Medtronic

Resolute Onyx™

Zotarolimus-Eluting Coronary Stent System
Rapid Exchange and Over-the-Wire Delivery Systems

Instructions for Use

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

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The components of the Resolute Onyx™ zotarolimus-eluting coronary stent system are sterile.

1 Symbol glossary

Explanation of symbols that may appear on package labeling

Refer to the device labeling to see which symbols apply to this product.

Standard title:

ISO 15223-1:2016 Cor 2017: Medical Devices — Symbols to be used with medical device labels, labeling and information to be supplied

Symbol	Reference	Symbol title	Explanatory text
	ISO 15223-1, Clause 5.4.3	Consult instructions for use	Indicates the need for the user to consult the instructions for use.
	ISO 15223-1, Clause 5.2.8	Do not use if package is damaged	Indicates a medical device that should not be used if the package has been damaged or opened.
	ISO 15223-1, Clause 5.4.2	Do not reuse	Indicates a medical device that is intended for one use, or for use on a single patient during a single procedure.
	ISO 15223-1, Clause 5.1.5	Lot number	Indicates the manufacturer's batch code so that the batch or lot can be identified.
	ISO 15223-1, Clause 5.1.1	Manufacturer	Indicates the medical device manufacturer.
	ISO 15223-1, Clause 5.1.6	Catalog number	Indicates the manufacturer's catalogue number so that the medical device can be identified.
	ISO 15223-1, Clause 5.2.3	Sterilized using ethylene oxide	Indicates a medical device that has been sterilized using ethylene oxide.
	ISO 15223-1, Clause 5.1.4	Use-by date	Indicates the date after which the medical device is not to be used.

2 Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System

The Medtronic Resolute Onyx™ zotarolimus-eluting coronary stent system (Resolute Onyx™ system) is a device/drug combination product that consists of the following device components: the Resolute Onyx™ coronary stent and delivery system and a drug component (a formulation of zotarolimus in a polymer coating). The characteristics of the Resolute Onyx™ system are described in **Error! Reference source not found.**.

Table 2-1: Device component description and nominal dimensions

Component	Resolute Onyx™ zotarolimus-eluting coronary stent system rapid exchange and over-the-wire delivery systems			
	Stent design 1 (small vessel)	Stent design 2 (medium vessel)	Stent design 3 (large vessel)	Stent design 4 (extra large vessel)
Available stent diameters (mm)	2.0, 2.25, 2.5	2.75, 3.0	3.5, 4.0	(RX only) – 4.5, 5.0
Available stent lengths (mm)	8, 12, 15, 18, 22, 26, 30, 34*, 38* *34, 38 mm lengths not available in 2.0 mm	8, 12, 15, 18, 22, 26, 30, 34, 38	8, 12, 15, 18, 22, 26, 30, 34, 38	(RX only) – 12, 15, 18, 22, 26, 30

Table 2-1: Device component description and nominal dimensions

Component		Resolute Onyx™ zotarolimus-eluting coronary stent system rapid exchange and over-the-wire delivery systems			
		Stent design 1 (small vessel)	**Stent design 2 (medium vessel)**	**Stent design 3 (large vessel)**	**Stent design 4 (extra large vessel)**
Stent material and geometry		A continuous sinusoid pattern stent manufactured from a composite metal material, consisting of a cobalt-based alloy shell conforming to ASTM F562 and a platinum-iridium alloy core conforming to ASTM B684.			
Drug component		A coating of polymers loaded with zotarolimus in a formulation applied to the entire surface of the stent at a dose of approximately 1.6 µg/mm^2 which results in a maximum nominal drug content of 317 µg on the stent with the largest surface area (4.0 x 38 mm).			
Delivery systems effective (working) length		140 cm			
Delivery system luer adapter ports	RX	Single access port to the inflation lumen. A guidewire exit port is located approximately 25 cm from the tip. Designed for guidewire less than or equal to 0.014 inch (0.36 mm).			
	OTW	Y-connector with side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen designed for guidewire less than or equal to 0.014 inch (0.36 mm).			
Stent delivery balloon		Single-layer Pebax balloon, wrapped over an inner member tubing with 2 radiopaque marker bands to locate the stent edges.			
Balloon inflation pressure		Nominal inflation pressure: 12 ATM (1216 kPa) Rated burst pressure: 2.0-4.0 mm = 18 ATM (1824 kPa), RX only: 4.5-5.0 mm = 16 ATM (1621kPa)			
Minimum guide catheter inner diameter		≥5 F (1.42 mm, 0.056 in)			
Catheter shaft outer diameter	RX	Proximal shaft OD: 2.1 F (0.69 mm) Distal shaft OD 2.0 – 4.0 mm: 2.7 F (0.91 mm) Distal shaft OD 4.5 and 5.0 mm: 3.2 F (1.07 mm)			
	OTW	Proximal shaft OD: 3.4 F (1.12 mm) Distal shaft OD: 2.7 F (0.91 mm)			

2.1 Device component description

The Medtronic Resolute Onyx™ zotarolimus-eluting coronary stent system (Resolute Onyx™ system) consists of a balloon-expandable, intracoronary, drug-eluting stent (DES) premounted on a rapid exchange (RX) or an over-the-wire (OTW) stent delivery system. The Resolute Onyx™ stent is manufactured from a composite material of cobalt alloy and platinum-iridium alloy and is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The stents are available in multiple lengths and diameters. The delivery system has 2 radiopaque markers to aid in the placement of the stent during fluoroscopy and is compatible with 0.014 inch (0.36 mm) guidewires and 1.42 mm (5 Fr / 0.056 in) minimum inner diameter guide catheters. The Resolute Onyx™ RX delivery system (Figure 2-1) and the Resolute Onyx™ OTW delivery system (Figure 2-2) have an effective length of 140 cm.

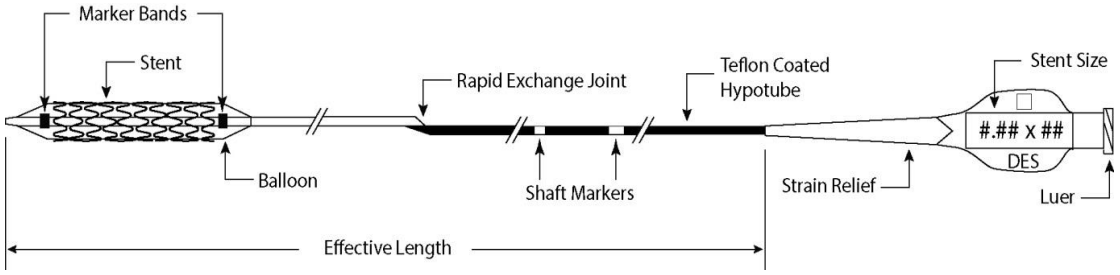

Figure 2-1: Resolute Onyx™ rapid exchange (RX) delivery system (with stent)
Illustration is not to scale

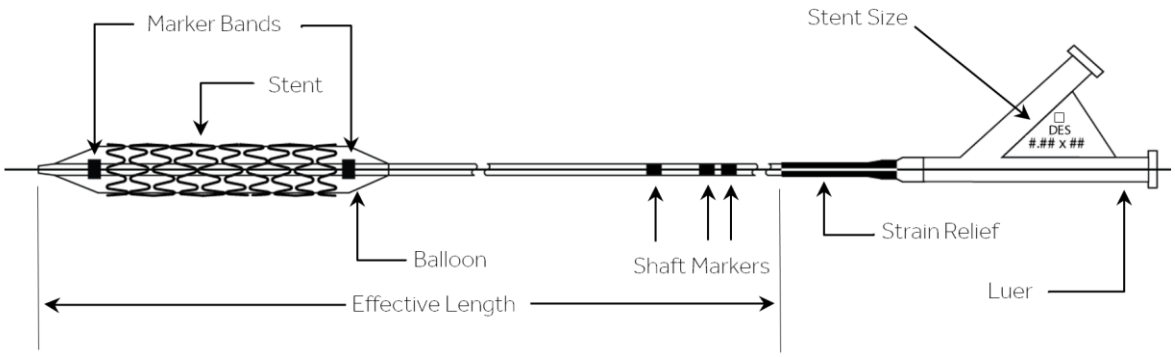

Figure 2-2: Resolute Onyx™ over-the-wire (OTW) delivery system (with stent)
Illustration is not to scale

The stent is crimped on various sizes of delivery catheter balloons, which range from 2.0 mm to 5.0 mm. The Resolute Onyx™ available stent sizes are listed in **Error! Reference source not found.**.

Table 2-2: Resolute Onyx™ stent sizes

Diameter (mm)	Stent length (mm)								
	8	12	15	18	22	26	30	34	38
2.0	✓	✓	✓	✓	✓	✓	✓	-	-
2.25	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.5	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.75	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.0	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.5	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.0	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.5	-	✓*	✓*	✓*	✓*	✓*	✓*	-	-
5.0	-	✓*	✓*	✓*	✓*	✓*	✓*	-	-

"-" Denotes stent length is not available
"*" Not available for OTW

2.2 Drug component description

The drug coating of the Resolute Onyx™ system consists of the drug zotarolimus (the active ingredient) and the BioLinx® polymer system (the inactive ingredient).

2.2.1 Zotarolimus

The active pharmaceutical ingredient utilized in the Resolute Onyx™ system is zotarolimus. It is a tetrazole-containing macrocyclic immunosuppressant.

The chemical name of zotarolimus is:
[3S-[3R*[S*(1R*,3S*,4R*)],6S*,7E,9S*,10S*,12S*,14R*,15E,17E,19E,21R*, 23R*, 26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[2-[3-methoxy-4-(1H-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

The chemical structure of zotarolimus is shown in Figure 2-3:

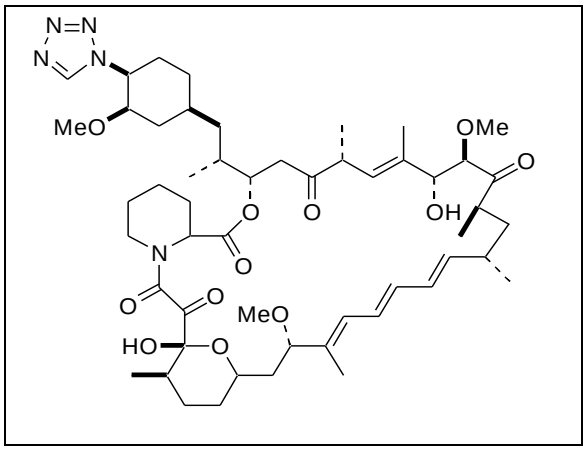

Figure 2-3: Zotarolimus chemical structure

Zotarolimus has extremely low water solubility and is a lipophilic compound that is freely soluble in propylene glycol, acetone, toluene, acetonitrile, ethanol, benzyl alcohol and DMSO. The molecular formula of zotarolimus is $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2.

Zotarolimus does not have any ionizable group(s) in the physiological pH range; therefore, its solubility is expected to be unaltered in this range.

2.2.2 Polymer system description

The Resolute Onyx™ stent consists of a bare metal stent with a Parylene C primer coat and a coating that consists of a blend of the drug zotarolimus and the BioLinx™ polymer system. BioLinx™ is a blend of the Medtronic proprietary components C10 and C19, and PVP (polyvinyl pyrrolidone). The structural formula of the BioLinx™ polymer subunits are shown in Figure 2-4:

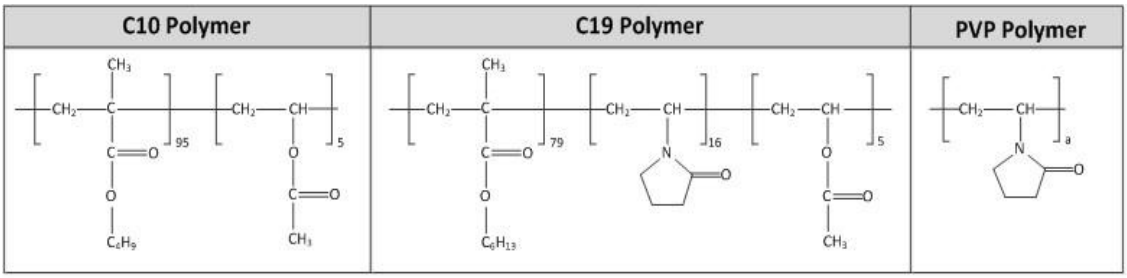

Figure 2-4: Chemical structure of the BioLinx™ polymer subunits

2.2.3 Product matrix and zotarolimus content

Table 2-3: Resolute Onyx™ zotarolimus-eluting coronary stent system product matrix and nominal zotarolimus doses

Product number RX	Product number OTW	Nominal expanded stent ID (mm)	Nominal unexpanded stent length (mm)	Nominal zotarolimus content (µg)
RONYX20008UX	RONYX20008W	2.0	8	51
RONYX22508UX	RONYX22508W	2.25	8	51
RONYX25008UX	RONYX25008W	2.5	8	51
RONYX27508UX	RONYX27508W	2.75	8	67
RONYX30008UX	RONYX30008W	3.0	8	67
RONYX35008UX	RONYX35008W	3.5	8	77
RONYX40008UX	RONYX40008W	4.0	8	77
RONYX20012UX	RONYX20012W	2.0	12	70
RONYX22512UX	RONYX22512W	2.25	12	70
RONYX25012UX	RONYX25012W	2.5	12	70
RONYX27512UX	RONYX27512W	2.75	12	94
RONYX30012UX	RONYX30012W	3.0	12	94
RONYX35012UX	RONYX35012W	3.5	12	108
RONYX40012UX	RONYX40012W	4.0	12	108
RONYX45012UX	-	4.5	12	132
RONYX50012UX	-	5.0	12	132
RONYX20015UX	RONYX20015W	2.0	15	85
RONYX22515UX	RONYX22515W	2.25	15	85
RONYX25015UX	RONYX25015W	2.5	15	85
RONYX27515UX	RONYX27515W	2.75	15	117
RONYX30015UX	RONYX30015W	3.0	15	117
RONYX35015UX	RONYX35015W	3.5	15	132
RONYX40015UX	RONYX40015W	4.0	15	132
RONYX45015UX	-	4.5	15	158
RONYX50015UX	-	5.0	15	158
RONYX20018UX	RONYX20018W	2.0	18	104
RONYX22518UX	RONYX22518W	2.25	18	104
RONYX25018UX	RONYX25018W	2.5	18	104
RONYX27518UX	RONYX27518W	2.75	18	140
RONYX30018UX	RONYX30018W	3.0	18	140
RONYX35018UX	RONYX35018W	3.5	18	156
RONYX40018UX	RONYX40018W	4.0	18	156
RONYX45018UX	-	4.5	18	188
RONYX50018UX	-	5.0	18	188
RONYX20022UX	RONYX20022W	2.0	22	127
RONYX22522UX	RONYX22522W	2.25	22	127
RONYX25022UX	RONYX25022W	2.5	22	127
RONYX27522UX	RONYX27522W	2.75	22	171

Table 2-3: Resolute Onyx™ zotarolimus-eluting coronary stent system product matrix and nominal zotarolimus doses

Product number RX	Product number OTW	Nominal expanded stent ID (mm)	Nominal unexpanded stent length (mm)	Nominal zotarolimus content (µg)
RONYX30022UX	RONYX30022W	3.0	22	171
RONYX35022UX	RONYX35022W	3.5	22	186
RONYX40022UX	RONYX40022W	4.0	22	186
RONYX45022UX	-	4.5	22	227
RONYX50022UX	-	5.0	22	227
RONYX20026UX	RONYX20026W	2.0	26	146
RONYX22526UX	RONYX22526W	2.25	26	146
RONYX25026UX	RONYX25026W	2.5	26	146
RONYX27526UX	RONYX27526W	2.75	26	198
RONYX30026UX	RONYX30026W	3.0	26	198
RONYX35026UX	RONYX35026W	3.5	26	221
RONYX40026UX	RONYX40026W	4.0	26	221
RONYX45026UX	-	4.5	26	265
RONYX50026UX	-	5.0	26	265
RONYX20030UX	RONYX20030W	2.0	30	168
RONYX22530UX	RONYX22530W	2.25	30	168
RONYX25030UX	RONYX25030W	2.5	30	168
RONYX27530UX	RONYX27530W	2.75	30	225
RONYX30030UX	RONYX30030W	3.0	30	225
RONYX35030UX	RONYX35030W	3.5	30	252
RONYX40030UX	RONYX40030W	4.0	30	252
RONYX45030UX	-	4.5	30	304
RONYX50030UX	-	5.0	30	304
RONYX22534UX	RONYX22534W	2.25	34	187
RONYX25034UX	RONYX25034W	2.5	34	187
RONYX27534UX	RONYX27534W	2.75	34	257
RONYX30034UX	RONYX30034W	3.0	34	257
RONYX35034UX	RONYX35034W	3.5	34	282
RONYX40034UX	RONYX40034W	4.0	34	282
RONYX22538UX	RONYX22538W	2.25	38	206
RONYX25038UX	RONYX25038W	2.5	38	206
RONYX27538UX	RONYX27538W	2.75	38	284
RONYX30038UX	RONYX30038W	3.0	38	284
RONYX35038UX	RONYX35038W	3.5	38	317
RONYX40038UX	RONYX40038W	4.0	38	317

3 Indications

The Resolute Onyx™ zotarolimus-eluting coronary stent system is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus or high bleeding risk, with symptomatic ischemic heart disease due to *de novo* lesions of length ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.0 mm to 5.0 mm. In addition, the Resolute Onyx™ zotarolimus-eluting coronary stent system is indicated for treating *de novo* chronic total occlusions.

4 Contraindications

The Resolute Onyx™ system is contraindicated for use in:

- Patients with known hypersensitivity or allergies to aspirin, heparin, bivalirudin, clopidogrel, prasugrel, ticagrelor, ticlopidine, drugs such as zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative.
- Patients with a known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum) or platinum-iridium alloy.
- Patients with a known hypersensitivity to the BioLinx® polymer or its individual components (see details in **Section 2.2.2 – Polymer system description**).

Coronary artery stenting is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system.

5 Warnings

- Ensure that the inner package has not been opened or damaged as this would indicate that the sterile barrier has been breached.
- The use of this product carries the same risks associated with coronary artery stent implantation procedures, which include subacute and late vessel thrombosis, vascular complications, and bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy.

6 Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Subsequent stent restenosis or occlusion may require repeat catheter-based treatments (including balloon dilatation) of the arterial segment containing the stent. The long-term outcome following repeat catheter-based treatments of previously implanted stents is not well characterized.
- The risks and benefits of stent implantation should be assessed for patients with a history of severe reaction to contrast agents.
- Do not expose or wipe the product with organic solvents such as alcohol.
- The use of a DES outside of the labeled indications, including use in patients with more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, myocardial infarction (MI), or death.
- Care should be taken to control the position of the guide catheter tip during stent delivery, stent deployment, and balloon withdrawal. Before withdrawing the stent delivery system, confirm complete balloon deflation using fluoroscopy to avoid arterial damage caused by guiding catheter movement into the vessel.
- Stent thrombosis is a low-frequency event that is frequently associated with MI or death. Data from the RESOLUTE clinical trials have been prospectively evaluated and

adjudicated using the definition developed by the Academic Research Consortium (ARC) (see **Section 10.7 – Pooled results of the Global RESOLUTE Clinical Trial Program** for more information).

6.1 Pre- and post-procedure antiplatelet regimen

In the Medtronic RESOLUTE ONYX Core (2.25 mm-4.0 mm) Clinical Study and RESOLUTE ONYX 2.0 mm Clinical Study, the protocols specified administration of clopidogrel or ticlopidine (or any approved P2Y12 platelet inhibitor), including dosages before the procedure, and for a period of at least 6 months post-procedure. Aspirin was administered before the procedure concomitantly with a P2Y12 platelet inhibitor and then continued post-procedure to reduce the risk of thrombosis.

- In the Medtronic RESOLUTE ONYX Core (2.25 mm-4.0 mm) Clinical Study, 93.3%, 93.2%, 89.2%, and 52.2% of the subjects remained on dual antiplatelet therapy at 6 months, 8 months, 12 months, and 36 months, respectively.
- In the Medtronic RESOLUTE ONYX 2.0 mm Clinical Study, 91.1%, 87.1%, and 51% of the subjects remained on dual antiplatelet therapy at 6 months, 12 months, and 36 months, respectively.

6.1.1 Oral antiplatelet therapy

Dual antiplatelet therapy (DAPT) using a combination treatment of aspirin with a P2Y12 platelet inhibitor after percutaneous coronary intervention (PCI), reduces the risk of stent thrombosis and ischemic cardiac events, but increases the risk of bleeding complications. The optimal duration of DAPT (specifically a P2Y12 platelet inhibitor in addition to aspirin) following DES implantation is unknown, and DES thrombosis may still occur despite continued therapy. It is very important that the patient is compliant with the post-procedural antiplatelet recommendations.

Per 2016 ACC/AHA guidelines,[1] a daily aspirin dose of 81 mg is recommended indefinitely after PCI. A P2Y12 platelet inhibitor should be given daily for at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS).

Consistent with the DAPT Study,[2] and the 2016 ACC/AHA guidelines, longer duration of DAPT may be considered in patients at higher ischemic risk with lower bleeding risk.

The Academic Research Consortium (ARC) proposed a standardized definition for identifying patients at high bleeding risk (HBR)[3]. Additionally, evidence from a dedicated study of Resolute Onyx in HBR patients and those who are unable to tolerate long term DAPT after PCI has been published[4].

Based on the Onyx ONE Clear Analysis, Resolute Onyx is safe and effective in patients at high risk of bleeding treated with one month of DAPT. The patients evaluated in the Onyx ONE Clear Analysis met the pre-defined criteria for high bleeding risk and were those whom

1 Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016; doi:10.1016/j.jacc.2016.03.513. For full text, please refer to the following website: http://content.onlinejacc.org/article.aspx?doi=10.1016/j.jacc.2016.03.513

2 Mauri L, et al. Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents. N Engl J Med. 2014; 371:2155–66.

3 Urban P, Mehran R, Colleran R, et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. Circulation 2019;140:240-6

4 Windecker S, Latib A, Kedhi E, et al. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. The New England Journal of Medicine 2020:10.1056/NEJMoa1910021.

in the opinion of their physician, the potential benefit of 1-Month DAPT outweighed the potential risk. In addition to at least one HBR risk factor, enrollment included 48.6% ACS patients (unstable angina 22.8%, Non-STEMI 21.7% and STEMI 4.2%). (see **Section 10.5.1 - Onyx ONE Clear Primary Analysis**).

Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of the benefit/risk ratio, and patient preference.

Premature discontinuation or interruption of prescribed antiplatelet medication could result in a higher risk of stent thrombosis, MI, or death. Before PCI, if premature discontinuation of antiplatelet therapy is anticipated, physicians should carefully evaluate with the patient whether a DES and its associated recommended DAPT regimen is the appropriate PCI choice.

Following PCI, if elective noncardiac surgery requiring suspension of antiplatelet therapy is considered, the risks and benefits of the procedure should be weighed against the possible risk associated with interruption of antiplatelet therapy.

Patients who require premature DAPT discontinuation should be carefully monitored for cardiac events. At the discretion of the patient's treating physician(s), the antiplatelet therapy should be restarted as soon as possible.

6.2 Use of multiple stents

The long-term effects of zotarolimus are currently unknown. The extent of the patient's exposure to the zotarolimus drug and the stent and polymer coating is directly related to the number of stents and total stent length implanted.

When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different materials in contact with each other may increase potential for corrosion. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.

Potential interactions of the Resolute Onyx™ stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

When using two wires, care should be taken when introducing, torquing, and removing one or both guidewires to avoid entanglement. In this situation, it is recommended that one guidewire be completely withdrawn from the patient before removing any additional equipment.

6.3 Use in conjunction with other procedures

The safety and effectiveness of using atherectomy devices with Resolute Onyx™ stent have not been established.

6.4 Brachytherapy

The safety and effectiveness of the Resolute Onyx™ stent in target lesions treated with prior brachytherapy, or the use of brachytherapy to treat in-stent restenosis of a Resolute Onyx™ stent, have not been established.

6.5 Use in special populations

Information on use of the Resolute Onyx™ stent in certain special patient populations is derived from clinical studies of the Resolute stent system, which uses the same drug (zotarolimus) – **See Section 8 – Overview of clinical trials**

6.5.1 Pregnancy

Pregnancy Category C. There are no well-controlled studies in pregnant women or men intending to father children. The Resolute Onyx™ stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus. Effective contraception should be initiated before implanting a Resolute Onyx™ stent and for 1 year after implantation. **See Section 7.6 – Pregnancy** under **Drug information**.

6.5.2 Lactation

It is not known whether zotarolimus is excreted in human milk. The pharmacokinetic and safety profiles of zotarolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from zotarolimus, a decision should be made whether to discontinue nursing or to implant a Resolute Onyx™ stent, taking into account the importance of the stent to the mother. **See Section 7.7 – Lactation** under **Drug information.**

6.5.3 Gender

Clinical studies of the Resolute™ stent did not suggest any significant differences in safety and effectiveness for male and female patients.

6.5.4 Ethnicity

Clinical studies of the Resolute™ stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity.

6.5.5 Pediatric use

The safety and effectiveness of the Resolute Onyx™ stent in patients below the age of 18 years have not been established.

6.5.6 Geriatric use

The RESOLUTE ONYX Core (2.25 mm-4.0 mm) Clinical Study, the RESOLUTE ONYX 2.0 mm Clinical Study, and the RESOLUTE clinical studies did not have an upper age limit. Among the 1,242 patients treated with the Resolute stent in the RESOLUTE US Main Study, which included 2.25 mm to 3.5 mm stents, 617 patients were age 65 or older and 88 patients were age 80 or older. A post hoc analysis of patients treated with the Resolute stent showed no significant differences in rates of cardiac death, target vessel MI, target lesion revascularization, ARC definite or probable stent thrombosis, or target lesion failure at 12 months. The rate of all-cause death at 12 months was 0.3% in patients under age 65 vs. 1.8% in patients age 65 or older.

6.5.7 Lesion/vessel characteristics

The safety and effectiveness of the Resolute Onyx™ stent have not been established in the cerebral, carotid, or peripheral vasculature or in the following coronary disease patient populations:

- Patients with coronary artery reference vessel diameters < 2.0 mm or > 5.0 mm.
- Patients with evidence of an acute ST-elevation MI within 72 hours of intended stent implantation.
- Patients with vessel thrombus at the lesion site.
- Patients with lesions located in a saphenous vein graft, in the left main coronary artery, ostial lesions, or bifurcation lesions.
- Patients with diffuse disease or poor flow distal to identified lesions.
- Patients with 3 vessel disease.

6.6 Drug interactions

The effect of potential drug interactions on the safety or effectiveness of the Resolute Onyx™ stent has not been investigated. While no specific clinical data are available, drugs like sirolimus that act through the same binding protein (FKBP12) may interfere with the efficacy of zotarolimus. Zotarolimus is metabolized by CYP3A4, a human cytochrome P450 enzyme. When administered concomitantly with 200 mg ketoconazole bid, a strong inhibitor of CYP3A4, zotarolimus produces less than a 2-fold increase in $AUC_{0\text{-}inf}$ with no effect on C_{max}. Therefore, consideration should be given to the potential for drug interactions when deciding to place a Resolute Onyx™ stent in a patient who is taking drugs that are known substrates or inhibitors of the cytochrome P450 isoenzyme CYP3A4. Systemic exposure of zotarolimus should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

Formal drug interaction studies have not been conducted with the Resolute Onyx™ stent.

6.7 Magnetic resonance imaging (MRI) safety information

Non-clinical testing has demonstrated that the Resolute Onyx™ stent is MR Conditional for single and overlapping lengths up to 120 mm. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 and 3 Tesla only
- Maximum spatial gradient magnetic field of 3000 gauss/cm (30 T/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2.0 W/kg (Normal Operating Mode)

Under the scan conditions defined above, the Resolute Onyx™ stent is expected to produce a maximum temperature rise of 4.3°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extended approximately 10 mm from the Resolute Onyx™ stent when imaged with a spin echo pulse sequence and a 3 Tesla MRI system. The artifact does obscure the device lumen.

6.8 Stent handling precautions

- For single use only. The Resolute Onyx™ system is provided sterile. Do not resterilize or reuse this product. Note the use-by date on the product label. Do not use the product if the package or product has been opened or damaged.
- Only the contents of the pouch should be considered sterile. The outside surface of the pouch is not sterile.
- Do not remove the contents of the pouch until the device will be used immediately.
- Do not remove the stent from the delivery balloon; removal may damage the stent and polymer coating and/or lead to stent embolization. The Resolute Onyx™ system is intended to perform as a system. The stent is not designed to be crimped onto another delivery device.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the rotating hemostatic valve and guide catheter hub.
- Do not try to straighten a kinked shaft or hypotube. Straightening a kinked metal shaft may result in breakage of the shaft.
- Stent manipulation (for example, rolling the mounted stent with your fingers) may cause coating damage, contamination, or dislodgement of the stent from the delivery system balloon.
- The Resolute Onyx™ system must not be exposed to any direct handling or contact with liquids before preparation and delivery as the coating may be susceptible to damage or premature drug elution**.**
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

- The Resolute Onyx™ stent delivery systems should not be used in conjunction with any other stents or for post-dilatation.

6.9 Stent placement precautions

- The vessel must be pre-dilated with an appropriately sized balloon. Refer to the pre-dilatation balloon sizing described in **Section 14.5 – Delivery procedure**. Failure to do so may increase the risk of placement difficulty and procedural complications.
- Do not prepare or pre-inflate the balloon before stent deployment other than as directed. Use the balloon purging technique described in **Section 14 – Directions for use.**
- Guide catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Device component description in** Error! Reference source not found.).
- After preparation of the stent delivery system, do not induce negative pressure on the delivery catheter before placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon or delivery difficulties.
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- In small or diffusely diseased vessels, the use of high balloon inflation pressures may over-expand the vessel distal to the stent and could result in vessel dissection.
- Implanting a stent may lead to a dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (for example, CABG, further dilatation, placement of additional stents, or other intervention).
- Do not expand the stent if it is not properly positioned in the vessel (see **Section 6** - **Precautions**–**Stent/system removal precautions**).
- Placement of the stent has the potential to compromise side branch patency.
- Do not attempt to pull an unexpanded stent back through the guide catheter, as dislodgement of the stent from the balloon may occur. Remove as a single unit per the instructions in **Section 6 - Precautions** –**Stent/system removal precautions**.
- Under-expansion of the stent may result in stent movement. Care must be taken to properly size the stent to ensure that the stent is in full contact with the arterial wall upon deflation of the balloon.
- Stent retrieval methods (for example, use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.
- Administration of appropriate anticoagulant, antiplatelet, and coronary vasodilator therapy is critical to successful stent implantation.

6.10 Stent/system removal precautions

If removal of a stent system is required before deployment, ensure that the guide catheter is coaxially positioned relative to the stent delivery system and cautiously withdraw the stent delivery system into the guide catheter. Should unusual resistance be felt at any time when withdrawing the stent towards the guide catheter, the stent delivery system and the guide catheter should be removed as a single unit. This must be done under direct visualization with fluoroscopy.

When removing the stent delivery system and guide catheter as a single unit:

- Do not retract the stent delivery system into the guide catheter. Maintain guidewire placement across the lesion and carefully pull back the stent delivery system until the proximal balloon marker of the stent delivery system is aligned with the distal tip of the guide catheter.

- The system should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guide catheter enters into the arterial sheath, the catheter will straighten, allowing safe withdrawal of the stent delivery system into the guide catheter and the subsequent removal of the stent delivery system and the guide catheter from the arterial sheath.

Failure to follow these steps and/or applying excessive force to the stent delivery system can potentially result in loss or damage to the stent and/or stent delivery system components such as the balloon.

6.11 Post-procedure

- Care must be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, an optical coherence tomography (OCT) catheter, a coronary guidewire, or a balloon catheter to avoid disrupting the stent placement, apposition, geometry, and coating.
- Post-dilatation: All efforts should be made to ensure that the stent is not under-dilated. If the deployed stent is not fully apposed to the vessel wall, the stent may be expanded further with a larger diameter balloon that is slightly shorter (about 2 mm) than the stent. The post-dilatation can be done using a low-profile, high-pressure, non-compliant balloon catheter. The balloon should not extend outside of the stented region. **Do not use the stent delivery balloon for post-dilatation.**
- If patient requires MR imaging, refer to **Section 6.7 – Magnetic resonance imaging (MRI) safety information** above.
- Antiplatelet therapy should be administered post-procedure (see **Precautions – Section 6.1 - Pre- and post-procedure antiplatelet regimen**). Patients who require early discontinuation of antiplatelet therapy (for example, secondary to active bleeding), should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.

7 Drug information

7.1 Mechanisms of action

The suggested mechanism of action of zotarolimus is to bind to FKBP12, leading to the formation of a trimeric complex with the protein kinase mTOR (mammalian target of rapamycin), inhibiting its activity. Inhibition of mTOR results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control.

7.2 Metabolism

Zotarolimus undergoes oxidative metabolism in the liver to form the demethyl and hydroxylated metabolites of the parent drug. Further metabolism can lead to the formation of hydroxyl-demethyl and dihydroxyl-demethyl metabolites. Enzymes of the CYP3A family are the major catalysts of oxidative metabolism of zotarolimus. Zotarolimus is a competitive inhibitor of CYP3A-dependent activities, however the IC_{50} values (3 µM and above) are many fold higher than the systemic concentrations expected following implantation of a drug-eluting stent. The anticipated zotarolimus blood levels in stented patients are expected to be less than 0.004 µM, suggesting that clinically significant drug-drug interactions are unlikely.

7.3 Pharmacokinetics of the Resolute Onyx™ stent

The pharmacokinetics information for the Resolute Onyx™ stent system is derived from a study conducted on the Resolute stent system. The Resolute Onyx™ stent system is similar to the Resolute stent system with regards to the stent design, the stent coating technology (dosing and drug to polymer ratio), and delivery system design and materials. Given these similarities and supportive bench and animal study information, the pharmacokinetics information from the RESOLUTE FIM PK Sub-study, as described below, is applicable to the Resolute Onyx™ stent system.

The pharmacokinetics (PK) of zotarolimus delivered from the Resolute stent have been determined in patients with coronary artery disease after stent implantation in the Medtronic RESOLUTE FIM Clinical Trial. The dose of zotarolimus was calculated per stent unit surface area and the key pharmacokinetic parameters determined from these patients are provided in **Error! Reference source not found.**.

Table 7-1: Zotarolimus pharmacokinetics in the Medtronic RESOLUTE FIM clinical trial PK Sub-study patients after implantation of Resolute zotarolimus-eluting coronary stents

PK parameter	Units	Group I (128 µg) N = 1†	Group II[a] (180 µg) N = 11	Group III[a] (240 µg) N = 7	Group IV[a] (300 µg) N = 3
C_{max}	(ng/mL)	0.129	0.210 ± 0.062	0.300 ± 0.075	0.346 ± 0.133
T_{max}	(h)	1.00	0.9 ± 0.7	0.9 ± 0.5	0.8 ± 0.5
$AUC_{0\text{-}last}$	(ng•h/mL)	15.08	16.04 ± 4.74	35.89 ± 12.79	31.19 ± 17.69
$AUC_{0\text{-}inf}$[$]	(ng•h/mL)	41.89	39.09 ± 11.77	52.41 ± 12.57	80.12 ± 51.00
β[$]	(1/h)	0.003	0.004 ± 0.001	0.004 ± 0.001	0.003 ± 0.002
$t_{½}$[‡,#]	(h)	263.4	195.5 ± 74.4	167.4 ± 29.7	208.3 ± 144.4
CL/F[$]	(L/h)	3.06	5.23 ± 2.55	4.80 ± 1.11	5.14 ± 3.55
$Vd_{β}/F$[$]	(L)	1161.2	1449.3 ± 221.6	1181.2 ± 336.4	1658.6 ± 494.8

Notes

C_{max}	Maximum observed blood concentration	a	Primary dose groups
T_{max}	Time to C_{max}	†	No SD was reported when N = 1
$AUC_{0\text{-}last}$	Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration	‡	Harmonic mean ± pseudo-standard deviation
$AUC_{0\text{-}inf}$	AUC from time 0 to infinity ($AUC_{0\text{-}inf}$).	#	Not a true estimate of the elimination half-life as the drug release from the stent was not complete during the course of the pharmacokinetic sampling
$t_{½}$	Harmonic mean half-life		
CL/F	Mean apparent clearance		
$Vd_{β}/F$	Apparent volume of distribution	$	Not a true sample

The results in **Error! Reference source not found.** show that the pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation (including dose groups with N > 1), 180, 240, and 300 µg, following the implantation of the Resolute stents as illustrated by dose proportional increases in maximum blood concentration (C_{max}), area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration ($AUC_{0\text{-}last}$) and AUC from time 0 to infinity($AUC_{0\text{-}inf}$). The mean apparent clearance (CL/F) and harmonic mean half-life ($t_{1/2}$) for the primary dose groups ranged from 4.80 to 5.23 L/h and 167.4 to 208.3 h, respectively. The mean time to reach peak systemic concentration (T_{max}) ranged from 0.8 to 0.9 h after stent implantation.

The data demonstrate dose proportionality and linearity similar to that seen with increasing zotarolimus doses from the Endeavor stent and intravenous administration. Based on available zotarolimus pharmacokinetic data, systemic safety margins of ≥78-fold have been established for the Resolute stent at 380 µg due to the extended elution of zotarolimus from the BioLinx® polymer.

7.4 Pharmacokinetics following multi-dose intravenous administration of zotarolimus

Zotarolimus pharmacokinetic activity has been determined following intravenous administration in healthy subjects. **Error! Reference source not found.** provides a summary of the pharmacokinetic analysis.

Table 7-2: Pharmacokinetic parameters (mean ± standard deviation) in patients following multi-dose intravenous administration of zotarolimus

PK parameters	Units	200 µg QD N = 15		400 µg QD N= 16		800 µg QD N=16	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C_{max}	(ng/mL)	11.41± 1.38¥	11.93 ± 1.25	21.99 ± 3.79	23.31± 3.15	37.72 ± 7.00	41.79 ± 6.68
T_{max}	(h)	1.05 ± 0.04¥	1.03 ± 0.04	1.00 ± 0.14	1.05 ± 0.04	1.03 ± 0.04	1.03 ± 0.05
$AUC_{0\text{-}24}$	(ng•h/mL)	34.19 ± 4.39¥	47.70 ± 6.68	68.43 ± 15.41	100.47 ± 18.02	123.48 ± 13.34	174.43 ± 19.88
$t_{1/2}$$	(h)		32.9 ± 6.8		37.6 ± 4.5		36.0 ± 4.7
CL[b]	(L/h)	4.2 ± 0.6	4.2 ± 0.6	4.0 ± 0.9	4.0 ± 0.9	4.6 ± 0.4	4.6 ± 0.4

Notes

¥ N = 16;

$ Harmonic mean ± pseudo-standard deviation

[b] Clearance data is calculated using compartmental methods.

All other data presented in Error! Reference source not found. is calculated using non-compartmental methods.

When administered intravenously for 14 consecutive days, zotarolimus showed dose proportionality. Renal excretion is not a major route of elimination for zotarolimus as approximately 0.1% of the dose was excreted as unchanged drug in the urine per day. In multiple doses of 200, 400, and 800 µg, zotarolimus was generally well tolerated by the subjects. No clinically significant abnormalities in physical examinations, vital signs, or laboratory measurements were observed during the study.

7.5 Mutagenesis, carcinogenicity and reproductive toxicology

7.5.1 Mutagenesis

Zotarolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the human peripheral lymphocyte chromosomal aberration assay, or the *in vivo* mouse micronucleus assay.

7.5.2 Carcinogenicity

No long-term studies in animals have been performed to evaluate the carcinogenic potential of zotarolimus. The carcinogenic potential of the Resolute stent is expected to be minimal based on the types and quantities of materials present.

7.5.3 Reproductive toxicology

No effect on fertility or early embryonic development in female rats was observed following the IV administration of zotarolimus at dosages up to 100 µg/kg/day (approximately 19 times the cumulative blood exposure provided by Resolute stents coated with 300 µg zotarolimus).

For male rats, there was no effect on the fertility rate at IV dosages up to 30 µg/kg/day (approximately 21 times the cumulative blood exposure provided by Resolute stents coated with 300 µg zotarolimus). Reduced sperm counts and motility, and failure in sperm release were observed in male rats following the IV administration of zotarolimus for 28 days at dosages of >30 µg/kg/day. Testicular germ cell degeneration and histological lesions were observed in rats following IV dosages of 30 µg/kg/day and above.

7.6 Pregnancy

Pregnancy Category C: There are no well-controlled studies in pregnant women, lactating women, or men intending to father children for this product.

Administration of zotarolimus to pregnant female rats in a developmental toxicity study at an intravenous dosage of 60 µg/kg/day resulted in embryolethality. Fetal ossification delays were also observed at this dosage, but no major fetal malformations or minor fetal anomalies were observed in this study. A 60 µg/kg/day dose in rats results in approximately 47 times the maximum blood level and about 11 times the cumulative blood exposure in patients receiving Resolute Onyx™ stents coated with 300 µg zotarolimus total dose.

No embryo-fetal effects were observed in pregnant rabbits administered zotarolimus in a developmental toxicity study at intravenous dosages up to 100 µg/kg/day. This dose in rabbits results in approximately 215 times the maximum blood level and about 37 times the cumulative blood exposure in patients receiving Resolute Onyx™ stents coated with 300 µg zotarolimus total dose.

Effective contraception should be initiated before implanting a Resolute Onyx™ stent and continued for one year post-stent implantation. The Resolute Onyx™ stent should be used in pregnant women only if potential benefits justify potential risks.

7.7 Lactation

It is not known whether zotarolimus is excreted in human milk. The potential adverse reactions in nursing infants from zotarolimus have not been determined. The pharmacokinetic and safety profiles of zotarolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from zotarolimus, 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 trials

8.1 The RESOLUTE ONYX Clinical Program

The RESOLUTE ONYX Clinical Program currently includes the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study, conducted in the United States (US), the RESOLUTE ONYX 2.0 mm Clinical Study conducted in the US and Japan, and the RESOLUTE ONYX Post-Approval Study (PAS) – which consists of the Primary Cohort, the XLV Cohort, and the Bifurcation Cohort.

Error! Reference source not found. summarizes the clinical trial designs for the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study, the RESOLUTE ONYX 2.0 mm Clinical Study, and the RESOLUTE ONYX PAS.

Table 8-1: The RESOLUTE ONYX Clinical Program

	RESOLUTE ONYX™ Core (2.25 mm – 4.0 mm) Clinical Study	RESOLUTE ONYX 2.0 mm Clinical Study	RESOLUTE ONYX™ Post-Approval Study Primary Cohort	RESOLUTE ONYX™ Post-Approval Study XLV Cohort	RESOLUTE ONYX™ Post-Approval Study Bifurcation Cohort
Study type	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Historical controlled trial	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Compared to a performance goal	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Compared to a performance goal	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Descriptively evaluate the TLF rate	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Compared to a performance goal
Study site location	United States	United States and Japan	United States and Europe	United States and Europe	United States and Europe
Number of subjects enrolled	75	101	416	101	205
Lesion criteria	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤35 mm ▪ Target vessel with RVD between 2.25 to 4.2 mm	▪ Single or two *de novo* lesions located in separate target vessels with at least one of the target lesions amenable to treatment with a 2.0 mm study stent ▪ Lesion(s) length ≤27 mm ▪ Target vessel with RVD between 2.0 to 2.25 mm	▪ Lesions located in separate target vessels with at least one of the target lesions amenable to treatment with a 2.0 to 4.0 mm stent ▪ Lesion(s) length ≤35 mm	▪ Lesions located in separate target vessels with at least one of the target lesions amenable to treatment with a 4.5 or 5.0 mm stent ▪ Lesion(s) length ≤35 mm	▪ Single *de novo* bifurcated lesion amenable to treatment with a 2.0 to 5.0 mm stent with provisional stenting technique ▪ Lesion(s) length ≤35 mm
Stent sizes (Resolute Onyx™)	Stent diameter: 2.25 to 4.0 mm Stent length: 8 to 38 mm	Stent diameter: 2.0 mm Stent length: 8 to 30 mm	Stent diameter: 2.0 to 4.0 mm Stent length: 8 to 38 mm	Stent diameter: 4.5 to 5.0 mm Stent length: 12 to 30 mm	Stent diameter: 2.0 to 5.0 mm Stent length: 8 to 38 mm
Product used	Resolute Onyx™ stent on a rapid exchange (RX) stent delivery system	Resolute Onyx™ stent on a rapid exchange (RX) stent delivery system	Resolute Onyx™ stent on a rapid exchange (RX) or over-the-wire (OTW) stent delivery system	Resolute Onyx™ stent on a rapid exchange (RX) or over-the-wire (OTW) stent delivery system	Resolute Onyx™ stent on a rapid exchange (RX) or over-the-wire (OTW) stent delivery system
Post-procedure antiplatelet therapy	Aspirin indefinitely and market approved thienopyridine (clopidogrel, prasugrel, ticagrelor, ticlopidine, etc.) for a minimum of 6 months in all subjects, and up to 12 months in subjects who are not at high risk of bleeding	Aspirin indefinitely and market approved thienopyridine (clopidogrel, prasugrel, ticagrelor, ticlopidine, etc.) for a minimum of 6 months in all subjects, and up to 12 months in subjects who are not at high risk of bleeding	Antiplatelet medication should be administered according to hospital routine and in line with the applicable guidelines on percutaneous coronary interventions and the Instructions for Use of the device.	Antiplatelet medication should be administered according to hospital routine and in line with the applicable guidelines on percutaneous coronary interventions and the Instructions for Use of the device.	Antiplatelet medication should be administered according to hospital routine and in line with the applicable guidelines on percutaneous coronary interventions and the Instructions for Use of the device.
Follow-up	30 days, 6 months, 1 to 3 years: clinical or contact 8 months: clinical and angiographic, IVUS (subset)	30 days, 6 months, 1 to 3 years: clinical or contact 13 months: clinical and angiographic, IVUS (subset)	30 days, 6 months, 1 year, 2 years, 3 years: clinical or contact	30 days, 6 months, 1 year, 2 years, 3 years: clinical or contact	30 days, 6 months, 1 year, 2 years, 3 years: clinical or contact

Table 8-1: The RESOLUTE ONYX Clinical Program

	RESOLUTE ONYX™ Core (2.25 mm – 4.0 mm) Clinical Study	RESOLUTE ONYX 2.0 mm Clinical Study	RESOLUTE ONYX™ Post-Approval Study Primary Cohort	RESOLUTE ONYX™ Post-Approval Study XLV Cohort	RESOLUTE ONYX™ Post-Approval Study Bifurcation Cohort
Status	8 months: clinical and angiographic follow-up is complete	13 months: clinical and angiographic follow-up is complete	12 months: clinical follow-up is complete	Enrollment complete, in follow-up	Enrollment complete, in follow-up

8.2 Supportive RESOLUTE and RESOLUTE INTEGRITY data:

The Resolute Onyx™ stent is an iterative design update to the Resolute Integrity™ stent, utilizing the same continuous sinusoid manufacturing technology with slight modifications incorporated to provide a lower crossing profile and thus improved deliverability over predicate products. Given the similarities between the Resolute stent system and the Resolute Onyx™ stent system, and supportive bench and animal study information, the findings from the RESOLUTE clinical studies are applicable to the Resolute Onyx™ stent system.

The principal safety and effectiveness information for the Resolute stent was derived from the Global RESOLUTE Clinical Trial Program, which consists of the following clinical trials – the RESOLUTE United States Clinical Trial (R-US), the RESOLUTE All-Comers Clinical Trial (R-AC), the RESOLUTE International Study (R-Int), the RESOLUTE First-in-Man (FIM) Clinical Trial, and the RESOLUTE Japan Clinical Trial (R-J). These 5 studies have evaluated the performance of the Resolute stent in improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to *de novo* lesions of length ≤35 mm in native coronary arteries with reference vessel diameters of 2.25 mm to 4.2 mm. Key elements of these studies are summarized below and in

Table 8-2: RESOLUTE and RESOLUTE INTEGRITY clinical trials overview

. The Resolute 38 mm Length Group was derived from subjects enrolled in the R-US and the RESOLUTE Asia study (R-Asia) (for 38 mm Length Group data see

Table 8-2: RESOLUTE and RESOLUTE INTEGRITY clinical trials overview

). In addition, the RESOLUTE INTEGRITY US Post Market Study, a prospective, multi-center evaluation of the procedural and clinical outcomes of subjects who were treated with the Medtronic Resolute Integrity™ zotarolimus-eluting coronary stent system was designed to assess the safety and efficacy of the Resolute Integrity™ stent for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) of 2.25 mm to 4.2 mm in two groups of patients, specifically those patients receiving stents ≤30 mm in length, referred to as the Primary Enrollment Group (PEG) and those patients who receive extended length stents (34 mm or 38 mm) referred to as the Extended Length (XL) Sub-study.

Table 8-2: RESOLUTE and RESOLUTE INTEGRITY clinical trials overview

summarizes the clinical trial designs for the Global RESOLUTE Clinical Trial Program and RESOLUTE INTEGRITY US Post-Market Study.

Table 8-2: RESOLUTE and RESOLUTE INTEGRITY clinical trials overview

Global RESOLUTE Clinical Trial Program						RESOLUTE Asia 38 mm Cohort	RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan		RESOLUTE INTEGRITY US (PEG)	RESOLUTE INTEGRITY US (XL Sub-study)
Study type	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Historical controlled trial*	▪ Prospective ▪ Multi-center ▪ Randomized (1:1 Resolute vs. Xience V®) ▪ Two-arm, non-inferiority trial ▪ Real World subject population	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Observational study ▪ Real World subject population	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Historical controlled trial ▪ PK Assessment	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Historical controlled trial	▪ Prospective ▪ Multi-center ▪ Non-randomized	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Post approval	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Post approval
Number of subjects enrolled	Total: 1516 - 2.25–3.5 mm Main Study - 1242 subjects - 2.25 mm Cohort - 150 subjects - 2.25–3.5 mm Angio/IVUS sub-study - 100 subjects - 4.0 mm Sub-study - 60 subjects - 38 mm Sub-study -114 subjects (38 mm Sub-study total patient population was 223 with 114 from RESOLUTE US and 109 from RESOLUTE Asia)	Total: 2292 (Resolute: 1140, Xience V®: 1152)	Total: 2349	Total: 139	Total: 100	Total: 109	Total:230	Total: 56

Table 8-2: RESOLUTE and RESOLUTE INTEGRITY clinical trials overview

	Global RESOLUTE Clinical Trial Program					RESOLUTE Asia 38 mm Cohort	RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	**RESOLUTE AC[1]**	**RESOLUTE Int[2]**	**RESOLUTE FIM[3]**	**RESOLUTE Japan**		**RESOLUTE INTEGRITY US (PEG)**	**RESOLUTE INTEGRITY US (XL Sub-study)**
Lesion criteria	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤27 mm for the Primary Enrollment Group, ≤35 mm for the 38 mm Length Group ▪ Target vessel with RVD between 2.25 to 4.2 mm	▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 to 4.0 mm	▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 to 4.0 mm	▪ Single *de novo* lesion ▪ Lesion length from 14 to 27 mm ▪ Target vessel with RVD between 2.5 and 3.5 mm	▪ Single or two *de novo* lesions located in separate coronary arteries ▪ Lesion(s) length ≤27 mm ▪ Target vessel with RVD between 2.5 to 3.5 mm	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤35 mm ▪ Target vessel with RVD between 3.0 to 4.0 mm ▪ Patients may have received treatment of up to two lesions second lesion RVD (2.25 to 4.2 mm), if the lesions were located in separate target vessels.	▪ Single target lesion or two target lesions located in separate target vessels **PEG:** ▪ Target lesion ≤27 mm ▪ Target vessel with RVD between 2.25 to 4.2 mm	▪ Single target lesion or two target lesions located in separate target vessels **XL:** ▪ Target lesion ≤35 mm treated or lesion length ▪ Target vessel with RVD between 2.25 to 4.2 mm
Stent sizes (Resolute)	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm for the Primary Enrollment Group, 38 mm for the 38 mm Length Group	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 38 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent length: 38 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent length: 34-38 mm
Product used	Resolute stent on the rapid exchange sprint delivery system	Resolute stent on the rapid exchange sprint delivery system	Resolute stent on the rapid exchange sprint delivery system	Resolute stent on the rapid exchange AV100 delivery system	Resolute stent on the rapid exchange sprint delivery system	Resolute stent on the rapid exchange sprint delivery system	Resolute Integrity stent on the rapid exchange MicroTrac delivery system	Resolute Integrity stent on the rapid exchange MicroTrac delivery system
Post-procedure antiplatelet therapy	Aspirin indefinitely and clopidogrel/ticlopidine for ≥6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine ≥6 months	Aspirin indefinitely and clopidogrel/ticlopidine for ≥6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥6 months in all subjects, up to 12 months if tolerated

Table 8-2: RESOLUTE and RESOLUTE INTEGRITY clinical trials overview

	Global RESOLUTE Clinical Trial Program					RESOLUTE Asia 38 mm Cohort	RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	**RESOLUTE AC[1]**	**RESOLUTE Int[2]**	**RESOLUTE FIM[3]**	**RESOLUTE Japan**		**RESOLUTE INTEGRITY US (PEG)**	**RESOLUTE INTEGRITY US (XL Sub-study)**
Follow-up	2.25 mm - 3.5 mm Main Study: 30 days and 9 months: clinical; 6, 12 and 18 months, 2-5 years: telephone 4.0 mm Sub-study: 8 months: clinical and angiographic; 6, 12 and 18 months, 2-5 years: telephone 2.25 mm - 3.5 mm Angio/IVUS Sub-study: 8 months: clinical and angiographic/ IVUS;6, 12 and 18 months, 2-5 years: telephone 38 mm Length Sub-study: 30 days (R-US) and 9 months clinical visits (preferred) or patient contact 30 days (R-Asia), 6, 12, 18 months then annually at 2, 3, 4, 5 years	30 days and 12 months: clinical 13 months (455 subject subset): angiographic 6 months and 2-5 years: telephone	30 days, 6 months, 1-3 years: clinical or telephone	30 days: clinical 4 (30 subject subset) and 9 months (100 subject subset): clinical and angiographic/IVUS 6 months and 1-5 years: telephone	30 days and 12 months: clinical 8 months: angiographic/IVUS 6, 9 and 18 months and 2-5 years: telephone	30 days, 6, 9 (clinical visit), 12, 18 months then annually at 2 - 5 years	30 days (contact); 6 months (contact); 12 months (clinic visit with 12-lead ECG) and 2 years: (contact)	30 days (contact); 6 months (contact); 12 months (clinic visit with 12-lead ECG) and 2 years: (contact) 3 years (contact)
Status	60-month follow-up is complete. 551 subjects qualified for 18-month follow-up	60-month follow-up is complete	36-month follow-up is complete	60-month follow-up complete	60-month follow-up is complete	60-month follow-up is complete	24-month follow-up is complete	36-month follow-up is complete

Table 8-2: RESOLUTE and RESOLUTE INTEGRITY clinical trials overview

Global RESOLUTE Clinical Trial Program						RESOLUTE Asia 38 mm Cohort	RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan		RESOLUTE INTEGRITY US (PEG)	RESOLUTE INTEGRITY US (XL Sub-study)

* The RESOLUTE US trial is composed of 4 studies. The 2.5 mm - 3.5 mm subset of the Main Study, the 2.25 mm – 3.5 mm Angio/IVUS Sub-study, the 38 mm Length Sub-study, and the 4.0mm Sub-study have historical control designs. The 2.25 mm Subset outcomes were compared to a performance goal.

[1] The term 'AC' refers to All-Comers.

[2] The term 'Int' refers to International.

[3] The term 'FIM' refers to First-In-Man.

9 Clinical outcomes

9.1 Clinical outcomes for RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study and RESOLUTE ONYX 2.0 mm Clinical Study

Table 9-1: Resolute Onyx™ clinical outcomes

Safety and effectiveness measures	RESOLUTE ONYX Core (2.25 mm - 4.0 mm) Clinical Study (N=75 subjects N=85 lesions) %(m/n)[1]	RESOLUTE ONYX 2.0 mm Clinical Study (N=101 subjects N=104 lesions) %(m/n)[1]
In-hospital		
Target lesion failure (TLF)[2]	4.0% (3/75)	2.0% (2/101)
Target vessel failure (TVF)[3]	4.0% (3/75)	2.0% (2/101)
MACE[4]	4.0% (3/75)	2.0% (2/101)
Cardiac death or target vessel MI (TVMI)[5]	2.7% (2/75)	2.0% (2/101)
Death or TVMI	2.7% (2/75)	2.0% (2/101)
Death	0.0% (0/75)	0.0% (0/101)
Cardiac death	0.0% (0/75)	0.0% (0/101)
Non-cardiac death	0.0% (0/75)	0.0% (0/101)
TVMI (extended historical definition)[6]	2.7% (2/75)	2.0% (2/101)
Clinically-driven TLR[7]	1.3% (1/75)	0.0% (0/101)
Clinically-driven TVR[8]	1.3% (1/75)	0.0% (0/101)
Stent thrombosis (ARC) definite/probable[9]	1.3% (1/75)	0.0% (0/101)
30 days		
MACE	4.0% (3/75)	2.0% (2/101)
Follow-up (12-months)		
Target lesion failure (TLF)[2]	9.3% (7/75)	5.0% (5/101)
Target vessel failure (TVF)[3]	14.7% (11/75)	5.0% (5/101)
MACE[4]	13.3% (10/75)	5.0% (5/101)
Cardiac death or target vessel MI (TVMI)[5]	4.0% (3/75)	3.0% (3/101)
Death or TVMI	6.7% (5/75)	3.0% (3/101)
Death	2.7% (2/75)	0.0% (0/101)
Cardiac death	0.0% (0/75)	0.0% (0/101)
Non-cardiac death	2.7% (2/75)	0.0% (0/101)
TVMI (extended historical definition) [6]	4.0% (3/75)	3.0% (3/101)
Clinically-driven TLR[7]	5.3% (4/75)	2.0% (2/101)
Clinically-driven TVR[8]	10.7% (8/75)	2.0% (2/101)
Stent thrombosis (ARC) definite/probable[9]	1.3% (1/75)	0.0% (0/101)
Early thrombosis (≤30 days)	1.3% (1/75)	0.0% (0/100)
Late thrombosis (31-360 days)	0.0% (0/75)	0.0% (0/101)
Latest follow-up (36-months)		
Target lesion failure (TLF)[2]	14.7% (11/75)	13.9% (14/101)

Table 9-1: Resolute Onyx™ clinical outcomes

Safety and effectiveness measures	RESOLUTE ONYX Core (2.25 mm - 4.0 mm) Clinical Study (N=75 subjects N=85 lesions) %(m/n)[1]	RESOLUTE ONYX 2.0 mm Clinical Study (N=101 subjects N=104 lesions) %(m/n)[1]
Target vessel failure (TVF)[3]	18.7% (14/75)	14.9% (15/101)
MACE[4]	21.3% (16/75)	14.9% (15/101)
Cardiac death or target vessel MI (TVMI)[5]	9.3% (7/75)	5.9% (6/101)
Death or TVMI	14.7% (11/75)	6.9% (7/101)
Death	8.0% (6/75)	3.0% (3/101)
Cardiac death	2.7% (2/75)	2.0% (2/101)
Non-cardiac death	5.3% (4/75)	1.0% (1/101)
TVMI (extended historical definition) [6]	8.0% (6/75)	4.0% (4/101)
Clinically-driven TLR[7]	8.0% (6/75)	7.9% (8/101)
Clinically-driven TVR[8]	13.3% (10/75)	10.9% (11/101)
Stent thrombosis (ARC) definite/probable[9]	1.3% (1/75)	0.0% (0/101)
Early thrombosis (≤30 days)	1.3% (1/75)	0.0% (0/101)
Late thrombosis (31-360 days)	0.0% (0/75)	0.0% (0/101)
Very late thrombosis (>360 days)	0.0% (0/75)	0.0% (0/101)

Table 9-1: Resolute Onyx™ clinical outcomes

Safety and effectiveness measures	RESOLUTE ONYX Core (2.25 mm - 4.0 mm) Clinical Study (N=75 subjects N=85 lesions) %(m/n)[1]	RESOLUTE ONYX 2.0 mm Clinical Study (N=101 subjects N=104 lesions) %(m/n)[1]

Notes

[1]N = The total number of subjects enrolled.
The numbers are % (count/number of eligible subjects).
Subjects are only counted once for each time period.
NA = Not applicable; variable and/or time point not calculated
In-hospital is defined as hospitalization less than or equal to the discharge date
12-month timeframe includes follow-up window (360 days ± 30 days).
36-month timeframe includes follow-up window (1080 days ± 30 days).
[2]Target lesion failure (TLF) is defined as any cardiac death, clinically-driven target lesion revascularization by PCI or CABG or target vesse MI.
[3]Target vessel failure (TVF) is defined as any cardiac death, clinically-driven target vessel revascularization by PCI or CABG or target vessel MI.
[4]Major adverse cardiac events (MACE) is defined as composite of death, MI (Q wave and non-Q wave), emergent bypass surgery, or clinically-driven target lesion revascularization (repeat PTCA or CABG).
[5]Cardiac death/TVMI is defined as cardiac death or myocardial infarction not clearly attributable to a non-target vessel.
[6]TVMI is composed of both Q wave and non-Q wave MI which are not clearly attributable to a non-target vessel.
Q wave MI defined when any occurrence of chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC, in the absence of timely cardiac enzyme data, or new pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data the CEC may adjudicate Q wave MI based on the clinical scenario and appropriate cardiac enzyme data.
Non-Q Wave MI is defined as elevated CK ≥ 2X the upper laboratory normal with the presence of elevated CK-MB (any amount above the institution's upper limit of normal) in the absence of new pathological Q waves.
[Note: Periprocedural MIs (events <48 hours post-PCI) that did not fulfill the criteria for Q-wave MI are included in Non-Q Wave MI category. Periprocedural MIs did not require clinical symptoms or ECG evidence of myocardial ischemia, and in the absence of CK measurements, were based on an elevated CKMB > 3 X the upper laboratory normal, an elevated troponin > 3 X the upper laboratory normal, or CEC adjudication of the clinical scenario.]
[7]Target lesion revascularization (TLR) is defined as a clinically-driven repeat intervention of the target lesion by PCI or CABG
[8]Target vessel revascularization (TVR) is defined as any clinically-driven repeat intervention of the target vessel by PCI or CABG.
[9] Academic Research Consortium (ARC) stent thrombosis is defined as follows.

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: Any unexplained death within the first 30 days following stent implantation. 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

See **Section 10 - Clinical studies** for a more complete description of the trial designs and results.

The Global RESOLUTE Clinical Trial Program has evaluated the performance of the Resolute stent in subjects, including those with diabetes mellitus, with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. The RESOLUTE INTEGRITY US Post-Market Approval Study assessed the safety and efficacy of the Resolute Integrity™ stent for the treatment of *de novo* lesions in native coronary arteries. Clinical outcomes are shown in

Table 9-2: Clinical outcomes from post-procedure through latest available follow-up

below.

Table 9-2: Clinical outcomes from post-procedure through latest available follow-up

	RESOLUTE US[1]	RESOLUTE AC		RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US	
	Resolute (N = 1402)	Resolute (N = 1140)	Xience V® (N = 1152)	Resolute (N = 2349)	Resolute (N = 139)	Resolute (N = 100)	Resolute (N = 223)	Resolute Integrity (PEG) (N=230)	RESOLUTE INTEGRITY US (XL Sub-study) (N=56)
In-hospital									
TLF	1.3% (18/1402)	3.7% (42/1140)	4.5% (52/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
TVF	1.3% (18/1402)	3.8% (43/1140)	4.7% (54/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
MACE	1.3% (18/1402)	3.8% (43/1140)	4.9% (56/1152)	2.7% (63/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
Total Death	0.0% (0/1402)	0.1% (1/1140)	0.8% (9/1152)	0.3% (7/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Cardiac death	0.0% (0/1402)	0.1% (1/1140)	0.6% (7/1152)	0.3% (6/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Non-cardiac death	0.0% (0/1402)	0.0% (0/1140)	0.2% (2/1152)	0.0% (1/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.0% (0/230)	0.0% (0/56)
TVMI[5]	1.1% (16/1402)	3.1% (35/1140)	3.6% (42/1152)	2.2% (51/2349)	4.3% (6/139)	2.0% (2/100)	3.1% (7/223)	1.7% (4/230)	1.8% (1/56)
Q wave MI	0.1% (1/1402)	0.3% (3/1140)	0.4% (5/1152)	0.3% (8/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Non-Q wave MI	1.1% (15/1402)	2.8% (32/1140)	3.2% (37/1152)	1.8% (43/2349)	4.3% (6/139)	2.0% (2/100)	2.7% (6/223)	1.7% (4/230)	1.8% (1/56)
Cardiac death or TVMI	1.1% (16/1402)	3.2% (36/1140)	4.0% (46/1152)	2.4% (56/2349)	4.3% (6/139)	2.0% (2/100)	3.6% ((8/223)	1.7% (4/230)	1.8% (1/56)
Clinically-driven TVR	0.1% (2/1402)	0.9% (10/1140)	0.9% (10/1152)	0.4% 10/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.4% (1/230)	0.0% (0/56)
TLR	0.1% (2/1402)	0.7% (8/1140)	0.7% (8/1152)	0.4% (10/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.4% (1/230)	0.0% (0/56)
Non-TL TVR	0.0% (0/1402)	0.4% (4/1140)	0.2% (2/1152)	0.0% (1/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.0% (0/230)	0.0% (0/56)
ARC Def/Prob ST	0.0% (0/1402)	0.6% (7/1140)	0.3% (4/1152)	0.4% (9/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	1.8% (1/56)
30 days									
MACE	1.4% (20/1399)	4.4% (50/1133)	5.2% (60/1146)	3.3% (78/2345)	4.3% (6/139)	3.0% (3/100)	4.5% (10/223)	3.0% (7/230)	3.6% (2/56)
12 months									
TLF	4.7% (65/1390)	8.1% (92/1132)	8.5% (97/1142)	7.1% (165/2337)	7.2% (10/139)	4.0% (4/100)	5.4% (12/222)	4.9% (11/226)	7.1% (4/56)
TVF	6.2% (86/1390)	8.9% (101/1132)	9.7% (111/1142)	7.7% (180/2337)	7.2% (10/139)	5.0% (5/100)	6.8% (15/222)	7.1% (16/226)	7.1% (4/56)
MACE	5.5% (77/1390)	8.6% (97/1132)	9.8% (112/1142)	8.3% (193/2337)	8.6% (12/139)	5.0% (5/100)	6.3% (14/222)	5.8% (13/226)	8.9% (5/56)
Total death	1.4% (19/1390)	1.6% (18/1132)	2.7% (31/1142)	2.4% (57/2337)	2.2% (3/139)	1.0% (1/100)	0.9% (2/222)	1.8% (4/226)	1.8% (1/56)
Cardiac death	0.7% (10/1390)	1.3% (15/1132)	1.7% (19/1142)	1.5% (34/2337)	0.7% (1/139)	0.0% (0/100)	0.9% (2/222)	1.3% (3/226)	1.8% (1/56)
Non-cardiac death	0.6% (9/1390)	0.3% (3/1132)	1.1% (12/1142)	1.0% (23/2337)	1.4% (2/139)	1.0% (1/100)	0.0% (0/222)	0.4% (1/226)	0.0% (0/56)

Table 9-2: Clinical outcomes from post-procedure through latest available follow-up

	RESOLUTE US[1]	RESOLUTE AC		RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US	
TVMI	1.3% (18/1390)	4.2% (48/1132)	4.2% (48/1142)	3.0% (71/2337)	5.8% (8/139)	4.0% (4/100)	3.6% (8/222)	2.2% (5/226)	5.4% (3/56)
Q wave MI	0.1% (2/1390)	0.8% (9/1132)	0.4% (5/1142)	0.5% (12/2337)	0.0% (0/139)	0.0% (0/100)	0.9% (2/222)	0.0% (0/226)	1.8% (1/56)
Non-Q wave MI	1.2% (16/1390)	3.5% (40/1132)	3.8% (43/1142)	2.5% (59/2337)	5.8% (8/139)	4.0% (4/100)	2.7% (6/222)	2.2% (5/226)	3.6% (2/56)
Cardiac death or TVMI	2.0% (28/1390)	5.3% (60/1132)	5.5% (63/1142)	4.2% (99/2337)	6.5% (9/139)	4.0% (4/100)	4.5% (10/222)	3.5% (8/226)	7.1% (4/56)
Clinically-driven TVR	4.6% (64/1390)	4.9% (55/1132)	4.8% (55/1142)	4.2% (99/2337)	0.7% (1/139)	1.0% (1/100)	2.7% (6/222)	4.4% (10/226)	1.8% (1/56)
TLR	2.9% (40/1390)	3.9% (44/1132)	3.4% (39/1142)	3.5% (81/2337)	0.7% (1/139)	0.0% (0/100)	1.4% (3/222)	2.2% (5/226)	1.8% (1/56)
Non-TL TVR	2.2% (30/1390)	1.9% (21/1132)	2.2% (25/1142)	1.2% (27/2337)	0.0% (0/139)	1.0% (1/100)	1.4% (3/222)	2.2% (5/226)	0.0% (0/56)
ARC Def/Prob ST	0.1% (2/1390)	1.6% (18/1132)	0.7% (8/1142)	0.9% (20/2337)	0.0% (0/139)	0.0% (0/100)	0.9% (2/222)	0.9% (2/226)	1.8% (1/56)
Latest follow-up	**60 months**	**60 months**		**36 months**	**60 months**	**60 months**	**60 months**	**24 months**	**36 months**
TLF	12.3% (164/1329)	17.0% (191/1123)	16.2% (183/1133)	11.4% (261/2284)	11.0% (15/136)	6.1% (6/98)	13.8% (30/217)	9.1% (20/219)	10.7% (6/56)
TVF	17.5% (233/1329)	20.0% (225/1123)	19.1% (216/1133)	12.9% (294/2284)	13.2% (18/136)	10.2% (10/98)	17.1% (37/217)	12.3% (27/219)	12.5% (7/56)
MACE	18.0% (239/1329)	21.9% (246/1123)	21.6% (245/1133)	14.4% (329/2284)	16.2% (22/136)	14.3% (14/98)	17.5% (38/217)	11.0% (24/219)	17.9% (10/56)
Total death	9.6% (127/1329)	11.0% (123/1123)	10.8% (122/1133)	6.1% (139/2284)	6.6% (9/136)	7.1% (7/98)	6.5% (14/217)	2.7% (6/219)	3.6% (2/56)
Cardiac death	4.1% (55/1329)	6.5% (73/1123)	5.7% (65/1133)	3.6% (82/2284)	1.5% (2/136)	1.0% (1/98)	4.1% (9/217))	1.8% (4/219)	1.8% (1/56)
Non-cardiac death	5.4% (72/1329)	4.5% (50/1123)	5.0% (57/1133)	2.5% (57/2284)	5.1% (7/136)	6.1% (6/98)	2.3% (5/217)	0.9% (2/219)	1.8% (1/56)
TVMI	3.2% (43/1329)	5.7% (64/1123)	5.7% (65/1133)	3.9% (89/2284)	6.6% (9/136)	4.1% (4/98)	6.0% (13/217)	4.1% (9/219)	5.4% (3/56)
Q wave MI	0.4% (5/1329)	1.3% (15/1123)	0.8% (9/1133)	0.9% (20/2284)	0.0% (0/136)	0.0% (0/98)	0.9% (2/217)	0.9% (2/219)	1.8% (1/56)
Non-Q wave MI	2.9% (38/1329)	4.6% (52/1123)	4.9% (56/1133)	3.0% (69/2284)	6.6% (9/136)	4.1% (4/98)	5.1% (11/217)	3.2% (7/219)	3.6% (2/56)
Cardiac death or TVMI	6.7% (89/1329)	11.5% (129/1123)	10.6% (120/1133)	7.0% (161/2284)	8.1% (11/136)	5.1% (5/98)	8.8% (19/217)	5.9% (13/219)	7.1% (4/56)
Clinically-driven TVR	12.5% (166/1329)	11.4% (128/1123)	10.9% (123/1133)	7.4% (168/2284)	5.1% (7/136)	5.1% (5/98)	9.7% (21/217)	8.2% (18/219)	7.1% (4/56)
TLR	6.5% (86/1329)	7.8% (88/1123)	7.1% (81/1133)	5.7% (130/2284)	2.9% (4/136)	1.0% (1/98)	6.0% (13/217)	5.0% (11/219)	5.4% (3/56)
Non-TL TVR	8.1% (107/1329)	6.1% (68/1123)	6.1% (69/1133)	2.6% (59/2284)	2.2% (3/136)	4.1% (4/98)	3.7% (8/217)	4.1% (9/219)	5.4% (3/56)
ARC Def/Prob ST	0.5% (7/1329)	2.4% (27/1123)	1.7% (19/1133)	1.1% (26/2284)	0.0% (0/136)	0.0% (0/98)	1.4% (3/217)	1.8% (4/219)	1.8% (1/56)

Table 9-2: Clinical outcomes from post-procedure through latest available follow-up

	RESOLUTE US[1]	RESOLUTE AC	RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US

Notes

N = The total number of subjects enrolled.
The numbers are % (count/number of eligible subjects).
Subjects are only counted once for each time period.
The definitions of the outcomes are presented as table notes to **Error! Reference source not found.**
In-hospital is defined as hospitalization less than or equal to the discharge date
12-month timeframe includes follow-up window (360 days ± 30 days).
24-month timeframe includes follow-up window (720 days ±30 days).
36-month timeframe includes follow-up window (1080 days ± 30 days).
60-month timeframe includes follow-up window (1800 days ± 30 days).
[1] Primary Enrollment Group consisted of 1402 subjects, including 1242 subjects in the 2.25 mm - 3.5 mm Main Study, 100 subjects in the 2.25 mm - 3.5 mm Angio/IVUS Sub-study and 60 subjects in the 4.0 mm Sub-study. The Primary Enrollment Group does not include the 38 mm Length Sub-study.

In the RESOLUTE All-Comers (R-AC) trial, a randomized trial comparing the Resolute™ ZES with the Xience V™* EES for treatment of patients with coronary lesions who had minimal exclusion criteria, there were similar safety and efficacy outcomes between the 2 stents. Through 5 years of follow-up, the clinical effectiveness of the Resolute ZES was sustained in the complex and non-complex cohorts as shown in **Error! Reference source not found.**, **Error! Reference source not found.**, and **Error! Reference source not found.** below.

Table 9-3: R-AC Clinical outcomes (complex cohort)

Composite safety and effectiveness	Complex cohort			
	12 months		60 months	
	Resolute (N = 764)	Xience V® (N = 756)	Resolute (N = 764)	Xience V® (N = 756)
TLF	8.8% (67/760)	10.0% (75/750)	18.2% (137/751)	18.4% (137/745)
TVF	9.7% (74/760)	11.3% (85/750)	22.1% (166/751)	21.3% (159/745)
MACE	9.1% (69/760)	11.7% (88/750)	22.5% (169/751)	24.6% (183/745)
Effectiveness				
Clinically-driven TVR	5.5% (42/760)	5.6% (42/750)	13.4% (101/751)	11.7% (87/745)
TLR	4.3% (33/760)	4.1% (31/750)	8.9% (67/751)	8.1% (60/745)
TLR, PCI	3.9% (30/760)	3.2% (24/750)	8.1% (61/751)	6.7% (50/745)
TLR, CABG	0.4% (3/760)	1.1% (8/750)	1.2% (9/751)	1.7% (13/745)
Safety				
Total death	1.4% (11/760)	3.3% (25/750)	10.4% (78/751)	13.2% (98/745)
Cardiac death	1.3% (10/760)	2.1% (16/750)	6.4% (48/751)	7.4% (55/745)
Non-cardiac death	0.1% (1/760)	1.2% (9/750)	4.0% (30/751)	5.8% (43/745)
Cardiac death or TVMI	5.4% (41/760)	6.4% (48/750)	11.9% (89/751)	12.2% (91/745)
TVMI	4.2% (32/760)	4.7% (35/750)	5.9% (44/751)	6.0% (45/745)
Q wave MI	0.7% (5/760)	0.5% (4/750)	1.3% (10/751)	0.9% (7/745)

Table 9-3: R-AC Clinical outcomes (complex cohort)

Composite safety and effectiveness	Complex cohort			
	12 months		60 months	
	Resolute (N = 764)	Xience V® (N = 756)	Resolute (N = 764)	Xience V® (N = 756)
Non-Q wave MI	3.7% (28/760)	4.1% (31/750)	4.8% (36/751)	5.1% (38/745)
Stent thrombosis ARC defined				
Definite/probable	1.7% (13/759)	0.9% (7/749)	2.5% (19/751)	2.0% (15/745)
Definite	1.2% (9/759)	0.4% (3/749)	1.7% (13/751)	0.9% (7/745)
Probable	0.7% (5/759)	0.5% (4/749)	0.9% (7/751)	1.1% (8/745)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

Numbers are % (count/number of eligible subjects).

The definitions of the outcomes are presented as table notes to **Error! Reference source not found.**.

12-month timeframe includes follow-up window (360 ± 30 days)

60-month timeframe includes follow-up window (1800 days ± 30 days).

Complex was defined as having one or more of the following patient or lesion characteristics: bifurcation, bypass graft, in stent restenosis, AMI < 72 hr., LVEF < 30%, unprotected left main, >2 vessels stented, renal insufficiency or failure (serum creatinine >2.5 mg/dl), lesion length > 27 mm, > 1 lesion per vessel, lesion with thrombus or total occlusion (pre procedure TIMI = 0).

Table 9-4: R-AC clinical outcomes (non-complex cohort)

Composite safety and effectiveness	Non-complex cohort			
	12 months		60 months	
	Resolute (N = 376)	Xience V® (N = 396)	Resolute (N = 376)	Xience V® (N = 396)
TLF	6.7% (25/372)	5.6% (22/392)	14.5% (54/372)	11.9% (46/388)
TVF	7.3% (27/372)	6.6% (26/392)	15.9% (59/372)	14.7% (57/388)
MACE	7.5% (28/372)	6.1% (24/392)	20.7% (77/372)	16.0% (62/388)
Effectiveness				
Clinically-driven TVR	3.5% (13/372)	3.3% (13/392)	7.3% (27/372)	9.3% (36/388)
TLR	3.0% (11/372)	2.0% (8/392)	5.6% (21/372)	5.4% (21/388)
TLR, PCI	2.2% (8/372)	1.8% (7/392)	4.3% (16/372)	4.6% (18/388)
TLR, CABG	0.8% (3/372)	0.3% (1/392)	1.9% (7/372)	0.8% (3/388)
Safety				
Total death	1.9% (7/372)	1.5% (6/392)	12.1% (45/372)	6.2% (24/388)
Cardiac death	1.3% (5/372)	0.8% (3/392)	6.7% (25/372)	2.6% (10/388)
Non-cardiac death	0.5% (2/372)	0.8% (3/392)	5.4% (20/372)	3.6% (14/388)
Cardiac death or TVMI	5.1% (19/372)	3.8% (15/392)	10.8% (40/372)	7.5% (29/388)
TVMI	4.3% (16/372)	3.3% (13/392)	5.4% (20/372)	5.2% (20/388)
Q wave MI	1.1% (4/372)	0.3% (1/392)	1.3% (5/372)	0.5% (2/388)
Non-Q wave MI	3.2% (12/372)	3.1% (12/392)	4.3% (16/372)	4.6% (18/388)
Stent thrombosis ARC defined				
Definite/probable	1.3% (5/372)	0.3%(1/392)	2.2% (8/372)	1.0% (4/388)
Definite	1.1% (4/372)	0.0%(0/392)	1.3% (5/372)	0.5% (2/388)
Probable	0.3% (1/372)	0.3%(1/392)	0.8% (3/372)	0.5% (2/388)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

Numbers are % (count/number of eligible subjects).

The definitions of the outcomes are presented as table notes to **Error! Reference source not found.**.

12-month timeframe includes follow-up window (360± 30 days)

60-month timeframe includes follow-up window (1800 days ± 30 days).

Complex was defined as having one or more of the following patient or lesion characteristics: bifurcation, bypass graft, in stent restenosis, AMI < 72 hr., LVEF < 30%, unprotected left main, >2 vessels stented, renal insufficiency or failure (serum creatinine > 2.5 mg/dl), lesion length > 27 mm, > 1 lesion per vessel, lesion with thrombus or total occlusion (pre procedure TIMI = 0).

Table 9-5: R-AC ARC defined definite/probable stent thrombosis through 60 months (all subjects, and complex and non-complex subjects)

	All Subjects		Non-complex		Complex	
	Resolute (N = 1140)	Xience V® (N = 1152)	Resolute (N = 376)	Xience V® (N = 396)	Resolute (N = 764)	Xience V® (N = 756)
Cumulative stent thrombosis through 1-Year	1.6% (18/1132)	0.7% (8/1142)	1.3% (5/372)	0.3% (1/392)	1.7% (13/760)	0.9% (7/750)
Cumulative stent thrombosis through 5 -Years	2.4% (27/1123)	1.7% (19/1133)	2.2% (8/372)	1.0% (4/388)	2.5% (19/751)	2.0% (15/745)
Acute (0 - 1 day)	0.4% (5/1123)	0.2% (2/1133)	0.3% (1/372)	0.0% (0/388)	0.5% (4/751)	0.3% (2/745)
Subacute (2 - 30 days)	0.7% (8/1123)	0.4% (4/1133)	0.3% (1/372)	0.3% (1/388)	0.9% (7/751)	0.4% (3/745)
Late (31 – 360 days)	0.6% (7/1123)	0.2% (2/1133)	0.8% (3/372)	0.0% (0/388)	0.5% (4/751)	0.3% (2/745)
Very Late (361 – 1800 days)	0.8% (9/1123)	1.0% (11/1133)	0.8% (3/372)	0.8% (3/388)	0.8% (6/751)	1.1% (8/745)

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (count/number of eligible subjects).
12-month timeframe includes follow-up window (360 ± 30 days)
60-month timeframe includes follow-up window (1800 days ± 30 days).
Complex was defined as having one or more of the following patient or lesion characteristics: bifurcation, bypass graft, in stent restenosis, AMI < 72 hr., LVEF <30%, unprotected left main, >2 vessels stented, renal insufficiency or failure (serum creatinine > 2.5 mg/dl), lesion length > 27 mm, > 1 lesion per vessel, lesion with thrombus or total occlusion (pre procedure TIMI = 0).

9.2 Potential adverse events

9.2.1 Potential adverse events related to zotarolimus

Patients' exposure to zotarolimus is directly related to the total amount of stent length implanted. The actual side effects/complications that may be associated with the use of zotarolimus are not fully known.
The adverse events that have been associated with the intravenous injection of zotarolimus in humans include but are not limited to:

- Anemia
- Diarrhea
- Dry skin
- Headache
- Hematuria
- Infection
- Injection site reaction
- Pain (abdominal, arthralgia, injection site)
- Rash

9.2.2 Potential adverse events related to BioLinx™* polymer

Although the type of risks of the BioLinx™* polymer coating are expected to be no different than those of other stent coatings, the potential for these risks are currently unknown as the coating has limited previous use in humans. These risks may include but are not limited to the following:

- Allergic reaction
- Focal inflammation at the site of stent implantation
- Restenosis of the stented artery

9.2.3 Potential risks associated with percutaneous coronary diagnostic and treatment procedures

Other risks associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks (in alphabetical order) may include but are not limited to the following:

- Abrupt vessel closure
- Access site pain, hematoma, or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- Arrhythmias, including ventricular fibrillation
- Balloon rupture
- Bleeding
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue, device, or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension or hypertension
- Incomplete stent apposition
- Infection or fever
- Myocardial infarction (MI)
- Pericarditis
- Peripheral ischemia or peripheral nerve injury
- Renal failure
- Restenosis of the stented artery
- Shock or pulmonary edema
- Stable or unstable angina
- Stent deformation, collapse, or fracture
- Stent migration or embolization
- Stent misplacement
- Stroke or transient ischemic attack
- Thrombosis (acute, subacute, or late)

10 Clinical studies

10.1 Results of the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study

Primary objective: The purpose of this study was to assess the safety and efficacy of the Resolute Onyx™ zotarolimus-eluting coronary stent system for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.25 mm to 4.2 mm.

Design: The Medtronic RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study is a single arm, open label, multi-center trial that enrolled 75 subjects with ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to percutaneous treatment with stenting. Subjects may have received treatment of one or two lesions with stent diameters 2.25 mm - 4.0 mm, one lesion per target vessel, for a maximum of two target vessels. Only one lesion may have been treated in a single target vessel. All treatments with the study stents were to be performed during a single index procedure. All enrolled subjects had an 8 month angiogram to assess late lumen loss. The first 20 subjects were to also undergo an IVUS assessment at baseline and 8 months.

Primary endpoint: In-stent late lumen loss (LL) at 8-months post-procedure as measured by quantitative coronary angiography (QCA).

Follow-up was performed at 30 days, 6, and 8 months, and annually out to 3 years. Following the index procedure, subjects were to be treated with aspirin indefinitely and clopidogrel/ticlopidine for a minimum of 6 months and up to 12 months in those who were not at a high risk of bleeding.

Demographics: The mean age was 66 years with 73.3% (55/75) of subjects being males. Of the subjects enrolled, 32.0% (24/75) had diabetes mellitus, 16.0% (12/75) were current smokers, 23.0% (17/74) had prior MI, 40.0% (30/75) had prior PCI, 73.3% (55/75) had hypertension, and 85.3% (64/75) reported hyperlipidemia. Baseline lesion characteristics include 49.3% (37/75) of subjects with LAD lesions, a mean lesion length of 14.28 ± 6.68 mm, and 85.9% (73/85) ACC/AHA type B2/C lesions. The mean RVD was 2.57 ± 0.48 mm and the percentage diameter stenosis was 62.98 ± 10.75%.

Results: The primary end point of in-stent late lumen loss (LL) at 8-months post-procedure as measured by quantitative coronary angiography (QCA) demonstrated not only non-inferiority ($p < 0.001$), but also superiority ($p = 0.027$), when compared to the historical control in-stent late loss value from the RESOLUTE US Angio/IVUS Sub-study.

The RESOLUTE ONYX Core (2.25 mm to 4.0 mm) Clinical Study outcomes at 8-months are consistent with the 9 month clinical outcomes of the RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study that evaluated a similar patient population (with mandated angiographic follow up at 8 months). These analyses are based on the intent-to-treat population. The results are presented in the following tables:

- **Table** 10-1: RESOLUTE ONYX™ - primary endpoint analysis
- Table 10-2: RESOLUTE ONYX™ - clinical and Angio / IVUS outcomes
- Table 10-3: RESOLUTE ONYX™ - ARC defined definite/probable stent thrombosis through 8 months

Table 10-1: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – primary endpoint analysis (non-inferiority test with propensity score adjustment)

Primary endpoint – In-stent late lumen loss at 8 months	RESOLUTE ONYX Core (N=75 subjects N=85 lesions)	Historical control Resolute (N=100 subjects N=104 lesions)	Difference: RESOLUTE ONYX Core - historical control[1]	Upper one-sided 95% CI[2]	Non-inferiority margin	Non-inferiority P value	Superiority P value[3]
Primary analysis with available data:							
– ITT set	0.24 ± 0.05 (73)	0.36 ± 0.05 (93)	-0.14	-0.02	0.20	< 0.001	0.027
– PP set	0.24 ± 0.05 (66)	0.35 ± 0.05 (89)	-0.15	-0.02	0.20	< 0.001	0.027
Secondary analysis with multiple imputation:							
– ITT set	0.23 ± 0.05	0.36 ± 0.05	-0.15	-0.03	0.20	< 0.001	0.023
– PP set	0.22 ± 0.05	0.35 ± 0.05	-0.16	-0.03	0.20	< 0.001	0.023

[1] The Resolute Onyx Core measure non-inferiority of 8-month in-stent late lumen loss compared to 8-month in-stent late lumen loss of the historical control
All target lesions are included in the analysis. The treatment differences have been adjusted with propensity score quintile.
[2] The CI is adjusted to propensity score, based on lesion-length, baseline RVD, age, sex, diabetes, history of MI, and worst Canadian Cardiovascular Society Angina Class as the independent variables.
[3] Superiority test was performed after non-inferiority was demonstrated.

Table 10-2: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – clinical and Angio / IVUS outcomes

	RESOLUTE ONYX (N=75 subjects N=85 lesions) %(m/n)[1]
Safety measures (to 180 days)	
Target lesion failure (TLF)	5.3% (4/75)
Target vessel failure (TVF)	8.0% (6/75)
MACE	8.0% (6/75)
Cardiac death or target vessel MI (TVMI)	2.7% (2/75)
Death or TVMI	4.0% (3/75)
Death	1.3% (1/75)
Cardiac death	0.0% (0/75)
Noncardiac death	1.3% (1/75)
TVMI (extended historical definition)	2.7% (2/75)
Clinically-driven TLR	2.7% (2/75)
Clinically-driven TVR	5.3% (4/75)
Stent thrombosis (ARC) definite/probable	1.3% (1/75)
Safety measures (to 240 days)	
Target lesion failure (TLF)	6.7% (5/75)
Target vessel failure (TVF)	12.0% (9/75)
MACE	9.3% (7/75)
Cardiac death or target vessel MI (TVMI)	2.7% (2/75)
Death or TVMI	4.0% (3/75)
Death	1.3% (1/75)
Cardiac death	0.0% (0/75)
Non-cardiac death	1.3% (1/75)
TVMI (extended historical definition)	2.7% (2/75)
Clinically-driven TLR	4.0% (3/75)
Clinically-driven TVR	9.3% (7/75)
Stent thrombosis (ARC) definite/probable	1.3% (1/75)
Early thrombosis (≤30 days)	1.3% (1/75)
Late thrombosis (31-240 days)	0.0% (0/75)
Safety measures (to 1080 days)	
Target lesion failure (TLF)	14.7% (11/75)
Target vessel failure (TVF)	18.7% (14/75)
MACE	21.3% (16/75)
Cardiac death or target vessel MI (TVMI)	9.3% (7/75)
Death or TVMI	14.7% (11/75)
Death	8.0% (6/75)

Table 10-2: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – clinical and Angio / IVUS outcomes

	RESOLUTE ONYX (N=75 subjects N=85 lesions) %(m/n)[1]
Cardiac death	2.7% (2/75)
Non-cardiac death	5.3% (4/75)
TVMI (extended historical definition)	8.0% (6/75)
Clinically-driven TLR	8.0% (6/75)
Clinically-driven TVR	13.3% (10/75)
Stent thrombosis (ARC) definite/probable	1.3% (1/75)
Early thrombosis (≤30 days)	1.3% (1/75)
Late thrombosis (31-240 days)	0.0% (0/75)
Very Late thrombosis (>360 days)	0.0% (0/75)
Angiography (8 months)	
Percent diameter stenosis (% DS)	
In-stent	
n	73
Mean±SD	15.56 ± 16.75
Median (1Q, 3Q)	14.86 (5.26, 22.24)
Min, max	-21.18, 82.89
In-segment	
n	73
Mean±SD	25.84 ± 14.20
Median (1Q, 3Q)	22.35 (17.71, 29.75)
Min, max	4.99, 82.89
Minimal lumen diameter (mm)	
In-stent	
n	73
Mean±SD	2.13 ± 0.55
Median (1Q, 3Q)	2.14(1.80, 2.45)
Min, max	0.45, 3.69
In-segment	
n	73
Mean±SD	1.88 ± 0.49
Median (1Q, 3Q)	1.89 (1.58, 2.19)
Min, max	0.45, 3.10
Late luminal loss (mm)	
In-stent	

Table 10-2: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – clinical and Angio / IVUS outcomes

	RESOLUTE ONYX (N=75 subjects N=85 lesions) %(m/n)[1]
n	73
Mean±SD	0.24 ± 0.39
Median (1Q, 3Q)	0.18 (0.03, 0.37)
Min, max	-0.49, 2.06
In-segment	
n	73
Mean±SD	0.16 ± 0.37
Median (1Q, 3Q)	0.13 (-0.03, 0.29)
Min, max	-0.65, 1.88
In-stent binary angiographic restenosis (BAR) rate	5.5% (4/73)
In-segment binary angiographic restenosis (BAR) rate	8.2% (6/73)
IVUS (8 months)	
Incomplete stent apposition	
Persistent	10.0% (2/20)
Late	0.0% (0/20)
Neointimal hyperplastic volume (mm^3)	
n	17
Mean±SD (N)	9.88 ± 9.38
Median (Q1,Q3)	6.80 (2.20, 18.10)
Min, max	0.00, 27.20
Percent volume obstruction	
n	17
Mean±SD (N)	6.88 ± 8.00
Median (Q1,Q3)	4.52 (1.48, 8.79)
Min, max	0.00, 31.38
Effectiveness measures	
Lesion success[2]	100.0% (85/85)
Device success[3]	100.0% (85/85)
Procedure success[4]	96.0% (72/75)

Table 10-2: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – clinical and Angio / IVUS outcomes

	RESOLUTE ONYX (N=75 subjects N=85 lesions) %(m/n)[1]

[1]Numerator (m) is the number of subjects with the specific classification, denominator (n) is the number of subjects in the study group with known values, and percentage (%) was calculated as 100 × (m/n)

The definitions of the outcomes are presented as table notes to **Error! Reference source not found.**

[2]The attainment of <30% residual stenosis by QCA (or <20% by visual assessment) AND TIMI Flow 3 after the procedure, using any percutaneous method.

[3]The attainment of <30% residual stenosis by QCA (or <20% by visual assessment) AND TIMI Flow 3 after the procedure, using the assigned device only.

[4]The attainment of <30% residual stenosis by QCA (or <20% by visual assessment) AND TIMI Flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay.

8-month timeframe includes follow-up window (240 days ± 14 days).

Extended historical definition of MI is used for all the composite endpoints.

Table 10-3: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – ARC defined definite/probable stent thrombosis through 36 months

	RESOLUTE ONYX™ (N=75 subjects N=85 lesions) %(m/n)[1]
Stent thrombosis	1.3% (1/75)
Early thrombosis (≤30 days)	1.3% (1/75)
Late thrombosis (31-360 days)	0.0% (0/75)
Very late thrombosis (>360 days)	0.0% (0/75)

Notes

[1]N = The total number of subjects enrolled.

Numbers are % (count/number of eligible subjects).

Subjects are only counted once for each time period.

36-month timeframe includes follow-up window (1080 days ± 30 days).

See **Error! Reference source not found.** for the definition of the ARC defined stent thrombosis.

10.2 Results of the RESOLUTE ONYX 2.0 mm Clinical Study

Primary objective: The purpose of this study is to assess the safety and efficacy of the Resolute Onyx™ zotarolimus-eluting coronary stent system for the treatment of *de novo* lesions in native coronary arteries that require the use of a 2.0 mm diameter stent.

Design: The Medtronic RESOLUTE ONYX 2.0 mm Clinical Study is a single arm, open label, multi-center trial that enrolled 101 subjects in the US and Japan with ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to percutaneous treatment with stenting. Subjects may have received treatment of one or two lesions with stent diameter 2.0 mm, one lesion per target vessel, for a maximum of two target vessels. Only one lesion may have been treated in a single target vessel. All treatments with the study stents were to be performed during a single index procedure. The first 20 subjects were to undergo an angiogram assessment at 13 months.

Primary endpoint: Target lesion failure (TLF) at 12-months post-procedure, defined as cardiac death, target vessel myocardial infarction (TVMI) (Q wave or non-Q wave) or target lesion revascularization by percutaneous or surgical methods.

Follow-up was performed at 30 days, 6, 12, and 13 months, and annually out to 3 years. Following the index procedure, subjects were to be treated with aspirin indefinitely and clopidogrel/ticlopidine for a minimum of 6 months and up to 12 months in those who were not at a high risk of bleeding.

Demographics: The mean age was 67.3 years with 70.3% (71/101) of subjects being males. Of the subjects enrolled, 46.5% (47/101) had diabetes mellitus, 11.9% (12/101) were current smokers, 35.7% (35/98) had prior MI, 59.4% (60/101) had prior PCI, 82.2% (83/101) had hypertension, and 94.1% (95/101) reported hyperlipidemia. Baseline lesion characteristics include 36.6% (37/101) of subjects with LAD lesions, a mean lesion length of 12.59 ± 6.27mm, and 65.4% (68/104) ACC/AHA type B2/C lesions. The mean RVD was 1.91 ± 0.26 mm and the percentage diameter stenosis was 65.83 ± 10.89%.

Results: The rate of TLF in the ITT primary analysis set at 12 months was 5.0% (5/100), fulfilling the pre-specified performance criterion (upper 1-sided 95% CI of 10.2%, compared with the performance goal of 19%, $p < 0.001$). The primary endpoint was also analyzed by gender, resulting in a TLF rate of 7.0% (5/71) in male subjects and 0.0% (0/30) in female subjects.

These analyses are based on the intent-to-treat population. The results are presented in the following tables:

- Table 10-4: RESOLUTE ONYX™ 2.0 mm - primary endpoint analysis
- Table 10-5: RESOLUTE ONYX™ 2.0 mm - clinical and angiographic outcomes
- Table 10-6: RESOLUTE ONYX™ 2.0 mm - ARC defined definite/probable stent thrombosis through 12 months
- Table 10-7: RESOLUTE ONYX™ 2.0 mm – primary endpoint analysis by gender

Table 10-4: RESOLUTE ONYX 2.0 mm Clinical Study – primary endpoint analysis

Primary endpoint - TLF at 12-month	Resolute Onyx 2.0mm (N = 101 subjects)	One-side upper 95% confidence interval[1]	Performance goal
Primary analysis – with analysis lesion only [2]			
– ITT set	5.0% (5/100)	10.2%	19%
– PP set	2.2% (2/90)	6.8%	19%
Secondary analysis – with all lesions included [3]			
– ITT set	5.0% (5/100)	10.2%	19%
– PP set	2.2% (2/90)	6.8%	19%

[1] The one-sided upper 95% CI is calculated by binomial (exact) distribution
[2] The lesions with a Resolute Onyx 2.0 mm stent are included in the analysis. For 2 or more lesions with Resolute Onyx 2.0 mm stents per subject, the lesion is randomly selected.
[3] All target lesions are included in the analysis.

Table 10-5: RESOLUTE ONYX 2.0 mm Clinical Study – clinical and angiographic outcomes

Safety and effectiveness measures	RESOLUTE ONYX 2.0 mm (N=101 subjects N=104 lesions) %(m/n)[1]
Safety measures (to 180 days)	
Target lesion failure (TLF)[2]	4.0% (4/101)
Target vessel failure (TVF)[3]	4.0% (4/101)

Table 10-5: RESOLUTE ONYX 2.0 mm Clinical Study – clinical and angiographic outcomes

Safety and effectiveness measures	RESOLUTE ONYX 2.0 mm (N=101 subjects N=104 lesions) %(m/n)[1]
MACE[4]	4.0% (4/101)
Cardiac death or target vessel MI (TVMI)	3.0% (3/101)
Death or TVMI	3.0% (3/101)
Death	0.0% (0/101)
Cardiac death	0.0% (0/101)
Non-cardiac death	0.0% (0/101)
TVMI (extended historical definition)	3.0% (3/101)
Clinically-driven TLR	1.0% (1/101)
Clinically-driven TVR	1.0% (1/101)
Stent thrombosis (ARC) definite/probable	0.0% (0/101)
Safety measures (to 360 days)	
Target lesion failure (TLF)[2]	5.0% (5/101)
Target vessel failure (TVF)[3]	5.0% (5/101)
MACE[4]	5.0% (5/101)
Cardiac death or target vessel MI (TVMI)	3.0% (3/101)
Death or TVMI	3.0% (3/101)
Death	0.0% (0/101)
Cardiac death	0.0% (0/101)
Non-cardiac death	0.0% (0/101)
TVMI (extended historical definition)	3.0% (3/101)
Clinically-driven TLR	2.0% (2/101)
Clinically-driven TVR	2.0% (2/101)
Stent thrombosis (ARC) definite/probable	0.0% (0/101)
Early thrombosis (≤30 days)	0.0% (0/101)
Late thrombosis (31-360 days)	0.0% (0/101)
Safety measures (up to 1080 days)	
Target lesion failure (TLF)[2]	13.9% (14/101)
Target vessel failure (TVF)[3]	14.9% (15/101)
MACE[4]	14.9% (15/101)
Cardiac death or target vessel MI (TVMI)	5.9% (6/101)
Death or TVMI	6.9% (7/101)
Death	3.0% (3/101)
Cardiac death	2.0% (2/101)
Non-cardiac death	1.0% (1/101)
TVMI (extended historical definition)	4.0% (4/101)
Clinically-driven TLR	7.9% (8/101)
Clinically-driven TVR	10.9% (11/101)
Stent thrombosis (ARC) definite/probable	0.0% (0/101)
Early thrombosis (≤30 days)	0.0% (0/101)

Table 10-5: RESOLUTE ONYX 2.0 mm Clinical Study – clinical and angiographic outcomes

Safety and effectiveness measures	RESOLUTE ONYX 2.0 mm (N=101 subjects N=104 lesions) %(m/n)[1]
Late thrombosis (31-360 days)	0.0% (0/101)
Very late thrombosis (>360 days)	0.0% (0/101)
Angiography (13 months)	
Percent diameter stenosis (% DS)	
In-stent	
N	25
Mean±SD	22.49 ± 26.89
Median (Q1, Q3)	15.66 (9.57, 31.72)
Min, max	-26.71, 100.00
In-segment	
N	25
Mean±SD	37.92 ± 21.54
Median (Q1, Q3)	31.72 (23.54, 42.50)
Min, max	14.06, 100.00
Minimal lumen diameter (mm)	
In-stent	
N	25
Mean±SD	1.55 ± 0.52
Median (Q1, Q3)	1.63 (1.53, 1.81)
Min, max	0.00, 2.20
In-segment	
N	25
Mean±SD	1.25 ± 0.46
Median (Q1, Q3)	1.44 (1.09, 1.52)
Min, max	0.00, 1.77
Late luminal loss (mm)	
In-stent	
N	25
Mean±SD	0.26 ± 0.48
Median (Q1, Q3)	0.06 (0.00, 0.33)
Min, max	-0.42, 1.58
In-segment	
N	25
Mean±SD	0.25 ± 0.41
Median (Q1, Q3)	0.21 (-0.08, 0.42)
Min, max	-0.39, 1.30
In-stent binary angiographic restenosis (BAR) rate	12.0% (3/25)
In-segment binary angiographic restenosis (BAR) rate	20.0% (5/25)
Effectiveness measures	

Table 10-5: RESOLUTE ONYX 2.0 mm Clinical Study – clinical and angiographic outcomes

Safety and effectiveness measures	RESOLUTE ONYX 2.0 mm (N=101 subjects N=104 lesions) %(m/n)[1]
Lesion success[5]	99.0% (103/104)
Device success[6]	96.2% (100/104)
Procedure success[7]	97.0% (98/101)

[1]Numerator (m) is the number of subjects with the specific classification, denominator (n) is the number of subjects in the study group with known values, and percentage (%) was calculated as 100 × (m/n).
[2]Cardiac death, target vessel myocardial infarction (Q wave and non-Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods.
[3]Cardiac death, target vessel myocardial infarction (Q wave and non-Q wave) or clinically-driven target vessel revascularization (TVR) by percutaneous or surgical methods.
[4]Defined as death, myocardial infarction (Q wave and non Q-wave), emergent coronary bypass surgery, or repeat target lesion revascularization (clinically-driven/clinically-indicated) by percutaneous or surgical methods.
[5]The attainment of <30% residual stenosis by QCA (or <20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method.
[6]The attainment of <30% residual stenosis by QCA (or <20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only.
[7]The attainment of <30% residual stenosis by QCA (or <20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay.
Extended historical definition of MI is used for all the composite endpoints.

Table 10-6: RESOLUTE ONYX 2.0 mm Clinical Study – ARC defined definite/probable stent thrombosis through 12 months

	RESOLUTE ONYX 2.0 mm (N=101 subjects N=104 lesions) %(m/n)[1]
Stent thrombosis	0.0% (0/101)
Early thrombosis (≤30 days)	0.0% (0/101)
Late thrombosis (31-360 days)	0.0% (0/101)

Table 10-7: RESOLUTE ONYX 2.0 mm - primary endpoint analysis by gender

Primary endpoint	Male (N = 71 subjects)	Female (N = 30 subjects)
Target lesion failure to 12 months	7.0% (5/71)	0.0% (0/30)

10.3 Subjects with diabetes mellitus in the RESOLUTE pooled analysis

Subjects with diabetes mellitus (DM) comprise an important patient subgroup that is at increased risk for cardiovascular morbidity and mortality[5,6]. A Global Statistical Analysis Plan (GSAP) was created with a pre-specified hypothesis to evaluate the safety and effectiveness of the Resolute stent to treat stenotic lesions in diabetic subjects with coronary artery disease. This section provides an overview of this plan and the results supporting the indication of the Resolute stent to treat coronary artery disease in subjects with diabetes mellitus.

Primary objective: To assess the safety and effectiveness of the Resolute zotarolimus-eluting coronary stent system (Resolute stent) for the treatment of *de novo* lesions in native coronary arteries in patients with DM with a reference vessel diameter (RVD) of 2.25 mm to 4.2 mm.

Population: The study population for the GSAP was selected by combining subjects with DM from the Global RESOLUTE Clinical Trial Program. The study population selected for this analysis met pre-defined general and angiographic inclusion and exclusion criteria. Analysis populations consisted of consecutively enrolled eligible diabetic subjects in the trials noted below.

The following global RESOLUTE clinical trials contributed subjects to the diabetes mellitus cohort:

- RESOLUTE FIM
- RESOLUTE All-Comers (AC)
- RESOLUTE International (Int)
- RESOLUTE United States (US), and
- RESOLUTE Japan

In total there were 878 subjects included in the RESOLUTE DM cohort. RESOLUTE US provided the highest percentage of subjects at 54.9% (482/878) while RESOLUTE Int contributed 27.6% (242/878), RESOLUTE AC 9.7% (85/878), RESOLUTE Japan 5.1% (45/878), and RESOLUTE FIM 2.7% (24/878).

Subjects from the 38 mm Length sub-study are not included in this Resolute Pooled Analysis of Subjects with Diabetes Mellitus. Additional information is provided in **Section 10.4** for the Resolute US 38 mm Length Group for subjects with Diabetes Mellitus.

Design: The Resolute stent performance for treatment of lesions in patients with DM was compared with a performance goal (PG) derived from a meta-analysis of published studies of coronary DES use in DM subjects and from data from the ENDEAVOR pooled studies.

Inclusion of study subjects in this analysis were required to have DM defined by either a history of DM or use of medications to treat DM (i.e., oral hypoglycemics or insulin) at time of enrollment. The Resolute stent DM subjects and those included in the meta-analysis were also required to have clinical characteristics of an on-label population, consistent with the enrollment criteria of the RESOLUTE US Clinical Trial. That is, subjects with the following clinical or lesion characteristics were excluded: total lesion length per vessel >27mm, >2 lesions per vessel, unprotected left main lesions, bifurcation lesions, total occlusions, bypass grafts, acute MI within 72 hours of the index procedure, thrombus-containing lesions, left ventricular ejection fraction <30%, or renal impairment (serum creatinine >2.5 mg/dl).

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5 American Heart Association. Heart Disease and Stroke Statistics - 2008 Update. *www.americanheart.org/statistics* [Online publication]. Accessed 12 November 2008, 2008.

6 Fang J, Alderman MH. Impact of the increasing burden of diabetes on acute myocardial infarction in New York City: 1990-2000. *Diabetes.* 2006;55(3):768-773.

The Resolute DM TVF rate at 12-month follow-up was compared to a performance goal to demonstrate the safety and effectiveness of the Resolute stent in diabetic subjects. The objective of the primary endpoint analysis in the RESOLUTE DM cohort was to assess whether the true primary endpoint rate of 12-month target vessel failure (TVF) for the Resolute stent met the PG established as 14.5% (which is a 31% increase over the expected rate of 11.08% for DES use in DM subjects derived from the meta-analysis). The hypothesis for this analysis accounted for the differences in the protocols of the individual studies in the published literature, the ENDEAVOR pooled studies, and the Global RESOLUTE Clinical Trial Program. Specifically, in calculating the meta-analytic PG for DM subjects, adjustments were made to the 12-month TVF rate based on protocol-required follow-up angiography and protocol-required post-PCI cardiac biomarker measurements.

Demographics: The mean age of subjects was 65.2 years and 66.4% (583/878) were male. 28.5% (250/878) of the subjects were insulin-dependent diabetics. Of the subjects included in this analysis, 24.9% (216/867) of the subjects had a prior MI and 28.9% (254/878) were undergoing revascularization for unstable angina.

Primary endpoint: The primary endpoint was Target Vessel Failure (TVF) at 12 months following the intervention. The TVF composite endpoint includes cardiac death, MI that cannot be attributed to vessel(s) other than the target vessel, and clinically-driven target vessel revascularization (TVR).

Results: The analysis met the primary endpoint's performance goal of 14.5%, as the TVF rate of the DM Cohort was 7.84% at 12 months with an upper bound of the 95% CI of 9.51%.

These analyses are based on the intent-to-treat population. The results are presented in the following tables:

- Table 10-8: RESOLUTE diabetes mellitus cohort - primary endpoint analysis
- Table 10-9: RESOLUTE diabetes mellitus (DM) cohort: all DM subjects, insulin-dependent DM subjects (IDDM), non-insulin dependent DM subjects (non-IDDM), and non-DM subjects – principal safety and effectiveness
- Table 10-10: RESOLUTE diabetes mellitus cohort - ARC defined definite/probable stent thrombosis events through 12 months

Table 10-8: RESOLUTE diabetes mellitus cohort - primary endpoint analysis

Primary endpoint	RESOLUTE DM (N = 878)	Upper bound of 95%CI[1]	Performance goal	P-value[2]
12-month TVF	7.84% (68/867)	9.51%	14.5%	< 0.001

Notes

N is the total number of subjects.

Numbers are % (count/number of eligible subjects).

Subjects are only counted once for each time period.

The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual lesions.

12-month timeframe includes follow-up window (360 days ± 30 days).

[1] One-sided confidence interval using exact method.

[2] One-sided p-value using exact test statistic to be compared at a 0.05 significance level.

Table 10-9: RESOLUTE diabetes mellitus (DM) cohort: all DM subjects, insulin-dependent DM subjects (IDDM), non-insulin dependent DM subjects (non-IDDM), and non-DM subjects – principal safety and effectiveness through 12 months

	All DM subjects (N = 878)	IDDM (N = 250)	Non IDDM (N = 628)	Non DM (N = 1903)
Composite safety and effectiveness				
TLF	6.6% (57/867)	10.6% (26/246)	5.0% (31/621)	4.9% (92/1867)
TVF	8.1% (70/867)	11.8% (29/246)	6.6% (41/621)	5.9% (110/1867)
MACE	7.5% (65/867)	11.8% (29/246)	5.8% (36/621)	5.7% (106/1867)
Effectiveness				
Clinically-driven TVR	5.1% (44/867)	6.5% (16/246)	4.5% (28/621)	3.1% (57/1867)
TLR	3.3% (29/867)	5.3% (13/246)	2.6% (16/621)	2.0% (38/1867)
TLR, CABG	0.2% (2/867)	0.8% (2/246)	0.0% (0/621)	0.3% (6/1867)
TLR, PCI	3.1% (27/867)	4.5% (11/246)	2.6% (16/621)	1.7% (32/1867)
Non-TL TVR	2.2% (19/867)	1.6% (4/246)	2.4% (15/621)	1.3% (24/1867)
Non-TL TVR, CABG	0.1% (1/867)	0.0% (0/246)	0.2% (1/621)	0.2% (4/1867)
Non-TL TVR, PCI	2.1% (18/867)	1.6% (4/246)	2.3% (14/621)	1.1% (20/1867)
Safety				
Total death	2.8% (24/867)	4.1% (10/246)	2.3% (14/621)	1.0% (19/1867)
Cardiac death	2.0% (17/867)	2.8% (7/246)	1.6% (10/621)	0.4% (8/1867)
Non-cardiac death	0.8% (7/867)	1.2% (3/246)	0.6% (4/621)	0.6% (11/1867)
Cardiac death or TVMI	3.6% (31/867)	6.1% (15/246)	2.6% (16/621)	3.2% (59/1867)
TVMI	1.8% (16/867)	4.1% (10/246)	1.0% (6/621)	2.7% (51/1867)
Q wave MI	0.3% (3/867)	0.8% (2/246)	0.2% (1/621)	0.3% (5/1867)
Non-Q wave MI	1.5% (13/867)	3.3% (8/246)	0.8% (5/621)	2.5% (46/1867)
Stent thrombosis ARC defined				
Definite/probable	0.3% (3/867)	0.8% (2/246)	0.2% (1/621)	0.3% (6/1867)
Definite	0.2% (2/867)	0.4% (1/246)	0.2% (1/621)	0.2% (4/1867)
Probable	0.1% (1/867)	0.4% (1/246)	0.0% (0/621)	0.1% (2/1867)

Notes
N = The total number of subjects.
Numbers are % (count/number of eligible subjects).
Subjects are only counted once for each time period.
12-month timeframe includes follow-up window (360 days ± 30 days).
The definitions of the outcomes are presented as table notes to **Error! Reference source not found.**.

Table 10-10: RESOLUTE diabetes mellitus cohort - ARC defined definite/probable stent thrombosis events through 12 months

	Resolute (N = 878)
Stent thrombosis	0.3% (3/867)
Acute (0 to 1 day)	0.1% (1/867)
Subacute (2 to 30 days)	0.1% (1/867)
Late (31 to 360 days)	0.1% (1/867)

Notes
N is the total number of subjects.
Numbers are % (count/number of eligible subjects).
12-month time frame includes follow-up window (360 days ± 30 days).
Subjects are only counted once for each time period.

10.4 Subjects with diabetes mellitus in the RESOLUTE 38 mm length group

Additional information is provided in **Error! Reference source not found.** for the RESOLUTE 38 mm length group in subjects with diabetes mellitus.

Table 10-11: RESOLUTE 38 mm length group: all 38 mm subjects, insulin-dependent DM subjects (IDDM), mon-insulin dependent DM subjects (non-IDDM), and non-DM subjects – principal safety and effectiveness through 12 months

	All diabetic 38 mm length group subjects (N = 84 patients)	38 mm length group IDDM (N = 23 patients)	38 mm length group – non-IDDM (N = 61 patients)	38 mm length group – non-DM (N = 139 patients)
Composite safety and effectiveness				
TLF	6.0% (5/84)	4.3% (1/23)	6.6% (4/61)	5.1% (7/138)
TVF	7.1% (6/84)	4.3% (1/23)	8.2% (5/61)	6.5% (9/138)
MACE	8.3% (7/84)	4.3% (1/23)	9.8% (6/61)	5.1% (7/138)
Effectiveness				
Clinically-driven TVR	3.6% (3/84)	0.0% (0/23)	4.9% (3/61)	2.2% (3/138)
TLR	2.4% (2/84)	0.0% (0/23)	3.3% (2/61)	0.7% (1/138)
Safety				
Total death	1.2% (1/84)	0.0% (0/23)	1.6% (1/61)	0.7% (1/138)
Cardiac death	1.2% (1/84)	0.0% (0/23)	1.6% (1/61)	0.7% (1/138)
Non-cardiac death	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	0.0% (0/138)
Cardiac death or TVMI	3.6% (3/84)	4.3% (1/23)	3.3% (2/61)	5.1% (7/138)
TVMI	2.4% (2/84)	4.3% (1/23)	1.6% (1/61)	4.3% (6/138)
Stent thrombosis ARC defined				
Stent thrombosis (ARC def/prob)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	1.4% (2/138)
Early (≤30 days)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	1.4% (2/138)
Late (>30 and ≤360 days)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	0.0% (0/138)

10.5 Subjects receiving short-term DAPT

The Onyx ONE Clear Primary Analysis subject population was formed by pooling data from eligible subjects enrolled into the Onyx ONE US & Japan Trial (a prospective, multi-center, single-arm trial, which enrolled subjects in the United States and Japan) with data from eligible subjects treated with Resolute Onyx only in the Onyx ONE Global RCT (a prospective, multi-center, randomized trial [See Section 10.5.2]).

10.5.1 Onyx ONE Clear Primary Analysis

Primary Objective: To assess the safety and effectiveness of the Resolute Onyx stent with use of one-month DAPT in subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment.

Population: Subjects with an indication for percutaneous coronary intervention deemed at high risk for bleeding and/or candidates for one-month DAPT who are acceptable candidates to receive treatment with the Resolute Onyx stent.

Design: The Onyx ONE US & Japan Trial is a prospective, multi-center, post-market single-arm study which enrolled subjects undergoing attempted PCI. Subjects received DAPT through one month, before transitioning to SAPT thereafter.

Eligible subjects enrolled in the Onyx ONE US & Japan Trial (N=751) combined with eligible subjects from the Resolute Onyx arm of the Onyx ONE Global RCT (N=1018) (See Section 10.5.2) to form an Onyx As Treated population (Onyx AT).

The one-month clear population excluded subjects who interrupted or discontinued DAPT (greater than 3 cumulative days) within the first month of procedure (2.1%), those who experienced adverse events that would prohibit them from discontinuing DAPT beyond one month (3.4%), who did not intend to transition from DAPT to SAPT one month after procedure (6.2%), and who were lost to follow-up (3.1%). Peri-procedural MIs did not exclude subjects from being considered as one-month clear.

Assessment of the use of Resolute Onyx stents in HBR patients was based on analyses combining outcomes from patients compared to a pre-specified performance goal (PG). The PG was based on a clinically acceptable margin added to an expected composite event rate of cardiac death, and myocardial infarction (CD/MI) rate at 12 months, adapted from historical short DAPT studies with high-bleeding risk patient populations (LEADERS FREE[7], ZEUS[8,9], and SENIOR[10]). The expected CD/MI rate between one month and one year was estimated to be 6.8%.

The PG for the composite event rate of CD/MI at one-year post-procedure in a one-month clear population was 9.7% based on an estimated CD/MI rate of 6.8% and a one sided 0.025 significance level.

[7] Urban P, Meredith IT, Abizaid A, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. N Engl J Med 2015;373:2038-4.

[8] Valgimigli M, Patialiakas A, Thury A, et al. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. J Am Coll Cardiol. 2015;65:805–15.

[9] Ariotti S, Adamo M, Costa F, et al. Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?: A Pre-Specified Analysis From the ZEUS Trial. JACC Cardiovasc Interv 2016;9:426-36.

[10] Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet. 2018 Jan 6;391(10115):41-50.

Demographics: The mean age was 74.0 ± 9.5, 67.7% (1019/1506) were male, 72.4% (1091/1506) reported dyslipidemia, 84.0% (1265/1506) had hypertension, 9.4% (141/1498) were current smokers, 39.4% (593/1506) were diabetic 13.7% (206/1506) reported as insulin dependent], 26.3% (396/1506) had a prior MI, and 48.6% (701/1441) were classified as having acute coronary syndrome.

The mean number of high bleeding risk criteria was 1.6±0.8. The most common HBR qualifying features were age ≥ 75 years, 59.0% (889/1506), long-term oral anticoagulation use, 41.0% (617/1506), anemia (hemoglobin level <11 g/dL) or recent transfusion, 14.4% (217/1506) and chronic kidney disease (creatinine clearance <40ml/min, 12.5% (188/1506).

Primary endpoint: The composite rate of cardiac death and myocardial infarction (CD/MI) at one year for a one-month clear population [timeframe: one month to one year].

Results: The Onyx As Treated (Onyx AT) one-month clear population was defined as the primary analysis population for the study. The CD/MI rate at one year for the Onyx ONE Clear cohort was 7.0% (104/1491) with the upper limit of 95% confidence interval of 8.4% which was lower than the prespecified performance goal of 9.7%.

The Onyx ONE Clear Primary Analysis results are presented in **Error! Reference source not found.** and **Error! Reference source not found.**.

Post hoc analyses by gender and ACS vs non-ACS presentation for the primary endpoint are presented in Table 10-14 and 10-15. For gender, CD/MI rates at one year were 7.6% (77/1010) in male subjects and 5.6% (27/481) in female subjects. Patients who presented with ACS had a CD/MI rate at 1 year of 7.9% (55/694) compared with 6.0% (44/733) for patients who did not present with ACS.

Table 10-12: Primary endpoint analysis – Onyx ONE Clear

Primary Endpoint at 12 month1	Resolute Onyx (N = 1506 Subjects)	Two-side 95% Confidence Interval2	Performance Goal	p-value	Primary Objective Met? (Yes or No)
Primary Analysis					
– Onyx ONE Clear	7.0% (104/1491)	[5.7%, 8.4%]	9.7%	<0.001	Yes
Best Case Analysis3					
– Onyx ONE Clear	6.9% (104/1506)	[5.7%, 8.3%]	9.7%	<0.001	Yes
Worst Case Analysis4					
– Onyx ONE Clear	7.9% (119/1506)	[6.6%, 9.4%]	9.7%	0.009	Yes

1 The primary endpoint is a composite of cardiac death, myocardial infarction at one year post-procedure.
2 The two-sided 95% CI was calculated by binomial (exact) distribution carried out to assess statistical significance at the 0.025 level.
3 Best case analysis imputed all the missing 12-month primary endpoint status as no.
4 Worst case analysis imputed all the missing 12-month primary endpoint status as yes.

Table 10-13: Principal safety and effectiveness results – Onyx ONE Clear

Safety and effectiveness measures	RESOLUTE ONYX (N=1506 subjects N=1960 lesions) %(m/n)[1]
Safety measures (to 180 days)	
Target lesion failure (TLF)2	4.1% (61/1500)
Target vessel failure (TVF)3	4.5% (67/1500)
MACE4	6.0% (90/1500)
Cardiac death, MI and definite/probable stent thrombosis	3.7% (56/1500)
Cardiac death or MI	3.7% (56/1500)
Cardiac death or target vessel MI (TVMI)	3.3% (50/1500)
Death or TVMI	4.9% (73/1500)
Death	2.5% (38/1500)
Cardiac death	1.0% (15/1500)
Non cardiac death	1.5% (23/1500)
TVMI (3rd UDMI)	2.5% (38/1500)
Clinically driven TLR	1.6% (24/1500)
Clinically driven TVR	2.2% (33/1500)
Stroke	0.7% (11/1500)
Stent thrombosis (ARC) definite/probable	0.4% (6/1500)
Bleeding	
All BARC	7.3% (110/1500)
BARC 3-5	2.3% (34/1500)
BARC 2-5	6.5% (97/1500)
Safety measures (to 365 days)	
Target lesion failure (TLF)2	8.1% (121/1491)
Target vessel failure (TVF)3	8.8% (131/1491)
MACE4	11.7% (174/1491)
Cardiac death, MI and definite/probable stent thrombosis	7.0% (104/1491)
Cardiac death or MI	7.0% (104/1491)
Cardiac death or target vessel MI (TVMI)	6.5% (97/1491)
Death or TVMI	9.7% (144/1491)
Death	6.0% (89/1491)
Cardiac death	2.6% (39/1491)
Non cardiac death	3.4% (50/1491)
TVMI (3rd UDMI)	4.4% (65/1491)
Clinically driven TLR	3.4% (50/1491)
Clinically driven TVR	4.3% (64/1491)

Table 10-13: Principal safety and effectiveness results – Onyx ONE Clear

Safety and effectiveness measures	RESOLUTE ONYX (N=1506 subjects N=1960 lesions) %(m/n)[1]
Stroke	1.5% (22/1491)
Stent thrombosis (ARC) definite/probable	0.7% (10/1491)
Bleeding	
All BARC	13.1% (195/1491)
BARC 3-5	4.0% (60/1491)
BARC 2-5	11.7% (175/1491)
Effectiveness measures	
Lesion success[5]	94.6% (1817/1920)
Device success[6]	93.3% (1790/1919)
Procedure success[7]	88.5% (1295/1463)

[1]Numerator (m) is the number of Subjects with the specific classification, denominator (n) is the number of Subjects in the study group with known values, and percentage (%) was calculated as 100 × (m/n)
[2]Cardiac death, target vessel myocardial infarction (Q wave and non Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods.
[3]Cardiac death, target vessel myocardial infarction (Q wave and non Q wave) or clinically-driven target vessel revascularization (TVR) by percutaneous or surgical methods.
[4]Defined as death, myocardial infarction (Q wave and non Q-wave), emergent coronary bypass surgery, or repeat target lesion
revascularization (clinically driven/clinically indicated) by percutaneous or surgical methods.
[5]The attainment of <30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure using any percutaneous method.
[6]The attainment of <30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure using the assigned device only.
[7]The attainment of <30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure using any percutaneous method without the occurrence of MACE during the hospital.
Third universal definition of MI is used for all the composite endpoints.

Table 10-14: Primary endpoint analysis by gender – Onyx ONE Clear

Primary endpoint	Male subjects Resolute Onyx (N=1019 subjects) % (m/n)	Female subjects Resolute Onyx (N=487 subjects) % (m/n)
CD/MI at 12 months	7.6% (77/1010)	5.6% (27/481)

Table 10-15: Primary endpoint analysis ACS vs. non-ACS patients- Onxy ONE Clear

Primary endpoint	Non-ACS (N=740 Subjects) (N=958 Lesions) %(m/n)[1]	ACS (N=701 Subjects) (N=914 Lesions) %(m/n)[1]
CD/MI at 12 months	6.0% (44/733)	7.9% (55/694)

10.5.2 The Onyx ONE Global RCT

Study design: The Onyx ONE Global RCT[11] was an international, randomized, single-blind trial, that compared zotarolimus-eluting stents (Resolute Onyx) with polymer-free umirolimus–coated stents in patients at high bleeding risk. After PCI, patients were treated with one-month of DAPT, followed by SAPT. A total of 1996 HBR patients were randomly assigned in a 1:1 ratio to receive Resolute Onyx stents (1003 patients) or polymer-free drug-coated stents (993 patients).

Objective: The purpose of this clinical study was to evaluate the clinical safety of the Resolute Onyx stent as compared to the polymer-free drug coated stents with use of 1 month DAPT in subjects deemed at HBR and/or medically unsuitable for more than 1 month DAPT treatment. In the LEADERS-FREE trial, the same polymer-free drug-coated stent showed superiority in safety and effectiveness to a bare-metal stent in a similar HBR population treated with 1 month of DAPT.

Primary Endpoint: The composite rate of cardiac death, myocardial infarction and stent thrombosis (definite/probable) at one year.

Results: At 1 year, the primary outcome was observed in 169 of 988 patients (17.1%) in the Resolute Onyx stent group and in 164 of 969 (16.9%) in the polymer-free drug-coated stent group (risk difference, 0.2 percentage points; upper boundary of the one-sided 97.5% confidence interval [CI], 3.5; noninferiority margin, 4.1; P = 0.01 for noninferiority). Among patients at HBR who received 1 month of DAPT after PCI, Resolute Onyx stents were noninferior to use of polymer-free drug-coated stents with regard to safety and effectiveness composite outcomes.

10.6 Subjects with chronic total occlusion

The PERSPECTIVE Study – RESOLUTE CTO cohort

The PERSPECTIVE Study included a retrospective and a prospective study arm. Both arms of this study enrolled approximately 250 patients at a single center experienced in CTO procedures. The prospective arm essentially comprised a separate substudy designed to evaluate procedural and 1-year clinical outcomes among consecutive patients undergoing attempted percutaneous Chronic Total Occlusion (CTO) revascularization. The prospective arm of the PERSPECTIVE study included a pre-specified subgroup analysis of patients treated with the Resolute family of drug-eluting stents (all were Resolute Integrity).

Primary objective: To assess the safety and effectiveness of the Resolute zotarolimus-eluting coronary stent system (Resolute ZES) for the treatment of chronic total occlusions.

Population: The population consisted of prospectively enrolled subjects undergoing attempted percutaneous CTO revascularization and treated with the Resolute ZES.

Design: The PERSPECTIVE Study (Prospective Arm/Prespecified Resolute ZES for CTO Analysis) was a single-center, investigator-initiated, observational study which prospectively enrolled approximately 250 subjects undergoing attempted CTO. Assessment of use of Resolute ZES stents in CTO revascularization was based on prospectively enrolled CTO patients compared to a pre-specified performance goal.

[11] Windecker S, Latib A, Kedhi E, et al. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. New England Journal of Medicine 2020.

An estimated MACE rate was derived based on a weighted average of the reported rates for drug-eluting stents from the PRISON II[12] and EXPERT CTO[13] studies. Due to difference in the definition of myocardial infarction used in the PRISON II study, an adjustment for the MACE rate was made to approximate the MACE rate if the ARC definition of myocardial infarction had been applied. The weighted average produced an estimated MACE rate of 16.6% using the ARC definition of MI. The performance goal (PG) for the pre-specified RESOLUTE CTO Cohort analysis was 25.2% based on the estimated MACE rate of 16.6% and a one-sided 95% CI.

Demographics: In the RESOLUTE CTO Cohort of the PERSPECTIVE Study, the mean age was 63.4 ± 9.5, 79.8% (146/183) were male, 98.4% (180/183) reported dyslipidemia, 88.5% (162/183) had hypertension, 18.0% (31/172) were current smokers, 35.5% (65/183) were diabetic including 12.6% (23/182) reported as insulin-dependent, 33.3% (61/183) had a prior MI, and 80.9% (140/173) were classified as having stable angina.

Primary endpoint: Major Adverse Cardiac Events (MACE) at one year; a composite of death, myocardial infarction (MI) (ARC defined), and clinically-driven target lesion revascularization (TLR).

Results: The observed MACE rate at one year for the RESOLUTE CTO Cohort was 18.2% (33/181) for the ITT population. The ITT population met the primary endpoint. The upper limit of the 95% confidence interval was 23.6% which is lower than the pre-specified performance goal (25.2%). A post hoc gender subgroup analysis of the primary endpoint resulted in MACE rates at one year of 18.8% (27/144) in male subjects and 16.2% (6/37) in female subjects.

The PERSPECTIVE Study results are presented in Table 10-, Table 10-, and **Error! Reference source not found.**:

Table 10-16: Primary endpoint analysis – MACE at 12 months (ITT)

Primary endpoint	RESOLUTE CTO cohort (N=183 Subjects)	One-side upper 95% confidence interval	Performance goal
MACE at 12 months			
ITT	18.2% (33/181)	23.6%	25.2%

Table 10-17: Principal safety and effectiveness results

Safety and effectiveness measures	RESOLUTE CTO cohort (N=183 subjects) %(m/n)
Safety measures (in-hospital)	
TLF	15.3% (28/183)
TVF	15.3% (28/183)
MACE	15.3% (28/183)
Cardiac death or MI	15.3% (28/183)
Death or MI	15.3% (28/183)
Death	1.1% (2/183)
Cardiac death	1.1% (2/183)

12 Suttorp MJ, Laarman GJ, Rahel BM, et al. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. Circulation 2006; 114(9); 921 – 928.

13 Kandzari DE, Kini AS, Karmpaliotis D, et al. Safety and Effectiveness of Everolimus-Eluting Stents in Chronic Total Coronary Occlusion Revascularization: Results From the EXPERT CTO Multicenter Trial (Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions). J Am Coll Cardiol Intv 2015; 8(6); 761 – 769.

Table 10-17: Principal safety and effectiveness results

Safety and effectiveness measures	RESOLUTE CTO cohort (N=183 subjects) %(m/n)
Non-cardiac death	0.0% (0/183)
MI	14.8% (27/183)
TLR	0.0% (0/183)
TVR	0.0% (0/183)
Safety measures (to 6 Months/183 days)	
TLF	17.5% (32/183)
TVF	17.5% (32/183)
MACE	17.5% (32/183)
Cardiacdeath or MI	17.5% (32/183)
Death or MI	17.5% (32/183)
Death	2.7% (5/183)
Cardiac death	2.2% (4/183)
Non-cardiac death	0.5% (1/183)
MI	15.8% (29/183)
TLR	0.5% (1/183)
TVR	0.5% (1/183)
All stent thrombosis (ARC definite/probable/possible)	1.6% (3/183)
Stent thrombosis ARC definite/probable	0.6% (1/183)
Stent thrombosis ARC possible	1.1% (2/183)
Early stent thrombosis (0 to 30 days)	0.6% (1/183)
Definite	0.6% (1/183)
Probable	0.0% (0/183)
Possible	0.0% (0/183)
Late stent thrombosis (31 days to 6 months)	1.1% (2/183)
Definite	0.0% (0/183)
Probable	0.0% (0/183)
Possible	1.1% (2/183)
Safety measures (to 1 year/365 days)	
TLF	18.2% (33/181)
TVF	18.2% (33/181)
MACE	18.2% (33/181)
Cardiac death or MI	17.7% (32/181)
Death or MI	17.7% (32/181)
Death	2.8% (5/181)
Cardiac death	2.2% (4/181)
Non-cardiac death	0.6% (1/181)
MI	16.0% (29/181)
TLR	1.1% (2/181)
TVR	1.1% (2/181)
All stent thrombosis (ARC definite/probable/possible)	1.7% (3/181)
Stent thrombosis ARC definite/probable	0.6% (1/181)
Stent thrombosis ARC possible	1.1% (2/181)
Early stent thrombosis (0 to 30 days)	0.6% (1/181)
Definite	0.6% (1/181)
Probable	0.0% (0/181)
Possible	0.0% (0/181)

Table 10-17: Principal safety and effectiveness results

Safety and effectiveness measures	RESOLUTE CTO cohort (N=183 subjects) %(m/n)
Late stent thrombosis (31 days to 1 year)	1.1% (2/181)
Definite	0.0% (0/181)
Probable	0.0% (0/181)
Possible	1.1% (2/181)
Effectiveness measures	
Clinical success[1]	92.3% (169/183)
Technical success[2]	96.2% (175/182)

1CTO procedural success as defined by achievement of <50% residual stenosis with ≥TIMI 2 antegrade flow

[2]Successful guidewire crossing with placement in distal true lumen of CTO target lesion

Table 10-18: RESOLUTE CTO cohort – primary endpoint analysis by gender

Primary endpoint	Male subjects RESOLUTE CTO cohort (N=146 subjects) % (m/n)	Female subjects RESOLUTE CTO cohort (N=37 subjects) % (m/n)
MACE at 12 months	18.8% (27/144)	16.2% (6/37)

Global RESOLUTE Clinical Program – RESOLUTE pooled CTO

Population: In order to provide additional support for the performance of the Resolute family of stents in the treatment of CTOs, a retrospective, pooled analysis was performed which was comprised of pooled CTO patients from the Global RESOLUTE Clinical Program.

The following Global RESOLUTE Clinical Trials contributed subjects to the CTO cohort:

- RESOLUTE International

  The RESOLUTE International Study (R-Int) was a prospective, multi-center, non-randomized, single-arm, observational study of the Resolute stent in a real world subject population. A total 2349 subjects were enrolled into the study. Subjects were followed for 3 years post-procedure. A total of 186 subjects from the R-Int study were included in the RESOLUTE Pooled CTO analysis.

- RESOLUTE China Randomized Controlled Trial

  The RESOLUTE China Randomized Controlled Trial (R-China RCT) was a prospective, multi-center, randomized, open-label study designed to assess the non-inferiority of the Resolute stent compared to the Taxus Liberte stent for in-stent late lumen loss. A total of 198 subjects were treated with the Resolute stent. Subjects were followed for 5 years post-procedure. A total of 15 subjects from the R-China RCT study were included in the RESOLUTE Pooled CTO analysis.

- RESOLUTE China Registry

The RESOLUTE China Registry (R-China Registry) was a prospective, multi-center, non-randomized, single-arm, observational study of the Resolute stent in a real-world patient population requiring stent implantation. A total of 1800 subjects were treated with the Resolute stent. Subjects were followed for 5 years post-procedure. A total of 157 subjects from the R-China Registry were included in the RESOLUTE Pooled CTO Analysis.

Design: The Resolute stent performance for the treatment of CTO lesions was analyzed from data collected in the R-Int, R-China RCT, and R-China Registry studies. The results pooled datasets from the 5-year data of R-China RCT, 4-year data of R-China Registry, and 3-year data from R-Int. In total, 358 subjects were evaluable for this CTO subset.

Demographics: The average age in the RESOLUTE Pooled CTO subset (n=358) was 60.4 ± 11.3 years and 84.4% (302/358) were male. For this population, 37.7% (133/353) experienced a prior MI, 65.1% (233/358) had hypertension, 50.3% (180/358) had hyperlipidemia and 26.5% (95/358) had diabetes.

Global RESOLUTE Clinical Program results are presented in the following table:

Table 10-19: RESOLUTE pooled CTO analysis – safety and effectiveness results

Safety and effectiveness endpoints	RESOLUTE pooled CTO (N=358 patients) (N=527 lesions) %(m/n)[9]
Effectiveness measures	
Lesion success[6]	100.0% (526/526)
Device success[7]	94.1% (496/527)
Procedure success[8]	97.5% (348/357)
1 Year	
TLF[1]	4.5% (16/352)
TVF[2]	4.8% (17/352)
MACE[3]	5.7% (20/352)
Composite endpoint[4]	12.2% (43/352)
Cardiac death or TVMI	3.1% (11/352)
Death or TVMI	4.0% (14/352)
Death	1.7% (6/352)
Cardiac death	0.9% (3/352)
Non-cardiac death	0.9% (3/352)
TVMI (extended historical definition)	2.3% (8/352)
Clinically-driven TLR	2.0% (7/352)
Clinically-driven TVR	2.3% (8/352)
Stent thrombosis (ARC) definite/probable)	0.6% (2/352)
Early thrombosis(≤30 days)	0.3% (1/352)
Late thrombosis(>30 and ≤360 days)	0.3% (1/352)
Significant bleeding complications[5]	1.1% (4/352)
Stroke	0.9% (3/352)
3 Years	
TLF[1]	8.9% (31/347)
TVF[2]	10.1% (35/347)
MACE[3]	10.1% (35/347)
Composite endpoint[4]	18.4% (64/347)
Cardiac death or TVMI	6.6% (23/347)
Death or TVMI	7.8% (27/347)
Death	5.5% (19/347)
Cardiac death	4.3% (15/347)

Table 10-19: RESOLUTE pooled CTO analysis – safety and effectiveness results

Safety and effectiveness endpoints	RESOLUTE pooled CTO (N=358 patients) (N=527 lesions) %(m/n)[9]
Non-cardiac death	1.2% (4/347)
TVMI (extended historical definition)	3.2% (11/347)
Clinically-driven TLR	3.2% (11/347)
Clinically-driven TVR	4.3% (15/347)
Stent thrombosis (ARC) definite/probable)	1.2% (4/347)
Early thrombosis(≤30 days)	0.3% (1/347)
Late thrombosis(>30 and ≤360 days)	0.3% (1/347)
Very late thrombosis(>360 days)	0.9% (3/347)
Significant bleeding complications[5]	1.2% (4/347)
Stroke	1.7% (6/347)

1.Cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods.
2.Cardiac death, target vessel myocardial infarction, or clinically-driven target vessel revascularization.
3.Death, myocardial infarction, (Q wave and non-Q-wave), emergent coronary bypass surgery, or repeat target lesion revascularization (clinically-driven/clinically-indicated) by percutaneous or surgical methods.
4.The combined clinical outcome of (all cause) mortality, myocardial infarction (Q-wave and non-Q wave), or (any) revascularization.
5.Bleeding complication is defined as a procedure related hemorrhagic event that requires a transfusion or surgical repair. These may include a hematoma requiring treatment of retroperitoneal bleed.
Significant bleeding complication is defined as the bleeding complication that has at least one of the following scenarios:
• Bleedings that led to an interruption of anti-platelet medication;
• Bleedings that require transfusion;
• Intracerebral bleedings; or
• Bleedings that resulted in substantial hemodynamic compromise requiring treatment
6.The attainment of <50% residual stenosis of the target lesion using any percutaneous method.
7.The attainment of <50% residual stenosis of the target lesion using only the assigned device.
8.The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE.
9.Numerator (m) is the number of patients (or lesions) with the specific classification, denominator (n) is the number of patients (or lesions) in the study group with known values, and percentage () was calculated as 100 × (m/n)
Extended historical definition of MI is used for all the composite endpoints.

10.7 Pooled results of the Global RESOLUTE Clinical Trial Program (RESOLUTE FIM, RESOLUTE US, RESOLUTE AC, RESOLUTE Int, RESOLUTE Japan)

In order to better estimate the incidence of low-frequency events or outcomes, a subject-level pooled analysis was conducted. Table 10- below provides the total number of subjects included in the analyses.

Table 10-20: Subjects included in the analyses by clinical study

	All subjects	On-label
RESOLUTE FIM	139	139
RESOLUTE All-Comers – Resolute	1140	376
RESOLUTE International	2349	763

Table 10-20: Subjects included in the analyses by clinical study

	All subjects	On-label
RESOLUTE US	1402	1402
RESOLUTE Japan	100	100
Pooled Resolute Data set	**5130**	**2780**
Subjects from the 38 mm length sub-study were not included in the RESOLUTE pooled analysis presented here		

The on-label subgroup includes all enrolled subjects except those that had a total occlusion, target lesions involving a bifurcation lesion, target lesions involving a saphenous vein graft lesion (SVG), an in-stent restenosis (ISR) target lesion, a subject having an acute myocardial infarction (AMI) (≤72 hrs), subjects with a demonstrated left-ventricular ejection fraction (LVEF) less than 30%, target lesions located in an unprotected left main artery, subjects with ≥3 treated vessels, subjects with a serum creatinine of >2.5 mg/dl, a lesion length >27 mm, 2 or more lesions treated per vessel, and target lesions with the presence of a thrombus.

It is acknowledged that the results of retrospective pooled analyses have limitations. Definitive proof of the presence or absence of any differences between sub-groups requires prospectively powered assessments in clinical trials. The results are presented in the following tables:

- Table 10-: RESOLUTE pooled analysis - principal safety and effectiveness through 60 months
- Table 10-: RESOLUTE pooled Analysis - ARC defined definite/probable stent thrombosis through 60 months
- Table 10-: RESOLUTE pooled analysis - subset outcomes through 12 months
- Table 10-: RESOLUTE pooled analysis – subset outcomes through 12 months
- Table 10-: RESOLUTE pooled analysis – subset outcomes through 12 months

Table 10-21: RESOLUTE pooled analysis - principal safety and effectiveness through 60 months

	All subjects (N = 5130)	On-label (N = 2780)
Outcomes at 12 months		
Composite safety and effectiveness		
TLF	6.6% (336/5098)	5.4% (150/2759)
TVF	7.5% (382/5098)	6.6% (181/2759)
MACE	7.5% (384/5098)	6.3% (174/2759)
Effectiveness		
Clinically-driven TVR	4.3% (220/5098)	3.7% (103/2759)
Clinically-driven TLR	3.3% (166/5098)	2.5% (69/2759)
Safety		
Total death	1.9% (98/5098)	1.6% (44/2759)
Cardiac-death	1.2% (60/5098)	0.9% (26/2759)
Non-cardiac death	0.7% (38/5098)	0.7% (18/2759)
TVMI	2.9% (149/5098)	2.4% (66/2759)
Cardiac death or TVMI	3.9% (200/5098)	3.3% (90/2759)

Table 10-21: RESOLUTE pooled analysis - principal safety and effectiveness through 60 months

	All subjects (N = 5130)	On-label (N = 2780)
Stent thrombosis ARC defined		
Definite/probable	0.8% (40/5098)	0.3% (9/2759)
Definite	0.6% (29/5098)	0.2% (6/2759)
Probable	0.3% (13/5098)	0.1% (3/2759)
Outcomes at 36 months		
Composite safety and effectiveness		
TLF	10.8% (539/5012)	9.2% (249/2709)
TVF	13.0% (652/5012)	12.0% (324/2709)
MACE	13.5% (679/5012)	12.0% (325/2709)
Effectiveness		
Clinically-driven TVR	7.9% (397/5012)	7.5% (204/2709)
Clinically-driven TLR	5.3% (267/5012)	4.4% (119/2709)
Safety		
Total death	5.5% (275/5012)	5.0% (135/2709)
Cardiac death	3.1% (156/5012)	2.6% (70/2709)
Non-cardiac death	2.4% (119/5012)	2.4% (65/2709)
TVMI	3.8% (188/5012)	3.1% (84/2709)
Cardiac death or TVMI	6.5% (324/5012)	5.4% (145/2709)
Stent thrombosis ARC defined		
Definite/probable	1.1% (54/5012)	0.5% (13/2709)
Definite	0.7% (37/5012)	0.3% (7/2709)
Probable	0.4% (19/5012)	0.2% (6/2709)
Outcomes at 60 months*		
Composite safety and effectiveness		
TLF	14.0% (376/2688)	12.3% (239/1937)
TVF	18.1% (486/2688)	16.5% (320/1937)
MACE	19.4% (521/2688)	18.2% (352/1937)
Effectiveness		
Clinically-driven TVR	11.4% (306/2688)	10.6% (205/1937)
TLR	6.7% (179/2688)	5.8% (112/1937)
Safety		
Total death	9.9% (266/2688)	9.7% (188/1937)
Cardiac death	4.9% (131/2688)	4.3% (83/1937)
Non-cardiac death	5.0% (135/2688)	5.4% (105/1937)

Table 10-21: RESOLUTE pooled analysis - principal safety and effectiveness through 60 months

	All subjects (N = 5130)	On-label (N = 2780)
TVMI	4.5% (120/2688)	3.9% (76/1937)
Cardiac death or TVMI	8.7% (234/2688)	7.5% (145/1937)
Stent thrombosis ARC defined		
Definite/probable	1.3% (34/2688)	0.8% (15/1937)
Definite	0.8% (22/2688)	0.5% (9/1937)
Probable	0.5% (13/2688)	0.3% (6/1937)

Notes

N = The total number of subjects enrolled.
Numbers are % (count/number of eligible subjects).
Subjects are only counted once for each time period.
12-month time frame includes follow-up window (360 days ± 30 days).
36-month timeframe includes follow-up window (1080 days ± 30 days).
60-month timeframe includes follow-up window (1800 days ± 30 days).
* Note: R-Int. follow-up ends at 3 years and is not included in this analysis.
The definitions of the outcomes are presented as table notes to **Error! Reference source not found.**.

Table 10-22: RESOLUTE pooled analysis - ARC defined definite/probable stent thrombosis through 60 months

	All subjects* (N = 2781)	On-label* (N = 2017)
Stent thrombosis	1.3% (34/2688)	0.8% (15/1937)
Early (0 to 30 days)	0.5% (13/2688)	0.2% (3/1937)
Late (31 to 360 days)	0.3% (8/2688)	0.2% (4/1937)
Very late (361 to 1440 days)*	0.5% (14/2688)	0.4% (8/1937)

N = The total number of subjects enrolled.
Numbers are % (count/number of eligible subjects).
Subjects are only counted once for each time period.
12-month time frame includes follow-up window (360 days ± 30 days).
60-month timeframe includes follow-up window (1800 days ± 30 days).
* Note: R-Int. follow-up ends at 3 years and is not included in this analysis.

Table 10-23: RESOLUTE pooled analysis - subset outcomes through 12 months

	On-label single lesion (N = 2466)	Age ≥65 yrs. (N = 2547)	Male (N = 3843)	Female (N = 1287)	B2/C lesions (N = 3636)	RVD ≤2.5 mm (N = 1956)	Lesion length ≥27 mm (N = 509)
Composite safety and effectiveness							
TLF	5.3% (128/2428)	7.0% (177/2515)	6.3% (239/3780)	7.4% (94/1264)	6.7% (239/3577)	7.3% (141/1928)	7.9% (39/495)
TVF	6.4% (155/2428)	8.0% (202/2515)	7.1% (270/3780)	8.6% (109/1264)	7.6% (272/3577)	8.5% (164/1928)	8.5% (42/495)
MACE	6.1% (147/2428)	8.4% (211/2515)	7.3% (277/3780)	8.0% (101/1264)	7.6% (271/3577)	8.1% (157/1928)	9.3% (46/495)
Effectiveness							
Clinically-driven TVR	3.6% (88/2428)	4.3% (108/2515)	4.3% (162/3780)	4.4% (55/1264)	4.4% (157/3577)	5.0% (96/1928)	5.7% (28/495)
TLR	2.4% (58/2428)	3.1% (79/2515)	3.3% (124/3780)	3.1% (39/1264)	3.3% (118/3577)	3.7% (71/1928)	5.1% (25/495)
Safety							
Total death	1.6% (39/2428)	3.1% (78/2515)	1.9% (70/3780)	2.1% (26/1264)	1.7% (62/3577)	1.7% (32/1928)	3.2% (16/495)
Cardiac death	0.9% (22/2428)	1.9% (48/2515)	1.0% (39/3780)	1.5% (19/1264)	1.0% (36/3577)	1.0% (20/1928)	1.8% (9/495)
Non-cardiac death	0.7% (17/2428)	1.2% (30/2515)	0.8% (31/3780)	0.6% (7/1264)	0.7% (26/3577)	0.6% (12/1928)	1.4% (7/495)
TVMI	2.3% (57/2428)	2.9% (74/2515)	2.8% (105/3780)	3.6% (45/1264)	3.2% (115/3577)	3.5% (67/1928)	1.8% (9/495)
Cardiac death or TVMI	3.2% (77/2428)	4.5% (113/2515)	3.6% (137/3780)	4.9% (62/1264)	4.0% (144/3577)	4.4% (84/1928)	3.4% (17/495)
Stent thrombosis ARC defined							
Definite/probable	0.3% (7/2428)	0.8% (19/2515)	0.8% (31/3780)	0.7% (9/1264)	0.9% (31/3577)	0.7% (14/1928)	1.0% (5/495)
Definite	0.2% (5/2428)	0.5% (12/2515)	0.6% (24/3780)	0.4% (5/1264)	0.7% (25/3577)	0.5% (10/1928)	0.6% (3/495)
Probable	0.1% (2/2428)	0.3% (8/2515)	0.2% (9/3780)	0.3% (4/1264)	0.2% (8/3577)	0.3% (6/1928)	0.4% (2/495)

Table 10-24: RESOLUTE pooled analysis – subset outcomes through 12 months

	Multiple stents (N = 1788)	Overlapping stents (N = 644)	Saphenous vein graft (N = 64)	Multi-vessel stenting (N = 770)	BMS in-stent restenosis (N = 199)
Composite safety and effectiveness					
TLF	7.8% (137/1758)	7.8% (49/632)	17.2% (11/64)	8.2% (62/756)	11.1% (22/198)
TVF	8.6% (152/1758)	8.7% (55/632)	17.2% (11/64)	8.9% (67/756)	12.1% (24/198)
MACE	8.8% (155/1758)	9.3% (59/632)	17.2% (11/64)	9.0% (68/756)	12.1% (24/198)
Effectiveness					
Clinically-driven TVR	5.1% (89/1758)	5.4% (34/632)	10.9% (7/64)	5.0% (38/756)	9.1% (18/198)
TLR	4.1% (72/1758)	4.4% (28/632)	7.8% (5/64)	4.4% (33/756)	8.1% (16/198)
Safety					
Total death	2.0% (36/1758)	3.0% (19/632)	3.1% (2/64)	1.9% (14/756)	3.0% (6/198)
Cardiac death	1.3% (22/1758)	1.4% (9/632)	3.1% (2/64)	1.3% (10/756)	2.0% (4/198)
Non-cardiac death	0.8% (14/1758)	1.6% (10/632)	0.0% (0/64)	0.5% (4/756)	1.0% (2/198)
TVMI	3.5% (62/1758)	3.3% (21/632)	7.8% (5/64)	3.3% (25/756)	3.0% (6/198)
Cardiac death or TVMI	4.5% (79/1758)	4.4% (28/632)	9.4% (6/64)	4.5% (34/756)	4.0% (8/198)
Stent thrombosis ARC defined					
Definite/probable	1.1% (20/1758)	1.1% (7/632)	1.6% (1/64)	1.2% (9/756)	2.5% (5/198)
Definite	0.9% (15/1758)	0.6% (4/632)	0.0% (0/64)	0.7% (5/756)	1.5% (3/198)
Probable	0.4% (7/1758)	0.6% (4/632)	1.6% (1/64)	0.7% (5/756)	1.0% (2/198)

Table 10-25: RESOLUTE pooled analysis – subset outcomes through 12 months

	Bifurcation (N = 702)	Total occlusion[1] (N = 505)	Unprotected left main (N = 57)	Renal insufficiency[2] (N = 135)	AMI <72 hours (N = 799)
Composite safety and effectiveness					
TLF	10.3% (71/690)	6.2% (31/497)	16.1% (9/56)	12.0% (16/133)	7.5% (59/788)
TVF	11.4% (79/690)	6.6% (33/497)	16.1% (9/56)	12.8% (17/133)	8.1% (64/788)
MACE	11.3% (78/690)	6.6% (33/497)	17.9% (10/56)	16.5% (22/133)	8.2% (65/788)
Effectiveness					
Clinically-driven TVR	6.1% (42/690)	4.2% (21/497)	7.1% (4/56)	4.5% (6/133)	5.6% (44/788)
TLR	4.8% (33/690)	3.6% (18/497)	7.1% (4/56)	3.0% (4/133)	4.7% (37/788)
Safety					
Total death	2.3% (16/690)	1.2% (6/497)	7.1% (4/56)	10.5% (14/133)	2.2% (17/788)
Cardiac death	1.6% (11/690)	1.0% (5/497)	5.4% (3/56)	6.8% (9/133)	1.5% (12/788)
Non-cardiac death	0.7% (5/690)	0.2% (1/497)	1.8% (1/56)	3.8% (5/133)	0.6% (5/788)
TVMI	5.9% (41/690)	2.4% (12/497)	7.1% (4/56)	5.3% (7/133)	2.4% (19/788)
Cardiac death or TVMI	7.1% (49/690)	3.4% (17/497)	10.7% (6/56)	9.8% (13/133)	3.8% (30/788)
Stent thrombosis ARC defined					
Definite/probable	2.0% (14/690)	2.0% (10/497)	3.6% (2/56)	2.3% (3/133)	2.2% (17/788)
Definite	1.6% (11/690)	1.0% (5/497)	1.8% (1/56)	0.8% (1/133)	1.5% (12/788)
Probable	0.6% (4/690)	1.0% (5/497)	1.8% (1/56)	1.5% (2/133)	0.8% (6/788)

Notes
N = The total number of subjects enrolled.
Numbers are % (count/number of eligible subjects).
Subjects are only counted once for each time period.
12-month time frame includes follow-up window (360 days ± 30 days).
The definitions of the outcomes are presented as table notes to **Error! Reference source not found.**
[1]Total occlusion is defined as pre procedure TIMI = 0.
[2]Renal insufficiency is defined as serum creatinine >2.5 mg/dl.
Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis

11 Patient selection and treatment

See also **Section 6.5 - Use in special populations**. The risks and benefits described above should be carefully considered for each patient before use of the Resolute Onyx™ system. Factors to be utilized for patient selection should include an assessment of the risk of prolonged anticoagulation. In accordance with the 2016 American College of Cardiology / American Heart Association guidelines, administration of $P2Y_{12}$ platelet inhibitor is recommended pre-procedure and for at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS). In patients at higher risk of bleeding, Resolute Onyx is safe and effective with one-month DAPT based on results of the Onyx ONE Clear Primary Analysis as described in **Section 6.1.1 - Pre- and post-procedure** antiplatelet regimen. Aspirin should be administered concomitantly with an approved antiplatelet medication and then continued indefinitely.

12 Patient counseling information

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

- Discuss the risks associated with stent placement
- Discuss the risks associated with a zotarolimus-eluting stent implant
- Discuss the risks and benefits tradeoff for the patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long term
- Discuss the risks of early discontinuation of the antiplatelet therapy

The following patient materials will be provided to physicians to educate their patients about the options available for treating coronary artery disease and provide contact information to the patient after their stent implant procedure:

- A Patient Guide which includes information on the Resolute Onyx™ zotarolimus-eluting coronary stent system, coronary artery disease, and the stent implantation procedure.
- A Stent Patient Implant Card that includes patient information, stent implant information and MRI guidelines. All patients should be instructed to keep this card in their possession at all times for procedure/stent identification.

13 How supplied

Sterile: This product is sterilized with ethylene oxide (EO) and is nonpyrogenic. Do not use the product if the package is opened or damaged. Do not resterilize the product. If the product or package is opened or damaged, return the product to Medtronic Returned Goods. Contact your local Medtronic representative for return information.

Contents: The package contains one (1) Resolute Onyx™ zotarolimus-eluting coronary stent mounted on either a rapid exchange (RX) or an over-the-wire (OTW) stent delivery system.

Storage: Store the product in the original container. Store at 25ºC (77ºF); excursions permitted to 15 - 30ºC (59 - 86ºF). Use by the use-by date noted on the package.

Disposal instructions: After use, dispose of the product and packaging in accordance with hospital, administrative and local government policy.

14 Directions for use

14.1 Access to package holding sterile stent delivery system

Remove the stent delivery system from the package. Special care must be taken not to handle the stent or in any way disrupt its placement on the balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through the rotating hemostatic valve and guiding catheter hub. Excessive manipulation, for example, rolling the mounted stent, may cause dislodgement of the stent from the delivery balloon.

14.2 Inspection before use

Before opening the product, carefully inspect the stent delivery system package, and check for damage to the sterile barrier. Do not use after the use-by date. If the sterile package is intact, carefully remove the system from the package and inspect it for bends, kinks, and other damage. Do not use the product if any damage to the packaging or system is noted.

A protective sheath covers the stent mounted on the balloon. After removal of the sheath, visually inspect the stent to ensure that it has not been damaged or displaced from its original position (between the proximal and distal marker bands) on the balloon.

14.3 Materials required

Quantity	Material
N/A	Guide catheter [≥ 5 Fr (1.42 mm, 0.056 in) inner diameter]
2 to 3	20 cc syringe
1,000 u /500 cc	Heparinized normal saline
1	Guidewire [≤ 0.014 in (0.36 mm) outer diameter]
1	Rotating hemostatic valve
N/A	Contrast medium diluted 1:1 with heparinized normal saline
1	Inflation device
1	Stopcock (3-way minimum)
1	Torque device
N/A	Appropriate anticoagulation and antiplatelet drugs

14.4 Preparation precaution

- **Do not** use product if the protective sheath is not present or the stent is damaged or displaced.
- **Avoid** manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.
- **Do not** apply positive pressure to the balloon during the delivery system preparation.

14.4.1 Guidewire lumen flush

Flush the stent system guidewire lumen with heparinized normal saline until the fluid exits the distal tip.

14.4.2 Delivery system preparation

Step	Action
1.	Prepare the guide catheter and guidewire according to the manufacturer's instructions.
2.	Remove the stent delivery system from the package.
3.	Remove the protective sheath covering from the stent/balloon. Removing the protective sheath will also remove the stylette.
4.	Inspect the stent to ensure that it has not been damaged or displaced from its original position on the balloon. Verify that the stent is positioned between the proximal and distal balloon markers. Verify that there is no visible damage to the stent or the balloon. ***Note**:* Should there be movement of or damage to the stent, do not use.
5.	Flush the stent delivery system guidewire lumen with heparinized normal saline in routine manner.
6.	Fill a 20 cc syringe with 5 cc of contrast/heparinized normal saline mixture (1:1).
7.	Attach to delivery system and apply negative pressure for 20 to 30 seconds.
8.	Slowly release pressure to allow negative pressure to draw the mixture into the balloon lumen.
9.	Detach the syringe and leave a meniscus of mixture on the hub of the balloon lumen.
10.	Prepare the inflation device in standard manner and purge to remove all air from the syringe and tubing.

Step	Action
11.	Attach the inflation device to the catheter directly, ensuring no bubbles remain at the connection.
12.	Leave on ambient pressure (neutral position).

Note: Do not apply negative pressure on the inflation device after balloon preparation and before delivering the stent.

14.5 Delivery procedure

Step	Action
1.	Prepare the vascular access site according to standard practice.
2.	**Pre-dilate the lesion with a PTCA catheter.** Pre-dilatation must be performed using a balloon with the following 3 characteristics: • A diameter at least 0.5 mm smaller than the treatment stent. • A length equal to or shorter than the lesion length to be dilated. • A length shorter than the stent to be implanted.
3.	Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible. ***Note:*** If resistance is encountered, **do not force passage**. Resistance may indicate a problem and may result in damage to the stent if it is forced. Remove the system and examine.
4.	Ensure guide catheter stability before advancing the Resolute Onyx™ system into the coronary artery. Carefully advance the Resolute Onyx™ system into the hub of the guide catheter.
5.	Advance the stent delivery system over the guidewire to the target lesion under direct fluoroscopic visualization. Use the radiopaque balloon markers to position the stent across the lesion; perform angiography to confirm the position of the stent. If the position of the stent is not optimal, it should be carefully repositioned or removed (see **Precautions – 6 stent/system removal precautions**). Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.
6.	Sufficiently tighten the rotating hemostatic valve. The stent is now ready to be deployed.

Note: Should unusual resistance be felt at any time during either lesion access or removal of the stent delivery system before stent implantation, do not force passage. Maintain guidewire placement across the lesion and remove the stent delivery system as a single unit. See **Precautions – 6 Stent/system removal precautions** for specific stent delivery system removal instructions. In the event the stent is not deployed, contact your local Medtronic representative for return information and avoid handling the stent with bare hands.

14.6 Deployment procedure

Step	Action
1.	Before stent expansion, utilize high-resolution fluoroscopy to verify that the stent has not been damaged or shifted during positioning.
2.	Maintain inflation pressure for 15 to 30 seconds for full expansion of the stent.
3.	**Do not exceed Rated Burst Pressure (RBP). The RBP is 18 atm for the 2.0 mm to 4.0 mm stent diameters and 16 atm for the 4.5 mm and 5.0 mm stent diameters. The Resolute Onyx™ stents should not be expanded to a diameter beyond the maximum diameter listed on the label. Do not dilate the 2.0, 2.25, and 2.5 mm stents to greater than 3.25 mm. Do not dilate the 2.75 and 3.0 mm stents greater than 3.75. Do not dilate the 3.5 and 4.0 mm stents to greater than 4.75 mm. Do not dilate the 4.5 mm and 5.0 mm stents to greater than 5.75 mm.**
4.	Fluoroscopic visualization during stent expansion should be used to properly judge the optimum stent diameter as compared to the proximal and distal native coronary artery

diameters (reference vessel diameters). Optimal stent expansion and proper apposition requires that the stent be in full contact with the arterial wall.

14.7 Removal procedure

Step	Action
1.	Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 30 seconds, for full balloon deflation. Longer stents may require more time for deflation. Deflation of the balloon should be confirmed by absence of contrast within the balloon.
2.	Open the hemostatic valve to allow removal of the delivery system.
3.	Maintain position of the guide catheter and guidewire. Very slowly, withdraw the balloon from the stent, maintaining negative pressure, allowing movement of the myocardium to gently dislodge the balloon from the stent.
4.	After removal of the delivery system, tighten the hemostatic valve.
5.	Repeat angiography and visually assess the vessel and the stent for proper expansion.

14.8 *In-vitro* information:

Table 14-1: Inflation pressure recommendations

Pressure		Nominal and rated burst pressure	Stent nominal inner diameter (mm)								
ATM	kPa		2.0	2.25	2.5	2.75	3.0	3.5	4.0	4.5 (RX only)	5.0 (RX only)
7 atm	709 kPa		1.85	2.05	2.25	2.45	2.75	3.05	3.60	4.10	4.55
8 atm	811 kPa		1.90	2.10	2.30	2.55	2.80	3.15	3.70	4.20	4.65
9 atm	912 kPa		1.90	2.15	2.35	2.60	2.90	3.25	3.80	4.30	4.80
10 atm	1013 kPa		1.95	2.20	2.45	2.65	2.95	3.35	3.85	4.40	4.90
11 atm	1115 kPa		2.00	2.25	2.50	2.70	3.00	3.40	3.95	4.45	4.95
12 atm	**1216 kPa**	**Nominal**	**2.05**	**2.30**	**2.55**	**2.75**	**3.05**	**3.45**	**4.00**	**4.50**	**5.05**
13 atm	1317 kPa		2.05	2.35	2.55	2.80	3.10	3.50	4.05	4.55	5.10
14 atm	1419 kPa		2.10	2.35	2.60	2.80	3.10	3.55	4.05	4.60	5.15
15 atm	1520 kPa		2.10	2.35	2.60	2.85	3.15	3.55	4.10	4.65	5.20
16 atm	1621 kPa		2.15	2.40	2.65	2.90	3.20	3.60	4.15	**4.70**	**5.25**
17 atm	1723 kPa		2.15	2.40	2.70	2.90	3.20	3.65	4.20	4.80	5.30
18 atm	**1824 kPa**	**RBP**	**2.20**	**2.45**	**2.70**	**2.95**	**3.25**	**3.70**	**4.25**	4.85	5.35
19 atm	1925 kPa		2.20	2.45	2.75	3.00	3.30	3.75	4.30	-	-
20 atm	2027 kPa		2.25	2.50	2.75	3.00	3.35	3.80	4.35	-	-
21 atm	2128 kPa		2.25	2.50	2.80	3.05	3.40	3.80	4.40	-	-

14.9 Further dilatation of stented segment

The stent delivery balloon may not be used for post-dilatation. Post-dilatation may be performed at the physician's discretion with appropriately sized (length and diameter) balloons to ensure that the stent is in full contact with the vessel wall. To achieve this, a balloon to artery ratio of 1.0 to 1.1:1.0 should be used to leave a residual diameter stenosis of near 0% (with a recommended maximum of no greater than 10%). Whenever possible, avoid the use of grossly oversized balloons (balloon: artery ratio > 1.2).

Precaution: Do not dilate the stent beyond the following limits:

Table 14-2: Nominal stent diameters and dilatation limits

Nominal stent diameter	Dilatation limits
2.00 mm	3.25 mm
2.25 mm	3.25 mm
2.50 mm	3.25 mm
2.75 mm	3.75 mm
3.00 mm	3.75 mm
3.50 mm	4.75 mm
4.00 mm	4.75 mm
4.50 mm (RX Only)	5.75 mm
5.00 mm (RX Only)	5.75 mm

All efforts should be taken to ensure 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 further. This further expansion should be performed using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guidewire to avoid dislodging or displacing the stent. The balloon should be centered within the stent and should not extend outside of the stented region. **The Resolute Onyx™ stents should not be expanded to a diameter beyond the maximum diameter listed on the label. Do not dilate the 2.0 mm, 2.25 mm, and 2.5 mm stents to greater than 3.25 mm, 2.75 mm and 3.0 mm stents to greater than 3.75 mm, 3.5 mm and 4.0 mm stents to greater than 4.75 mm, and 4.5 mm and 5.0 mm stents to greater than 5.75 mm.**

14.10 Instructions for simultaneous use of 2 devices in guide catheter (kissing balloon technique)

RX only:

6 Fr (2 mm) compatibility: Any combination of one Resolute Onyx™ RX stent (models 2.0 mm to 4.0 mm) and one balloon catheter (Sprinter Legend™ RX models 1.25 mm to 3.5 mm up to 30 mm length, Euphora™ RX models 1.5 to 3.5 mm up to 30 mm length, or NC Euphora™ RX models 2.0 mm to 3.5 mm up to 27 mm length) can be used simultaneously within a 6 Fr (2 mm)/GC/MID 1.8 mm (0.070 in) guide catheter.

The technique can be performed as per the instructions listed below:

1. Insert the Resolute Onyx™ RX stent using the instructions provided (refer to **Section 14.5**).

2. Insert a second guidewire and a balloon catheter, track to the target site and inflate the balloon.
3. Removing the catheters: Remove one catheter and its associated guidewire completely before removing the other catheter and its associated guidewire.

15 Reuse precaution statement

For single use only.

Do not resterilize or reuse.

Disclaimer of warranty

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This educational booklet provides valuable information about the causes and treatment options for coronary artery disease.

For more information on treatment options for coronary artery disease, visit **www.medtronic.com**.

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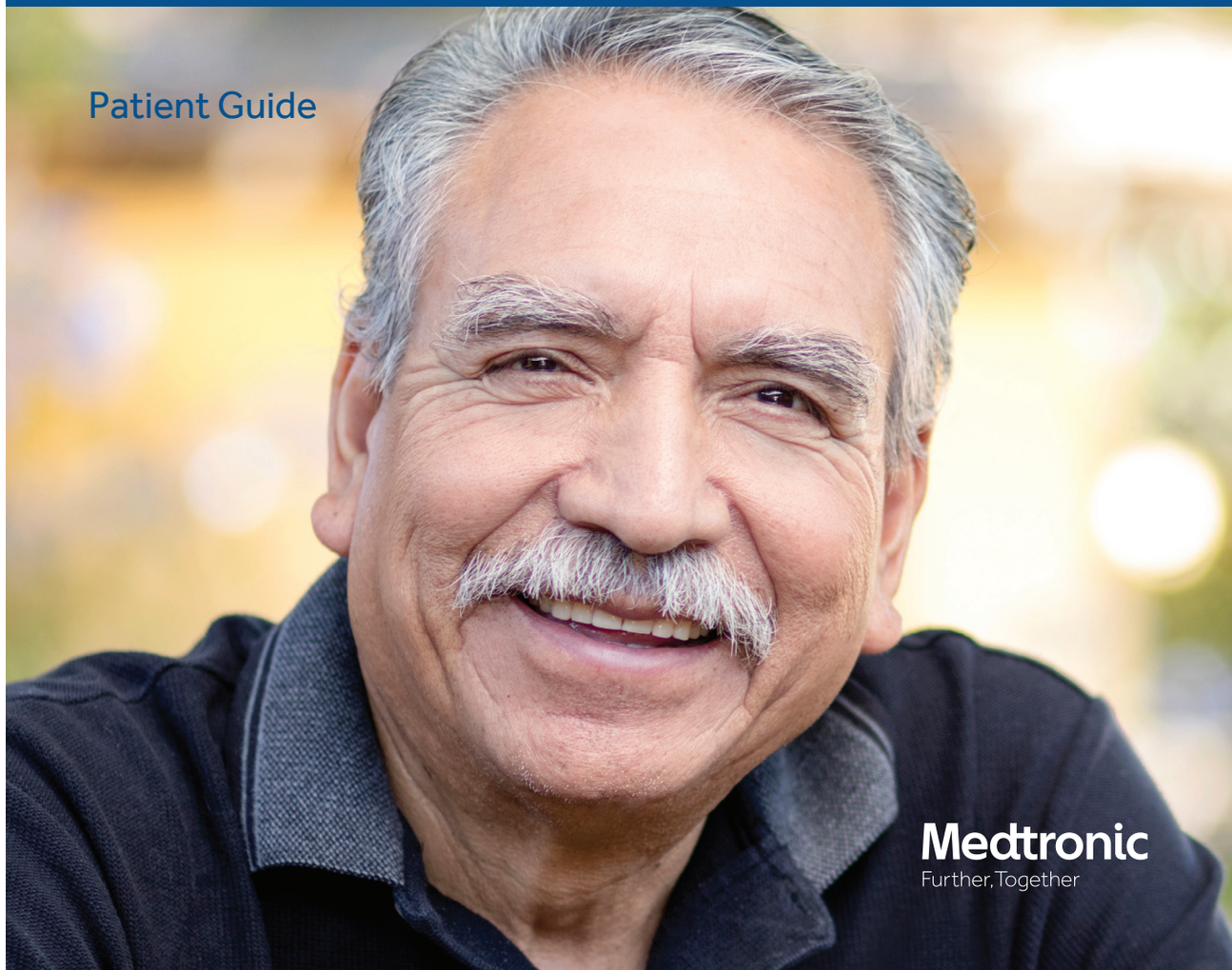
Coronary Artery Disease

UNDERSTANDING YOUR DRUG-ELUTING STENT PROCEDURE

Resolute Onyx™
Zotarolimus-Eluting Coronary Stent System

Patient Guide



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This booklet is provided to doctors for use in educating their patients about the options available for treating coronary artery disease. This information does not replace medical advice. Only a doctor can diagnose your health problem and determine which treatment is best for you.

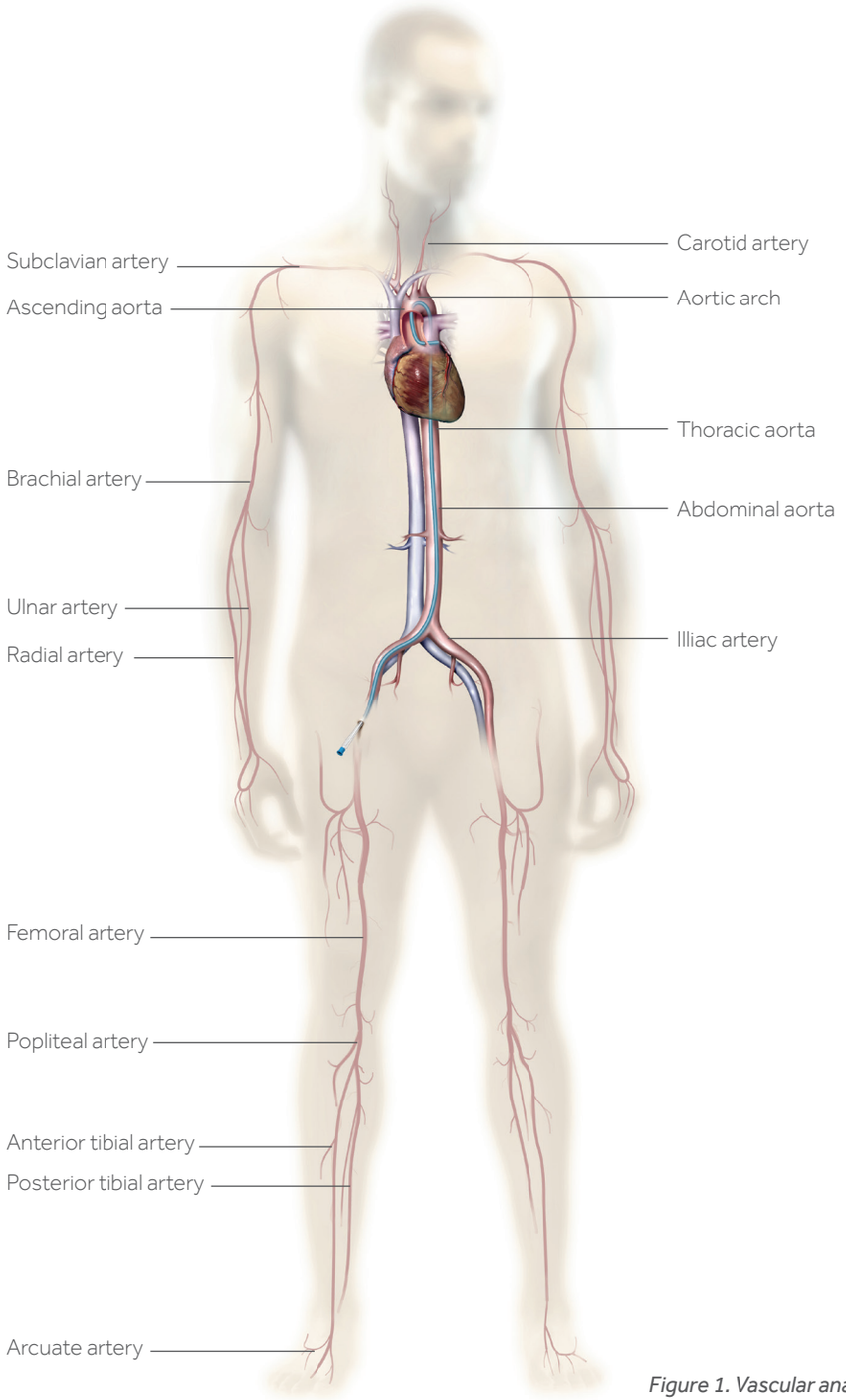


Figure 1. Vascular anatomy

Your Heart

Your heart is a muscle that pumps blood throughout your body (see **Figure 1**). The blood carries oxygen and nutrients that your body needs to work correctly. For the heart to be able to function properly, it also needs a constant supply of oxygen-filled blood. The vessels that supply this blood to the heart are called coronary arteries (see **Figure 2**).

If these arteries become narrowed or blocked resulting in reduced blood flow to the heart muscle, treatment is usually required.

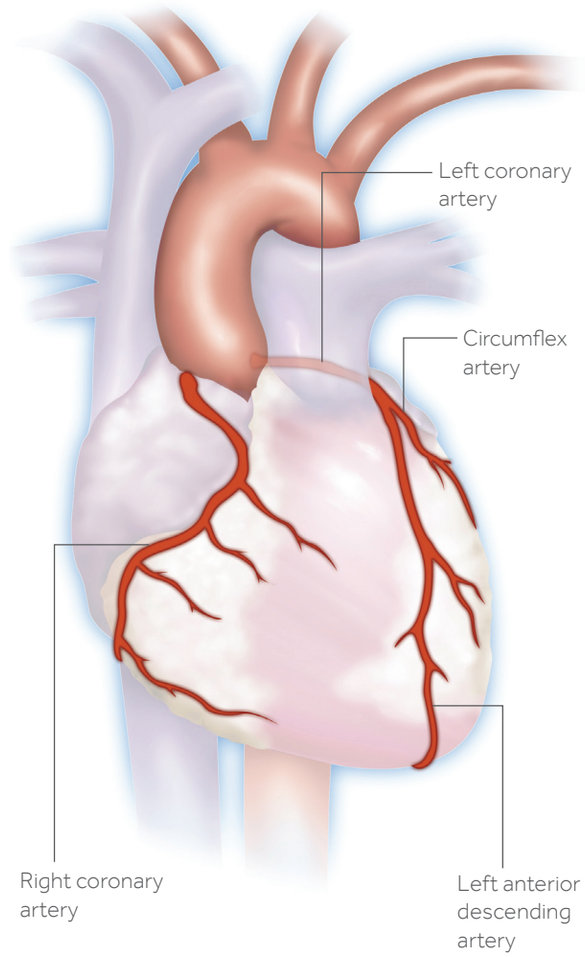


Figure 2. Coronary arteries

Understanding Coronary Artery Disease

What Causes It?

Fatty, waxy deposits called plaque (fat, cholesterol, calcium and other substances in your blood) can build up on the inside of your coronary arteries in a process known as atherosclerosis. These plaque deposits can narrow or clog the inside of your arteries, decreasing the supply of blood and oxygen to your heart (see **Figure 3**). This process is known as coronary artery disease (CAD). CAD is the leading cause of death for both men and women in the United States.[1]

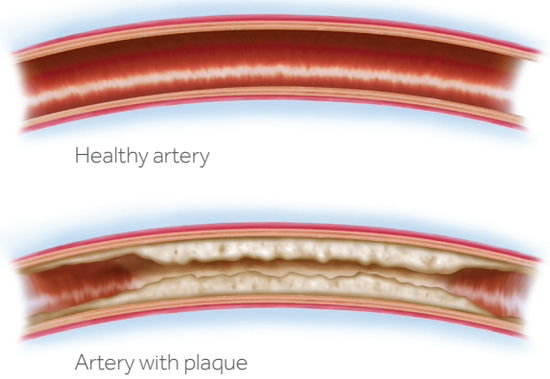


Figure 3. Comparison of coronary arteries

[1]National Heart, Lung and Blood Institute

What Are the Signs and Symptoms?

Some of the most common signs of reduced blood flow and oxygen to the heart include:

- Angina (chest pain)

Sometimes mistaken for heartburn or indigestion, angina can spread to the arms, shoulders, back and jaw. In some cases, if a coronary artery becomes completely blocked, you could have a heart attack, also known as a myocardial infarction.

- Shortness of breath
- Nausea
- Sweating

Did you know?

Although the most common symptom of a heart attack is chest pain or pressure, women are more likely to also have symptoms unrelated to chest pain such as:

- Neck, jaw, shoulder and upper back pain
- Burning sensation in the chest or upper abdomen
- Shortness of breath or irregular heartbeat
- Lightheadedness or dizziness
- Unusual or unexplained fatigue
- Nausea or vomiting
- Sweating or "cold sweat"

Source: www.mayoclinic.com

Who Is at Risk?

Some hardening and plaque accumulation within the arteries is expected as you grow older. However, certain risk factors, which include behaviors, conditions or habits, can speed up the process of your developing CAD. Also, the more risk factors you have, the higher your chances of developing CAD. For more information about risk factors, see Page 12.

Although some risk factors are beyond your control, such as your age and family history, others can be managed or eliminated to lower your risk. These include smoking, diabetes, high blood pressure, high cholesterol, obesity, and lack of exercise (leading a sedentary lifestyle). Your doctor can support your efforts to make healthier choices regarding your diet, tobacco use, activity level and stress management. For more steps you can take to prevent or slow CAD, see Page 19.

How Is It Diagnosed?

When making a diagnosis, your doctor will review your medical and family history, your risk factors and symptoms. If your doctor suspects you have CAD, you may be referred to a cardiologist — a doctor who specializes in problems of the heart, arteries and veins.

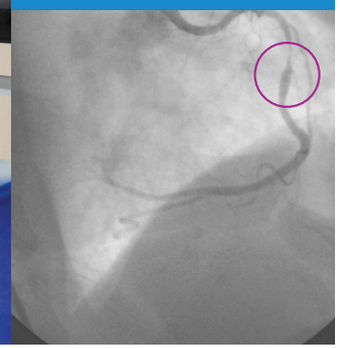
Before deciding on a treatment plan, your doctor or cardiologist may order some blood tests, a chest X-ray and other tests to measure how well your heart is working. A baseline electrocardiogram (ECG or EKG) is a simple test that records your heart's activity while you sit quietly. An exercise EKG, or stress test, shows how your heart responds to physical activity. Both tests can determine whether or not your heart is working properly due to a lack of oxygen.

Risk factors for CAD:

- High blood pressure
- High "bad" cholesterol; low "good" cholesterol
- Certain diseases, such as diabetes
- Obesity and being overweight
- Smoking
- Lack of exercise
- Stress
- Age (over 45 for men, over 55 for women)
- Family history of CAD
- Ethnicity (Hispanics and African Americans are at higher risk)

Source: American Heart Association

Figure 4. Typical cardiac catheterization laboratory



A coronary angiogram can identify the exact location of a narrowed or blocked artery.

Angiogram and heart catheterization

If one or more tests suggest that you may have CAD, your doctor may perform a coronary angiogram. The results of this test can help your doctor decide which treatment option is best for you.

The procedure consists of an imaging technique called fluoroscopy, which uses X-ray technology and a special fluid called contrast dye to obtain real-time moving pictures of the blood flow in your arteries. The fluoroscopic images can identify the exact location of your narrowed or blocked arteries and show the degree of your plaque buildup. This test, which usually takes 20 to 40 minutes, is performed in a cardiac catheterization laboratory, or cath lab, which is a room designed especially for the procedure (see **Figure 4**).

Procedure

For the heart catheterization, you may be given a mild sedative to help you relax. Small sticky pads, called electrodes, will be placed on your chest to monitor your heart rate and rhythm. Other devices will monitor your oxygen level and blood pressure. Your doctor will determine the best entry point for evaluating your heart arteries — leg, wrist, or arm. That area will be cleaned, shaved and numbed before a tiny puncture is made. After the artery puncture is made, a short tube known as a sheath will be placed in the artery to provide a temporary passageway for the necessary medical devices to reach your heart. Your doctor will next insert a long, thin, flexible hollow tube, or catheter, to access your coronary artery (see **Figure 5**). The contrast dye will be injected through the catheter and into your bloodstream to allow your doctor to view your arteries on the X-ray monitor, much like a television screen, and measure the extent of your CAD. It is normal to feel a warm but temporary sensation when the contrast dye is injected. Tell your doctor or nurse if you feel any pain or discomfort during the procedure.

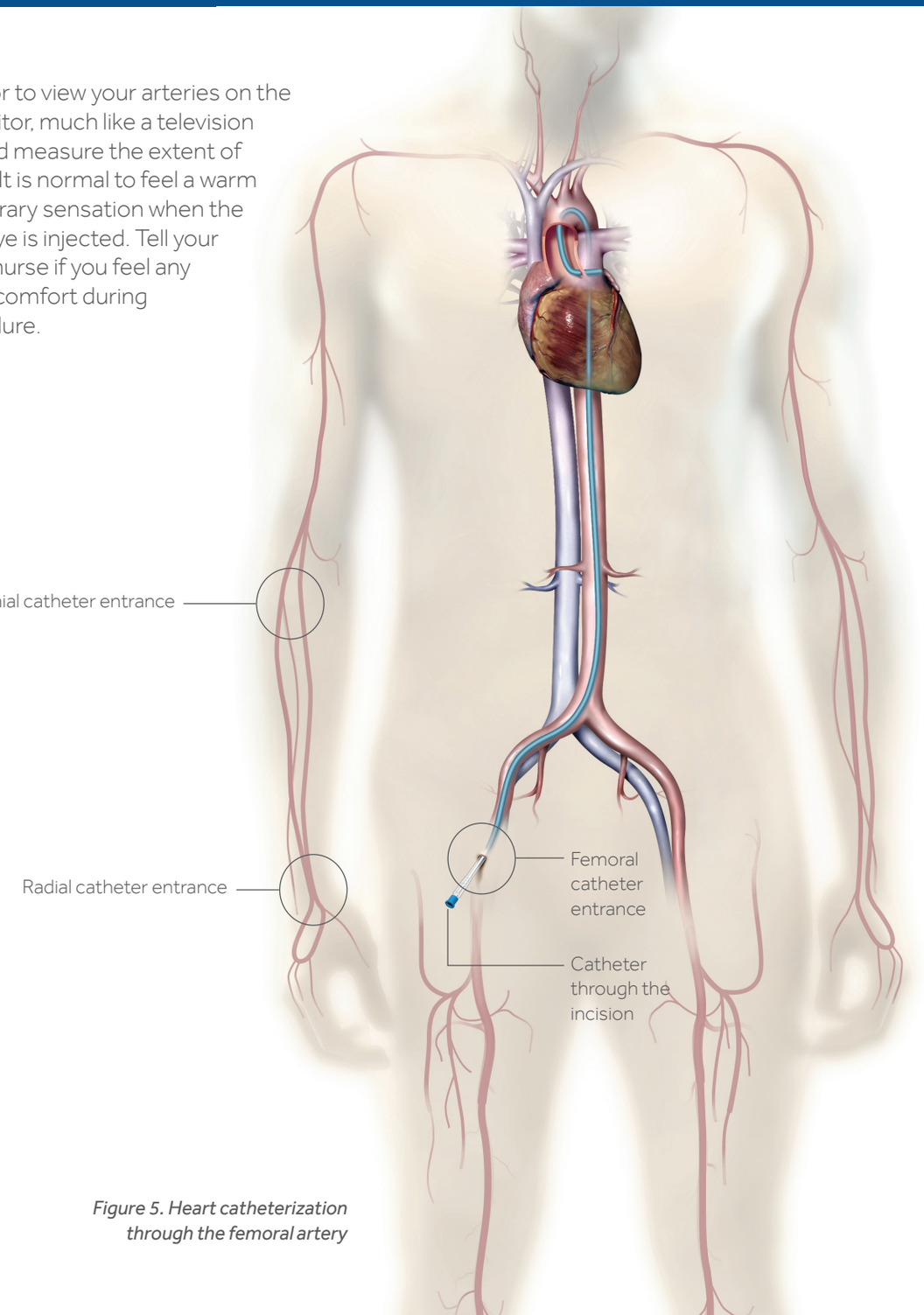


Figure 5. Heart catheterization through the femoral artery

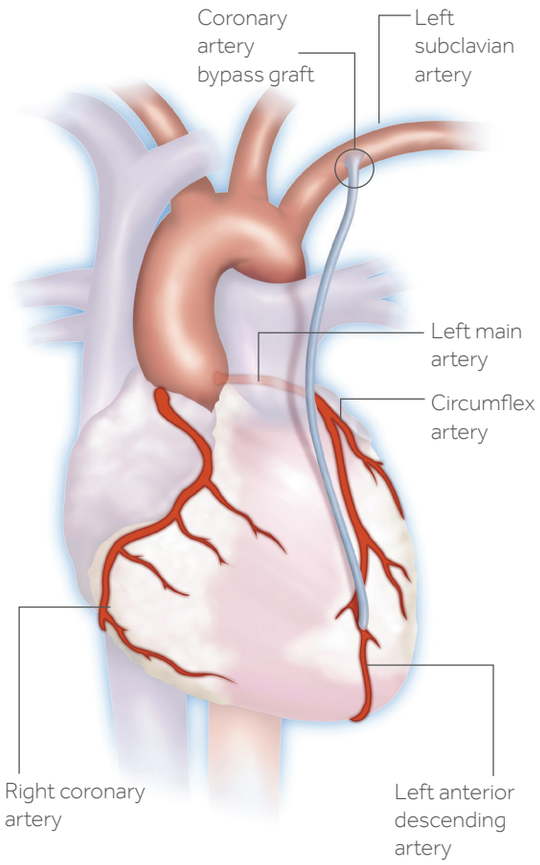


Figure 6. Coronary artery bypass grafting

Treatment Options for Coronary Artery Disease

CAD can be managed in several ways. Your doctor will recommend a treatment plan based on your symptoms, test results, medical history and future potential risks. This plan may include medications to relieve your chest pain, heart bypass surgery, and/or stenting to expand your coronary arteries and increase blood flow to your heart. Each of the treatment options discussed below has potential benefits and risks. Your doctor will discuss which of the choices is likely to be best for you.

Medical Therapy

Nitroglycerin may be given to relieve chest discomfort due to coronary blockages. Drugs such as beta blockers and cholesterol-lowering medications may be given to slow the disease's progress or to ease certain symptoms.

Surgery

Heart bypass surgery, also known as coronary artery bypass graft (CABG) surgery, is an open heart procedure. Typically, a section of vein from your leg (and sometimes an artery from your wrist) is removed. Then an artery from your chest and the section of the vein from your leg are attached (grafted) onto your coronary artery just past the blockage site (see **Figure 6**), creating a new path for blood to flow (bypass) around the blocked artery.

Today, there are options regarding the surgical approaches for CABG surgery with respect to the type and location of chest incisions. The heart surgeon may discuss these options with you. Following successful CABG surgery, patients typically stay in the hospital for less than one week and continue their recovery at home.

Balloon Angioplasty

Balloon angioplasty is one type of a group of heart procedures known as percutaneous coronary intervention (PCI) and is performed in the catheterization laboratory — the same room where you may have had a coronary angiogram. Balloon angioplasty does not require open surgery. A local anesthetic will be used to numb the puncture site, and you may be given a sedative to help you relax. Your doctor will determine the best entry point for evaluating your heart arteries — leg, wrist, or arm. That area will be cleaned, shaved, and numbed before the artery puncture is made. After the artery puncture is made, a short tube known as a sheath will be placed in the artery to provide a temporary passageway for the necessary medical devices to reach your heart. During the coronary angiogram, your doctor will inject a contrast dye through a catheter into your bloodstream, which allows your doctor to view your arteries on the X-ray monitor. A catheter with a small balloon on its tip is inserted through the sheath and threaded through your arteries until it reaches your blocked coronary artery. Then the balloon is inflated to flatten the plaque against the wall of the artery. It is normal to have some chest pain when the balloon is inflated. Tell your doctor or nurse if you feel any pain or discomfort during the procedure. The balloon is then deflated and the catheter is removed from your artery. This procedure opens the narrowing in your coronary artery, and increases blood flow through the artery (see **Figure 7**).

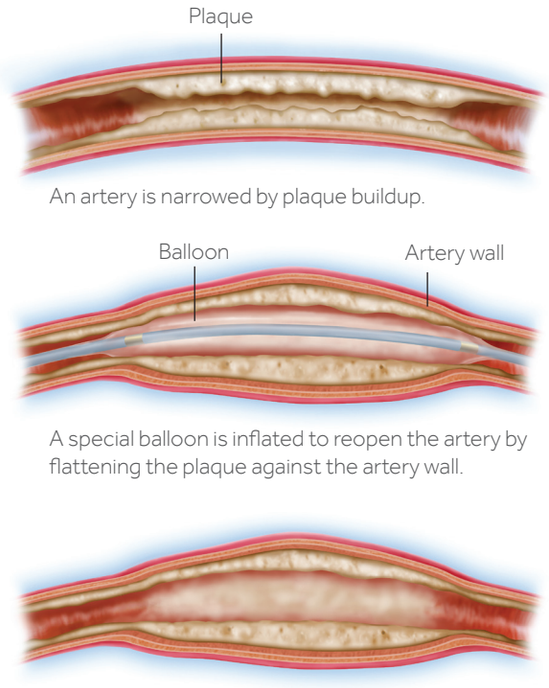


Figure 7. Balloon angioplasty inside an artery

Stent Therapy

In many cases, balloon angioplasty alone may not be successful in effectively opening your blocked artery. Therefore, your doctor may recommend placing a coronary stent at the site of the artery blockage. Stent implantation in a heart artery is another type of PCI procedure. Implanting a stent does not require open surgery.

A stent is a tiny, metallic, expandable mesh-like tube that supports the artery and helps to keep it open (see **Figure 8**). You will likely already have a short tube known as a sheath in an artery in your leg, wrist, or arm. Your doctor will insert a specially designed balloon catheter through the sheath and deliver the stent to the blocked area of the coronary artery. The balloon is inflated to expand the stent. As the stent expands, it helps flatten the plaque against the artery wall, increasing blood flow. Once the stent is properly expanded, the balloon is deflated and the catheter is removed from your body. The stent stays in your artery permanently to help keep it open to maintain blood flow.

Restenosis

Restenosis is the renarrowing of the artery due to the overgrowth of tissue within the stent during the healing process. Although stenting is a less invasive way to open clogged arteries compared with CABG surgery, restenosis may occur in some patients who receive stents.

Drug-Eluting Stents for Coronary Artery Disease

To help prevent restenosis from occurring, scientists developed drug-eluting stents. Drug-eluting stents reduce the risk of restenosis and reduce the potential need for future treatment. They provide the same support to the artery wall as uncoated stents, except they have a coating on the stent that includes a drug that is released over time. The drug helps limit the overgrowth of tissue within the stent as the artery heals, preventing renarrowing (see **Figure 9**).

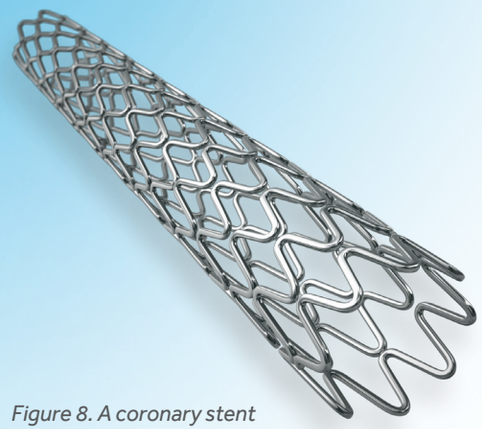


Figure 8. A coronary stent

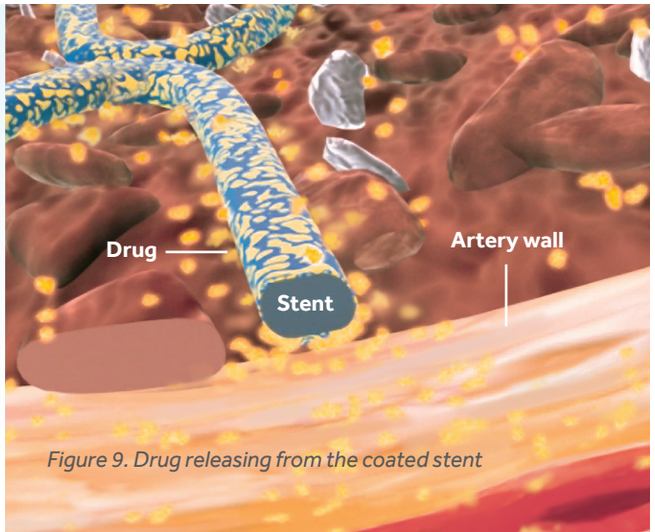


Figure 9. Drug releasing from the coated stent

Did you know?

- Since the introduction of stents, millions of people around the world have been treated with this therapy.
- Stents come in a variety of sizes so that doctors can best match the size of the diseased artery.

Source: American Heart Association

Diabetes and heart disease

If you have diabetes, you are at an increased risk for having a heart attack. Therefore, in addition to all the measures aimed at lowering the risk of CAD, diabetic individuals should pay attention to the following measures to lower the chances of CAD:

- Adopt a heart-healthy diet rich in fiber, fruits and vegetables
- Aim for at least 30 minutes of physical activity daily
- Take your medications as directed
- Keep your blood glucose under control
- Check your feet daily for cuts, blisters, sores, swelling, redness or sore toenails
- Brush and floss your teeth daily
- Manage your blood pressure and cholesterol
- Maintain a healthy weight
- Do not smoke

Source: National Diabetes Information Clearinghouse

Resolute Onyx™ Zotarolimus-Eluting Coronary Stent

Medtronic Resolute Onyx™ zotarolimus-eluting coronary stents are drug-eluting stents (see **Figure 10**). They are made of an alloy containing the following metals: cobalt, chromium, molybdenum, nickel, and platinum-iridium. They are coated with a drug called zotarolimus, which is contained within a polymer (a plastic material designed specifically to control the drug release). The drug helps limit the growth of tissue in the artery where the stent is placed. Each stent is polished for a smooth surface and shaped to allow it to pass through your arteries on a specially designed balloon catheter.

Contraindications

You should not receive the Resolute Onyx™ stent if you have a known allergy to:

- Drugs used for suppression of the immune system such as zotarolimus, tacrolimus, sirolimus or related drugs
- Cobalt, nickel, chromium, molybdenum, or platinum-iridium
- The polymer or its individual components, including: polybutyl methacrylate, polyhexyl methacrylate, polyvinyl acetate and PVP (polyvinyl pyrrolidone)

Coronary artery stenting is contraindicated for use in the following:

- If you are unable to take aspirin or other blood-thinning drugs (also called antiplatelet or anticoagulation therapy) such as heparin, bivalirudin, clopidogrel, prasugrel, ticagrelor, or ticlopidine
- If your doctor decides that your blockage will not allow complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system

A drug-eluting stent for people with diabetes:

- Diabetes affects 25.8 million people in the United States[1] and is on the rise. People with diabetes are more likely to have high blood pressure, heart disease or suffer a stroke. In fact, CAD is the leading cause of death in patients with diabetes.[1]
- Resolute™ stents, including Resolute Onyx™ DES, have been evaluated in people with diabetes and have been approved by the FDA as safe and effective treatment options for this patient population.
- If you have diabetes, it is important to adopt healthy habits (see Page 5) and talk with your doctor about ways you can further reduce your risk of CAD.

[1] *American Diabetes Association*

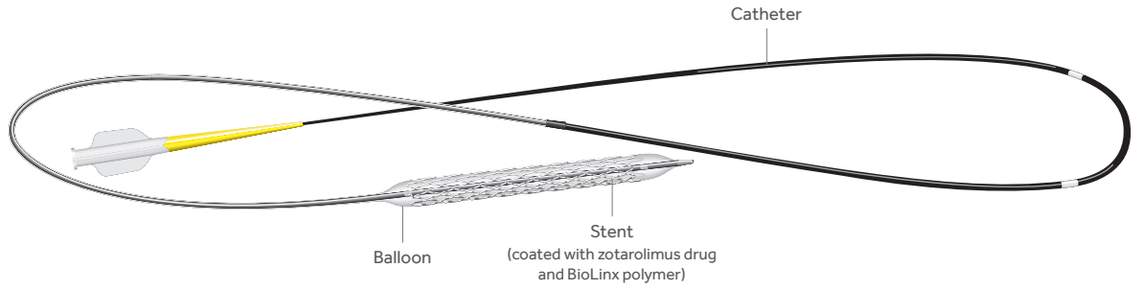


Figure 10. Resolute Onyx™ coronary stent and delivery system

Potential Adverse Events

The risks of using the Resolute Onyx™ stent are similar to those associated with any stent procedure. Discuss all of your available treatment options with your doctor, who can advise you as to whether or not a drug-eluting stent is right for you. If the stent clots, you may need another angioplasty procedure. It may also lead to a heart attack, the need for urgent bypass surgery, or death. Even with successful stent implants, there is a chance of renarrowing (restenosis). This may require additional treatment, such as repeat angioplasty and/or bypass surgery, to reopen the artery and to increase blood flow to the heart. The risks from using balloon catheters within a previously implanted stent are similar to the risks that may occur during the initial stent implant. These may be serious enough to require additional surgery or cause death.

Some risks associated with standard balloon angioplasty and stenting include, but are not limited to:

- Bruise or bleeding at the catheter insertion site in the leg, wrist or arm
- Pain at the catheter insertion site
- Irregular heartbeats, possibly life-threatening
- Chest pains during and after the procedure
- Decreased or increased blood pressure
- Renarrowing of the coronary artery
- Tearing, puncture or rupture of the coronary artery
- Air, pieces of devices or fragments of clots blocking the coronary artery
- Complete blockage of the coronary artery, which may require a repeat procedure to reopen the coronary artery
- Bleeding around the heart
- Heart attack or death
- Stent deformation, collapse or fracture
- Damage to the stent or injury to the coronary artery requiring emergency heart surgery
- Bleeding requiring transfusion or surgery
- Allergic reaction, which may be due to contrast dye, antiplatelet therapy, stent material (cobalt, chromium, nickel, and platinum-iridium), drug or polymer coating
- Infection or fever
- Nerve injury
- Aneurysm (weakening of a portion of the wall of a blood vessel)
- Failure to release the stent from the catheter
- Stent misplacement in the artery
- Movement of the stent from where it was placed
- The balloon used to expand the stent may break
- Shock
- Stroke/transient ischemic attack
- Renal failure

The risks of the zotarolimus drug are not yet fully known. The risks that might occur include but are not limited to:

- Blood in the urine and/or diarrhea
- Diarrhea
- Dry skin
- Fatigue
- Headache
- Infection
- Pain (abdominal, joint, injection site)
- Skin reaction (at injection site)
- Tingling feeling around the mouth

Exposure to zotarolimus and the Resolute Onyx™ polymer coating is directly related to the number of implanted stents. The use of multiple Resolute Onyx™ stents will result in your receiving larger amounts of drug and polymer.

Questions to ask your doctor:

- Do I have a blocked or clogged artery?
- How severe is my CAD?
- What are my treatment options and the benefits and risks of each?
- What happens if I wait to receive treatment?
- Is stent implantation an option?
- What kind of stent is best for me?
- What will I need to do to take care of myself after the procedure?

Clinical Studies

The safety and effectiveness of the Resolute Onyx™ stent was based on data from the RESOLUTE ONYX studies and a series of clinical studies that evaluated the Resolute™ stent and Resolute Integrity™ stent. The Resolute Onyx™, Resolute Integrity™, and Resolute™ stents are similar with regard to their metal stent design and identical with respect to their drug and polymer coating. Given the similarities between the three stents, plus additional laboratory tests, the findings described below for the Resolute Onyx™, Resolute Integrity™, and Resolute™ stent clinical studies apply to the Resolute Onyx™ stent

RESOLUTE ONYX Core Clinical Study

In the RESOLUTE ONYX Core (2.25 mm–4.0 mm) Clinical Study, 75 patients in the United States were treated with Resolute Onyx™ drug-eluting stents. After eight months, angiogram data showed that the Resolute Onyx™ stent was noninferior to another approved drug-eluting stent at reducing the renarrowing of the artery where the stent was placed.

RESOLUTE ONYX 2.0 mm Clinical Study

In the RESOLUTE ONYX 2.0 mm Clinical Study, 101 patients in the United States and Japan received at least one Resolute Onyx™ stent measuring 2.0 mm in diameter to treat a blocked artery. After one year, 5% of patients who received a Resolute Onyx™ stent had a heart-related death, heart attack, or need for a repeat procedure at the site of the originally placed stent.

The Global RESOLUTE Clinical Trial Program

There have been five clinical studies that together show the safety and effectiveness of Resolute™ coronary stents in patients with coronary artery disease. A short description of these studies is provided below:

1. RESOLUTE First-In-Man (FIM): RESOLUTE FIM was the first clinical study conducted with the Resolute™ stent. This study had 139 patients and was performed in Australia and New Zealand. After nine months, the Resolute™ stent was noninferior to another approved drug-eluting stent in reducing the renarrowing of the artery where the stent was placed. At four years after the initial procedure, 2.2% of patients who had received the Resolute™ stent needed a repeat procedure at the site of the originally placed stent.

2. RESOLUTE US: RESOLUTE US (R-US) was conducted in the United States to evaluate the safety and effectiveness of the Resolute™ stent. There were a total of 1516 patients enrolled in the RESOLUTE US study; 1242 patients in the main study (which included 100 patients towards the 150 patients in the 2.25 mm cohort[1]), 100 patients in the Angiographic and Intravascular Ultrasound (IVUS) Substudy, 60 patients in the 4.00 mm Substudy and 114 patients in the R-US 38 mm Substudy (the 38 mm Substudy included a total of 223 patients; 114 from the R-US study and 109 from the R-Asia study).

- **2.50 mm–3.50 mm Substudy:** A total of 1112 patients received at least one Resolute™ stent to treat blocked heart arteries measuring 2.50 mm to 3.50 mm in diameter. After one year, 3.8% of patients had a heart-related death, heart attack, or need for a repeat procedure at the site of the originally placed stent
- **Angiographic and Intravascular Ultrasound (IVUS) Substudy:** A total of 100 patients received a Resolute™ stent. Eight months later, the patients had a repeat angiogram and an ultrasound test to look at whether renarrowing of the artery had occurred. The angiogram at eight months showed that the Resolute™ stent was noninferior to another approved drug-eluting stent at reducing the renarrowing of the artery where the stent was placed.
- **2.25 mm Cohort:** A total of 150 patients received at least one Resolute™ stent measuring 2.25 mm in diameter to treat a blocked artery. After one year, 5.5% of patients who received a Resolute™ stent had a heart-related death, heart attack, or need for a repeat procedure at the site of the originally placed stent.
- **4.00 mm Substudy:** A total of 60 patients received at least one Resolute™ stent measuring 4.00 mm in diameter to treat a blocked artery. After eight months, the Resolute™ stent was noninferior to an approved bare metal stent in reducing the renarrowing of the artery segment where the stent was placed.
- **38 mm Length Substudy:** A total of 223 patients, 114 in the USA and 109 in Asia, received at least one stent measuring 38 mm in length. After 12 months 4.5% of patients had a heart-related death, heart attack or a need for a repeat procedure at the site of the originally placed stent.

3. RESOLUTE All Comers: In RESOLUTE All Comers, 1140 patients received at least one Resolute™ stent. Many patients had coronary artery disease that was more complicated than in the RESOLUTE FIM, RESOLUTE US and RESOLUTE Japan studies. This study was conducted in Europe. After one year, 8.1% of patients treated with Resolute™ stents had a heart-related death, heart attack, or need for a repeat procedure at the site of an originally placed stent. After two years, 11.2% of patients treated with Resolute™ stents had a heart-related death, heart attack, or need for a repeat procedure at the site of an originally placed stent.

4. RESOLUTE International: In RESOLUTE International, a total of 2349 patients received at least one Resolute™ stent. Many patients had coronary artery disease that was more complicated than in the RESOLUTE FIM, RESOLUTE US and RESOLUTE Japan studies. This study was conducted in Europe, India, South Africa and Argentina. After one year, 4.3% of patients had a heart-related death or heart attack.

5. RESOLUTE Japan: This study involved 100 Japanese patients. After eight months, the Resolute™ stent was noninferior to an approved drug-eluting stent at reducing the renarrowing of the artery where the stent was placed.

Resolute™ Stent in Patients with Diabetes: The safety and effectiveness of the Resolute™ stent in diabetic patients was evaluated by combining the results of 878 diabetic patients from the five studies noted above. After one year, 8.1% of diabetic patients who received a Resolute™ stent had a heart-related death, heart attack, or need for a repeat procedure in the same vessel where the original stent was placed.

Resolute Integrity™ Stent in Patients with Chronic Total Occlusions (CTO): The safety and effectiveness of the Resolute Integrity™ stent in CTOs was evaluated by assessing the results of 183 patients from the PERSPECTIVE investigator-initiated study in the United States. After one year, 18.2% of CTO patients who received a Resolute Integrity stent had a heart-related death, heart attack, or need for a repeat procedure in the same vessel where the original stent was placed.

Resolute Onyx™ Stent Treated with 1-Month Dual Antiplatelet Therapy (DAPT): The safety and effectiveness of the Resolute Onyx™ stent in patients at high bleeding risk who stopped taking one of their DAPT medications after 1 month were evaluated in the Onyx ONE Clear Primary Analysis.

After one year, combined analysis from 601 patients from the Onyx ONE US/Japan Trial, with 905 patients from the Onyx ONE Global RCT, showed that from 1 month to 12 months after the procedure, 7.0% of the patients had a heart-related death or heart attack.

[1] The 2.25 mm cohort included 130 patients who were part of the main study and 20 patients who were part of the 2.25–3.50 mm Angio/IVUS substudy.

Your Stent Procedure: What to Expect

Preparing for your procedure

If you know in advance that you will be getting a coronary stent, ask your doctor any questions you may still have.

Before you receive a Resolute Onyx™ stent

In the days prior to your treatment, make sure you:

- Take all of your prescribed medicines.
- Tell your doctor if you cannot take aspirin and/or blood-thinning medications such as Plavix®, also known as clopidogrel, or if you have a history of bleeding problems.
- Tell your doctor about any medications you are taking.
- Tell your doctor about your drug allergies, or if you are allergic to any metals or plastics. Ask your doctor which medications are safe for you to continue taking.
- Follow all instructions given to you by your doctor or nurse, including limits on what you eat and drink before your procedure, arrangements for going home after your procedure, what activities are safe to do after your procedure, and when you should see your physician after you go home.

Be sure to tell your doctor if you:

- Cannot take aspirin or other blood-thinning medications
- Are allergic to drugs/metals/plastics/shellfish
- Have a history of bleeding problems
- Are or might be pregnant, or are nursing
- Are planning other surgeries or dental work soon

Implanting the stent

Your stent procedure will be performed in a cath lab by an interventional cardiologist, a doctor who specializes in this procedure. You will be awake for the procedure and will receive fluids and drugs to relax you. Your procedure will begin with an angiogram to determine the number and location of the blockage(s), and will usually include a balloon angioplasty prior to implanting the stent.

Using X-ray images to guide the way, your physician will insert an unexpanded stent mounted onto a deflated balloon through the sheath placed in an artery in your leg, wrist or arm. You might feel pressure at the sheath site while this is being done. You won't be able to feel the catheter as it moves through your body. The stent and balloon are carefully guided to the site of the blockage in the artery. Then the balloon is inflated, expanding the stent, flattening the plaque against the artery wall. It is common to feel some mild discomfort as the stent is expanded, but this should subside when the balloon is deflated.

Once the stent is in place, more X-ray images are taken to ensure that the stent is fully expanded and that blood flow to your heart has improved. Your doctor may inflate and deflate the balloon several times to make sure the stent is firmly pressed against the artery wall. When your doctor sees that blood is flowing properly, the catheter will be removed from your body. The stent will remain permanently inside the artery to hold it open and maintain blood flow to your heart **(see Figure 11)**. After the procedure is completed, the sheath in the artery in your leg, wrist or arm will be removed, and the puncture site will be sealed with a special closure device or by applying pressure over the artery. The stenting procedure lasts 30 minutes to two hours.

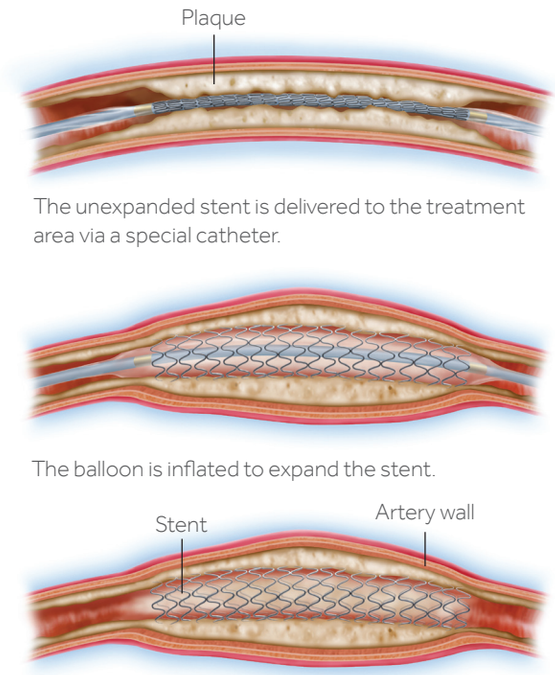
After Your Procedure

Resting in the hospital

Immediately after the procedure, you will be instructed to lie still and not bend your leg, wrist or arm where the catheter was inserted. You will probably stay in a special hospital unit for several hours or up to one or two days while nurses monitor your heart, blood pressure and catheter insertion site. It is normal to feel some bruising and soreness at the insertion site in your leg, arm or wrist. You may also feel groggy or forgetful from the sedating medication. Gradually, you will be allowed to get up and walk around — most people are up within two to six hours.

Going home

- Before leaving the hospital, your cardiologist or nurse will give you instructions about what drugs you will need to take.
- You will also receive a stent implant identification (ID) card.
- It is important to rest and drink plenty of fluids to rid your body of the contrast dye.



The unexpanded stent is delivered to the treatment area via a special catheter.

The balloon is inflated to expand the stent.

The balloon is deflated and withdrawn from the body, leaving the stent to support the artery and maintain blood flow.

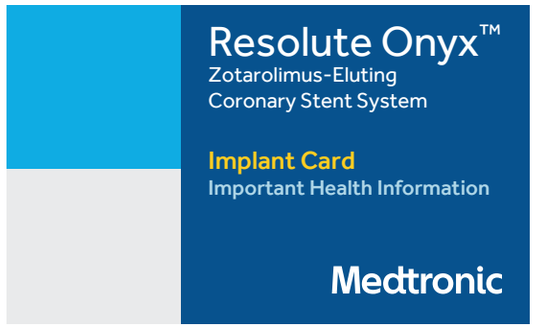
Figure 11. Implanting a stent inside a narrowed artery

- Do not lift heavy objects or exercise for at least 24 hours after going home.
- If you are a smoker, talk to your doctor about quitting.
- You should be able to return to your normal activities quickly, but be sure to discuss this with your doctor.

Your stent implant identification card

Your stent implant ID card identifies you as a patient who has had a stent implanted. It contains important information including the kind of stent you have and its location inside your body, the date of your stent implant procedure, and your doctor's name and contact information.

Keep your stent implant ID card with you at all times and be prepared to show it to other doctors and dentists you may see in the future. They may need to take special precautions when treating you. If you require a magnetic resonance imaging (MRI) scan, tell your doctor or MRI technician that you have a stent implant.



Signs to watch for:

Call your doctor or hospital staff immediately if:

- Your catheter insertion site is painful, or starts to bleed or swell
- You have signs of infection such as fever or warmth, redness, swelling, or drainage at the catheter insertion site
- You feel chest pain, discomfort or shortness of breath
- You feel faint, dizzy or weak

Caution: If you experience any of these symptoms and your doctor is unavailable, call for an ambulance to take you to the nearest hospital emergency room.

Recovering from Your Stent Procedure

Before you leave the hospital, your doctor will ask you to take certain drugs. It is important to precisely follow your doctor's advice about taking these medications.

Blood-thinning drugs

Blood-thinning or antiplatelet medicine helps prevent blood clots from forming on your stent, a condition called stent thrombosis. Stent thrombosis is a dangerous condition that can cause a heart attack or sudden death. The most commonly used antiplatelet medications are Plavix®, also known as clopidogrel, Ticlid®, also known as ticlopidine, Effient®, also known as prasugrel, and Brilinta®, also known as ticagrelor. You will need to take one of these blood thinners for up to a year or more after your procedure, but be sure to let your doctor know if you have bleeding problems. Most people will also need to take aspirin for life. It is extremely important to take the full dose your doctor prescribes and to not miss any doses.

Caution: Call your doctor if you cannot continue taking your medications because of side effects such as rash, bleeding or upset stomach.

Caution: Do not stop taking your prescribed medications unless you are instructed to do so by the doctor who performed your stent procedure.

Caution: If your dentist or another doctor has told you to stop taking your medication, talk to your cardiologist before you stop taking your antiplatelet medications — even if you are asked to stop for only a short time. If surgery or dental work that would require you to stop taking antiplatelet medications is recommended after you have received the stent, you and your doctor should carefully consider the risks and benefits of this surgery or dental work vs. the possible risks from early discontinuation of these medications.

Follow-up visits

Along with taking your medications, seeing your doctor on a regular basis is very important to your recovery. Your first visit is usually within four weeks after your stent is implanted. Be sure to keep all appointments for follow-up care, including blood tests. If you receive a drug-eluting stent, your doctor will monitor you for possible side effects of this drug. It is also very important to work with your doctor to keep coronary artery disease risk factors (high cholesterol, diabetes, obesity, high blood pressure, and smoking) under control.

Caution: Notify your doctor immediately if you experience new, severe or frequent chest pain, especially in the first month after your procedure. These symptoms may indicate a renarrowing in your coronary arteries.

Staying Healthy with a Stent Implant

Although CAD can be treated effectively, it has no cure. Along with learning everything you can about the disease, you can help slow or prevent its advancement by making some healthy lifestyle changes.

Heart-healthy choices

Smoking, leading a sedentary or stressful lifestyle, and consuming a diet high in fat and low in fruits and vegetables all increase your risk for CAD. Ask your doctor how you can learn to:

- Stop smoking — it is the single most important thing you can do for your health
- Control diabetes
- Control blood pressure
- Eat heart-healthy food
- Exercise
- Maintain a healthy weight
- Manage stress
- Learn more about living with CAD

Frequently Asked Questions

Are stents safe?

More than two million people receive stents each year, and doctors have been recommending them to their patients for more than ten years. However, a stent may not be the right treatment option for you. If you cannot take aspirin or other blood-thinning (antiplatelet) medicines, or if you are allergic to certain metals and plastics, then a stent is not right for you. Talk with your doctor about the risks of stent therapy and how it may affect you. For more information, see Page 12.

How long does the procedure take and when can I go home?

A stent procedure lasts 30 minutes to two hours depending on the extent of your CAD. Some patients are discharged the same day that the stent is implanted, but you should expect to stay overnight in the hospital and return home the next day. However, your hospital stay may be longer.

Do I need to be worried about contrast dye and its impact on my kidneys?

Like any procedure requiring use of contrast dye, there are risks that may include kidney damage. Your doctor will explain the risks involved and try to minimize the amount of contrast dye you receive during your procedure. Afterwards, be sure to drink plenty of water to help your kidneys flush away the dye.

Will drug-coated stents interfere with other over-the-counter or prescription medicines I may be taking?

Although drug interactions are uncommon, certain drugs may interact with the specific medication used on drug-coated stents. It is important to tell your doctor about any drugs you may be taking.

How long will the stent stay in my body?

Stents are designed to stay in your body permanently.

Will I be able to feel the stent inside me? Will it move?

No, you will not be able to feel the stent once it has been implanted in your artery. Once the stent is implanted and pressed against the artery wall, it will remain there permanently. Tissue will grow over the stent and hold it in place so it will not move.

Can the stent rust? What is it made of?

The Resolute Onyx™ stents are made of a non-rusting alloy containing the following metals: cobalt, chromium, molybdenum, nickel, and platinum-iridium.

When can I resume my regular activities (for example, working, exercising, sexual activity, traveling, playing sports)?

Your doctor will advise you. Most patients can return to work and follow their normal routines in about one week.

Do I need to contact my private insurance before or after the procedure?

As with any medical procedure, it is a good idea to contact your insurance company in advance to check on the specific benefits, limitations, copayments and deductibles that may apply to your treatment.

If I have a drug-coated stent, what medications do I need to take, for how long, and what do they do?

After your stent is implanted, you will need to take blood-thinning medicines for up to a year or more to prevent stent thrombosis, which is the formation of blood clots within the stent. Most people will need to take aspirin for the rest of their lives. The most important thing that you can do to minimize the risk of stent thrombosis is to take the medicines your doctor prescribes. Do not stop taking them until your doctor tells you to, even if you are feeling better. Follow your doctor's instructions exactly.

What follow-up care is required for drug-coated stents?

You will need to return to see your doctor for regular follow-up visits after undergoing stent implantation. It is very important not to miss any scheduled follow-up visits with your doctor. Along with taking your prescribed medications, your doctor will monitor you for possible side effects and help keep your risk factors under control. See Page 3 for more information.

Why should I carry a stent implant identification card?

Your stent implant ID card notifies medical personnel that you have a stent implanted in your body. It tells them the type of stent you have, its location and that you are likely to be taking antiplatelet medication. Carry your card with you at all times and present it whenever you see a new doctor, have a medical test or procedure, go to the emergency room or see your dentist.

Will my stent set off metal detectors at airports or security checkpoints in stores?

No, your stent implant will not trigger alarms at airports or security checkpoints.

Is it safe to have an MRI/mammogram/ CAT scan?

Mammography, CAT scans, X-rays and nuclear stress tests are safe for people with stents. However, if you need an MRI, the technician will need to operate the machine within certain limits. Be sure to tell all doctors treating you that you have a stent, and show them your stent implant ID card.

Do I need to be careful around microwaves?

You can safely use a microwave oven. A microwave oven will not harm your stent.

Could I have recurring symptoms?

Yes, it is possible that you will experience symptoms again, either due to a reblockage in the artery with the stent or a new blockage in a different heart artery. Notify your doctor if you have recurring symptoms.

How can I prevent a recurrence of symptoms?

While there is no sure way to prevent a recurrence of symptoms, you can reduce your risk through exercise, not smoking and adopting a healthy diet. Your doctor can advise you about lifestyle changes.

What if my arteries renarrow?

If this happens, you may experience symptoms similar to those you experienced before your stent procedure. These symptoms may include chest pain or shortness of breath, especially during physical activity. Inform your doctor immediately if you experience any of these symptoms. You may need additional treatment.

Resources

These resources provide additional information about heart disease and treatment options:

- **American Heart Association** (www.heart.org)
- **American College of Cardiology** (www.cardiosource.org)
- **Food and Drug Administration** (www.fda.gov/forconsumers)
- **National Heart Lung and Blood Institute** (www.nhlbi.nih.gov)
- **Mayo Clinic** (www.mayoclinic.com)

Glossary

Angina. Pain or discomfort in the chest because of reduced blood flow and oxygen supply to the heart muscle.

Angiogram. Special X-ray test that indicates the number, exact location and extent of narrowed or blocked coronary arteries.

Angioplasty. Procedure used to unblock an artery clogged with plaque; also known as percutaneous transluminal coronary angioplasty (PTCA), or balloon angioplasty. Often followed by the placement of a stent.

Antiplatelet medications. Drugs that inhibit the function of platelets, the blood cells that clump together to begin the process of blood clot formation. Examples include Plavix, also known as clopidogrel, Ticlid, also known as ticlopidine, Effient, also known as prasugrel, and Brilinta, also known as ticagrelor.

Arrhythmia. Irregular heart beat or abnormal heart rhythm.

Atherosclerosis. Disease process involving the buildup of a waxy substance called plaque on the inside of arteries.

Balloon angioplasty. Nonsurgical medical procedure in which a specially designed balloon catheter is used to open a narrowed or blocked artery.

Bare metal stent (BMS). Stent not coated with a drug that prevents renarrowing of a heart artery. Also known as an uncoated stent.

Cardiac catheterization. Procedure in which a thin, hollow tube (catheter) is inserted into an artery for the purposes of visualizing the heart and blood vessels, and diagnosing and treating heart disease.

Cardiac catheterization laboratory. A hospital room designed especially for the catheterization procedure.

Catheter. A thin, flexible hollow tube used to access a body cavity; in angioplasty, a catheter provides access to the artery for the delivery of a balloon or stent.

Cholesterol. Used by your body to build healthy cells and some vital hormones. High blood cholesterol can lead to the buildup of fatty deposits in your blood vessels (atherosclerosis) and may lead to restricted blood flow to your arteries.

Contrast dye. Liquid injected into your blood to improve the visibility of veins and arteries on an X-ray. It is later eliminated from your body through your kidneys and your urine.

Coronary artery disease (CAD). Atherosclerosis (blockage) in the coronary arteries. Also called coronary heart disease

Coronary arteries. Blood vessels on the outside of the heart that provide oxygen-rich blood to the heart.

Coronary artery bypass graft (CABG) surgery. Open-heart surgery that uses a vein from another part of your body to create a different route for blood to flow around a blocked coronary artery. Also called open heart or bypass surgery.

Drug-coated or drug-eluting stent (DES). A stent coated with a drug, such as zotarolimus, that helps prevent restenosis (renarrowing of the arteries) after a stent has been implanted.

Electrocardiogram (ECG or EKG). Medical test in which several electronic sensors are placed on your body to monitor electrical activity associated with the heartbeat.

Fluoroscopy. Examination of the tissue and deep structures of the body by using X-rays.

Hematoma. An abnormal, localized collection of blood outside a blood vessel. Caused by a break in the wall of a blood vessel.

Hemorrhage. Escape of blood from an injured blood vessel.

Myocardial infarction (MI). Damage or death of an area of your heart muscle, resulting from a blocked blood supply to the area. Commonly referred to as a heart attack.

Plaque. Waxy substance consisting of fats and cholesterol that can build up on the inner lining of your arteries and restrict blood flow to the heart muscle.

Polymer. Plastic material that when combined with a drug and coated on a stent, helps control the release of the drug into the heart vessel wall to help prevent restenosis.

Restenosis. Renarrowing of an artery at the site of angioplasty and/or an implanted stent, due to the overgrowth of tissue at the treatment site.

Thrombosis. Vessel blockage caused by a blood clot. Stent thrombosis refers to the blockage of the stent by a blood clot.