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Drug eluting balloons: should we use them more?

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Take Home Messages

- Drug-eluting balloons (DEB) are safe and efficient in treating in-stent restenosis and small de-novo coronary artery lesions leaving no metal inside the coronary artery.
- DEB is a good option for high bleeding risk patients who need shortened duration of DAPT compared with drug-eluting stents.
- Lesion preparation is pivotal to achieving the best results from DEB angioplasty.
- DEB use is easy and similar to any other balloon in delivery and inflation (typically 30-60s).

Introduction

Balloon angioplasty was first used to recanalise arteries in 1977 but its use was associated with significant complications like abrupt vessel closure, subintimal dissection and restenosis (1-4). To tackle these issues, bare metal stents (BMS) and drug-eluting stents (DES) were introduced in 1986 and 1999 (4). However, their use can cause delayed healing, local inflammation, and endothelial dysfunction resulting in-stent thrombosis as well as in-stent restenosis (ISR) (5,6). Furthermore, there are some limitations for stent use in small or tortuous vessels and diffuse calcific lesions due to difficulties in stent delivery. Also, stent struts can obstruct large side branches or bifurcation lesions (7). The drug-eluting balloon (DEB) or drug-coated balloon (DCB) was introduced in 2004 to overcome some of these limitations (8).

How does the DEB work?

DEB is a semi-compliant balloon coated with a cytotoxic antiproliferative drug which is released homogeneously into the vessel wall during balloon inflation (8). Targeted-drug therapy prevents smooth muscle proliferation, minimises endothelial dysfunction and neoatherosclerosis (9,10). Paclitaxel has been the main drug of choice with more recent data promoting the use of sirolimus; both have a lipophilic property which allows better tissue absorption (11). The release of these drugs is controlled by polymeric materials which adhere to the balloon before inflation and to the vessel wall after (9,12). The balloon catheters are flexible with high mechanical strength and thin walls to facilitate their deliverability, tractability and crossability (defined in **Table 1**) (13-15).

About the author

Ahmed Ayuna graduated from the University of Baghdad in 2009, and completed a postgraduate diploma and MSc in preventative cardiology and MD in 2016. He is currently a cardiology speciality trainee in the North Western deanery. His main research interests are in coronary artery disease and he plans to pursue a career in coronary intervention.

Table 1. Drug-eluting balloon properties (13-15)	
Deliverability	Delivering the balloon to the target lesion which could face some challenges like very distal lesions, extreme tortuosity and excessive calcifications.
Tractability	The ability of the balloon to curve while translated within the vessel.
Crossability	The ability of the balloon to pass through a stenotic segment of the vessel.

Table 2. Angiographic criteria for pre DEB delivery (15)
• The predilatation balloon should be fully inflated with the correct balloon-vessel size (1:1).
• 30% or less residual stenosis.
• Good flow down the vessel i.e. Thrombolysis In Myocardial Infarction (TIMI) grade III.
• No flow-limiting dissection. Type A and B were always considered safe to leave after DEB. There is much debate about type C dissection and the current practice is to seal it with a stent.

DEB deployment is similar to any other balloon. It is advisable to avoid touching the DEB with your hands while handling the balloon catheter and minimise transit time before inflation to maximise its effect (4,15). It is essential to prepare the lesion adequately before deploying the DEB to reduce the risk of further ISR (**Figure 1**) (34,35). Depending on the manufacturer's recommendations, the balloon should be inflated for 30-60 seconds. The international DCB consensus (2020) outlined criteria for DEB use, outside which DES should be used. These criteria are outlined in **Table 2**.

DEB and Dual anti-platelet therapy (DAPT)

It is recommended to use DAPT for one month after DEB-percutaneous coronary intervention (DEB-PCI) for stable coronary artery disease (CAD) versus three to six months in DES-PCI (37-40). The data is limited to support DAPT for less than 12 months in acute coronary syndrome (ACS); however, the DEBUT trial and another retrospective study suggested one month DAPT after DEB-PCI for stable CAD and ACS showed low 9-month MACE (1% DEB vs.14% BMS) and 12-month total mortality (2.3% stable CAD vs. 9.3% ACS) respectively (41,42). The shorter duration of DAPT required after DEB as compared to DES, makes DEB a good option for high bleeding risk patients.

Benefits of DEB?

One of the earliest randomised controlled trials (RCT) demonstrated a significant reduction in the rate of ISR for DEB versus plain-balloon angioplasty (POBA) after 6 and 12-month follow-up (16). Despite the small sample size (N=52), the results were very promising: 43% vs. 5% 6-month restenosis, and 31% vs. 4% 12-month MACE (16).

Similar results were shown in larger trials like the PACOCATH-ISR I and II: 5-year MACE 27.8% vs.59.3% (P=0.009) in the DEB vs. DES groups(16).

DEB has also been shown to be of benefit in treating patients with established ISR, where deployment of stents within stents may be less desirable. The PEPCADII trial compared DEB with DES to treat BMS-ISR and also showed a significant reduction in MACE at 1 and 3 years (9% vs.22% and 34.8% vs.41.5% in the DEB v DES groups respectively) and target-lesion revascularisation (TLR) (6% vs.15%)(17). Similar results were shown for DEB use to treat DES-ISR compared with POBA and DES in the PEPCAD-DES, PEPCAD-CHINA-ISR, RIBS-IV and RESTORE studies (18-21).

DEB use for treating small vessel de-novo disease (<3.0 mm) is still debatable (15). In the earliest trial PICCOLETO, DEB failed to show equivalence to DES with higher 9-month MACE rates (35.7% vs.13.8% DEB vs DES). However, in the PICCOLETO study an older generation paclitaxel-DEB was used and since this data a newer generation has been released which has been shown to deliver the drug more efficiently (29). Subsequently, several nonrandomised trials and registries have shown efficacy and safety to treat smaller vessels with up to 3 years follow up (22-26). More recent randomised trials like the RESTORE-SVD and BASKET-SMALL2 showed non-inferiority in 9-month in-segment percentage diameter stenosis and 12-months MACE (7.5% vs 7.3%) respectively compared to DES (27-28).

Furthermore, DEB use in de-novo large vessel lesions has shown efficacy and safety in non-randomised trials (24,30,31). This encouraging data needs to be further supported by randomised trials.

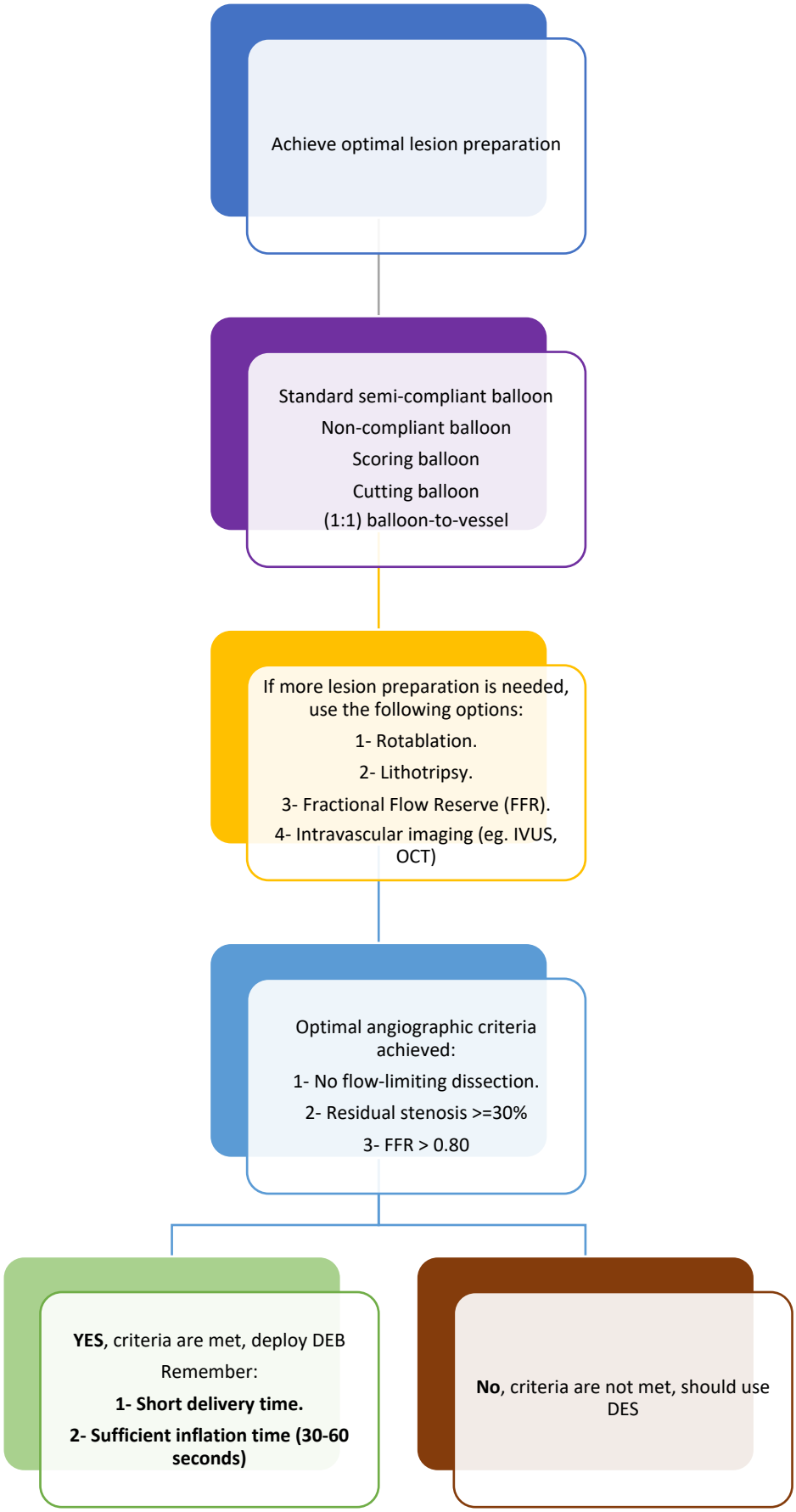

Figure 1. Flow diagram demonstrating the criteria for DEB deployment [adapted from Jeger *et al*. J Am Coll Cardiol Interv. 2020;13(12):1391-402] (15).
DEB = Drug-eluting balloon; DES = Drug-eluting stents; FFR = Fractional Flow Reserve; IVUS = Intravascular ultrasound; OCT = Optical Coherence Tomography.

Table 3. Summary of benefits and potential limitations of DEB use.	
Benefits	**Potential limitations**
In-stent restenosis	Acute vessel closure and recoil
Small vessel de-novo disease	Flow limiting dissection
Large vessel de-novo disease	Focal vessel wall necrosis
Bifurcation	
High bleeding risk patient (shorter duration of DAPT)	

DAPT = dual antiplatelet therapy; DEB = drug-eluting balloon.

Moreover, in bifurcation lesions, data from observational studies has also suggested a low rate of restenosis and TLR for DEBs in bifurcation lesions (side branch >=2mm) (32,33).

Limitations of DEB

Some concerns were raised about releasing large doses of the cytotoxic drug into the bloodstream following balloon inflation, as well as focal-wall necrosis (36). Specifically, one meta-analysis showed increased mortality when Paclitaxel-DEB and DES were used in peripheral arterial disease (PAD) (36). The 2-year mortality (12 RCTs) and 4-5 year mortality (3 RCTs) for DEB in PAD versus DES was high (7.2 % vs 3.8% and 14.7% versus 8.1% respectively). There is no such data in coronary PCI, also balloon sizes used in coronaries are smaller and many manufacturers are now using non-paclitaxel drug. Furthermore, the dose of paclitaxel used in DEB is very low and even using multiple balloons do not even come close to the level which can cause toxicity (175 mg/mm^2) The benefits and possible limitations of DEB are summarised in **Table 3** (43,44).

Conclusion

DEB is a novel innovation in PCI which is simple and easy to use. There is evidence that it is safe and effective in treating ISR as well as de-novo disease in small and large vessels, and bifurcation lesions. Leaving no metal behind will reduce risks related to stenting which makes DEB a wonderful device in coronary intervention.

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