

# Drug-coated balloon catheters. Discussing mortality from the coronary perspective

## *Balones liberadores de fármaco. Discusión sobre la mortalidad desde la perspectiva coronaria*

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### INTRODUCTION

The history of coronary balloon angioplasty began in 1997 with the first percutaneous transluminal coronary angioplasty (PTCA) ever performed by Andreas Grüntzig.<sup>1</sup> Some of the limitations of this technology were solved with the introduction of stents.<sup>2</sup> Added to an improved pharmacological concomitant therapy in the form of dual platelet inhibition,<sup>3</sup> the local drug delivery initially through stents (drug-eluting stents, DES)<sup>4</sup> and then balloons (drug-coated balloons, DCB)<sup>5</sup> improved long-term outcomes significantly. The history of coronary angioplasty was summarized in detail in various articles on the 40<sup>th</sup> anniversary of this technology.<sup>6,7</sup>

The local application of paclitaxel through DCB had begun to revolutionize the treatment of peripheral arterial disease (PAD).<sup>8</sup> This advance was very helpful for patients regarding primary patency and quality of life, but received a severe setback in a meta-analysis that claimed that the use of paclitaxel DES and DCB was associated with a higher mortality rate at the 2- and 5-year follow-up.<sup>9</sup>

The objective of this editorial is to discuss the safety profile of drug-coated devices in the historical context of the 2006 "European Society of Cardiology (ESC) firestorm" on coronary DES, data available on the coronary use of paclitaxel coated devices, and the potential role of limus-based agents in DCB.

### FIRST-GENERATION DES AND THE 2006 "ESC FIRESTORM"

After the publication of the RAVEL clinical trial on the Cypher sirolimus-eluting stent<sup>4</sup> and the TAXUS trials on the Taxus paclitaxel-eluting stent,<sup>10</sup> the DES rapidly gained momentum thanks to their significantly lower rate of restenosis compared to uncoated bare metal stents (BMS). In a direct comparison with the Cypher stent, the Taxus showed a higher rate of recurrence at the 9- to 12-month follow-up.<sup>11</sup> The common view that sirolimus is more effective than paclitaxel is essentially based on these data. However, it should be emphasized that the Taxus stent was almost as effective as the Cypher stent beyond the 12-month follow-up and up to 10 years.<sup>12</sup> The progress made by these first-generation DESs compared to modern DESs was based on the nowadays better controlled coating processes especially after improving stent platforms with thinner stent struts.<sup>13</sup>

However, there were also critical remarks to be made on the safety profile of coronary DESs. It has been reported that the delayed drug delivery from the stent struts prevents the implant endothelialization and increases the risk of thrombotic occlusion of the stent.<sup>14</sup> The BASKET-LATE trial reported between 3 and 4 times more late deaths or myocardial infarctions<sup>15</sup> with first-generation DESs. A hotline session held in Barcelona at the ESC congress of 2006 reported on 2 meta-analyses on a safety risk after sirolimus DES implantation.<sup>16,17</sup> In both meta-analyses the events published at study level were divided by the total number of patients with intention-to-treat without observation of cross-over treatments and lost to follow-up numbers. This is similar to the recently controversial meta-analysis on paclitaxel coated devices for the management of PAD.<sup>9</sup> The first DES meta-analysis showed significant differences in the mortality and Q-wave myocardial infarction rate at the late follow-up when the Cypher and bare metal stents were compared.<sup>16</sup> This finding may be explained by a possibly higher rate of late stent thrombosis. However, the second meta-analysis showed that the higher mortality rate associated with the Cypher stent was due to a higher non-cardiac mortality rate, thus contradicting the mechanism of stent thrombosis.<sup>17</sup> Despite these conflicting results, the government regulatory agencies worldwide were alarmed. The Food and Drug Administration (FDA) published several warning letters that eventually limited the indications for DESs.<sup>18</sup> However, further analyses did not confirm such an increased risk.<sup>19</sup> Also, the clinical trials that compared the Taxus stent to the BMS or the Cypher did not show higher rates of myocardial infarction or death.<sup>10,12</sup> Thus, DES became the standard treatment for the management of coronary heart disease.<sup>20</sup> Similarly, large contemporary registry studies and randomized studies have not confirmed any mortality signals for paclitaxel devices for the management of PAD.<sup>21-24</sup> It remains to be seen whether a similar comeback as with coronary DES will eventually happen.

### PACLITAXEL-COATED BALLOONS

Currently, the clinical practice guidelines recommend DCBs for the management of in-stent restenosis (ISR) only.<sup>20</sup> However, there is an increasing number of positive data on the treatment of de novo stenoses, particularly in small coronary vessels<sup>25,26</sup> and risk indications.<sup>27,28</sup> A patient-based meta-analysis of the trials that compared DCBs and DESs in DES-treated ISRs showed a similar 3-year safety

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profile for DCBs and DESs with numerically lower rates of events with DCB.<sup>29</sup> Even individual studies that compared DCB with first-generation DES,<sup>30</sup> BMS,<sup>27</sup> or plain old balloon angioplasty<sup>31,32</sup> reported significantly lower mortality rates after DCB implantation in the long term. However, these studies did not have enough statistical power to analyze this question. A recent meta-analysis of all randomized data on DCBs showed no differences in the mortality rate of DCBs and alternative treatments at the 1- and 2-year follow-up, but a significant survival benefit for DCBs regarding all-cause mortality and cardiac mortality at the 3-year follow-up.<sup>33</sup>

### SIROLIMUS VS PACLITAXEL FOR LOCAL DRUG DELIVERY

When comparing paclitaxel and sirolimus regarding local drug delivery it is often said that sirolimus has a wider therapeutic window and paclitaxel is cytotoxic. However, these statements are not correct.

Cell culture experiments tell us that the exposure of smooth muscle cells or endothelial cells to paclitaxel leads to more pronounced dose-dependent growth inhibition compared to sirolimus.<sup>34,35</sup> There is an increasing release of cytosolic lactate dehydrogenase—a marker for cell death—when incubating the cells with paclitaxel from a concentration of  $\geq 100$  ng/mL.<sup>34</sup> It should be mentioned that the paclitaxel DES only released 10% of the total amount of drug just as the comparable sirolimus DES because of this stronger antiproliferative effect. Regarding DCB, there are typically acute tissue levels of less than 100 ng/mg in the vessel wall.<sup>36</sup> Also, only about 10 ng/mg of paclitaxel are biologically active. Otherwise, the solubility product in the tissue is exceeded. While toxic concentrations may well be reached in the DES in the area of the stent struts, distribution in the vessel wall is very homogeneous with local drug delivery through DCB.<sup>37</sup> Also, tissue concentration decreases very rapidly after DCB treatment.<sup>36</sup> Therefore, the theoretically possible cytotoxicity of paclitaxel is not a factor in the clinical use of DCB.

The second myth is the therapeutic window. A typical total dose of a paclitaxel DCB equals 0.4 mg (3  $\mu\text{g}/\text{mm}^2$ , 20 mm length, 3 mm diameter). The single dose per cancer treatment cycle is 100-175 mg/m<sup>2</sup> of body surface area through intravenous administration,<sup>38</sup> usually 300 mg per infusion. This results in a factor of 750 for paclitaxel as therapeutic window compared to systemic therapy. The typical daily oral dose of sirolimus for restenosis prevention is 2 mg.<sup>39</sup> Depending on the specific sirolimus DCB used, the balloon dose is somewhere between 0.2 and 0.6 mg (1-4  $\mu\text{g}/\text{mm}^2$ , 20 mm length, 3 mm diameter). So far, clinical efficacy could only be proved for the high dose of sirolimus,<sup>40</sup> which means a factor of 3 only compared to systemic therapy, a clearly smaller therapeutic window. If a sirolimus DCB is implanted on the superficial femoral artery, the dose delivered through the balloon is already above the systemic dose and should be contraindicated (table 1).

### DISCUSSION AND FINAL REMARKS

The 2006 "ESC Firestorm" can be seen as a blueprint for the current paclitaxel controversy on the management of PAD. Interestingly enough, discussion at that time focused on sirolimus and not on paclitaxel. The current meta-analysis on the management of PAD with paclitaxel devices has several methodical flaws and has already been refuted. In any case, it has caused great damage to the entire field of local drug delivery for restenosis prevention. Too many patients are currently not receiving the therapy that works best for them and have to receive unnecessary revascularizations.

Regarding coronary paclitaxel DCB no associated mortality signals were seen. Just the opposite, there are indications that the therapy

**Table 1.** Systemic vs local treatment. Therapeutic window of paclitaxel and sirolimus.

	Paclitaxel	Sirolimus
Systemic treatment	300 mg Single IV dose of 100-175 mg/m <sup>2</sup> per cancer treatment cycle <sup>38</sup>	2 mg Daily oral dose for restenosis prevention <sup>39</sup>
Local treatment (DCB)	0.4 mg CAD 3.0/20 mm at 3 $\mu\text{g}/\text{mm}^2$ 5.5 mg PAD 5.0/80 mm at 3.5 $\mu\text{g}/\text{mm}^2$	0.2-0.6 mg CAD 3.0/20 mm at 1-4 $\mu\text{g}/\text{mm}^2$ 1.6-6.4 mg PAD 5.0/80 mm at 1-4 $\mu\text{g}/\text{mm}^2$
Therapeutic window	CAD $\times$ 750 PAD $\times$ 55	CAD $\times$ 3-10 PAD none

CAD, coronary artery disease; DCB, drug-coated balloons; IV, intravenous; PAD, peripheral arterial disease.

could even offer survival advantages in the longer term by avoiding permanent implants. The alternative of a sirolimus-coated balloon endorsed by many interventional cardiologists still has to prove its clinical efficacy. However, considering the necessary local doses compared to systemic therapy, the use of a sirolimus DCB for the management of PAD is questionable.

### CONFLICTS OF INTEREST

B. Scheller is a shareholder of InnoRa GmbH, Berlin, and co-inventor on patent applications filed by Charité university hospital, Berlin, Germany.

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