Editorial

Feasibility of emergent reperfusion therapy using paclitaxel-coated balloons for acute coronary syndrome: lessons from the PEBSI Study

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García-Touchard *et al*. reported the results of an 8-year follow-up from a randomized clinical trial (PEBSI Study) with a very high percentage (97–98%) of clinical follow-up (1). The PEBSI Study was a multicenter, single-blind, randomized controlled trial involving patients experiencing their first ST-segment elevated myocardial infarction (STEMI), which revealed the benefits of paclitaxel/drug coated balloons (PCBs/DCBs) after bare-metal stent (BMS) implantation (DCB-combined strategy) compared to the outcomes associated with BMS alone (BMS-only therapy). In this long interval, a brief and single application of PCB after BMS implantation exhibited sustained safety and efficacy in patients with STEMI compared to the reperfusion rates associated with BMS alone. At present, since BMS is unavailable, this strategy cannot be applied in daily practice. Drug-eluting stents (DES) are now the preferred therapy in STEMI. However, this DCB-combined strategy is associated with a low frequency of late-phase cardiac events, including very low frequencies of target lesion revascularization (TLR) (2.8%), target vessel revascularization (TVR) (3.7%), and no episodes of stent thrombosis, that is, none of major adverse cardiac events (MACEs), as reported in a meta-analysis of the outcomes (2). This highlights the favorable long-term clinical outcomes of this unique strategy from the perspective of post-hoc analyses.

The PEBSI Study (DCB-combined therapy) revealed the beneficial impacts of PCB angioplasty with BMS for the reperfusion therapy of STEMI, particularly with regards to early (3) and late coronary healing, at the affected site of STEMI. Optical coherence tomography (OCT) revealed a low rate of uncovered struts (3.2%), a high rate of covered and apposed struts (96.1%), and, compared to BMS-alone therapy, showed significant reductions of major coronary evaginations (approximately 42.2%), as well as a significantly higher rate of development of thin homogeneous neointimal layer (approximately 3.5 times), after only a brief but effective application of paclitaxel after BMS implantation (3). Therefore, additional PCB angioplasty is likely to reduce the probability of the mal-apposition of BMS, with the drug (paclitaxel) facilitating acute coronary healing by suppressing evagination on the BMS. Moreover, paclitaxel may diffuse into the vessel lumens via the BMS struts, enabling a reduction in the BMS restenosis rate in STEMI due to the frequency of in-BMS restenosis in cases where STEMI is relatively high, which is the most significant issue associated with BMI reperfusion therapy (2). Since no cumulative adverse clinical outcomes occurred during the late phase from index percutaneous coronary intervention (PCI), the late coronary healing were stable without significant neo-atherosclerosis after the index PCB-combination therapy (1).

Herdeg *et al*. (4) reported on the impact of the DCB +

BMS strategy (in a reverse order compared to that reported by the PEBSI Study) on *de novo* coronary lesions compared to that of BMS and the first-generation (1st-G) paclitaxel-eluting stent (PES). The DCB + BMS strategy retained the metal struts of BMS to prevent acute post-angioplasty recoil and supplemented the local release of anti-proliferative agents by being combining with a prior DCB angioplasty. According to a recent network meta-analysis (5), the DCB + BMS strategy is superior to BMS alone. However, the DCB + BMS strategy is inferior to DES in terms of MACEs, TLR, and angiographic outcomes (late luminal loss and binary restenosis). Therefore, the order of treatment administered in the PEBSI Study, that is, initially scaffolding the vessel followed by the suppression of the culprit plaque with PCB to diffuse the paclitaxel on the plaque material protrusion inside the BMS, to bring about the beneficial impacts described above.

At present, both of the DCB-combined therapies (1,4) cannot be applied in clinical settings due to the fact that BMS have been unavailable. In addition, all of the frequencies of the OCT-detected parameters of the PEBSI Study (3) have been significantly improved in more recent DES (6). Consequently, adverse late coronary healing due to MACE have significantly reduced due to the use of recent DES. Therefore, based on the improved intravascular findings (6) and the results of the aforementioned network meta-analysis (5), the combination of the DCB and BMS strategies can be considered a historical therapeutic strategy.

The long-term efficacy of a brief and single application of a paclitaxel (PCB-alone angioplasty) in patients with STEMI and acute coronary syndrome (ACS) compared to that of DES has been highlighted in recent reperfusion therapies (5,7). Changes in the main devices of mechanical reperfusion therapy for STEMI, namely the transition from plain old balloon angioplasty (POBA) and primary stenting using BMS to the use of DES, were as follows. Just 20 years ago, the CADILLAC study (8) reported that even if an optimal acute POBA result (residual diameter stenosis <30% without significant dissection) is achieved after primary POBA in acute myocardial infarction (AMI), both the early and late clinical outcomes could be further improved with routine BMS implantation. Subsequently, the use of primary stenting using BMS was widely adopted as the standard reperfusion therapy for patients with STEMI, until the safety and efficacy of 1st-G DES were established. In 568 Japanese patients with STEMI, although more complex lesions and high-risk patients were included in the 1st-G sirolimus-eluting stent (SES) group, the 1st-G SES showed significant angiographic efficacy by reducing the frequency of in-stent restenosis and TLR without increasing MACE [mortality, myocardial infarction (MI), and all definite stent thrombosis] (9). This study was integrated in the meta-analysis to compare the long-term (>3 years) outcomes of the 1st-G DES with those of BMS for the treatment of STEMI (2). The use of 1st-G DES (1st-G SES and 1st-G PES) as the first choice for primary stenting for STEMI resulted in decreased repeat revascularization with no increase in stent thrombosis, mortality, or recurrent MI. The superiority of 2nd-G DES (everolimus; EES) and biolimus-eluting stent for STEMI in terms of clinical outcomes and intravascular findings were consistently shown by the EXAMINATION (10) and COMFORTABLE AMI studies (11). The BIOSTEMI study (12) reported that biodegradable polymer SES (3rd-G SES) were superior to durable polymer EES (2nd-G EES) with respect to target lesion failure at one year, largely driven by a reduction in ischemia-driven TLR. Thus, due to advances in the PCI devices used for reperfusion therapy for STEMI, the outcomes have significantly improved. All therapies and devices associated with reperfusion therapy for STEMI have improved, including methods of intravascular assessment with intravascular ultrasound (IVUS) and OCT/optical frequency domain imaging (OFDI), the non-compliant balloon dilation enabling high-pressure dilation; secondary prevention pharmacotherapies, including dual anti-platelet agents (DAPTs), for the reduction of the early stent thrombosis; simplified and efficacious mechanical circulatory support, such as intra-aortic balloon pumping and venoarterial extracorporeal membrane oxygenation; and the out-of-hospital emergent care system (13). These medical and social environments have helped significantly reduce mortality in patients with STEMI. Therefore, the outcomes of reperfusion therapy for ACS, including STEMI, need to be re-evaluated, and use should be made of previous reports for subsequent reperfusions.

Aside from DCB (PCB) and BMS combination therapies (1,4), an important factor addressed by the PEBSI Study was the use of DCB in reperfusion therapy for the treatment of STEMI. Recently, PCBs have emerged as viable alternatives to DES in coronary angioplasty, and PCB has been widely used as the representative therapy of "stent-less PCI" (7,14). However, issues remain regarding the persistent relative rates of TLR, TVR, and stent thrombosis, as well as the duration of DAPT after the placement of the DES. In recent years, significant efforts have been made to investigate the role of PCB angioplasty (7,14), regardless of vessel size (15), in large vessels (16), in complex lesions,

such as bifurcations, chronic total occlusions, and severely calcified lesions using a rotablator, in lesions from which plaques have been removed by direct coronary atherectomy, in ostial lesions, and in diffuse long lesions, particularly in patients with stable chronic coronary syndrome (CCS). According to reports on PCB angioplasties in elective cases for CCS, increasing evidence highlights the effects of PCB angioplasty in patients with ACS administered via emergent procedures (5,17-19). Although the use of PCB angioplasty has spread in percutaneous coronary interventions, as well as an increasing number of reports summarizing the relevant data in daily practice (7,14), PCB angioplasty tends to be used for less complex lesions than DES placement in cases of CCS (15) and ACS (17-19). However, PCB angioplasty has demonstrated similar efficacies as DES in terms of propensity score-matched adjusted baselines in both CCS (15) and ACS (18). Factors to be considered include the presence of non-calcified lesions with a total PCB length of approximately 20 mm (non-diffuse lesion) and a maximum PCB size of approximately 3.0 mm (non-small vessels) (15,16,18). This PCB-efficacious length-dependent baseline is also followed in cases of small vessels of ACS (20) and DES-instent restenosis (ISR) (21). The benefits of PCB angioplasty for DES-ISR are limited to non-diffuse (<20 mm) DES-ISR and could not be found in diffuse (≥20 mm) ISR compared to recurrent DES placement (DES-in-DES strategy). Thus, we proposed a lesion length-dependent PCB angioplasty, using a 3.0-mm size with a 20-mm length of PCB for non-calcified lesions in cases of ACS (17).

PCB angioplasty should be promoted concomitantly with advances in DES outcomes. Therefore, the feasibility of PCB angioplasty for ACS should be compared to that of DES. In contrast to DES, DCB involves hydrophilic polymers and anti-proliferation agents, and there is no metal platform. As a result, it directly inhibits the process of neointimal hyperplasia and negative remodeling. One of the consistent advantages of PCB angioplasty was observed in the follow-up stages of angiographic outcomes in the chronic phase (5,7). Therein, the mean values of late luminal loss in PCB angioplasty lesions ranged from 0 to approximately 0.10 mm (7). Late lumen enlargement (LLE), defined as the minus late luminal loss, occurs in approximately half or more of the angiographic follow-up lesions (7,15,22). Although the precise mechanism of this unique LLE phenomenon are under investigation, the relationship between LLE and final insignificant dissection (i.e., types A or B without coronary flow limitation) has been consistently reported in cases of elective procedures (15,22). We previously reported on a potential mechanism for LLE (15), to which we attributed four factors: (I) balloon angioplasty enlarged the lumen and vessel areas (vessel enlargement); (II) the distribution of paclitaxel suppressed the plaque and induced its regression; (III) minor dissections formed at any step further facilitated the diffusion of paclitaxel into the plaques; (IV) almost all minor dissections formed perioperatively were sealed in the chronic phase without late lumen loss. However, to fully elucidate the feasibility of PCB angioplasty in the treatment of ACS, further details on the long-term clinical outcomes of LLE after PCB angioplasty must be compared with those of DES placement.

In summary, the PEBSI Study highlighted the significance of a brief and single application of paclitaxel in coronary lesions in the context of the history of mechanical reperfusion therapy for STEMI, particularly regarding the importance of coronary healing. In addition to established PCB and BMS combination therapies, the feasibility of PCB-alone angioplasty for reperfusion therapy in patients with ACS via emergent procedures must be determined. To this end, the indications and procedural endpoints of PCB angioplasty, as well as the non-inferior outcomes of PCB angioplasty, including LLE, compared to those of recent DES should be examined not only in CCS, but also in ACS cases.

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