Review

# Should paclitaxel be considered an old generation DCB? The limus era

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Since their introduction Drug Coated Balloons (DCBs) have slowly gained their spot into everyday cath-lab practice, first for treatment of in-stent restenosis (ISR), more recently for small vessels disease; today a growing body of evidence start supporting their use in more complex lesions, from bifurcations, to large vessels, to acute lesions. Although the new generation of DCBs showed a better performance and safety than the older one, the drug of choice has always been the Paclitaxel; last year some concerns were raised on the safety of Paclitaxel devices, in particular the balloons mining their use. Recently Sirolimus ventured in the DCBs world, making its appearance on cath-lab shelves and becoming a good alternative to Paclitaxel (DCB).

*Keywords*

DCB; Sirolimus; Paclitaxel

## 1. Introduction

Since the first stent implanted in 1986, the field of interventional cardiology and percutaneous coronary intervention (PCI) changed radically from a "balloon approach" to a metal implantation strategy [1]. Although in the last 30 years most of efforts were directed to improve stent technology and performance, their use is still burdened with complications, mainly restenosis and late or very-late thrombosis [2]. The introduction of drug-coated balloons (DCB) still represents the most attractive innovation in interventional cardiology field, in recent years; paclitaxel-coated balloon (PCB) earned their spot in the cath-lab for treatment of in-stent restenosis (ISR) and certain *de novo* coronary lesions [3]. Despite being relatively new, sirolimus-coated balloon (SCB) are rapidly gaining a role as an alternative to PCB, due to the fast updating technology in this field [4–6].

## 2. Drug-coated balloon technology

PCI with DCB is based on the principle of delivering an anti-proliferative drug to the vessel wall, during balloon inflation, leaving no permanent implant. In order to obtain a good result lesion preparation is of paramount importance. A common mistake is using the DCB directly, without adequate lesion preparation [7]. After DCB delivery is important to look for optimal balloon expansion, less than 30% residual stenosis, no flow limiting dissection [7–9].

First recognized clinical indication for DCBs was in-stent restenosis (ISR), both in case of bare-metal stent (BMS) or drug-eluting stent (DES); this approach showed to be safe and feasible, better than plain old balloon angioplasty (POBA) and comparable to DES in terms of clinical outcomes [4, 10, 11].

Robust evidence from four landmark trials (BELLO, BASKET-SMALL 2, RESTORE SVD and PICCOLETO II) [5, 12–14], supported the use of PCBs also for *de novo* small-vessel coronary disease; recent data opened a new pathway in different scenarios such as large coronary arteries, multivessel disease, bifurcations and acute coronary syndrome (ACS) [15–18].

## 3. Sirolimus vs paclitaxel, some biomolecular considerations

Not all DCBs are created equally; balloon design, polymeric coating, and the drug used affect DCB efficacy, safety and outcome.

Paclitaxel and sirolimus are two well know anti-proliferative drugs. Both reduce cell proliferation and cell migration. Clinical data suggests sirolimus-eluting stent proved to be superior to paclitaxel-eluting stent in terms of target lesion revascularization (TLR), target vessel revascularization (TVR), re-stenosis rate and major adverse cardiovascular events (MACE) [19, 20]; of course this cannot be extended entirely to all DCBs.

Paclitaxel mechanism of action is based on binding and disabling the microtubules, which are crucial during cellular mitosis by giving a strong structure to the cell for building the mitotic apparatus, which in turn helps to capture and separate chromosomes (Fig. 1).

The final result is cell death and impairment of proliferation, a potent antitumoral activity. Moreover, paclitaxel is a highly lipophilic cytostatic drug that can reside in tissue for a prolonged period of time, but at high doses can become cytotoxic and apoptotic, its biggest limitations (Table 1) [21, 22].

Sirolimus reversibly binds the cytosolic protein FKBP12, creating an immunosuppressive complex that blocks the activation of the cell-cycle-specific kinase, mTOR. This in turn results in blockage of cell-cycle progression at the level of G1

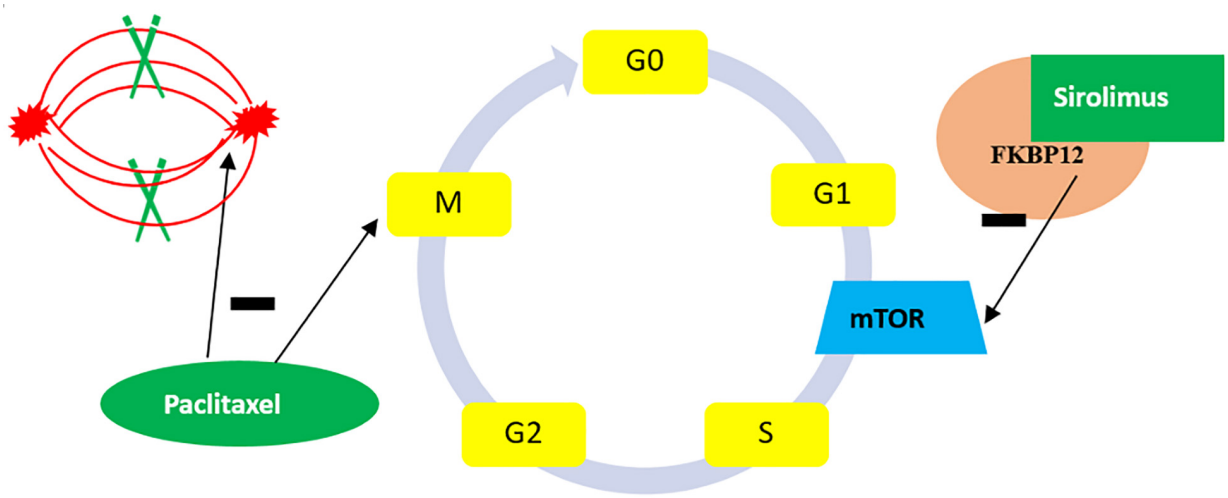


**Fig. 1. Sirolimus and Paclitaxel mechanism of action at an endothelial cell.** At the center of the figure, cell proliferation cycle can be note with the typical phases 0, G1, S, G2 and Mitosis (M). To the left, Paclitaxel disabling the microtubules (red), which helps to capture the chromosomes (green), during M phase. To the right, Sirolimus interacting with FKBP12 protein and inhibiting the mTOR kinase (blue), which works at the level of G1 to S phase.

**Table 1. Main biochemical and balloon differences between Sirolimus and Paclitaxel.**

| | Sirolimus | Paclitaxel |
|---|---|---|
| Biochemical characteristics | | |
| Antiproliferative | √ | √ |
| Cytostatic | √ | √ |
| Cytotoxic | × | √ |
| Apoptotic | × | √ |
| Suppress neutrophilic leukocyte activation | √ | × |
| Lipophilic | × | √ |
| Broader therapeutic window | √ | × |
| Effects in normoxic conditions | √ | √ |
| Highly effective during hypoxia | √ | × |
| Drug-coated balloon characteristics | | |
| Late vessel remodeling | × | √ |
| Similar coating method | × | √ |

and S phase of the cell proliferation (Fig. 1). Even though sirolimus is less lipophilic than paclitaxel, it has a broader therapeutic window, providing an additional benefit (Table 1) [21, 22]. Neutrophilic leukocyte activation and transmigration should be avoided since it may precipitate adverse coronary events such as restenosis and stent thrombosis. In animal studies sirolimus effectively suppresses this process but paclitaxel tends to cause the opposite effect [23].

In normoxic conditions, sirolimus and paclitaxel share similar inhibitory power on the proliferation of endothelial and smooth muscle cells. One of the advantages of the first over the second one is based on the performance comparison under hypoxia micro-environment in a vessel with atherosclerosis; under these circumstances, the hypoxia inducible factor promotes endothelial cell and smooth muscle cell proliferation. Glycolysis may cause vascular inflammation and mitochondrial dysfunction; vessel arterial wall becomes thicker and oxygen diffusion to the intima can be reduced. In "*in vitro*" studies on hypoxia, sirolimus showed a sustained anti-proliferative effect, while paclitaxel effect resulted reduced; this limitation of the latter is overcome at high doses, with a higher risk of systemic toxic effects, because of its narrow therapeutic window [24].

Interesting, paclitaxel used in coronary vessels has shown a lumen enlargement effect caused by a positive vessel remodeling, due to the capacity to reach the tunica adventitia; on the other hand, this effect has not already been tested for sirolimus, but future studies will answer this question [8].

In terms of DCB technology, either drug needs a coating method or a carrier to bind to the balloon and help drug delivery to the vessel wall, upon inflation.

The coating method can vary hugely between different balloons, ranging from simpler ones to more complex carriers with excipients. This difference is crucial and impacts their drug concentration and ability to transfer to the vessel wall [7].

For paclitaxel, different types of water-soluble matrix have been used, all relying on the same concept firstly developed in the Paccocath® technology (Bayer Schering Pharma AG, Berlin, Germany). The coating excipient in this case has a moderate importance since paclitaxel is a highly lipophilic drug, and transfer to the vessel wall is easier. Elutax® first generation (achen Resonance, Aachen, Germany) and Dior® (urocor Tech, Bonn, Germany) used no carrier, while In.Pact Falcon® and Prevail® (Medtronic, Minneapolis, MN, USA) use urea as a matrix, a non-toxic and ubiquitous endogenous compound. Paccocath® technology and SeQuent Please Neo® (B. Braun, Melsungen, Germany) use iopromide, which greatly enhances the solubility of Paclitaxel. Pantera Lux® (Biotronik, Berlin, Germany) and Danubio® (Minvasys, Gennevilliers, France) use n-Butyryl tri-n-hexyl citrate (BTHC), used also in various medical devices and cosmetics. Elutax III® (AR Baltic, Vilnius, Lithuania) uses a hydrogel (dextran) carrier with a technology called "snow and ice", which allows a lower drug concentration (2.2 $\mu$g/mm$^2$ instead of the common 3 $\mu$g/mm$^2$).

Still in term of DCB adoption, sirolimus is a more challenging drug, since, having a lower lipophilicity, its transfer to the vessel wall is more difficult. To overcome this problem several excipient and technologies have been studied. Magic Touch® (Concept Medical, Gujarat, India) was the first CE marketed SCB; this technology is based on a sprayed coating with sirolimus sub-micron particles, encapsulated into a phospholipid carrier. Selution SLR® (Med Alliance, Nyon, Switzerland) uses a biodegradable polymer as carrier, which in turn forms micro-reservoirs. In a simpler way, using butylated hydroxytoluene, SeQuent Please SCB® (B. Braun, Melsungen, Germany) uses a crystalline form of sirolimus.

Because of all these different technologies we cannot assume that all DCBs are equals and, therefore, a DCB class effect does not exist.

## 4. Paclitaxel-coated balloon: overview of clinical studies

Since the PACCOCATH ISR I study [25], the management of ISR changed radically. This was the first published clinical study suggesting the feasibility and safety of PCB for ISR, and subsequently other clinical trials supported this approach. Current European guidelines recommend the use of DCB for coronary in class I [3].

The ISAR-DESIRE-3, compared PCB to POBA and paclitaxel DES in 402 patients with ISR, demonstrating the non-inferiority of DCB against DES in terms of TLR at 3 years follow-up [26, 27].

Recently the DAEDALUS study, a large meta-analysis of 10 RCTs concluded that, at 3 years follow up, PCB is effective as DES for BMS-ISR in terms of TLR, while it has a lower efficacy in case of DES ISR, with no differences in terms of hard clinical endpoints including long-term mortality [28].

While DCBs have a clear indication in ISR, more data on *de novo* lesions are emerging.

Small vessel disease (SVD) ($\leq$2.75 or $<$3.0 mm) is one of the most investigated scenario; earlier studies failed to prove a superior efficacy of DCB compared to DES in SVD setting, while recently published adequate designed trials, offered new and interesting insights.

Notably the BASKET-SMALL 2 [12] was the first large study with clinical endpoints comparing a PCB with a DES, demonstrating the non-inferiority of the first strategy. Since then other studies confirmed these results [5, 13, 29, 30].

Recently in the PICCOLETO II study [14] a new-generation DCB, Elutax III, showed a lower 6-month Late Lumen Loss (LLL) as compared to everolimus-eluting DES (DCB 0.04 $\pm$ 0.28 mm vs. DES 0.17 $\pm$ 0.39 mm) and similar clinical outcome at 12 months.

There is a growing evidence supporting the feasibility and safety of DCBs in many clinical scenarios such as large vessels, bifurcation, ACS (Table 2, Ref. [5, 12–16, 25, 30–38]). More recently complex lesions and more complex patients have been tested. In bifurcations, DCB for the side branch (SB) has shown to be safe and feasible in small studies [39, 40] and in a randomized trial DCB for the SB showed to be superior to POBA [17].

## 5. Paclitaxel and mortality risk

In 2018, a large metanalysis by Katsanos *et al.* [41] encompassing 28 randomized controlled trials (RCT) raised some concerns showing an increased mortality risk in patients with peripheral arterial disease treated with paclitaxel DES and DCB. Bittl *et al.* [42], in a new analysis done applying the Bayes factors to the available studies and several other drawbacks showed the results of Katsanos' meta-analysis to be inconclusive in terms of hard clinical events [43–45].

It is important to highlight the concept that not all PCBs are equal and there is not a class effect, these devices reported a high percent of drug loss during manipulation and before reaching the lesion while newer technologies showed better performances, protecting the drug until the delivering site, and allowing a better transferring to the vessel wall during the upcoming weeks in order to exert an effective inhibition of restenosis, limiting the drug loss.

Moreover, Scheller *et al.* [46] in a meta-analysis including all available RCTs comparing PCBs with non-PCB devices, for the treatment of both coronary ISR or *de novo* lesions, showed was no difference in all-cause mortality after 12 months, and a significant reduction after 3 years in DCB-treated patients. Despite all these results, such controversial messages led to a decreased the use of paclitaxel-eluting devices for both peripheral and coronary interventions.

## 6. Sirolimus coated balloon: overview of clinical studies

Although SCBs are relatively new, there is a growing body of evidence supporting their use. Magic Touch® (Concept Medical, Gujarat, India), has the most robust evidence and is

**Table 2. Main randomized trials of Paclitaxel-coated balloon in coronary artery disease.**

| First Author/Study (Ref. Nu.) | Type of lesion | PCB | Comparator | n | Outcome LLL, mm ($p$ value) | Outcome MACE, % ($p$ value) |
|---|---|---|---|---|---|---|
| PACCOCATH ISR [25] | BMS ISR | PACOCATH | POBA | 108 | 0.03 ± 0.48 vs. 0.74 ± 0.86 ($p < 0.0002$) | 4 vs. 31 ($p < 0.01$) |
| PEPCAD II [31] | BMS ISR | SeQuent Please | PES | 131 | 0.17 ± 0.42 vs. 0.38 ± 0.61 ($p < 0.03$) | 9 vs. 22 ($p < 0.08$) |
| RIBS V [32] | BMS ISR | | EES | 189 | 0.14 ± 0.5 vs. 0.04 ± 0.5 ($p < 0.14$) | 8 vs. 6 ($p < 0.6$) |
| PEPCAD-DES [30] | DES ISR | SeQuent Please | POBA | 110 | 0.43 ± 0.61 vs. 1.03 ± 0.77 ($p < 0.001$) | 16.5 vs. 50 ($p < 0.001$) |
| PEPCAD CHINA ISR [33] | DES ISR | SeQuent Please | PES | 220 | 0.46 ± 0.51 vs. 0.55 ± 0.61 ($p = 0.0005$) | 16.5 vs. 16 ($p = 0.92$) |
| RIBS IV [34] | DES ISR | SeQuent Please | EES | 309 | - | 18 vs. 10 ($p = 0.04$) |
| DARE [35] | DES ISR + BMS ISR | SeQuent Please | EES | 278 | 1.71 ± 0.51 vs. 1.74 ± 0.61 ($p < 0.0001$) [a] | 10.9 vs. 9.2 ($p = 0.66$) |
| BELLO [5] | Small arteries | IN.PACT Falcon | TAXUS - PES | 182 | 0.08 ± 0.38 vs. 0.29 ± 0.44 ($p = 0.001$) | 10 vs. 16.3 ($p = 0.21$) |
| BASKET-SMALL 2 [12] | Small arteries | SeQuent Please | TAXUS element PES and Xience EES | 758 | 0.13 vs. 0.10 ($p = 0.72$) | 7.5 vs. 7.3 ($p = 0.92$) |
| RESTORE SVD [13] | Small arteries | Restore | Resolute onyx ZES | 230 | 0.26 ± 0.42 vs. 0.30 ± 0.35 ($p < 0.41$) | 9.6 vs. 96 ($p = 1.0$) |
| PICCOLETO [36] | Small arteries | Dior | TAXUS PES | 57 | 1.11 ± 0.65 vs. 1.94 ± 0.72 ($p = 0.0002$) [a] | 35.7 vs. 13.8 ($p = 0.054$) |
| PICCOLETO II [14] | Small arteries | Elutax SV | EES | 232 | 0.04 vs. 0.17 ($p = 0.001$) | 5.6 vs. 7.5 ($p = 0.55$) |
| DEBUT [15] | Large arteries – High bleeding risk | SeQuent Please | BMS | 208 | - | 1 vs. 14 ($p < 0.00001$) |
| PEPCAD-NSTEMI [16] | NSTEMI | SeQuent Please | BMS/DES | 210 | - | 6.7 vs. 14.2 ($p = 0.11$) |
| REVELATION [37] | STEMI | Pantera Lux | SES | 120 | 0.92 ± 0.05 vs. 0.91 ± 0.06 ($p = 27$) [b] | - |
| Gobic *et al.* [38] | STEMI | SeQuent Please | SES | 75 | –0.09 ± 0.09 vs. 0.10 ± 0.19 ($p < 0.05$) | 0 vs. 5.4 ($p = 0.29$) |

DCB, drug-coated balloon; BMS, bare metal stent; ISR, in-stent restenosis; DES, drug-eluting stent; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; PCB, paclitaxel-coated balloon; POBA, plain old balloon angioplasty; PES, paclitaxel-eluting stent; EES, everolimus-eluting stent; ZES, zotarolimus-eluting stent; SES, sirolimus-eluting stent; LLL, late lumen loss; TLF, target lesion failure; FFR, fractional flow reserve; MACE, major adverse cardiovascular outcomes.

[a] Mean luminal diameter (mm); [b] Mean fractional flow reserve.

**Table 3. Registries design with the use of Sirolimus-coated balloon.**

| Characteristics | FASICO [6] | NATIVES [48] | SELFIE [50] | NANOLUTE [49] | EASTBOURNE[a] [18] |
|---|---|---|---|---|---|
| N patients/lesions | 32/34 | 27[b] | 62 | 408/435 | 642 |
| Presentation | | | | | |
| Stable CAD, n (%) | 21 (66) | 16 (80) | 0 | 196 (48) | 353 (55) |
| ACS, n (%) | 10 (31) | 4 (20) | 62 (100) | 194 (47.5) | 289 (45) |
| Multi-vessel, n (%) | 17 (50) | 17 (85) | - | 26 (6.4) | 372 (58.1) |
| Lesion type | | | | | |
| De-novo, n (%) | 18 (53) | 27 (100) | 32 (52) | 240 (55.2) | 364 (57) |
| ISR, n (%) | 16 (47) | 0 | 30 (48) | 195 (44.8) | 278 (43) |
| Procedural Success (%) | 100 | 74 | 100 | 98.9 | 98.6 |
| Follow-up, months | 6, clinical | 6, angiographic and clinical | 12, clinical | 24, clinical | 12, clinical |
| Final outcomes | | | | | |
| MACE, n (%) | 3 (9.4) | - | 3 (4.8) | 17 (4.2) | 37 (5.8) |
| TLR, n (%) | 3 (9.4) | - | 2 (3.2) | 13 (3.2) | 16 (2.5) |
| C death, n (%) | 0 | 0 | 1 (1.6) | 3 (0.7) | 6 (0.9)[c] |
| MI, n (%) | 0 | 0 | 2 (3.2) | 1 (0.2) | 15 (2.3) |
| LLL, mm (mean ± SD) | - | 0.09 ± 0.34 | - | - | - |

N, number; CAD, coronary artery disease; ACS, acute coronary syndrome; ISR, in-stent restenosis; MACE, major adverse cardiovascular events; TLR, target vessel revascularization; C, cardiac; MI, myocardial infarction; LLL, late lumen loss.

[a] Interim analysis; [b] 7 patients were excluded due to stent implantation during the index procedure; [c] Total death.

the first Conformité Européenne (CE) marketed SCB; first experiences go back to 2016 showing good safety and feasibility [47]. Thereafter several more evidences were published (Table 3, Ref. [6, 18, 48–50]). The FASICO registry included an all-comers population, demonstrating excellent efficacy (100% procedural success and TLR 9.4%) and outcomes (MACE 9.4%) [6]. On the other side the FASICO NATIVES registry, enrolling only patients with *de novo* coronary lesions, with angiographic follow-up at 6 months, confirmed the safety and efficacy of the device with a LLL of 0.09 ± 0.34 mm and a minimal lumen diameter (MLD) of 1.68 ± 0.48 mm post-procedure vs. 1.59 ± 0.59 mm during follow-up [48]. Few years after, the NANOLUTE Indian registry demonstrated good clinical outcome of Magic Touch SCB at 24 months in more than 400 patients in terms of MACE [49].

EASTBOURNE registry is an international, multicenter, investigator-driven prospective registry is to date the largest with 2123 patients treated with SCB Magic Touch. An interim analysis presented by B. Cortese during EuroPCR 2021, showed that 41% were diabetic and 56% had multivessel coronary disease. Half of patients presented with ISR, 83% being attributed to previously implanted DES. Only 7.5% of patients received bailout stenting. TLR occurred in 2.5%, myocardial infarction in 2.3%, total death in 1% and MACE in 5.8% with a good safety and efficacy profile at 12 months [18].

Another SCB, the Virtue angioplasty balloon (Caliber Therapeutics, New Hope, Pennsylvania), investigated in the SABRE trial, showed excellent procedural success and safety. The primary safety endpoint, target lesion failure was 0% at 30 days follow-up and LLL 0.31 ± 0.52 mm at 6 months [51].

In the setting of peripheral artery disease the recent first-in-human study with the use of Selution SLR® DCB in femoropopliteal lesions, showed the safety and efficacy in reducing LLL at 6 months [52].

## 7. Sirolimus vs. paclitaxel: clinical stand point

Scientific literature is still poor of comparisons between SCB and PCB. The first direct comparison was presented by Ali *et al.* [53] in 2019; they presented a randomized controlled trial comparing SeQuent Please SCB® (B. Braun, Melsungen, Germany) to SeQuent Please Neo® (B. Braun, Melsungen, Germany), in 50 patients presenting with DES ISR. The LLL after 6 months was 0.17 ± 0.55 mm (sirolimus) vs. 0.21 ± 0.54 mm (paclitaxel) with no significant differences between groups also in terms of clinical endpoints [53].

More recently, the SIRPAC study compared 544 patients from the DCB RISE registry using Elutax SV/III PCB to 596 patients from the EASTBOURNE interim analysis registry with Magic Touch. After a propensity score matching, 290 patients per group were selected (Table 4); at 12 months clinical follow-up, there was no difference in terms of TLR between PCB and SCB (8.3% vs. 7.9%, respectively, $p = 0.879$), and MACE (10.7% vs. 10.3%, respectively, $p = 0.892$) at 12 months [54].

The currently ongoing randomized trial TRANSFORM I is comparing Magic Touch SCB to SeQuent Please Neo PCB for the management of *de novo* coronary lesions in small vessels of ≤2.75 mm; after lesion preparation, patients are randomized 1:1 to receive either SCB or PCB and will undergo OCT analysis for the actual vessel sizing. The primary outcome will be net lumen diameter gain at 6 months assessed with QCA [55].

**Table 4. Patients characteristics and procedural details in the SIRPAC study.**

| | EASTBOURNE (n = 290) | DCB RISE (n = 290) | *p* value |
|---|---|---|---|
| Patients characteristics after PSM | | | |
| Age (mean ± SD) | 66 ± 12 | 67 ± 11 | 0.507 |
| Diabetes (%) | 131 (45) | 103 (35) | 0.018 |
| Previous PCI (%) | 215 (74) | 212 (73) | 0.885 |
| CKD (%) | 36 (12) | 46 (16) | 0.233 |
| Small vessels (%) (<2.5 mm) | 134 (46) | 117 (40) | 0.154 |
| ACS | 155 (53) | 150 (52) | 0.678 |
| ISR n (%) | 184 (63) | 175 (60) | 0.442 |
| Procedural details after PSM | | | |
| Pre-dilation n (%) | 261 (90) | 263 (91) | 0.779 |
| Angiographic success n (%) | 283 (98) | 282 (97) | 0.794 |
| Balloon inflation pressure (atm) (mean ± SD) | 11 ± 4 | 11 ± 4 | 0.400 |
| Balloon inflation time (sec) (mean ± SD) | 58 ± 13 | 56 ± 30 | 0.188 |
| Balloon diameter (mm) (mean ± SD) | 2.8 ± 0.6 | 2.8 ± 0.5 | 0.984 |
| Balloon length (mm) (mean ± SD) | 22 ± 7 | 19 ± 5 | 0.001 |

PSM, propensity score matching; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; ACS, acute coronary syndrome; ISR, in-stent restenosis.

## 8. Conclusions and future perspectives

Since its first use in DES, sirolimus has proven to be superior and better suitable for coronary interventions compared to paclitaxel. This assumption clearly demonstrated for metallic stents cannot be currently made for the DCB technology. While either drugs share some common biochemical characteristics, the safety profile and the broader therapeutic window favors sirolimus.

Results from studies currently ongoing such as TRANSFORM I [55], will help to clear the fog.

Future relevant studies are already in the making:

- The TRANSFORM II (ClinicalTrials.gov Identifier: NCT04893291), an investigator-driven international randomized controlled trial, will compare Magic Touch against everolimus-eluting DES in 1300 patients with small and mid-sized coronary vessels (≤3.0 mm). The primary endpoint will be TLF at 12 months, and patients will be followed up for 5 years.

- The PICCOLETO III trial will compare the 3 technologies of DES, SCB and PCB in patients with highly complex coronary lesions.

## Author contributions

GdP and EFSJ designed the drugs comparison, figures and tables. LL and BC designed the research in clinical studies and clinical comparison. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.


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## Conflict of interest

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