences in the occurrence of all-cause death, cardiac death, reinfarction, or stent thrombosis between the groups; (III) there were no cardiac death, no TVR, no TLR in the DCB-combined group beyond the 5-year follow-up; (IV) in contrast, the BMS group experienced an additional cardiac death, one case of TVR, one case of TLR, and one case of stent thrombosis during the period from year 5 to 8.

Although this study provides additional clinical data to support the favorable anti-atherosclerotic effect of DCB-combined strategy, several limitations should be considered when interpreting the findings. First, the control group in this study was BMS, not new-generation DES, which is the first-line treatment for STEMI in the modern era. Therefore, it is not possible to assess whether the DCB-combined strategy is worth changing the current treatment strategy. Belkacemi *et al.* reported conflicting results with the present study, in which the BMS implantation after DCB dilatation strategy failed to demonstrate angiographic superiority over BMS alone; furthermore, in that study first-generation DES demonstrated angiographic superiority over both BMS and the BMS after DCB strategy, as well as a reduction in future in-stent restenosis and adverse cardiac events (15). Second, this study included only cases with successful BMS implantation, which may introduce the selection bias. Since this study included only cases of successful procedures, it is not surprising that the number of subsequent events in long-term follow-up was suppressed. Third, because the DCB-combined strategy significantly suppressed TVR rather than TLR, it may not have been able to demonstrate a significant effect on the suppression of neoatherosclerosis formation at the treated lesions, which is important in contrast to the conventional DES strategy. The Kaplan-Meier curve of TLR suggests that the early neointimal proliferation inhibition by DCB suppressed the restenosis better than the BMS group, but the nearly parallel curves in the chronic phase do not indicate a conferred effect of DCB for suppressing neoatherosclerosis formation. Fourth, the authors emphasized that TVR, TLR, and stent thrombosis did not occur after 5 years in the DCB-combined group, but only one case occurred in the BMS group during the same period. Given the small sample size of this study, which was set up to compare late lumen loss rather than clinical outcomes, it is unclear whether the difference in this small number of events makes sense. Fifth, the DCB-combined strategy uses both BMS and DCB, which may make revascularization procedure more expensive and time-consuming.

The novel and interesting concept of the DCB-combined strategy has proven to be effective in BMS-controlled studies, but caution is needed in interpreting the results. Further dedicated studies with new-generation DES-controlled, with large sample, and perhaps requiring long-term follow-up are needed to determine whether the DCB-combined strategy can be alternative to the current new-generation DES strategy.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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