

Head-to-Head Trial Compares Low- to Higher-Dose Drug-Coated Balloons at a Critical Time

BY MICHAEL R. JAFF, DO

For as many as 200 million people around the world affected by peripheral artery disease (PAD),¹ the evolution of endovascular innovations certainly provides a source of optimism. Within 3 decades, we have moved from treating patients with uncoated percutaneous transluminal angioplasty (PTA) to utilizing advanced drug-coated balloons (DCBs). These latest innovations deliver doses of the drug paclitaxel to inhibit cell proliferation and migration in arterial tissue, thereby limiting the amount of restenosis after treatment.

Considering that the use of DCBs for femoropopliteal interventions was challenged by a 2018 meta-analysis identifying a late mortality signal beyond 2 years in patients treated with paclitaxel-coated devices compared with uncoated devices,² there is growing interest in a new-generation DCB that has benefits comparable to earlier drug-coated devices, but uses significantly reduced doses of drug. Although an association between paclitaxel dose and all-cause mortality was postulated in this meta-analysis, subsequent publications of individual patient-level data and registries did not corroborate this assumption, proving it is still a critical time to study and compare the efficacy and safety of higher- and low-dose DCBs.³⁻⁸

In January 2020, at the Leipzig Interventional Course (LINC) Congress in Leipzig, Germany, expert trialists in endovascular therapies unveiled the results from the world's first head-to-head, prospective, randomized trial comparing a low-dose and a higher-dose DCB. The COMPARE trial, simultaneously published in the *European Heart Journal*,⁹ demonstrated that a new DCB called the Ranger™ Drug-Coated Balloon* (Boston Scientific Corporation; Figure 1) coated with a lower dose (2 µg/mm²) of paclitaxel is “non-inferior” to the higher-dose (3.5 µg/mm²) IN.PACT™ Admiral™ Drug-Coated Balloon (Medtronic).

With long-term patient outcomes in mind, the COMPARE trial was designed to advance the level of

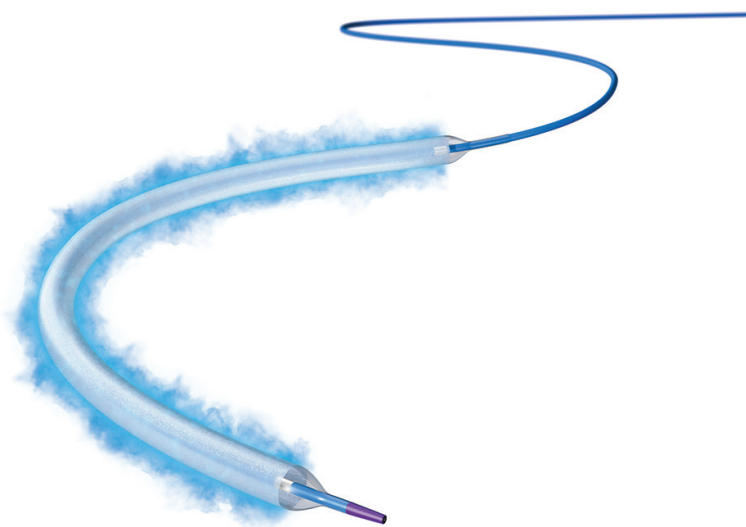


Figure 1. Ranger Drug-Coated Balloon.

evidence of vascular trials to a broad group of stakeholders, including physicians, regulators, payers, and most importantly, patients who want to know they are getting the safest and most effective therapies to improve their quality of life.

DOSE AND DELIVERY

When a physician recommends treatment for a patient with femoropopliteal PAD, there may be questions about the need for a coated balloon versus an uncoated PTA balloon. The answer lies in PTA-related restenosis rates as high as 70% in complex lesions.¹⁰ One can point to abundant evidence that coating inhibits neointimal hyperplasia and smooths muscle cell proliferation. But what is the optimal dose and how is the drug best delivered to the surrounding tissue?

To answer such questions, we can turn to the COMPARE study that evaluated the safety and efficacy of two different coating technologies and paclitaxel doses

RANGER DRUG-COATED BALLOON

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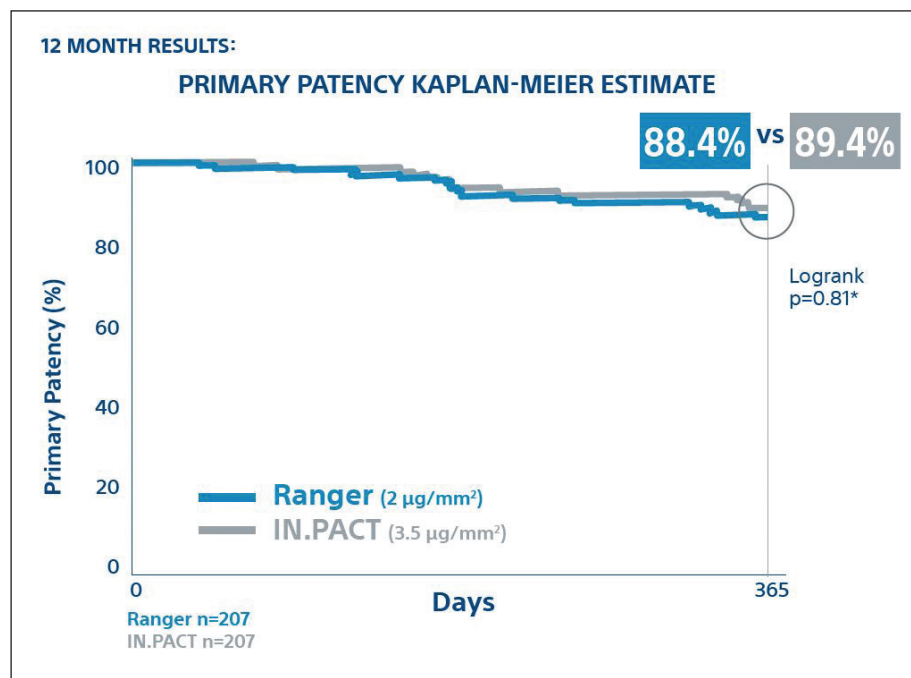


Figure 2. Primary patency rates per Kaplan-Meier estimate at 12 months. *Log-rank *P*-value compares the entire Kaplan-Meier curves from time zero to full 1-year follow-up window.

in patients with symptomatic femoropopliteal lesions. By intention, the trial included complex patients with lesion length of approximately 120 mm, approximately 40% had chronic total occlusions (CTOs), and approximately 30% of patients had diabetes mellitus. More than half of enrolled lesions exhibited moderate-to-severe calcification.

Technical success was defined as final in-lesion residual diameter stenosis $\leq 50\%$, while procedural success was determined by the combined absence of periprocedural mortality or complications such as target limb amputation, thrombosis of the target lesion, or need for repeat revascularization through 12 months. The primary safety endpoint was a composite of freedom from device- or procedure-related death, target limb amputation, or clinically driven target lesion revascularization (CD-TLR) for 12 months following the index procedure. The main efficacy endpoint was primary patency at 12 months, defined as the absence of CD-TLR. All-cause mortality was one of the key secondary endpoints.

NON-INFERIORITY OF LOW DOSE

The goal of the trial was to test the hypothesis that a low-dose DCB is non-inferior to higher-dose DCBs in terms of antirestenotic safety and efficacy through the first 12 months, with an overall sample size—414 patients—large enough to ensure adequate statisti-

cal power. The COMPARE trial demonstrated the non-inferiority of the low-dose Ranger DCB for both primary safety and efficacy endpoints at 12 months.

Primary patency was observed in 83% of patients in the low-dose arm and 81.5% of patients in the higher-dose DCB arm (Figure 2; reflects primary patency rates per Kaplan-Meier estimate). Not surprisingly, most restenotic events were observed in the long-lesion subgroup with lesions > 200 mm. The primary safety endpoint—freedom from major adverse events—was met in 91% of patients in the low-dose group and 96.2% of patients in the higher-dose cohort were event-free at 12 months, meeting the test of non-inferiority ($P \leq .01$).

All-cause mortality was low, with 5 and 3 deaths in the low- and higher-dose cohorts, respectively.

The COMPARE trial demonstrated the non-inferiority of the Ranger DCB coated with low-dose paclitaxel compared with the higher-dose IN.PACT DCB for both safety and efficacy at 12 months. Researchers observed no statistically significant difference in patency, although the Ranger DCB exposes patients to approximately half as much paclitaxel.

INNOVATIVE DESIGN

Although COMPARE may offer some of the most compelling data on the Ranger DCB, it is hardly an isolated example. More than 1,500 patients are involved in studies of this device, including Boston Scientific-sponsored trials and physician-sponsored programs.

In fact, at the 2020 LINC Congress, the full cohort from the RANGER II SFA trial was presented. In that study, the Ranger DCB demonstrated a primary patency rate of 89.8% at 12 months, which was significantly higher than that demonstrated in patients treated with uncoated PTA (74%) at 12 months ($P = .0005$). Despite the inclusion of complex patients (approximately 42% diabetics, approximately 85% smokers, approximately 48% of lesions with moderate/severe calcium), those treated with the Ranger DCB had a significantly lower TLR rate

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of 5.5% in contrast to 16.5% observed with standard PTA ($P = .0011$), thus substantially reducing a patient's need for repeat procedures.

The Ranger DCB has shown consistent results in randomized trials and a real-world registry. This is the culmination of more than 20 years studying paclitaxel in a variety of devices with a series of design innovations.

Aside from the recent controversy surrounding paclitaxel in endovascular devices for patients with PAD, using a lower but effective drug dose is a generally accepted principle in designing new drugs or devices. A lower drug dose allows physicians to minimize potential side effects for the patient, and in bench and pre-clinical studies, we have observed that the Ranger DCB releases approximately 10 times fewer drug particulates than the IN.PACT DCB and approximately eight times fewer drug particulates than the Lutonix® Drug-Coated Balloon (BD Interventional).¹¹

CONCLUSION

The seminal COMPARE trial has demonstrated the non-inferiority of the Ranger DCB coated with a low dose of paclitaxel compared with the higher-dose IN.PACT DCB at 12 months, meeting both the safety and efficacy endpoints. Primary patency and CD-TLR were non-inferior through 12 months for femoropopliteal interventions including a wide range of lesion complexities. Both devices showed excellent efficacy with a similar and reassuring safety profile.

Researchers will continue to track patency over the next year as part of the study follow-up built into the revised protocol design, and they will monitor TLR and mortality for up to 5 years. This should yield even more important insights including patterns of restenosis in lesions of varying complexity, helping endovascular specialists and their patients confidently design the optimum course of treatment. In addition, COMPARE sets a new standard of expectation of what clinicians and patients demand as treatment strategies are established. ■

Disclaimer: *In the United States, the Ranger DCB is an investigational device and is not available for sale. The Ranger DCB gained CE Mark in 2014. CAUTION: The law restricts these devices to sale by or on the order of a physician. Indications, contraindications, warnings and instructions for use can be found in the product labelling supplied with each device. Information for the use only in countries with applicable health authority product registrations. This material not intended for use in France. Ranger™ Paclitaxel PTA Balloon Catheter is manufactured by Hemotek AG. All cited trademarks are the property of their respective owners.

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