Editorial

Drug coated balloons and bare metal stents in ST-elevation myocardial infarction: eternal life or return of the living dead?

Ahmed Farah[1], Raban V. Jeger[2]

[1]Knappschaftskrankenhaus Dortmund, Klinikum Westfalen, Dortmund, Germany; [2]Triemli Hospital Zürich, Zürich, Switzerland, and University of Basel, Basel, Switzerland

Correspondence to: Ahmed Farah, MD. Knappschaftskrankenhaus Dortmund, Klinikum Westfalen, Am Knappschaftskrankenhaus 1,44309 Dortmund, Germany. Email: farahahmed_dr@yahoo.com.

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During the dawn of interventional treatment of coronary artery disease, bare metal stents (BMS) were developed to treat acute vessel closure and restenosis after plain balloon angioplasty (1). Since their efficacy was limited due to high rates of restenosis (2), first- and later second-generation drug-eluting stents (DES) were used more and more frequently. However, despite their beneficial efficacy and safety profile, modern DES continue to exhibit a constant occurrence of stent-related events at a rate of 2% per year (3). Therefore, new approaches to overcome this limitation were sought, e.g., biodegradable scaffolds and drug-coated balloons (DCB). While the use of biodegradable scaffolds was limited by high rates of stent thrombosis (4), drug-coated balloons are a novel and promising tool in the armamentarium of interventional cardiologists (5).

Currently, most interventions in the coronary field are performed using either DES or DCB, limiting the use of BMS in the real world to only 3.5% (6). However, in ST-elevation myocardial infarction (STEMI) some interventional cardiologists still may prefer BMS over DES (6,7) despite worse outcomes (8) and the clear recommendation of the current STEMI guidelines (9). The main motive of this preference is the long-term unfavorable safety and efficiency profile of DES and the risk of late and very late stent thrombosis (10).

In this context, the 8-year follow-up of the PEBSI study opens up new vistas (11). PEBSI randomized 223 patients with STEMI to either an interventional treatment with BMS (PRO-Kinetic Energy, Biotronik, Berlin, Germany) alone or to a combined therapy with BMS followed by a post-dilatation with a DCB (Pantera Lux, Biotronik, Berlin, Germany) and showed a median late lumen loss of 0.80 mm [interquartile range (IQR) 0.36–1.26 mm] in the BMS group *vs.* 0.31 mm (IQR 0.00–0.58 mm) in the combined BMS/DCB group after nine months (P<0.0001) (12). The long-term follow-up shows the very interesting finding of a target vessel failure (TVF) rate of only 3.7% in the combined BMS/DCB treatment group (*vs.* 14.3% in the BMS comparator group, P=0.006), which is one of the lowest TVF rates in BMS or DES studies ever published. While the very long follow up duration of 8 years and the low TVF rate of less than 4% are very intriguing, the fact that the PEBSI investigators randomized the patients after a successful BMS-Implantation needs special attention.

The combination of BMS and DCB has been tested in other settings already. In 2009, the results of the PEPCAD III trial were presented at the AHA Scientific Sessions in Orlando FL, but have never been published in a scientific journal. In this trial, the combination of a paclitaxel DCB and a BMS mounted on the same device was compared with DES in 637 patients with stable *de-novo* coronary artery disease and showed a target vessel revascularization (TVR) rate of 13.8% for the combined DCB/BMS and 6.9% for DES group (P<0.1). The difference between the

PEPCAD III and PEBSI trials was not only the selection of devices and the patient population, but also the strategy. In PEPCAD III, BMS and DCB were used concomitantly in a combined device, whereas in PEBSI, the BMS and the DCB were used sequentially with individual devices. It is possible that the assembly of the simultaneous-use device impaired the efficacy of the DCB, while the sequential use of the devices allowed for a proper transfer of the drug to the vessel wall.

Apart from these considerations, the results of the combined BMS/DCB group in PEBSI may be related to various characteristics of the devices used, such as the DCB itself, the drug used on the DCB, the absence of polymer on the stent, or the thin stent strut design.

Is it the strut design? In the observational BIOHELIX-I study (13), the Prokinetik Energy platform, that was used for the present study as well, is characterized by very thin struts of only 60 μm and showed target-vessel failure rate of 9%. In the BIO-STEMI trial, the same stent platform combined with a biodegradable polymer (Orsiro, Biotronik) showed a target-lesion failure rate of only 5.1%, while the comparator durable-polymer DES (Xience, Abbott) showed a target lesion failure rate of 8.1% (14). In another STEMI study, the HEROES investigators (15) reported a target failure rate of only 0.6% in 353 STEMI patients treated with the same stent (Orsiro, Biotronik). Therefore, the thin stent strut design might have contributed to the result.

Is it the absence of the polymer? Although long-term presence of a polymer can cause inflammation and thrombogenesis, previous studies demonstrated that current second-generation durable-polymer DES is non-inferior to biodegradable or even polymer-free DES (16). Specifically, polymer-free DES were investigated in many trials in acute coronary syndromes (ACS) and STEMI, such as the LEADERS-FREE ACS sub-study (17) showing polymer-free DES being superior to DES in the setting of ACS with a target lesion failure of 3.9% *vs.* 9.0%, and the ISAR-5 study (18) showing no difference between polymer-free DES und durable-polymer DES in STEMI patients up to 5 years follow up with a major adverse cardiovascular event (MACE) of 18% *vs.* 20%. The results of these studies support the theory that the success of the present DCB/BMS combination may be eased by the absence of a polymer.

Is it the DCB itself? The DEB-AMI trial failed to show an equipoise of DCB combined with BMS to BMS or DES (19). In this trial, DES was superior to the other two groups, while BMS alone was even better than the combined strategy with DCB and BMS. However, in this trial the STEMI patients were randomized to one of the 3 groups before dilatation. In two other studies, the use of DCB alone was compared to DES in STEMI patients (20,21). In these studies, DCB were non-inferior regarding the primary endpoint, but there was a high percentage of patients requiring stent implantations due to dissections. Just recently, Merinopoulos *et al.* (22) assessed the use of DCB alone versus DES in more than 1,000 STEMI patients. This observational study showed non-inferiority of DCB *vs.* DES for up to 3 years regarding mortality and target lesion revascularization. Therefore, the effect of DCB in the setting of STEMI may be favorable but its use may be limited by flow-limiting dissections after the first balloon dilatation leading to stent implantation.

Is it the drug on the DCB? Paclitaxel, which has been used as drug coating on the balloon in the current trial, has a potent antiproliferative effect by binding to the β subunit of tubulin, resulting in arrest of microtubule function, and thus preventing restenosis (23). The PEBSI authors evaluated 53 patients with optical coherence tomography after 9 months (24), which revealed a significantly lower rate of major coronary evaginations and development of a thin homogeneous neointimal layer in the DCB/BMS combined group, suggesting distinct superior healing at 3 months compared to BMS alone. Major coronary evaginations were mainly present with first-generation sirolimus stents, but not with later-generation DES (25). Therefore, the 9-month optical coherence tomography data of the current trial support the theory that the potent antiproliferative effect of paclitaxel delivered by the DCB prevented intimal hyperplasia and instent restenosis, but allowed for a thin neointimal layer, thus prevented instent thrombosis.

Therefore, all of these four device characteristics may have been contributed to the favorable long-term outcome of PEBSI. However, it is fair to say that the postdilatation of the BMS with DCB may have prevented the unfavorable consequences of the stent, i.e., restenosis, by adding an antiproliferative drug, while the stent may have prevented the unfavorable consequences of angioplasty, i.e., high-grade dissections or relevant residual stenosis.

Based on the presented data showing an excellent long-term outcome of a combined treatment strategy of BMS implantation followed by DCB postdilatation, the question remains whether PEBSI will change our daily practice. Based on the presented data, a combined BMS/DES-

treatment strategy for STEMI may be a feasible approach. However, in the light of the conflicting PEPCAD data, a combined DCB/BMS strategy cannot be recommended to be pursued at the time being. However, these appealing results may encourage the interventional community to intensively evaluate of the role of DCB in a STEMI population, in order to overcome current limitations of DES in this indication. These investigations may answer the question if DCB are going to give BMS an eternal life or if it is just a return of the living dead.

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Footnote

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