Medtronic

IN.PACT™ AV

Paclitaxel-coated PTA Balloon Catheter

Instructions for Use

USA **Caution:** Federal law (USA) restricts this device to sale by or on the order of a physician.

Explanation of symbols on package labeling

STERILE EO	Sterilized using ethylene oxide
REF	Catalog number
LOT	Lot number
	Manufacturer
	Manufactured in
	Use-by date
	Quantity
www.medtronic.com/manuals	Consult instructions for use at this website: www.medtronic.com/manuals
	Do not reuse
	Do not resterilize
	Keep away from sunlight
	Keep dry
	Do not use if package is damaged
	Outer diameter
	Temperature limit
	Nonpyrogenic
OTW	Over the wire
NP	Nominal pressure
RBP	Rated burst pressure
RBP	Do not exceed rated burst pressure
IP	Inflation pressure
BALLOON ∅	Balloon diameter
≥	Minimum sheath inner diameter
	Maximum guidewire diameter
BALLOON	Balloon length
	Usable catheter length

IN.PACT™ AV

Paclitaxel-coated PTA Balloon Catheter

Table of contents

1. Product Name

IN.PACT™ AV paclitaxel-coated percutaneous transluminal angioplasty (PTA) balloon catheter

2. Product Description

The IN.PACT AV paclitaxel-coated PTA balloon catheter, hereafter referred to as the IN.PACT AV DCB, is an over-the-wire (OTW) balloon catheter with a drug-coated balloon (DCB) at the distal tip. The drug component, referred to as the FreePac™ coating, consists of the drug paclitaxel and the excipient urea. The device component physically dilates the vessel lumen by PTA, and the drug is intended to reduce the proliferative response that is associated with restenosis. Product Component Description (Table 1) summarizes the characteristics of the device.

Table 1. Product Component Description

<table>
<tr><td rowspan="10">Available Balloon Diameters (mm) and Lengths (mm)</td><td rowspan="2">Balloon Diameter</td><td colspan="4">Balloon Length</td></tr>
<tr><td>40 mm</td><td>60 mm</td><td>80 mm</td><td>120 mm</td></tr>
<tr><td>4.0 mm</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>5.0 mm</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>6.0 mm</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>7.0 mm</td><td>X</td><td>X</td><td>X</td><td>---</td></tr>
<tr><td>8.0 mm</td><td>X</td><td>X</td><td>X</td><td>---</td></tr>
<tr><td>9.0 mm</td><td>X</td><td>X</td><td>X</td><td>---</td></tr>
<tr><td>10.0 mm</td><td>X</td><td>---</td><td>---</td><td>---</td></tr>
<tr><td>12.0 mm</td><td>X</td><td>---</td><td>---</td><td>---</td></tr>
<tr><td colspan="5">Note: “---” indicates sizes not offered; “X” indicates sizes offered</td></tr>
<tr><td>Balloon Coating (Drug Component)</td><td colspan="4">Paclitaxel (Active Pharmaceutical Ingredient) and Urea (excipient)</td></tr>
<tr><td>Catheter Design</td><td colspan="4">Over-the-Wire (OTW)</td></tr>
<tr><td>Usable Catheter Lengths</td><td colspan="4">40 cm, 80 cm and 130 cm</td></tr>
<tr><td rowspan="9">Balloon Inflation Pressure</td><td>Balloon Diameter</td><td colspan="2">Nominal Pressure</td><td>Rated Burst Pressure</td></tr>
<tr><td>4.0 mm</td><td colspan="2" rowspan="6">811 kPa / 8 atm</td><td rowspan="4">1419 kPa / 14 atm</td></tr>
<tr><td>5.0 mm</td></tr>
<tr><td>6.0 mm</td></tr>
<tr><td>7.0 mm</td></tr>
<tr><td>8.0 mm</td><td rowspan="2">1013 kPa / 10 atm</td></tr>
<tr><td>9.0 mm</td></tr>
<tr><td>10.0 mm</td><td colspan="2" rowspan="2">608 kPa / 6 atm</td><td rowspan="2">912 kPa / 9 atm</td></tr>
<tr><td>12.0 mm</td></tr>
<tr><td rowspan="10">Minimum Introducer Sheath Compatibility</td><td>Balloon Diameter</td><td colspan="2">Max. Crossing Profile</td><td>Introducer Sheath</td></tr>
<tr><td>4.0 mm</td><td colspan="2">5.6 F (1.88 mm)</td><td>5 F</td></tr>
<tr><td>5.0 mm</td><td colspan="2">6.0 F (2.00 mm)</td><td rowspan="2">6 F</td></tr>
<tr><td>6.0 mm</td><td colspan="2">6.3 F (2.10 mm)</td></tr>
<tr><td>7.0 mm</td><td colspan="2" rowspan="4">7.0 F (2.33 mm)</td><td rowspan="4">7 F</td></tr>
<tr><td>8.0 mm</td></tr>
<tr><td>9.0 mm</td></tr>
<tr><td>10.0 mm</td></tr>
<tr><td>12.0 mm</td><td colspan="2">9.0 F (3.00 mm)</td><td>9 F</td></tr>
<tr><td>Guidewire Compatibility</td><td colspan="4">The catheter is compatible with a guidewire diameter of 0.035 in (0.89 mm).</td></tr>
</table>

2.1. Device Component Description

The balloon catheter consists of a proximal hub, dual-lumen shaft, and a distal dilatation balloon. The central lumen extends to the distal tip and is used to pass the catheter over a guidewire with a diameter of 0.035 in (0.89 mm). The balloon-inflation lumen is used to inflate and deflate the balloon with a mixture of contrast medium and saline solution. Two radiopaque platinum-iridium markers indicate the working length of the balloon to position the balloon across the target lesion during fluoroscopy. See IN.PACT AV Paclitaxel-coated PTA Balloon Catheter (Figure 1).

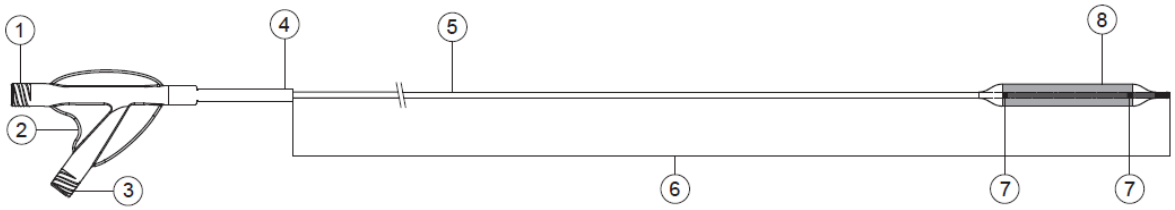


Figure 1. IN.PACT AV Paclitaxel-coated PTA Balloon Catheter

1. Guidewire port
2. Hub
3. Inflation port
4. Strain relief
5. Shaft
6. Usable catheter length
7. Radiopaque marker
8. Drug-coated balloon

2.2. Drug Component Description

The FreePac™ drug coating on the balloon of the IN.PACT AV DCB consists of the drug paclitaxel and the excipient urea. The balloon surface has a nominal paclitaxel dose density of 3.5 µg/mm^2.

2.2.1. Paclitaxel

The active pharmaceutical ingredient in the IN.PACT AV DCB is paclitaxel. The principal mechanism by which paclitaxel inhibits neointimal growth is through the stabilization of microtubules by preventing their depolymerization during the final G2/M phase of cell division.

The CAS Registry number of paclitaxel is 33069-62-4. The chemical name of paclitaxel is:

Benzenepropanoic acid, ß-(benzoylamino)-α-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy) -2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-ylester,[2aR-[2aα,4β,4aβ,6β,9α(αR, βS),11α,12α,12aα,12bα]]

See Chemical Structure of Paclitaxel (Figure 2) below.

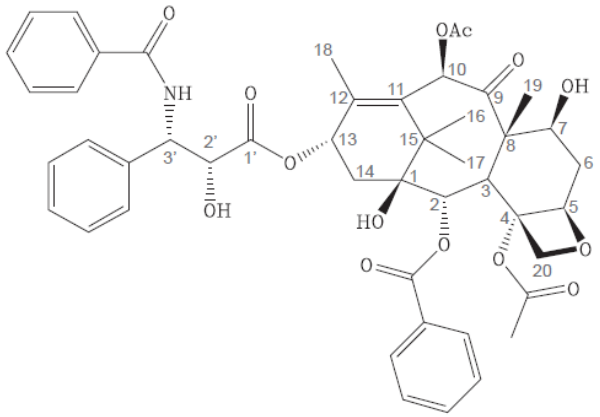


Figure 2. Chemical Structure of Paclitaxel

Paclitaxel is a diterpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol, and a molecular formula of $C_{47}H_{51}NO_{14}$. It is a white powder, has extremely low water solubility, is highly lipophilic, and is freely soluble in methanol, ethanol, chloroform, ethyl acetate, and dimethyl sulfoxide.

2.2.2. Urea

The coating utilizes the inactive ingredient urea as an excipient to facilitate the release and transfer of paclitaxel into the vessel wall. See Chemical Structure of Urea (Figure 3) below.

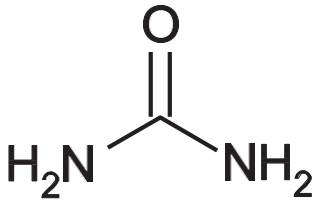


Figure 3. Chemical Structure of Urea

2.2.3. Product Matrix and Paclitaxel Content

Table 2. Product Matrix and Paclitaxel Content

Product Code (40 cm Usable Catheter Length)	Product Code (80 cm Usable Catheter Length)	Product Code (130 cm Usable Catheter Length)	Nominal Balloon Diameter (mm)	Nominal Balloon Length (mm)	Nominal Paclitaxel Content (µg)
IAV 040 040 04P	IAV 040 040 08P	IAV 040 040 13P	4.0	40	1969
IAV 040 060 04P	IAV 040 060 08P	IAV 040 060 13P	4.0	60	2848
IAV 040 080 04P	IAV 040 080 08P	IAV 040 080 13P	4.0	80	3728
IAV 040 120 04P	IAV 040 120 08P	IAV 040 120 13P	4.0	120	5487
IAV 050 040 04P	IAV 050 040 08P	IAV 050 040 13P	5.0	40	2553
IAV 050 060 04P	IAV 050 060 08P	IAV 050 060 13P	5.0	60	3653
IAV 050 080 04P	IAV 050 080 08P	IAV 050 080 13P	5.0	80	4752

Product Code (40 cm Usable Catheter Length)	Product Code (80 cm Usable Catheter Length)	Product Code (130 cm Usable Catheter Length)	Nominal Balloon Diameter (mm)	Nominal Balloon Length (mm)	Nominal Paclitaxel Content (µg)
IAV 050 120 04P	IAV 050 120 08P	IAV 050 120 13P	5.0	120	6951
IAV 060 040 04P	IAV 060 040 08P	IAV 060 040 13P	6.0	40	3170
IAV 060 060 04P	IAV 060 060 08P	IAV 060 060 13P	6.0	60	4489
IAV 060 080 04P	IAV 060 080 08P	IAV 060 080 13P	6.0	80	5809
IAV 060 120 04P	IAV 060 120 08P	IAV 060 120 13P	6.0	120	8448
IAV 070 040 04P	IAV 070 040 08P	IAV 070 040 13P	7.0	40	3819
IAV 070 060 04P	IAV 070 060 08P	IAV 070 060 13P	7.0	60	5358
IAV 070 080 04P	IAV 070 080 08P	IAV 070 080 13P	7.0	80	6897
IAV 080 040 04P	IAV 080 040 08P	IAV 080 040 13P	8.0	40	4494
IAV 080 060 04P	IAV 080 060 08P	IAV 080 060 13P	8.0	60	6253
IAV 080 080 04P	IAV 080 080 08P	IAV 080 080 13P	8.0	80	8012
IAV 090 040 04P	IAV 090 040 08P	IAV 090 040 13P	9.0	40	5204
IAV 090 060 04P	IAV 090 060 08P	IAV 090 060 13P	9.0	60	7183
IAV 090 080 04P	IAV 090 080 08P	IAV 090 080 13P	9.0	80	9162
IAV 100 040 04P	IAV 100 040 08P	IAV 100 040 13P	10.0	40	5943
IAV 120 040 04P	IAV 120 040 08P	IAV 120 040 13P	12.0	40	7522

3. Indications for Use

The IN.PACT AV paclitaxel-coated PTA balloon catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae with reference vessel diameters of 4 to 12 mm.

4. Contraindications

The IN.PACT AV DCB is contraindicated for use in the following anatomy and patient types:

- Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries
- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system
- Patients with known allergies or sensitivities to paclitaxel
- Women who are breastfeeding, pregnant, or are intending to become pregnant, or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and whether there is a potential for adverse reaction in nursing infants from paclitaxel exposure

5. Warnings

- **A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel-eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel-coated device exposure. Inadequate information is available to evaluate the potential mortality risk associated with the use of paclitaxel-coated devices for the treatment of other diseases/conditions, including this device indicated for use in arteriovenous dialysis fistulae. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options for their specific disease/condition with their patients. See Section 11.1 for further information.**
- Use the product prior to the Use-by date specified on the package.
- Contents are supplied sterile. Do not use the product if the inner packaging is damaged or opened.
- Do not use air or any gaseous medium to inflate the balloon. Use only the recommended inflation medium (equal parts contrast medium and saline solution).
- Do not move the guidewire during inflation of the IN.PACT AV DCB.
- Do not exceed the rated burst pressure (RBP). The RBP is based on the results of in vitro testing. Use of pressures higher than RBP may result in a ruptured balloon with possible intimal damage and dissection. Refer to Product Component Description (Table 1) for RBP information.
- The safety of using multiple IN.PACT AV DCBs with a total drug dosage exceeding 15,105 µg paclitaxel has not been evaluated clinically.

6. Precautions

6.1. General Precautions

- This product should only be used by physicians trained in percutaneous transluminal angioplasty (PTA).
- Assess risks and benefits before treating patients with a history of severe reaction to or inability to tolerate contrast agents. Identify allergic reactions to contrast media and antiplatelet therapy before treatment and consider alternatives for appropriate management prior to the procedure.
- Administer appropriate drug therapy to the patient according to standard protocols for PTA before insertion of the dilatation catheter.
- Take precautions to prevent or reduce clotting when any catheter is used. Flush and rinse all products entering the vascular system with heparinized normal saline or a similar solution. For the IN.PACT AV DCB catheter, flush the guidewire lumen through the guidewire port with heparinized normal saline until the fluid exits the distal tip. **Do not rinse or wipe the IN.PACT AV DCB catheter.**
- Prior to the procedure, inspect the product to verify that the product is intact.
- Handle the product with caution to avoid any damage to the balloon coating or folded balloon.
- This product is not intended for the expansion or delivery of a stent or graft.
- Do not use the IN.PACT AV DCB for pre-dilatation or for post-dilatation.
- This product is designed for single patient use only. Do not reuse, reprocess, or resterilize this product. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or create a risk of contamination of the device, which could result in patient injury, illness, or death.
- Do not expose the product to organic solvents such as alcohol.
- To reduce the potential for vessel damage, the inflated diameter of the balloon should approximately match the inner diameter of the vessel just distal to the lesion.
- The use of this product carries the risks associated with percutaneous transluminal angioplasty, including thrombosis, vascular complications, and/or bleeding events.

6.2. Pre-procedure and Post-procedure Medication Regimen

It is recommended that single antiplatelet therapy (e.g. aspirin, clopidogrel, ticlopidine, or prasugrel), at a minimum, should be administered before the procedure and for at least 4 weeks after the procedure. Prolonged antiplatelet therapy can be given at the discretion of the physician.

6.3. Use of Multiple Balloons

The extent of the patient's exposure to the drug coating is directly related to the number of balloons used. Refer to Using Multiple IN.PACT AV DCBs (Section 13.9) and Product Matrix and Paclitaxel Content (Table 2) for details regarding the use of multiple balloons and a product matrix containing the nominal paclitaxel content for each device size, respectively.

6.4. Use in Conjunction with Other Procedures

The safety and effectiveness of the IN.PACT AV DCB used in conjunction with other drug-eluting stents or drug-coated balloons in the same procedure has not been evaluated.

6.5. Drug Interaction

Formal drug interaction studies have not been conducted with the IN.PACT AV DCB. In the clinical pharmacokinetic (PK) sub-study of the IN.PACT SFA Trial, systemic levels of paclitaxel following treatment were low and cleared rapidly, reducing possible impact of drug-drug interactions due to concomitant medications. Consideration for both systemic and local drug interactions should be given when deciding to use IN.PACT AV DCB(s) in a patient who is taking a drug with known interactions to paclitaxel or when deciding to initiate therapy with such a drug in a patient who has recently been treated with IN.PACT AV DCB(s). Please refer to Drug Information (Section 8).

6.6. Balloon Handling and Preparation Precautions

- Do not remove the device from the pouch until it is needed for immediate use.
- Handle the device with caution to avoid any damage to the balloon coating or folded balloon.
- Keep the protective sheath in place when purging the balloon catheter of air bubbles.
- Carefully remove and discard the balloon's protective sheath.
- Do not use the protective sheath as an introduction aid or a rewrapping tool.
- Do not apply positive pressure to the balloon during preparation.

6.7. Balloon Placement Precautions

- Do not move the guidewire during inflation of the balloon.
- Do not manipulate the IN.PACT AV DCB while inflated.
- Catheter applications vary. Select the technique on the basis of the patient's condition and the experience of the physician.
- Introducer sheaths used must have lumen sizes that are suitable to accommodate the IN.PACT AV DCB. See Product Component Description (Table 1) for the introducer sheath compatibility and crossing profile of each device size.
- If resistance occurs during manipulation, ascertain the cause via fluoroscopy, road mapping, or digital subtraction angiography (DSA) before moving the IN.PACT AV DCB backward or forward.
- Do not manipulate the IN.PACT AV DCB without sufficient fluoroscopy.
- Use a pressure-monitoring device to prevent over-pressurization. Refer to Product Component Description (Table 1) for RBP information.
- To ensure full coverage of the entire lesion, the balloon diameter must match the inner diameter of the reference vessel distal to the lesion and the balloon length must exceed the lesion length by approximately 1 cm on both ends. When using multiple balloons, do so only as described in Using Multiple IN.PACT AV DCBs (Section 13.9).
- Never advance the IN.PACT AV DCB without the guidewire extending from the tip.
- Balloon inflation must be for at least 180 seconds. Adequate drug transfer occurs in the first 60 seconds of inflation. The additional 120 seconds is intended solely for mechanical dilatation purposes for optimal PTA.
- Appropriate vessel preparation is required prior to use of the IN.PACT AV DCB. Vessel preparation of the target lesion using high-pressure PTA for pre-dilatation was studied in the IN.PACT AV Access clinical study. Other methods of vessel preparation, such as atherectomy, have not been studied clinically with IN.PACT AV DCB.
- Appropriate vessel preparation as determined by the physician to achieve residual stenosis of ≤ 30% is required prior to use of the IN.PACT AV DCB.

6.8. Balloon Catheter Removal Precautions

- Prior to withdrawing the balloon catheter from the lesion, completely deflate the balloon under vacuum.
- Center the IN.PACT AV DCB relative to the introducer sheath when withdrawing, and use caution when removing the IN.PACT AV DCB.
- Should unusual resistance be felt at any time when withdrawing the balloon catheter back into the introducer sheath, remove the balloon catheter and the introducer sheath as a single unit to reduce the risk of vascular damage. This must be done under direct visualization with fluoroscopy.
- If removal of the IN.PACT AV DCB is required prior to deployment and a repeat attempt is desired, use a new IN.PACT AV DCB.

6.9. Post-procedure Precautions

- Administer post-procedure antiplatelet therapy as described in Pre-procedure and Post-procedure Medication Regimen (Section 6.2).

7. Use in Special Populations

7.1. Pregnancy and Lactation

The IN.PACT AV DCB is contraindicated in women who are breastfeeding, pregnant, or are intending to become pregnant, or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and whether there is a potential adverse reaction in nursing infants from paclitaxel exposure

7.2. Gender

The outcomes are shown in Table 10. The results of an interaction analysis indicate that the treatment differences between the IN.PACT AV DCB study group and the PTA control group are consistent between male and female subjects.

7.3. Ethnicity

Due to the nature of the global trial design, the IN.PACT AV DCB study did not include a sufficient number of patients to assess treatment differences in safety or effectiveness due to ethnicity.

7.4. Pediatric Use

The safety and effectiveness of the IN.PACT AV DCB in pediatric patients has not been established.

7.5. Geriatric Use

The IN.PACT AV DCB study had an upper age limit of 94 years, and had predefined study subgroups of ≤ the median age of 67.0 years and > the median age of 67.0 years. Within both subgroups, the IN.PACT AV DCB study group showed improvement on the primary effectiveness endpoints, and no statistically significant difference between treatment groups on the primary safety endpoint. The results of an exploratory analysis indicate that the treatment differences between IN.PACT AV DCB and PTA groups are generally consistent between 2 age groups defined by median age.

8. Drug Information

8.1. Mechanism of Action

The mechanism(s) by which the IN.PACT AV DCB affects neointimal production has not been fully established. The principal mechanism by which paclitaxel inhibits neointimal growth is through the stabilization of microtubules by preventing their depolymerization during the final G2/M phase of cell division. Consequently, the microtubule network may not maintain the dynamic rearrangement required for a normal mitotic process.

8.2. Pharmacokinetics

Human pharmacokinetics was investigated as a sub-study of the IN.PACT SFA Trial in 25 patients receiving 2850 µg to 16,900 µg of paclitaxel. Paclitaxel systemic exposure in the treated subjects was low and cleared rapidly with a bi-phasic decline. The C_{max} ranged from 1.0 to 35.9 ng/mL and the $AUC_{0-\infty}$ ranged from 11.4 to 128.8 hr*ng/mL. The pharmacokinetic sub-study demonstrated low systemic exposure with rapid clearance of paclitaxel.

8.3. Metabolism

Metabolic transformation of paclitaxel occurs predominantly in the liver through cytochromes P450 2C8 (CYP2C8) and 3A4 (CYP3A4). Agents which could compete with or inhibit the activity of the CYP2C8 and CYP3A4 isoenzymes may increase paclitaxel plasma levels. For more information on potential drug interactions, see Drug Interaction (Section 6.5).

8.4. Carcinogenicity, Genotoxicity, and Reproductive Toxicity

No long-term studies in animals have been published in peer-reviewed literature to evaluate the carcinogenic potential of paclitaxel. Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay. However, the mechanism by which paclitaxel interferes with cellular proliferation may give rise to loss of chromosomes during cell division as a result of microtubule stabilization during cell division. Paclitaxel is an established aneugenic drug in vitro on human normal cells and will also produce a positive response in the mouse bone marrow micronucleus assay. It has not been established that paclitaxel exerts any direct action on DNA to induce strand fragmentation

Reproductive toxicity has been previously evaluated in vivo in both rabbits and rats. When administered during rabbit fetal organogenesis, paclitaxel doses of 3.0 mg/kg/day caused embryo- and fetotoxicity; maternal toxicity was also observed. No teratogenic effects were observed at 1.0 mg/kg/day; effects at higher doses could not be assessed due to fetal mortality. In rats, fertility impairment was observed at doses ≥ 1.0 mg/kg/day. For comparison, the average dose of paclitaxel in the IN.PACT SFA PK Sub-study was 7454 µg, with an average subject weight of 91 kg, for a theoretical normalized dose of 0.082 mg/kg (assuming all the paclitaxel from the coating enters the systemic circulation).

9. Potential Adverse Effects

Potential adverse effects which may be associated with balloon catheterization may include, but are not limited to, the following:

- Abrupt vessel closure
- Allergic reaction

- Arrhythmias
- Arterial or venous aneurysm
- Arterial or venous thrombosis
- Death
- Dissection
- Embolization
- Hematoma
- Hemorrhage
- Hypotension/hypertension
- Infection
- Ischemia or infarction of tissue/organ
- Loss of permanent access
- Pain
- Perforation or rupture of the artery or vein
- Pseudoaneurysm
- Restenosis of the dilated vessel
- Shock
- Stroke
- Vessel spasms or recoil

Potential complications of peripheral balloon catheterization include, but are not limited to, the following:

- Balloon rupture
- Detachment of a component of the balloon and/or catheter system
- Failure of the balloon to perform as intended
- Failure to cross the lesion

These complications may result in adverse effects.

Although systemic effects are not anticipated, potential adverse effects not captured above that may be unique to the paclitaxel drug coating include, but are not limited to, the following:

- Allergic/immunologic reaction
- Alopecia
- Anemia
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leucopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
- Myalgia/arthralgia
- Myelosuppression
- Peripheral neuropathy

Refer to the Physician's Desk Reference for more information on the potential adverse effects observed with paclitaxel. There may be other potential adverse effects that are unforeseen at this time.

10. Patient Counseling Information

Physicians should consider the following when counseling patients about this product:

- Discuss the risks associated with percutaneous transluminal angioplasty procedures.
- Discuss the risks associated with the IN.PACT AV DCB.
- Discuss the risks and benefits of the treatment specific to the patient.
- Discuss the risks of early discontinuation of the antiplatelet therapy.
- Discuss short- and long-term post-procedure changes to the patient's lifestyle.

11. Summary of Clinical Study

11.1. Late Mortality Signal for Paclitaxel-Coated Devices

A meta-analysis of randomized controlled trials published in December 2018 by Katsanos et. al. identified an increased risk of late mortality at 2 years and beyond for paclitaxel-coated balloons and paclitaxel-eluting stents used to treat femoropopliteal arterial disease. In response to these data, FDA performed a patient-level meta-analysis of long-term follow-up data from the pivotal premarket randomized trials of paclitaxel-coated devices used to treat femoropopliteal disease using available clinical data through May 2019. The meta-analysis also showed a late mortality signal in study subjects treated with paclitaxel-coated devices compared to patients treated with uncoated devices. Specifically, in the 3 randomized trials with a total of 1090 patients and available 5-year data, the crude mortality rate was 19.8% (range 15.9% - 23.4%) in patients treated with paclitaxel-coated devices compared to 12.7% (range 11.2% - 14.0%) in subjects treated with uncoated devices. The relative risk for increased mortality at 5 years was 1.57 (95% confidence interval 1.16 – 2.13), which corresponds to a 57% relative increase in mortality in patients treated with paclitaxel-coated devices. As presented at the June 2019 FDA Advisory Committee Meeting, an independent meta-analysis of similar patient-level data provided by VIVA Physicians, a vascular medicine organization, reported similar findings with a hazard ratio of 1.38 (95% confidence interval 1.06 - 1.80). Additional analyses have been conducted and are underway that are specifically designed to assess the relationship of mortality to paclitaxel-coated devices.

The presence and magnitude of the late mortality risk should be interpreted with caution because of multiple limitations in the available data, including wide confidence intervals due to a small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data, no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths.

Paclitaxel-coated balloons and stents improve blood flow to the legs and decrease the likelihood of repeat procedures to reopen blocked blood vessels compared to uncoated devices. The benefits of paclitaxel-coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks (e.g., late mortality).

Inadequate information is available to evaluate the potential mortality risk associated with the use of paclitaxel-coated devices for the treatment of other diseases/conditions including this device indicated for use in arteriovenous dialysis fistulae.

In the IN.PACT AV Access study, Kaplan Meier mortality estimates at 6 and 12 months are 5.5% [2.7%, 9.7%], and 9.4% [5.5%, 14.6%], respectively, for the IN.PACT™ AV DCB treatment device and 2.0% [0.5%, 5.2%] and 9.6% [5.5%, 15.0%], respectively, for the standard PTA control device. Additional information regarding long-term outcomes can be found in the following sections.

11.2. Investigational Design

11.2.1. Description of Study Design and Plan

The IN.PACT AV Access study was a prospective, global, multicenter, single-blinded, randomized (1:1) clinical study evaluating the IN.PACT™ AV DCB (study group) vs. standard PTA (control group) for the treatment of de novo or non-stented restenotic obstructive lesions up to 100 mm in length in the arteriovenous dialysis fistulae. Eligible subjects who provided informed consent and met all inclusion/exclusion criteria were randomized 1:1 based upon lesion type (de novo, restenotic) to the control or study group. Total enrollment was 330 subjects at 29 global sites, with 204 (62%) of subjects coming from U.S. sites, 112 (34%) of subjects coming from Japan sites, and 14 (4%) of subjects coming from New Zealand sites. There was no minimum enrollment requirement at each site; however, individual sites were not allowed to enroll more than 20% of the total study subjects. Follow-up was completed at 30 days and 6 months. Subjects will be followed up out to 5 years.

11.2.2. Discussion of Design

Primary endpoints for the study are as follows:

Primary Effectiveness Endpoint: Target Lesion Primary Patency Rate through 6 Months

Defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis measured through 6 months post-procedure.

Primary Safety Endpoint: Serious Adverse Event Rate within 30 Days

Defined as the Serious Adverse Event (SAE) rate involving the AV access circuit through 30 days post-procedure.

There were 2 primary hypotheses for the study. One was for the primary safety endpoint through 30 days and one was for the primary effectiveness endpoint through 6 months. Each hypothesis was tested on the Intent-To-Treat (ITT) subjects at a one-sided significance level of 2.5%, as pre-specified in the Statistical Analysis Plan. The control group is standard percutaneous transluminal angioplasty (PTA), which is an active alternative treatment outcome. The control treatment is a legally marketed alternative with similar indications for use.

For the primary safety endpoint, the study and control groups were compared in a non-inferiority format under the following hypothesis.

H_0: $\pi_T \geq \pi_c + 0.075$

H_A: $\pi_T < \pi_c + 0.075$

For the primary effectiveness endpoint, the study (p_T) and control (p_C) groups were compared in a superiority format under the following hypothesis:

H_0: $p_T \leq p_C$

H_A: $p_T > p_C$

To control the overall Type I error the study was deemed successful only if both primary effectiveness and primary safety endpoints passed the hypothesis testing. Once the 2 primary endpoints have succeeded the hypothesis tests, the following key secondary endpoints were compared between treatment groups sequentially by using ITT analysis set in a superiority manner, each at a one-sided significance level of 0.025, in the following order. The testing procedure would stop at the first failure to reject null hypothesis.

1. Cumulative (any) target lesion revascularizations (TLR) measured through 6 months post procedure;
   H_0: $t_T \geq t_C$
   H_A: $t_T < t_C$
   t_x refers to as the expected cumulative TLR rate through 6 months (x = T for DCB ; x = C for PTA). One-sided Z-test was performed at a significance level of 0.025.
2. Number of interventions required to maintain target lesion patency through 6 months post procedure;
   H_0: $l_T \geq l_C$
   H_A: $l_T < l_C$
   l_x refers to the expected number of interventions to maintain target lesion patency through 6 months (x = T for DCB ; x = C for PTA). The comparison was performed at one-sided significance level of 0.025 using Wilcoxon Rank Sum Test.
3. Number of interventions required to maintain access circuit patency through 6 months post procedure;
   H_0: $c_T \geq c_C$
   H_A: $c_T < c_C$
   c_x refers to the expected number of interventions to maintain access circuit patency through 6 months (x = T for DCB ; x = C for PTA). The comparison was performed at one-sided significance level of 0.025 using Wilcoxon Rank Sum Test.
4. Access circuit primary patency through 6 months post procedure;
   H_0: $a_T \leq a_C$
   H_A: $a_T > a_C$
   a_x refers to the expected access circuit primary patency rate through 6 months (x = T for DCB ; x = C for PTA). One-sided Z-test will be performed at a significance level of 0.025.

11.2.3. Sample Size

Globally, 330 subjects at 29 global sites, with 204 (62%) of subjects coming from U.S. sites, 112 (34%) of subjects coming from Japan sites, and 14 (4%) of subjects coming from New Zealand sites. There was no minimum enrollment requirement at each site; however, individual sites were not allowed to enroll more than 20% of the total study subjects.

11.2. Demographic and Clinical Characteristics

Site reported baseline demographic and clinical characteristics for all 330 enrolled subjects are provided in Table 3 below. Treatment groups were well balanced with no statistically significant differences in baseline demographics and clinical characteristics between IN.PACT AV DCB and PTA subjects. IN.PACT AV DCB subjects had a mean age of 65.8 years, 65.9% were male, 62.9% had diabetes, and 91.2% had hypertension. Similarly, PTA subjects had a mean age of 65.5 years, 63.1% were male, 68.8% had diabetes, and 94.4% had hypertension. All subjects (100%) reported renal insufficiency, have been receiving hemodialysis for a mean of 4.3 years, and have had their target AVF for a mean of 3.3 years. The most common type of AVF is radiocephalic (50.3% (166/330)), followed by brachiocephalic (36.4% (120/330)), brachiobasilic (9.7% (32/330)), and other (3.6% (12/330)). All subjects (100% (330/330)) presented with clinical symptoms indicating AV access dysfunction at baseline. Overall, baseline characteristics and comorbidities were well matched.

Table 3. Baseline Demographic and Clinical Characteristics – ITT Analysis Set

Subject Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Total (N=330 Subjects)	p-value[a]
Age (yrs)				
N	170	160	330	
Mean ± SD	65.8 ± 13.1	65.5 ± 13.4	65.6 ± 13.3	0.837
Median (Q1, Q3)	67.0 (58, 75)	68.0 (57, 75)	67.0 (57, 75)	
Min, Max	29, 94	29, 90	29, 94	
Male	65.9% (112/170)	63.1% (101/160)	64.5% (213/330)	0.646
Ethnicity				
Hispanic/Latino	9.0% (15/167)	8.9% (14/157)	9.0% (29/324)	1.000
Race				0.920
White	24.7% (42/170)	28.8% (46/160)	26.7% (88/330)	
Black or African American	31.8% (54/170)	30.0% (48/160)	30.9% (102/330)	
Asian	37.1% (63/170)	35.6% (57/160)	36.4% (120/330)	
Native Hawaiian or Other Pacific Islander	3.5% (6/170)	2.5% (4/160)	3.0% (10/330)	
American Indian or Alaska Native	0.0% (0/170)	0.0% (0/160)	0.0% (0/330)	
Other	2.9% (5/170)	3.1% (5/160)	3.0% (10/330)	
Hypertension	91.2% (155/170)	94.4% (151/160)	92.7% (306/330)	0.295
Hyperlipidemia	54.1% (92/170)	52.5% (84/160)	53.3% (176/330)	0.825
Diabetes Mellitus	62.9% (107/170)	68.8% (110/160)	65.8% (217/330)	0.297
Type I	2.4% (4/170)	3.8% (6/160)	3.0% (10/330)	0.532
Type II	60.6% (103/170)	65.0% (104/160)	62.7% (207/330)	0.427
Renal Insufficiency	100.0% (170/170)	100.0% (160/160)	100.0% (330/330)	> 0.999
Carotid Artery Disease	4.1% (7/170)	8.8% (14/160)	6.4% (21/330)	0.114
Congestive Heart Failure	22.9% (39/170)	24.4% (39/160)	23.6% (78/330)	0.796
Coronary Heart Disease	35.9% (61/170)	38.8% (62/160)	37.3% (123/330)	0.649
Peripheral Artery Disease	19.4% (33/170)	15.1% (24/159)	17.3% (57/329)	0.312
Current Smoker	11.2% (19/170)	16.3% (26/160)	13.6% (45/330)	0.201
Former Smoker	37.6% (64/170)	28.1% (45/160)	33.0% (109/330)	0.079
AVF Type				0.918
Radiocephalic	50.6% (86/170)	50.0% (80/160)	50.3% (166/330)	
Brachiocephalic	36.5% (62/170)	36.3% (58/160)	36.4% (120/330)	
Brachiobasilic	10.0% (17/170)	9.4% (15/160)	9.7% (32/330)	
Other	2.9% (5/170)	4.4% (7/160)	3.6% (12/330)	
Dominant Arm	22.4% (38/170)	24.4% (39/160)	23.3% (77/330)	0.697
Previous peripheral revascularization	74.1% (126/170)	75.0% (120/160)	74.5% (246/330)	0.900
Years since AVF creation[b]				
N	170	160	330	
Mean ± SD	3.2 ± 3.0	3.5 ± 3.8	3.3 ± 3.4	0.436
Median (Q1, Q3)	2.2 (1, 4)	2.2 (1, 5)	2.2 (1, 5)	
Min, Max	0, 17	0, 28	0, 28	
Years of Hemodialysis History[c]				
N	170	159	329	
Mean ± SD	4.3 ± 5.1	4.2 ± 5.2	4.3 ± 5.1	0.755

Subject Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Total (N=330 Subjects)	p-value[a]
Median (Q1, Q3)	2.7 (1, 6)	2.3 (1, 6)	2.6 (1, 6)	
Min, Max	0, 32	0, 41	0, 41	

[a] p-values for continuous variables were based on independent t-test, for binary variables were based on Fisher's Exact test, for nominal variables were based on Cochran-Mantel-Haenszel (CMH) general association test, for ordinal variables were based on CMH score test. The p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.
[b] 41 subjects had partial dates and their years since AVF creation was calculated based on the imputed dates using the middle of the month or middle of the year.
[c] 51 subjects had partial dates and their years of hemodialysis history was calculated based on the imputed dates using the middle of the month or middle of the year.

Table 4. Site-Reported Baseline Lesion Characteristics – ITT Analysis Set

Lesion Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Total (N=330 Subjects)	p-value[a]
Target Arm				0.449
Right Arm	23.5% (40/170)	27.5% (44/160)	25.5% (84/330)	
Left Arm	76.5% (130/170)	72.5% (116/160)	74.5% (246/330)	
Target Lesion Access				0.765
Venous	97.1% (165/170)	96.3% (154/160)	96.7% (319/330)	
Arterial	2.9% (5/170)	3.8% (6/160)	3.3% (11/330)	
Lesion Type				0.905
De Novo	30.0% (51/170)	30.6% (49/160)	30.3% (100/330)	
Restenotic	70.0% (119/170)	69.4% (111/160)	69.7% (230/330)	

[a] p-values for continuous variables were based on independent t-test, for binary variables were based on Fisher's Exact test, for nominal variables were based on CMH general association test, for ordinal variables were based on CMH score test. Note: Site reported data. The p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

Table 5. Baseline / Procedural Angiographic Core Lab Characteristics– ITT Analysis Set

Procedural Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value[a]
Treated Vessel				
Anastomosis	33.7% (57/169)	31.6% (50/158)	2.1% [-8.8%, 12.9%]	0.724
Arterial Inflow	0.0% (0/169)	0.0% (0/158)	NA	> 0.999
Cephalic Arch	16.6% (28/169)	22.8% (36/158)	-6.2% [-17.0%, 4.6%]	0.166
In Cannulation Zone	26.6% (45/169)	20.9% (33/158)	5.7% [-5.1%, 16.5%]	0.244
Swing Point	19.5% (33/169)	20.9% (33/158)	-1.4% [-12.2%, 9.5%]	0.784
Venous Outflow	3.6% (6/169)	3.8% (6/158)	-0.2% [-11.1%, 10.6%]	1.000
Subjects with Tandem Lesion	12.4% (21/170)	16.3% (26/160)	-3.9% [-14.7%, 6.9%]	0.346
Target Lesion Length (mm)				
N	170	159		
Mean ± SD	46.3 ± 28.1	41.9 ± 25.2	4.4 [-1.4, 10.2]	0.137
Median (Q1, Q3)	42.7 (25, 61)	37.5 (23, 58)		
Min, Max	3, 160	3, 157		
Minimum Lumen Diameter (mm)				
N	170	159		
Mean ± SD	2.7 ± 1.6	2.8 ± 1.7	-0.1 [-0.4, 0.3]	0.731
Median (Q1, Q3)	2.6 (2, 4)	2.4 (1, 4)		
Min, Max	0, 9	0, 9		
Reference Vessel Diameter (mm)				
N	170	159		
Mean ± SD	7.5 ± 2.3	7.7 ± 2.6	-0.2 [-0.7, 0.3]	0.442
Median (Q1, Q3)	7.2 (6, 9)	7.3 (6, 9)		
Min, Max	2, 13	3, 15		
Pre-procedure % Diameter Stenosis				
N	170	159		
Mean ± SD	64.8 ± 13.3	64.8 ± 14.5	0.0 [-3.0, 3.0]	0.986
Median (Q1, Q3)	64.7 (56, 74)	65.6 (55, 76)		
Min, Max	27, 100	2, 100		
Subjects with Occluded Lesions	1.2% (2/169)	0.6% (1/159)	0.6% [-10.3%, 11.4%]	1.000
Length of Occlusion				
N	2	1		
Mean ± SD	37.5 ± 40.5	26.3 ± NA	11.2 [NA, NA]	NA
Median (Q1, Q3)	37.5 (9, 66)	26.3 (26, 26)		
Min, Max	9, 66	26, 26		
Dissection	0.0% (0/170)	0.0% (0/159)		NA
Aneurysm	25.3% (43/170)	22.0% (35/159)	3.3% [-7.6%, 14.0%]	0.518
Pseudoaneurysm	0.0% (0/170)	0.0% (0/159)	NA	> 0.999
Perforation	0.0% (0/170)	0.0% (0/159)	NA	> 0.999
Thrombus	0.6% (1/170)	0.6% (1/159)	-0.0% [-10.8%, 10.8%]	1.000
Embolism	0.0% (0/170)	0.0% (0/159)	NA	> 0.999

Core Laboratory reported data.

[a] p-values for continuous variables were based on independent t-test, for binary variables were based on Fisher's Exact test, for nominal variables were based on CMH general association test, for ordinal variables were based on CMH score test. The p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

11.3. Treatment Devices Used

As shown in Table 6 the mean number of balloons used per subject was 1.2 in the IN.PACT AV DCB study group and 1.0 in the PTA control group (p<0.001). The mean total balloon length per subject was 73.5 mm in the IN.PACT AV DCB study group and 48.0 mm in the PTA control group (p<0.001). One subject in each treatment group received provisional stenting.

Table 6. Treatment Devices Used During Index Procedure – All ITT Subjects

Subject Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	p-value[a]
Subjects with			< 0.001
No Balloon	0.0% (0/170)	1.9% (3/160)	
One Balloon	75.3% (128/170)	95.0% (152/160)	
Two Balloons	24.7% (42/170)	3.1% (5/160)	
Three Balloons	0.0% (0/170)	0.0% (0/160)	
More than Three Balloons	0.0% (0/170)	0.0% (0/160)	
Total Balloon Length per Subject (mm)			
N	170	160	
Mean ± SD	73.5 ± 30.6	48.0 ± 18.5	< 0.001
Median (Q1, Q3)	80.0 (40, 100)	40.0 (40, 60)	
Min, Max	40, 160	0, 120	
Number of Treatment Balloons per Subject			
N	170	160	
Mean ± SD	1.2 ± 0.4	1.0 ± 0.2	< 0.001
Median (Q1, Q3)	1.0 (1, 1)	1.0 (1, 1)	
Min, Max	1, 2	0, 2	
Subjects received provisional stents[b]	0.6% (1/170)	0.6% (1/160)	1.000
Number of provisional stents per subject[b]			
N	170	160	
Mean ± SD	0.0 ± 0.1	0.0 ± 0.1	0.966
Median (Q1, Q3)	0.0 (0, 0)	0.0 (0, 0)	
Min, Max	0, 1	0, 1	
Reasons for Provisional Stenting[b, c]			
Persistent residual stenosis	0.0% (0/169)	0.6% (1/160)	0.486
Major flow-limiting dissection	0.0% (0/169)	0.0% (0/160)	> 0.999

[a] p-values for continuous variables were based on independent t-test, for binary variables were based on Fisher's Exact test, for nominal variables were based on CMH general association test, for ordinal variables were based on CMH score test. The p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.
[b] Provisional stents are not allowed in Japan patients.
[c] One IN.PACT AV DCB study group subject received provisional stenting for a grade C dissection (not considered flow-limiting) for subject safety, and therefore does not appear in the reasons for provisional stenting.

11.4. Methods

Subjects presenting with a stenosed AV fistula in the arm, confirmed by site angiography, were enrolled in the study. After the target lesion size and stenosis were confirmed by angiography, pre-dilatation of the target vessel was performed. After successful pre-dilatation in both treatment arms, subjects with documented angiographic residual stenosis ≤ 30% were enrolled and randomized 1:1 for subsequent treatment with IN.PACT™ AV DCB (Study) or standard PTA (Control). Subjects that were randomized and had an adjunct procedure will be followed for the entire duration of the study. Any adjunct procedures were done according to standard of care and were captured on the electronic case report forms.

All deaths, adverse events leading to AV access circuit re-interventions, procedure. device or therapy related adverse events, and SAEs involving the access circuit were adjudicated by an independent (blinded) Clinical Events Committee (CEC).

The Intent-To-Treat (ITT) population consists of all randomized subjects, irrespective of the treatment actually delivered.

11.5. Clinical Results – ITT Subjects

11.5.1. Primary Safety Results

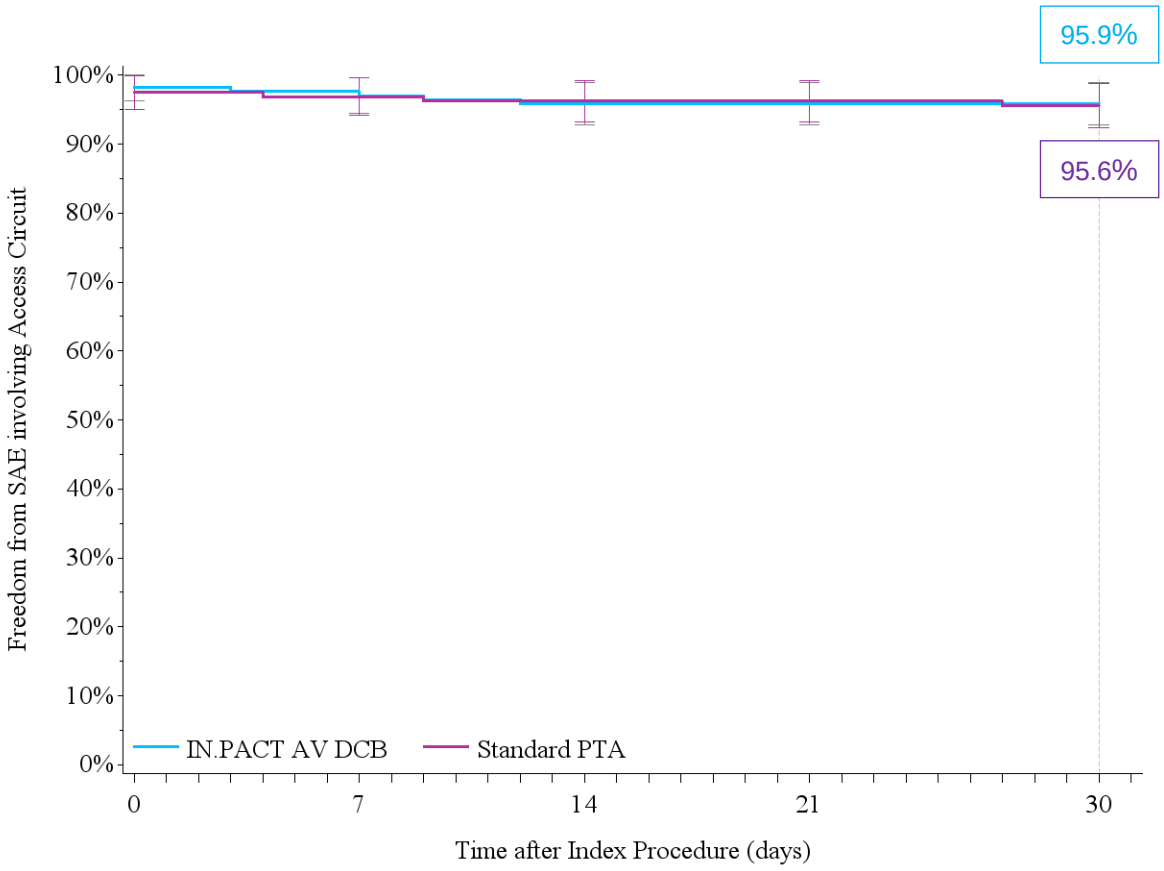
The primary safety endpoint was Serious Adverse Event (SAE) rate involving the AV access circuit through 30-day post procedure. The 30-day SAE rate involving the AV access circuit was 4.2% in the IN.PACT AV DCB study group and 4.4% in the PTA control group (noninferiority p=0.002). The upper limit of 95% confidence interval for the risk difference was 5%, less than the noninferiority margin (7.5%), demonstrating that IN.PACT AV DCB was noninferior to PTA in terms of the primary safety endpoint.

Table 7. Primary Safety Endpoint– ITT Analysis Set

	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value[a]
Primary Safety Endpoint			Non-inferiority Test with 7.5% Margin	
SAE involving the AV access circuit within 30 days	4.2% (7/166)	4.4% (7/158)	-0.2% [-5.5%, 5.0%]	0.002
Arteriovenous Fistula Occlusion	14.3% (1/7)	0.0% (0/7)		
Arteriovenous Fistula Site Complication	71.4% (5/7)	57.1% (4/7)		
Arteriovenous Fistula Thrombosis	14.3% (1/7)	14.3% (1/7)		
Haemodialysis Complication	14.3% (1/7)	0.0% (0/7)		
Vasospasm	0.0% (0/7)	14.3% (1/7)		
Vessel Puncture Site Haematoma	0.0% (0/7)	14.3% (1/7)		

[a]Non-inferiority p-values for the primary safety endpoint was based on the Farrington-Manning non-inferiority test with a margin of 7.5%.

A Kaplan-Meier analysis of SAEs involving the AV access Circuit within 30 days (primary safety endpoint) is shown below in Figure 4 for all ITT subjects. The Kaplan-Meier survival curve estimated freedom from SAE involving the access circuit through 30 days was 95.9% in the IN.PACT AV DCB study group vs. 95.6% in the PTA control group.


95.9%
95.6%
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Freedom from SAE involving Access Circuit
IN.PACT AV DCB
Standard PTA
0
7
14
21
30
Time after Index Procedure (days)

From day X To day Y	0 0	1 7	8 14	15 21	22 30
IN.PACT AV Access DCB (N=170 Subjects)					
# Entered	170	166	164	161	159
# Censored	1	0	1	2	1
# Events	3	2	2	0	0
Survival rate [%]	98.2%	97.1%	95.9%	95.9%	95.9%
STANDARD PTA (N=160 Subjects)					
# Entered	160	154	153	152	152
# Censored	2	0	0	0	0
# Events	4	1	1	0	1
Survival rate [%]	97.5%	96.9%	96.2%	96.2%	95.6%

Figure 4. Kaplan-Meier Plot – Freedom from SAE involving Access Circuit through 30 Days – ITT Analysis Set. The arrow bars are confidence intervals at each time point. The arrow bars and the log-rank p-value should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified (please refer to Table 7 above for SAEs involving the AV access circuit within 30 days. The same SAEs involving the AV access circuit are collected through the entire study duration).

11.5.2. Primary Effectiveness Results

The primary effectiveness endpoint was target lesion primary patency through 6 months post procedure. The 6-month target lesion primary patency rate was 82.2% in the IN.PACT AV DCB study group and 59.5% in the PTA control group (p < 0.001). The IN.PACT AV DCB group showed statistical superiority against the PTA group.

Table 8. Primary Effectiveness Endpoints – ITT Analysis

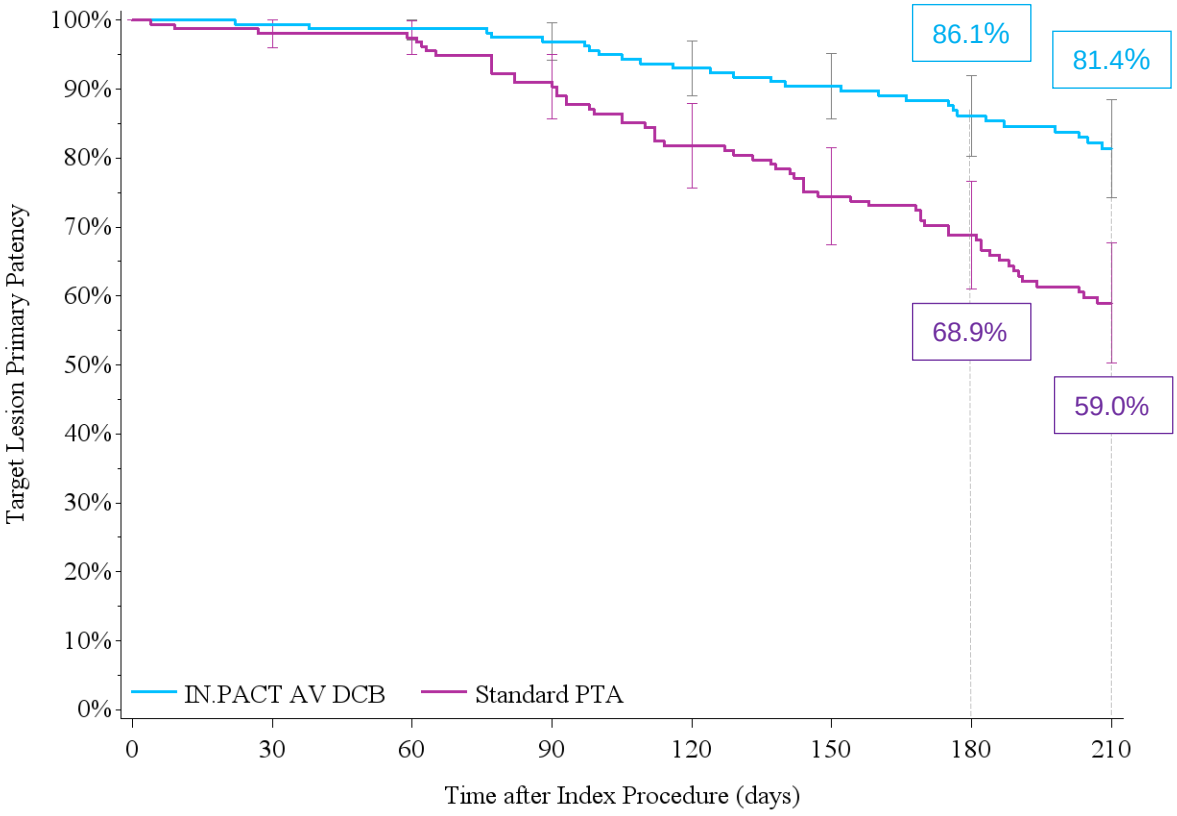
	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value[†]
Primary Effectiveness Endpoint				
Target Lesion Primary Patency[a] through 6 Months - freedom from	82.2% (125/152)	59.5% (88/148)	22.8% [12.8%, 32.8%]	< 0.001
CD-TLR	16.4% (25/152)	38.5% (57/148)		

	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value[†]
Access circuit thrombosis	2.0% (3/151)	3.4% (5/146)		

[†]p-values for the primary effectiveness endpoint were based on one-sided Z-test.

[a] Target Lesion Primary Patency (TLPP) is defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis post index procedure.

A Kaplan-Meier analysis of the primary effectiveness endpoint is shown below in Figure 5 for all ITT subjects. The Kaplan-Meier survival curve shows target lesion primary patency through 210 days and it was 81.4% in the IN.PACT AV DCB study group vs. 59.0% in the PTA control group.



From day X To day Y	0 0	1 30	31 60	61 90	91 120	121 150	151 180	181 210
IN.PACT AV DCB (N=170 Subjects)								
# Entered	170	169	164	158	152	144	136	115
# Censored	1	4	5	3	2	4	15	14
# Events	0	1	1	3	6	4	6	6
Survival rate [%]	100.0%	99.4%	98.8%	96.9%	93.0%	90.4%	86.1%	81.4%
STANDARD PTA (N=160 Subjects)								
# Entered	160	158	155	152	138	123	111	93
# Censored	2	0	2	3	2	1	10	8
# Events	0	3	1	11	13	11	8	13
Survival rate [%]	100.0%	98.1%	97.5%	90.3%	81.8%	74.4%	68.9%	59.0%

Survival Curves Comparison				
Analysis Method	Test	Chi Square	Degr. Freedom	p-value
Kaplan-Meier Analysis	Log-Rank	18.3761	1	<.0001

Figure 5. Kaplan-Meier Plot – Target Lesion Primary Patency through 210 Days – ITT Analysis Set. The arrow bars are confidence intervals at each time point. The arrow bars and the log-rank p-value should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

11.6. Key Secondary Endpoints

Table 9 shows key secondary endpoints through 6 months, which shows superiority of the IN.PACT AV DCB study group results against the PTA control group.

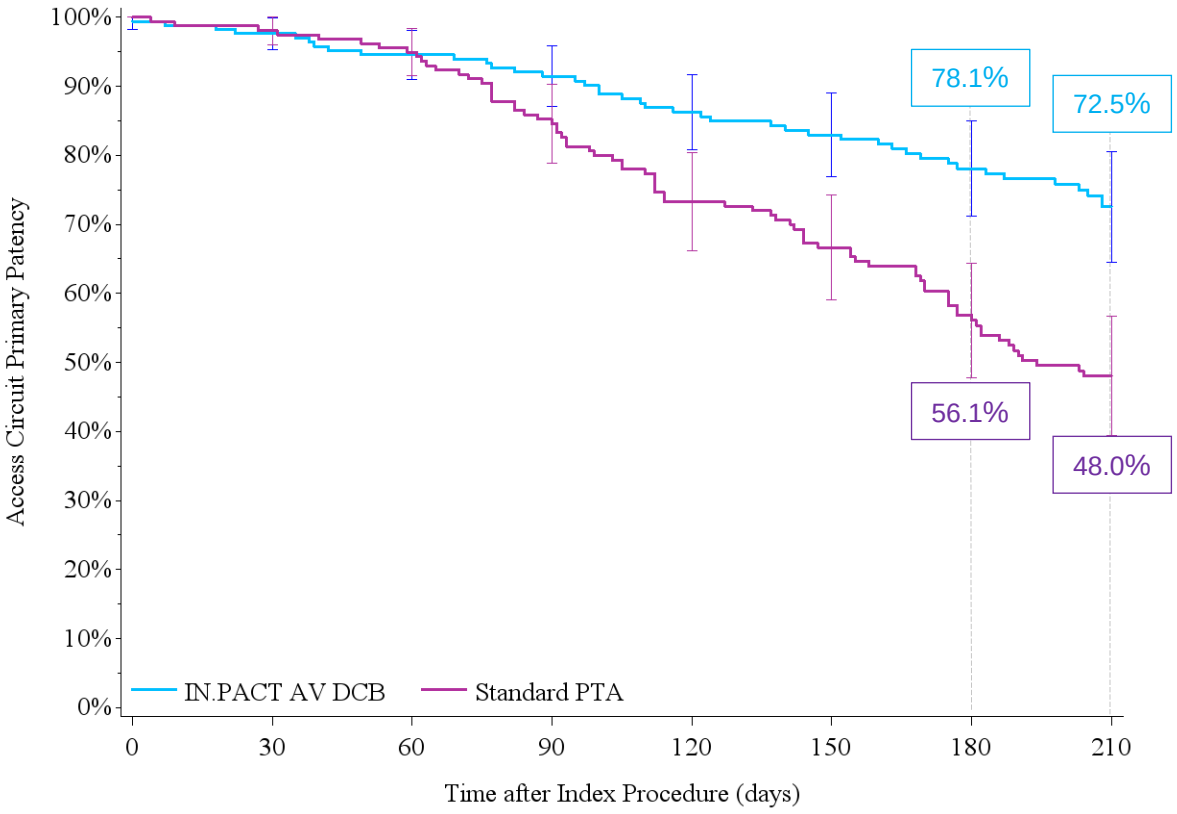
Table 9. Key Secondary Endpoints– ITT Analysis Set

	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value[†]
Key Secondary Endpoints Through 6-months				
Any TLR	16.3% (25/153)	39.9% (59/148)	-23.5% [-33.4%, -13.7%]	< 0.001
Number of interventions required to maintain target lesion patency[a]				
Total number of interventions	40	91		
Subjects with at least one intervention	18.2% (31/170)	43.8% (70/160)		
Number of interventions per subject				< 0.001
N	170	160		
Mean ± SD	0.2 ± 0.6	0.6 ± 0.7	-0.3 [-0.5, -0.2]	
Median (Q1, Q3)	0.0 (0, 0)	0.0 (0, 1)		
Min, Max	0, 4	0, 3		
Number of interventions required to maintain access circuit patency[b]				
Total number of interventions	54	103		
Subjects with at least one intervention	22.9% (39/170)	46.9% (75/160)		
Number of interventions per subject				< 0.001
N	170	160		
Mean ± SD	0.3 ± 0.7	0.6 ± 0.8	-0.3 [-0.5, -0.2]	
Median (Q1, Q3)	0.0 (0, 0)	0.0 (0, 1)		
Min, Max	0, 4	0, 3		
Access circuit primary patency[c] - freedom from	73.2% (112/153)	48.0% (71/148)	25.2% [14.6%, 35.9%]	< 0.001
Re-intervention in access circuit	25.5% (39/153)	50.7% (75/148)		
Access circuit thrombosis	2.0% (3/151)	3.4% (5/146)		

[†]p-values for the binary key secondary endpoints were based on one-sided Z-test. p-values for the endpoints on number of interventions required were based on one-sided Wilcoxon sum rank test

[a] Number of interventions required to maintain target lesion patency is defined as number of TLR post index procedure
[b] Number of interventions required to maintain access circuit patency is defined as number of re-interventions in the target lesion and/or access circuit post index procedure
[c] Access Circuit Primary Patency is defined as freedom from re-intervention in the access circuit or access circuit thrombosis post index procedure

A Kaplan-Meier analysis of the access circuit primary patency is shown below in Figure 6 for all ITT subjects. The Kaplan-Meier survival curve shows access circuit primary patency through 210 days and it was 72.5% in the IN.PACT AV DCB study group vs. 48.0% in the PTA control group.



From day X To day Y	0 0	1 30	31 60	61 90	91 120	121 150	151 180	181 210
IN.PACT AV DCB (N=170 Subjects)								
# Entered	170	168	161	151	143	133	125	106

# Censored	1	4	5	3	2	3	12	13
# Events	1	3	5	5	8	5	7	7
Survival rate [%]	99.4%	97.6%	94.6%	91.4%	86.2%	83.0%	78.1%	72.5%
STANDARD PTA (N=160 Subjects)								
# Entered	160	158	155	148	129	110	99	78
# Censored	2	0	2	3	2	1	6	5
# Events	0	3	5	16	17	10	15	11
Survival rate [%]	100.0%	98.1%	94.9%	84.6%	73.3%	66.6%	56.1%	48.0%

Survival Curve Comparison				
Analysis Method	**Test**	**Chi Square**	**Degr. Freedom**	**P-Value**
Kaplan-Meier Analysis	Log-Rank	18.1873	1	<.0001

Figure 6. Kaplan-Meier Plot – Access Circuit Primary Patency through 210 Days – ITT Analysis Set. The arrow bars are confidence intervals at each time point. The arrow bars and the log-rank p-value should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

11.7. Subgroup and Subset Analysis

Gender

Clinical benefit of the IN.PACT AV DCB at 6-months was observed in both male (TLPP: 83.0% DCB vs. 61.7% PTA) and female subjects (TLPP: 80.8% DCB vs. 55.6% PTA). In addition, primary safety events at Day 30 were similar in both males (4.5% DCB vs. 4.0% PTA) and females (3.6% DCB vs. 5.3% PTA)

Table 10. Primary Endpoint Analysis by Gender

Primary Analysis	Gender	AV DCB (N=112 Male, N=58 Female)	Standard PTA (N=101 Male, N=59 Female)	Difference
Primary Safety	Male	4.5% (5/111)	4.0% (4/101)	0.5%
	Female	3.6% (2/55)	5.3% (3/57)	-1.6%
Primary Effectiveness	Male	83.0% (83/100)	61.7% (58/94)	21.3%
	Female	80.8% (42/52)	55.6% (30/54)	25.2%

11.8. Serious Adverse Events

A Serious Adverse Event (SAE) is an adverse event that a) led to death, b) led to a serious deterioration in the health of the subject, resulting in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Table 11 provides a summary of the events that were classified by the site as SAEs, whether or not related to the device, procedure or therapy. In total 62.9% of IN.PACT AV DCB study group subjects experienced one or more serious adverse events and 71.9% of standard PTA control arm subjects experienced one or more serious adverse events within 360 days. SAEs which led to death were CEC adjudicated as not related to the study device, procedure, or therapy.

Additional analysis on SAEs is presented in Table 12

Table 11. Number of Subjects with One or More Serious Adverse Events by MedDRA System-Organ Class and Preferred Term Within 360 Days – ITT Analysis Set

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
SUBJECTS WITH ONE OR MORE SERIOUS ADVERSE EVENTS	62.9% (107/170)	71.9% (115/160)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1.8% (3/170)	1.3% (2/160)
ANAEMIA	1.2% (2/170)	1.3% (2/160)
LEUKOCYTOSIS	0.6% (1/170)	0.0% (0/160)
THROMBOCYTOPENIA	0.6% (1/170)	0.0% (0/160)
CARDIAC DISORDERS	15.9% (27/170)	14.4% (23/160)
ACUTE CORONARY SYNDROME	0.6% (1/170)	0.0% (0/160)
ACUTE MYOCARDIAL INFARCTION	0.0% (0/170)	1.9% (3/160)
ANGINA PECTORIS	1.8% (3/170)	1.3% (2/160)
ANGINA UNSTABLE	0.6% (1/170)	0.0% (0/160)
AORTIC VALVE STENOSIS	0.0% (0/170)	0.6% (1/160)
ATRIAL FIBRILLATION	2.4% (4/170)	2.5% (4/160)
ATRIAL FLUTTER	0.6% (1/170)	0.0% (0/160)
BRADYCARDIA	1.2% (2/170)	0.6% (1/160)
CARDIAC ARREST	2.4% (4/170)	1.9% (3/160)
CARDIAC FAILURE	0.6% (1/170)	0.0% (0/160)
CARDIAC FAILURE CHRONIC	0.6% (1/170)	0.6% (1/160)
CARDIAC FAILURE CONGESTIVE	2.9% (5/170)	3.1% (5/160)
CARDIO-RESPIRATORY ARREST	0.0% (0/170)	0.6% (1/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
CARDIOMYOPATHY	0.0% (0/170)	0.6% (1/160)
CORONARY ARTERY DISEASE	1.2% (2/170)	1.3% (2/160)
CORONARY ARTERY OCCLUSION	0.6% (1/170)	0.0% (0/160)
CORONARY ARTERY STENOSIS	1.8% (3/170)	1.3% (2/160)
DIASTOLIC DYSFUNCTION	0.6% (1/170)	0.0% (0/160)
ISCHAEMIC CARDIOMYOPATHY	1.2% (2/170)	0.0% (0/160)
MITRAL VALVE INCOMPETENCE	0.6% (1/170)	0.0% (0/160)
MYOCARDIAL ISCHAEMIA	0.0% (0/170)	0.6% (1/160)
PERICARDIAL EFFUSION	1.2% (2/170)	0.6% (1/160)
EAR AND LABYRINTH DISORDERS	0.6% (1/170)	0.0% (0/160)
DEAFNESS NEUROSENSORY	0.6% (1/170)	0.0% (0/160)
EYE DISORDERS	1.8% (3/170)	0.0% (0/160)
CATARACT	1.2% (2/170)	0.0% (0/160)
VITREOUS HAEMORRHAGE	0.6% (1/170)	0.0% (0/160)
GASTROINTESTINAL DISORDERS	4.7% (8/170)	6.9% (11/160)
ASCITES	0.6% (1/170)	0.0% (0/160)
COLITIS ISCHAEMIC	0.6% (1/170)	0.0% (0/160)
DIARRHOEA	0.6% (1/170)	0.0% (0/160)
DIVERTICULUM	0.6% (1/170)	0.0% (0/160)
DYSPHAGIA	0.0% (0/170)	1.3% (2/160)
GASTRIC POLYPS	0.0% (0/170)	0.6% (1/160)
GASTROINTESTINAL HAEMORRHAGE	1.2% (2/170)	1.3% (2/160)
HAEMATEMESIS	0.0% (0/170)	0.6% (1/160)
HAEMORRHOIDS	0.6% (1/170)	0.0% (0/160)
INGUINAL HERNIA	0.0% (0/170)	0.6% (1/160)
LARGE INTESTINAL STENOSIS	0.0% (0/170)	0.6% (1/160)
LOWER GASTROINTESTINAL HAEMORRHAGE	0.0% (0/170)	0.6% (1/160)
MESENTERIC HAEMATOMA	0.6% (1/170)	0.0% (0/160)
NAUSEA	0.6% (1/170)	0.0% (0/160)
PANCREATITIS ACUTE	0.0% (0/170)	0.6% (1/160)
UPPER GASTROINTESTINAL HAEMORRHAGE	0.0% (0/170)	0.6% (1/160)
VOMITING	0.6% (1/170)	0.6% (1/160)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2.4% (4/170)	3.8% (6/160)
CHEST PAIN	1.8% (3/170)	1.3% (2/160)
COMPLICATION ASSOCIATED WITH DEVICE	0.0% (0/170)	0.6% (1/160)
DEATH	0.0% (0/170)	0.6% (1/160)
MULTIPLE ORGAN DYSFUNCTION SYNDROME	0.6% (1/170)	0.0% (0/160)
PERIPHERAL SWELLING	0.0% (0/170)	0.6% (1/160)
VASCULAR STENT STENOSIS	0.0% (0/170)	0.6% (1/160)
HEPATOBILIARY DISORDERS	4.1% (7/170)	0.0% (0/160)
BILE DUCT STONE	0.6% (1/170)	0.0% (0/160)
CHOLANGITIS	0.6% (1/170)	0.0% (0/160)
CHOLECYSTITIS	0.6% (1/170)	0.0% (0/160)
CHOLECYSTITIS ACUTE	0.6% (1/170)	0.0% (0/160)
CHOLELITHIASIS	0.6% (1/170)	0.0% (0/160)
HEPATIC CIRRHOSIS	0.6% (1/170)	0.0% (0/160)
PORTAL VEIN THROMBOSIS	0.6% (1/170)	0.0% (0/160)
IMMUNE SYSTEM DISORDERS	0.0% (0/170)	0.6% (1/160)
KIDNEY TRANSPLANT REJECTION	0.0% (0/170)	0.6% (1/160)
INFECTIONS AND INFESTATIONS	17.1% (29/170)	11.3% (18/160)
ABDOMINAL ABSCESS	0.6% (1/170)	0.0% (0/160)
ABSCESS LIMB	0.6% (1/170)	0.0% (0/160)
APPENDICITIS	0.6% (1/170)	0.0% (0/160)
BACTERAEMIA	0.6% (1/170)	0.0% (0/160)
BRONCHITIS	0.6% (1/170)	0.0% (0/160)
CELLULITIS	2.4% (4/170)	0.6% (1/160)
CLOSTRIDIUM DIFFICILE COLITIS	0.0% (0/170)	0.6% (1/160)
CLOSTRIDIUM DIFFICILE INFECTION	0.0% (0/170)	0.6% (1/160)
ENDOCARDITIS	0.6% (1/170)	0.0% (0/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
ENTEROCOCCAL INFECTION	0.0% (0/170)	0.6% (1/160)
ESCHERICHIA BACTERAEMIA	0.6% (1/170)	0.0% (0/160)
GANGRENE	0.6% (1/170)	0.6% (1/160)
GASTROENTERITIS	0.6% (1/170)	0.0% (0/160)
GASTROINTESTINAL INFECTION	0.6% (1/170)	0.0% (0/160)
INFECTED SKIN ULCER	0.6% (1/170)	0.0% (0/160)
INFECTION	0.0% (0/170)	0.6% (1/160)
INFLUENZA	0.0% (0/170)	1.9% (3/160)
LOCALISED INFECTION	0.6% (1/170)	0.0% (0/160)
NECROTISING FASCIITIS	0.0% (0/170)	0.6% (1/160)
OSTEOMYELITIS	1.2% (2/170)	0.0% (0/160)
PNEUMONIA	7.1% (12/170)	3.1% (5/160)
PNEUMONIA STAPHYLOCOCCAL	0.0% (0/170)	0.6% (1/160)
POSTOPERATIVE WOUND INFECTION	0.0% (0/170)	0.6% (1/160)
PYELONEPHRITIS	0.6% (1/170)	0.6% (1/160)
SEPSIS	2.4% (4/170)	2.5% (4/160)
SEPTIC SHOCK	0.6% (1/170)	0.0% (0/160)
STAPHYLOCOCCAL BACTERAEMIA	0.6% (1/170)	0.6% (1/160)
SUBCUTANEOUS ABSCESS	0.6% (1/170)	0.0% (0/160)
UPPER RESPIRATORY TRACT INFECTION	0.6% (1/170)	0.6% (1/160)
URINARY TRACT INFECTION	1.2% (2/170)	2.5% (4/160)
URINARY TRACT INFECTION BACTERIAL	0.0% (0/170)	0.6% (1/160)
UROSEPSIS	0.0% (0/170)	0.6% (1/160)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	38.8% (66/170)	57.5% (92/160)
ACETABULUM FRACTURE	0.6% (1/170)	0.0% (0/160)
ARTERIOVENOUS FISTULA ANEURYSM	1.8% (3/170)	3.1% (5/160)
ARTERIOVENOUS FISTULA OCCLUSION	1.8% (3/170)	3.8% (6/160)
ARTERIOVENOUS FISTULA SITE COMPLICATION	31.8% (54/170)	49.4% (79/160)
ARTERIOVENOUS FISTULA SITE HAEMATOMA	0.6% (1/170)	0.6% (1/160)
ARTERIOVENOUS FISTULA SITE HAEMORRHAGE	0.6% (1/170)	1.3% (2/160)
ARTERIOVENOUS FISTULA THROMBOSIS	0.6% (1/170)	2.5% (4/160)
CORONARY ARTERY RESTENOSIS	0.6% (1/170)	0.0% (0/160)
DIALYSIS RELATED COMPLICATION	0.6% (1/170)	0.0% (0/160)
FEMORAL NECK FRACTURE	0.6% (1/170)	0.0% (0/160)
FEMUR FRACTURE	0.0% (0/170)	0.6% (1/160)
HAEMODIALYSIS COMPLICATION	1.8% (3/170)	0.0% (0/160)
HEAD INJURY	0.6% (1/170)	0.0% (0/160)
HIP FRACTURE	0.0% (0/170)	0.6% (1/160)
INCARCERATED INCISIONAL HERNIA	0.0% (0/170)	0.6% (1/160)
LIMB INJURY	0.0% (0/170)	0.6% (1/160)
MULTIPLE FRACTURES	0.0% (0/170)	0.6% (1/160)
OVERDOSE	0.6% (1/170)	0.0% (0/160)
POST PROCEDURAL HAEMORRHAGE	0.0% (0/170)	0.6% (1/160)
RECTAL INJURY	0.6% (1/170)	0.0% (0/160)
SKULL FRACTURE	0.6% (1/170)	0.0% (0/160)
SPINAL COMPRESSION FRACTURE	0.0% (0/170)	1.3% (2/160)
SUBDURAL HAEMATOMA	0.6% (1/170)	0.0% (0/160)
TIBIA FRACTURE	0.0% (0/170)	0.6% (1/160)
TOXICITY TO VARIOUS AGENTS	0.0% (0/170)	0.6% (1/160)
UPPER LIMB FRACTURE	0.0% (0/170)	0.6% (1/160)
INVESTIGATIONS	0.0% (0/170)	0.6% (1/160)
TROPONIN INCREASED	0.0% (0/170)	0.6% (1/160)
METABOLISM AND NUTRITION DISORDERS	5.9% (10/170)	8.1% (13/160)
FLUID OVERLOAD	2.4% (4/170)	1.9% (3/160)
HYPERGLYCAEMIA	0.6% (1/170)	0.6% (1/160)
HYPERKALAEMIA	1.8% (3/170)	3.1% (5/160)
HYPERNATRAEMIA	0.0% (0/170)	0.6% (1/160)
HYPERVOLAEMIA	0.6% (1/170)	0.6% (1/160)
HYPOGLYCAEMIA	0.6% (1/170)	0.0% (0/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
HYPOVOLAEMIA	0.0% (0/170)	0.6% (1/160)
LACTIC ACIDOSIS	0.6% (1/170)	0.6% (1/160)
MALNUTRITION	0.6% (1/170)	0.0% (0/160)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3.5% (6/170)	1.9% (3/160)
ARTHRITIS REACTIVE	0.6% (1/170)	0.0% (0/160)
BACK PAIN	0.6% (1/170)	0.6% (1/160)
CHONDROCALCINOSIS PYROPHOSPHATE	0.6% (1/170)	0.0% (0/160)
COSTOCHONDRITIS	0.6% (1/170)	0.0% (0/160)
FLANK PAIN	0.0% (0/170)	0.6% (1/160)
LUMBAR SPINAL STENOSIS	0.6% (1/170)	0.0% (0/160)
MUSCULAR WEAKNESS	0.0% (0/170)	0.6% (1/160)
SPINAL COLUMN STENOSIS	0.6% (1/170)	0.0% (0/160)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1.8% (3/170)	2.5% (4/160)
ANGIOSARCOMA	0.0% (0/170)	0.6% (1/160)
BLADDER CANCER	0.6% (1/170)	0.0% (0/160)
BREAST ANGIOSARCOMA	0.0% (0/170)	0.6% (1/160)
HEPATIC CANCER	0.6% (1/170)	0.0% (0/160)
LUNG ADENOCARCINOMA	0.0% (0/170)	0.6% (1/160)
METASTASES TO PERITONEUM	0.0% (0/170)	0.6% (1/160)
PROSTATE CANCER METASTATIC	0.6% (1/170)	0.0% (0/160)
RENAL CANCER	0.0% (0/170)	0.6% (1/160)
NERVOUS SYSTEM DISORDERS	3.5% (6/170)	6.9% (11/160)
BRAIN STEM STROKE	0.0% (0/170)	0.6% (1/160)
CAROTID ARTERY STENOSIS	0.0% (0/170)	0.6% (1/160)
CEREBRAL HAEMORRHAGE	0.6% (1/170)	0.0% (0/160)
CEREBROVASCULAR ACCIDENT	1.2% (2/170)	0.0% (0/160)
CERVICAL RADICULOPATHY	0.0% (0/170)	0.6% (1/160)
ENCEPHALOPATHY	0.6% (1/170)	1.3% (2/160)
HEPATIC ENCEPHALOPATHY	0.6% (1/170)	0.0% (0/160)
HYPERTENSIVE ENCEPHALOPATHY	0.0% (0/170)	0.6% (1/160)
ISCHAEMIC STROKE	0.6% (1/170)	0.6% (1/160)
METABOLIC ENCEPHALOPATHY	0.0% (0/170)	1.3% (2/160)
NARCOLEPSY	0.0% (0/170)	0.6% (1/160)
NEUROPATHY PERIPHERAL	0.6% (1/170)	0.0% (0/160)
PRESYNCOPE	0.0% (0/170)	0.6% (1/160)
SYNCOPE	0.0% (0/170)	0.6% (1/160)
TRANSIENT ISCHAEMIC ATTACK	0.6% (1/170)	0.0% (0/160)
PSYCHIATRIC DISORDERS	0.6% (1/170)	1.3% (2/160)
DELIRIUM TREMENS	0.6% (1/170)	0.0% (0/160)
MENTAL STATUS CHANGES	0.0% (0/170)	1.3% (2/160)
RENAL AND URINARY DISORDERS	1.2% (2/170)	1.9% (3/160)
END STAGE RENAL DISEASE	0.0% (0/170)	1.3% (2/160)
RENAL CYST	0.6% (1/170)	0.0% (0/160)
RENAL MASS	0.6% (1/170)	0.0% (0/160)
URINARY RETENTION	0.0% (0/170)	0.6% (1/160)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8.2% (14/170)	5.6% (9/160)
ACUTE PULMONARY OEDEMA	0.0% (0/170)	0.6% (1/160)
ACUTE RESPIRATORY FAILURE	1.8% (3/170)	0.6% (1/160)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0.6% (1/170)	0.0% (0/160)
DYSPNOEA EXERTIONAL	0.6% (1/170)	0.0% (0/160)
HYPOXIA	0.6% (1/170)	0.0% (0/160)
PLEURAL EFFUSION	2.9% (5/170)	0.0% (0/160)
PNEUMOTHORAX	0.0% (0/170)	0.6% (1/160)
PULMONARY HYPERTENSION	0.0% (0/170)	0.6% (1/160)
PULMONARY OEDEMA	0.6% (1/170)	1.3% (2/160)
RESPIRATORY ARREST	0.6% (1/170)	0.0% (0/160)
RESPIRATORY FAILURE	1.8% (3/170)	3.8% (6/160)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1.2% (2/170)	1.9% (3/160)
DECUBITUS ULCER	0.0% (0/170)	0.6% (1/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
DIABETIC FOOT	0.6% (1/170)	0.0% (0/160)
ISCHAEMIC SKIN ULCER	0.0% (0/170)	0.6% (1/160)
PSORIASIS	0.0% (0/170)	0.6% (1/160)
SKIN ULCER	0.6% (1/170)	0.0% (0/160)
SOCIAL CIRCUMSTANCES	0.6% (1/170)	0.0% (0/160)
REFUSAL OF TREATMENT BY PATIENT	0.6% (1/170)	0.0% (0/160)
SURGICAL AND MEDICAL PROCEDURES	0.6% (1/170)	2.5% (4/160)
ARTERIOVENOUS FISTULA OPERATION	0.0% (0/170)	1.3% (2/160)
INTERVERTEBRAL DISC OPERATION	0.0% (0/170)	0.6% (1/160)
PERIPHERAL REVASCULARISATION	0.6% (1/170)	0.0% (0/160)
RENAL TRANSPLANT	0.0% (0/170)	0.6% (1/160)
VASCULAR DISORDERS	7.1% (12/170)	8.8% (14/160)
AORTIC ANEURYSM	0.6% (1/170)	0.0% (0/160)
AORTIC STENOSIS	0.6% (1/170)	0.0% (0/160)
BRACHIOCEPHALIC VEIN STENOSIS	0.0% (0/170)	0.6% (1/160)
HYPERTENSION	0.6% (1/170)	0.0% (0/160)
HYPOTENSION	2.9% (5/170)	1.3% (2/160)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	1.2% (2/170)	2.5% (4/160)
PERIPHERAL ARTERY OCCLUSION	0.6% (1/170)	0.0% (0/160)
PERIPHERAL ARTERY STENOSIS	0.0% (0/170)	1.3% (2/160)
PERIPHERAL ISCHAEMIA	0.6% (1/170)	0.0% (0/160)
SHOCK HAEMORRHAGIC	0.6% (1/170)	0.0% (0/160)
STEAL SYNDROME	0.6% (1/170)	1.9% (3/160)
SUBCLAVIAN VEIN THROMBOSIS	0.0% (0/170)	0.6% (1/160)
VENOUS STENOSIS	0.0% (0/170)	0.6% (1/160)
VENOUS THROMBOSIS LIMB	0.6% (1/170)	0.0% (0/160)
TOTAL SERIOUS ADVERSE EVENTS	**321**	**350**

Note:
Percentages are calculated as no. of subjects with each event / total no. of subjects in the analysis set.
Event verbatim terms are reported by sites. The events listed in this table are then coded using MedDRA version 19.1 and then stratified by System-Organ Class (SOC) and Preferred Term. Patients are only counted once in each specific SOC and PT event term.
Site reported data.

Table 12 below provides additional analysis on infections and infestations, and pneumonia. The Kaplan-Meier estimated cumulative incidence of infections and infestations through 180 and 360 days was 10.6% [6.4%, 15.9%], and 18.9% [13.1%, 25.5%] respectively in the IN.PACT AV DCB group and 3.9% [1.6%, 7.9%], and 12.2% [7.6%, 18.1%] respectively in the standard PTA group. The Kaplan-Meier estimated cumulative incidence of pneumonia through 180 and 360 days was 3.8% [1.5%, 7.6%], and 7.9% [4.3%, 13.0%] respectively in the IN.PACT AV DCB group and 1.3% [0.3%, 4.2%] and 4.1% [1.7%, 8.3%] respectively in the standard PTA group. As summarized in Table 12, infections and infestations, and pneumonia, are numerically higher in the IN.PACT AV DCB group than in the standard PTA group though 360 days.

Table 12. Number of Subjects with One or More Serious Infections and Infestations or Pneumonia – ITT Analysis Set

Serious Adverse Events	IN.PACT AV DCB (N = 170 Subjects)		Standard PTA (N = 160 Subjects)		Log-rank p-value
	% (n)	95% CI	% (n)	95% CI	
Infections and Infestations through 180 Days	10.6% (17)	6.4%, 15.9%	3.9% (6)	1.6%, 7.9%	0.022
Pneumonia† through 180 Days	3.8% (6)	1.5%, 7.6%	1.3% (2)	0.3%, 4.2%	0.172
Infections and Infestations through 360 Days	18.9% (29)	13.1%, 25.5%	12.2% (18)	7.6%, 18.1%	0.092
Pneumonia† through 360 Days	7.9% (12)	4.3%, 13.0%	4.1% (6)	1.7%, 8.3%	0.164

Note:
Percentages are Cumulative Incidence based on Kaplan-Meier estimate (number of subjects with event)
CI – Confidence Interval
† Include 'Pneumonia' and 'Pneumonia Staphylococcal'
The Log-rank p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

12. How Supplied

STERILE: The IN.PACT AV DCB is sterilized by ethylene oxide (EtO) and is nonpyrogenic. It is intended for single use only. Do not resterilize. Do not use if package is opened or damaged.

CONTENTS: The package contains 1 IN.PACT AV DCB.

STORAGE: Store the device in the original container. Store between 15°C and 30°C (59°F and 86°F). Use product by the Use-by Date noted on the package. Do not store near radiation or ultraviolet light sources.

DISPOSAL INSTRUCTIONS: After use, this product may be a biohazard. Handle and dispose of all such devices in accordance with accepted medical practice and applicable hospital, administrative, and government regulations.

DEVICE RETURN INSTRUCTIONS: In the case of a product failure or malfunction related to the product, contact a Medtronic clinical representative for return or replacement. Any ancillary devices involved in the incident should also be returned to Medtronic, if possible. To obtain return instructions or for any other product return inquiries, contact US Customer Service / Product Inquiries at 1 888 283 7868.

13. Instructions for Use

Reference Figure 1 (IN.PACT AV Paclitaxel-coated PTA Balloon Catheter) for a device schematic.

13.1. Equipment

- 0.035 in Guidewire
- Introducer sheath
- Vessel preparation device
- Contrast medium
- Sterile saline
- Inflation device with manometer
- Luer lock syringe for purging

13.2. Balloon Catheter Size Selection

- The nominal balloon diameter must match the inner diameter of the reference vessel distal to the target lesion. The balloon length must exceed the lesion length by approximately 1 cm on the proximal and distal ends.
- If the lesion is longer than the longest available IN.PACT AV DCB, use multiple IN.PACT AV DCBs to treat the lesion, using the recommended overlap, as described in Using Multiple IN.PACT AV DCBs (Section 13.9), Recommended Overlap When Using Multiple IN.PACT AV DCBs (Figure 8), and Treatment of a Tandem Lesion with Multiple IN.PACT AV DCBs (Figure 10).

13.3. Recommendations for Optimal Treatment

- Appropriate vessel preparation is required prior to use of the IN.PACT AV DCB. Vessel preparation of the target lesion using high-pressure PTA for predilatation was studied in the IN.PACT AV Access clinical study. Other methods of vessel preparation, such as atherectomy, have not been studied clinically with IN.PACT AV DCB.
- Use appropriate vessel preparation as determined by the physician to achieve residual stenosis of ≤ 30% prior to use of the IN.PACT AV DCB.
- When using an uncoated high-pressure PTA balloon catheter, use a PTA balloon with a diameter matching the reference vessel diameter distal to the target lesion to facilitate the passage of the appropriately sized IN.PACT AV DCB.

  Note: Following vessel preparation, if the lesion cannot be crossed with the first inserted IN.PACT AV DCB, the second attempt must be made with a new IN.PACT AV DCB in order to ensure effective drug delivery.
- As noted in Delivery and Dilatation Procedure (Section 13.7), for optimal mechanical dilatation of the vessel, inflate the balloon for at least 180 seconds. Adequate drug transfer occurs in the first 60 seconds of inflation. The additional 120 seconds is intended solely for mechanical dilatation purposes for optimal PTA.
- Post-dilatation should be completed according to the physician's discretion. If adequate PTA results are not obtained after the IN.PACT AV DCB(s) balloon inflation, post-dilatation using a non–drug-coated PTA balloon catheter of shorter length than the previously used IN.PACT AV DCB is recommended.
- It is important to provide drug delivery to the entire length of the treated vessel prior to post-dilatation or provisional stenting.

13.4. PTA Preparation

1. Prepare the inflation device, introducer sheath, and guidewire according to the manufacturer's instructions. See Table 1 for help selecting the appropriately sized introducer sheath.
2. Administer the appropriate medication to the patient prior to treatment as described in Pre-procedure and Post-procedure Medication Regimen (Section 6.2).
3. Prepare the vascular access site according to standard practice.
4. Insert a guidewire through the hemostatic valve following the manufacturer's instructions or standard practice. Advance the guidewire carefully into the introducer sheath.
5. Attach a torque device to the wire, if desired. Under fluoroscopy, advance the guidewire to the desired vessel, then across the stenosis. Remove the torque device once the guidewire is positioned.

13.5. IN.PACT AV DCB Preparation

1. The catheter is packaged in a protective tray. Verify that the catheter and sterile packaging have not been damaged in shipment. After all preparation has been completed, carefully remove the catheter from the package. Do not remove the IN.PACT AV DCB from the packaging until it is ready for insertion.

   Note: Avoid exposing the balloon drug coating to excessive handling or contact with liquids prior to preparation and delivery as the coating may be susceptible to damage or premature drug release.
2. The folded balloon catheter may contain air that should be purged prior to use. Connect a stopcock to the balloon inflation port of the catheter hub. Connect a luer-lock syringe partially filled with saline solution to the stopcock. Open the stopcock. Keeping the syringe in a downward vertical position, draw back the plunger of the syringe and create a vacuum for 30 seconds in the balloon inflation line until air is completely evacuated.

   Caution: If the air bubbles cannot be completely evacuated, there may be a leak in the catheter. Discard the device and select a new IN.PACT AV DCB.

   Note: It is important to maintain the vacuum seal in order to keep the balloon profile tight before insertion into the introducer sheath.

   Note: Keep the protective sheath in place during the purging procedure.
3. After air is completely evacuated, close the stopcock and remove the syringe.
4. Remove the protective sheath from the balloon and discard. Do not use the protective sheath as an introduction aid or rewrapping tool.
5. Connect the filled syringe to the guidewire port. Flush the guidewire lumen through the guidewire port with heparinized normal saline until the fluid exits the distal tip.

   Caution: Do not rinse or wipe the IN.PACT AV DCB catheter.

   Note: Drops of saline must emerge from the device tip.

   Note: To minimize the introduction of air, aspirate and flush the system and keep a tight catheter connection throughout the procedure.

13.6. Inflation Device Connection to the IN.PACT AV DCB

1. Fill the inflation device with 10 mL of saline-contrast mixture. Do not use air or any gaseous medium to inflate the balloon. Use only the recommended inflation medium (equal parts contrast medium and saline solution). Do not apply positive pressure to the balloon during preparation.
2. Evacuate all air present in the inflation device.

   Note: The inflation device should have no air bubbles present, either in the tube or in the cylinder; to remove any air lodged, keeping the tip upward, purge approximately 1 cc of saline-contrast mixture.
3. With the stopcock connected to the balloon port in the closed position, securely couple the inflation device to the stopcock. Verify that no air is evident in both the stopcock and the inflation device's connection.

13.7. Delivery and Dilatation Procedure

1. Load the distal tip of the balloon catheter over the prepositioned guidewire, which has been placed through the lesion.
2. Advance the catheter under direct fluoroscopic visualization. To avoid kinking, advance the catheter through the hemostatic valve slowly and in small increments while the stopcock is closed. Open the hemostatic valve to allow for easy passage of the balloon and to prevent damage to the balloon coating. Once the balloon has passed through, the hemostatic valve should be closed as much as is needed to prevent blood return while still permitting easy movements of the catheter.

   Note: If significant resistance is encountered, do not advance the catheter through the introducer sheath.
3. Under fluoroscopy, use the balloon radiopaque markers to position the balloon within the lesion to be dilated. If the inflation device has not already been connected, connect the inflation device according to instructions in Inflation Device Connection to the IN.PACT AV DCB (Section 13.6).
4. Open the stopcock and inflate the balloon to the appropriate pressure as described in the Compliance Chart included in the device packaging, then close the stopcock to maintain pressure. For optimal mechanical dilatation of the vessel, inflate the balloon for at least 180 seconds. Adequate drug transfer occurs in the first 60 seconds of inflation. If the IN.PACT AV DCB was inflated for at least 60 seconds but the vessel requires additional dilatation due to suboptimal PTA results, a plain PTA balloon catheter of the operator's choice can be used (PTA balloon length should be of shorter length compared to the IN.PACT AV DCB).

   Warning: Do not exceed rated burst pressure as indicated on the device label. Use of pressures higher than those specified on the device label may result in a ruptured balloon with possible intimal damage and dissection.

Note: The IN.PACT AV DCB is intended for single inflation only.

13.8. Removal Procedure

1. Open the stopcock and deflate the balloon by applying negative pressure to the inflation device. Allow approximately 60 seconds for full balloon deflation. Larger balloons may require more time for deflation. Deflation of the balloon should be confirmed by absence of contrast medium within the balloon.

   Note: The balloon must be completely deflated before removal.
2. Upon confirmation of full deflation, disconnect the inflation device, then open the hemostatic valve and withdraw the deflated balloon catheter from the introducer sheath, through the hemostatic valve. Tighten the knurled knob on the hemostatic valve.
3. If necessary, the balloon catheter can be exchanged for different balloon types or sizes using the guidewire/ introducer that remains in the vessel.

   Note: If further dilatation is required, post-dilatation should be performed with a non–drug-coated PTA balloon catheter of shorter length than the IN.PACT AV DCB.
4. When complete, withdraw the guidewire/introducer, and close the hemostatic valve.

   Note: After use, this device may be a biohazard. Handle and dispose of all such devices in accordance with accepted medical practice and applicable hospital, administrative, and government regulations.

13.9. Using Multiple IN.PACT AV DCBs

Warning: The safety of using multiple IN.PACT AV DCBs with a total drug dosage exceeding 15,105 µg paclitaxel has not been evaluated clinically.

Additional IN.PACT AV DCBs should be used to treat a lesion only under either of the following circumstances:

- The first IN.PACT AV DCB bursts prior to 60 seconds of inflation time.
- The lesion length requires more than 1 IN.PACT AV DCB to fully cover the lesion and extend approximately 1 cm at both the proximal and distal edges.

If multiple IN.PACT AV DCBs are required due to a lesion length greater than the longest available DCB, the balloons must overlap by approximately 1 cm. The size of additional DCBs should not be longer than required to allow for this overlap and complete the lesion coverage with approximately 1 cm extended beyond the lesion both proximally and distally. Proper size selection is important to avoid excessive overlap. Refer to Figure 7 through Figure 10 for further guidance.

Note: In order to reduce procedure-related complications, use only the minimum number of devices needed to cover the lesion(s).

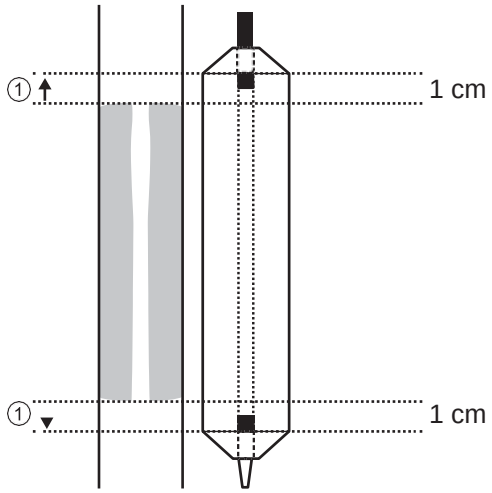


Figure 7. Treatment of a Single Lesion

1. Approximately 1 cm

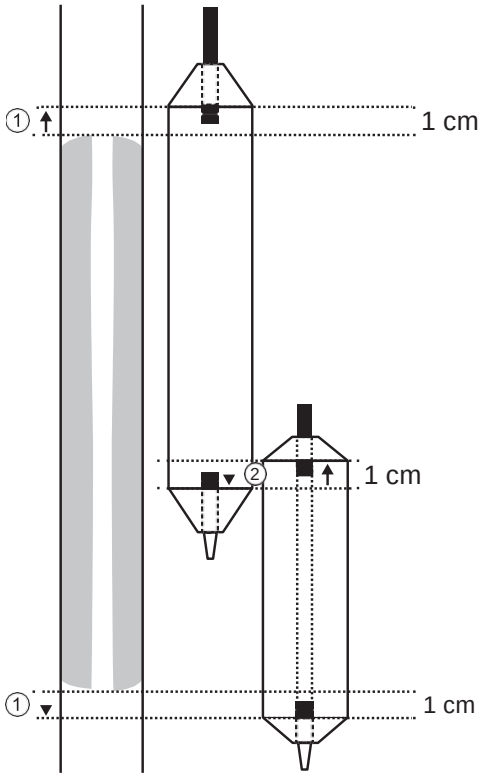


Figure 8. Recommended Overlap When Using Multiple IN.PACT AV DCBs

1. Approximately 1 cm
2. Approximately 1 cm balloon overlap

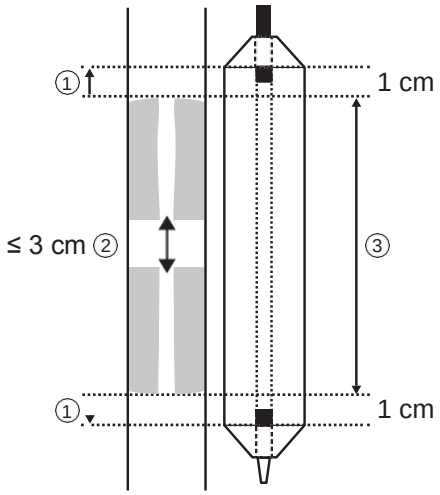


Figure 9. Treatment of a Tandem Lesion with a Single IN.PACT AV DCB

1. Approximately 1 cm
2. Lesion gap ≤ 3 cm
3. Total lesion length ≤ 100 mm

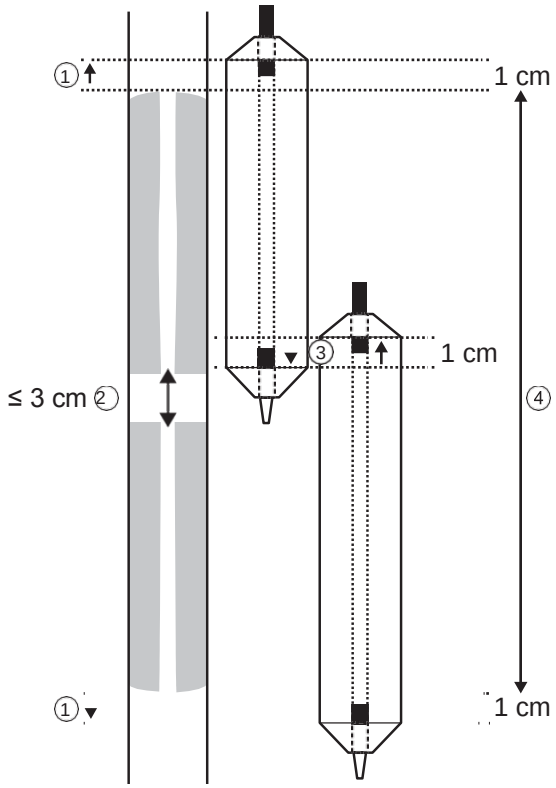


Figure 10. Treatment of a Tandem Lesion with Multiple IN.PACT AV DCBs

1. Approximately 1 cm
2. Lesion gap ≤ 3 cm
3. Approximately 1 cm balloon overlap
4. Total lesion length ≤ 100 mm

14. DISCLAIMER OF WARRANTY

The warnings contained in the product labeling provide more detailed information and are considered an integral part of this disclaimer of warranty. Although the product has been manufactured under carefully controlled conditions, Medtronic has no control over the conditions under which this product is used. Medtronic, therefore, disclaims all warranties, both express and implied, with respect to the product, including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. Medtronic shall not be liable to any person or entity for any medical expenses or any direct, incidental, or consequential damages caused by any use, defect, failure, or malfunction of the product, whether a claim for such damages is based upon warranty, contract, tort, or otherwise. No person has any authority to bind Medtronic to any representation or warranty with respect to the product.

The exclusions and limitations set out above are not intended to, and should not be construed so as to, contravene mandatory provisions of applicable law. If any part or term of this disclaimer of warranty is held to be illegal, unenforceable, or in conflict with applicable law by a court of competent jurisdiction, the validity of the remaining portions of this disclaimer of warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this disclaimer of warranty did not contain the particular part or term held to be invalid.

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