Medtronic

Instructions for Use

ENDEAVOR® Zotarolimus-Eluting Coronary Stent System
Over-the-Wire Delivery System

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

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1 Endeavor Zotarolimus-Eluting Coronary Stent System

The Endeavor Zotarolimus-Eluting Coronary Stent System (Endeavor stent) is a device/drug combination product comprised of device components (Driver® Coronary Stent and Micro-Driver® Coronary Stent and the Endeavor delivery systems) and a drug component (a formulation of zotarolimus contained in a polymer coating).

The Endeavor Coronary Stent System is supplied sterile.

The characteristics of the Endeavor stent are described in **Table 1-1**.

Table 1-1: Device Component Description

Component	Endeavor Stent on the Over-the-Wire (OTW) Delivery System	
Available Stent Diameters (mm):	2.5	3.0, 3.5
Available Stent Lengths (mm):	8†, 12, 14, 18, 24, 30	9†, 12, 15, 18, 24, 30
Stent Material:	A cobalt-based alloy (MP35N)–the Driver and Micro-Driver stents	
Drug Component:	A spray coating of polymer carrier loaded with zotarolimus is applied to the stent at a drug loading of 10 µg/mm stent length. The maximum nominal drug content on the longest stent (30 mm) is 300 µg.	
Delivery System Usable Length:	135 cm	
Delivery System Luer Adapter Ports:	Y-Connector (side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014" (0.36 mm).	
Stent Delivery Balloon:	A semi-compliant balloon mounted on the distal end of the catheter to facilitate stent deployment. There are proximal and distal pillows formed on either side of the stent which aid in holding the stent in position. Two radiopaque balloon markers are located on the distal section of the inner member and are positioned to mark the working length of the balloon.	
Balloon Inflation Pressure:	Nominal Pressure: 9 atm (912 kPa, 9.12 bar) Rated Burst Pressure: 16 atm (1621 kPa, 16.21 bar)	
Guide Catheter Compatibility:	0.056" minimum (5 F)	
Distal Section Outer Diameter:	Distal = 2.7 F	
	Proximal = 3.0 F	
Proximal Outer Diameter:	3.3 F	

† The 8 mm and 9 mm stent lengths are used for bailout procedures or insufficient lesion coverage.

1.1 Device Component Description

The device component consists of the Driver or Micro-Driver balloon-expandable coronary stent pre-mounted onto a stent delivery system (SDS). The range of stent diameters is made possible by varying the element lengths and number of crowns on the stent. The 2.5 mm diameter cobalt-based alloy stent (Micro-Driver) has 1.2 mm length elements and seven crowns; the 3.0 and 3.5 mm diameter cobalt-based stents (Driver) have 1.0 mm length elements and ten crowns. The

stent is crimped onto various size delivery catheter balloons, which are sized from 2.5 mm to 3.5 mm.

1.2 Drug Component Description

The drug component of the Endeavor Coronary Stent System consists of zotarolimus (the active ingredient) and Phosphorylcholine (PC) polymer (the inactive ingredient).

1.2.1 Zotarolimus

The active pharmaceutical ingredient utilized in the Endeavor stent 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 below:

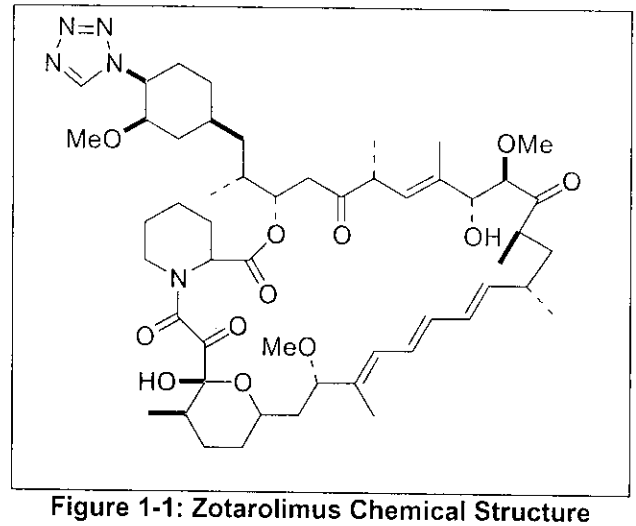


Figure 1-1: Zotarolimus Chemical Structure

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 dimethyl sulfoxide (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 groups in the physiological pH range; therefore, its solubility is expected to be unaltered in this range.

1.2.2 Polymer Component Description

The only inactive ingredient in the Endeavor stent is the Phosphorylcholine (PC) polymer, which acts as a carrier for zotarolimus. The PC polymer consists of 2-methacryloyloxyethyl phosphorylcholine that is synthesized and then used in the preparation of crosslinked polymer membranes with lauryl methacrylate, hydroxypropyl methacrylate and trimethoxysilylpropyl methacrylate (crosslinker) co-monomers. The PC polymer contains a biocompatible component which mimics the body's own chemistry, a hydrophobic component for adhesion and stability, and a crosslinking component for robustness.

The molecular weight of PC polymer was estimated using viscometry and resulted in values of Mv ranging from 160,000 to 270,000. These figures were supported by light scattering values of Mw (g/mol) ranging from 100,000 to 200,000.

PC polymer in a solvent carrier (ethanol) is applied to the Driver stent to form the base layer coat of the Endeavor stent. The polymer is also mixed with the drug zotarolimus and then applied to the base layer-coated stents. Finally, a drug-free overspray of PC polymer is applied after the stent has been coated with the drug/polymer formulation and it has been crimped onto the balloon. The drug/polymer coating is applied to the entire surface (i.e. luminal and abluminal) of the stent. The structural formula of the polymer is shown below:

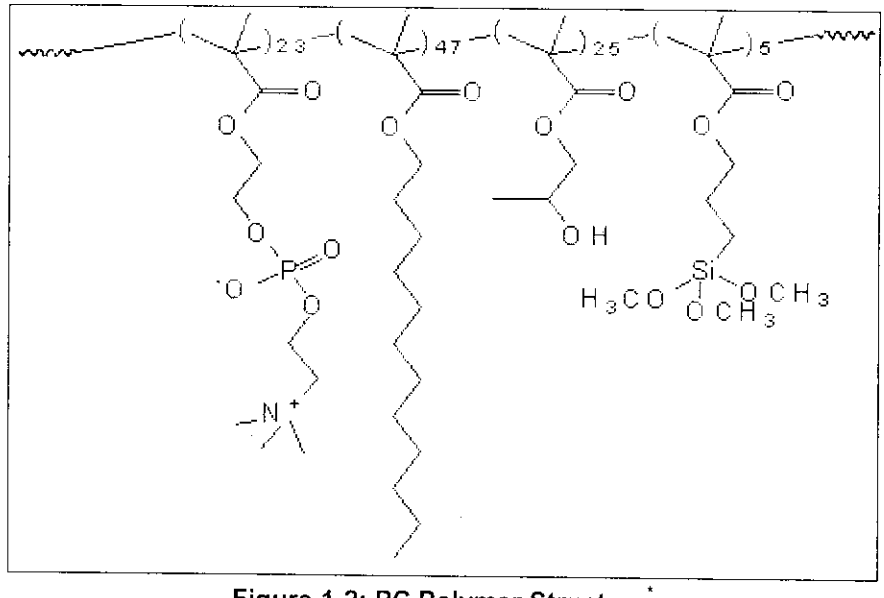


Figure 1-2: PC Polymer Structure*

* PC Technology™ is licensed under patents or patent applications owned by Biocompatibles.

1.2.3 Product Matrix and Zotarolimus Content

Table 1-2: Endeavor Zotarolimus-Eluting Coronary Stent System Product Matrix and Nominal Zotarolimus Doses

Product Number OTW	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
EN25008W	2.50	8*	84
EN30009W	3.00	9	90
EN35009W	3.50	9	90
EN25012W	2.50	12	120
EN30012W	3.00	12	120
EN35012W	3.50	12	120
EN25014W	2.50	14*	144
EN30015W	3.00	15	150
EN35015W	3.50	15	150
EN25018W	2.50	18	180
EN30018W	3.00	18	180
EN35018W	3.50	18	180
EN25024W	2.50	24	240
EN30024W	3.00	24	240
EN35024W	3.50	24	240
EN25030W	2.50	30	300
EN30030W	3.00	30	300
EN35030W	3.50	30	300

* *Note*: The 8 mm and 14 mm stent lengths have a total nominal drug content of 84 µg and 144 µg, respectively, since the actual stent length for the 8 mm stent is 8.4 mm, and the actual stent length for the 14 mm stent is 14.4 mm.

2 Indications

The Endeavor Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.5 mm to ≤ 3.5 mm.

3 Contraindications

The Endeavor Zotarolimus-Eluting Coronary Stent System is contraindicated for use in:

- Patients with a known hypersensitivity to zotarolimus or structurally-related compounds.
- Patients with a known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum).
- Patients with a known hypersensitivity to Phosphorylcholine polymer or its individual components (see **Section 1.2.2 Polymer Component Description** for details).

Coronary artery stenting is contraindicated for use in:

- Patients who cannot receive recommended antiplatelet and/or anticoagulation therapy (see **Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen** for more information).
- 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.

4 Warnings

- Please ensure that the inner package has not been opened or damaged, as this indicates the sterile barrier has been breached.
- The use of this product carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events. .
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy.

5 Precautions

5.1 General Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized stents is not well characterized.
- Risks and benefits of the stent should be assessed for patients with history of severe reaction to contrast agents.
- Do not expose or wipe the product with organic solvents such as alcohol or detergents (see **Section 5.10 Stent Handling Precautions** for more information).
- Stent thrombosis is a low-frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Stent thrombosis is frequently associated with myocardial infarction (MI) or death. Data from the ENDEAVOR randomized clinical trials have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used (see **Section 9.5.1 Stent Thrombosis in Endeavor Pooled Analysis** for more information). In the ENDEAVOR clinical trials analyzed to date, the differences in the incidence of stent thrombosis observed with the Endeavor stent compared to bare metal stents have not been associated with an increased risk of cardiac death, MI, or all-cause mortality. Additional data from longer-term follow-up in the ENDEAVOR randomized clinical trials and analyses of DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.
- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the pivotal clinical trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In the ENDEAVOR I, ENDEAVOR II, and ENDEAVOR III studies, clopidogrel or ticlopidine was administered pre-procedure and for a minimum of 3 months post-procedure (75 mg per day). In ENDEAVOR IV, clopidogrel or ticlopidine was administered pre-procedure and for a minimum of 6 months post-procedure (75 mg per day). Aspirin was administered pre-procedure and continued indefinitely (a minimum of 75 mg per day). Based on the case report forms from the Endeavor randomized clinical trials (ENDEAVOR II, ENDEAVOR III, and ENDEAVOR IV), approximately 82% of the patients remained on dual antiplatelet therapy at 6 months. See **Section 9 Clinical Studies**, for more specific information.
- The optimal duration of dual antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies on sirolimus-eluting or paclitaxel-eluting stents suggest that a longer duration of clopidogrel than was recommended post-procedurally in DES pivotal trials may be beneficial. Current guidelines recommend that patients receive aspirin indefinitely and that clopidogrel therapy be extended to 12 months in patients at low risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines[1,2]).
- It is very important that the patient is compliant with the post-procedural antiplatelet therapy recommendations. Early discontinuation of prescribed antiplatelet medication could result in a

[1] Smith et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2006; 47: e1-121

[2] King III et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2008; 51:172-209

higher risk of thrombosis, MI or death. Prior to percutaneous coronary intervention (PCI), if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI treatment of choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risks associated with early discontinuation of antiplatelet therapy. Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

5.3 Use of Multiple Stents

The long-term effects of zotarolimus are currently unknown. In clinical trials of the Endeavor stent, the protocols specified that patients were to be treated with no more than 30 mm of total Endeavor stent length, except in situations involving bailout stenting. The extent of the patient's exposure to the drug and polymer coating is directly related to the number of stents and 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. Data obtained from *in vitro* corrosion tests using an MP35N (ASTM F562) stent (Medtronic Driver coronary stent) in combination with a 316L stainless steel alloy stent (Medtronic S7 coronary stent) do not suggest an increased risk of *in vivo* 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 Endeavor stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

5.4 Brachytherapy

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

5.5 Use in Conjunction with Other Procedures

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

5.6 Use in Special Populations

5.6.1 Pregnancy

Pregnancy Category C. See **Section 6.7 Pregnancy** under **Drug Information**. There are no adequate and well-controlled studies in pregnant women or men intending to father children. The Endeavor 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 an Endeavor stent and for 3 months after implantation.

5.6.2 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 the stent, taking into account the importance of the stent to the mother.

5.6.3 Gender

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

5.6.4 Ethnicity

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

5.6.5 Pediatric Use

The safety and effectiveness of the Endeavor stent in pediatric patients below the age of 18 years have not been established.

5.6.6 Geriatric Use

Clinical studies of the Endeavor stent did not suggest that patients age 65 years and over differed with regard to safety and efficacy compared to younger patients.

5.7 Lesion/Vessel Characteristics

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

- Patients with vessel thrombus at the lesion site
- Patients with coronary artery reference vessel diameters < 2.5 mm or > 3.5 mm
- Patients with coronary artery lesions longer than 27 mm or requiring more than one Endeavor stent
- Patients with lesions located in saphenous vein grafts, in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation
- Patients with diffuse disease or poor flow distal to the identified lesions
- Patients with multi-vessel disease
- Patients with tortuous vessels in the region of the obstruction or proximal to the lesion
- Patients with a recent acute MI or evidence of thrombus in the target vessel
- Patients with longer than 48 months of follow-up
- Patients with in-stent restenosis
- Patients with moderate or severe calcification in the lesion or a chronic total occlusion

5.8 Drug Interactions

The effect of potential drug interactions on the safety or efficacy of the Endeavor 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 200mg ketoconazole bid, a strong inhibitor of CYP3A4, zotarolimus produces less than a 2-fold increase in $AUC_{0\text{-}inf}$ (area under the blood concentration-time curve (AUC) from time 0 to infinity) with no effect on C_{max} (maximum blood concentration). Therefore, consideration should be given to the potential for drug interactions when deciding to place an Endeavor Coronary 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.

See **Section 6.5 Drug Interactions.**

5.9 Magnetic Resonance Imaging (MRI)

Non-clinical testing on single and overlapped stents has demonstrated that the Endeavor stent is MR Conditional. It can be scanned safely under the following conditions:

Single Stenting (Stent Length 30 mm)	Overlapped Stenting (Total Length 55 mm)
Static magnetic field of 3-Tesla	Static magnetic field of 3-Tesla
Spatial gradient field of 525 Gauss/cm	Spatial gradient field of 720 Gauss/cm
Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of scanning	Maximum whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning
In non-clinical testing, the Endeavor stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of MR scanning in a 3-Tesla, Signa, General Electric Medical Systems (software version 9.0) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.	In non-clinical testing, the Endeavor stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of MR scanning in a 3-Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.
The Endeavor stent should not move or migrate when exposed to MR scanning immediately post-implantation.	
The image artifact extends approximately 9 mm from the device/lumen centerline when scanned in non-clinical testing using a 3-Tesla, Signa, General Electric Medical Systems (software version 9.0) MR system with a send-receive RF body coil.	The image artifact extends approximately 10 mm from the device/lumen centerline when scanned in non-clinical testing using a 3-Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR system with a send-receive RF body coil.

5.10 Stent Handling Precautions

- For single use only. The Endeavor Coronary Stent System is provided sterile. Do not resterilize or reuse this product. Note the "Use By" date on the product label (see **Section 14 Reuse Precaution Statement**). Do not use if package or product has been opened or damaged.
- The foil pouch is not a sterile barrier. The pouch contained within the foil pouch is the sterile barrier. **Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is not sterile.**
- Do not remove the contents of foil pouch until immediately prior to the use of device.
- Do not remove the stent from the delivery balloon–removal may damage the stent and polymer coating and/or lead to stent embolization. The Endeavor Coronary Stent 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.
- Stent manipulation (e.g., rolling the mounted stent with your fingers) may cause coating damage, contamination or dislodgement of the stent from the delivery system balloon.

- The Endeavor stent must not be exposed to any direct handling or contact with liquids prior to 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 Endeavor coronary stent delivery system should not be used in conjunction with any other stents or for post-dilatation.
- In the event the Endeavor stent is not deployed, contact your local Medtronic representative for return information.

5.11 Stent Placement Precautions

- The vessel should be pre-dilated with an appropriately sized balloon. Refer to the pre-dilatation balloon sizing described in **Section 13.5 Delivery Procedure**.
- Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in **Section 13 Operator's Manual**.
- Guide catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Device Component Description** in **Table 1-1**).
- Do not induce negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgement of the stent from the balloon.
- 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 smaller 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 (e.g., 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 5.12 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 instructions in **Section 5.12 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 (e.g., 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.

5.12 Stent/System Removal Precautions

If removal of a stent system is required prior to 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 should 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 subsequent removal of the 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.

5.13 Post-Procedure

- Care should be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guidewire, or balloon catheter to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Post-dilatation: All efforts should be made to assure 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 (see **Operator's Manual – 13.9 Further Dilatation of Stented Segment**). **Do not use the stent delivery balloon for post-dilatation.**
- Non-clinical testing on single and overlapped stents has demonstrated that the Endeavor stent is MR Conditional (see **Section 5.9 Magnetic Resonance Imaging (MRI)**). MR imaging quality may be compromised if the area of interest is in the same area of the position of the stent.
- Antiplatelet therapy should be administered post-procedure (see **Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen** and **Section 7 Overview of Clinical Studies**). Patients who require early discontinuation of antiplatelet therapy (e.g., 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.

6 Drug Information

6.1 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.

6.2 Metabolism

Zotarolimus undergoes oxidative metabolism in the liver to form the desmethyl 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 DES. 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. Radiolabeled studies confirm that the major route of elimination is via feces (82.0%) with a total of 6.2% of the administered dose excreted in urine.

6.3 Intravenous Administration of Zotarolimus

6.3.1 Pharmacokinetics

Zotarolimus pharmacokinetic activity has been determined following intravenous (IV) administration in healthy patients. **Table 6-1** provides a summary of the pharmacokinetic analysis.

Table 6-1: Pharmacokinetic Parameters (Mean ± standard deviation) in Patients Following 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_{0-24}	(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 £	(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

¥ N = 16

$ Harmonic mean ± pseudo-standard deviation

£ Clearance data is calculated using compartmental methods. All other data presented in Table 6-1 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 patients. No clinically significant changes in physical examination, vital signs, or laboratory measurements were observed during the course of the study. For a total stent length of 48 mm (480 µg drug dose), a C_{max} of 4.0 ng/mL and AUC_{0-inf} of 162 ng•h/mL were estimated as seen in **Table 6-2** below. These calculations are based on the mean C_{max} and AUC_{0-inf} values calculated from the IV dosing studies conducted on zotarolimus.

Table 6-2: Zotarolimus Dose Exposure

Units	480µg Dose Stent	Exposure Multiples
C_{max} (ng/ml)	4.0	27.69¥
AUC_{0-inf} (ng•h/mL)	162	15.06#

¥ Calculated based on the mean C_{max} value (110.78) from the highest dose group (900 µg) from human single escalation IV dose study conducted on zotarolimus

Based on the mean all day AUC_{0-inf} (Day 1 to 14); 2440ng•h/mL) value from the highest dose regimen (800 µg QD x 14 days) from human multiple escalation IV dose study conducted on zotarolimus

6.3.2 Adverse Event Profile

The incidence of adverse events attributed to the drug zotarolimus was determined in IV escalating and multiple-dose studies. In the single-escalating dose study, the proportion of patients reporting treatment-emergent adverse events was slightly lower among patients who received doses of zotarolimus than those who received placebo for zotarolimus. The most common treatment-emergent adverse events associated with zotarolimus were application site reaction, injection site reaction, pain, and hematuria. There were no deaths or other serious adverse events reported in this study. No clinically significant changes in physical examination, vital signs, or laboratory measurements were observed during the course of the study. **Table 6-3** provides a summary of the analysis.

Table 6-3: Summary of Treatment-Emergent Adverse Events Reported by Two or More Patients in Any One Treatment by Body Systems and Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART Term) in the Single-escalating Dose Study.

BODY SYSTEMS	COSTART Term	All Placebo N = 20 (%)	Zotarolimus 100 µg N = 8 (%)	Zotarolimus 300 µg N = 8 (%)	Zotarolimus 500 µg N = 8 (%)	Zotarolimus 700 µg N = 8 (%)	Zotarolimus 900 µg N = 8 (%)
Body as a whole	Headache	3 (15%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)
	Injection site Reaction	1(5%)	0 (0%)	0 (0%)	3 (38%)	0 (0%)	0 (0%)
	Pain	7 (35%)	1 (13%)	0 (0%)	5 (63%)	5 (63%)	2 (25%)
Digestive System	Diarrhea	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin and Appendage	Application site Reaction	8 (40%)	1 (13%)	5 (63%)	2 (25%)	1 (13%)	5 (63%)
Urogenital System	Hematuria	1 (5%)	0 (0%)	1 (13%)	0 (0%)	1 (13%)	1 (13%)

In the multiple-dose study, the proportion of patients reporting treatment-emergent adverse events was similar among patients who received doses of zotarolimus, and the most common treatment-emergent adverse events associated with zotarolimus were headache, pain, injection site reaction, dry skin, abdominal pain, diarrhea, and rash. There were no deaths or other serious adverse events. Results of other safety analyses including individual patient changes, changes over time and individual clinically significant values for vital signs, laboratory safety assessments and physical examinations were unremarkable for each treatment group. No clinically significant changes in physical examination, vital signs, or laboratory measurements were observed during the course of the study. No differences were seen among the doses with respect to adverse event profiles or overall drug safety. **Table 6-4** provides a summary of the analysis.

Table 6-4: Summary of Treatment-Emergent Adverse Events Reported by Two or More Patients in Any One Treatment by Body Systems and COSTART Term in the Multiple-dose Study.

BODY SYSTEM	COSTART Term	All Placebo (N = 16) N (%)	200 µg QD (N = 16) N (%)	400 µg QD (N = 16) N (%)	800 µg QD (N = 16) N (%)
Body as a whole	Headache	1 (4)	2 (13)	2 (13)	2 (13)
	Pain	1 (4)	2 (13)	1 (6)	0 (0)
	Injection Site Reaction	2 (8)	0 (0)	0 (0)	2 (13)
	Injection Site Pain	2 (8)	0 (0)	0 (0)	0 (0)
	Abdominal Pain	1 (4)	1 (6)		0 (0)
Digestive System	Diarrhea	1 (4)	0 (0)	1 (6)	0 (0)
Skin and Appendage	Dry Skin	0 (0)	0 (0)	2 (13)	0 (0)
	Rash	0 (0)	1 (6)	1 (6)	0 (0)

6.4 Pharmacokinetics of the Endeavor Stent

The pharmacokinetics of zotarolimus delivered from the Endeavor stent have been determined in patients with coronary artery disease after stent implantation in the ENDEAVOR US Pharmacokinetic trial. The dose of zotarolimus was calculated from the total implanted stent length; the parameters determined from these patients are provided in **Table 6-5**.

Table 6-5: Zotarolimus Pharmacokinetics in Patients after Implantation of Endeavor Zotarolimus-Eluting Coronary Stent

PK Parameter	Units	Group I (90 µg) N = 1†	Group II (168 µg) N = 1†	Group III[a] (180 µg) N = 24	Group IV[a] (240 µg) N = 6	Group V (270 µg) N = 2†	Group VI[a] (300 µg) N = 7	Group VII (360 µg) N = 1†	Group VIII (420 µg) N = 1†
C_{max}	(ng/mL)	0.847	2.176	1.513 ± 0.616	1.83 ± 0.210	1.584	2.658 ± 0.998	2.539	3.133
T_{max}	(h)	1.00	4.00	1.2 ± 0.6	1.4 ± 1.3	1.5	1.5 ± 1.3	2.00	1.3
$AUC_{0\text{-last}}$	(ng•h/mL)	46.51	71.73	57.02 ± 13.46	63.83 ± 15.27	125.18	90.77 ± 19.51#	95.21	87.45
$AUC_{0\text{-inf}}$	(ng•h/mL)	56.57	78.28	66.61 ± 14.86	72.84 ± 19.96	136.65	101.45 ± 23.48#	113.85	99.82
β	(1/h)	0.010	0.013	0.012 ± 0.003	0.012 ± 0.002	0.010	0.012 ± 0.003	0.010	0.012
$t_{½}$‡	(h)	71.5§	53.7§	59.7 ± 14.4	57.5 ± 7.6	68.3	59.5 ± 16.1#	66.67§	58.4§
Vd_{β}/F	(L)	164.1	166.3	254.7 ± 74.5	288.5 ± 53.6	261.6	291.6 ± 113.7#	304.2	354.6
CL/F	(L/h)	1.6	2.1	2.8 ± 0.7	3.5 ± 1.0	2.9	3.1 ± 0.8#	3.2	4.2

Vdβ/F Apparent volume of distribution
C_{max} Maximum blood concentration
T_{max} Time to Cmax
$AUC_{0\text{-inf}}$ AUC from time 0 to infinity ($AUC_{0\text{-inf}}$).
$t_{½}$ Harmonic mean half-life
$AUC_{0\text{-last}}$ Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration
a. Primary dose groups
‡ Harmonic mean ± pseudo-standard deviation
† No SD was reported when N ≤ 2
# N = 6
CL/F Mean apparent clearance
§ Mean only

The results in **Table 6-5** show that the pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation, consisting of dose groups with N > 2 (180, 240 and 300 µg), following the implantation of Endeavor stents as illustrated by dose proportional increases in C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$. Mean apparent clearance and harmonic mean half-life for the primary dose groups ranged from 2.8 to 3.5 L/h and 57.5 to 59.7 h, respectively. The mean time to reach peak systemic concentration (T_{max}) ranged from 1.2 to 1.5 h after stent implantation.

6.5 Drug Interactions

The effect of potential drug interactions on the safety or efficacy of the Endeavor 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 200mg 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 an Endeavor Coronary 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 Endeavor stent.

6.6 Mutagenesis, Carcinogenicity and Reproductive Toxicology

6.6.1 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.

6.6.2 Carcinogenicity

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

6.6.3 Reproductive Toxicology

No effect on fertility and early embryonic development in female rats was observed following the IV administration of zotarolimus at dosages up to 100 µg/kg/day (approximately 14 times the cumulative blood exposure provided by Endeavor stents coated with 300 µg zotarolimus[3]).

For male rats, there was no effect on fertility rate at IV dosages up to 30 µg/kg/day (approximately 17 times the cumulative blood exposure provided by Endeavor 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 (approximately 30 times the cumulative blood exposure provided by Endeavor stents coated with 300 µg zotarolimus).

6.7 Pregnancy

Pregnancy Category C: Zotarolimus was embryo/feto-toxic in rats at IV dosages of 25 µg/kg/day and above (approximately 3 times the cumulative blood exposure provided by Endeavor stents coated with 300 µg zotarolimus). Embryotoxicity was manifested as reduced fetal body weights and fetal ossification delays, but no major fetal malformations, deaths, or minor fetal abnormalities were observed. No embryo-fetal effects were observed in pregnant rabbits at the maternally toxic dosage of 30 µg/kg/day (approximately 13 times the cumulative blood exposure provided by Endeavor stents coated with 300 µg zotarolimus). The Endeavor stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

6.8 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.

7 Overview of Clinical Studies

The principal safety and efficacy information for the Endeavor stent is presented from the following clinical studies – the ENDEAVOR I trial, the ENDEAVOR II trial, the ENDEAVOR III trial and the ENDEAVOR IV trial. These studies have evaluated the performance of the Endeavor Stent in patients with symptomatic ischemic heart disease in single *de novo* lesions of native coronary arteries. Major study characteristics are summarized in **Table 7-1**.

The ENDEAVOR I trial was the first-in-man study for the Endeavor stent. ENDEAVOR I was a non-randomized, prospective, multi-center, single-arm trial. The purpose of the trial was to assess the initial safety of the Endeavor stent. The primary endpoints in this trial were the rate of major adverse cardiac events (MACE) defined as composite of death, myocardial infarction (MI), emergent bypass surgery, or target lesion revascularization (TLR) at 30 days and in-segment late loss at 4 months as measured by quantitative coronary angiography (QCA). Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR II trial was a prospective, multi-center, double-blind, two-arm randomized and controlled, superiority trial that compared the Endeavor stent to a control bare metal stent (the Driver stent). Eligibility was based on assessments of lesion reference vessel diameter and lesion length. The primary endpoint in this trial was the target vessel failure (TVF) rate, defined as the composite of cardiac death, MI, or clinically-driven target vessel revascularization (TVR) of the treated vessel at 9 months post-procedure. The powered secondary endpoint was in-segment late loss at 8 months measured by QCA. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

[3] The 30 mm Endeavor stent contains a nominal dose of 300 µg zotarolimus

The ENDEAVOR III trial was a prospective, multi-center, single-blind, two-arm randomized and controlled, non-inferiority trial that compared the Endeavor stent to a control DES (the Cypher stent). Eligibility was based on the assessments of a lesion reference vessel diameter and lesion length. The primary endpoint of this study was in-segment late loss at 8 months as measured by QCA and defined as the difference between post-procedure minimum lumen diameter (MLD) and the MLD at time of follow-up within the stented region and 5 mm proximal and distal to the edges of the stent. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR IV trial was a prospective, multi-center, single-blind, two-arm randomized and controlled, non-inferiority trial that compared the Endeavor stent to a control DES (the Taxus stent). Eligibility was based on the assessments of a lesion reference vessel diameter and lesion length. The primary clinical endpoint in this non-inferiority study was the TVF rate, defined as the composite of cardiac death, MI, or clinically-driven TVR of the treated vessel at 9 months post-procedure. The powered secondary endpoint was in-segment late loss at 8 months, measured by QCA. Post-procedure, patients received aspirin indefinitely and clopidogrel for a minimum of 6 months.

Table 7-1: Clinical Trial Comparisons

	ENDEAVOR I	ENDEAVOR II	ENDEAVOR III	ENDEAVOR IV
Study Type	Multi-center (n=8) Prospective Non-randomized	Multi-center (n=72) Prospective Randomized	Multi-center (n=29) Prospective Randomized	Multi-center (n=80) Prospective Randomized
Number of Patients	Total: 100 (Endeavor)	Total: 1197 (Endeavor: 598, Driver: 599)	Total: 436 (Endeavor: 323, Cypher:113)	Total: 1548 (Endeavor: 773, Taxus: 775)
Lesion Criteria	Single *de novo* lesion in native coronary artery ≤ 15 mm in length and ≥ 3.0 mm to ≤ 3.5 mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥ 2.25 mm to ≤3.5 mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥ 2.5 mm to ≤3.5 mm in diameter	Single *de novo* lesion in native coronary artery ≤ 27 mm in length and ≥ 2.5 mm to ≤3.5 mm in diameter
Product Used	Endeavor Stent on the Rapid Exchange Stent Delivery System	Endeavor Stent on the Rapid Exchange Stent Delivery System	Endeavor Stent on the Over-The -Wire Stent Delivery System	Endeavor Stent on the Over-The -Wire Stent Delivery System
Antiplatelet Therapy	Aspirin indefinitely and clopidogrel or ticlopidine for ≥ 3 months.	Aspirin indefinitely and clopidogrel or ticlopidine for ≥ 3 months.	Aspirin indefinitely and clopidogrel or ticlopidine for ≥ 3 months.	Aspirin indefinitely and clopidogrel or ticlopidine for ≥ 6 months
Follow up	30 days: clinical 4 & 12 months: clinical and angiographic/IVUS 9 month: clinical 1-5 years: telephone	30 days: clinical 8 months: clinical and angiographic/IVUS 9 month: clinical 6 month, 1-5 years: telephone	30 days: clinical 8 months: clinical and angiographic/IVUS 9 month: clinical 6 month, 1-5 years: telephone	30 days: clinical 8 months: clinical and angiographic/IVUS 9 month: clinical 6 month, 1-5 years: telephone
Status	48 month follow-up complete. Yearly follow up to 5 years is ongoing.	36 month follow-up is complete. Yearly follow up to 5 years is ongoing.	24 month follow-up is complete. Yearly follow up to 5 years is ongoing.	9 month follow-up is complete. Yearly follow up to 5 years is ongoing.

Two additional single-arm non-randomized trials were reviewed by FDA: the ENDEAVOR II Continued Access study and the ENDEAVOR PK study. The objective of the ENDEAVOR II Continued Access registry was to collect additional acute safety information and performance data of the Endeavor stent. The primary endpoint was MACE at 30 days. The objective of the ENDEAVOR PK study was to assess the pharmacokinetic profile of the Endeavor stent (see Section 6.4 Pharmacokinetics of the Endeavor Stent). These trials provide additional data on

Endeavor stent use. Results of these studies have been pooled with the patients treated with Endeavor stents in Endeavor I, II, III, and IV studies described above in a post-hoc patient-level analysis to provide an enhanced estimate of the incidence of low-frequency events and outcomes in specific patient subgroups (see Section 9.5 Overall Results of the ENDEAVOR Clinical Program (ENDEAVOR I, II, II-CA, III, IV and USPK)).

8 Adverse Events

8.1 Observed Adverse Events

Observed adverse event experience with the Endeavor stent comes from four clinical studies: the ENDEAVOR IV, the ENDEAVOR III, the ENDEAVOR II, and the ENDEAVOR I trials. See **Section 9 Clinical Studies** for a more complete description of the study designs and results.

The ENDEAVOR IV, III, II, and I trials have evaluated the performance of the Endeavor stent in patients with symptomatic ischemic heart disease in single *de novo* lesions of native coronary arteries. Principal adverse events are shown in **Table 8-1**.

ıble 8-1: ENDEAVOR IV, III, II and I - Principal Adverse Events from Post-procedure to Latest Follow-up

	ENDEAVOR IV		ENDEAVOR III		ENDEAVOR II		ENDEAVOR I
	Endeavor N = 773	Taxus N = 775	Endeavor N = 323	Cypher N = 113	Endeavor N = 598	Driver N = 599	Endeavor N = 100
In-Hospital							
MACE	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Total Death	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.0% (0/596)	0.0% (0/100)
Cardiac Death	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.0% (0/596)	0.0% (0/100)
Non-Cardiac Death	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
MI	0.8% (6/773)	2.1% (16/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.7% (16/596)	0.0% (0/100)
Q wave MI	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.3% (2/596)	0.0% (0/100)
Non-Q wave MI	0.5% (4/773)	1.9% (15/775)	0.6% (2/323)	3.5% (4/113)	2.3% (14/597)	2.3% (14/596)	0.0% (0/100)
TVR	0.4% (3/773)	0.6% (5/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
TLR	0.4% (3/773)	0.5% (4/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Non-TLR	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Cardiac death or MI	0.8% (6/773)	2.1% (16/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.7% (16/596)	0.0% (0/100)
TVF	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Stent thrombosis (protocol)	0.3% (2/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.3% (2/597)	0.3% (2/596)	0.0% (0/100)
ıta at 9 Months							
MACE	5.7% (42/740)	5.7% (42/734)	7.5% (24/321)	7.1% (8/113)	7.3% (43/592)	14.4% (85/591)	2.0% (2/100)
Total Death	0.7% (5/740)	0.8% (6/734)	0.6% (2/321)	0.0% (0/113)	1.2% (7/592)	0.5% (3/591)	0.0% (0/100)
Cardiac Death	0.4% (3/740)	0.3% (2/734)	0.0% (0/321)	0.0% (0/113)	0.8% (5/592)	0.5% (3/591)	0.0% (0/100)
Non-Cardiac Death	0.3% (2/740)	0.5% (4/734)	0.6% (2/321)	0.0% (0/113)	0.3% (2/592)	0.0% (0/591)	0.0% (0/100)
MI	1.5% (11/740)	2.5% (18/734)	0.6% (2/321)	3.5% (4/113)	2.7% (16/592)	3.9% (23/591)	1.0% (1/100)
Q wave MI	0.3% (2/740)	0.1% (1/734)	0.0% (0/321)	0.0% (0/113)	0.3% (2/592)	0.8% (5/591)	0.0% (0/100)
Non-Q wave MI	1.2% (9/740)	2.3% (17/734)	0.6% (2/321)	3.5% (4/113)	2.4% (14/592)	3.0% (18/591)	1.0% (1/100)
TVR	5.5% (41/740)	5.0% (37/734)	11.2% (36/321)	8.0% (9/113)	5.6% (33/592)	12.5% (74/591)	2.0% (2/100)
TLR	4.2% (31/740)	2.7% (20/734)	6.2% (20/321)	3.5% (4/113)	4.6% (27/592)	11.8% (70/591)	2.0% (2/100)
Non-TLR	2.0% (15/740)	2.9% (21/734)	5.9% (19/321)	5.3% (6/113)	1.5% (9/592)	2.2% (13/591)	0.0% (0/100)
Cardiac death or MI	1.9% (14/740)	2.7% (20/734)	0.6% (2/321)	3.5% (4/113)	3.4% (20/592)	4.4% (26/591)	1.0% (1/100)
TVF	6.8% (50/740)	7.4% (54/734)	11.8% (38/321)	11.5% (13/113)	7.9% (47/592)	15.1% (89/591)	2.0% (2/100)
Stent thrombosis (protocol)	0.8% (6/740)	0.1% (1/734)	0.0% (0/321)	0.0% (0/113)	0.5% (3/592)	1.2% (7/591)	1.0% (1/100)
1-year MACE	NA	NA	7.8% (25/320)	8.0% (9/112)	8.8% (52/590)	15.6% (92/589)	2.0% (2/99)
2-year MACE	NA	NA	9.3% (29/313)	11.6% (13/112)	9.9% (58/587)	18.1% (106/586)	3.0% (3/99)
3-year MACE	NA	NA	NA	NA	12.0% (69/577)	20.7% (120/579)	6.1% (6/98)
4-year MACE	NA	NA	NA	NA	NA	NA	7.2% (7/97)

Table 8-1: ENDEAVOR IV, III, II and I - Principal Adverse Events from Post-procedure to Latest Follow-up

	ENDEAVOR IV		ENDEAVOR III		ENDEAVOR II		ENDEAVOR I
	Endeavor N = 773	Taxus N = 775	Endeavor N = 323	Cypher N = 113	Endeavor N = 598	Driver N = 599	Endeavor N = 100
Latest Data Available	9 Months		24 Months		36 Months		48 Months
MACE	5.7% (42/740)	5.7% (42/734)	9.3% (29/313)	11.6% (13/112)	12.0% (69/577)	20.7% (120/579)	7.2% (7/97)
Total Death	0.7% (5/740)	0.8% (6/734)	1.6% (5/313)	4.5% (5/112)	3.3% (19/577)	4.5% (26/579)	4.1% (4/97)
Cardiac Death	0.4% (3/740)	0.3% (2/734)	0.0% (0/313)	0.9% (1/112)	1.6% (9/577)	2.4% (14/579)	0.0% (0/97)
Non-Cardiac Death	0.3% (2/740)	0.5% (4/734)	1.6% (5/313)	3.6% (4/112)	1.7% (10/577)	2.1% (12/579)	4.1% (4/97)
MI	1.5% (11/740)	2.5% (18/734)	0.6% (2/313)	3.6% (4/112)	3.3% (19/577)	4.3% (25/579)	1.0% (1/97)
Q wave MI	0.3% (2/740)	0.1% (1/734)	0.0% (0/313)	0.0% (0/112)	0.3% (2/577)	1.0% (6/579)	0.0% (0/97)
Non-Q wave MI	1.2% (9/740)	2.3% (17/734)	0.6% (2/313)	3.6% (4/112)	2.9% (17/577)	3.3% (19/579)	1.0% (1/97)
TVR	5.5% (41/740)	5.0% (37/734)	13.7% (43/313)	9.8% (11/112)	9.5% (55/577)	17.6% (102/579)	5.2% (5/97)
TLR	4.2% (31/740)	2.7% (20/734)	7.0% (22/313)	4.5% (5/112)	7.3% (42/577)	14.7% (85/579)	3.1% (3/97)
Non-TLR	2.0% (15/740)	2.9% (21/734)	8.3% (26/313)	6.3% (7/112)	2.9% (17/577)	4.8% (28/579)	2.1% (2/97)
Cardiac death or MI	1.9% (14/740)	2.7% (20/734)	0.6% (2/313)	3.6% (4/112)	4.5% (26/577)	6.7% (39/579)	0.0% (0/0)
TVF	6.8% (50/740)	7.4% (54/734)	14.4% (45/313)	13.4% (15/112)	12.8% (74/577)	21.4% (124/579)	5.2% (5/97)
Stent thrombosis (protocol)	0.8% (6/740)	0.1% (1/734)	0.0% (0/313)	0.0% (0/112)	0.5% (3/577)	1.2% (7/579)	1.0% (1/97)

NA= Not Applicable; variable and/or time point not calculated
= The maximum number of eligible patients.
numbers are % (Count/Sample Size).
,or adverse cardiac events (MACE) is defined as composite of death, MI (Q wave and non-Q wave), emergent bypass surgery, or target lesion revascularization (repeat PTCA or CABG).
Q wave MI (QMI) 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 (NQMI) 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.
Stent Thrombosis: See section 9.5.1 for the per protocol stent thrombosis definition.
Target vessel failure (TVF) is defined as a composite of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization.
Target lesion revascularization (TLR) is defined as any clinically-driven repeat intervention of the target lesion by PCI or CABG of the target vessel.
Target vessel revascularization (TVR) is defined as any clinically driven repeat intervention of the target vessel by PCI or CABG.

8.2 Potential Adverse Events

8.2.1 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 IV injection of zotarolimus in humans include:

- Anemia
- Application site reaction
- Diarrhea
- Dry skin
- Headache
- Hematuria

- Infection
- Injection site reaction
- Pain (abdominal, arthralgia, injection site)
- Rash

8.2.2 Potential Adverse Events Associated with Percutaneous Coronary Diagnostic and Treatment Procedures

Other adverse events associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks 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
- Balloon rupture
- 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/hypertension
- Incomplete stent apposition
- Infection or fever
- Late or very late thrombosis
- Myocardial infarction (MI)
- Myocardial ischemia
- Peripheral ischemia/peripheral nerve injury
- Renal failure
- Restenosis of the stented artery
- Rupture of native or bypass graft
- Shock/pulmonary edema
- Stent deformation, collapse, or fracture
- Stent migration
- Stent misplacement
- Stroke/transient ischemic attack
- Thrombosis (acute and subacute)
- Unstable angina
- Ventricular fibrillation

9 Clinical Studies

9.1 Results of the ENDEAVOR IV Trial

Primary Objective: To demonstrate the non-inferiority in safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System when compared to the Taxus Paclitaxel-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5 mm to 3.5 mm and lesion length of ≤ 27 mm.

Design: This was a prospective, multi-center, single-blind, two-arm, randomized and controlled non-inferiority trial that compared the Endeavor stent to a control DES (the Taxus stent). A total of 1548 patients were enrolled at 80 study sites in the United States who presented with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that were amenable to treatment by stenting. Patients were stratified by diabetic status and subsequently randomized to receive either the Endeavor or Taxus stent in a 1:1 ratio. Multiple stents were allowed for bailout only.

Follow-up was performed at 30 days, 6, 8, and 9 months, and will be performed at 12 months, and annually thereafter out to 5 years. The first 328 consecutively enrolled patients (across all sites) were scheduled to have angiographic and IVUS evaluations at 8 months. Following the index procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 6 months.

Demographics: The mean age was 63.5 years for patients in the Endeavor arm and 63.6 years for patients in the Taxus arm. The Endeavor arm had 66.9% (517/773) males, and the Taxus arm had 68.5% (531/775) males. In the Endeavor arm, 28.2% (218/773) of patients had prior percutaneous coronary revascularization, compared to 29.5% (229/775) of patients in the Taxus arm. In the Endeavor arm, 31.2% (241/773) of patients had a history of diabetes mellitus, compared to 30.5% (236/775) of patients in the Taxus arm. Patients were well-matched for baseline demographics with no statistically significant differences between treatment arms.

Results: The primary and secondary endpoints, protocol-defined stent thrombosis, and the latest available follow-up results are presented below (**Table 9-1, Table 9-2, Table 9-3 and Figure 9-1**).

The primary endpoint of TVF at 9 months was met with 6.8% (50/740) for the Endeavor arm and 7.4% (54/734) for the Taxus arm ($p < 0.001$ for non-inferiority).

The pre-specified secondary endpoint of in-segment late loss at 8 months was not met with measurements of 0.36 ± 0.47 mm (143) for the Endeavor arm and 0.23 ± 0.45 mm (135) for the Taxus arm ($p = 0.0890$ for non-inferiority).

Table 9-1: ENDEAVOR IV Clinical Results

	Outcomes at 9 Months		
	Endeavor (N = 773)	Taxus (N = 775)	P-Value
PRIMARY ENDPOINT			
TVF[§]	6.8% (50/740)	7.4% (54/734)	< 0.001*
§ 9-month primary endpoint. * Test for non-inferiority.			
EFFICACY			
TVR	5.5% (41/740)	5.0% (37/734)	0.727**
TLR	4.2% (31/740)	2.7% (20/734)	0.154**
TLR, PCI	3.8% (28/740)	1.9% (14/734)	0.041**
TLR, CABG	0.5% (4/740)	0.8% (6/734)	0.546**
Non-TLR	2.0% (15/740)	2.9% (21/734)	0.316**
Non-TLR, PCI	1.8% (13/740)	2.5% (18/734)	0.370**
Non-TLR, CABG	0.4% (3/740)	0.4% (3/734)	1.000**
SAFETY			
Total Death	0.7% (5/740)	0.8% (6/734)	0.773**
Cardiac Death	0.4% (3/740)	0.3% (2/734)	1.000**
Non-Cardiac Death	0.3% (2/740)	0.5% (4/734)	0.450**
Cardiac Death or MI	1.9% (14/740)	2.7% (20/734)	0.303**
MI	1.5% (11/740)	2.5% (18/734)	0.194**
Q wave MI	0.3% (2/740)	0.1% (1/734)	1.000**
Non-Q wave MI	1.2% (9/740)	2.3% (17/734)	0.117**
Stent Thrombosis (protocol)	0.8% (6/740)	0.1% (1/734)	0.124**

** P-values for outcome differences are not adjusted for multiple comparisons.

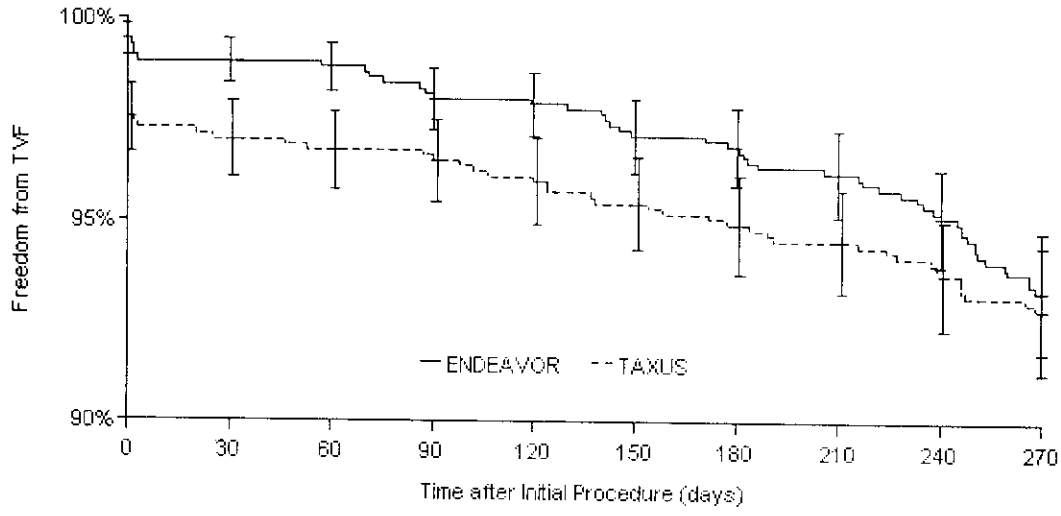
Notes:

Fisher's Exact test was used for P-values.

This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.

Numbers are % (Count/Sample Size).

To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.



TVF	Event Free	Event rate	P-Value*
ENDEAVOR	93.3%	6.7%	0.626
TAXUS	92.8%	7.2%	

*Log-rank P-value. P-value is not adjusted for multiple comparisons.

Figure 9-1: Survival Free from Target Vessel Failure (at 270 days)

Table 9-2: Endeavor IV 8-Month Angiographic and IVUS Results

	Endeavor (N = 773)	Taxus (N = 775)	P-Value
SECONDARY ENDPOINT			
Late Loss, In-segment (mm)¥	0.36 ± 0.47 (143)	0.23 ± 0.45 (135)	0.089*
¥ Powered secondary endpoint. * Test for non-inferiority.			
OTHER ANGIOGRAPHIC RESULTS			
MLD (mm), In-stent			
Post-Procedure	2.62 ± 0.43 (763)	2.61 ± 0.44 (763)	0.703**
8-Month	1.95 ± 0.61 (143)	2.25 ± 0.61 (135)	< 0.001**
MLD (mm), In-segment			
Post-Procedure	2.22 ± 0.47 (770)	2.19 ± 0.50 (772)	0.196**
8-Month	1.80 ± 0.55 (144)	1.98 ± 0.56 (135)	0.008**
% DS, In-stent			
Post-Procedure	5.50 ± 9.61 (763)	5.01 ± 10.49 (763)	0.348**
8-Month	26.41 ± 19.74 (143)	16.09 ± 17.99 (135)	< 0.001**
% DS, In-segment			
Post-Procedure	20.47 ± 9.54 (770)	20.97 ± 11.12 (772)	0.344**
8-Month	32.28 ± 17.02 (144)	26.61 ± 15.52 (135)	0.004**
Late Loss, In-stent (mm)	0.67 ± 0.49 (142)	0.42 ± 0.50 (135)	< 0.001**
Binary Restenosis			
In-stent Restenosis	13.3% (19/143)	6.7% (9/135)	0.075**
In-segment Restenosis	15.3% (22/144)	10.4% (14/135)	0.284**
IVUS RESULTS			
Neointimal Volume (mm^3)	24.14 ±19.38 (74)	14.88 ±16.62 (77)	0.002**
% Volume Obstruction	15.72 ±10.40 (74)	9.88 ±9.24 (77)	< 0.001**
Incomplete Apposition			
Post-procedure	12.5% (17/136)	11.8% (15/127)	1.000**
8-Month	10.0% (12/120)	14.7% (17/116)	0.324**
Resolved	3.8% (4/106)	2.1% (2/95)	0.686**
Persistent	8.5% (9/106)	10.5% (10/95)	0.638**
Late Acquired	0.9% (1/106)	3.2% (3/95)	0.346**

** P-values for outcome differences are not adjusted for multiple comparisons.
Note:
Fisher's Exact test or Student's t-test was used for P-values.

Table 9-3: ENDEAVOR IV Protocol-Defined Stent Thrombosis* Through 9 Months

	Endeavor (N = 773)	Taxus (N = 775)	P-Value
Cumulative ST through 9 Months	0.8% (6/740)	0.1% (1/734)	0.124**
Acute ST (≤ 24 hrs)	0.0% (0/770)	0.0% (0/771)	--
Subacute ST (> 24 hrs and ≤ 30days)	0.4% (3/770)	0.1% (1/771)	0.374**
Late ST (> 30 days and ≤ 9 months)	0.4% (3/740)	0.0% (0/734)	0.250**

* See section 9.5.1 for the per protocol stent thrombosis definition.
** P-values for outcome differences are not adjusted for multiple comparisons.
Notes:
Fisher's Exact test was used for P-values.
This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.
Numbers are % (Count/Sample Size).

9.2 Results of the ENDEAVOR III Clinical Trial

Primary Objective: To demonstrate non-inferiority in in-segment late loss at 8 months between the Endeavor Zotarolimus-Eluting Coronary Stent System and the Cypher Sirolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5 mm to 3.5 mm and lesion lengths of ≥ 14 mm and ≤ 27 mm.

Design: This was a prospective, multi-center, single-blind, two-arm, randomized and controlled non-inferiority trial that compared the Endeavor stent to a control DES (the Cypher stent). A total of 436 patients were enrolled at 29 study sites in the United States who presented with symptomatic ischemic heart disease attributable to stenotic lesions of native coronary arteries that were amenable to treatment by stenting. Patients were randomized to receive either an Endeavor or a Cypher stent in a 3:1 ratio. Multiple stents were allowed for bailout only.

Follow-up was performed at 30 days, 6, 8, 9, 12 months, and at 2 years, and will be performed annually thereafter out to 5 years. All patients were scheduled to have angiographic and IVUS evaluations at 8 months. Following the index procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

Demographics: The mean age was 61.4 years for patients in the Endeavor arm and 61.7 years for patients in the Cypher arm. The Endeavor arm had 65.3% (211/323) males and the Cypher arm had 81.4% (92/113) males. In the Endeavor arm, 22.6% (73/323) of patients had prior percutaneous coronary revascularization compared to 16.8% (19/113) of patients in the Cypher arm. In the Endeavor arm, 29.7% (96/323) of patients had a history of diabetes mellitus compared to 28.3% (32/113) of patients in the Cypher arm. Patients were well matched for baseline demographics, with gender being the only significant difference between treatment arms.

Results: The primary and secondary endpoints, protocol-defined stent thrombosis, and the latest available follow-up results are presented below (**Table 9-4, Table 9-5, and Table 9-6**).

The primary endpoint of in-segment late loss at 8 months was not met with measurements of 0.36 ± 0.46 mm (277) for the Endeavor arm and 0.13 ± 0.33 mm (94) for the Cypher arm ($p < 0.791$ for non-inferiority). Differences noted in baseline demographics (gender) did not result in a significant impact on study outcomes.

Table 9-4: Endeavor III 8-Month Angiographic and IVUS Results

	Endeavor (N = 323)	Cypher (N = 113)	P-Value
PRIMARY ENDPOINT			
Late Loss, In-segment (mm) §	0.36 ± 0.46 (277)	0.13 ± 0.33 (94)	0.791*
§ 8-month primary endpoint.			
* Test for non-inferiority.			
OTHER ANGIOGRAPHIC RESULTS			
MLD (mm), In-stent			
Post-Procedure	2.67 ± 0.42 (323)	2.67 ± 0.40 (112)	0.993**
8-Month	2.06 ± 0.57 (277)	2.52 ± 0.56 (94)	< 0.001**
MLD (mm), In-segment			
Post-Procedure	2.27 ± 0.45 (323)	2.28 ± 0.47 (113)	0.836**
8-Month	1.91 ± 0.53 (277)	2.16 ± 0.50 (94)	< 0.001**
% DS, In-stent			
Post-Procedure	4.33 ± 9.77 (323)	5.92 ± 9.07 (112)	0.132**
8-Month	24.90 ± 17.45 (277)	11.01 ± 15.91 (94)	< 0.001**
% DS, In-segment			
Post-Procedure	19.38 ± 9.25 (323)	20.17 ± 11.74 (113)	0.522**
8-Month	30.42 ± 15.57 (277)	23.86 ± 13.87 (94)	< 0.001**
Late Loss, In-stent (mm)	0.62 ± 0.49 (277)	0.15 ± 0.34 (94)	< 0.001**
Binary Restenosis			
In-stent Restenosis	9.7% (27/277)	2.1% (2/94)	0.014**
In-segment Restenosis	12.3% (34/277)	4.3% (4/94)	0.029**
IVUS RESULTS			
Neointimal Volume (mm^3)	24.09 ± 21.16 (209)	3.74 ± 5.20 (67)	< 0.001**
% Volume Obstruction	15.94 ± 10.94 (187)	2.66 ± 3.11 (61)	< 0.001**
Incomplete Apposition			
Post-procedure	12.4% (31/251)	17.7% (17/96)	0.224**
8-Month	7.5% (17/226)	17.1% (13/76)	0.025**
Resolved	5.8% (11/189)	7.4% (5/68)	0.770**
Persistent	7.9% (15/189)	11.8% (8/68)	0.332**
Late Acquired	0.5% (1/189)	5.9% (4/68)	0.018**

** P-values for outcome differences are not adjusted for multiple comparisons.
Note:
Fisher's Exact test or Student's t-test was used for P-values.

Table 9-5: ENDEAVOR III Clinical Results

	Outcomes at 9 Months			Outcomes at 24 Months (latest available follow-up)		
	Endeavor (N = 323)	Cypher (N = 113)	P-Value	Endeavor (N = 323)	Cypher (N = 113)	P-Value
EFFICACY						
TVF	11.8% (38/321)	11.5% (13/113)	1.000**	14.4% (45/313)	13.4% (15/112)	0.875**
TVR	11.2% (36/321)	8.0% (9/113)	0.375**	13.7% (43/313)	9.8% (11/112)	0.325**
TLR	6.2% (20/321)	3.5% (4/113)	0.346**	7.0% (22/313)	4.5% (5/112)	0.498**
TLR, PCI	5.3% (17/321)	3.5% (4/113)	0.612**	5.8% (18/313)	4.5% (5/112)	0.808**
TLR, CABG	0.9% (3/321)	0.0% (0/113)	0.571**	1.3% (4/313)	0.0% (0/112)	0.577**
Non-TLR	5.9% (19/321)	5.3% (6/113)	1.000**	8.3% (26/313)	6.3% (7/112)	0.545**
Non-TLR, PCI	5.6% (18/321)	5.3% (6/113)	1.000**	7.7% (24/313)	6.3% (7/112)	0.832**
Non-TLR, CABG	0.3% (1/321)	0.0% (0/113)	1.000**	1.0% (3/313)	0.0% (0/112)	0.570**
SAFETY						
Total Death	0.6% (2/321)	0.0% (0/113)	1.000**	1.6% (5/313)	4.5% (5/112)	0.138**
Cardiac Death	0.0% (0/321)	0.0% (0/113)	--	0.0% (0/313)	0.9% (1/112)	0.264**
Non-Cardiac Death	0.6% (2/321)	0.0% (0/113)	1.000**	1.6% (5/313)	3.6% (4/112)	0.252**
Cardiac Death or MI	0.6% (2/321)	3.5% (4/113)	0.042**	0.6% (2/313)	3.6% (4/112)	0.044**
MI	0.6% (2/321)	3.5% (4/113)	0.042**	0.6% (2/313)	3.6% (4/112)	0.044**
Q wave MI	0.0% (0/321)	0.0% (0/113)	--	0.0% (0/313)	0.0% (0/112)	--
Non-Q wave MI	0.6% (2/321)	3.5% (4/113)	0.042**	0.6% (2/313)	3.6% (4/112)	0.044**
Stent Thrombosis (protocol)	0.0% (0/321)	0.0% (0/113)	--	0.0% (0/313)	0.0% (0/112)	--

** P-values for outcome differences are not adjusted for multiple comparisons.

Notes:

Fisher's Exact test was used for P-values.

This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.

Numbers are % (Count/Sample Size).

To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.

Table 9-6: ENDEAVOR III Protocol-Defined Stent Thrombosis* Through 24 Months

	Endeavor (N = 323)	Cypher (N = 113)	P-Value
Cumulative ST through 24 Months	0.0% (0/313)	0.0% (0/112)	--
Acute ST (≤ 24 hrs)	0.0% (0/323)	0.0% (0/113)	--
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/323)	0.0% (0/113)	--
Late ST (> 30 days and ≤ 12 months)	0.0% (0/320)	0.0% (0/112)	--
Very late ST (> 12 months and ≤ 24 months)	0.0% (0/313)	0.0% (0/112)	--

* See section 9.5.1 for the per protocol stent thrombosis definition.
Notes:
This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.
Numbers are % (Count/Sample Size).

9.3 Results of the ENDEAVOR II Clinical Trial

Primary Objective: To demonstrate superiority in the safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System when compared to the Driver Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.25 mm to 3.5 mm in diameter and lesion lengths of ≥ 14 mm and ≤ 27 mm.

Design: This was a prospective, multi-center, double-blind, two-arm randomized and controlled superiority trial that compared the Endeavor stent to a control bare metal stent (BMS), the Driver stent. A total of 1197 patients were enrolled at 72 study sites in Asia, Australia, Europe, Israel and New Zealand who presented with symptomatic ischemic heart disease attributable to stenotic lesions of native coronary arteries that were amenable to treatment by stenting. Patients were randomized to receive either an Endeavor or a Driver stent in a 1:1 ratio. Multiple stents were allowed for bailout only.

Follow-up was performed at 30 days, 6, 8, 9, 12 months, at 2 and 3 years, and will be performed annually thereafter out to 5 years. The first 600 consecutively enrolled patients (across all sites) were scheduled to receive angiographic evaluation at 8 months, and 300 patients were scheduled to receive IVUS evaluation at 8 months at pre-specified sites. Following the index procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

Demographics: The mean age was 61.6 years for patients in the Endeavor arm and 61.9 years for patients in the Driver arm. The Endeavor arm had 77.2% (461/597) males, and the Driver arm had 75.3% (449/596) males. In the Endeavor arm, 21.7% (129/595) of patients had prior percutaneous coronary revascularization, compared to 18.0% (107/594) of patients in the Driver arm. In the Endeavor arm, 18.2% (108/595) of patients had a history of diabetes mellitus, compared to 22.2% (132/595) of patients in the Driver arm. Patients were well matched for baseline demographics, with no statistically significant differences between treatment arms.

Results: The primary and secondary endpoints, protocol-defined stent thrombosis, and the latest available follow-up results are presented below (**Table 9-7, Table 9-8, Table 9-9 and Figure 9-2**).

The primary endpoint of TVF at 9 months was met with 7.9% (47/592) for the Endeavor arm and 15.1% (89/591) for the Driver arm ($p < 0.001$ for superiority).

The pre-specified secondary endpoint of in-segment late loss at 8 months was met, with measurements of 0.36 mm ± 0.46 mm (264) for the Endeavor arm and 0.72 mm ± 0.61 mm (263) for the Driver arm ($p < 0.001$ for superiority).

Table 9-7: ENDEAVOR II Clinical Results

	Outcomes at 9 Months			Outcomes at 36 Months (latest available follow-up)		
	Endeavor (N = 598)	Driver (N = 599)	P-Value	Endeavor (N = 598)	Driver (N = 599)	P-Value
PRIMARY ENDPOINT						
TVF[§]	7.9% (47/592)	15.1% (89/591)	< 0.001*	12.8% (74/577)	21.4% (124/579)	< 0.001**
§ 9-month primary endpoint * Test for superiority.						
EFFICACY						
TVR	5.6% (33/592)	12.5% (74/591)	< 0.001**	9.5% (55/577)	17.6% (102/579)	< 0.001**
TLR	4.6% (27/592)	11.8% (70/591)	< 0.001**	7.3% (42/577)	14.7% (85/579)	< 0.001**
TLR, PCI	4.2% (25/592)	11.3% (67/591)	< 0.001**	6.9% (40/577)	13.8% (80/579)	< 0.001**
TLR, CABG	0.3% (2/592)	0.5% (3/591)	0.687**	0.5% (3/577)	1.0% (6/579)	0.506**
Non-TLR	1.5% (9/592)	2.2% (13/591)	0.400**	2.9% (17/577)	4.8% (28/579)	0.128**
Non-TLR, PCI	1.4% (8/592)	2.2% (13/591)	0.282**	2.8% (16/577)	4.7% (27/579)	0.119**
Non-TLR, CABG	0.2% (1/592)	0.0% (0/591)	1.000**	0.2% (1/577)	0.3% (2/579)	1.000**
SAFETY						
Total Death	1.2% (7/592)	0.5% (3/591)	0.342**	3.3% (19/577)	4.5% (26/579)	0.362**
Cardiac Death	0.8% (5/592)	0.5% (3/591)	0.726**	1.6% (9/577)	2.4% (14/579)	0.400**
Non-Cardiac Death	0.3% (2/592)	0.0% (0/591)	0.500**	1.7% (10/577)	2.1% (12/579)	0.830**
Cardiac Death or MI	3.4% (20/592)	4.4% (26/591)	0.372**	4.5% (26/577)	6.7% (39/579)	0.125**
MI	2.7% (16/592)	3.9% (23/591)	0.260**	3.3% (19/577)	4.3% (25/579)	0.443**
Q wave MI	0.3% (2/592)	0.8% (5/591)	0.287**	0.3% (2/577)	1.0% (6/579)	0.287**
Non-Q wave MI	2.4% (14/592)	3.0% (18/591)	0.481**	2.9% (17/577)	3.3% (19/579)	0.866**
Stent Thrombosis (protocol)	0.5% (3/592)	1.2% (7/591)	0.224**	0.5% (3/577)	1.2% (7/579)	0.342**

** P-values for outcome differences are not adjusted for multiple comparisons.

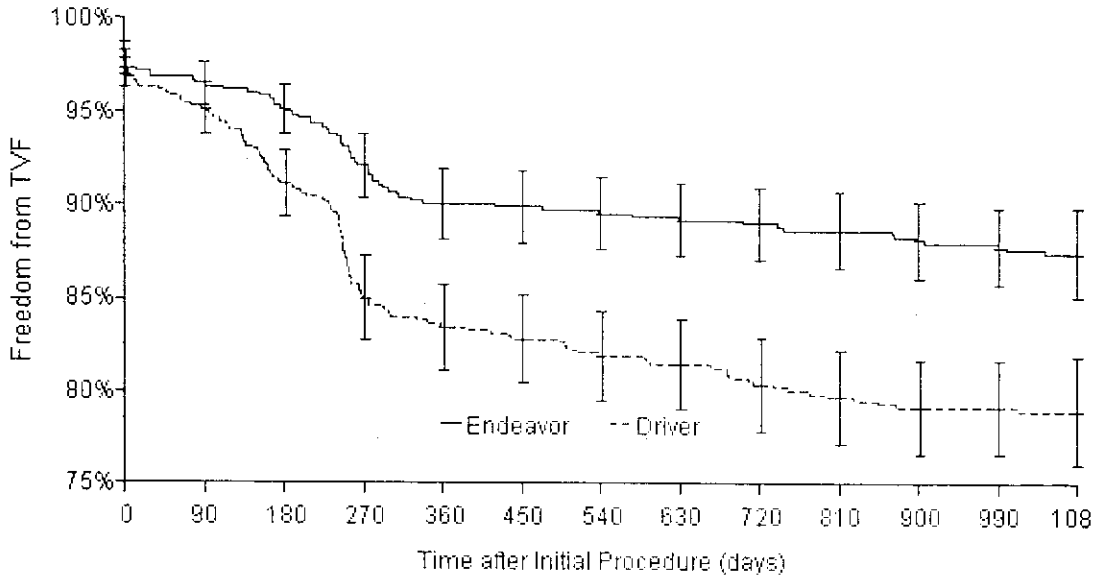
Notes:

Fisher's Exact test was used for P-values.

This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.

Numbers are % (Count/Sample Size).

To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.



TVF	Event free	Event Rate	P-Value*
Endeavor	87.4%	12.6%	< 0.001
Driver	78.9%	21.1%	

* Log-rank P-value. P-value is not adjusted for multiple comparisons.

Figure 9-2: Survival Free from Target Vessel Failure (at 1080 days)

Table 9-8: Endeavor II 8-Month Angiographic and IVUS Results

	Endeavor (N = 598)	Driver (N = 599)	P-Value
SECONDARY ENDPOINT			
Late Loss, In-segment (mm) ¥	0.36 ± 0.46 (264)	0.72 ± 0.61 (263)	< 0.001*
¥ Powered secondary endpoint. * test for superiority.			
OTHER ANGIOGRAPHIC RESULTS			
MLD (mm), In-stent			
Post-Procedure	2.59 ± 0.43 (588)	2.61 ± 0.44 (589)	0.436**
8-Month	1.99 ± 0.56 (264)	1.62 ± 0.70 (265)	< 0.001**
MLD (mm), In-segment			
Post-Procedure	2.21 ± 0.49 (589)	2.24 ± 0.49 (590)	0.302**
8-Month	1.86 ± 0.55 (264)	1.56 ± 0.67 (265)	< 0.001**
% DS, In-stent			
Post-Procedure	6.04 ± 10.43 (588)	6.23 ± 10.03 (589)	0.757**
8-Month	27.91 ± 17.30 (264)	42.24 ± 21.73 (265)	< 0.001**
% DS, In-segment			
Post-Procedure	20.39 ± 10.26 (589)	20.11 ± 9.38 (590)	0.622**
8-Month	32.67 ± 16.27 (264)	44.33 ± 20.45 (265)	< 0.001**
Late Loss, In-stent (mm)	0.62 ± 0.46 (264)	1.03 ± 0.59 (263)	< 0.001**
Binary Restenosis			
In-stent Restenosis	9.5% (25/264)	33.2% (88/265)	< 0.001**
In-segment Restenosis	13.3% (35/264)	34.7% (92/265)	< 0.001**
IVUS RESULTS			
Neointimal Volume (mm^3)	30.15 ± 21.66 (90)	53.51 ± 39.80 (81)	< 0.001**
% Volume Obstruction	17.34 ± 10.27 (90)	29.55 ± 17.58 (81)	< 0.001**
Incomplete Apposition			
Post-procedure	24.8% (36/145)	19.6% (28/143)	0.322**
8-Month	16.8% (21/125)	14.5% (16/110)	0.721**
Resolved	7.0% (8/114)	6.7% (7/104)	1.000**
Persistent	17.5% (20/114)	14.4% (15/104)	0.583**
Late Acquired	0.0% (0/114)	0.0% (0/104)	--

** P-values for outcome differences are not adjusted for multiple comparisons.
Note:
Fisher's Exact test or Student's t-test was used for P-values.

Table 9-9: ENDEAVOR II Protocol-Defined Stent Thrombosis* Through 36 Months

	Endeavor (N = 598)	Driver (N = 599)	P-Value
Cumulative ST through 36 Months	0.5% (3/577)	1.2% (7/579)	0.342**
Acute ST (≤ 24 hrs)	0.2% (1/596)	0.2% (1/594)	1.000**
Subacute ST (> 24 hrs and ≤ 30 days)	0.3% (2/596)	1.0% (6/594)	0.178**
Late ST (> 30 days and ≤ 12 months)	0.0% (0/590)	0.0% (0/589)	--
Very late ST (> 12 months and ≤ 36 months)	0.0% (0/577)	0.0% (0/579)	--

* See section 9.5.1 for the per protocol stent thrombosis definition.
** P-values for outcome differences are not adjusted for multiple comparisons.
Notes:
Fisher's Exact test was used for P-values.
This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.
Numbers are % (Count/Sample Size).

9.4 Results of the ENDEAVOR I Clinical Trial

Primary Objective: To demonstrate the safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 3.0 mm to 3.5 mm and lesion length of ≤ 15 mm.

Design: The ENDEAVOR I trial was the first-in-man study for the Endeavor stent. This was a non-randomized, prospective, multi-center, single-arm trial. A total of 100 patients were enrolled at 8 study sites in Australia and New Zealand who presented with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that were amenable to treatment by stenting.

Follow-up was performed at 30 days, 4, 9, 12 months, at 2, 3 and 4 years, and will be performed at 5 years. All patients were scheduled to have angiographic follow-up at 4 and 12 months. Following the index procedure, patients were treated with aspirin indefinitely and clopidogrel for a minimum of 3 months.

Demographics: The mean age was 59 years, and 79% were male. Diabetes was present in 16%, and 47% had a prior MI.

Results: The primary and secondary endpoint, protocol-defined stent thrombosis, and the latest available follow-up results are presented below (**Table 9-10, Table 9-11, and Table 9-12**).

The primary endpoint of 30-day MACE was 1.0% (1/100), and the co-primary endpoint of in-segment late loss at 4 months was 0.22 ± 0.43 mm (98).

Table 9-10: ENDEAVOR I Clinical Results

	Endeavor (N = 100)	Endeavor (N = 100)
PRIMARY ENDPOINT		
MACE at 30 days[§]	1.0% (1/100)	
[§]30 day primary endpoint.		
	Outcomes at 9 Months	Outcomes at 48 Months (latest available follow-up)
EFFICACY		
TVF	2.0% (2/100)	5.2% (5/97)
TVR	2.0% (2/100)	5.2% (5/97)
TLR	2.0% (2/100)	3.1% (3/97)
TLR, PCI	2.0% (2/100)	3.1% (3/97)
TLR, CABG	1.0% (1/100)	1.0% (1/97)
Non-TLR	0.0% (0/100)	2.1% (2/97)
Non-TLR, PCI	0.0% (0/100)	1.0% (1/97)
Non-TLR, CABG	0.0% (0/100)	1.0% (1/97)
SAFETY		
Total Death	0.0% (0/100)	4.1% (4/97)
Cardiac Death	0.0% (0/100)	0.0% (0/97)
Non-Cardiac Death	0.0% (0/100)	4.1% (4/97)
Cardiac Death or MI	1.0% (1/100)	1.0% (1/97)
MI	1.0% (1/100)	1.0% (1/97)
Q wave MI	0.0% (0/100)	0.0% (0/97)
Non-Q wave MI	1.0% (1/100)	1.0% (1/97)
Stent Thrombosis (protocol)	1.0% (1/100)	1.0% (1/97)

Notes:
Numbers are % (Count/Sample Size).
This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.

Table 9-11: ENDEAVOR I 12-Month Angiographic and IVUS Results

	Endeavor (N = 100)
PRIMARY ENDPOINT	
In-segment Late loss at 4 Months (mm) §	0.22 ± 0.43(98)
§ 4-month primary endpoint	
ANGIOGRAPHIC RESULTS	
MLD (mm), In-stent	
Post-Procedure	2.84 ± 0.35 (100)
12-Month	2.26 ± 0.49 (92)
MLD (mm), In-segment	
Post-Procedure	2.52 ± 0.42 (100)
12-Month	2.08 ± 0.47 (92)
% DS, In-stent	
Post-Procedure	5.37 ± 7.51 (100)
12-Month	21.75 ± 15.35 (92)
% DS, In-segment	
Post-Procedure	16.54 ± 8.40 (100)
12-Month	28.00 ± 13.41 (92)
Late Loss, In-stent (mm)	0.58 ± 0.44 (92)
Late Loss, In-segment (mm)	0.43 ± 0.44 (92)
Binary Restenosis	
In-stent Restenosis	4.3% (4/92)
In-segment Restenosis	5.4% (5/92)
IVUS RESULTS	
Neointimal Volume (mm^3)	14.15 ±11.82 (86)
% Volume Obstruction	9.73 ±8.50 (86)
Incomplete Apposition	
Post-procedure	12.6% (12/95)
12-Month	4.7% (4/86)
Resolved	8.1% (7/86)
Persistent	4.7% (4/86)
Late Acquired	0.0% (0/86)

Table 9-12: ENDEAVOR I Protocol-Defined Stent Thrombosis* Through 48 Months

	Endeavor I (N = 100)
Cumulative ST through 48 Months	1.0% (1/97)
Acute ST (≤ 24 hrs)	0.0% (0/100)
Subacute ST (> 24 hrs and ≤ 30 days)	1.0% (1/100)
Late ST (> 30 days and ≤ 12 months)	0.0% (0/99)
Very Late ST (> 12 months and ≤ 48 months)	0.0% (0/97)

* See section 9.5.1 for the per protocol stent thrombosis definition.
Notes:
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.
Numbers are % (Count/Sample Size).

9.5 Overall Results of the ENDEAVOR Clinical Program (ENDEAVOR I, II, II-CA, III, IV and USPK)

In order to better estimate the incidence of low-frequency events or outcomes in various specific patient subgroups, a patient-level pooled analysis was conducted. This analysis compared pooled Endeavor stent patients (across all trials) to Driver stent patients from ENDEAVOR II. Although ENDEAVOR I (100), ENDEAVOR II-CA (296) and ENDEAVOR USPK (43) are not randomized trials, for the purpose of this analysis, they are pooled with the randomized trials -- ENDEAVOR II (596), ENDEAVOR III (323) and ENDEAVOR IV (770) -- to allow the broadest comparison of the Endeavor stent (1287 patients) vs. the Driver stent patients (599) to 2 years of follow-up. Across the ENDEAVOR program, 2133 patients received the Endeavor stent. The patient-level data was included until the latest available time point depending on the follow-up status for each trial -- ENDEAVOR I (97% complete at 4 years), ENDEAVOR II (97.8% completed at 3 years), ENDEAVOR II-CA (97.3% complete at 2 years), ENDEAVOR III (96.9% complete at 2 years), ENDEAVOR IV (96.1% complete at 9 months), and ENDEAVOR USPK (97.7% complete at 9 months).

Table 9-13: Patient Follow-up

	30 Days	6 Months	9 Months	12 Months	24 Months	36 Months	48 Months
ENDEAVOR I	100	100	100	99	99	98	97
ENDEAVOR II	596	593	592	590	587	577	-
ENDEAVOR II CA	296	295	293	292	288	-	-
ENDEAVOR III	323	321	321	320	313	-	-
ENDEAVOR IV	770	766	740	-	-	-	-
ENDEAVOR PK	43	43	42	-	-	-	-
Total	**2128**	**2118**	**2088**	**1301**	**1287**	**675**	**97**

It is acknowledged that the results of such retrospective pooled analyses are hypothesis-generating in nature. Definitive proof of the presence or absence of any differences between sub-groups requires prospectively powered assessment in dedicated clinical trials.

The results of the pooled analysis show the Endeavor stent significantly reduces the need for repeat revascularization vs. the Driver stent that is maintained throughout long-term follow-up as shown in **Figure 9-3**.

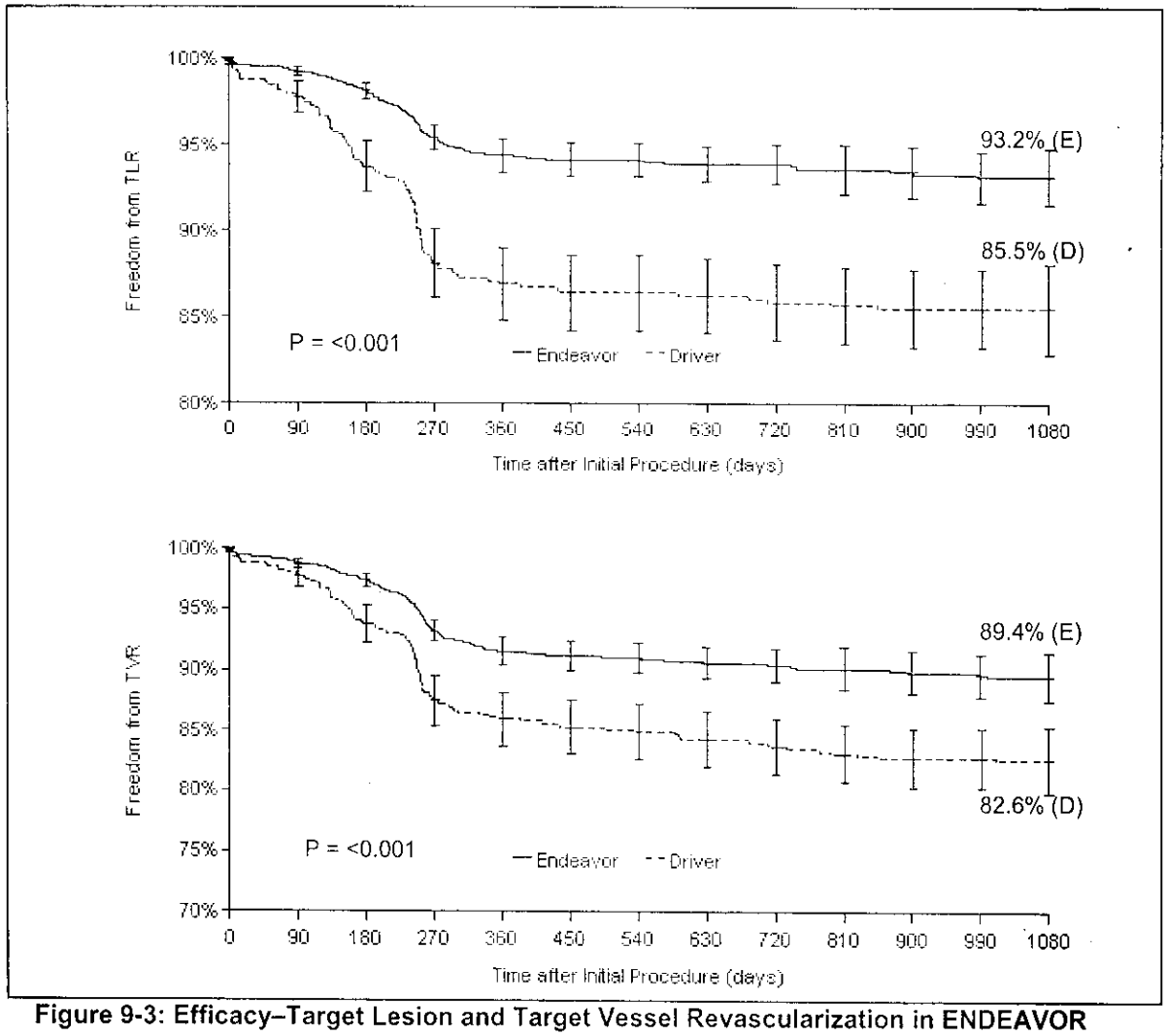


Figure 9-3: Efficacy–Target Lesion and Target Vessel Revascularization in ENDEAVOR Pooled Analysis

Kaplan-Meier rates %.
P-values are from the Log-rank test and are not adjusted for multiple comparisons.

The Endeavor stent is more effective than the Driver stent in reducing the need for revascularization, as shown in **Figure 9-3**. The analyses shown in **Figure 9-4** suggest a lower rate of cardiac death in pooled Endeavor patients compared to Driver patients from ENDEAVOR II. The pooled analysis addressed total death as well as cardiac death and non-cardiac death as its components. There were no differences noted in non-cardiac or total death between groups.

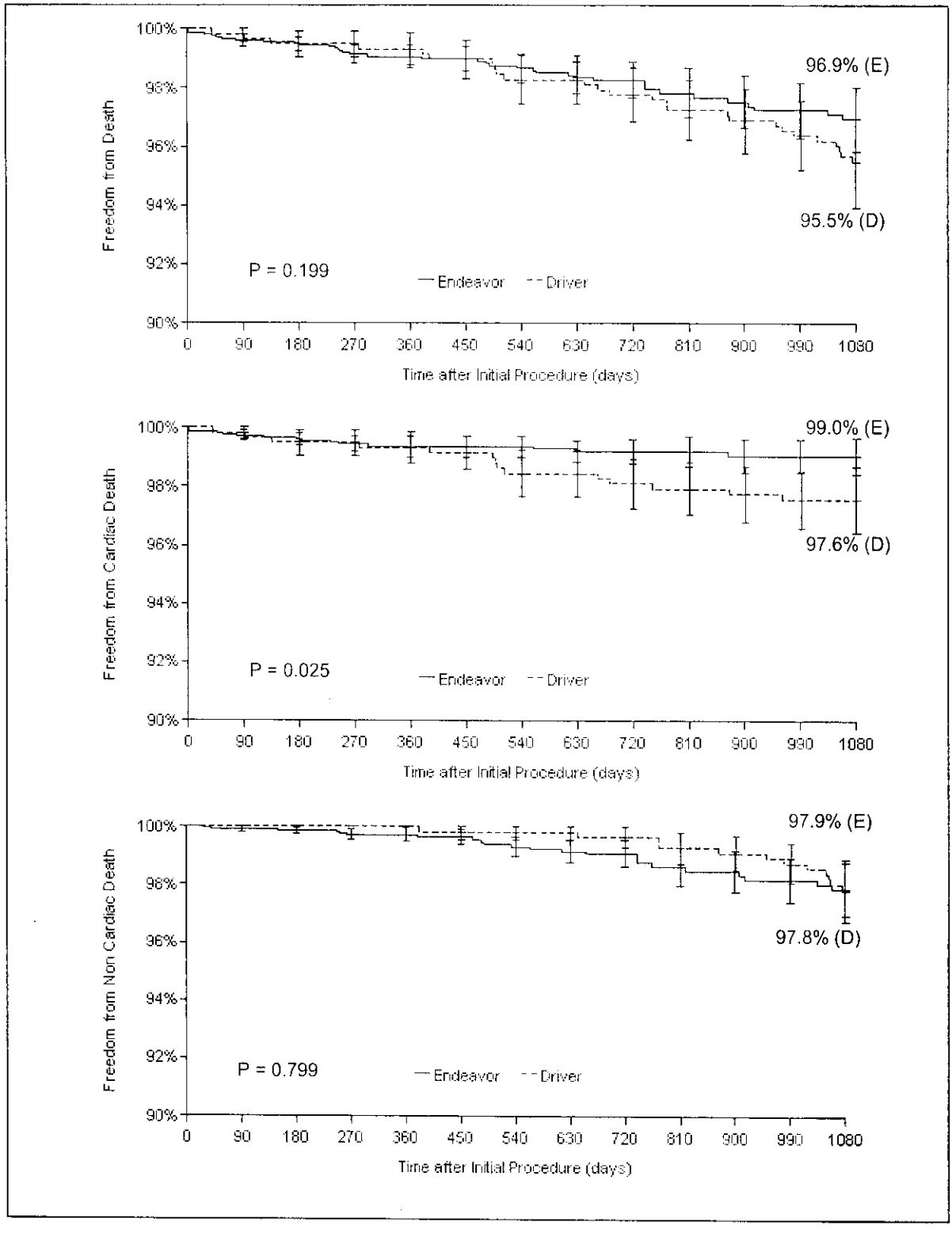


Figure 9-4: Safety–Mortality in ENDEAVOR Pooled Analysis

Kaplan-Meier rates %.

P-values are from the Log-rank test and are not adjusted for multiple comparisons.

The MI rates in patients receiving the Endeavor stent vs the Driver control stent were also examined. At three years, any differences noted favored the Endeavor stent as shown in **Figure 9-5**.

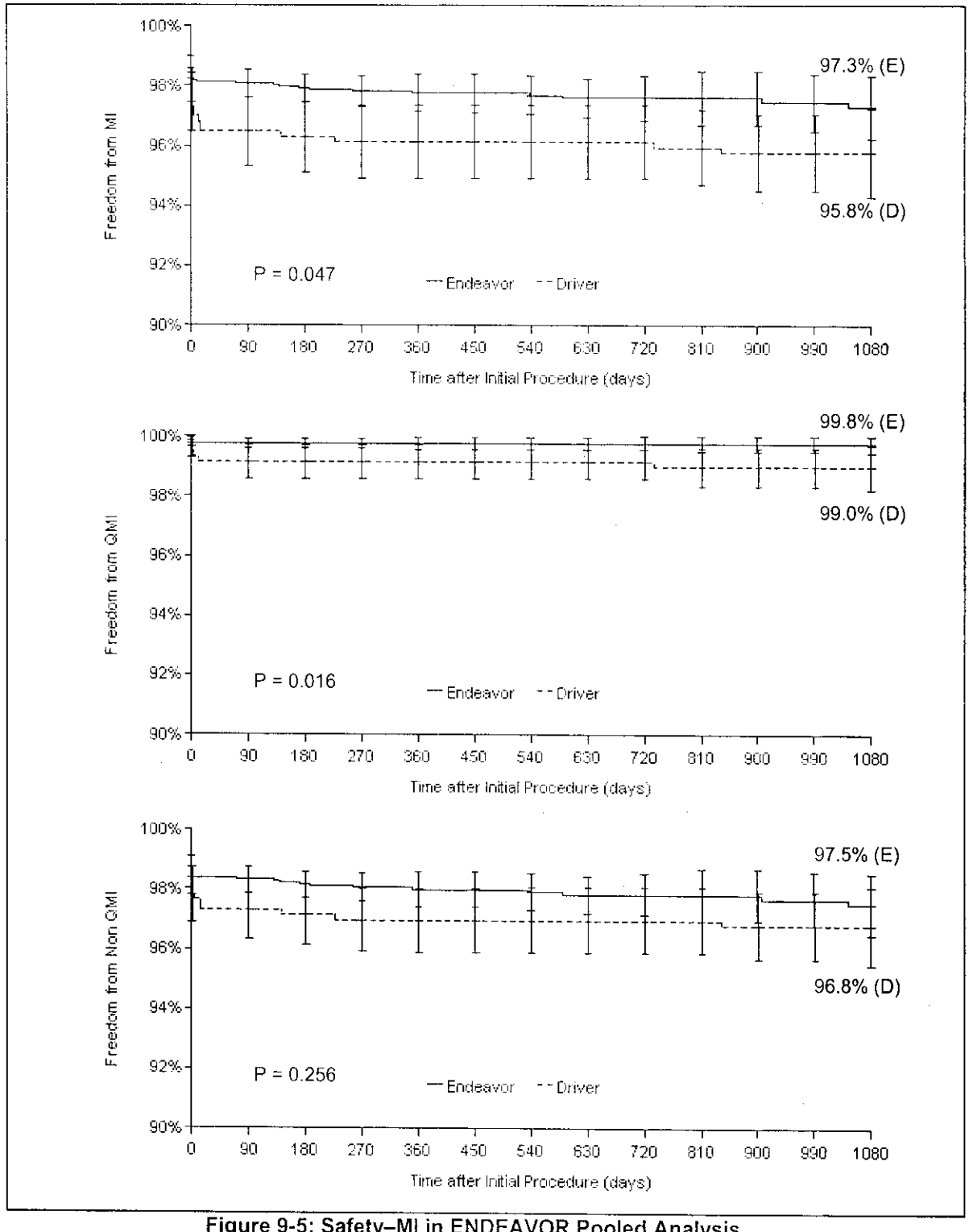


Figure 9-5: Safety–MI in ENDEAVOR Pooled Analysis

Kaplan-Meier rates %.
P-values are from the Log-rank test and are not adjusted for multiple comparisons.

9.5.1 Stent Thrombosis in ENDEAVOR Pooled Analysis

For the critical safety endpoint of stent thrombosis, Endeavor rates have been reported using two different reporting mechanisms: the pre-specified protocol definition and the retrospective Academic Research Consortium (ARC)[4] definition. Stent thrombosis was defined (per protocol) in the ENDEAVOR clinical trials as the occurrence of any of the following:

- Angiographic thrombus or subacute closure within the stented vessel at the time of the clinically-driven angiographic restudy for documented ischemia (chest pain and ECG changes).
- Any death not attributed to a non-cardiac cause within the first 30 days.
- Late stent thrombosis is reported according to the following criteria: MI > 30 days after index and attributable to the target vessel, angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and freedom from interim revascularization of the target vessel.

All events were re-adjudicated based on FDA recommendation using the ST definitions proposed by ARC. This was performed by an independent events committee blinded to the treatment groups of the individual patients. According to ARC, each incident of ST is categorized by timing, level of evidence, and relationship to TLR as follows:

Timing:
Acute stent thrombosis[5]: 0–24 hours post stent implantation
Subacute stent thrombosis[5]: > 24 hours–30 days post stent implantation
Late stent thrombosis: > 30 days–1 year post stent implantation
Very late stent thrombosis: > 1 year post stent implantation

Level of Evidence:

- Definite stent thrombosis: Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.
- Probable stent thrombosis: Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
  - Any unexplained death within the first 30 days
  - Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
- Possible stent thrombosis: Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

Stent Thrombosis After TLR: Censored vs. Non-Censored:

- Censoring stent thrombosis events that occur post-TLR performed for stent restenosis may be appropriate, as the thrombosis may be related to the treatment chosen to treat restenosis (e.g., brachytherapy) rather than the type of stent used in the index procedure. Alternatively, censoring stent thrombosis events that occur after TLR may bias results in favor of devices with higher restenosis risks. Therefore, stent thrombosis data presented in this review will report both TLR-censored and TLR-uncensored rates as follows:
  - ARC Definite + probable (TLR-censored): Adjudicated stent thrombosis meeting the definite or probable ARC definition with censoring of any definite or probable stent thrombosis events that may have occurred after a TLR.
  - ARC Definite + probable (TLR-uncensored): Adjudicated stent thrombosis meeting the definite or probable ARC definition including any definite or probable stent thrombosis events that may have occurred after a TLR.

[4] Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circ 2007;115:2344-51.
[5] Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 – 30 days) will be used in the remainder of this document.

In the ENDEAVOR clinical program comprised of six multi-center trials, 2133 patients were assigned to receive the Endeavor Stent (1287 patients were followed out to two years and 675 patients out to three years). When all patients who received the Endeavor stent across trials were pooled and compared to the patients who received the Driver stent in ENDEAVOR II, the Endeavor stent did not appear to pose an increased stent thrombosis risk. Regardless of the method for reporting the pre-specified protocol definition or the retrospective ARC definition, in the randomized ENDEAVOR II trial and the FDA-requested pooled analysis, the Endeavor stent exhibited low event rates that were similar to or lower than the Driver stent.

The cumulative rates of stent thrombosis (per protocol and per the ARC definite + probable definitions) in patients treated with Endeavor stents from the pooled ENDEAVOR trials are shown in **Table 9-14** below. (Stent thrombosis rates observed in patients treated with Driver stents in ENDEAVOR II are shown for reference.) ARC definite + probable stent thrombosis is reported both as TLR-censored and uncensored.

Table 9-14: Stent Thrombosis (Protocol) and Definite + Probable Stent Thrombosis (ARC)

	Endeavor (N=2132)	95% CI	Driver (N=596)	95% CI
Thrombosis (0-30 Days)				
Stent Thrombosis (Protocol)	0.3% (7/2128)	[0.1%, 0.7%]	1.2% (7/594)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-censored)	0.3% (7/2128)	[0.1%, 0.7%]	1.2% (7/594)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-uncensored)	0.3% (7/2128)	[0.1%, 0.7%]	1.2% (7/594)	[0.5%, 2.4%]
Thrombosis (0-6 Months)				
Stent Thrombosis (Protocol)	0.5% (10/2118)	[0.2%, 0.9%]	1.2% (7/593)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-censored)	0.5% (11/2118)	[0.3%, 0.9%]	1.2% (7/593)	[0.5%, 2.4%]
ARC definite + probable (TLR-uncensored)	0.5% (11/2118)	[0.3%, 0.9%]	1.2% (7/593)	[0.5%, 2.4%]
Thrombosis (0-12 Months)				
Stent Thrombosis (Protocol)	0.3% (4/1301)	[0.1%, 0.8%]	1.2% (7/589)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-censored)	0.4% (5/1301)	[0.1%, 0.9%]	1.4% (8/589)	[0.6%, 2.7%]
ARC Definite + Probable (TLR-uncensored)	0.5% (6/1301)	[0.2%, 1.0%]	1.4% (8/589)	[0.6%, 2.7%]
Thrombosis (0-24 Months)				
Stent Thrombosis (Protocol)	0.3% (4/1287)	[0.1%, 0.8%]	1.2% (7/586)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-censored)	0.5% (6/1287)	[0.2%, 1.0%]	1.4% (8/586)	[0.6%, 2.7%]
ARC Definite + Probable (TLR-uncensored)	0.5% (7/1287)	[0.2%, 1.1%]	1.4% (8/586)	[0.6%, 2.7%]
Thrombosis (0-36 Months)				
Stent Thrombosis (Protocol)	0.6% (4/675)	[0.2%, 1.5%]	1.2% (7/579)	[0.5%, 2.5%]
ARC Definite + Probable (TLR-censored)	0.9% (6/675)	[0.3%, 1.9%]	1.4% (8/579)	[0.6%, 2.7%]
ARC Definite + Probable (TLR-uncensored)	0.9% (6/675)	[0.3%, 1.9%]	1.6% (9/579)	[0.7%, 2.9%]

Beyond one year, the Endeavor stent showed zero stent thrombosis by the pre-specified protocol definition and one stent thrombosis event by the *post hoc* ARC definition (definite + probable).

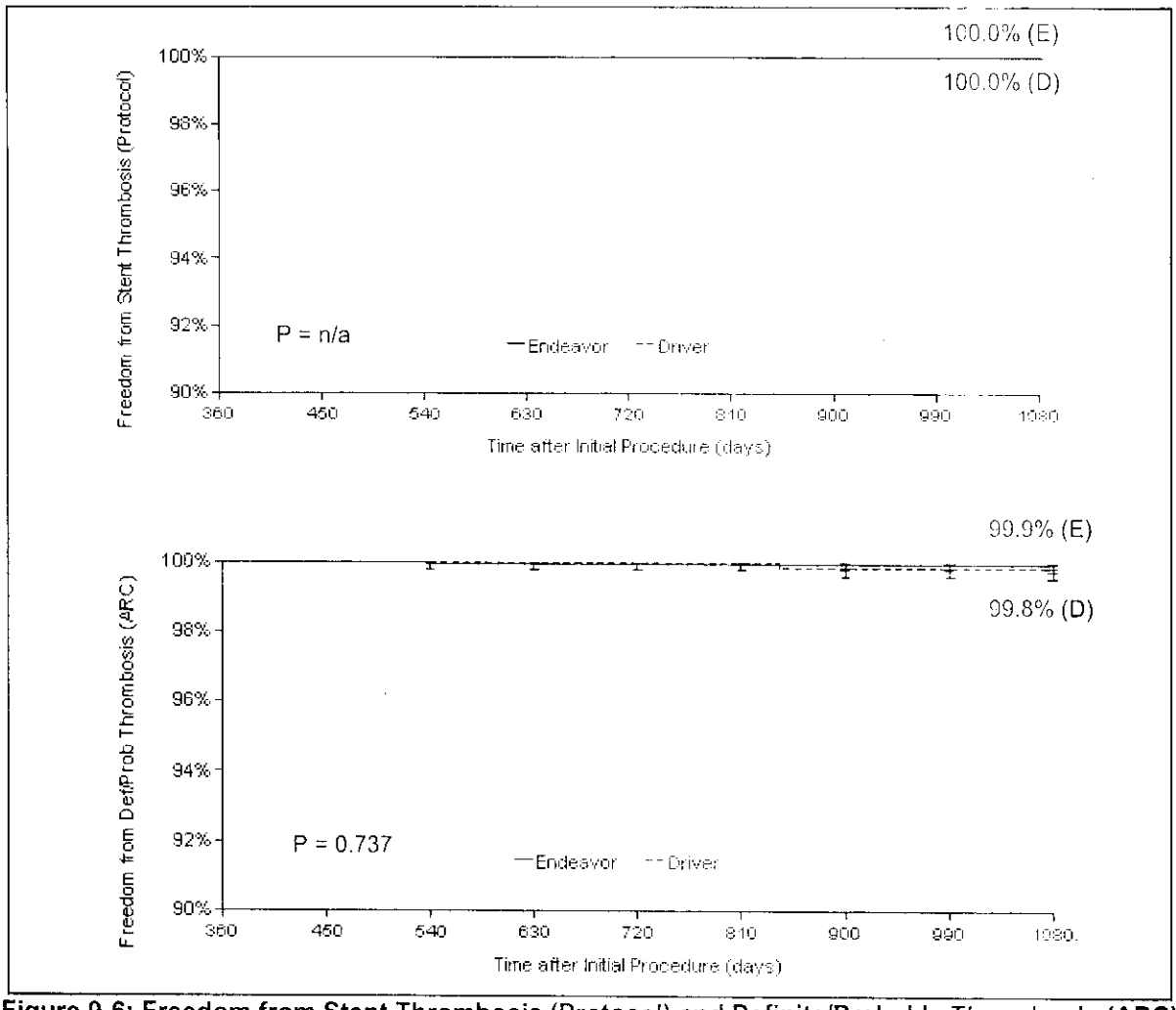


Figure 9-6: Freedom from Stent Thrombosis (Protocol) and Definite/Probable Thrombosis (ARC)
Kaplan-Meier rates %.
P-values are from the Log-rank test and are not adjusted for multiple comparisons.

9.5.2 Diabetic Patients in ENDEAVOR Pooled Analysis

Diabetic patients comprise an important patient subgroup that is at increased risk for cardiovascular morbidity and mortality. Although diabetic patients were included in the ENDEAVOR clinical trials, there were no pre-specified hypotheses or trial design features to warrant a specific labeled indication for the use of the Endeavor stent in diabetic individuals.

Table 9-15 shows clinical outcomes through 9 months in patients pooled from the ENDEAVOR trials and stratified by non-diabetics, all diabetics, insulin-dependent diabetics, and non-insulin dependent diabetics. As expected, TLR and TVR rates were numerically increased in diabetics vs. non-diabetics, with no observed safety signals with respect to the rates of death, cardiac death, MI, or stent thrombosis.

Table 9-15: Clinical Events Through 9 Months

	Non-Diabetics N = 1549	All Diabetics N = 537	Insulin-Dependent N = 154	Non-Insulin-Dependent N = 381
Death	0.8%	0.8%	0.7%	0.8%
Cardiac Death	0.5%	0.6%	0.0%	0.8%
MI	2.4%	1.5%	2.0%	1.4%
Cardiac Death or MI	2.8%	1.9%	2.0%	1.9%
Protocol ST	0.5%	0.6%	0.7%	0.5%
Definite and Probable ST ARC (TLR-censored)	0.5%	0.8%	1.3%	0.5%
Definite and Probable ST ARC (TLR-uncensored)	0.5%	0.8%	1.3%	0.5%
TLR	4.1%	6.3%	6.0%	6.5%
TVR	5.8%	9.4%	8.0%	9.8%

From the pooled ENDEAVOR studies, clinical outcomes through 9 months are shown in **Table 9-16** stratified by all diabetics, insulin-dependent diabetics, and non-insulin dependent diabetics. Event rates for the Driver patients in the ENDEAVOR II study are shown for reference. These data show no observed safety signals with respect to the rates of death, cardiac death, MI, or stent thrombosis with the Endeavor stent compared to the Driver stent.

Table 9-16: Clinical Events in Diabetics (Endeavor Compared to Driver BMS) Through 9 Months

	All Diabetics		Insulin-Dependent		Non-Insulin-Dependent	
	Endeavor N=537	Driver N=132	Endeavor N=154	Driver N=44	Endeavor N=381	Driver N=88
Death	0.8%	1.5%	0.7%	2.3%	0.8%	1.1%
Cardiac Death	0.6%	1.5%	0.0%	2.3%	0.8%	1.1%
MI	1.5%	3.8%	2.0%	2.3%	1.4%	4.5%
Cardiac Death or MI	1.9%	5.3%	2.0%	4.5%	1.6%	5.7%
Protocol ST	0.6%	2.3%	0.7%	0.0%	0.5%	3.4%
Definite and Probable ST ARC (TLR-censored)	0.8%	2.3%	1.3%	0.0%	0.5%	3.4%
Definite and Probable ST ARC (TLR-uncensored)	0.8%	2.3%	1.3%	0.0%	0.5%	3.4%
TLR	6.3%	15.2%	6.0%	13.6%	6.5%	15.9%
TVR	9.4%	15.9%	8.0%	13.6%	9.8%	17.0%

10 Individualization of Treatment

See also **Section 5.6 Use in Special Populations** and Section 5.7 **Lesion/Vessel Characteristics.**

The risks and benefits described above should be carefully considered for each patient before use of the Endeavor Zotarolimus-Eluting Coronary Stent System. Factors to be utilized for patient selection should include an assessment of the risk of prolonged anticoagulation. Stenting is generally avoided in patients at risk of bleeding and for those with contraindicated anticoagulation therapy.

11 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/benefits issues for this particular 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 information is provided in the package or online for physicians to provide to their patients:

- A Patient Guide which includes information on the Endeavor Zotarolimus-Eluting Coronary Stent System, coronary artery disease, and the implantation procedure
- A Patient Implant Card that is used to record information about the patient and the stent

12 How Supplied

STERILE: FOR SINGLE USE ONLY. This product is sterilized with ethylene oxide (EO) and is nonpyrogenic. Do not use if the package is opened or damaged. Do not resterilize. Return product if package is opened or damaged to Medtronic Returned Goods. Contact your local Medtronic, Inc. Representative for return information.

CONTENTS for one (1) Endeavor Over-the-Wire Zotarolimus-Eluting Coronary Stent System:

- One (1) Endeavor Over-the-Wire Zotarolimus-Eluting Coronary Stent System
- One (1) Patient Implant Card
- One (1) Reference Card to the electronic Instructions for Use
- One (1) Compliance Card

STORAGE: Store in the original container. Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F). Use by the "Use By" date noted on the package.

DISPOSAL INSTRUCTIONS:

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

13 Operator's Manual

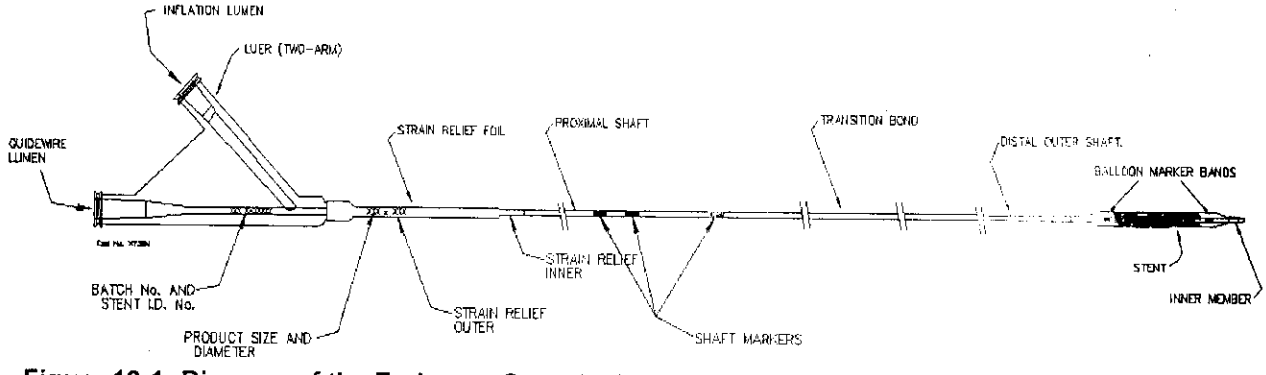


Figure 13-1: Diagram of the Endeavor Over-the-Wire (OTW) Zotarolimus-Eluting Coronary Stent System

13.1 Access to Package Holding Sterile Stent Delivery System

Tear open the outer foil pouch to reveal the inner pouch. Do not drop or hand the inner pouch into the sterile field. Remove the inner pouch from the outer foil pouch.
***Note*: The outer surface of the inner pouch is not sterile.**

13.2 Inspection Prior to 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 is noted. Peel open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
***Note*: The outer surface of the inner pouch is not sterile.**

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 proximal and distal marker bands) on the balloon.

13.3 Materials Required

Quantity	Material
1	Guide catheter [≥ 5 F (1.4 mm, 0.056 inch) inner diameter]
2-3	20 cc syringe
1,000 u/500 cc	Heparinized normal saline
1	Guidewire [≤ 0.014 inch (0.36 mm) 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

13.4 Preparation Precautions

- DO NOT use product if the protective sheath is not present or the stent is damaged/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 negative or positive pressure to the balloon during the delivery system preparation.

13.4.1 Guidewire Lumen Flush

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

13.4.2 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-mounted balloon.
4.	Fill a 20 cc syringe with 5 cc of contrast/heparinized normal saline mixture (1:1).
5.	Attach the syringe to the delivery system and apply negative pressure for 20-30 seconds.
6.	Slowly release pressure to allow negative pressure to draw mixture into the balloon lumen.
7.	Detach the syringe and leave a meniscus of mixture on the hub of the balloon lumen.
8.	Prepare the inflation device in the standard manner and purge to remove all air from the syringe and tubing.

9. Attach the inflation device to the catheter directly, ensuring no bubbles remain at the connection.
10. Leave on ambient pressure (neutral position).
Note: Do not apply negative pressure on inflation device after balloon preparation and prior to delivering the stent.

13.5 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 three 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 Endeavor stent delivery system into the coronary artery. Carefully advance the Endeavor stent delivery 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 – 5.12 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 – 5.12 Stent/System Removal Precautions** for specific stent delivery system removal instructions.

13.6 Deployment Procedure

Step	Action
1.	Prior to stent expansion, utilize high-resolution fluoroscopy to verify the stent has not been damaged or shifted during positioning.
2.	Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3.	Do not exceed Rated Burst Pressure. The Endeavor stent should not be expanded to a diameter beyond 0.5 mm of its nominal expansion.
4.	Fluoroscopic visualization during stent expansion should be used in order 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.

13.7 Removal Procedure

Step	Action
1.	Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 15 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 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. ***Note***: Observation of the patient and angiographic evaluation of the stent site should be performed periodically within the first 30 minutes after stent placement. If stent placement is associated with the onset of thrombus or suspected thrombus in the region of the stented segment, an intracoronary infusion of a thrombolytic agent is recommended.

13.8 *In Vitro* Information

Table 13-1: Inflation Pressure Recommendations

Pressure				Stent Nominal Inner Diameter (mm)		
atm	kPa	bar		2.5	3.0	3.5
6	608	6.08		2.3	2.9	3.3
7	709	7.09		2.3	2.9	3.4
8	811	8.11		2.4	3.0	3.4
9	912	9.12	Nominal	2.4	3.0	3.5
10	1013	10.13		2.5	3.1	3.5
11	1115	11.15		2.5	3.1	3.6
12	1216	12.16		2.5	3.2	3.6
13	1317	13.17		2.6	3.2	3.6
14	1419	14.19		2.6	3.2	3.7
15	1520	15.20		2.6	3.3	3.7
16	1621	16.21	RBP*	2.6	3.3	3.8
17	1723	17.23		2.7	3.3	3.8
18	1824	18.24		2.7	3.4	3.8

*Do not exceed the rated burst pressure (RBP)

13.9 Further Dilatation of Stented Segment

The stent delivery balloon may not be used for post-dilatation. Post-dilatation may be performed 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:

Nominal Stent Diameter	Dilatation Limits
2.50 mm	3.00 mm
3.00 mm	3.50 mm
3.50 mm	4.00 mm

All efforts should be taken to assure that the stent is not underdilated. 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 the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

14 Reuse Precaution Statement

For single use only. Do not resterilize or reuse.

Disclaimer of Warranty and Limitation of Remedy

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Manufacturer:

Medtronic, Inc.
710 Medtronic Pkwy NE,
Minneapolis, MN 55432 USA
www.medtronic.com

Manufactured In:

Medtronic Ireland
Parkmore Business Park West
Galway, IRELAND

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For Technical Information:

Medtronic, Inc.
3576 Unocal Place
Santa Rosa, CA 95403 USA

Product Services:

Tel: (888) 283-7868
Fax: (800) 838-3103

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This educational booklet is provided to all patients for whom the stent procedure is being considered as general information about treatment options for coronary artery disease.

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

Medtronic Vascular
3576 Unocal Place
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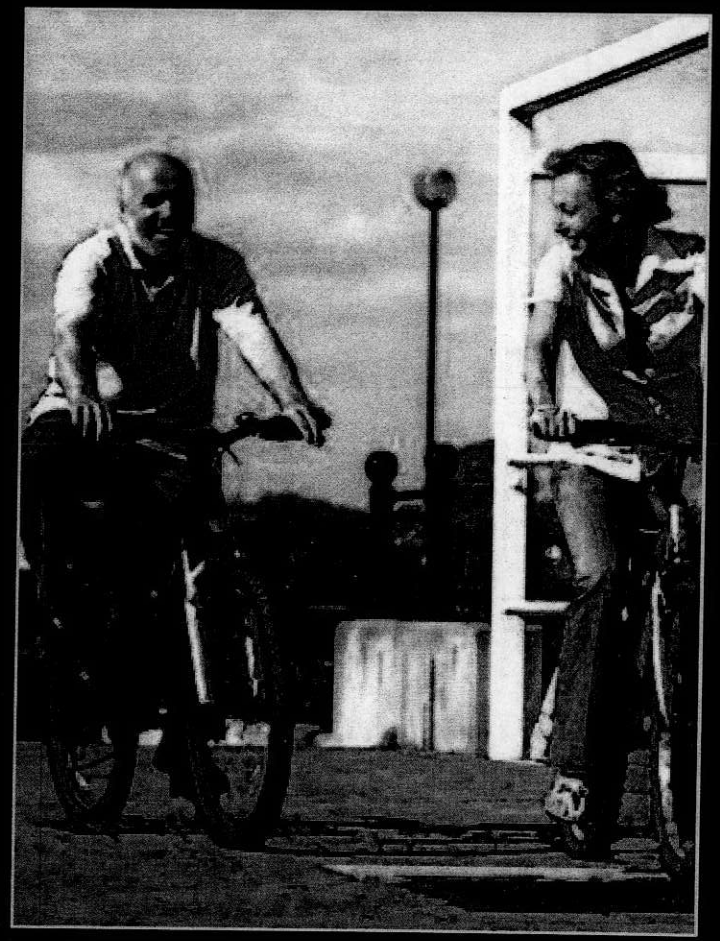
Understanding Your Stent Procedure



ENDEAVOR®

Zotarolimus-Eluting
Coronary Stent System

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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.

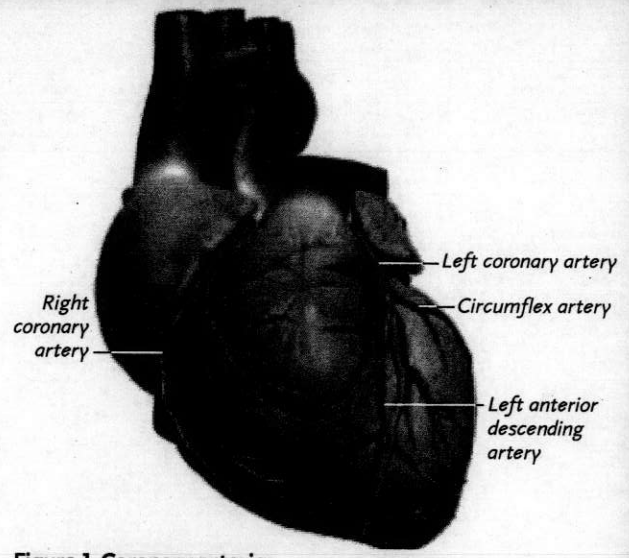


Figure 1. Coronary arteries

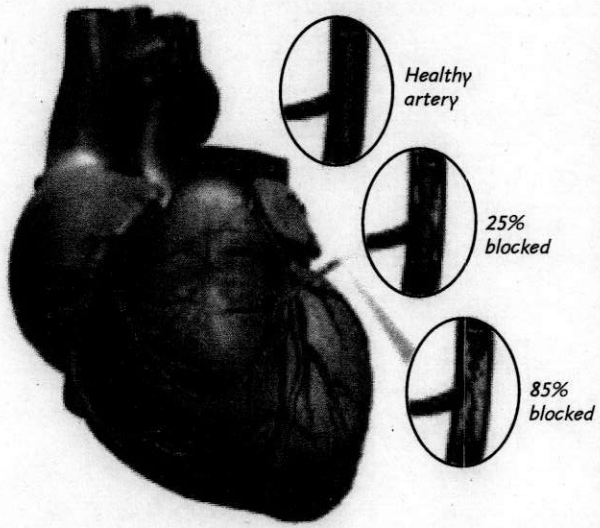


Figure 2. Plaque deposits build up inside the coronary arteries, decreasing blood flow

Your Heart

Your heart is a muscle that pumps blood throughout your body. 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 1**). If these arteries become blocked or narrowed, treatment is usually required to restore blood flow and the vital supply of oxygen to the heart.

Coronary Artery Disease

Coronary artery disease occurs when a waxy substance called *plaque* builds up on the inside of your arteries, in a process known as *atherosclerosis*. These plaque deposits can cause a narrowing of the inside of the arteries, which decreases the supply of blood and oxygen (see **Figure 2**). When atherosclerosis occurs in the arteries that supply your heart, it is called coronary artery disease. When it occurs in the arteries that supply oxygen-rich blood to your arms and legs, it is called peripheral vascular disease.

The reduced blood flow to the heart can lead to chest pain or pressure (called *angina*) and may spread to the arms, shoulders, back and jaw. In some cases, it can cause a heart attack (*myocardial infarction* or *MI*), or even death.

TABLE 1. RISK FACTORS FOR CORONARY ARTERY DISEASE

> High blood pressure (also called hypertension)
> High levels of cholesterol and triglycerides in your blood
> Diabetes
> Obesity and overweight
> Gender (sex)
> Smoking
> Lack of physical activity
> Age over 65 years
> Family history of coronary artery disease

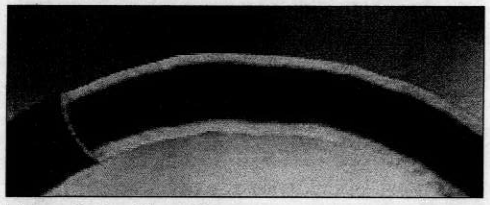


Figure 3. Healthy artery

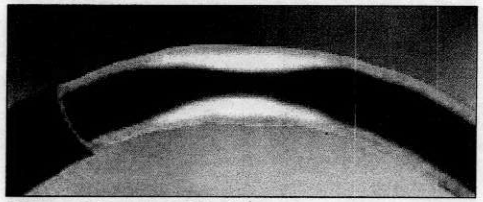


Figure 4. Artery with plaque

Risk Factors

Several factors can increase your risk of coronary artery disease (see **Table 1**). The more risk factors you have, the higher your risk.

Some proven risk factors are beyond your control, such as your age, sex and family history. Other risk factors can be managed or eliminated to lower your risk. These risk factors are smoking, diabetes, high blood pressure, high cholesterol, obesity and having 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 information on steps you can take to prevent heart disease, see Page 23.

Diagnosis

When making a diagnosis, your doctor will consider:
> Your current symptoms and previous medical history.
> Your family history.
> Your risk factors.

Before deciding on a treatment plan, your doctor may also recommend that you have a chest X-ray and/or blood tests. You may also have a test to measure how well your heart is functioning. A baseline *electrocardiogram* (ECG or EKG) records your heart's electrical activity while you sit quietly. An exercise ECG, or "stress test," shows how your heart responds to increasing physical activity. Both tests are designed to show if your heart is not working properly due to a lack of oxygen.

Coronary Angiogram

Your doctor also may perform a special X-ray test called a coronary *angiogram* (also called a *cardiac catheterization*). It will show the exact location and

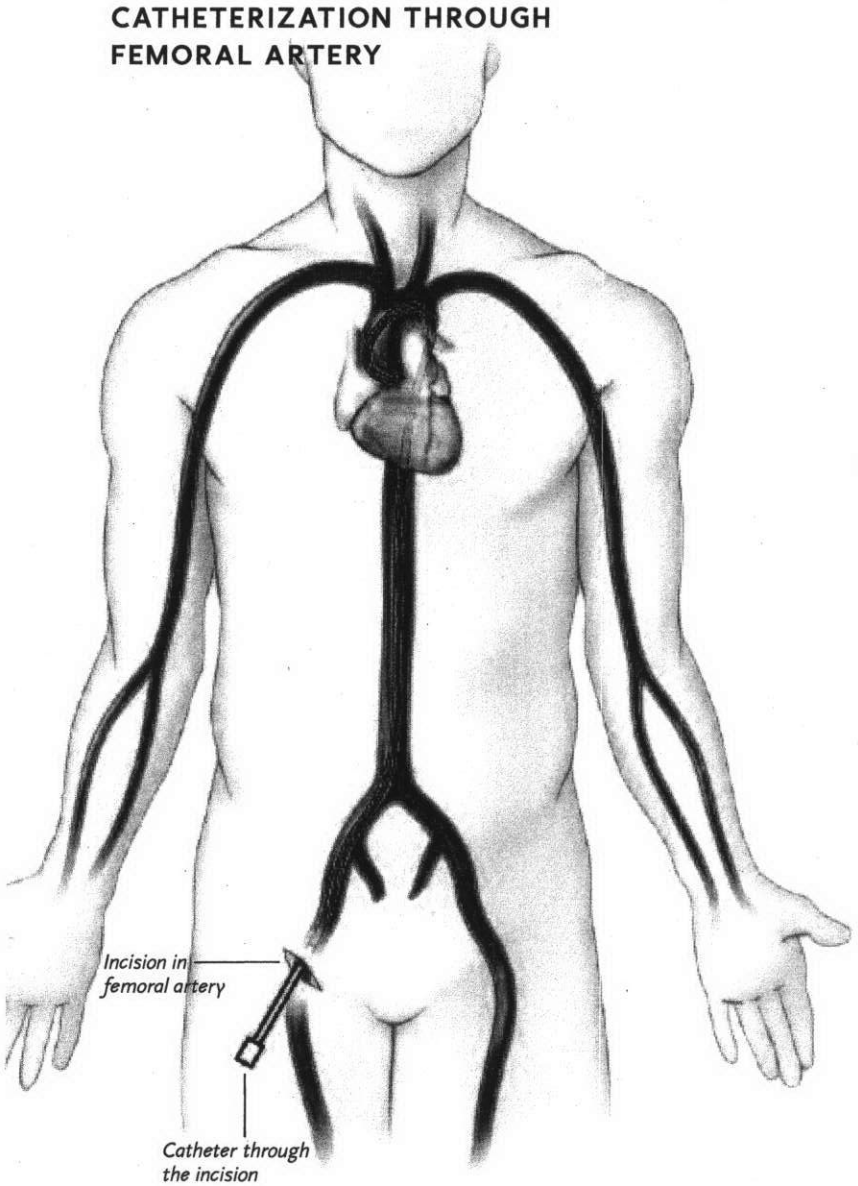


Figure 5. Heart catheterization through femoral artery

extent of your narrowed or blocked coronary arteries. This test, which usually takes 20 to 40 minutes, is performed in a cardiac catheterization laboratory ("cath lab"), a room designed especially for the procedure.

For the procedure, you will be given a mild sedative to help you relax. Small sticky patches, called electrodes, will be placed on your chest to monitor your heart rate and rhythm. Your doctor will insert a short, hollow tube into an artery in your arm or leg, after numbing the area with a local anesthetic (see **Figure 5**).Through this tube, the doctor can move small metal wires, called guidewires, and thin, flexible shafts, called catheters, to the arteries in your heart. A special dye will be injected through the catheter and into your bloodstream to allow your doctor to view your arteries on an X-ray monitor, much like a television screen.

Results of this angiogram can help your doctor decide which treatment option is best for you. It is normal to feel a warm but temporary "flush" when the dye is injected. Tell your doctor or nurse if you feel any pain or discomfort during the procedure.

Treatment Options for Coronary Artery Disease

Your doctor will recommend a treatment plan for you, depending on your symptoms, test results and medical history. The plan may include medications to relieve your chest pain and/or to expand the coronary arteries, increasing blood flow to your heart.

However, because medicine alone may not clear blocked arteries, you may need more treatment, including surgery, angioplasty and/or stenting.

BALLOON ANGIOPLASTY

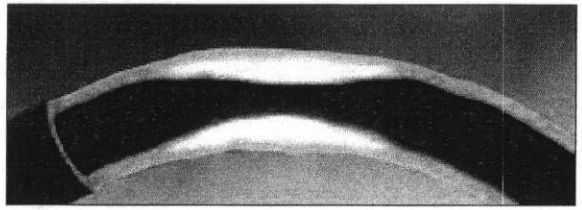


Figure 6a. Artery narrowed by plaque deposits

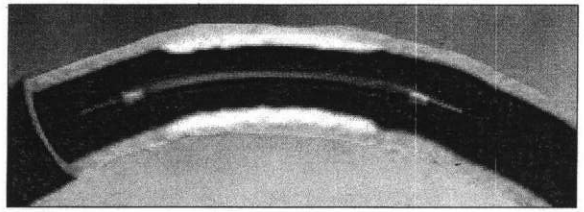


Figure 6b. Balloon is inflated to flatten plaque and reopen the artery

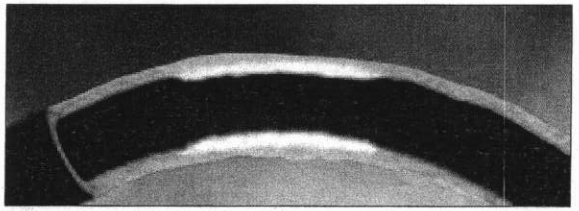


Figure 6c. Balloon is deflated and withdrawn, restoring blood flow

Surgery

Coronary artery bypass grafting is a common surgical procedure that removes a section of artery or vein from another part of your body. This vessel is then connected (grafted) to the coronary artery at the blockage site. This creates a new path for blood to flow around (bypass) the blocked artery and to your heart. Often, several blocked arteries are bypassed during the same operation. Most coronary bypass patients remain in the hospital for about a week, followed by a recovery period at home.

Balloon Angioplasty

Balloon angioplasty is performed in the catheterization laboratory—the same room where you may have had a coronary angiogram. Like with coronary angiograms, your doctor will inject a special dye through a catheter into your bloodstream, which allows your doctor to view your arteries on the X-ray monitor. A local anesthetic will be used to numb the puncture site, and you may be given a sedative to help you relax. A catheter with a small balloon on its tip is inserted through an artery in your groin or your forearm 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. This increases blood flow through the artery (see **Figures 6a–c**).

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.

STENTING PROCEDURE

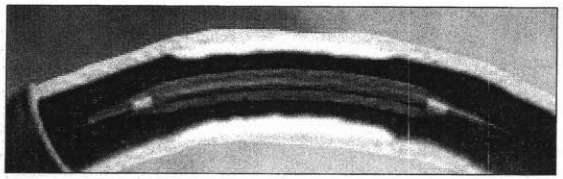


Figure 7a. The unexpanded stent is delivered to the treatment area via a special catheter

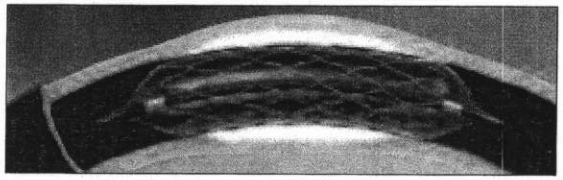


Figure 7b. The balloon is inflated to expand the stent

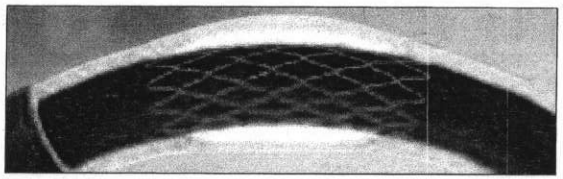


Figure 7c. The balloon is deflated and withdrawn from the body, leaving the stent to support the artery and maintain good blood flow

Stenting

Your doctor also may recommend placing a coronary stent in the narrowed part of your artery during the balloon angioplasty procedure (see **Figures 7a–c**). A stent is a tiny, expandable, mesh-like tube made of metal that acts as a scaffold inside the artery and helps keep the artery open after balloon angioplasty.

Implanting the stent does not require open surgery. Instead, your doctor will make a small incision in your groin or forearm and insert a catheter into the artery, similar to the balloon angioplasty procedure. A specially designed balloon catheter is used to 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 fully expanded, the balloon is deflated and removed from your body. The stent is designed to stay in your artery permanently.

Stenting is less invasive than traditional surgery. It involves a shorter hospital stay—usually one to three days—and faster recovery than surgery. However, a condition called *restenosis* occurs in some patients who receive uncoated metal stents. This is the renarrowing of the artery where the stent was placed, due to the overgrowth of normal tissue within the stent during the healing process.

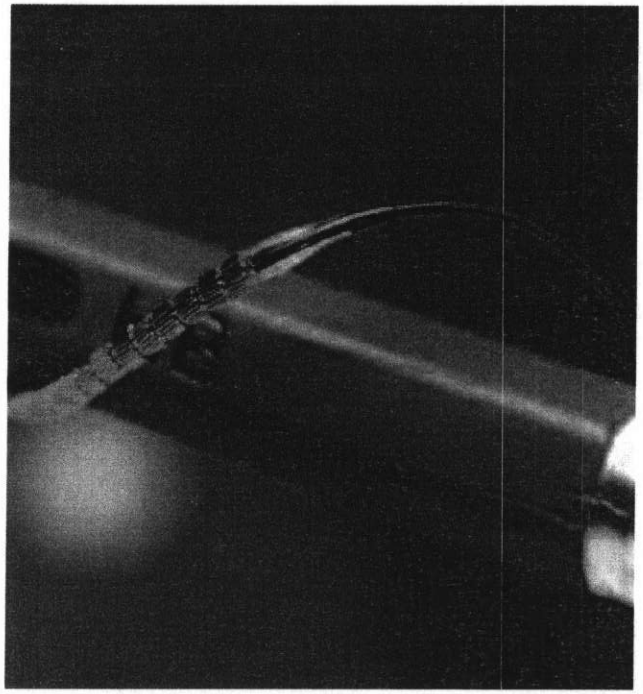


Figure 8. A stent is a tiny, expandable mesh-like tube that helps support the artery, increasing blood flow

Drug-Eluting Stents

To help prevent restenosis, *"drug-eluting" stents* have been developed. These stents provide the same structural support as uncoated stents, but they also have a drug applied to them. The drug is released over time, helping to prevent restenosis by limiting the overgrowth of normal tissue within the stent.

Medtronic Endeavor Zotarolimus-Eluting Coronary Stent

Medtronic's Endeavor zotarolimus-eluting coronary stent has a drug (called zotarolimus) contained within a biocompatible polymer that coats the surface of the stent. The Endeavor stent provides mechanical support in the artery, and the zotarolimus drug is released into the artery wall around the stent. The zotarolimus drug is designed to limit the growth of scar tissue, which results in restenosis.

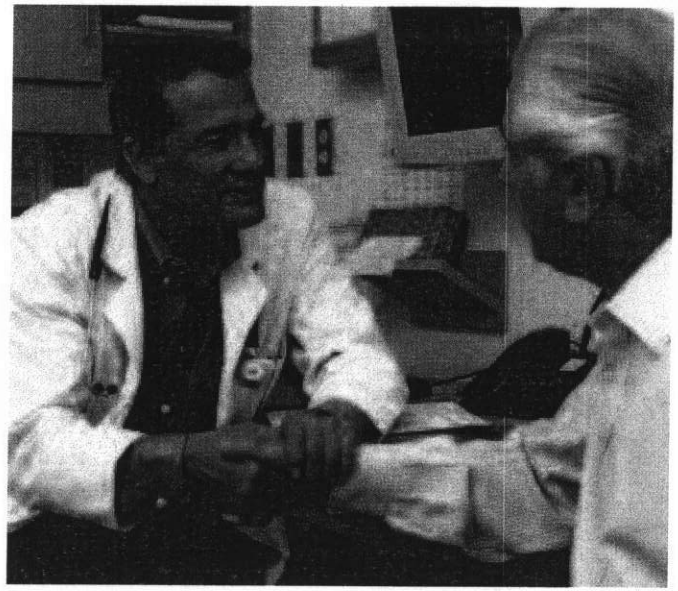
Contraindications

You should not receive the Endeavor stent if you have a known allergy to:

> Drugs such as zotarolimus, rapamycin, tacrolimus, everolimus or any other analogue or derivative.
> The cobalt-based alloy (cobalt, nickel, chromium and molybdenum).
> The polymer (phosphorylcholine) or its individual components (including but not limited to polymethacrylates).

Coronary artery stenting is contraindicated for use in:

> Patients who cannot receive recommended antiplatelet and/or anticoagulation therapy.
> 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.



Before You Receive an Endeavor Stent

Your doctor might tell you to take aspirin and other medications before your stent procedure. It is important to tell your doctor if you cannot take aspirin or have a history of bleeding problems. Also, be sure to tell your doctor if you are taking any other medications, have drug allergies, or are allergic to any metals or plastics.

Potential Adverse Events Associated with the Endeavor Stent

The risk of using the Endeavor stent are similar to those that are associated with standard stent procedures. If the stent clots, you may need another angioplasty. 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 in the first six months. This may require more therapy, 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 after stent implants are similar to the risks that may occur during the stent implant. These may be serious enough to require surgery or cause death.

Like other permanently placed medical devices, the Endeavor stent is composed of an alloy containing the following metals: cobalt, chromium, molybdenum and nickel.

Other risks from these devices are the same as treatment procedures for a narrowed heart artery. Some problems with standard balloon angioplasty and stenting include but are not limited to:

Most Likely Risks

> Bruise or bleeding at the catheter insertion site in the groin 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 heart artery.

Rare Risks

> Tearing, puncture or rupture of the heart artery.
> Air, pieces of devices or fragments of clots blocking the coronary artery.
> Complete blockage of the heart artery, which may require a repeat procedure to reopen the heart artery.
> Bleeding around the heart.
> Heart attack.
> Damage to the stent or injury to the heart artery requiring emergency heart surgery.
> Bleeding requiring transfusion or surgery.
> Allergic reaction (may include X-ray dye, cobalt, chromium, nickel, zotarolimus [an analog of rapamycin] and phosphorylcholine [the stent's base coating]).
> Infection.
> 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.
> Death.

The actual risks of the zotarolimus drug are not yet fully known. Your exposure to zotarolimus is directly related to the total amount of stent length implanted. The risks that might occur include but may not be 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 Endeavor polymer coating is directly related to the number of implanted stents. Use of more than one Endeavor stent has not been adequately evaluated. Use of more than two Endeavor stents will result in your exposure to a larger amount of zotarolimus and polymer coating than experienced in the ENDEAVOR clinical studies.

There is no clinical experience in the performance of the Endeavor stent before or after the use of brachytherapy.

The safety and effectiveness of the Endeavor stent was compared to the Driver stent (an uncoated stent) in the ENDEAVOR II study that included 1197 patients. All patients were followed for three years. The study results showed that patients who received an Endeavor stent had a significantly lower incidence of repeat procedures when compared to the uncoated Driver stent. Additionally, patients treated with the Endeavor stent had an in-lesion restenosis rate of 9.5% while patients treated with the Driver stent had an in-lesion restenosis rate of 33.2%. The combined occurrence of death, heart attacks, bypass surgery and repeat

angioplasty was 7.3% for Endeavor stent patients and 14.4% for Driver patients after 9 months, and 12.0% and 20.7% after 36 months for the Endeavor and Driver stents respectively.

The safety and effectiveness of the Endeavor stent was compared to the Cypher drug-eluting stent in the ENDEAVOR III study that included 436 patients. All patients were followed for two years. The Endeavor stent had an in-lesion restenosis rate of 9.7% while patients treated with the Cypher stent had an in-lesion restenosis rate of 2.1%. The combined occurrence of death, heart attacks, bypass surgery and repeat angioplasty was 7.5% for Endeavor stent patients and 7.1% for Cypher stent patients after 9 months, and 9.3% and 11.6% after 24 months for the Endeavor and Cypher stents respectively.

The safety and effectiveness of the Endeavor stent was compared to the Taxus drug-eluting stent in the ENDEAVOR IV study that included 1548 patients. All patients were followed for 9 months. The Endeavor stent had an in-lesion restenosis rate of 13.3% while patients treated with the Taxus stent had an in-lesion restenosis rate of 6.7%. The combined occurrence of death, heart attacks, bypass surgery and repeat angioplasty was 5.7% for Endeavor stent patients and 5.7% for Taxus stent patients after 9 months.

For patients treated with the Endeavor stent in indications not studied in these clinical trials, clinical results may vary.

Long-term risks and benefits (*i.e.*, beyond two years) associated with the Endeavor stent are currently unknown.

What to Expect After Your Stent Procedure

Immediately After Procedure

You will be asked to lie flat for four to six hours following the procedure and to not bend your leg or arm, depending on which area your doctor used to insert the catheters. Pressure will also be placed on the area.

A vascular closure device may be used to seal the puncture site in your groin or arm. You will be allowed to get up and walk around sooner if this type of device is used. Your hospital stay may range from one to three days.

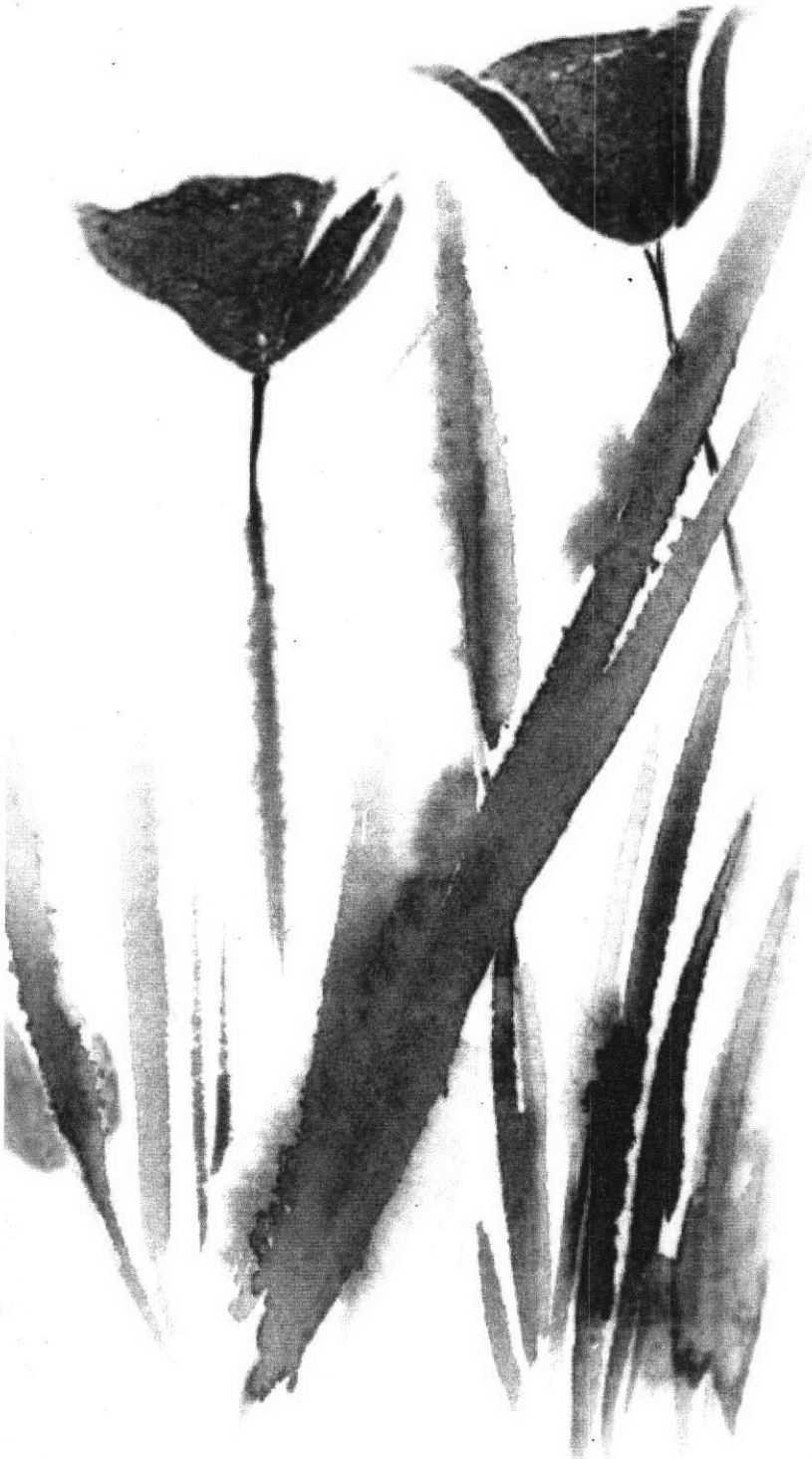
Medications will be prescribed for you before and after stent placement. Aspirin and antiplatelet medications (also called platelet inhibitors) are the most commonly prescribed. They help prevent a blood clot (thrombus) from forming and adhering to the surface of the stent. You may need to have periodic blood tests while taking these medications. Your doctor or nurse will give you instructions about your medications before you leave the hospital.

Caution: If you have any chest pain, discomfort or bleeding from your puncture site, call your doctor immediately. If your doctor is unavailable, call for an ambulance to take you to the nearest hospital emergency room.

Take All Medications as Instructed

After you leave the hospital, your cardiologist may instruct you to take a small daily dose of aspirin indefinitely. Your doctor will tell you how long you should continue taking the antiplatelet drugs. It is very important that you take these medications exactly as your doctor instructs you:

> Follow your medication schedule exactly to avoid possible complications after you receive your stent. Do not miss any doses.



- Call your doctor if you cannot keep 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:** Notify your cardiologist or family doctor if you are scheduled to see the dentist while on antiplatelet medication. Your doctor may prescribe antibiotics to avoid the potential of an infection. You should review with your doctor any recommendations from your dentist to stop your prescribed medications.

Follow-Up Care

You will be discharged to the care of your cardiologist or family doctor. You should be able to return to your normal activities soon.

Caution: Notify your doctor immediately if you experience chest pain (angina) or notice any changes such as more severe or frequent chest discomfort, especially in the first month after a procedure. These symptoms may indicate a renarrowing in your coronary arteries.

Your doctor will ask you to return for follow-up visits. The first visit is usually two to four weeks after your stent is implanted, with follow-up visits every six months for the first year. Be sure to keep all appointments for follow-up care, including blood tests.

Keep Your ID Card Handy

Caution: Show your identification card if you report to an emergency room. This card identifies you as a patient who has had a stent implanted.

If you require a magnetic resonance imaging (MRI) scan, tell your doctor or MRI technician that you have a stent implant.

Preventing Coronary Artery Disease

Coronary artery disease can be treated effectively, but it has no cure. You can help to prevent your coronary artery disease from progressing by carefully following your doctor's advice. Your doctor may prescribe medications to help control your blood pressure, diabetes and/or high cholesterol. Your doctor may also recommend some lifestyle changes. Among the healthy choices you can make:

Stop smoking. If you smoke, quitting is the single most important thing you can do to lower your risk of coronary artery disease. Chemicals in cigarette smoke may make it easier for plaque to build up on your artery walls. And smoking increases your heart rate and blood pressure, raising your risk of heart attack and stroke. If you're ready to quit, ask your doctor for advice—he or she can recommend smoking cessation aids to help you quit.

Increase your activity. A sedentary lifestyle increases your risk. Your doctor can recommend an activity program tailored for your situation. Regular exercise can help you lower your blood pressure and blood cholesterol and reach a healthy weight. It can also help you manage the daily stresses of modern life more easily.

Choose a healthy diet. A diet low in saturated fats and cholesterol and rich in lean protein, fresh fruits, vegetables and whole grains can help you achieve a healthy weight and control your blood pressure and cholesterol levels.

Manage your stress. Stress is an inescapable aspect of modern day living, but you can help lessen its negative health effects by practicing the "relaxation response." Research has shown that relaxation techniques can improve your ability to cope with stressful events while decreasing your heart rate, blood pressure and stress hormone levels.

Frequently Asked Questions

How long will the stent stay in my body?
Stents are designed to stay in your body permanently.

What are the restrictions or cautions?
If you require magnetic resonance imaging (MRI), tell your doctor or MRI technician that you have an implanted stent.

When can I resume my regular activities?
Your doctor will advise you. Many patients can return to work and follow their normal routine about a week after their stent procedure.

Will my stent set off the metal detector at airport security checkpoints?
No, your stent implant will not trigger alarms at security checkpoints.

Will I be able to feel the stent inside me?
No, you will not be able to feel the stent once it has been implanted in your artery.

Could I have recurring symptoms?
Yes, it is possible that you will experience symptoms again, either due to a new blockage in the treated region or another blockage in your arteries. Your doctor will monitor your progress.

How can I help prevent a recurrence of symptoms?
While there is no sure way to prevent a recurrence of symptoms, you can reduce the risk through exercise, not smoking and eating a healthy diet. Your doctor can advise you about lifestyle changes.

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.

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 aspirin and Plavix® (also known as clopidogrel).

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.

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 room designed especially for the catheterization procedure.

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

Coronary artery bypass graft. Common surgical procedure that grafts an artery from your chest or a vein from your leg to create an alternate route around a narrowed or blocked coronary artery.

Drug-eluting stent (DES). Used to refer to stents that carry drugs that help keep arteries from renarrowing 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.

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

Plaque. Waxy substance consisting of fats and cholesterol that can build up on the inner lining of your arteries.

Restenosis. Renarrowing of an artery at the site of angioplasty and/or a stent implant, due to the over-growth of normal tissue.

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