



A Retrospective Look at Paclitaxel Use in the Coronary Arteries

A review of the safety and efficacy profile of paclitaxel treatment in patients with coronary artery disease.

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A recent meta-analysis of randomized clinical trials has identified a potential “signal” for increased long-term mortality in patients treated with paclitaxel-coated balloons (PCBs) and paclitaxel-eluting stents (PESs) in the peripheral arteries.¹ This finding was both surprising and controversial, given the extensive body of evidence for paclitaxel use in the coronary arteries, where its track record of safety and efficacy is well-established. Nevertheless, given the potential implications of this meta-analysis, the FDA issued a warning letter to health care providers in January 2019 expressing potential concerns about the risk of paclitaxel-coated devices for the treatment of peripheral vascular disease and indicated that further study was needed.² The FDA also acknowledged that a specific cause for potential increased mortality was unknown. No specific regulatory action was taken on FDA-approved or investigational paclitaxel-coated devices because it was believed that “the benefits continue to outweigh the risks.”

An FDA advisory panel was convened in June 2019, and again, although no definitive conclusions were reached, it was emphasized that the individual studies included in the meta-analysis required cautious interpretation, as there was a large amount of missing follow-up (up to 30% at 5 years), no clear mechanism identified for the mortality signal on review of animal and human studies, and poor correlations between paclitaxel dose and mortality.³ Nevertheless, a thoughtful discussion of the potential risks and benefits of paclitaxel-coated devices in patients with peripheral vascular disease was recommended.

These findings in patients with peripheral vascular disease prompted a retrospective review of patients treated with paclitaxel for coronary artery disease, which included substantially more patients, albeit at lower delivered paclitaxel dose. Although paclitaxel-coated coronary stents are no longer routinely used in current practice in the United States, there are a number of studies currently evaluating PCBs for native coronary artery disease and the

treatment of in-stent restenosis (ISR).⁴⁻⁶ This article reviews the safety and efficacy profile of paclitaxel in patients with coronary artery disease (Table 1).^{4,7-20}

PACLITAXEL MECHANISM OF ACTION

The commercial availability of bare-metal stents (BMSs) in the early 1990s was transformational for patients undergoing percutaneous coronary intervention (PCI), improving the safety of the procedure by treating coronary dissections associated with balloon-induced barotrauma and lessening the rate of late restenosis by 30% to 50%. Despite these beneficial effects, restenosis still occurred in 20% to 30% of patients treated with BMSs, particularly in those with diabetes mellitus, small vessels, and long lesions. A number of drug-eluting stents (DESs) were developed in the early 2000s to address the vexing process of restenosis. These DESs were composed of a metallic scaffold, durable polymer, and antiproliferative drug, most commonly sirolimus, another mTOR inhibitor analog, or paclitaxel.

Paclitaxel was originally isolated from the Pacific Yew tree (*Taxus brevifolia*) and is an antiproliferative agent that stabilizes intracellular microtubules and prevents mitosis in the G₀-G₁ and G₂-M phases of the cell cycle.²¹ Paclitaxel was originally approved by the FDA in 1992 and has been used extensively in oncology, particularly for breast and ovarian cancer. Paclitaxel toxicity is well-characterized and includes neutropenia, neurotoxicity, and hypersensitivity reactions.²² Cardiac side effects are rare. Notably, the plasma levels of paclitaxel in oncology patients are 100 to 1,000 times higher than the cumulative doses of PESs. Highlighting its perceived safety, paclitaxel was deemed safe when given during pregnancy after organogenesis.²³

PACLITAXEL-ELUTING CORONARY STENTS

Several DESs were developed to deliver paclitaxel to the coronary artery to inhibit arterial smooth muscle cell proliferation and reduce neointimal stenosis after



TABLE 1. PACLITAXEL DRUG-ELUTING CORONARY SYSTEMS

Study	Platform	Manufacturer	Dose Formulation	Elution Agent
Drug-eluting stents				
BARDDS ⁷	QuaDS-QP2 316 L stainless steel stent	Quanam Medical Corporation	4,000 µg	Polymer sleeves are made of an acrylic copolymer configured as a seamless tube
JACTAX ⁸	Jactax DES made from a precrimped 316 L stainless steel Taxus Liberté stent with a strut thickness of 0.0038 inches (96.5 µm)	Boston Scientific Corporation	0.6 µg/mm of stent length	Bioresorbable DLPLA applied to the abluminal surface on a premounted stent
DELIVER ⁹	Multi-Link Penta stainless steel stent	Guidant Corporation	3 µg/mm ² stent surface area	No polymer
TAXUS I, ¹⁰ TAXUS II, ¹¹ TAXUS III ¹²	Taxus NIRx stainless steel stent	Boston Scientific Corporation	1 µg/mm ²	Translute polymer
TAXUS IV, ¹³ TAXUS V ¹⁴	Taxus Express stainless steel stent	Boston Scientific Corporation	1 µg/mm ²	Translute polymer
TAXUS VI ¹⁵	Taxus Express stainless steel stent	Boston Scientific Corporation	1 µg/mm ²	Translute polymer: SR and MR
Drug-coated balloons				
DEBUT ⁴	SeQuent Please	B. Braun Interventional Systems, Inc.	3 µg/mm ²	Iopromide excipient
PACCOCATH ISR ¹⁶	Paccocath	Bayer HealthCare	3 µg/mm ²	Radiographic contrast
PEPCAD II ¹⁷	SeQuent Please	B. Braun Interventional Systems, Inc.	3 µg/mm ²	Iopromide excipient
ISAR-DESIRE 3 ¹⁸	SeQuent Please	B. Braun Interventional Systems, Inc.	3 µg/mm ²	Iopromide excipient
PEPCAD I ¹⁹	SeQuent Please	B. Braun Interventional Systems, Inc.	3 µg/mm ²	Iopromide excipient
PICCOLETO ²⁰	Dior	Eurocor GmbH	3 µg/mm ²	Microcrystals

Abbreviations: DLPLA, D-lactic polylactic acid; MR, moderate release; SR, slow release.

stent placement (Table 1).^{7-15,24,25} The QuaDS-QP2 stent (Quanam Medical Corporation) provided a metallic scaffold, polymeric sleeve, and high quantities (up to 4 g) of paclitaxel.⁷ This stent had very brief clinical use, owing to high rates of vessel thrombosis, likely due to the very narrow efficacy-toxicity window with paclitaxel. The Jactax DES system (Boston Scientific Corporation) was a precrimped BMS that was coated on its abluminal aspect with an ultrathin (< 1 µm) one-to-one mixture of biodegradable polylactide polymer and paclitaxel applied as discrete microdots.^{8,26} The Achieve stent (Guidant Corporation) that released paclitaxel from a stainless

steel stent without a polymer provided no significant benefit over BMS, likely due to the rapid elution of the paclitaxel.⁹

The predominant evidence base for PESs was developed with the TAXUS program studying Boston Scientific's Taxus product line. These slotted-tube stainless steel stents included the Taxus NIRx stent (TAXUS I, II, and III studies),¹⁰⁻¹² the Taxus Express stent (TAXUS IV, V, and VI studies),¹³⁻¹⁵ and the Taxus Liberté stent (ATLAS studies).²⁷ Most clinical studies were performed with the slow-release (SR) formulation of the proprietary Translute polymer, which was designed to control paclitaxel release with an initial



burst phase over the first 48 hours after implantation, followed by a low-level release phase for 10 days. The Taxus moderate-release (MR) device provided an eightfold higher 10-day drug release, and clinical studies showed no significant change in the antiproliferative effect but also no additional toxicity.¹⁵ Of the total loaded dose, approximately 90% remained sequestered within the SR polymer and 75% remained sequestered within the MR.

The TAXUS I study included 61 patients with de novo or restenotic coronary lesions who were randomized to receive a PES or BMS and showed a trend toward a decrease in restenosis in the PES group (0%) compared with the BMS group (10%).¹⁰ The TAXUS II trial evaluated PES in SR and MR formulations compared with BMS and showed a lower rate restenosis in the PES group.¹¹ The TAXUS III trial was a small feasibility study of 28 patients with ISR treated with the PES.¹²

The TAXUS IV study enrolled 1,314 patients with noncomplex coronary artery disease who were assigned treatment with a BMS, and 662 were assigned to receive treatment with an SR, polymer-based PES.¹³ Target lesion revascularization (TLR) was required in 3% of patients who received a PES and 11.3% of patients who received a BMS (relative risk, 0.27; 95% confidence interval [CI], 0.16–0.43; $P < .001$). The rate of angiographic restenosis was reduced from 26.6% to 7.9% with the PES (relative risk, 0.30; 95% CI, 0.19–0.46; $P < .001$). As a result, the FDA approved the Taxus stent based on a totality of clinical evidence, including the TAXUS IV study. In long-term follow-up at 1 and 5 years, the PES demonstrated superior efficacy with lower TLR and showed similar safety with no difference in major adverse cardiovascular events compared with a BMS (Figure 1).^{28,29} The TAXUS V study found similar results in patients with complex coronary artery disease.¹⁴ Shortly thereafter, the Taxus PES and sirolimus-eluting Cypher stent (Cordis, a Cardinal Health company) became standard of care in patients undergoing PCI. Within 10 months of approval, the Taxus stent had been implanted in over 1 million patients.³⁰

Based on the safety and efficacy of PESs, despite the high rate of late lumen loss with the PESs compared with sirolimus-eluting stents,³¹ the Taxus stent became the comparator in a number of noninferiority stent versus stent trials that provided long-term clinical trial outcomes in a large number of patients treated with PESs.^{32,33}

LATE STENT THROMBOSIS AND THE 2006 FDA ADVISORY PANEL MEETING

By the summer of 2006, DESs had become the default therapy for 80% to 90% of patients undergoing PCI due to the dramatic reduction in restenosis. Dual antiplatelet therapy was generally only continued for 1 year after

the procedure. After a small series description of late stent thrombosis (> 1 year after the procedure),³⁴ a meta-analysis of randomized trials showed higher late mortality in patients receiving either a sirolimus-eluting or paclitaxel-eluting coronary stent.³⁵ As a result of these concerns, the FDA convened a meeting of the Circulatory System Devices Panel in 2006. This landmark advisory panel shed light on the limitations of the clinical trial design with DESs, including follow-up limited to 1 year, “off-label” use in patients with complex coronary disease (eg, bifurcation lesions, coronary artery bypass grafts, acute myocardial infarction, chronic total occlusion, and with overlapping stents), and variations in the definitions used for endpoint events.³⁰ As a result of these analyses, it became apparent that there was an off-setting impact of the reduction of restenosis with the DES with the small but late risk of stent thrombosis.³⁶ It was also believed that the type and amount of durable polymer also contributed to late stent thrombosis with early DESs, which could be lessened in part with the use of extended dual antiplatelet therapy. No particular toxicity related to paclitaxel or sirolimus was identified, but the overall use of DESs fell dramatically.

Newer-generation DESs were then developed with thinner stent filaments, lower polymer burden with more bio-comparable polymers, and more effective antiproliferative agents. In a network meta-analysis that included 50,844 patients, the rates of 1-year definite stent thrombosis were significantly lower with cobalt-chromium everolimus-eluting stents (CoCr-EEs) compared with PESs, permanent

5-year Mortality in TAXUS trials (N=2,797)

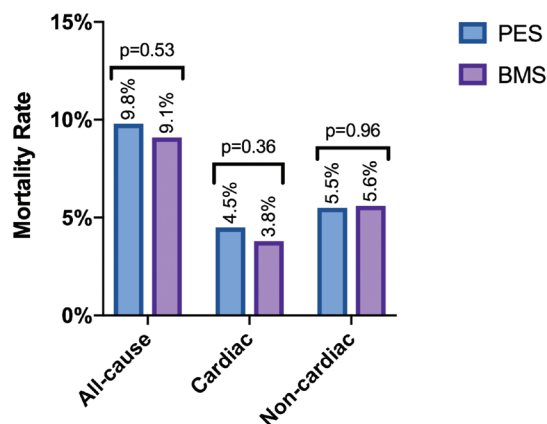


Figure 1. Five-year mortality pooled patient-level data from the TAXUS trials. Data from Stone GW, Ellis SG, Colombo A, et al. Long-term safety and efficacy of paclitaxel-eluting stents final 5-year analysis from the TAXUS clinical trial program. *JACC Cardiovasc Interv.* 2011;4:530-542.



polymer-based sirolimus-eluting stents, phosphorylcholine-based zotarolimus-eluting stents, and the Resolute zotarolimus-eluting stent (Medtronic).³⁷ At 2-year follow-up, CoCr-EESs were still associated with significantly lower rates of definite stent thrombosis than BMSs and PESs. The beneficial effects of EESs over paclitaxel stents were mechanistically related enhanced efficacy with reduced TLR and stent thrombosis rather than toxicity related to paclitaxel.³⁸ No late safety signals were detected in long-term follow-up of these studies with paclitaxel, but their availability was terminated due to lower efficacy compared with the latest-generation devices.

PACLITAXEL-COATED CORONARY BALLOONS

PCBs may have value in patients with ISR, small vessels, and those at high risk for bleeding. Scheller and colleagues reported a reduction in restenosis compared with balloon angioplasty alone in patients with ISR using early drug-coated balloon (DCB) technology.¹⁶ The superiority of PCBs in terms of target vessel revascularization persisted at 5-year follow-up. The PEPCAD II trial randomized 131 patients with ISR within BMSs to treatment with PCBs or PESs and showed that there was no difference in major adverse cardiac events in the two groups and no deaths at 12 months.¹⁷ The ISAR-DESIRE 3 trial demonstrated the noninferiority of DCB use compared with PES in percent diameter stenosis at 6 to 8 months.¹⁸

The first study investigating PCB use in small vessels was the PEPCAD I study, a single-arm trial investigating the SeQuent Please balloon (B. Braun Interventional Systems, Inc.), which showed that the DCB-only group had superior angiographic and clinical results at 6 months.¹⁹ Other randomized trials of DCBs in small vessels have been completed,²⁰ and it appears that a DCB-only strategy with provisional BMSs might be a reasonable approach in this population.

A final subset of patients was evaluated in the DEBUT trial that randomized 208 patients with native coronary artery disease who were at high bleeding risk and were treated with a PCB or BMS. Patients treated with a PCB had a significantly lower rate of major adverse cardiac events compared with those in the BMS arm.⁴ A post hoc analysis showed that total mortality was higher in the BMS group.⁴ Additional studies with PCBs in these patient subsets are ongoing. No significant safety concerns have been identified to date.

CONCLUSION

Between the approval of PESs by the FDA in 2004 and the availability of next-generation DESs by 2010, millions of patients were treated with paclitaxel in coronary arteries. Because PESs were the default control stent in testing

a number of new-generation DESs, extended follow-up to 5 years is available for thousands of patients. To date, there have been no late mortality signals in late cardiovascular or noncardiovascular deaths attributable to paclitaxel toxicity. PESs fell out of favor due to reduced efficacy compared with next-generation DESs rather than any identified paclitaxel toxicity. PCBs, which have not been approved in the United States, may have a particular benefit in patients with ISR, smaller vessels, or those at high risk for bleeding. Longer-term studies in larger numbers of patients with long-term follow-up should be performed. ■

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Disclosures: Receives institutional grants from Medtronic, Abbott Vascular, Boston Scientific Corporation, Cook Medical, Terumo, and Phillips; receives consulting fees from Boston Scientific Corporation for participating on a medical advisory board.