Boston Scientific

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ION™

MONORAIL®

OVER-THE-WIRE

Paclitaxel-Eluting Platinum Chromium Coronary Stent System

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℞ ONLY

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

This device is supplied in sterile condition. All materials inside the sterile barrier pouch (the delivery system and stent, as well as the carrier tube and pouch liner) are sterile. The external surface of the sterile barrier pouch, as well as the product carton, should not be considered sterile.

1 WARNING

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Boston Scientific representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

...ICE DESCRIPTION

...Paclitaxel-Eluting Platinum Chromium Coronary ...ystem

The ION Paclitaxel-Eluting Platinum Chromium Stent System (hereinafter referred to as ION Stent System) is a device/drug combination product comprised of two regulated components: a device (ION Stent System) and a drug product (a formulation of paclitaxel contained in a polymer coating). The characteristics of the ION Stent System are described in Table 2.1.

Table 2.1 ION Stent System Product Description

	ION Monorail Stent Delivery System	ION Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38	
Available Stent Diameters (mm)	2.25*, 2.50*, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.0032 in (0.081 mm) for diameters 2.25 mm to 3.5 mm 0.0034 in (0.086 mm) for diameter 4.0 mm	
Drug Product	A conformal coating of a polymer carrier loaded with 1 µg/mm² paclitaxel applied to the stent with a maximum nominal drug content of 247 µg on the largest stent (4.00 x 38 mm).	
Delivery System		
Effective Length	144 cm	143 cm
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 26 cm from tip. Designed for guidewire ≤ 0.014 in (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014 in (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.385 mm (0.015 in) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm; 11 atm (1115 kPa)	
	Rated Burst Inflation Pressure: • Diameters 2.25 mm; 18 atm (1824 kPa) • Diameters 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm; 16 atm (1621 kPa)	
Catheter Shaft Outer Diameter	2.3 F (0.80 mm) proximal and 2.7 F (0.95 mm) distal.	3.4F (1.20 mm) proximal for 2.25 to 4.00 mm sizes 2.4F (0.85 mm) distal for 2.25 to 2.75 mm sizes 2.7F (0.95 mm) distal for 3.00 to 4.00 mm sizes
Guide Catheter Minimum Inner Diameter Requirement	≥ 0.056 in (1.42 mm) for 2.25 to 3.50 mm sizes. ≥ 0.058 in (1.47 mm) for 4.00 mm sizes.	≥ 0.066 in (1.68 mm)

*2.25 and 2.50 mm sizes are available in 8, 12, 16, 20, 24, 28, 32 mm lengths

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2.1 Device Component Description

The ION™ Stent is the paclitaxel-coated member of the platinum chromium (PtCr) Stent Series. The ION Stent System is available in four stent models each engineered for specific diameters to provide consistent stent-to-artery ratios across the range of reference vessel diameters indicated:

- Small Vessel (SV): 2.25 mm
- Small Workhorse (SWH): 2.50, 2.75 mm
- Workhorse (WH): 3.00, 3.50 mm
- Large Vessel (LV): 4.00 mm

CONTENTS for (1) ION Over-the-Wire Stent System

- One (1) ION Over-the-Wire Stent System

CONTENTS for (1) ION Monorail® Stent System

- One (1) ION Monorail Stent System
- Two (2) CLIPIT™ Coil clips
- One (1) Flushing needle with luer fitting

2.2 Drug Component Description

The stent component of the ION Stent System is a PtCr stent with a drug/polymer coating formulation consisting of paclitaxel (the active ingredient) and Translute™ Polymer carrier (the inactive ingredient). The drug/polymer coating formulation is identical to the drug/polymer coating formulation used in the following TAXUS products: TAXUS Express Paclitaxel-Eluting Stent and TAXUS Liberté Paclitaxel-Eluting Stent.

2.2.1 Paclitaxel

The active pharmaceutical ingredient in the ION Stent is paclitaxel. It is a white powder, isolated from a spectrum of Taxus species and hybrids. The chemical name of paclitaxel is: Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-,6,12bbis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12bdodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester,[2a *R*-[2aα,4β,4aβ,6β,9α (α*R**,β*S**),11α,12α,12aα,12bα]]-. The chemical structure of paclitaxel is shown in Figure 2.1.

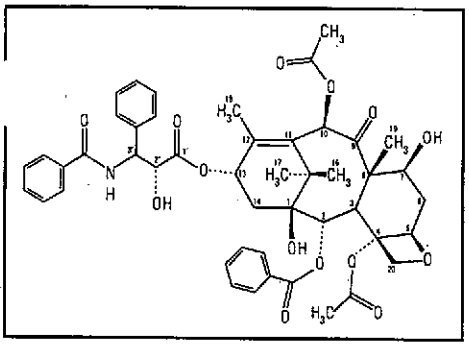

Figure 2.1 The Chemical Structure of Paclitaxel

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 C47H51NO14. It is highly lipophilic, insoluble in water, but freely soluble in methanol, ethanol, chloroform, ethyl acetate and dimethyl sulfoxide.

2.2.2 Translute Polymer Carrier

The only inactive ingredient in the ION Stent is SIBS [poly(styrene-b-isobutyleneb-styrene)], a tri-block copolymer (trade name: Translute), composed of polystyrene and polyisobutylene units. It is a hydrophobic elastomeric copolymer with a molecular weight (Mn-number average molecular weight) of 80,000 to 130,000 g/mol and a polydispersity index of 1.0 to 2.0. The polymer is mixed with paclitaxel and conformally applied to the stent. There is no primer or topcoat layer. The structural formula for the polymer is shown in Figure 2.2.

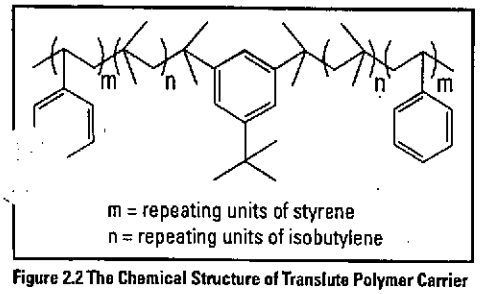

Figure 2.2 The Chemical Structure of Translute Polymer Carrier

2.2.3 Product Matrix and Paclitaxel Content

Table 2.2 ION Stent System Product Matrix and Paclitaxel Content

Product Code MR	Product Code OTW	Nominal Expanded Stent Inner Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Paclitaxel Content (µg)
H7493902408220	H7493902308220	2.25	8	39
H7493902408250	H7493902308250	2.50	8	40
H7493902408270	H7493902308270	2.75	8	40
H7493902408300	H7493902308300	3.00	8	43
H7493902408350	H7493902308350	3.50	8	43
H7493902408400	H7493902308400	4.00	8	57
H7493902412220	H7493902312220	2.25	12	58
H7493902412250	H7493902312250	2.50	12	62
H7493902412270	H7493902312270	2.75	12	62
H7493902412300	H7493902312300	3.00	12	61
H7493902412350	H7493902312350	3.50	12	61
H7493902412400	H7493902312400	4.00	12	82
H7493902416220	H7493902316220	2.25	16	74
H7493902416250	H7493902316250	2.50	16	80
H7493902416270	H7493902316270	2.75	16	80
H7493902416300	H7493902316300	3.00	16	86
H7493902416350	H7493902316350	3.50	16	86
H7493902416400	H7493902316400	4.00	16	107
H7493902420220	H7493902320220	2.25	20	94
H7493902420250	H7493902320250	2.50	20	97
H7493902420270	H7493902320270	2.75	20	97
H7493902420300	H7493902320300	3.00	20	104
H7493902420350	H7493902320350	3.50	20	104
H7493902420400	H7493902320400	4.00	20	131
H7493902424220	H7493902324220	2.25	24	109
H7493902424250	H7493902324250	2.50	24	115
H7493902424270	H7493902324270	2.75	24	115
H7493902424300	H7493902324300	3.00	24	123
H7493902424350	H7493902324350	3.50	24	123
H7493902424400	H7493902324400	4.00	24	156
H7493902428220	H7493902328220	2.25	28	129
H7493902428250	H7493902328250	2.50	28	133
H7493902428270	H7493902328270	2.75	28	133
H7493902428300	H7493902328300	3.00	28	141
H7493902428350	H7493902328350	3.50	28	141
H7493902428400	H7493902328400	4.00	28	181
H7493902432220	H7493902332220	2.25	32	148
H7493902432250	H7493902332250	2.50	32	155
H7493902432270	H7493902332270	2.75	32	155
H7493902432300	H7493902332300	3.00	32	166
H7493902432350	H7493902332350	3.50	32	166
H7493902432400	H7493902332400	4.00	32	206
H7493902438270	H7493902338270	2.75	38	181
H7493902438300	H7493902338300	3.00	38	197
H7493902438350	H7493902338350	3.50	38	197
H7493902438400	H7493902338400	4.00	38	247

3 INTENDED USE/INDICATIONS FOR USE

The ION Stent System is indicated for improving luminal diameter for the treatment of *de novo* lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 34 mm in length.

4 CONTRAINDICATIONS

Use of the ION Stent System is contraindicated in patients with:

- Known hypersensitivity to 316L stainless steel or platinum.
- Known hypersensitivity to paclitaxel or structurally-related compounds.
- Known hypersensitivity to the polymer or its individual components (see Section 2.2.2., Translute Polymer Carrier for more information).

Coronary Artery Stenting is contraindicated for use in:

- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy (see Section 6.2 Pre- and Post-Procedure Antiplatelet Regimen for more information).
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

5 WARNINGS

- To maintain sterility, the inner package should not be opened or damaged prior to use.
- The use of this product carries the risks associated with coronary artery stenting, including stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with recommended antiplatelet therapy.

6 PRECAUTIONS

6.1 General Precautions

- Only physicians who have received adequate training should perform stent implantation.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized stents is not well characterized.
- Consideration should be given to the risks and benefits of use in patients with history of severe reaction to contrast agents.
- Do not expose the delivery system to organic solvents such as alcohol or detergents.
- Care should be taken to control the position of the guide catheter tip during stent delivery, deployment and balloon withdrawal.
- Before withdrawing the Stent Delivery System (SDS), visually confirm complete balloon deflation by fluoroscopy (See Table 6.1 System Deflation Time Specifications). Failure to do so may cause increased SDS withdrawal forces, and result in guide catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Stent thrombosis is frequently associated with myocardial infarction (MI) or death. Data from the PERSEUS Clinical Program, which evaluated the ION Stent System, have been evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used. In the clinical trials analyzed to date, evaluated on earlier generations of TAXUS Stents, the differences in the incidence of stent thrombosis observed with a paclitaxel-eluting stent compared to bare-metal stents have not been associated with an increased risk of cardiac death, myocardial infarction, or all-cause mortality. Additional data from longer-term follow-up in the PERSEUS clinical trials and in previous trials in the TAXUS program and analyses of DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.
- When drug-eluting stents are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the pivotal clinical trials.
- Compared to use within the specified Indications for Use, the use of drug-eluting stents in patients and lesions outside of the labeled Indications, may have an increased risk of adverse events, including stent thrombosis, stent embolization, myocardial infarction, or death.

6.2 Pre-and Post-Procedure Antiplatelet Regimen

In the PERSEUS Clinical Program, which evaluated the ION Stent System, clopidogrel or ticlopidine was administered pre-procedure and for a period of 6 months post procedure and for 12 months in patients who were not at high risk of bleeding. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. See Section 10 Clinical Studies, for more specific information.

The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies suggest that a longer duration of antiplatelet therapy than was recommended post-procedurally in certain drug-eluting stent pivotal clinical trials (including TAXUS clinical trials which evaluated the earlier generation stents with the same drug/polymer coating

formulation as the ION™ Stent System) may be beneficial. Provided herein are recent recommendations from the ACC/AHA/SCAI 2007 Guideline for anti-thrombotic adjunctive therapies for Percutaneous Coronary Intervention (PCI), Section 6.2.1.

6.2.1 Oral Antiplatelet Therapy

Continuation of combination treatment with aspirin and clopidogrel after PCI appears to reduce rates of cardiovascular ischemic events. On the basis of randomized clinical trial protocols, aspirin 162 mg to 325 mg daily should be given for at least 6 months after paclitaxel eluting stent (PES) implantation, after which daily chronic aspirin should be continued indefinitely at a dose of 75 to 162 mg. Likewise, clopidogrel 75 mg daily should be given for at least 12 months in patients who are not at high risk of bleeding. To reduce the incidence of bleeding complications associated with dual antiplatelet therapy, lower-dose aspirin (75 to 162 mg daily) is recommended for long-term therapy.

Full guidelines are provided at the following website:

http://www.acc.org

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to PCI, if a surgical or dental procedure is anticipated which requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a drug-eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy. Generally, it is recommended to postpone elective surgery for one year and among those patients for whom surgery cannot be deferred, ASA should be considered during perioperative period in high risk DES patients.

Patients who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding should be monitored carefully for cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.

of Multiple Stents

PERSEUS Clinical Program, which evaluated the ION Stent System, the protocols specified that patients were to be treated with no more than one ION Stent, except in situations involving bailout stenting. The use of multiple drug-eluting stents will expose the patient to larger amounts of drug and polymer.

When multiple overlapping stents are used resulting in stent-to stent contact, it is suggested that the stents be adequately overlapped to avoid the potential for gap restenosis. It is recommended that overlapping stents be of similar composition to minimize the likelihood of dissimilar metal corrosion.

Potential interactions of the ION Stent with other drug eluting or coated stents have not been evaluated in the PERSEUS Clinical Program.

6.4 Brachytherapy

The safety and effectiveness of the ION Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of the use of brachytherapy to treat in-stent restenosis in an ION Stent have not been established. Both vascular brachytherapy and the ION Stent alter arterial remodeling. The synergy between these two treatments has not been determined.

6.5 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with ION Stent implantation have not been established.

6.6 Use in Special Populations

6.6.1 Pregnancy

Pregnancy "Category C". See Drug Information – Section 7.5, Pregnancy. There are no adequate or well-controlled studies in pregnant women or men intending to father children. ION Stents should be used in pregnant women only if the potential benefit justifies the potential risk to the embryo or fetus. Because some paclitaxel remains on the stent indefinitely, use of the ION Stent in women who are of childbearing potential or in men intending to father children should be given careful consideration.

6.6.2 Lactation

See Drug Information – Section 7.6, Lactation. A decision should be made whether to discontinue nursing prior to implanting the stent, taking into account the importance of the stent to the mother.

6.6.3 Gender

See Clinical Information - Section 10, Clinical Studies. Clinical studies of the ION Stent did not include formal analysis of differences in safety and effectiveness between male and female patients.

6.6.4 Ethnicity

See Clinical Information - Section 10, Clinical Studies. Clinical studies of the ION Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity, either by individual category or when grouped by Caucasian and non-Caucasian.

6.6.5 Pediatric Use

The safety and effectiveness of the ION Stent in pediatric patients have not been established.

6.6.6 Geriatric Use

Clinical studies of the ION Stent did not have an upper age limit. In the PERSEUS Workhorse study, there were 402 patients in the ION Stent group who were age 65 or older, and 124 in the PERSEUS Small Vessel study. There were 22 ION Stent patients in the PERSEUS Workhorse study who were over 80 years of age, and 10 ION Stent patients in the PERSEUS Small Vessel study. There were no statistically significant differences in outcomes between patients under 65 and over 65 years of age in the ION Stent group.

6.7 Lesion/Vessel Characteristics

The safety and effectiveness of the ION Stent have not been established in the cerebral, carotid, or peripheral vasculature or the following patient populations:

- Patients with vessel thrombus at the lesion site.
- Patients with coronary artery reference vessel diameters < 2.25 or > 4.00 mm.
- Patients with coronary artery lesions longer than 34 mm or requiring more than one ION Stent.
- Patients with lesions located in the saphenous vein grafts, in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with diffuse disease or poor flow distal to the identified lesions.
- Patients with tortuous vessels (> 60 degrees) in the region of the obstruction or proximal to the lesion.
- Patients with a recent acute myocardial infarction where there is evidence of thrombus or poor flow.
- Patients with in-stent restenosis.
- Patients with moderate or severe calcification in the lesion or a chronic total occlusion.
- Patients with multi-vessel disease.

6.8 Drug Interaction

Because systemic levels of paclitaxel have not been detected post-stent placement in clinical trials, possible interactions of paclitaxel with concomitantly administered medications are unlikely to be detectable. The effect of potential drug interactions on the safety and efficacy of the ION Stent has not been formally investigated. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

See Drug Information - Section 7.3 Drug Interactions for more information.

6.9 Magnetic Resonance Imaging (MRI)

The ION Stent has been shown to be MR Conditional (poses no known hazards under specified conditions) through non-clinical testing of single and overlapped configurations up to 74 mm in overall length. The conditions are as follows:

- Field strengths of 1.5 and 3 Tesla
- Static magnetic field gradient < 9 T/m (extrapolated)
- Normal operational mode (maximum whole body averaged specific absorption rate (SAR) of lower than 2.0 W/kg) for a total active MR scan time (with RF exposure) of 15 minutes or less

The ION Stent should not migrate in this MRI environment. MR imaging within these conditions may be performed immediately following the implantation of the stent. This stent has not been evaluated to determine if it is MR Conditional beyond these conditions.

3.0 Tesla Temperature Information

Non-clinical testing of RF-induced heating was performed at 123 MHz in a 3.0 Tesla Magnetom Trio®, Siemens Medical Solutions MR system, software version Numaris/4, Syngo® MR A30. RF power was applied for 15 minutes and the measured conductivity of the phantom material was about 0.3 S/m. The phantom average SAR was calculated using calorimetry to be 2.2 W/kg. The maximal in-vitro temperature rise was calculated as 2.6°C for a measured stent length of 74 mm with the whole-body SAR scaled to 2.0 W/kg. The calculations did not include the cooling effects due to blood flow.

1.5 Tesla Temperature Information

Non-clinical testing of RF-induced heating was performed at 64 MHz in a 1.5 Tesla Intera® Philips Medical Systems, software version Release 10.6.2.0, 2006-03-10 whole body coil MR scanner. RF power was applied for 15 minutes and the measured conductivity of the phantom material was about 0.3 S/m. The phantom average SAR was calculated using calorimetry to be 2.1 W/kg. The maximal in-vitro temperature rise was calculated as 2.6°C for a measured stent length of 74 mm with the whole-body SAR scaled to 2.0 W/kg. The calculations did not include the cooling effects due to blood flow.

In vivo, local SAR depends on MR Field strength and may be different than the estimated whole body averaged SAR, due to body composition, stent position within the imaging field, and scanner used, thereby affecting the actual temperature rise.

Image Artifact Information

The calculated image artifact extends approximately 7 mm from the perimeter of the device diameter and 5 mm beyond each end of the length of the stent when scanned in non-clinical testing using a Spin Echo sequence. With a Gradient Echo sequence the calculated image artifact extends 5 mm beyond the perimeter of the diameter and 6 mm beyond each end of the length with both sequences partially shielding the lumen in a 3.0 Tesla Intera (Achieva Upgrade), Philips Medical Solutions, software version Release 2.5.3.0 2007-09-28 MR system with a transmit/receive head coil.

Medical Registration

It is recommended that patients register the conditions under which the implant can be scanned safely with the MedicAlert Foundation (www.medicalert.org) or equivalent organization.

Magnetic Resonance Conditional

6.10 Stent Handling

(also see Section 14, Operational Instructions)

- For single use only. Do not resterilize or reuse this product. Note product "Use By" date. (See Warning - Section 1)
- The premounted ION Stent and its delivery system are designed for use as a unit. The stent is not to be removed from its delivery balloon. The stent is not designed to be crimped onto another balloon. Removing the stent from its delivery balloon may damage the stent and coating and/ or lead to stent embolization.
- Special care must be taken not to handle or in any way disrupt the stent position on the delivery balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through hemostasis valve adapter and guide catheter hub.
- Excessive manipulation or handling may cause coating damage, contamination, or dislodgment of the stent from the delivery balloon.
- Use only the appropriate balloon inflation media (see Operational Instructions - Section 14.3.3, Balloon Preparation). Do not use air or any gas medium to inflate the balloon.
- In the event the ION Stent is not deployed, do not use the product and contact your local Boston Scientific Representative for return information.

6.11 Stent Placement

Preparation

- Do not prepare or pre-inflate balloon prior to stent deployment other than as directed. Use the balloon purging technique described in Operational Instructions - Section 14.3.3 Balloon Preparation.
- If unusual resistance is felt at any time during lesion access before stent implantation, the stent system and the guide catheter should be removed as a single unit (See Precautions - Section 6.12, Stent System Removal).
- An unexpanded stent should be introduced into the coronary arteries one time only. An unexpanded stent should not be subsequently moved in and out through the distal end of the guide catheter as stent or coating damage or stent dislodgment from the balloon may occur.

Placement

- The vessel should be pre-dilated with an appropriate sized balloon. Failure to do so may increase the risk of placement difficulty and procedural complications.

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- Do not expand the stent if it is not properly positioned in the vessel (see Precautions - Section 6.12, Stent System Removal).
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on product label (see Table 14.5.1. Typical **ION™ Stent System compliance**). ' of pressures higher than specified on product label may :lt in a ruptured balloon and potential intimal damage .d dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.
- Placement of the stent has the potential to compromise side branch patency.
- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stented portion, and may cause acute closure of the vessel requiring additional intervention (e.g. CABG, further dilation, placement of additional stents, or other).
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the more proximal lesion(s). Stenting in this order alleviates the need to cross the proximal stent in placement of the distal stent and reduces the chances of dislodging the proximal stent.

6.12 Stent System Removal

- If unusual resistance is felt at any time during lesion access before stent implantation, the stent system and the guide catheter should be removed as a single unit.
- Do not attempt to pull an unexpanded stent back into the guide catheter, as stent or coating damage or stent dislodgment from the balloon may occur.
- Stent retrieval methods (use of additional wires, snares and/ or forceps) may result in additional trauma to the vascular site. Complications can include bleeding, hematoma, or pseudoaneurysm.

  When removing the entire stent system and guide catheter as a single unit (NOTE: The following steps should be executed under direct visualization using fluoroscopy):
- Following stent placement, confirm complete balloon deflation (See Table 6.1 System Deflation Time Specifications). If greater than usual resistance is felt during delivery system withdrawal, pay particular attention to guide catheter :tion. In some cases it may be necessary to pull back :tly on the guide catheter in order to prevent deep :ting (unplanned advancement) of the guide catheter and subsequent vessel damage. In cases where unplanned guide catheter movement has occurred, angiographic assessment of the coronary tree should be undertaken to ensure that there is no damage to the coronary vasculature.
- Maintain guidewire placement across the lesion during the entire removal process.
- Carefully pull back the stent system until the proximal balloon marker of the stent system is just distal to the guide catheter distal tip.
- The stent system and the guide catheter should be pulled back until the tip of the guide catheter is just distal to the arterial sheath, allowing the guide catheter to straighten. Carefully retract the stent system into the guide catheter and remove the stent system and the guide catheter from the patient as a single unit while leaving the guidewire across the lesion.

Failure to follow these steps, and/or applying excessive force to the stent system, can potentially result in stent or coating damage, stent dislodgment from the balloon, and/or damage to the delivery system.

Table 6.1 System Deflation Time Specifications (seconds)

Balloon Length/ Diameter	8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm	38 mm
2.25 mm	≤ 16			≤ 16		≤ 16		N/A
2.50 mm								
2.75 mm						≤ 21		≤ 30
3.00 mm								
mm				≤ 21				
mm								

6.13 Post-Procedure

- Care must be exercised when crossing a newly deployed stent with any wire, catheter or ancillary device to avoid disrupting the stent placement, apposition, and/or coating.
- In the PERSEUS Clinical Program, which evaluated the ION Stent System, clopidogrel or ticlopidine was administered pre-procedure and for a period of 6 months post-procedure and for 12 months in patients who were not at high risk of bleeding. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. See Section 10 – Clinical Studies, for more specific information.
- If the patient requires imaging, see Precautions – Section 6.9, Magnetic Resonance Imaging (MRI).

7 DRUG INFORMATION

7.1 Mechanism of Action

The mechanism (or mechanisms) by which an ION Stent affects neointimal production as seen in clinical studies has not been fully established. Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

7.2 Pharmacokinetics

Given that the drug/polymer coating formulation of the ION Stent is identical to that of the TAXUS Express Stent and the TAXUS Liberté Stent, the evaluation of the TAXUS Express Stent and the TAXUS Liberté Stent is applicable. In the clinical studies TAXUS I, II, and III (which evaluated the TAXUS Express Stent), no paclitaxel levels were detected after stent implantation using an analytical method with a lower limit of quantification (LLOQ) of 10 ng/ml. These findings were confirmed in preclinical studies using multiple stents with total loaded doses above the clinically available stent system and an assay with an LLOQ of 0.03 ng/ml. Hence, in the absence of systemically detectable levels, standard pharmacokinetic parameters were not established.

7.3 Drug Interactions

Paclitaxel is metabolized in the liver via CYP2C8 to 6-alphahydroxypaclitaxel and via CYP3A4 to 3'-p-hydroxypaclitaxel and 6-alpha, 3'-p-dihydroxypaclitaxel. Paclitaxel is a substrate of P-glycoprotein. Because metabolism appears to play an important role in the elimination of paclitaxel, agents that could compete with or inhibit the CYP2C8 and CYP3A4 isoenzymes may increase paclitaxel plasma levels. Potential drug interactions may occur with any drug that affects these isoenzymes.

Formal drug interaction studies have not been conducted with the ION Stent. Consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place an ION Stent 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 that has recently received an ION Stent.

7.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicology

No long-term studies in animals have been performed to evaluate the carcinogenic potential of paclitaxel. Paclitaxel interacts with microtubules; this is the major mechanism by which it inhibits cell growth. One consequence is the loss of whole chromosomes via interactions with spindle microtubules during cell division. As such, Paclitaxel is defined as an aneugen (agent causing an alteration in chromosome number). This indirect action is consistent with positive responses in in vitro and in vivo micronucleus genotoxicity assays, which detect DNA fragments. Positive results have also been reported for chromosomal aberrations in primary human lymphocytes. It is not known whether paclitaxel has a separate direct action on DNA in the generation of DNA strand breaks or fragments. It is negative in assays for gene mutation, including salmonella and CHO/HPRT. Paclitaxel administered via IV prior to and during mating produced impairment of fertility in male and female rats at doses > 1 mg/kg (approximately 39 times the dose provided by the largest ION Stent coated with 247 µg paclitaxel adjusted for body surface area).

7.5 Pregnancy

Pregnancy Category C: There are no adequate and well controlled studies in pregnant women of paclitaxel or ION Stents. Studies performed in rats and rabbits receiving IV paclitaxel during organogenesis revealed evidence of maternal toxicity, embryotoxicity, and fetotoxicity at dosages of 1 and 3 mg/kg, respectively (approximately 39 and 236 times the dose provided by the largest ION Stent coated with 247 µg paclitaxel adjusted for body surface area). The drug resulted in increased resorptions and increased fetal deaths. No teratogenicity was observed in gravid rats receiving daily IV paclitaxel doses of 1 mg/kg (approximately 39 times the dose provided by the largest ION Stent coated with 247 µg paclitaxel adjusted for body surface area). ION Stents should be used in pregnant women only if the potential benefit justifies the potential risk. Because some paclitaxel remains on the stent indefinitely, use of the ION Stent in women who are of childbearing potential should be given careful consideration.

7.6 Lactation

It is not known whether paclitaxel is distributed in human milk. However, in lactating rats given radio labeled paclitaxel, levels of radioactivity in plasma and milk were similar. Mothers should be advised of the potential for serious adverse reactions to paclitaxel in nursing infants.

Prior to implantation of an ION Stent, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

8 OVERVIEW OF CLINICAL STUDIES

The PERSEUS Clinical Trial Program[1] evaluates the ION Stent for the treatment of single, *de novo* atherosclerotic lesions in 2 parallel studies, PERSEUS Workhorse (WH) and PERSEUS Small Vessel (SV). This overview includes a summary of each trial design as well as data generated from each trial. A summary of the PERSEUS WH and SV trial designs is presented in Table 8.1.

8.1 PERSEUS Workhorse

The PERSEUS Workhorse (WH) study is a prospective, randomized, controlled, single-blind, non-inferiority trial to evaluate the safety and efficacy of the 1 µg/mm² (loaded drug/ stent surface area) ION Stent in the treatment of *de novo* coronary lesions. Subjects with *de novo* target lesion length ≤ 28 mm and target vessel diameter ≥ 2.75 mm to ≤ 4.0 mm were considered for enrollment. The trial employs a 3:1 randomization to the ION or the TAXUS Express Paclitaxel-Eluting Stent respectively. The TAXUS Express Stent is an earlier generation stent with the same drug/polymer coating formulation as the ION Stent System.

The primary endpoint is the rate of target lesion failure (TLF; including any ischemia-driven revascularization of the target lesion [TLR], myocardial infarction [MI; Q-wave and non-Q-wave] related to the target vessel, or cardiac death related to the target vessel) at 12 months post-index procedure, testing non-inferiority of the ION Stent relative to the TAXUS Express Paclitaxel-Eluting Stent control. In-segment percent diameter stenosis at 9 months post-index procedure as measured by quantitative coronary angiography (QCA) is the secondary endpoint.

Enrollment of 1264 subjects was planned; 1262 (942 ION Stent and 320 TAXUS Express Stent) were enrolled and randomized at 90 sites. A total of 330 subjects were randomly assigned to protocol-mandated 9-month angiographic follow-up (angiographic subset). The protocol mandated antiplatelet therapy compliance in accordance with the ACC/AHA/SCAI Guidelines for PCI.[2]

The study is now considered complete with regard to the 12-month primary endpoint. Additional follow-up is ongoing to 5 years.

8.2 PERSEUS Small Vessel

The PERSEUS Small Vessel (SV) study is a prospective, single-arm, superiority trial to evaluate the safety and efficacy of the 1 µg/mm² (loaded drug/stent surface area) 2.25 mm and 2.5 mm ION Stents in the treatment of *de novo* coronary lesions in small vessels. Subjects with *de novo* target lesion length ≤ 20 mm and target vessel diameter ≥ 2.25 mm to < 2.75 mm in a native coronary artery were considered for enrollment. The trial compares the ION Stent to a matched bare metal (Express Stent) historical control group comprised of subjects with reference vessel diameter (RVD) ≥ 2.25 to < 2.75 mm and lesion length ≤ 20 mm from the TAXUS V trial.

All subjects in PERSEUS SV were required to undergo a 9-month angiographic assessment. The primary endpoint is in-stent late loss by quantitative coronary angiography (QCA) on 9-month follow-up (ION Stent compared to bare metal Express Stent) and the secondary endpoint is TLF at 12 months (ION Stent compared to a performance goal based on TAXUS Express Stent results from the TAXUS IV and TAXUS V trials).

A total of 224 patients were enrolled at 28 sites. The control group consisted of 125 matched bare metal Express Stent subjects from the TAXUS V trial, including 108 with 9-month QCA follow-up. The protocol mandated antiplatelet therapy compliance in accordance with the ACC/AHA/SCAI Guidelines for PCI.[2]

The study is now considered complete with regard to the primary endpoint. Additional follow-up is ongoing to 5 years.

Table 8.1. Comparison of PERSEUS Clinical Studies

	PERSEUS Workhorse	PERSEUS Small Vessel
Purpose	To evaluate the safety and effectiveness in workhorse lesions	To evaluate the safety and effectiveness in small vessel lesions
Design	Prospective, multicenter, randomized, single-blind, non-inferiority to PES	Prospective, multicenter, single-arm, open-label superiority to BMS
Primary Endpoint	12-month TLF	9-month in-stent late loss
Number of Subjects (ITT)	Total: 1264 planned; 1262 enrolled and randomized ION™ Stent: 942 TAXUS Express Stent: 320	Total: 224 ION Stent: 224 BMS Control Group: 125
Polymer	Translute™ Polymer	
PTx Dose Density	1 μg/mm²	
Lesion Criteria: Vessel Diameter (by visual estimate)	≥ 2.75 mm to ≤ 4.00 mm	≥ 2.25 mm to < 2.75 mm
Lesion Criteria: Lesion Length (by visual estimate)	≤ 28 mm	≤ 20 mm
Number of stents	Single	
Stent Matrix	2.75-4.0 mm diameter 8, 12, 16, 20, 24, 28, 32 mm length	2.25-2.50 mm diameter 8, 12, 16, 20, 24 mm length
Post-Procedure Antiplatelet Therapy	Clopidogrel or ticlopidine: at least 6 months, ideally for 12 months in patients who are not at high risk for bleeding. ASA: indefinitely	
Follow-Up	Clinical: 30 day, 9 month, 1 year, 18 month, annually 2-5 years Angiographic (330 subject subset): 9 month	Clinical: 30 day, 9 month, 1 year, 18 month, annually 2-5 years Angiographic (all): 9 month

Abbreviations: ASA=aspirin; BMS=bare metal stent; ITT=intent-to-treat; PES=paclitaxel-eluting stent; PTx=paclitaxel; TLF=target lesion failure

9 ADVERSE EVENTS

9.1 Observed Adverse Events

Observed adverse event experience comes from two studies which evaluated the ION Stent System: PERSEUS Workhorse and PERSEUS Small Vessel. Principal adverse events for these trials are shown in Table 9.1.1.

Table 9.1.1. PERSEUS Workhorse and PERSEUS Small Vessel Major Adverse Cardiac Events (MACE) and Stent Thrombosis From Post-Procedure to 1 Year Follow-Up

	PERSEUS Workhorse to 1 Year		PERSEUS Small Vessel to 1 Year	
	ION Stent (N=942)	TAXUS Express Stent[2] (N=320)	ION Stent (N=224)	Express Stent[2] (N=125)
Hospital MACE	1.9% (18/942)	2.5% (8/320)	0.0% (0/224)	1.6% (2/125)
30-Day MACE	2.2% (21/939)	3.1% (10/319)	0.9% (2/221)	2.4% (3/124)
9-Month MACE	5.6% (52/932)	6.3% (20/317)	7.8% (17/218)	14.6% (18/123)
Cardiac Death	0.3% (3/932)	0.3% (1/317)	0.9% (2/218)	0.8% (1/123)
MI	2.0% (19/932)	2.8% (9/317)	0.9% (2/218)	2.4% (3/123)
Q-Wave MI	0.4% (4/932)	0.0% (0/317)	0.5% (1/218)	0.0% (0/123)
Non-Q-Wave MI	1.6% (15/932)	2.8% (9/317)	0.5% (1/218)	2.4% (3/123)
TVR	4.0% (37/932)	4.4% (14/317)	6.9% (15/218)	12.2% (15/123)
TLR	2.6% (24/932)	3.5% (11/317)	3.7% (8/218)	10.6% (13/123)
Non-TLR	1.9% (18/932)	1.3% (4/317)	5.0% (11/218)	4.1% (5/123)
1-Year MACE	7.4% (68/922)	7.7% (24/313)	12.4% (27/218)	27.3% (33/121)
Cardiac Death	0.5% (5/922)	0.3% (1/313)	1.4% (3/218)	0.8% (1/121)
MI	2.2% (20/922)	2.9% (9/313)	0.9% (2/218)	2.5% (3/121)
Q-Wave MI	0.5% (5/922)	0.0% (0/313)	0.5% (1/218)	0.0% (0/121)
Non-Q-Wave MI	1.6% (15/922)	2.9% (9/313)	0.5% (1/218)	2.5% (3/121)
TVR	5.6% (52/922)	5.8% (18/313)	11.5% (25/218)	24.8% (30/121)
TLR	3.8% (35/922)	4.5% (14/313)	6.0% (13/218)	20.7% (25/121)
Non-TLR	2.5% (23/922)	1.9% (6/313)	7.8% (17/218)	7.4% (9/121)
1-Year ARC Stent Thrombosis				
Definite or Probable	0.4% (4/918)	0.3% (1/313)	0.5% (1/215)	0.8% (1/119)
Definite	0.3% (3/918)	0.3% (1/313)	0.5% (1/215)	0.8% (1/119)
Probable	0.1% (1/918)	0.0% (0/313)	0.0% (0/215)	0.0% (0/119)

Abbreviations: ARC=Academic Research Consortium; BMS=bare metal stent; DES=drug-eluting stent; MACE=major adverse cardiac events (cardiac death, Q- or non-Q-wave MI, TVR); MI=myocardial infarction; TLR=target lesion revascularization; TVR=target vessel revascularization.
[1] DES Control
[2] BMS Control

Angiographic core laboratory review of all available angiograms in the PERSEUS Clinical Trials revealed a total of 3 stent fractures [illegible] stent fractures (Type 3[1]) that were seen on angiograms performed at 286 and 259 days post-stent implantation and 1 Taxus Express stent fracture (Type 4[1]) noted on an angiogram performed 861 days post-stent implantation. Only the fracture that occurred with the Taxus Express stent was associated with a major adverse cardiovascular event (a TLR).

REFERENCE

[1] From Table 1 in Popma, JJ, Tiroch, K, Almonacid, A, Cohen, SA, Kandzari, DE, and Leon, MB. A Qualitative and Quantitative Angiographic Analysis of Stent Fracture Late Following Sirolimus-Eluting Stent Implantation. Am J Cardiol 103: 923–929, 2009.

9.2 Potential Adverse Events

Potential adverse events (in alphabetical order) which may be associated with the use of a coronary stent in native coronary arteries include but are not limited to:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction to anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation and ventricular tachycardia
- Arteriovenous fistula
- Cardiac tamponade
- Cardiogenic shock/pulmonary edema
- Coronary aneurysm
- Death
- Dissection
- Emboli, distal (air, tissue or thrombotic material or material from devices(s) used in the procedure)
- Heart failure
- Hematoma
- Hemorrhage, required transfusion
- Hypotension/hypertension
- Infection, local or systemic
- Ischemia, myocardial
- Pain, access site
- Perforation or rupture of coronary artery
- Pericardial effusion
- Pseudoaneurysm, femoral
- Renal failure
- Respiratory failure
- Restenosis of stented segment
- Stent embolization or migration
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident /TIA
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma requiring surgical repair or reintervention

Potential adverse events not captured above, that may be unique to the paclitaxel drug coating:

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or the polymer stent coating (or its individual components)
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia/arthralgia
- Peripheral neuropathy

There may be other potential adverse events that are unforeseen at this time.

10 CLINICAL STUDIES

10.1 PERSEUS Workhorse

Primary Objective: The primary objective of the PERSEUS WH study was to evaluate the safety and efficacy of the ION™ Paclitaxel-Eluting Platinum Chromium Coronary Stent System for the treatment of *de novo* atherosclerotic lesions of up to 28 mm in length (by visual estimate) in native coronary arteries of 2.75 mm to 4.0 mm diameter (by visual estimate) compared to the TAXUS Express Stent control. The TAXUS Express Stent is an earlier generation stent with the same drug/polymer coating formulation as the ION Stent System.

Design: PERSEUS Workhorse is a prospective, randomized, controlled, single-blind, non-inferiority trial which employs a 3:1 randomization to the ION or the TAXUS Express Paclitaxel-Eluting Stent respectively. Eligible patients were those ≥ 18 years old with documented stable angina pectoris, unstable angina pectoris, or documented silent ischemia and left ventricular ejection fraction (LVEF) ≥ 30%. *De novo* target lesions in a native coronary artery with diameter stenosis ≥ 50%, reference vessel diameter ≥ 2.75 mm to ≤ 4.0 mm, and cumulative lesion length ≤ 28 mm coverable by a single study stent were eligible. Multiple stenting was allowed for bail-out only. The protocol mandated antiplatelet therapy compliance in accordance with the ACC/AHA/SCAI Guidelines for PCI.[2]

The primary endpoint is the rate of target lesion failure (TLF; including any ischemia-driven revascularization of the target lesion [TLR], myocardial infarction [MI; Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) at 12 months post-index procedure, testing non-inferiority of the ION Stent relative to the TAXUS Express Paclitaxel-Eluting Stent control. In-segment percent diameter stenosis at 9 months post-index procedure as measured by quantitative coronary angiography (QCA) is the secondary endpoint.

Enrollment of 1264 subjects was planned. A total of 1262 (942 ION Stent and 320 TAXUS Express Stent) were enrolled and randomized at 90 centers. Of the 1262 subjects included in the intent-to-treat analysis set, a total of 1235 subjects (922 ION Stent and 313 TAXUS Express Stent) were evaluable for the 12-month primary endpoint. A total of 330 subjects (256 ION Stent, 74 TAXUS Express Stent) were randomly assigned to protocol-mandated 9-month angiographic follow-up (angiographic subset). Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and the areas immediately 5 mm proximal and distal from the stent margins (analysis segment).

Follow-up included clinical assessments at 30 days, 9, 12 and 18 months, and 2, 3, 4 and 5 years post index procedure. After the 12-month follow-up, the study population was reduced to a pre-specified cohort (Safety Population), which consists of all patients who received a study stent (ION Stent or TAXUS Express Stent). The study is now considered complete with regard to the 12-month primary endpoint.

Both the primary and secondary endpoints were analyzed under a Bayesian framework. Bayesian analyses can be interpreted in a more intuitive way than conventional frequentist analyses through the posterior distributions they produce. These posterior distributions give the probability that a parameter of interest (e.g. the difference in the rate of TLF across treatment groups) lies within a certain range, given the data observed. Therefore Bayesian methods can provide a posterior probability that the non-inferiority hypothesis is true given the data observed, whereas a frequentist P value provides the probability of observing data as or more extreme than that observed assuming the non-inferiority hypothesis is false.

Results are presented below (Tables 10.1.1 - 10.1.6, Figure 10.1.1 and Figure 10.1.2).

Demographics: Patients were well-matched for baseline demographics. There were no significant differences between the randomized treatment groups with the exception of slightly lower age in the ION Stent group compared to the TAXUS Express Stent control (62.2±9.6 versus 63.5±9.5, P=0.03). Approximately 71% of patients in the ION Stent group and 69% of patients in the TAXUS Express Stent group were male. Approximately 93% of patients in both the ION and TAXUS Express Stent groups were Caucasian, and 25% were medically treated diabetics.

Baseline lesion characteristics: Reference vessel diameter was 2.78±0.48 mm and 2.75±0.47 mm in the ION Stent and TAXUS Express Stent groups, respectively, with baseline lesion length of 14.2±6.1 mm and 14.1±5.8 mm, respectively.

12-Month Clinical and 9-Month Angiographic Outcomes

Table 10.1.1. PERSEUS Workhorse Clinical Results

	1-year (ITT population)	
	ION Stent[1] (N=942)	TAXUS Express Stent[1] (N=320)
EFFICACY		
TVR, Overall	5.6% (52/922)	5.8% (18/313)
TLR, Overall	3.8% (35/922)	4.5% (14/313)
TLR, PCI	3.6% (33/922)	4.2% (13/313)
TLR, CABG	0.3% (3/922)	0.6% (2/313)
Non-TLR, Overall	2.5% (23/922)	1.9% (6/313)
Non-TLR, PCI	2.3% (21/922)	1.6% (5/313)
Non-TLR, CABG	0.3% (3/922)	1.0% (3/313)
SAFETY		
Total Death	0.7% (6/922)	0.6% (2/314)
Cardiac Death or MI	2.5% (23/922)	2.9% (9/313)
Cardiac Death	0.5% (5/922)	0.3% (1/313)
MI	2.2% (20/922)	2.9% (9/313)
Q-wave MI	0.5% (5/922)	0.0% (0/313)
Non-Q-wave MI[2]	1.6% (15/922)	2.9% (9/313)
ARC Stent Thrombosis		
Definite or Probable	0.4% (4/918)	0.3% (1/313)
Definite	0.3% (3/918)	0.3% (1/313)
Probable	0.1% (1/918)	0.0% (0/313)

[1] DES Control
[2] Timing of non-Q-wave MI: 15/15 ION events and 8/9 TAXUS Express events occurred peri-procedurally.
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Primary Endpoint (12-Month TLF): The primary endpoint was met: There is a 99.96% Bayesian posterior probability that the ION Stent is non-inferior to TAXUS Express Stent (given the data observed), demonstrating non-inferiority of the ION Stent versus the TAXUS Express Stent.

Table 10.1.2. PERSEUS Workhorse Primary Endpoint

12-Month Target Lesion Failure (TLF)[2]	ION Stent	TAXUS Express Stent	Difference		Δ	Posterior Probability of NI[3]
	Posterior Mean (SD)	Posterior Mean (SD)	Posterior Mean (SD)	95% CP		
Per Protocol[1]	5.568% (0.0076)	6.138% (0.0136)	-0.570% (0.0155)	1.85%	4.1%	0.9996

[1] Primary analysis for assessing hypothesis of non-inferiority and study success criterion. For per protocol analyses, only ITT PERSEUS Workhorse trial subjects who had the randomly assigned study stent implanted in the target coronary artery were included.
[2] 1-Sided 95% posterior credible interval, based off the 95th percentile of the posterior distribution.
[3] Posterior probability that the difference in the rate of 12-month TLF between ION Stent and TAXUS Express Stent is less than the pre-specified margin of 4.1%, given the data.
12-Month TLF: the proportion of patients who experience a TLF up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Secondary Endpoint (9-Month %DS): The secondary endpoint was met: There is a 99.70% Bayesian posterior probability that the ION Stent is non-inferior to the TAXUS Express Stent (given the data observed), demonstrating non-inferiority of the ION Stent versus the TAXUS Express Stent.

Table 10.1.3. PERSEUS Workhorse Secondary Endpoint

Ln (9-Month In-Segment %DS)	ION Stent	TAXUS Express Stent	Difference		Δ	Posterior Probability of NI[3]
	Posterior Mean (SD)	Posterior Mean (SD)	Posterior Mean (SD)	95% CP[2]		
Per Protocol[1]	3.087 (0.0374)	3.117 (0.0736)	-0.0294 (0.08253)	.0.1078	0.20	0.9970

[1] Primary analysis for assessing hypothesis of non-inferiority. For per protocol analyses, only ITT PERSEUS Workhorse trial subjects who had the randomly assigned study stent implanted in the target coronary artery were included.
[2] 1-Sided 95% posterior credible interval, based off the 95th percentile of the posterior distribution.
[3] Posterior probability that the difference in mean ln (9-month %DS) between the ION Stent and the TAXUS Express Stent is less than the pre-specified margin of 0.20, given the data.
The secondary endpoint is 9-month in-segment %DS. For the secondary endpoint, a natural log (ln) transformation was used to improve the normality of the distribution. Analyses are performed on the transformed data.

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Table 10.1.4. PERSEUS Workhorse Angiographic Results

Angiographic Outcomes[1]	ION™ Stent (N=228)	TAXUS Express Stent[2] (N=61)
MLD (mm), In-stent		
Post-Procedure	2.68±0.39 (228)	2.54±0.36 (61)
1onth	2.34±0.67 (228)	2.28±0.64 (61)
(mm), Analysis Segment		
Post-Procedure	2.25±0.49 (228)	2.16±0.37 (61)
9-Month	2.08±0.63 (228)	2.00±0.56 (61)
Acute Gain (mm), In-stent	1.93±0.41 (228)	1.83±0.40 (61)
Acute Gain, Analysis Segment (mm)	1.51±0.48 (228)	1.45±0.40 (61)
% DS, In-stent		
Post-Procedure	4.1±10.13 (228)	5.64±8.05 (61)
9-Month	16.37±20.86 (228)	16.02±20.61 (61)
% DS, Analysis Segment		
Post-Procedure	20.21±9.71 (228)	19.87±7.57 (61)
9-Month	26.10±17.71 (228)	26.37±17.47 (61)
Late Loss, In-stent (mm)	0.34±0.55 (228)	0.26±0.52 (61)
Late Loss, Analysis Segment (mm)	0.17±0.48 (228)	0.16±0.45 (61)
Binary Restenosis		
In-stent restenosis	7.9% (18/228)	6.6% (4/61)
Analysis segment restenosis	8.8% (20/228)	9.8% (6/61)

[1] Includes all patients in the angiographic subset with paired lesion data.
[2] DES Control
Abbreviations: DES=drug-eluting stent; DS=diameter stenosis; MLD=minumum lumen diameter.

Table 10.1.5. PERSEUS Workhorse Stent Thrombosis

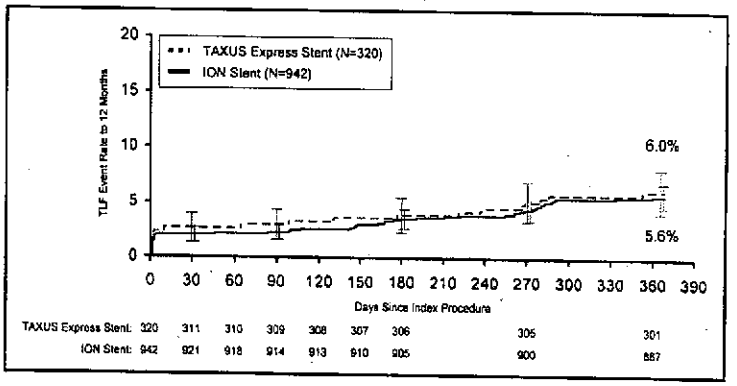
Intent-to-Treat Population	ION Stent (N=942)	TAXUS Express Stent[2] (N=320)
Protocol Defined Stent Thrombosis[1]		
Cumulative through 1 year	0.4% (4/918)	0.3% (1/313)
Acute ST (≤ 24 hrs)	0.2% (2/942)	0.3% (1/320)
)acute ST (24 hrs and ≤ 30 days)	0.0% (0/939)	0.0% (0/319)
Late ST (> 30 days and ≤ 12 months)	0.2% (2/936)	0.0% (0/317)
ARC Definite & Probable Stent Thrombosis[3]		
Cumulative through 1 year	0.4% (4/918)	0.3% (1/313)
Acute ST (≤ 24 hrs)	0.2% (2/942)	0.3% (1/320)
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/939)	0.0% (0/319)
Late ST (> 30 days and ≤ 12 months)	0.2% (2/936)	0.0% (0/317)

To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 37-365 days inclusive) or they had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).
[1] Per protocol, stent thrombosis is defined as the occurrence of any of the following:
1. Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis:
   a. Angiographic documentation of a complete occlusion (TIMI flow 0 or 1) of a previously successfully treated artery (TIMI flow 2 to 3 immediately after stent placement and diameter stenosis ≤ 30%) and/or
   b. Angiographic documentation of a flow-limiting thrombus within or adjacent to a previously successfully treated lesion.
2. Acute MI of the distribution of the treated vessel.
3. Death within the first 30 days (without other obvious cause) is considered a surrogate for stent thrombosis when angiography is not available.

[3] Academic Research Consortium (ARC) stent thrombosis is defined as follows[5]:
1. Definite ST is considered to have occurred after intracoronary stenting by either angiographic or pathologic confirmation of stent thrombosis.
2. Probable ST is considered to have occurred after intracoronary stenting in the following cases:
   a. Any unexplained death within the first 30 days following stent implantation.
   b. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.

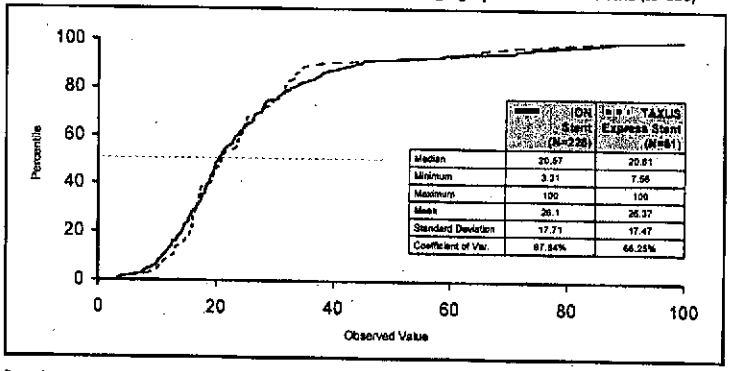
[2] DES Control
Numbers are % (Count/Sample Size).
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

Figure 10.1.1. PERSEUS Workhorse Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, Event Rate ± 1.5 SE, All Patients (N=1262)



	Event Rate	Event Free
ION Stent	5.6%	94.4%
TAXUS Express Stent DES Control	6.0%	94.0%

Figure 10.1.2. PERSEUS Workhorse Cumulative Frequency Distribution of 9-Month In-Segment Percent Diameter Stenosis by QCA, Intent-to-Treat, All Angiographic Subset Patients (N=330)



Results in patients with and without diabetes: Patients with diabetes mellitus represent a high-risk group for adverse events following percutaneous coronary intervention. Table 10.1.6 shows 1-year outcomes in patients with and without medically treated diabetes (defined as treatment with oral hypoglycemic agents or insulin at enrollment). While the PERSEUS WH study randomization was stratified for diabetic status, this trial was not adequately powered to study safety or effectiveness of the TAXUS Express Stent versus the ION Stent in patients with or without diabetes and was not designed to specifically support an approval for use in diabetic patients. These exploratory analyses suggest that in patients treated with the ION Stent, 1-year TLR rates were 4.9% in diabetic and 3.4% in non-diabetic patients.

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Table 10.1.6. PERSEUS Workhorse Clinical Results in Patients with and Without Medically Treated Diabetes

	1-year (ITT Population)	
	ION™ Stent Patients With Medically Treated Diabetes (N=232)	ION Stent Patients Without Medically Treated Diabetes (N=710)
EFFICACY		
TVR, Overall	7.6% (17/223)	5.0% (35/699)
TLR, Overall	4.9% (11/223)	3.4% (24/699)
TLR, PCI	4.5% (10/223)	3.3% (23/699)
TLR, CABG	0.4% (1/223)	0.3% (2/699)
Non-TLR, Overall	3.6% (8/223)	2.1% (15/699)
Non-TLR, PCI	2.7% (6/223)	2.1% (15/699)
Non-TLR, CABG	0.9% (2/223)	0.1% (1/699)
SAFETY		
Total Death	1.4% (3/222)	0.4% (3/700)
Cardiac Death or MI	3.1% (7/223)	2.3% (16/699)
Cardiac Death	1.3% (3/223)	0.3% (2/699)
MI	2.2% (5/223)	2.1% (15/699)
Q-wave MI	0.9% (2/223)	0.4% (3/699)
Non-Q-wave MI	1.3% (3/223)	1.7% (12/699)
ARC Stent Thrombosis		
Definite or Probable	0.5% (1/220)	0.4% (3/698)
Definite	0.0% (0/220)	0.4% (3/698)
Probable	0.5% (1/220)	0.0% (0/698)

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.
[1] DES Control

10.2 PERSEUS Small Vessel Clinical Trial

Primary Objective: The primary objective of the PERSEUS SV study was to evaluate the safety and efficacy of the ION Paclitaxel-Eluting Platinum Chromium Coronary Stent System for the treatment of *de novo* atherosclerotic lesions of ≤ 20 mm in length in native coronary arteries with visual RVD ≥ 2.25 mm to < 2.75 mm diameter.

PERSEUS Small Vessel is a prospective, single-arm, superiority trial that compares the ION to a matched bare metal (Express Stent) historical control group comprised of subjects with reference vessel diameter (RVD) ≥ 2.25 mm to < 2.75 mm and lesion length ≤ 20 mm garnered from the TAXUS V trial. Eligible patients were those ≥ 18 years old with documented stable angina pectoris, unstable angina pectoris, or documented silent ischemia and left ventricular ejection fraction (LVEF) ≥ 30%. *De novo* target lesions in a native coronary artery with diameter stenosis ≥ 50%, reference vessel diameter ≥ 2.25 mm to < 2.75 mm, and cumulative lesion length ≤ 20 mm coverable by a single study stent were eligible. Multiple stenting was allowed for bail-out only. The protocol mandated antiplatelet therapy compliance in accordance with the ACC/AHA/SCAI Guidelines for PCI.[2]

The primary endpoint is in-stent late loss by QCA on 9-month follow-up (ION Stent compared to bare metal Express Stent) and the secondary endpoint is target lesion failure (TLF; including any ischemia-driven revascularization of the target lesion [TLR], myocardial infarction [MI; Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) at 12 months (ION Stent compared to a performance goal based on TAXUS Express Stent results from the TAXUS IV and TAXUS V trials). (The TAXUS Express Stent is an earlier generation stent with the same drug/polymer coating formulation as the ION Stent System.) The study success criteria are met when both the primary and secondary endpoints are met, that is, when mean in-stent late loss at 9 months post-index procedure for the ION Stent group is shown to be superior to that of the historical control and the 12-month TLF rate for the ION Stent group is shown to be less than the 19.5% performance goal, which is based on TAXUS Express Stent results in lesion-matched patients in TAXUS IV and TAXUS V.

Enrollment of 224 subjects was planned. A total of 224 subjects were enrolled at 28 centers. Of the 224 subjects included in the intent-to-treat analysis set, a total of 197 subjects were evaluable for the 9-month primary endpoint of in-stent late loss. The control group consisted of 125 matched bare metal Express subjects from the TAXUS V trial, including 108 with 9-month QCA follow-up.

Follow-up included clinical assessments at 30 days, 9, 12 and 18 months, and 2, 3, 4 and 5 years post index procedure. All 224 enrolled subjects were required to undergo protocol-mandated 9-month angiographic follow-up. Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and the areas immediately 5 mm proximal and distal from the stent margins (analysis segment). After the 12-month follow-up, the study population was reduced to a pre-specified cohort (Safety Population), which consists of all subjects who received a study stent (ION Stent). The study is now considered complete with regard to the 9-month primary and 12-month secondary endpoints.

Results are presented below (Tables 10.2.1 - 10.2.6 and Figure 10.2.1).

raphics: The ION Stent group had a higher rate of prior congestive heart failure (8.1% versus previous smoking (48.6% versus 36.8%) and higher baseline ejection fraction (57.9±9.4 versus ±9.2) as compared with the historical BMS control group. The ION Stent group had lower rates of baseline unstable angina (20.1% versus 29.6%) and current smoking (13.6% versus 22.2%).

Baseline lesion characteristics: Differences in the ION Stent group compared to the historical BMS control group included shorter lesion length (11.7±5.1 versus 12.9±5.1), lower incidence of ACC/AHA Type B2/C lesions (58.0% versus 77.6%), and lower incidence of tortuosity (8.9% versus 18.4%). However, baseline RVD and MLD were lower in ION Stent subjects than in the BMS historical control (2.08±0.28 versus 2.19±0.35 for RVD and 0.55±0.23 versus 0.62±0.24 for MLD, respectively). These differences were not expected to affect outcomes variables, as propensity score adjustments showed no change in the outcome or conclusion of the trial.

12-Month Clinical and 9-Month Angiographic Results

Table 10.2.1 PERSEUS Small Vessel Clinical Results

	1 year (ITT population)	
	ION Stent (N=224)	Historical Control Express BMS (N=125)
EFFICACY		
TVR, Overall	11.5% (25/218)	24.8% (30/121)
TLR, Overall	6.0% (13/218)	20.7% (25/121)
TLR, PCI	5.5% (12/218)	19.0% (23/121)
TLR, CABG	0.5% (1/218)	1.7% (2/121)
Non-TLR, Overall	7.8% (17/218)	7.4% (9/121)
Non-TLR, PCI	7.3% (16/218)	6.6% (8/121)
Non-TLR, CABG	0.5% (1/218)	0.8% (1/121)
SAFETY		
Total Death	1.4% (3/218)	1.7% (2/121)
Cardiac Death or MI	2.3% (5/218)	3.3% (4/121)
Cardiac Death	1.4% (3/218)	0.8% (1/121)
MI	0.9% (2/218)	2.5% (3/121)
Q-wave MI	0.5% (1/218)	0.0% (0/121)
Non-Q-wave MI[1]	0.5% (1/218)	2.5% (3/121)
ARC Stent Thrombosis		
Definite or Probable	0.5% (1/215)	0.8% (1/119)
Definite	0.5% (1/215)	0.8% (1/119)
Probable	0.0% (0/215)	0.0% (0/119)

[1] Non-Q-wave MI timing: Events occurred at day 218 post-procedure in the ION Stent group and at days 0, 8, and 187 post-procedure in the historical BMS control group.
Abbreviations: ARC=Academic Research Consortium; BMS=bare metal stent; CABG=coronary artery bypass graft; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization;TVR=target vessel revascularization.
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

Table 10.2.2. PERSEUS Small Vessel Primary Endpoint

9-Month In-stent Late Loss	ION Stent (N=224)	Historical Control Express BMS[1] (N=125)	Difference (95% CI)	*P* Value
Intent-to-Treat[1]	0.38±0.51 (197) (-0.38, 2.28)	0.80±0.53 (108) (-0.15, 2.10)	-0.42 [-0.54, -0.30]	< 0.0001
Propensity score adjusted	0.37	0.81	-0.45[-0.59, -0.31]	< 0.0001

[1] Primary analysis set for assessing hypothesis of superiority and study success criterion.

Table 10.2.3. PERSEUS Small Vessel Secondary Endpoint

12-Month TLF	Performance Goal	ION Stent (N=224)	Upper 95% Confidence Limit	*P* Value
Intent-to-Treat[1]	19.5%	7.34% (16/218)	10.80%	< 0.0001

[1] Primary analysis set for assessing hypothesis of superiority and study success criterion.

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Table 10.2.4. PERSEUS Small Vessel Angiographic Results

Angiographic Outcomes[1]	ION™ Stent (N=197)	Historical Control Express BMS (N=108)
MLD (mm), In-stent		
Post-Procedure	2.11±0.21 (197)	2.09±0.30 (108)
Month	1.73±0.53 (197)	1.29±0.55 (108)
(mm), Analysis Segment		
Post-Procedure	1.70±0.29 (197)	1.76±0.38 (108)
9-Month	1.50±0.48 (197)	1.22±0.50 (108)
Acute Gain (mm), In-stent	1.57±0.27 (197)	1.47±0.33 (108)
Acute Gain, Analysis Segment (mm)	1.16±0.30 (197)	1.14±0.39 (108)
% DS, In-stent		
Post-Procedure	0.31±10.76 (197)	6.63±10.97 (108)
9-Month	18.48±23.31 (197)	40.72±23.64 (108)
% DS, Analysis Segment		
Post-Procedure	20.12±9.42 (197)	22.34±10.69 (108)
9-Month	29.82±19.82 (197)	43.85±21.44 (108)
Late Loss, In-stent (mm)	0.38±0.51 (197)	0.80±0.53 (108)
Late Loss, Analysis Segment (mm)	0.21±0.41 (197)	0.53±0.52 (108)
Binary Restenosis		
In-stent restenosis	11.7% (23/197)	34.3% (37/108)
Analysis segment restenosis	13.7% (27/197)	38.0% (41/108)

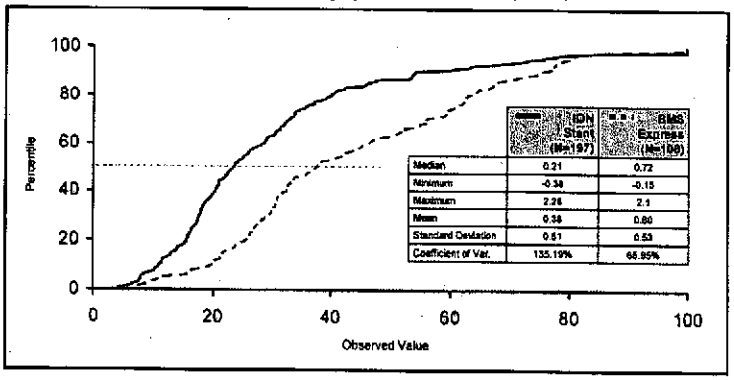
[1] Includes all patients with paired lesion data.
Abbreviations: BMS=bare metal stent; DS=diameter stenosis; MLD=minumum lumen diameter.

Table 10.2.5. PERSEUS Small Vessel Stent Thrombosis

Intent-to-Treat Population	ION Stent (N=224)	Historical Control Express BMS (N=125)
Protocol Defined Stent Thrombosis		
Cumulative through 1 year	0.5% (1/215)	0.8% (1/119)
Acute ST (≤ 24 hrs)	0.0% (0/224)	0.0% (0/125)
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/221)	0.8% (1/125)
ST 30 days and ≤ 12 months)	0.5% (1/217)	0.0% (0/124)
ARC Definite & Probable Stent Thrombosis		
Cumulative through 1 year	0.5% (1/215)	0.8% (1/119)
Acute ST (≤ 24 hrs)	0.0% (0/224)	0.0% (0/125)
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/221)	0.8% (1/125)
Late ST (> 30 days and ≤ 12 months)	0.5% (1/217)	0.0% (0/124)

See definitions provided with Table 10.1.5
Numbers are % (Count/Sample Size).
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Abbreviations: BMS=bare metal stents; ST=stent thrombosis.

Figure 10.2.1. PERSEUS Small Vessel Cumulative Frequency Distribution of 9-Month In-Stent Late Loss by QCA, Intent-to-Treat, All Angiographic Subset Patients (N=349)



Results in patients with and without diabetes: Table 10.2.6 shows 1-year outcomes in patients with and without medically treated diabetes (defined as treatment with oral hypoglycemic agents or insulin at enrollment). The PERSEUS SV study was not stratified for diabetic status, was not adequately powered to study safety or effectiveness of the BMS Express Stent versus the ION Stent in patients with or without diabetes, and was not designed to specifically support an approval for use in diabetic patients. These exploratory analyses suggest that in patients treated with the ION Stent, 1-year TLR rates were 6.2% in diabetic and 5.8% in non-diabetic patients, and lower compared to the historical BMS Express control.

Table 10.2.6. PERSEUS Small Vessel Clinical Results in Patients with and Without Medically Treated Diabetes

	1-year (ITT Population)	
	ION Stent Patients With Medically Treated Diabetes (N=82)	ION Stent Patients Without Medically Treated Diabetes (N=142)
EFFICACY		
TVR, Overall	9.9% (8/81)	12.4% (17/137)
TLR, Overall	6.2% (5/81)	5.8% (8/137)
TLR, PCI	6.2% (5/81)	5.1% (7/137)
TLR, CABG	0.0% (0/81)	0.7% (1/137)
Non-TLR, Overall	6.2% (5/81)	8.8% (12/137)
Non-TLR, PCI	6.2% (5/81)	8.0% (11/137)
Non-TLR, CABG	0.0% (0/81)	0.7% (1/137)
SAFETY		
Total Death	2.5% (2/81)	0.7% (1/137)
Cardiac Death or MI	3.7% (3/81)	1.5% (2/137)
Cardiac Death	2.5% (2/81)	0.7% (1/137)
MI	1.2% (1/81)	0.7% (1/137)
Q-wave MI	1.2% (1/81)	0.0% (0/137)
Non-Q-wave MI	0.0% (0/81)	0.7% (1/137)
ARC Stent Thrombosis		
Definite or Probable	1.3% (1/79)	0.0% (0/136)
Definite	1.3% (1/79)	0.0% (0/136)
Probable	0.0% (0/79)	0.0% (0/136)

Abbreviations: ARC=Academic Research Consortium; BMS=bare metal stent; CABG=coronary artery bypass graft; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization;TVR=target vessel revascularization.
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

10.3 Prevalence of CAD and Outcome Differences by Gender and Race

In the United States, an estimated 17,600,000 adults age 20 and older (9.1% of men and 7.0% of women) suffer from coronary artery disease (CAD)[4].

Once diagnosed and treated, poorer revascularization outcomes have been reported in women due to smaller coronary arteries and increased baseline comorbidity including advanced age, diabetes, hypertension, and peripheral vascular disease compared with men.

Boston Scientific conducted a retrospective pooled analysis of patients enrolled in five randomized trials and two 'real world' registries to evaluate the influence of gender on long-term outcomes after percutaneous coronary intervention with the paclitaxel-eluting coronary stent. The proportion of women included in our studies is reflective of the 15-35% enrollment of women reported in percutaneous coronary intervention trials.

Despite significantly more adverse baseline risk factors in women, recent randomized trials of drug-eluting stents have demonstrated comparable safety and effectiveness outcomes in men and women. However, the influence of gender on long-term drug-eluting stent outcomes has not been fully elucidated.[5]

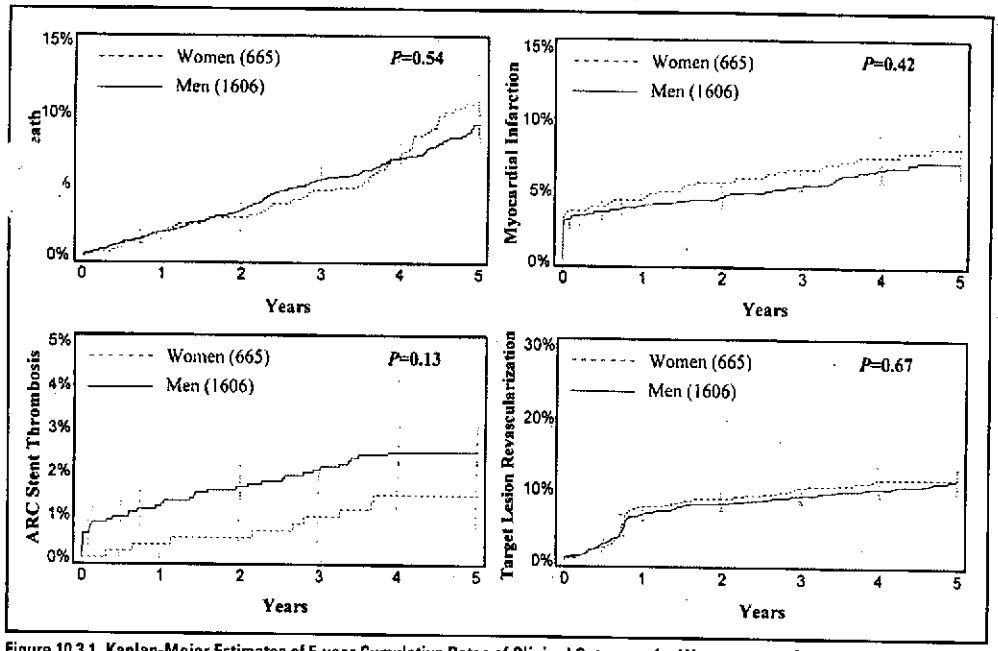


Figure 10.3.1 Kaplan-Meier Estimates of 5-year Cumulative Rates of Clinical Outcomes for Women versus Men for Patients Receiving Paclitaxel-eluting Stents in the Randomized Trials

Similarly, race-specific differences have also been reported in the diagnosis and treatment of CAD. Although differences in coronary anatomy do not solely explain racial difference in revascularization rates, several studies of clinically diverse persons undergoing coronary angiography have found less obstructive CAD in Black patients compared with clinically similar White patients.

Boston Scientific has also conducted a retrospective pooled analysis of patients enrolled in six trials to compare the long-term outcomes after percutaneous coronary intervention with the paclitaxel-eluting coronary stents in Black versus White patients. Of the 2,428 pooled patients 127 (5.2%) were Black.[5]

To evaluate for possible sex-based differences in outcome of treatment with the ION Stent, sex/gender-specific analyses were performed on safety and effectiveness endpoints. The results suggest that the general conclusions of the overall study regarding both safety and effectiveness can be generalized for males and females.

The PERSEUS WH study was not powered to study safety or effectiveness of the ION Stent versus the TAXUS Express Stent in sex-specific subgroups. PERSEUS WH primary and secondary endpoint data were assessed for differences between male and female subgroups, as well as for any interaction between treatment group and gender. These post hoc analyses suggest that in patients with the ION stent,12-month TLF rates were 7.0% in females and 5.1% in males, and 9-month %DS was 26.95±18.62 in females and 25.71±17.32 in males. Numerical differences were observed in the treatment effect (i.e., the difference between the ION Stent and TAXUS Express Stent), as shown in Table 10.3.1 below. No significant treatment-by-gender interaction effect was observed for the primary endpoint of 12-month TLF (P=0.5485). A marginally significant treatment-by-gender interaction effect was observed for the secondary endpoint of 9-month in-segment %DS under the natural log transformation (P=0.0628). However, this analysis is limited by the small sample size; fifteen female TAXUS Express patients have available 9-month in-segment %DS data, and the mean %DS for those patients was markedly low. Considering the small sample size and the lack of observed interaction effect for the primary endpoint of 12-month TLF, there does not appear to be a clinically significant treatment-by-gender interaction in the PERSEUS WH trial. This suggests that the overall conclusions of this trial regarding both safety and effectiveness of the ION Stent can be generalized for males and females.

Table 10.3.1. PERSEUS Workhorse Primary and Secondary Endpoint Results by Gender, Intent-to-Treat, All Patients (N=887)

	TAXUS Express	ION Stent	Relative Risk [95% CI]	Difference [95% CI]	P value	Interaction p-Value
12-month TLF (Primary Endpoint)						
	(N=220)	(N=667)				
Male	4.7% (10/214)	5.1% (33/650)	1.09 [0.54, 2.17]	0.4% [-2.9%, 3.7%]	0.8136	
	(N=100)	(N=275)				0.5485
Female	9.1% (9/99)	7.0% (19/272)	0.77 [0.36, 1.64]	-2.1% [-8.5%, 4.3%]	0.4971	
9-month Percent Diameter Stenosis In-Segment (Secondary Endpoint)						
	(N=53)	(N=180)				
Male	28.57±19.16 (46) (7.56, 100.00)	25.71±17.32 (156) (3.31, 100.00)	NA	-2.86 [-8.70, 2.97]	0.3373	
	(N=21)	(N=76)				0.0628
Female	19.60±7.91 (15) (9.71, 31.66)	26.95±18.62 (72) (4.22, 95.29)	NA	7.34 [-2.29, 16.97]	0.1389	

Table 10.3.2 shows PERSEUS Workhorse12-month clinical results in male and female patients.

Table 10.3.2. PERSEUS Workhorse 12-Month Clinical Endpoints, All ION™ Male and Female Patients, Intent-to-Treat, (N=942)

Endpoint	ION Male Stent Patients (N=667)	ION Female Stent Patients (N=275)
'ICACY		
:, Overall	5.7% (37/650)	5.5% (15/272)
TLR, Overall	3.4% (22/650)	4.8% (13/272)
TLR, PCI	3.2% (21/650)	4.4% (12/272)
TLR, CABG	0.3% (2/650)	0.4% (1/272)
Non-TLR, Overall	2.8% (18/650)	1.8% (5/272)
Non-TLR, PCI	2.5% (16/650)	1.8% (5/272)
Non-TLR, CABG	0.5% (3/650)	0.0% (0/272)
SAFETY		
Total Death	0.8% (5/650)	0.4% (1/272)
Cardiac Death or MI	2.3% (15/650)	2.9% (8/272)
Cardiac Death	0.6% (4/650)	0.4% (1/272)
MI	2.0% (13/650)	2.6% (7/272)
Q-wave MI	0.5% (3/650)	0.7% (2/272)
Non-Q-wave MI	1.5% (10/650)	1.8% (5/272)
ARC Stent Thrombosis		
Definite or Probable	0.6% (4/647)	0.0% (0/271)
Definite	0.5% (3/647)	0.0% (0/271)
Probable	0.2% (1/647)	0.0% (0/271)

Figures 10.3.2 and **10.3.3** show the cumulative TLF rate through 12-months for males and females, respectively. This post-hoc analysis suggests that within each sex-specific subgroup, non-inferiority of ION to TAXUS Express for this endpoint is maintained at all follow-up time-points (30d, 90d, 180d, 270d, 360d).

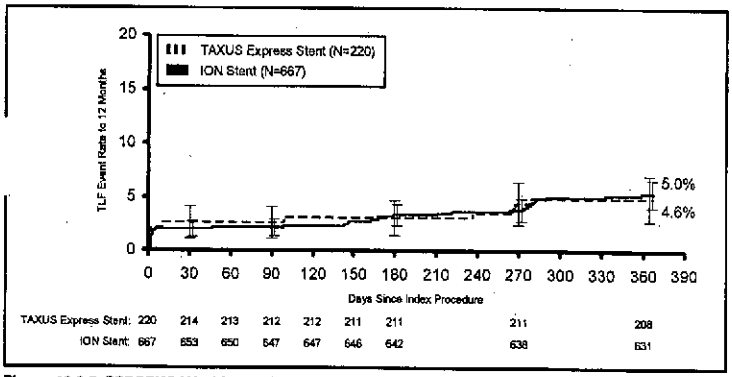


Figure 10.3.2. PERSEUS Workhorse Cumulative Rate of Target Lesion Failure to 12 Month, All Male Patients, Intent-to-Treat, Event Rate ± 1.5 SE (N=887)

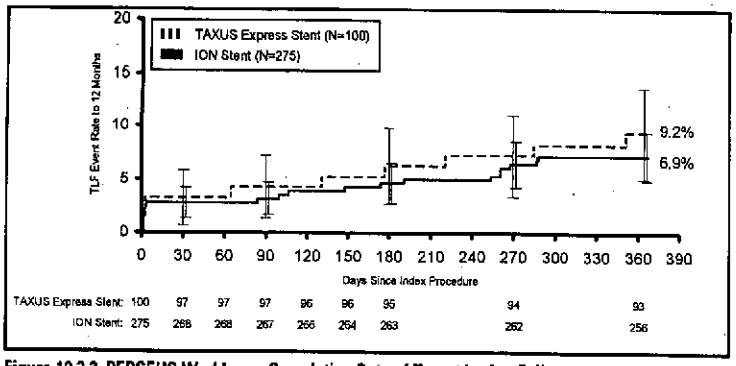


Figure 10.3.3. PERSEUS Workhorse Cumulative Rate of Target Lesion Failure to 12 Month, All Female Patients, Intent-to-Treat, Event Rate ± 1.5 SE (N=375)

To evaluate for possible sex-based differences in outcome of treatment with the ION Stent when used in small vessels, sex/gender-specific analyses were performed on safety and effectiveness endpoints. The results suggest that the general conclusions of the overall study regarding both safety and effectiveness can be generalized for males and females.

The PERSEUS SV study was not powered to study safety or effectiveness of the ION Stent in sex-specific subgroups. PERSEUS SV primary and secondary endpoint data were assessed for differences between male and female subgroups, as well as for any interaction between treatment group and gender. These post hoc analyses suggest that in patients treated with the ION stent in small vessels, 9-month in-segment late loss was 0.41±0.48 in females and 0.36±0.52 in males, and12-month TLF was 5.0% in females and 8.7% in males. In the BMS Express historical control group, rates of 12-month TLF were also numerically higher in males (25.2%) than females (16.8%). These observations are limited by the small sample size available for these analyses. Treatment effect (i.e., superiority of ION Stent to historical control BMS) was demonstrated for both males and females, as shown in **Table 10.3.3** below. No significant treatment-by-gender interaction effect was observed for the primary endpoint of 9-month in-stent late loss (P=0.7255) or 12-month TLF (P=0.9246). This suggests that the overall conclusions of this trial regarding both safety and effectiveness of the ION Stent in small vessels can be generalized for males and females.

Table 10.3.3. PERSEUS Small Vessel Primary and Secondary Endpoint Results, by Gender, Intent-to-Treat, All Patients (N=219)

	Historical Control BMS	ION Stent	Relative Risk [95% CI]	Difference [95% CI]	P value	Interaction p-Value
9-month Late Loss In-Stent (Primary Endpoint)						
	(N=76)	(N=143)				0.7255
Male	0.80±0.54 (70) (-0.15, 2.08)	0.36±0.52 (127) (-0.38, 2.28)	NA	-0.44 [-0.59, -0.28]	<.0001	
	(N=49)	(N=81)				
Female	0.80±0.50 (38) (-0.09, 2.10)	0.41±0.48 (70) (-0.34, 1.59)	NA	-0.39 [-0.59, -0.20]	0.0001	
12-month TLF (Secondary Endpoint)						
	(N=76)	(N=143)				0.9246
Male	25.7% (19/74)	8.7% (12/138)	0.34 [0.17, 0.66]	-17.0% [-28.0%, -6.0%]	0.0009	
	(N=49)	(N=81)				
Female	17.0% (8/47)	5.0% (4/80)	0.29 [0.09, 0.92]	-12.0% [NA]	0.0549	

Table 10.3.4. shows PERSEUS Small Vessel 12-month clinical results in male and female patients.

Table 10.3.4. PERSEUS Small Vessel 12-Month Clinical Endpoints, All ION Male and Female Patients, Intent-to-Treat, (N=224)

Endpoint	ION Male Stent Patients (N=143)	ION Female Stent Patients (N=81)
EFFICACY		
TVR, Overall	13.8% (19/138)	7.5% (6/80)
TLR, Overall	7.2% (10/138)	3.8% (3/80)
TLR, PCI	6.5% (9/138)	3.8% (3/80)
TLR, CABG	0.7% (1/138)	0.0% (0/80)
Non-TLR, Overall	9.4% (13/138)	5.0% (4/80)
Non-TLR, PCI	8.7% (12/138)	5.0% (4/80)
Non-TLR, CABG	0.7% (1/138)	0.0% (0/80)
SAFETY		
Total Death	1.4% (2/138)	1.3% (1/80)
Cardiac Death or MI	2.9% (4/138)	1.3% (1/80)
Cardiac Death	1.4% (2/138)	1.3% (1/80)
MI	1.4% (2/138)	0.0% (0/80)
Q-wave MI	0.7% (1/138)	0.0% (0/80)
Non-Q-wave MI	0.7% (1/138)	0.0% (0/80)
ARC Stent Thrombosis		
Definite or Probable	0.7% (1/136)	0.0% (0/79)
Definite	0.7% (1/136)	0.0% (0/79)
Probable	0.0% (0/136)	0.0% (0/79)

In the PERSEUS SV Trial, the study success criterion for 12-month TLF was met for both sexes (greater than performance goal of 19.5%). Figures 10.3.4 and 10.3.5 show the cumulative TLF rate through 12-months for males and females, respectively. This post-hoc analysis suggests that within each sex-specific subgroup, the ION group had lower TLF rates than the BMS Express historical control group at all follow-up time-points (30d, 90d, 180d, 270d, 360d), although confidence intervals are wide and overlap at earlier time points.

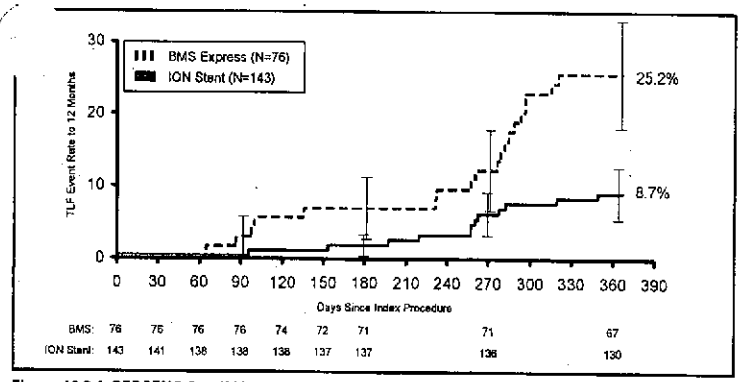


Figure 10.3.4. PERSEUS Small Vessel Cumulative Rate of Target Lesion Failure to 12 Month, All Male Patients, Intent-to-Treat, Event Rate ± 1.5 SE (N=219)

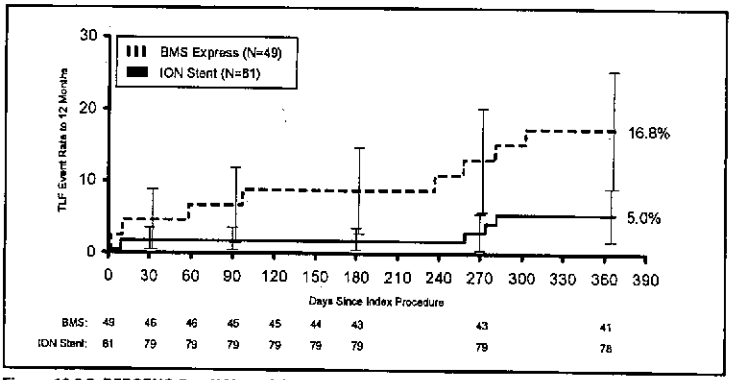


Figure 10.3.5. PERSEUS Small Vessel Cumulative Rate of Target Lesion Failure to 12 Month, All Female Patients, Intent-to-Treat, Event Rate ± 1.5 SE (N=130)

ICES

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11 INDIVIDUALIZATION OF TREATMENT

See also Precautions - Section 6.6, Use in Special Populations and Section 6.7, Lesion/Vessel Characteristics.

The risks and benefits should be carefully considered for each patient before use of the ION Stent System. Patient selection factors to be assessed should include a judgment regarding risk of prolonged anticoagulation therapy. On the basis of randomized clinical trial protocols, administration of clopidogrel or ticlopidine should be given for at least 6 months after paclitaxel-eluting stent (PES) implantation and ideally up to 12 months. Aspirin should be administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g. those patients with recently active ...is or peptic ulcer disease) in which anticoagulation therapy would be contraindicated.

...id conditions that increase the risk of poor initial results or the risks of emergency referral ...ass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

12 PATIENT COUNSELING INFORMATION

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

- Discuss the risks associated with stent placement.
- Discuss the risks associated with a paclitaxel-eluting stent.
- Discuss the risks/benefits issues for this particular patient.
- Discuss alteration to current lifestyle immediately following the procedure and over the long term.
- A Patient Information Guide (included in the package or available on-line) which includes both product information and a stent implant card.
- An Angioplasty Education Guide (available on-line or by request) which includes information on coronary artery disease, the implant procedure and frequently asked questions.

13 HOW SUPPLIED

Sterile: This product is sterilized with ethylene oxide gas. It is intended for single use only. Do not resterilize. Non-pyrogenic. Do not use if package is opened or damaged.

Handling and Storage: Protect from light. Do not remove from carton or foil pouch until ready for use. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

The foil pouch is not a sterile barrier.

Disposal Instructions: After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

14 OPERATIONAL INSTRUCTIONS

14.1 Inspection Prior to Use

Check foil pouch for "Use By" date. Do not use the product after the "Use By" date.

Carefully inspect the foil pouch and the sterile package before opening.

If the integrity of the foil pouch or the sterile package has been compromised prior to the product "Use By" date (e.g., damage of the package), contact your local Boston Scientific representative for return information. Do not use if any defects are noted.

Note: At any time during use of the Monorail® Stent System, if the proximal shaft (hypotube) has been bent or kinked, do not continue to use the catheter.

14.2 Materials Required

(not included in Stent System package)

Quantity	Material
1	Appropriate guide catheter (see Table 2.1, ION™ Stent System Product Description)
2-3	20 ml (cc) syringe
1,000u / 500cc	Normal heparinized sterile saline
1	≤ 0.014 in (0.36 mm) guidewire
1	Rotating hemostatic valve Diluted contrast medium 1:1 with normal heparinized sterile saline
1	Inflation device
1	Torque device
1	Pre-deployment dilation catheter
1	Three-way stopcock
1	Appropriate arterial sheath

14.3 Preparation

14.3.1 Packaging Removal

Step Action

1. Open the outer box to reveal the foil pouch and carefully inspect the foil pouch for damage.
2. Carefully open the foil pouch by tearing along the tear strip as indicated on the foil pouch to access the sterile barrier package containing the stent delivery system.
3. Carefully inspect the sterile barrier package for damage.
4. Carefully peel open the sterile barrier using aseptic techniques and extract the stent delivery system.
5. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a Monorail system, do not bend or kink hypotube during removal.
6. Remove the product mandrel and stent protector by grasping the catheter just proximal to the stent (or just proximal to the balloon bond site), and with the other hand, grasp the stent protector and gently remove distally.

Note: If unusual resistance is felt during product mandrel and stent protector removal, do not use this product and replace with another.

7. Examine the device for any damage. If it is suspected that the sterility or performance of the device has been compromised, the device should not be used.
8. A Monorail Catheter may be coiled once and secured using the CLIPIT™ Coil Clips provided in the catheter package. Only the proximal shaft should be inserted into the CLIPIT device; the clip is not intended for the distal end of the catheter.

Note: Care should be taken not to kink or bend the shaft upon application or removal of the CLIPIT Coil Clip.

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14.3.2 Guidewire Lumen Flush

Step Action

1. (Over-The-Wire only) Flush stent system guidewire lumen with normal heparinized saline through the back port of the manifold.
2. (Monorail system only) Flush stent system guidewire lumen with normal heparinized saline using the flushing needle supplied for the Monorail system at the distal end.
3. Verify that the stent is positioned between the proximal and distal balloon markers. Check for bends, kinks and other damage. Do not use if any defects are noted.

Note: Avoid manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.

14.3.3 Balloon Preparation

Step Action

1. Stent contact with any fluid is not recommended, as there is a possibility of initiating drug release. However, if it is absolutely necessary to flush the stent with saline, contact time should be limited (1 minute maximum).
2. Prepare inflation device/syringe with diluted contrast medium.
3. Attach inflation device/syringe to stopcock; attach to inflation port. Do not bend the proximal shaft when connecting to inflation device/syringe.
4. With tip down, orient stent system vertically.
5. Open stopcock to stent system; pull negative for 15 seconds; release to neutral for contrast fill.
6. Close stopcock to stent system; purge inflation device/syringe of all air.
7. Repeat steps 4 through 6 until all air is expelled. If bubbles persist, do not use product.
8. If a syringe was used, attach a prepared inflation device to stopcock.
9. Open stopcock to stent system.
10. Leave on neutral.

14.3.4 Delivery Procedure

Step Action

1. Prepare the vascular access site according to standard PTCA practice.
2. Predilate the lesion/vessel with appropriate diameter balloon.
3. Maintain neutral pressure on inflation device attached to stent system.
4. Backload stent system onto proximal portion of guidewire while maintaining guidewire position across target lesion.
5. Fully open rotating hemostatic valve to allow for easy passage of the stent and prevent damage to the stent.
6. Carefully advance the stent system into the hub of the guide catheter. When using a Monorail system be sure to keep the proximal shaft straight. Ensure guide catheter stability before advancing the stent system into the coronary artery.

Note: If unusual resistance is felt before the stent exits the guide catheter, do not force passage. Resistance may indicate a problem, and use of excessive force may result in stent damage or stent dislodgment from the balloon. Maintain guidewire placement across the lesion, and remove the stent system and guide catheter as a single unit.

7. Advance the stent system over the guidewire to target lesion under direct fluoroscopic visualization. Utilize the proximal and distal radiopaque balloon markers as a reference point. If the position of the stent is not optimal, it should be carefully repositioned or removed (See also Precautions - 6.12, Stent System Removal). The inside edges of the marker bands indicate both the stent edges and balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.

Note: If unusual resistance is felt at any time during lesion access before stent implantation, the stent system and the guide catheter should be removed as a single unit. (See also Precautions - 6.12, Stent System Removal).

8. Sufficiently tighten the rotating hemostatic valve. The stent is now ready to be deployed.

14.3.5 Deployment Procedure

Step Action

1. Inflate the delivery system expanding the stent to a minimum pressure of 11 atm (1115 kPa). Higher pressure may be necessary to optimize stent apposition to the arterial wall. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter of about 1.1 times the reference vessel diameter (see Table 14.5.1). Balloon pressure must not exceed rated burst pressure of 18 atm (1824 kPa) for the 2.25 mm stents and 16 atm (1621 kPa) for the 2.50-4.00 mm stent sizes. (see Table 14.5.1).
2. Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3. Deflate balloon by pulling negative pressure on inflation device until balloon is fully deflated, see Table 6.1 System Deflation Time Specifications.
4. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).
5. If stent sizing/apposition requires optimization, readvance the stent system balloon, or another high-pressure, balloon catheter of the appropriate size, to the stented area using standard angioplasty techniques.
6. Inflate the balloon to the desired pressure while observing under fluoroscopy. Deflate the balloon (refer to product labeling and/or Table 14.5.1 for proper stent inflation pressure).
7. If more than one ION Stent is needed to cover the lesion and balloon treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents, the balloon marker bands of the second ION Stent should be positioned inside of the deployed stent prior to expansion.
8. Reconfirm stent position and angiographic result. Repeat inflations until optimal stent deployment is achieved.

14.3.6 Removal Procedure

Step Action

1. Ensure balloon is fully deflated before delivery system withdrawal.
2. Fully open rotating hemostatic valve.
3. While maintaining guidewire position and negative pressure on inflation device, withdraw delivery system.
4. Monorail catheters may be coiled once and secured using the CLIPIT Coil Clip (see Operational Instructions – Section 14.3.1, Packaging Removal).
5. Repeat angiography to assess the stented area. If an adequate expansion has not been obtained, exchange back to the original stent delivery catheter or exchange to another balloon catheter of appropriate balloon diameter to achieve proper stent apposition to the vessel wall.

14.4 Post-Deployment Dilatation of Stented Segments

Precaution: Do not dilate the stent beyond the limits tabulated below.

Nominal Stent Diameter (ID)	Dilatation Limits (ID)
2.25 mm	2.75 mm
2.50 mm - 2.75 mm	3.50 mm
3.00 mm - 3.50 mm	4.25 mm
4.00 mm	5.75 mm

All efforts should be taken to assure that the stent is not under-dilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent. The stent may be expanded using a low profile and high pressure balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

Note: In line with Precaution 6.13 Post-Procedure: Care must be exercised when crossing a newly deployed stent with any wire, catheter or ancillary device to avoid disrupting the stent placement, apposition, geometry, and/or coating.

14.5 In Vitro Information

Table 14.5.1 Typical ION™ Stent System compliance

Pressure Atm (kPa)		2.25 mm Stent I.D. (mm)	2.50 mm Stent I.D. (mm)	2.75 mm Stent I.D. (mm)	3.00 mm Stent I.D. (mm)	3.50 mm Stent I.D. (mm)	4.00 mm Stent I.D. (mm)
9.0 (911)		NA	2.32	2.58	2.84	3.26	3.71
9.5 (962)		2.11	2.38	2.65	2.92	3.35	3.80
10.0 (1013)		2.16	2.45	2.72	3.00	3.44	3.89
11.0 (1115)	Nominal	2.22	2.51	2.78	3.07	3.52	3.98
12.0 (1216)		2.27	2.59	2.86	3.13	3.61	4.07
13.0 (1317)		2.32	2.64	2.91	3.18	3.67	4.13
14.0 (1419)		2.37	2.69	2.96	3.22	3.72	4.19
15.0 (1520)		2.41	2.73	3.00	3.26	3.77	4.24
16.0* (1621)		2.46	2.77	3.04	3.29	3.81	4.29
17.0 (1723)		2.49	NA	NA	NA	NA	NA
18.0* (1824)		2.53	NA	NA	NA	NA	NA

* RATED BURST PRESSURE. DO NOT EXCEED.
Note: The Stent I.D. values listed are actual average stent inner diameters at the specific balloon inflation pressures obtained during in vitro testing at 37°C.

15 WARRANTY

Boston Scientific Corporation (BSC) warrants that reasonable care has been used in the design and manufacture of this instrument. **This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.** Handling, storage, cleaning and sterilization of this instrument as well as other factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond BSC's control directly affect the instrument and the results obtained from its use. BSC's obligation under this warranty is limited to the repair or replacement of this instrument and BSC shall not be liable for any incidental or consequential loss, damage or expense directly or indirectly arising from the use of this instrument. BSC neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this instrument. **BSC assumes no liability with respect to instruments reused, reprocessed or resterilized and makes no warranties, express or implied, including but not limited to merchantability or fitness for a particular purpose, with respect to such instruments.**

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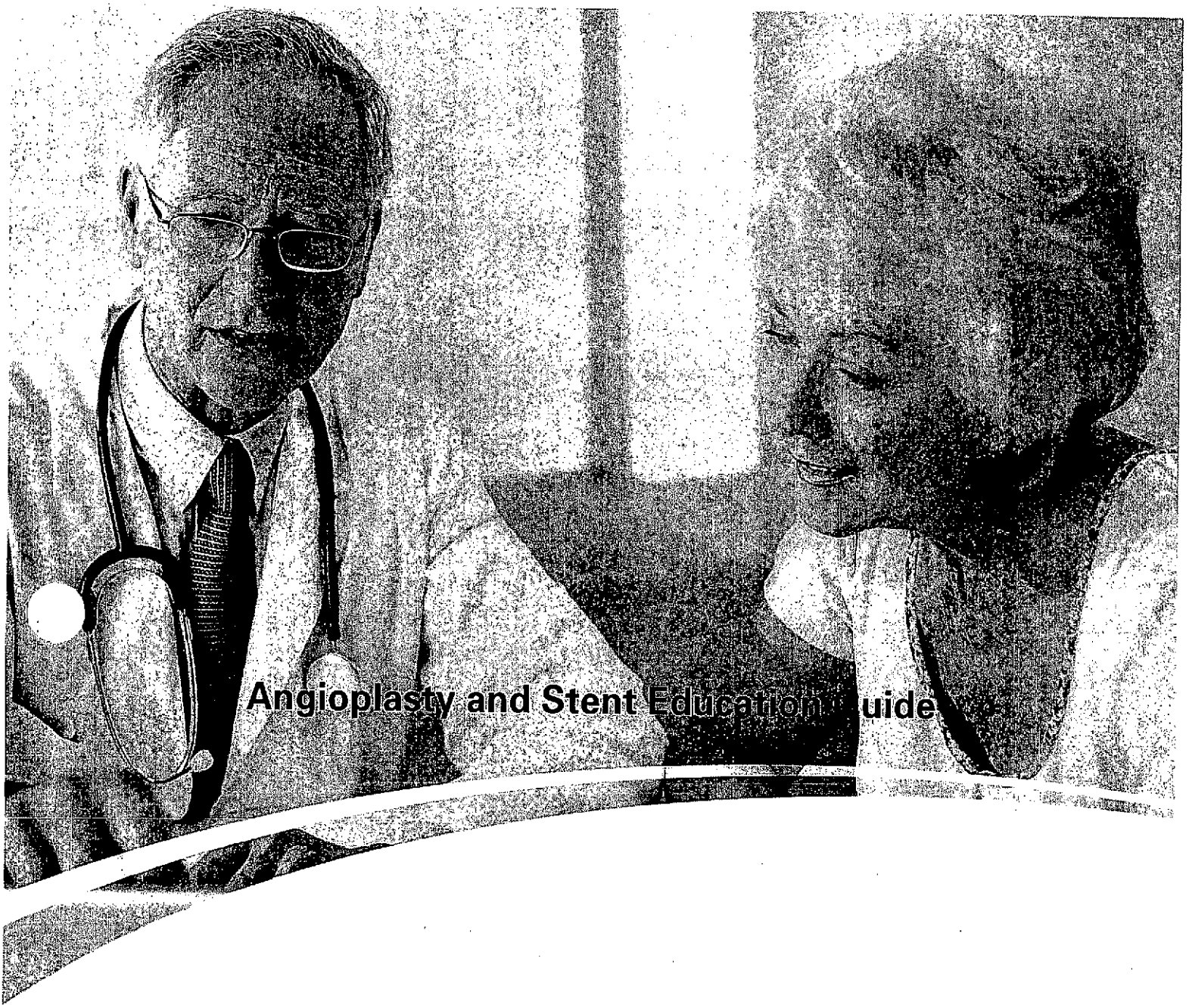
A N G I O T E C H



Angioplasty and Stent Education Guide

Boston Scientific

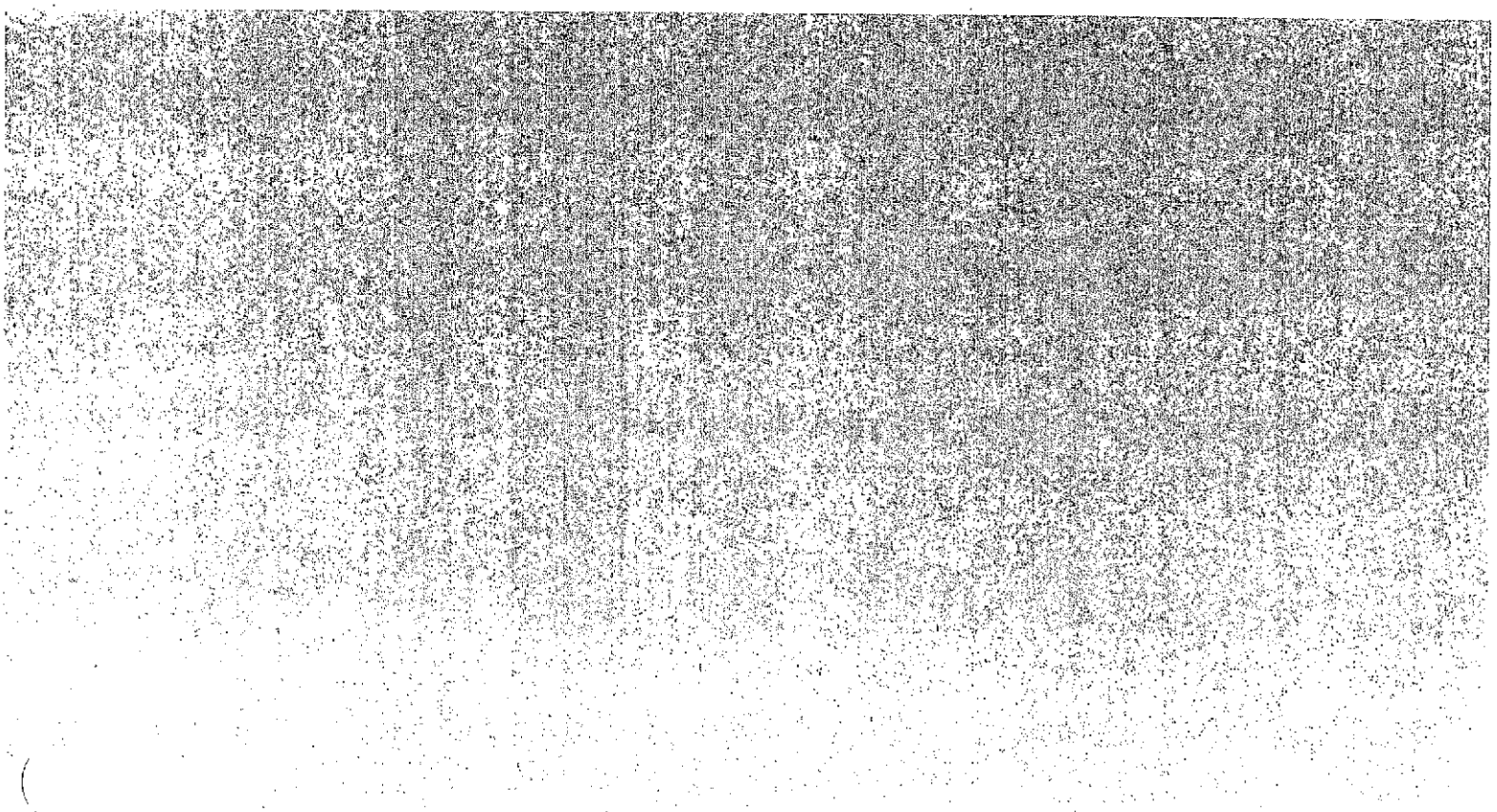


Table of Contents

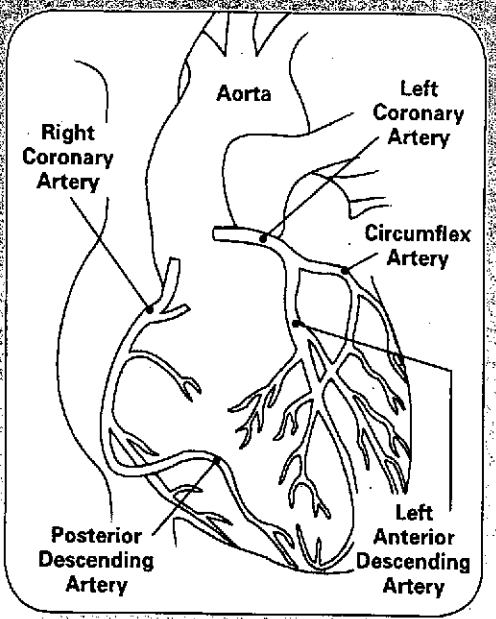
Treating coronary artery disease

Your doctor may want you to have a stent placed in your coronary artery. This is to help treat your coronary artery disease. This guide explains the procedure and what you can expect from start to finish. A glossary at the end of this guide defines common medical terms about this procedure.

You will also learn steps you can take to live a healthier life with coronary artery disease.

What is coronary artery disease

Coronary Artery Disease (CAD) is the narrowing of the arteries in the heart. This narrowing can also be called stenosis. It is usually caused by a build up of fat or calcium deposits called *plaque*. Over time, this *plaque* can build to a total blockage of the artery. This process is called *atherosclerosis*.



When the heart doesn't receive enough blood flow due to blockage in the artery, it may cause mild to severe chest pain or pressure. This pain or pressure can also spread to the arms or jaw. If the arteries are completely blocked, it can result in a heart attack. Anyone who experiences symptoms should promptly call 911. More than 13 million Americans suffer from CAD each year. However, the treatment of CAD has changed in recent years, and many CAD patients are able to return to a normal lifestyle shortly after treatment.

Who is at risk?

If you have a history of high cholesterol, diabetes, smoking, high blood pressure, being overweight or a family history of CAD, you have an increased chance of developing blockage in your *coronary arteries*. As you get older, you have a greater chance of developing CAD. In addition, women who have reached menopause have a greater chance of having CAD.

How do I know if I have Coronary Artery Disease?

There are a number of tests that your doctor can perform to help determine if you have CAD. A test that measures the electrical activity in your heart is called an *electrocardiogram (ECG or EKG)*. A *stress test* can be done to measure the electrical activity in your heart while you are exercising. These tests may show your doctor if part of your heart has been damaged or is not receiving enough blood. To directly determine if your arteries may be blocked or narrowing, your doctor may schedule a procedure with a cardiologist. This procedure is called a *coronary angiogram* and is performed in a Cardiac *Catheter*ization Lab by inserting a dye into your *coronary arteries*. By doing this procedure, the cardiologist can see your *coronary arteries* on an X-ray screen and can make a decision of how best to treat you.

Coronary artery disease treatment options

There are many different treatment options for treating coronary artery disease. The options focus on increasing blood flow to the heart, along with changes to your every day lifestyle, including diet, physical activity and medications. The type of treatment your doctor recommends for you depends on your symptoms and how much damage has been done to your heart.

Treatment Options for Coronary Artery Disease may include:

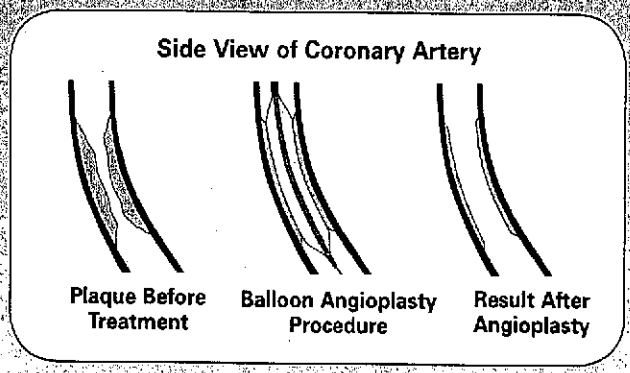
1. Medications
2. *Balloon angioplasty*
3. Coronary artery stenting
4. *Coronary artery bypass graft surgery (CABG)*

1. Medications

Nitroglycerin may be given to relieve chest discomfort due to coronary blockages. It does not treat the blockage itself. Your cardiologist may prescribe a number of medications (aspirin, beta-blockers, cholesterol medications, etc.) to thin your blood and to help prevent blockage of the arteries.

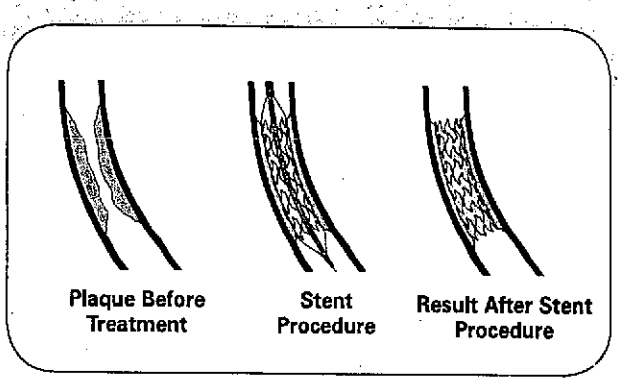
2. *Angioplasty*

A procedure known as *angioplasty* can also treat artery narrowing. A thin tube known as a *guide catheter* is inserted into the artery at the groin or wrist. A small balloon located on the top of a second *catheter* is moved through the *guide catheter* to the site of the narrowing. The balloon is then inflated to reduce the blockage. The balloon is deflated and removed after the *angioplasty* is done. The patient remains awake while the cardiologist performs the procedure. The procedure may end here or you could have a bare-metal or drug-eluting *stent* implanted to help keep the artery open.



3. Coronary artery stenting

During this procedure a small mesh tube is implanted into the artery to widen the artery and restore adequate blood flow to the heart. This mesh tube is called a *stent*. Once the *stent* is placed into the coronary artery, it is expanded with the inflation of a balloon *catheter*. The *stent* is left in the artery to keep it open and help prevent further narrowing of the coronary artery.



4. *Coronary artery bypass graft surgery (CABG)*

This surgery is also called a heart bypass or open heart surgery. Your surgeon will need to take a short length of artery from your inner chest wall and/or a vein from your leg and surgically attach it above and below the blocked area of the heart artery.

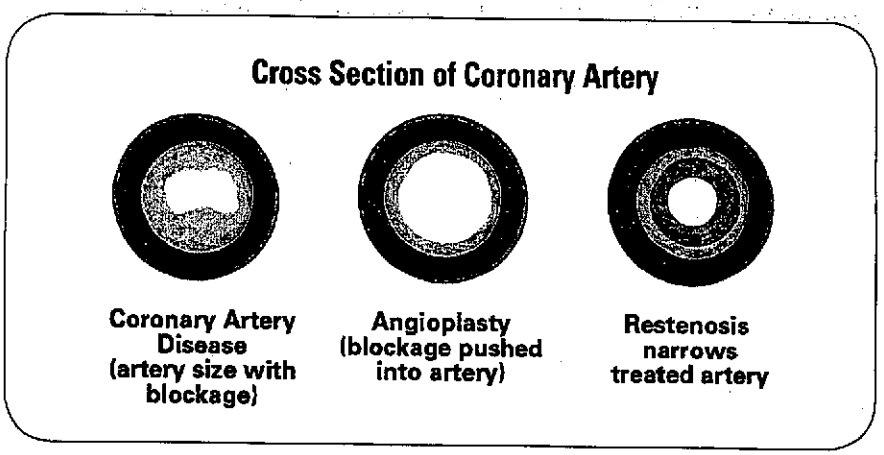
What are coronary artery stents

Coronary artery *stents* are small mesh tubes that can help to reduce blockage of a coronary artery. The *stent* is implanted into an artery and expanded to fit the size, shape and bend of the coronary artery. The *stent* is propped open to help prevent any more blockages. Once the *stent* is in place, the *stent* will remain in your artery. Over time, the artery wall will heal around the *stent* as it continues to support the artery.

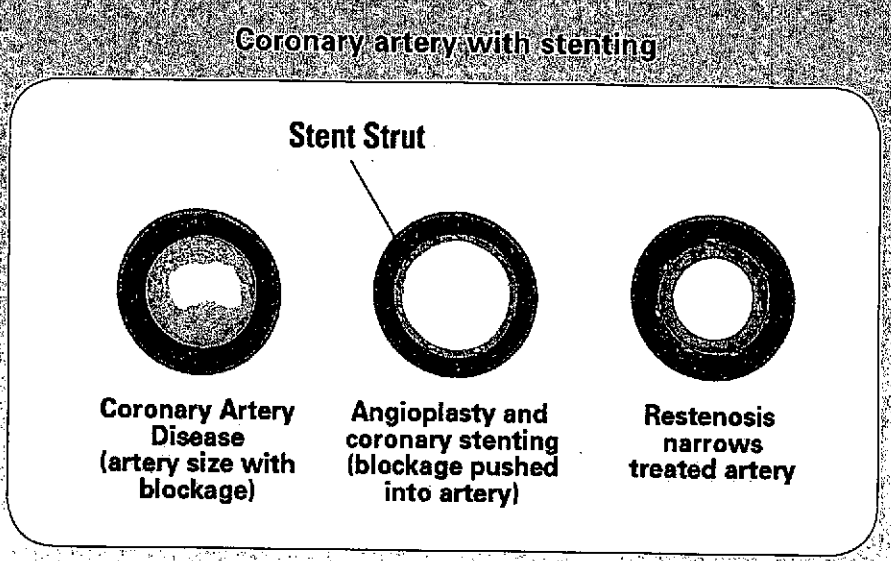
Why are *stents* used?

Many patients who undergo *balloon angioplasty* treatment will experience a re-narrowing of the artery. This re-narrowing is called *restenosis*. This re-narrowing of the coronary artery can happen more often following a *balloon angioplasty* procedure than for patients who receive a *stent*. The re-narrowing can be caused by a combination of factors including the blockage reforming or new tissue growth within the treated area.

Coronary artery with angioplasty



What are coronary artery stents continued



What are the different types of coronary stents?

There are two kinds of *stents*, bare-metal and drug-coated. Bare-metal *stents* provide support to help keep the artery open after *angioplasty*. A drug-coated *stent* is a bare-metal *stent* with a special drug coating added to help reduce the chance of the artery becoming blocked again. The drug is released from the *stent* over the period of time during which re-blockage is most likely to occur. The *stents* were designed to be very flexible, allowing them to fit the shape of your artery.

Boston Scientific offers bare-metal and drug-eluting *stents*. Depending upon your specific needs, your doctor may choose to place a bare metal, drug-eluting or some combination of these *stents*. There are differences between the two *stent* types (such as the need for longer-term dual antiplatelet therapy with drug-eluting *stents*) that you should discuss with your doctor. Please reference the ION Patient Information Guide for more details about the *stent*.

How does the drug coating and polymer work on a drug-eluting stent?

Polymer Coating
The *stent* is coated with a proprietary polymer, which was developed specifically for drug-eluting *stents*. The polymer carries and protects the drug before and during the procedure. Once the *stent* is implanted, it helps control drug release into the coronary arterial wall. This contributes to even and consistent distribution of the drug from the *stent*.

Drug Release
The drug-eluting *stent* is coated with a drug and polymer and has been designed to allow for a consistent and controlled release of the drug from the *stent* surface into the artery walls. Both the amount of drug and release rate have been determined so that healing can occur while allowing the processes leading to *restenosis* to be minimized, thus reducing the need for additional treatment in the stented area.

Risks of treatment options

You should not have a drug eluting *stent* placed in your coronary artery if you have any of the following conditions:

- You are allergic to the drug or related drugs
- You are allergic to the polymer
- You are allergic to stainless steel or platinum chromium
- You are unable to take medicines that make your blood take longer to clot (also called anticoagulants)
- You are unable to take medicines that make your blood cells slippery and make it more difficult for your blood to clot (also called antiplatelets)
- You have a blockage that will not allow proper placement of the *stent*
- You are allergic to the dye used during the procedure (also called contrast agent)
- Your doctor decides that you are not able to have the required medication prior to *stent* placement

Your doctor and the medical staff will monitor you during and after the procedure for complications. If a complication does occur, your doctor will decide what type of treatment you may need.

Risks of treatment options continued

The placement of *stents* in arteries is done to treat blockages and to try to prevent re-narrowing.

As with any *stent* procedure, there is a chance that complications may occur, including, but not limited to, the following:

- Air bubbles, tissue or clots which can block the artery (emboli)
- Allergic reaction to the drug
- Allergic reaction to the polymer
- Allergic reaction to the metal used to make the *stent* (stainless steel or platinum chromium)
- Allergic reaction to the contrast dye (which could cause kidney failure)
- Aneurysm
- Bleeding (which may require a blood transfusion)
- Bruising at the access site
- Bruising which occurs on a blood vessel (pseudo-aneurysm)
- Chest pain or discomfort
- Collection of blood in the lining of the heart
- Coronary spasm
- Death
- Emergency bypass surgery
- Heart attack
- High or low blood pressure
- Inadequate supply of blood to the heart
- Infection and/or pain at the access site
- Injury or tearing of artery
- Irregular heartbeat (arrhythmia)
- Movement of the *stent* to an unintended location
- Plugging of the *stent* with blood clots
- Re-narrowing of the treated artery (*restenosis*)
- Shock/pulmonary edema
- Side effects due to contrast dye, heparin or other medications
- Stroke or other neurological problems
- Total blockage (occlusion) of the artery
- Unnatural connection between vein and artery (asterio-venous fistula)
- Arterial trauma requiring surgical repair or reintervention
- Worsening of heart and lung function

There is a chance that complications may occur relating to the drug (based on studies of patients who used the drug for a prolonged period of time) or the polymer which include:

- Abnormal liver test levels
- Allergic or immunologic reaction to the drug
- Allergic reaction to the polymer or polymers with similar chemical structures
- Anemia
- Blood transfusion
- Changes in blood profile (decrease in the number of white and red blood cells and platelets)
- Changes of the tissue in the arterial wall including inflammation, cell injury and cell death
- Disturbances of the gastrointestinal (GI) tract and stomach
- Loss of hair
- Muscle pain/joint pain
- Nerve disease in arms and legs

There may be other potential adverse events that are unforeseen at this time.

Before your coronary artery stenting procedure

Before your coronary artery stenting procedure:

- Tell your doctor about any medications you are taking.
- Let your doctor know about any allergies you have. It is important he or she knows about allergies to contrast dye, iodine, cobalt, chromium, nickel, titanium, stainless steel, platinum or plastics.
- Tell your doctor if you cannot take aspirin or blood thinning medicines. These medications are usually prescribed before and after your procedure.
- Make sure you understand the possible risks and benefits of your coronary *stent* procedure.

Below is a typical checklist. Your doctor may ask you to go through this before your procedure:

- Do not eat or drink anything after midnight on the night before your procedure.
- Follow the instructions you receive from your doctor and nurses.
- Take all your medications with you.
- You may be given a sedative to relax you before starting your *stent* procedure. The sedative can make you sleepy.

During a typical coronary artery stenting procedure

1. You will be taken to an area of the hospital called the Cardiac *Catheter*ization Laboratory. While in the cath lab, you may be given a sedative that will make you feel sleepy during the procedure.

2. A small puncture is made in your arm or groin. A needle is used to gain access to your artery and a guide *catheter* and guide wire are fed through the artery and moved up into the coronary artery. All of this is done using X-rays for a guide.

3. The diseased artery first needs to be enlarged to make room for the *stent*. To do this, the doctor places a small, deflated balloon over the guide wire and through the *catheter* to the blocked area of the coronary artery. When the balloon is in the correct position, it is inflated. This pushes the *plaque* buildup aside and reopens the artery to restore blood flow.

4. The balloon is deflated and removed, and a small metal mesh tube called a *stent* is advanced into the same blocked area of the artery and expanded against the artery wall to fit the shape of your artery. Your doctor may choose to expand the *stent* by using another balloon. This is to make sure the *stent* is in better contact with the artery.

5. If your doctor places a drug-eluting *stent* into your artery, a drug will be released from the *stent* over a slow period of time.

6. After the *stent* is implanted, the *catheter* and wire are removed and the puncture site is closed. The *stent* remains in place permanently and is designed to help keep the artery open and prevent future narrowing of the coronary artery.

After a typical coronary artery stenting procedure

- You may feel sleepy from the sedative given to you. This will wear off over the next few hours.
- You will be taken to a unit where nurses and doctors can monitor you.
- You will be asked to stay in bed for several hours. You will be asked to keep your arm or leg straight so the entry site can heal.
- You may need to stay in the hospital before you can go home.
- You should follow your doctor's recommendations and let them know if you are experiencing any of the following:
  - Chest pain
  - Shortness of breath
  - Sudden weakness or paralysis of the face, arm or leg
  - Pain, bleeding or infection at the entry site in your arm or leg
  - Any other unexplained symptoms
- You can return to normal activities gradually. Check with your doctor about physical activities.
- You should not stop taking your medications unless you are asked to stop by the doctor who implanted your *stent*.
- You should keep all of your follow-up appointments, including blood testing.
- You should carry your *Stent* Implant Card.
- You should always show your dentist or medical doctor your *Stent* Implant Card.

Medications

Your cardiologist may prescribe a number of medications to thin the blood and prevent blood clots from forming and adhering to the surface of the *stent*. These medications will include aspirin and blood thinning drugs such as Plavix®, Ticlid® or Effient® (Prasugrel). It is extremely important that you follow your doctor's instructions on what medications to take. **If you stop taking these medications before being instructed to do so by your cardiologist, the chances of blood clot formation on the *stent*, subsequent heart attack or even death are increased.**

If you plan to have any type of surgery or dental work which may require you to stop taking these medications prematurely, you and your cardiologist should discuss whether or not placement of a *stent* is the right treatment for you.

If surgery or dental work is recommended which would require you to stop taking these medications prematurely after you've received the *stent*, you and your doctor should carefully consider the risks and benefits of this additional surgery or dental work versus the possible risks from early discontinuation of these medications.

If you do require premature discontinuation of these medications because of significant bleeding, then your cardiologist will be carefully monitoring you for possible complications. Once your condition has stabilized, your cardiologist will probably put you back on these medications.

Follow-Up Examinations

You will need to see the cardiologist who implanted your *stent* for routine follow-up examinations. During these visits, your doctor will monitor your progress and evaluate your medications, the clinical status of your coronary artery disease, and how the *stent* is working for you.

Frequently Asked Questions

Can the stent move or rust?
Once positioned by your doctor, the *stent* does not move on its own. It is manufactured so that it will not rust.

Can I walk through metal detectors with a stent?
Yes, without any fear of setting them off.

How soon can I go back to work?
The majority of people return to work within a few days following the procedure.

What if I still have pain?
If you experience pain, immediately inform your cardiologist or the center where the procedure was performed.

Can I undergo MRI or scanner testing with a stent?
MRI safety testing has shown that the coronary *stent* is MR Conditional and that a patient with a coronary *stent* may safely undergo an MRI scan under certain conditions listed on the *Stent* Implant Card. Prior to undergoing an MRI scan, inform your doctor or MR technologist that you have a coronary *stent* and show them your *Stent* Implant Card.

Can I play sports?
Your doctor will tell you what sports you can play and when you can start them.

What should I change in my diet?
Your doctor may prescribe a low-fat, low-cholesterol diet to help reduce the levels of fat in your blood and reduce your risk.

Glossary

Angina Pectoris
Symptoms experienced when the heart muscle is not receiving adequate oxygen (may include chest, arm, jaw or back pain, shortness of breath, nausea, vomiting).

Angioplasty
A minimally invasive treatment to open blocked *coronary arteries*. Also known as *percutaneous transluminal coronary angioplasty (PTCA)*.

Atherosclerosis
A disease in which the flow of blood to the heart is restricted with *plaque* deposits and, therefore, less oxygen and other nutrients reach the heart muscle. This may lead to chest pain (*angina pectoris*) or to a heart attack (*myocardial infarction*).

Balloon Angioplasty
Opening the blocked artery by using a balloon *catheter* that is inflated inside the artery.

Catheter
A small, thin plastic tube used to provide access to parts of the body, such as the *coronary arteries*.

Coronary Angiogram
A test in which contrast dye is injected into the *coronary arteries* allowing the doctor to see the arteries on an X-ray machine.

Coronary Arteries
The arteries that surround the heart and supply blood containing oxygen and nutrients to the heart muscle.

Coronary Artery Bypass Graft Surgery (CABG)
Open heart or bypass surgery. A section of an artery or vein from your chest or leg is harvested and surgically attached to a coronary artery below the blocked area of the heart.

Coronary Artery Disease (CAD)
Disease affecting the *coronary arteries* that surround the heart and supply blood to the heart muscle.

Electrocardiogram (ECG/EKG)
A test that records changes in the electrical activity of the heart. May show whether sections of the heart muscle have been damaged due to insufficient blood or oxygen flow to the heart.

Glossary *continued*

In-Stent Restenosis
Recurrent blockage or narrowing of a previously stented area in an artery.

Lumen
The inner channel of an artery.

Magnetic Resonance Imaging (MRI)
A non-invasive way to take pictures of the body. MRI uses powerful magnets and radio waves, unlike x-rays and computed tomographic (CT) scans which use radiation.

Myocardial Infarction
Permanent damage to the heart tissue and muscle due to the interruption of the blood supply to the area. Commonly referred to as a heart attack.

Percutaneous Transluminal Coronary Angioplasty (PTCA)
See *Angioplasty.*

Plaque
Accumulation or buildup of cholesterol, fatty deposits, calcium and collagen in a coronary vessel that leads to blockages in the *coronary arteries.*

Restenosis
Recurrent blockage or re-narrowing of a previously treated artery.

Stent
An expandable metal tubular structure (lattice) that supports the vessel wall and maintains blood flow through the opened artery.

Stress Test
A test that records the heart's electrical activity while the patient exercises. May show whether parts of the heart muscle have been damaged and if there is insufficient blood or oxygen flow to the heart.

Indications, contraindications, warnings and instructions for use can be found in the product labeling supplied with each product. CAUTION: Federal (U.S.A.) law and governing law outside the U.S.A. restricts these products to sale by or on the order of a physician.

Boston Scientific

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To order product or for more information, contact customer service at 1.888.272.1001.

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Prior to use, please see the complete "Directions for Use" and "Instructions for Use" at www.bostonscientific.com for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events and Operator's Instructions.

Boston Scientific

ION™

Paclitaxel-Eluting Platinum Chromium Coronary Stent System

Patient Information Guide

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ION™

Paclitaxel-Eluting Platinum Chromium Coronary Stent System

PATIENT INFORMATION GUIDE

You have recently had an ION drug-coated stent implanted in the coronary arteries of your heart. The following information is important for you to know, including the possible risks associated with having a stent implant along with medication recommendations and questions you may have about your stent.

ION Drug Eluting Stent

The ION stent is a bare-metal stent with a special drug coating added to help reduce the chance of the artery becoming blocked again. The drug is released from the stent over the period of time during which re-blockage is most likely to occur. The stent was designed to be very flexible, allowing it to fit the shape of your artery.

Polymer Coating

The stent is coated with a proprietary polymer, which was developed specifically for drug-eluting stents. The polymer carries and protects the drug before and during the procedure. Once the stent is implanted, it helps control drug release into the coronary arterial wall. This contributes to even and consistent distribution of the drug from the stent.

Drug Release

The ION drug-eluting stent is coated with a drug and polymer and has been designed to allow for a consistent and controlled release of the drug from the stent surface into the artery walls. Both the amount of drug and release rate have been determined so that healing can occur while allowing the processes leading to restenosis to be minimized, thus reducing the need for additional treatment in the stented area.

Potential adverse events (in alphabetical order) which may be associated with the use of a coronary stent in native coronary arteries include but are not limited to:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction to anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation and ventricular tachycardia
- Arteriovenous fistula
- Cardiac tamponade
- Cardiogenic shock/pulmonary edema
- Coronary aneurysm
- Death
- Dissection
- Emboli, distal (air, tissue or thrombotic material or material from devices(s) used in the procedure)
- Heart failure
- Hematoma
- Hemorrhage, required transfusion
- Hypotension/hypertension
- Infection, local or systemic
- Ischemia, myocardial
- Pain, access site
- Perforation or rupture of coronary artery
- Pericardial effusion
- Pseudoaneurysm, femoral
- Renal failure
- Respiratory failure
- Restenosis of stented segment
- Stent embolization or migration
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/TIA
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma requiring surgical repair or reintervention

Potential adverse events related to the drug paclitaxel or the stent polymer include:

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or the polymer stent coating (or its individual components)
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia/arthralgia
- Peripheral neuropathy

Exposure to paclitaxel and the polymer coating is directly related to the number of implanted stents. Use of more than one ION stent has not been adequately evaluated. Use of multiple stents will result in your exposure to a larger amount of paclitaxel and polymer coating than experienced in the clinical studies. There is no clinical experience on the performance of the ION stent when used with other types of coated or drug-eluting stents.

There may be other potential adverse events that are unforeseen at this time.

Medications

Your cardiologist may prescribe a number of medications to thin the blood and prevent blood clots from forming and adhering to the surface of the stent. These medications will include aspirin and blood thinning drugs such as Plavix®, Ticlid® or Effient® (Prasugrel). It is extremely important that you follow your doctor's instructions on what medications to take. If you stop taking these medications

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before being instructed to do so by your cardiologist, the chances of blood clot formation on the stent, subsequent heart attack or even death are increased.

If you plan to have any type of surgery or dental work which may require you to stop taking these medications prematurely, you and your cardiologist should discuss whether or not placement of a stent is the right treatment for you.

If surgery or dental work is recommended which would require you to stop taking these medications prematurely after you've received the stent, you and your doctor should carefully consider the risks and benefits of this additional surgery or dental work versus the possible risks from early discontinuation of these medications.

If you do require premature discontinuation of these medications because of significant bleeding, then your cardiologist will be carefully monitoring you for possible complications. Once your condition has stabilized, your cardiologist will probably put you back on these medications.

Clinical Data Summary

The safety and effectiveness of the ION Stent were compared to the TAXUS Express Stent, in the PERSEUS Workhorse clinical trial that included 1262 patients with a planned five-year clinical follow-up. The study results showed that patients who received an ION Stent had a similar incidence of bypass surgery or repeat angioplasty in the lesion where the stent was placed when compared to patients who received a TAXUS Express Stent (3.8% ION vs. 4.5% TAXUS Express) at 12 months. The combined occurrence of Major Adverse Cardiac Events, which is comprised of cardiac death, heart attacks, bypass surgery and repeat angioplasty, was 7.4% (ION) vs. 7.7% (TAXUS Express) at 12 months.

Full study results are provided in the ION Directions for Use, found on www.bostonscientific.com.

AFTER THE PROCEDURE

After the stent is implanted, you will be moved to a cardiology ward for a short period where you can be monitored closely as you begin to recover. On average, your hospital stay may last one to three days before you are discharged.

ACTIVITY

- Follow your doctor's guidelines.
- Return to normal activities gradually, pacing your return to activity as you feel better. Check with your doctor about strenuous activities.
- Let your doctor know about any changes in lifestyle you make during your recovery period.
- Report side effects from medications immediately. These may include headaches, nausea, vomiting or rash.
- Do not stop taking your medications unless you are asked to stop by the doctor who implanted your stent.
- Keep all follow-up appointments, including laboratory blood testing.
- Carry your Stent Implant Card at all times. If you receive dental or medical care or report to an emergency room/center, show your Stent Implant Card.

FREQUENTLY ASKED QUESTIONS

Can the stent move or rust?

Once positioned by your physician, the stent does not move on its own. It is manufactured so it will not rust.

Can I walk through metal detectors with a stent?

Yes, without any fear of setting them off.

How soon can I go back to work?

The majority of people return to work within a few days following the procedure.

What if I still get pains?

If you experience pain, immediately inform your cardiologist or the center where the procedure was performed.

Can I undergo MRI or scanner testing with a stent?

MRI safety testing has shown that the stent should not migrate in the MRI environment typically used in a clinical setting (≤3T), and that MRI may be performed immediately following stent implantation. Testing also demonstrated that stent heating due to the MRI is less than 2.6 degrees Celsius and should not affect performance of the implanted stent or the drug coating.

Can I play sports?

Your doctor will tell you what sports you can play and when you can start them.

What should I change in my diet?

Your doctor may prescribe a low-fat, low-cholesterol diet to help reduce the levels of fat in your blood and reduce your risk.

Does paclitaxel have any drug interactions that I should be concerned about?

Formal drug interaction studies with paclitaxel-based stents have not been conducted. Since some paclitaxel will remain on the stent, interactions at the location of the stent itself affecting the performance of the drug cannot be ruled out. Be sure to discuss with your doctor any drugs you are taking or planning to take.

What if I have taken paclitaxel before and had a reaction to it?

Be sure to let your doctor know if you have had a previous reaction to paclitaxel.

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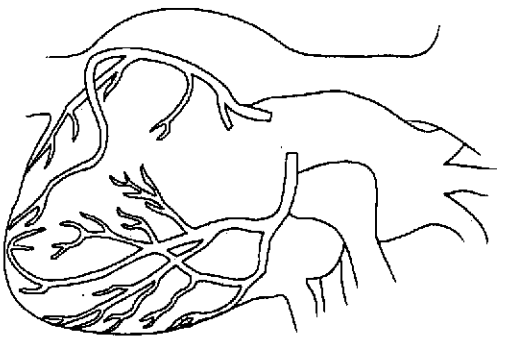

Stent Implant Location

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www.bostonscientific.com
www.stent.com

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Paclitaxel-Eluting Platinum Chromium Coronary Stent System

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Paclitaxel-Eluting Platinum Chromium Coronary Stent System

If you require a magnetic resonance imaging (MRI) scan, tell your doctor or MRI technician technologist that you have a stent implant. Test results indicate that the ION Stent is MR Conditional. Patients with single or overlapped ION Stents up to 74 mm in total length can undergo MRI scans safely under the following conditions:

- Field strengths of 1.5 Tesla and 3 Tesla
- Static magnetic field gradient < 9 T/m (extrapolated)
- Normal operating mode (maximum whole body averaged specific absorption rate (SAR) of lower than 2.0 W/kg) for a total active MR scan time (with RF exposure) of 15 minutes or less

The stent(s) should not migrate in this MRI environment and MRI may be performed immediately following the implantation of an ION Stent(s). Prior to undergoing an MRI scan, inform your doctor that you have an ION Stent.

MR image quality will be compromised if the area of interest is in the same area or relatively close to the position of the stent. Please contact 1.888.272.1001 for more information about MR image artifact.

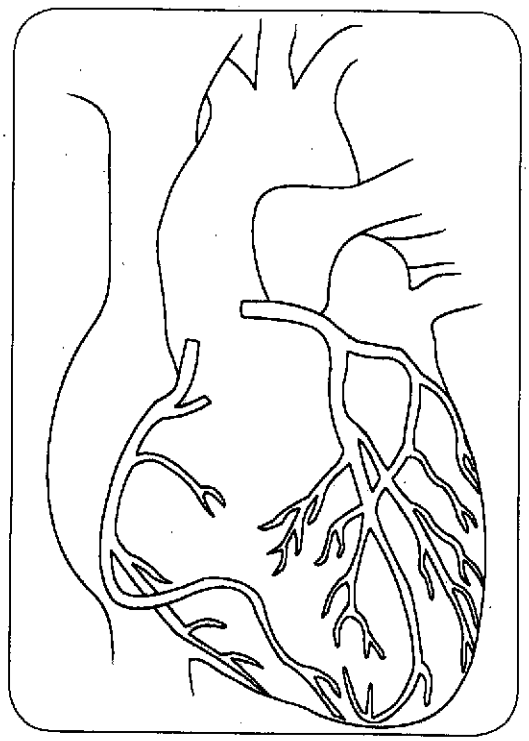
PLEASE CARRY YOUR CARD AT ALL TIMES

Your cardiologist has prescribed a number of medications to thin the blood and prevent blood clots after your implant. It is extremely important to follow the medication regimen as prescribed by your cardiologist. Before considering any surgery or dental work which would require you to stop taking these medicines early, you and your doctors should consider the risks from premature discontinuation of these medications. **For questions regarding your Coronary Stent System or other procedures (e.g., MRI), please contact your implanting cardiologist.**

Stent Identification Information

Patient Name	Patient Phone Number
Implanting Physician's Name	Stent Material
Physician's Phone Number	Date of Implant
Product Name	Product Name
Product Lot Number	Product Lot Number
Stent Location	Stent Location

Indications, contraindications, warnings and instructions for use can be found in the labeling supplied with each product. CAUTION: Federal (U.S.A.) law and governing law outside the U.S.A. restricts these products to sale by or on the order of a physician. ION™ Paclitaxel-Eluting Platinum Chromium Coronary Stent System is a product of Boston Scientific Corporation.



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