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Drug-eluting balloons for coronary use in clinical practice: why, where and how?

In-stent restenosis is one of the key challenges following the deployment of stents in coronary care. For some time, drug-eluting balloons have offered a therapeutic option for the management of this complication. However, they can also be used for the management of *de novo* lesions. Following the first International Course on drug-eluting balloon angioplasty, held in Milan, *Confluence* caught up with Course Director Dr Bernardo Cortese, A.O. Fatebenefratelli Milano, Italy, and Faculty member, Dr Pierfrancesco Agostoni, University Medical Center Utrecht, Netherlands, to find out more.

Could you explain the underlying mechanism of action for drug-eluting balloons?

Dr Pierfrancesco Agostoni (PA): Drug-eluting balloons (DEBs) can be used to treat *de novo* lesions or in-stent restenosis; however, we should always remember that DEBs are not meant to be balloons used to open up the vessel but as carriers of an anti-proliferative drug, normally paclitaxel. Only once we have a good result with pre-dilatation with conventional balloons should we use DEBs.

Following deployment, the immediate result is the disruption of the plaque or the in-stent restenosis. Subsequently, the paclitaxel on the balloon's surface works to prevent recurrence of restenosis in the case of in-stent restenosis and also long-term negative vessel remodelling in the case of *de novo* lesions. Data suggest that in some patients with type A, B and sometimes C dissections, we observe beneficial remodelling, so that is encouraging. For in-stent restenosis, we have recently shown that we see regression of the restenosis in the first 6 months following use of DEBs, although some balloons perform better than others. The most important aspect that determines the performance of balloons is the way the paclitaxel is delivered from the balloon to the vessel wall. Some balloons may deliver less drug, or they don't deliver the drug to the vessel wall efficiently enough to allow for sufficient effect.

What accounts for the different performance in balloons?

PA: In general, there are two groups. The first group comprises all the balloons where there is an excipient that allows the drug, the paclitaxel, to be properly attached to the balloon in a matrix. This excipient also allows easy delivery of the paclitaxel once the balloon is in place. This includes balloons such as the IN.PACT Falcon (Medtronic, Inc., Minnesota, USA).

The second group only contains one balloon licensed at present, the DIOR balloon (Eurocor GmbH, Bonn, Germany), in which the paclitaxel is embedded in shellac. However, while the amount of paclitaxel in the balloon is the same, in my experience the delivery of the paclitaxel from this plastic material may be insufficient.

Dr Bernardo Cortese (BC): That is totally correct, although we have also tested another balloon with a similar shellac composition that has shown more promising results in the initial patients in which it has been deployed. In my opinion, the excipient is a very important issue, and the degree to which it keeps paclitaxel on the balloon until you arrive at the lesion and how it leaves the balloon upon deployment are crucial important points.

There is another type of DEB that does not have any excipient and tests are currently ongoing to see if the delivery of paclitaxel is similar to the other DEBs with the excipient. In this case they don't have an excipient but they have a type of gel that, at least in bench testing and in some preliminary animal tests, appears to show paclitaxel delivery similar to that of current balloons.

Drug-eluting stents (DES) have been around for a very long time as well. In what situations would you choose to use a DEB rather than a DES?

BC: In our cath lab we use DEBs quite a lot in clinical practice (around 25% of coronary cases). For example, if we have an in-stent restenosis our first choice is to use a DEB. We insert it into the lesion and if we don't see major dissections we use a DEB and then we stop – no further therapy is required.

We are also using it quite a lot in *de novo* lesions, even in small vessels. Around 60% of small vessels in our cath lab are treated with DEBs. Even there if we don't have the major dissection or Thrombolysis in Myocardial Infarction (TIMI) flow <3, we use a DEB alone with good outcomes. We try not to place a stent in the vast majority of the cases, ideally fewer than 10% of patients. We know that if you correctly deliver the paclitaxel using a DEB you will see very good results and improvements at the angiographic follow-up.

Furthermore, often we don't want to stent the side branch of a bifurcation and so dilatation of the side branch after main vessel stenting is usually performed with a DEB in our cath lab.

The PICCOLETO and BELLO studies investigated DCBs in in *de novo* disease: could tell us about the results and impact of these trials?

BC: The paclitaxel-coated balloon versus DES during PCI of small coronary vessels (PICCOLETO) randomized 60 patients with *de novo* stenosis (vessel <2.75 mm diameter) to either TAXUS Liberté DES (Boston Scientific, Boston, Massachusetts) or to management with a first-generation DIOR balloon without shellac excipient.[1] However, the study had a number of limitations: firstly, the device was a normal balloon and not a coated balloon, despite the desire of the company at that time; secondly, many patients did not undergo standard balloon pre-dilatation before DEBs because we didn't recognize the importance of this at that time. This resulted in a failure of the DIOR DEB to show equivalence to the DESs with regards to angiographic endpoints in small vessels, and a failure in terms of target lesion revascularization rates.

Subsequent to PICCOLETO, the Balloon Elution and Late Loss Optimization (BELLO) trial examined the efficacy of the Medtronic IN.PACT Falcon balloon. The BELLO trial included patients assigned randomly to the IN.PACT Falcon paclitaxel DEB or TAXUS Libertè paclitaxel-eluting stents.[2] While the Medtronic balloon has the same amount of paclitaxel as the DIOR balloon, it had a different excipient that effectively delivers paclitaxel to the vessel wall.[2] This was reflected in the study results where use of a DEB delivered less angiographic late loss and similar rates of restenosis and revascularization as DESs.

How do you think that the results of these trials have impacted on clinical practice?

PA: I think it varies between practitioners; for example, I am more conservative than Bernardo in treating *de novo* lesions, but I have to say that the latest results in this area, as well as the course I have just been part of with Bernardo, have caused me to more strongly consider DEBs, especially in distal lesions and diffuse disease. This is especially the case where you would like to stay away from deploying a stent: for example, if surgery might be required in the future or you think you don't have a really good landing zone for a stent because the disease starts somewhere mid-way in the vessel and goes all the way up to the distal part of the vessel. If you think that is the real cause of the patient's symptoms then a DEB would be a very good option, provided that you get a good result without dissection after pre-dilatation; that is always the bottom line.

We have also done stent-wide pre-dilation, where you use incrementally larger balloons and higher pressures to slowly break the plaques to avoid major dissection. This strategy can be time-consuming, and this is something that we, as interventionalists, are not used to doing as inserting stents is so quick. However this strategy offers the advantage of having a result without any residual metal in the vessel, which can be a long-term advantage if the patient needs surgery, for example, in the future.

I have my doubts more on proximal lesions of the left anterior descending (LAD), circumflex or other major proximal arteries as there is unlikely to be surgical intervention here, so stenting offers a good solution.

BC: I also agree that the proximal native large vessels shouldn't be treated with DEBs, at least at present. We have done some cases where the patient cannot undergo prolonged dual antiplatelet therapy (DAPT), where DEBs might be an option, otherwise DESs should be the first choice in big

vessels, e.g., >3 mm of diameter. In fact, in this type of vessels the risk of recoil after balloon dilatation may be higher given the larger amount of elastic tissue. However, I have to say that few physicians around the world are having some preliminary and encouraging experiences even in this anatomical setting.

May I give a suggestion? If a physician wants to start to gain experience with DEBs, at the beginning he should focus on in-stent restenosis because in this setting it is more difficult to have dissections. After that, once he feels comfortable with the technology, he should be guided by data and try DEBs in new scenarios, like small vessel disease, where at least two of the currently available devices have shown good results.

How does the DAPT differ between someone who has been treated with a DEB and with a DES?

BC: DESs have improved considerably over time and there is now evidence that you can reduce the dual antiplatelet therapy (DAPT) for 6 months and perhaps sometimes 3 months in some selected cases. However, as we wrote in the Italian consensus document on DEBs,[3] we suggest that following the use of DEBs, DAPT is prescribed for 1 month in all the cases and up to 3 months where stent implantation is required. However, anecdotal evidence suggests that stopping DAPT after 15 days may be as safe as after 30 days with DEBs. A shorter duration of DAPT leads to less bleeding and means the patient may undergo any type of surgery. I have to underline that this is not a reason for starting to use a DEB instead of a stent, but if you have used it for other reasons you have an advantage for the standard patient.

What additional evidence is required to support the use of DCBs?

PA: One important issue would be to test the combination of DEBs and DESs, because if we are going to use DEBs more regularly for patients with *de novo* lesions, we need more understanding of the risks. Potential solutions, such as the use of increased concentrations or combinations of anti-proliferative agents, also warrant further investigation in terms of toxicity and animal studies will be required here. Once the safety of such interventions has been assessed in animals then you can more easily move to patients.

BC: We would like to expand the findings from BELLO to include other devices and different primary endpoints. We are trying to organise such a study being our centre the coordinator. Moreover, I think it is now time to test DEBs against new-generation DECs. It is unlikely, however, that we will ever have large randomised clinical trials with 3,000 patients, due to a variety of reasons.

What role might registries play in providing more data about these balloons?

BC: Registries are really important. There are now data from a number of DEB registries. We have data from the SeQuent Please (B. Braun Melsungen AG, Berlin, Germany) worldwide registry and also other registries.

I am also on the steering committee for the international IN.PACT Falcon registry, which will recruit at least 1,000 patients. This registry will be very helpful in investigating current use and indications for DEBs. For example, until 2 or 3 years ago, 90% of the cases of DEB use were for in-stent restenosis, but it now seems that in many other cath labs, *de novo* lesions and multi-vessel disease accounts for 30–40% DEB use. The primary endpoint that will be measured in this registry is target lesion revascularisation after 1 year. This means that this study will provide longer-term data than others. A clinical target lesion revascularisation (TLR) <10% will be a good result and is expected. There will also be angiographic follow-up of some patients if required during their care.

PA: Interestingly, IN.PACT Falcon has already been in use and there are already angiographic data from our in-stent restenosis study. Again, the late loss of the IN.PACT is pretty much between 0 and 0.1, so it is very good.[4] In this way I think it is a good device. In this view, of course, 1,000 patients in a prospective registry will definitely confirm it is, but we need to have a TLR rate <10% to demonstrate the efficacy conclusively.

What are the limitations of using DEBs?

PA: It is important to underline the importance of pre-dilatation is and we must reinforce that you shouldn't use DEB as a dilatation tool. It is just a drug carrier.

I was born in the "stent era", so now that I am involved with DEB studies I have had to re-think the way I do angioplasty using DEBs. People that want to use DEBs need to perform angioplasty in

another way, not a 10-second, go in, inflate, go out. They have to wait a bit longer, you have to properly dilate, perhaps even in a step-wise manner; the optimal inflation time for a DEB ranges between 30 and 60 seconds, although in my clinical practice, to stay on the safe side, I tend to always inflate the DEB for 60 seconds. It is not a limitation *per se*, but it is something we have to take care of to train properly people that want to approach the DEB technology to be sure that they are working in the best possible way.

Are DEBs cost-effective?

PA: There is now good evidence that DEBs are cost-effective.[5-7] Perhaps you have to pay a little more in the beginning but you avoid many sequelae of recurrent restenosis and so on, that you might experience with stent-in-stent revascularization. You would probably have similar results using DESs. Furthermore, the price of DEBs and DESs are similar to my knowledge.

BC: There are several studies that demonstrate the cost-effectiveness of DEBs, to my knowledge. There is a study from Klaus Bonaventura, from Berlin, saying that DEB for in-stent restenosis is cost effective.[5] A further German study in the same setting provides similar results.[6] Finally there is a study from the UK, which again finds the use of DEBs cost effective.[7]

PA: For *de novo* lesions, efficacy is comparable between DEB and DES, so again if the prices are comparable then it wouldn't be a real advantage in terms of money. However, there is a clinical advantage again in the sense that you avoid putting in a stent. The advantage for me would be that these patients would be potential future candidates for surgery and if you put stents in this artery would never be accessible again for surgery in the future. These are very specific types of patients where building up major evidence is difficult and you have to do more with the feeling of the physician. Again, as long as the price is comparable and is not tied between DEB and DES in terms of comparable results, then in my opinion the device should be supported by the authorities.

What is the reimbursement status of DEBs at present?

PA: This is a big limitation. DEB are reimbursed also in the Netherlands and it is my understanding that in Germany the use of DEBs there has increased considerably in some countries after they got it.

BC: At our DEB Course in Milano Dr Levenson, a colleague from Germany, explained how reimbursement worked in that country (Fig. 1). There they get reimbursement that is similar to DES, so in Germany they dot have reasons to prefer DESs over DEB only for economic reasons, and that is important. We are now trying to organise a "group of pressure" involving our Italian Society of Interventional Cardiology (GISE) to see if our Government would be willing to carry out a socioeconomic study, to see if reimbursement is feasible, because we would like to have the similar reimbursement than the one that we have with the DES, like in other european countries.

fig. 1

Reimbursement of DEBs in selected countries.

Figure presented by B. Levenson at the first International DEB Course, Milano, May 30th 2014.

Country	Market approval	Clinical recommendations	Reimbursement
United Kingdom	2009	2010 NICE 2010 ESC GL	To be negotiated with trust fund
Switzerland	2009	2010 ESC GL	Mandatory health basket list since 7/2012; financed within DRG
Germany	2009	2010 ESC GL 2011+2013 Consensus Group recommendation (German Cardiac Society)	'Zusatzentgelt' (additional fee) per DEB: 2013 €930 2014 €836
Japan	2013	Not official, 2 local trials (BMS-ISR, DED-ISR)	Negotiated with Ministry of Health; approximately €1300

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