Premarket Approval (PMA) Package for Dockets Management Branch

PMA Number P950020
Docket # 00M-1298

Interventional Technologies, Inc.
Cutting Balloon

Includes:

Approval Order
Summary of Safety and Effectiveness Data (SSED)
Labeling

00M-1298

AAVI

7523 '00 MAY 24 P1:38

APPROVAL ORDER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

APR 18 2000

Paul Mason, Ph.D.
Director, Regulatory Affairs/Compliance Standards
Interventional Technologies, Inc.
3574 Ruffin Road
San Diego, CA 92123

Re: P950020
Cutting Balloon™
Filed: November 13, 1995
Amended: December 4 and 19, 1995, February 6, April 11, and May 6, 1996, July 15, August 3 and 11, October 22, and November 18, 1999, February 15, and April 12, 2000

Dear Dr. Mason:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Cutting Balloon. This device is indicated for the dilatation of stenoses in coronary arteries for the purpose of improving myocardial perfusion in those circumstances where a high pressure balloon resistant lesion is encountered. In addition, the target lesion should possess the following characteristics: discrete (≤15 mm in length) or tubular (10 to 20 mm in length) with a reference vessel diameter ranging from 2.0 mm to 4.0 mm; readily accessible to the device; light to moderate tortuosity of proximal vessel segment, non-angulated lesion segment (<45°), smooth angiographic contour; and absence of angiographically-visible thrombus and/or calcification. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 18 months. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Judy Danielson at (301) 443-8243.

Sincerely yours,

Kimber C. Richter

Kimber C. Richter, M.D.
Deputy Director for Clinical
and Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1) May have caused or contributed to a death or serious injury; or

(2) Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

SUMMARY OF SAFETY AND EFFECTIVENESS

1. GENERAL INFORMATION

Classification (Generic) Name:	Percutaneous Transluminal Coronary Angioplasty Catheter
Device Trade Name:	Cutting Balloon™
Applicant's Name and Address:	Interventional Technologies, Inc. 3574 Ruffin Road San Diego, CA 92123
PMA Number:	P950020
Date of Panel Recommendation:	Refer to Section 12
Date of Notice of Approval to Applicant:	APR 18 2000

2. INDICATIONS FOR USE

The Cutting Balloon is indicated for dilatation of stenoses in coronary arteries for the purpose of improving myocardial perfusion in those circumstances where a high pressure balloon resistant lesion is encountered. In addition, the target lesion should possess the following characteristics: discrete (≤15 mm in length) or tubular (10 to 20 mm in length) with a reference vessel diameter ranging from 2.0 mm to 4.0 mm; readily accessible to the device; light to moderate tortuosity of proximal vessel segment, non-angulated lesion segment (<45°), smooth angiographic contour; and absence of angiographically-visible thrombus and/or calcification.

3. DEVICE DESCRIPTION

The Cutting Balloon consists of a non-compliant balloon with 3 or 4 atherotomes™ (microsurgical blades) mounted longitudinally on its outer surface. When the Cutting Balloon is inflated, the atherotomes score the plaque, creating initiation sites for crack propagation. This process, referred to as atherotomy®, allows dilatation of the target lesion with less force.

The Cutting Balloon catheter shaft consists of two lumens. The outer lumen is used to inflate and deflate the balloon. The inner lumen permits the passage of a PTCA guidewire to aid placement of the Cutting Balloon. At the proximal end of the catheter is a Y-connector with standard luer fittings.

4 CONTRAINDICATIONS

The Cutting Balloon is contraindicated for use in:

Coronary artery spasm in the absence of a significant stenosis.

5. WARNINGS AND PRECAUTIONS

See Warnings and Precautions in the final labeling (Instructions for Use).

6. ADVERSE EVENTS

6.1 Observed Adverse Events

The Adverse Events reported in this section were those observed in two clinical investigations: the Resistant Lesion Registry (RLR), which demonstrated the ability of the Cutting Balloon to dilate lesions in a series of patients whose lesions could not be dilated with conventional balloon angioplasty; and the Global Randomized Trial (GRT), a multi-centered, randomized trial designed to compare the Cutting Balloon with conventional angioplasty. Twenty-nine patients were entered into the RLR and a total of 1245 patients were randomized in the GRT; 622 to the Cutting Balloon arm and 623 to the PTCA arm. Seven patients (5 in the Cutting Balloon arm and 2 in the PTCA arm) were deregistered after randomization but before receiving the assigned treatment. Therefore, there were 1238 valuable patients in the GRT.

In the RLR, dissection was the only in-lab complication recorded. Dissections occurred 14 times: six times prior to Cutting Balloon treatment; two times after Cutting Balloon treatment; and six times as part of the post-Cutting Balloon adjunctive treatment.

One patient death from a cardiac arrest and acute pulmonary edema occurred in the RLR 24-48 hours post-procedure. This patient was treated for a mid-RCA lesion with a series of four inflations with a PTCA balloon catheter, followed by a single inflation with the Cutting Balloon. A dissection was noted following use of the Cutting Balloon. Adjunctive treatment included two inflations with a second PTCA balloon catheter followed by placement of a stent.

The major adverse events occurring in the GRT are listed below (Table 1).

Table 1. Global Randomized Trial (GRT) Major adverse events occurring within 270 days (1238 patients)

Adverse Event	*Cutting Balloon**	*Conventional Balloon**	*Difference [95% CI†]*
MACE‡	13.6% (84/617)	15.1% (94/621)	-1.5% [-5.4%, 2.4%]
Death	1.3% (8/617)	0.3% (2/621)	1.0% [0.0%, 2.0%]
MI	4.7% (29/617)	2.4% (18/621)	1.8% [-0.3%, 3.9%]
Q Wave MI	1.5% (9/617)	1.1% (7/621)	0.3% [-0.9%, 1.6%]
Non-Q Wave MI	3.2% (20/617)	1.3% (11/621)	1.5% [-0.3%, 3.2%]
Emergent CABG	1.0% (6/617)	1.0% (6/621)	0% [-2.3%, 1.7%]
TLR§	11.7% (72/617)	14.8% (92/621)	-3.1% [-6.9%, 0.6%]
CABG (per pt.)	1.5% (9/617)	2.1% (13/621)	-0.6% [-2.1%, 0.8%]
PTCA (per pt.)	10.5% (65/617)	12.7% (79/621)	-2.2% [-5.8%, 1.4%]
Subacute Closure	1.3% (8/617)	1.6% (10/621)	-0.3% [-1.5%, 3.0%]
Bleeding Complications	0.3% (2/617)	0.0% (0/621)	0.3% [-1.9%, 0.7%]
Vascular Complications¶	0.3% (2/617)	0.2% (1/621)	0.1% [-1.9%, 1.0%]
Clinical Perforations	0.8% (5/617)	0.0% (0/621)	0.8% [-0.4%, 2.3%]

* - Numbers are % (counts/sample size).

† - Difference = $S_{CB} - S_{PTCA}$ $SE_{Diff} = sqrt[(SE_{CB}^2 + SE_{PTCA}^2]$ $CI = Diff \pm 1.96 * SE_{Diff}$

‡ - Major Adverse Cardiac Events (MACE): Death, Q Wave MI, emergent CABG, target lesion CABG or TL-PTCA.

§ - Target lesion revascularization (TLR) at 9 months: any "clinically-driven" PTCA (TL-PTCA) or bypass surgery (TL-CABG) performed on the target lesion after documentation of recurrent angina and/or evidence of myocardial ischemia by stress testing.

¶ - Vascular complications: Any vascular complication requiring surgical repair.

There were eight deaths among the patients randomized to the Cutting Balloon arm. Two deaths occurring during the procedure involved perforations. In the first case, the perforation was associated with contrast extravasation and a Grade F dissection which was treated with balloon angioplasty and one stent. QCA reported TIMI 3 flow with a 35% residual stenosis and persistent contrast extravasation at the end of the procedure. Tamponade developed and the patient died during surgery. An intramyocardial hematoma was identified. In the second case, the coronary artery ruptured at the Cutting Balloon site and the patient developed ventricular fibrillation. The patient was resuscitated and

treated emergently for tamponade, but expired following CABG. In both of these cases, the Cutting Balloon was oversized. The balloon:artery ratio, as determined by QCA, was 1.25:1 and 1.8:1, respectively.

A perforation also occurred in the death of another patient who was randomized to the Cutting Balloon arm, but treated with a PTCA balloon because of a failure to cross the lesion with the Cutting Balloon. This patient died 105 days post-procedure due to complications of a CABG performed at that time.

One patient died within an hour of the procedure from a presumed re-occlusion.

A fifth patient died at 130 days post-procedure from a reported heart attack. Two deaths occurred following exacerbation of a pre-existing chronic obstructive pulmonary disease and respiratory failure (20 days), and emergency surgery for an abdominal aortic aneurysm (50 days). The remaining death was reported as the result of respiratory failure caused by chronic obstructive pulmonary disease.

Perforation was observed in five cases, all in the Cutting Balloon arm. As described above, in two of these cases the patient died acutely. Perforations were treated with PTCA, a stent or both.

6.2 Potential Adverse Events

Potential adverse events include, but are not limited to, the following:

Death
Acute myocardial infarction
Total occlusion of the coronary artery or bypass graft
Coronary vessel dissection, perforation, rupture, or injury
Aneurysm
Restenosis of the dilated vessel
Unstable angina
Embolism
Arrhythmias, including ventricular fibrillation
Hypo/hypertension
Coronary artery spasm
Hemorrhage or hematoma
Arteriovenous fistula
Drug reactions, allergic reactions to contrast medium
Infection.

6.3 Observed Device Malfunctions

There were no cutting Balloon malfunctions in the RLR.

A total of 15 Cutting Balloon malfunctions were recorded in the GRT. Two devices failed to inflate. Thirteen cases of balloon leak or rupture were reported: 9 with the first inflation and 4 with the second inflation.

7. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative treatments for patients with high pressure balloon resistant lesions are conventional balloon angioplasty, stents, atherectomy devices or medical therapy.

8. MARKETING HISTORY

The Cutting Balloon carries the CE Mark and is available for commercial distribution in Japan, Canada, Australia and New Zealand, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, the Netherlands, Norway, Portugal, Russia, Spain, Sweden, Switzerland, Turkey and the United Kingdom. The Cutting Balloon has never been withdrawn from any market for reasons related to the safety and effectiveness of the device.

9. SUMMARY OF PRECLINICAL STUDIES

9.1 Biocompatibility Testing

The Cutting Balloon was tested for biocompatibility in accordance with ISO 10993-1 using Good Laboratory Practices (GLP). The following tests were conducted: USP systemic toxicity, intracutaneous reactivity, cytotoxicity, Guniea Pig sensitization, hemolysis, and C3a complement activation. The results of all biocompatibility testing were acceptable.

9.2 Bench Testing

Comprehensive bench testing of the physical properties of sterilized devices was conducted as recommended in the "FDA Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: PTCA Catheters, Atherectomy Catheters, Lasers, Intravascular Stents."

Balloon minimum burst strength.-- A total of 20 Cutting Balloons of various diameters and lengths were tested for burst strength. Statistical analysis shows that, with 95% confidence, at least 99.9% of the balloons have a burst strength above the labeled recommended rated burst pressure (RBP) of 10 atmospheres (Table 2).

Table 2. Balloon Minimum Burst Strength

$\bar{x} \pm s$*	$\bar{x} - Ks$ †	$\bar{x} - Ks > RBP?$†
19.5 ± 1.2 atm	14.2 atm	Yes.

* Mean burst pressure ±standard deviation, based on a sample of 20.

† Statistical tolerance limit test for RBP of 10 atm.

Balloon Compliance (distensibility).-- A total of 90 Cutting Balloons (five devices of each diameter and length) were tested for compliance and distensibility. Over the pressure range of 2-8 atmospheres, the diameters for all balloon sizes were consistent with the labeled diameter (Figures 1 and 2). Testing was repeated with 10 balloons (5 each of 2.25×10 mm and 4.00×10 mm) with similar results.

Balloon Inflation/Deflation Performance.-- A total of 36 Cutting Balloons (two devices of each diameter and length) were tested. Average times required to fully inflate and deflate the Cutting Balloon with radiopaque contrast media were found to be suitable for human use. Inflation times ranged from 0.5 to 2.1 seconds; deflation times ranged from 3.2 to 16.5 seconds.

Crossing Profile.-- To determine the crossing profile of the Cutting Balloon, 5 samples of each balloon diameter were measured. The crossing profile of the Cutting Balloon averaged 0.041 inches for the 2.0 mm to 3.25 balloons, 0.044 inches for the 3.5 mm to 3.75 mm balloons and 0.046 inches for the 4.0 mm balloon.

Balloon Fatigue (Repeated Balloon Inflation).-- A total of 30 Cutting Balloons of various diameters and lengths were tested. All Cutting Balloons passed the test of 40 consecutive inflation/deflation cycles to 10 atmospheres without failure.

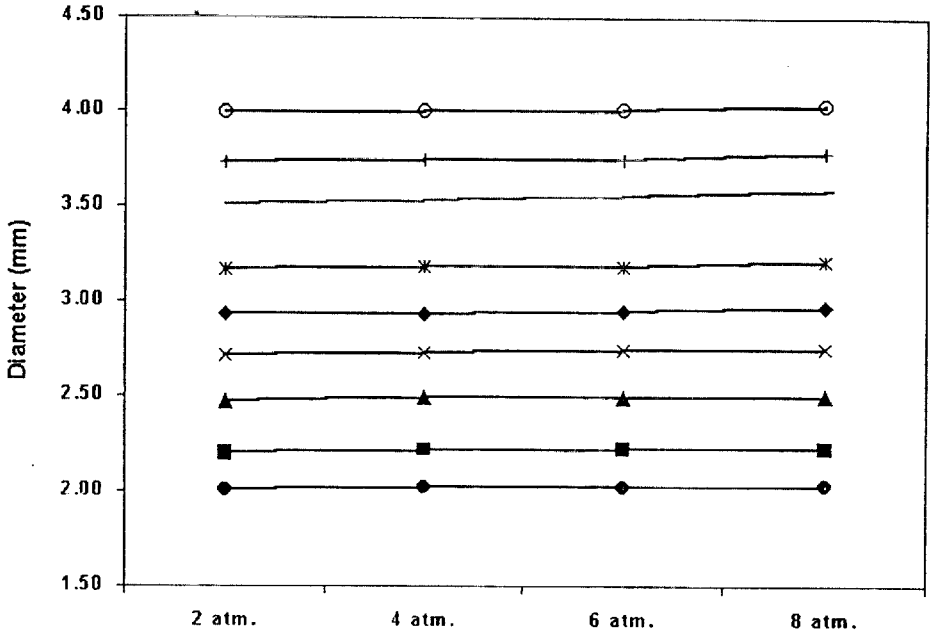


Figure 1. Balloon compliance (distensibility), 10 mm models with nominal inflated diameters of 2.00 to 4.00 mm, in 0.25 mm increments.

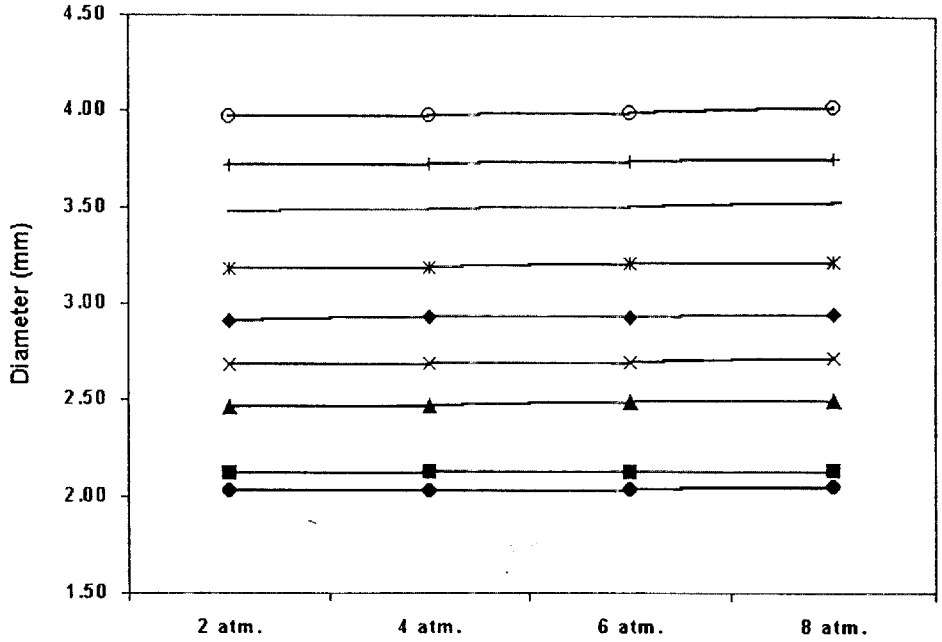


Figure 2. Balloon compliance (distensibility), 15 mm models with nominal inflated diameters of 2.00 to 4.00 mm, in 0.25 mm increments.

Bond Strength.-- A minimum of 15 Cutting Balloons of various diameter and length were tested to demonstrate the strength of the bonded joints. The results of all tensile testing determined that the bond strength was acceptable (Table 3). The blades were also pull-tested (Table 4). The force at failure and the failure mode were recorded. In the majority of cases (84% of the 10 mm test samples, 91% of the 15 mm test samples) the failure involved blade fracture at the clamping point. In these cases, the bond strength exceeded the structural strength of the blade. In the remaining cases, the pad separated from the balloon surface. The forces involved in this testing exceed the forces observed during clinical use.

Table 3. Bond Strength

Bond tested	$\bar{x} \pm sd^*$ ***(n)***
Balloon-to-catheter	2.70 ± 0.23 lb (15)
Catheter transition joint	3.14 ± 0.38 lb (15)
"Y" Body to Catheter	8.45 ± 0.59 lb (15)
"Y" body to luer	28.86 ± 2.38 lb (15)
Marker to Guidewire Tubing	1.03 ± 0.09 lb (20)
Wireport to Guidewire tubing	1.04 ± 0.09 lb (20)

* Mean force at failure ± standard deviation, sample size in parentheses.

Table 4. Blade Pull Strength

Nom. Infl. Diameter	$\bar{x}$ ±*sd** *10 mm*	$\bar{x}$ ± *sd** *15 mm*
2.00 mm	0.58 ± 0.08 lb	0.82 ± 0.18 lb
2.25 mm	0.70 ± 0.14 lb	0.76 ± 0.15 lb
2.50 mm	0.72 ± 0.17 lb	0.65 ± 0.19 lb
2.75 mm	0.47 ± 0.04 lb	0.75 ± 0.09 lb
3.00 mm	0.57 ± 0.16 lb	0.70 ± 0.16 lb
3.25 mm	0.45 ± 0.09 lb	0.72 ± 0.13 lb
3.50 mm	0.62 ± 0.09 lb	0.68 ± 0.18 lb
3.75 mm	0.55 ± 0.08 lb	0.68 ± 0.06 lb
4.00 mm	0.70 ± 0.18 lb	0.66 ± 0.15 lb

* Mean force at failure ± standard deviation, in lbs, based on a sample of 5.

9.3 Sterility and Shelf-life Qualification Studies

Sterilility Testing.-- The Cutting Balloon is sterilized via e-beam radiation. The product was validated for dosimetric release based on the Sterilization of Healthcare Products-- Requirements for Validation and Routine Control, Radiation Sterilization, ANSI/AAMI/ISO 11137-1994, Method 1.

Pyrogen Testing.-- Pyrogen testing, based on a USP-based *Limulus* amoebocyte lysate (LAL) pyrogen test procedure, occurs on a lot-by-lot basis prior to product release.

Shelf-life Testing.-- The Cutting Balloon has a shelf-life of 18 months, based on the comparison of sterilized devices (n = 20) to accelerated-aged (18 months, n = 20) and real time aged (19 months, n = 20) devices. The testing sequence subjected each device in each of the three groups to: microscopic examination for damage; verification of the continuity of the lumen; various measurements of dimensional conformance; burst testing; and pull testing of multiple bonds. All three groups met all acceptance criteria, demonstrating that device functionality is unaffected after 19 months of real-time aging.

9.4 Animal Testing

The Cutting Balloon was evaluated in the non-diseased arteries of pigs. The Cutting Balloon maintained its physical and structural integrity and could be inflated and deflated in succession with no measurable decrease in the device's performance. Cine angiography was conducted before, during and after the use of the Cutting Balloon and there was no evidence or indication of vessel damage or perforations at the site of balloon inflation. The Cutting Balloon could be maneuvered to each site of interest under fluoroscopic guidance, including marginal branches. The Cutting Balloon demonstrated no evidence of guide catheter backout caused by over-stiffness of the catheter shaft or excessive resistance to catheter movement within the guide catheter. No significant thrombosis was observed upon removal of the Cutting Balloon catheters.

9.5 Cadaver Study

The Cutting Balloon was tested in the atherosclerotic coronary arteries of eight human cadaver hearts. There was no evidence of blade breakage, detachment or other malfunction.

10. SUMMARY OF CLINICAL STUDIES

10.1 Resistant Lesion Registry (RLR)

The Resistant Lesion Registry (RLR) contains registry data on 30 lesions in 29 patients. All patients were enrolled at a single site between November 1996 and November 1999.

Study Endpoints: The primary endpoint was acute lesion success defined as a reduction in lumen narrowing of at least 20%. The secondary endpoint was procedural success. Procedural success was defined as lesion success, a final residual stenosis of ≤ 50% after all devices are used and no major adverse events (MACE, defined as death, CABG, or non-fatal MI).

Study Population: The RLR patients were selected for treatment on the basis of failed conventional angioplasty, defined as failure to reduce the lumen diameter narrowing by >20% and a final residual stenosis by ≥50% with PTCA balloon inflation pressures > 10 atmospheres. The demographics, risk factors and prior history of these patients are shown in Table 5.

Table 5. Demographics, Risk Factors and Prior Procedures, Resistant Lesion Registry (RLR).

Demographics:	% Male	69% (20/29)
	Age	65 ± 8.4
	Angina Class (CCS)	2.8 ± 0.8
Risk Factors:	Diabetes	14% (4/28)
	Smoking	39% (11/28)
	High Blood Pressure	29% (8/28)
	Hyperlipidemia	48% (13/27)
Prior Procedures:	Myocardial Infarction	33% (9/27)
	CABG	22% (6/27)
	PTCA	22% (6/27)

Methods: Patient data were obtained prospectively on 6 patients under a formal clinical protocol and retrospectively on 23 patients. For both prospective and retrospective patient groups, conventional balloon angioplasty was used as the initial treatment in all but two cases. In these two cases the Cutting Balloon was used as the first treatment for dilatation of an unprotected left main, a vessel known to be resistant to PTCA dilatation. Physician discretion was used to further decrease the residual stenosis with additional adjunctive devices following treatment with the Cutting Balloon.

Results: Of the 29 patients entered into the RLR, balloon resistant lesions were treated in 26 native vessels and 4 saphenous vein grafts (SVGs). Patients were treated with a sequence of devices including the Cutting Balloon. The Cutting Balloon was usually used as the second (14 cases) or third (10 cases) device in each treatment sequence. In three cases, the Cutting Balloon failed to cross the lesion on the initial attempt. Successful crossing was achieved with the second attempt (2 cases) following an additional crossing with a PTCA balloon. In the third case there were no further attempts to cross the lesion.

In most cases, the Cutting Balloon was inflated once (78%, 25/32); while the number of inflations with the PTCA catheter, prior to the Cutting Balloon, varied from 1 (31%, 14/45), 2 (36%, 16/45), 3 (18%, 8/45), to ≥4 (16%, 7/45) inflations. Inflation pressures ranged from 8-16 atmospheres for the Cutting Balloon and 4-25 atmospheres for the PTCA catheters. The average inflation pressure for the Cutting Balloon was significantly less than the average pressure used for the PTCA catheters [9.3±1.8 atmospheres (n=32) versus 15.4±3.6 atmospheres (n = 45), $p < 0.0001$].

The principal safety and efficacy results of the RLR are shown in Table 6. The primary and secondary endpoints, used for the prospectively enrolled patients, were also applied to the patients enrolled retrospectively.

Table 6. Prinicpal Effectiveness and Safety Results Resistant Lesion Registry (n=29 patients, 30 lesions)

Effectiveness Measures:	*Cutting Balloon, %, (freq.), [95% CI]*
Acute Lesion Success	78% (18/23) [56%, 93%]
Procedural Success	74% (17/23) [52%, 90%]
% Diameter Stenosis - Initial	73% (30) [70%, 77%]
Post-PTCA	51% (17) [44%, 59%]
Post-Cutting Balloon	36% (22) [28%, 45%]
Final	16% (30) [8%, 23%]
Safety Measures:	
MACE	3% (1/30) [1%, 10%]
Dissection, Prior to Cutting Balloon	20% (6/30) [8%, 39%]
Dissection, Cutting Balloon + Adjunctive Use	27% (8/30) [12%, 47%]

There were 20 (69%) males and 9 (31%) females treated with the Cutting Balloon in the RLR study. This gender distribution is similar to that of patients undergoing percutaneous balloon angioplasty procedures, as described in the medical literature. Although a higher percentage of females than males achieved acute lesion success [89% (8/9) versus 50% (10/20)] and procedural success [78% (7/9) versus 50% (10/20)], the small sample size does not allow a valid statistical comparison between these two subgroups. The only MACE event in the RLR study occurred in a female patient.

10.2 Global Randomized Trial (GRT)

The Global Randomized Trial (GRT) was a multi-centered, randomized trial designed to compare the Cutting Balloon with conventional angioplasty. Patient enrollment in the GRT occurred between June 1994, and November 1996, at 31 centers in the US, Canada, France, Belgium and the Netherlands. Of the 1245 patients enrolled, 622 were assigned to the Cutting Balloon arm and 623 to the PTCA arm. Seven patients (5 in the Cutting Balloon and 2 in the PTCA arm) were deregistered after randomization but before receiving the assigned treatment. Deregistration occurred for the following reasons: resolution of the stenosis between the prior angiogram and the index procedure (3 cases), the presence of calcification requiring atherectomy (1 case), and

failing to meet the inclusion criteria (3 cases).

Study Endpoints: The primary endpoint was angiographic restenosis at 6 months. Secondary endpoints included TLR and MACE at 9 months. A clinical events committee blinded to treatment assignment adjudicated all major clinical events.

Study Population: Patients, between the ages of 25 and 75 years, with atherosclerotic coronary artery disease were eligible for enrollment in the GRT if they were suitable candidates for coronary artery bypass graft surgery and the target lesions were *de novo* Type A or B lesions in native arteries without total obstructions or visible thrombus, and were accessible to the Cutting Balloon.

Methods: Patients were prospectively randomized to treatment with either the Cutting Balloon or PTCA. Access to the target lesion was gained through the femoral artery approach. The reference vessel diameter (located just proximal to the target lesion) was measured by quantitative angiography.

Selection of the Cutting Balloon with the appropriately sized balloon diameter was based on the reference vessel diameter. If necessary, tandem dilatations were allowed for lesion lengths ≤ 20 mm. Oversizing of the balloon was not recommended in the PTCA arm.

The protocol allowed for a single inflation of the Cutting Balloon up to 8 atmospheres for a maximum of 90 seconds. Subsequent dilatation(s) with a PTCA balloon were allowed only if the residual stenosis was > 40%. In the PTCA arm, the inflation times and pressures were left to the discretion of the investigator. Serial inflations with a single balloon, or subsequent inflations with increased diameter PTCA balloons were allowed to achieve a ≥20% reduction in stenosis and a ≤50% residual stenosis. Multiple violations of the procedural protocol were reported in the Cutting Balloon arm [33% (212/617) of the Cutting Balloon subjects were not treated per protocol].

Clinical follow-up was performed at 6 weeks, 6 months and 9 months. Baseline quantitative coronary angiography (QCA) was performed pre-procedure, following device use, and after the final treatment in all patients. Follow-up quantitative coronary angiography at 6 months was required in all patients. Anticoagulation included aspirin 325 mg/day throughout the study.

Results: The acute and 6 month angiographic and clinical results demonstrated that the Cutting Balloon was similar to PTCA with respect to Procedure Success (defined as achievement of <50% residual diameter stenosis and freedom from in-hospital major adverse cardiac events [MACE, defined as death, Q wave MI, emergent coronary artery bypass surgery, or repeat target lesion revascularization]), 30-Day incidence of MACE, and Angiographic

Restenosis (defined as >50% minimum lumen diameter stenosis at follow-up angiography). The principal safety and efficacy results are shown in Table 7.

Table 7. Principal Effectiveness and Safety Results (Intent-to-Treat)
All Randomized Lesions Treated (1238 Patients, 1385 Lesions)

Efficacy Measures (per lesion)	Cutting Balloon (N=689)	PTCA (N=696)	Relative Risk [95% C.I.]	Difference [95% C.I.]
Lesion Success	95.5% (642/672)	96.5% (668/692)	0.99 [0.97,1.01]	-1.0% [-3.1%,1.1%]
Device Success	77.7% (473/609)	77.8% (460/617)	1.00 [0.94,1.06]	-0.1% [-4.8%,4.5%]
Procedure Success	92.9% (566/609)	94.7% (584/617)	0.98 [0.95,1.01]	1.0% [-1.1%,3.1%]
MLD after Device (mm) Range (min,max)	2.05±0.52 (672) (0.00, 4.14)	2.13±0.53 (692) (0.00, 4.07)	N/A	-0.08 [-0.14,-0.03]
%DS after Device Range (min, max)	29%±14% (672) (-13%, 100%)	27%±13% (692) (-12%, 100%)	N/A	1.6% [0.1%,3.0%]
MLD after 6 months (mm) Range (min,max)	1.63±0.62 (551) (0.00, 3.44)	1.65±0.61 (559) (0.00, 3.40)	N/A	-0.02 [-0.10,0.05]
%DS after 6 months Range (min, max)	42%±19 (551) (-11%, 100%)	42%±19% (559) (-4%, 100%)	N/A	0.1% [-2%,2%]
Restenosis Rate at 6 months	31.4% (173/551)	30.4% (170/559)	1.03 [0.87,1.23]	1.0% [-4.5%,6.4%]
TLR-free at 9 months*	89.3%	86.1%	1.04 [1.00,1.08]	3.2% [-0.3%,6.7%]
TVR-free at 9 months†	88.5%	84.6%	1.05 [1.00,1.09]	3.9% [0.3%,7.5%]
TVF-free at 9 months‡	86.9%	84.8%	1.03 [0.98,1.07]	2.2% [-1.7%,6.1%]

Safety Measures and Other Clinical Events (per patient)	(N=617)	(N=621)	Relative Risk [95% C.I.]	Difference [95% C.I.]
MACE ≤ 30 days	3.7% (23/617)	2.7% (17/621)	1.36 [0.74,2.52]	1.0% [-1.0%,3.0%]
MACE> 30 days	10.0% (62/617)	12.9% (80/621)	0.78 [0.57,1.06]	-2.8% [-6.4%,0.7%]
Perforations	0.8% (5/617)	0% (0/621)	N/A	0.8% [-0.4% 2.3%]
Vascular Complications	0.3% (2/617)	0.2% (1/621)	2.01 [0.19,21.11]	0.2% [-0.4%,0.7%]

Numbers are % (counts/sample size) or Mean ± 1 SD. CI = Confidence interval.
Survival estimates by Kaplan-Meier method; Standard Error estimates by Greenwood formula.
Relative Risk = S_{CB}/S_{PTCA} SE_{RR}= sqrt[$(SE_{CB}/S_{CB})^2 + (SE_{PTCA}/S_{PTCA})^2$] CI=RR*exp(1.96*$SE_{RR}$)
Difference = $S_{CB} - S_{PTCA}$ SE_{Diff}= sqrt[$(SE_{CB}^2 + SE_{PTCA}$] CI=Diff±1.96*SE_{Diff}
Lesion success: Lesion success was defined as the achievement of a final residual dimater stenosis of <50% (by QCA core laboratory) using any percutaneous method.
Device success: Achievement of a final residual diameter stenosis of <50% (by QCA core laboratory) in the absence of unplanned coronary stenting, randomized treatment failure or crossover.
Procedure success: Achievement of a final residual diameter stenosis of <50% (by QCA core laboratory) in the absence of : In-Hospital MACE or target lesion revascularization within 7 days after the index procedure.
* - TLR-free: Survival free from target lesion revascularization at 9 months estimated using Kaplan-Meier methods.
† - TVR-free: Survival free from target vessel revascularization at 9 months estimated using Kaplan-Meier methods.
‡ - TVF-free: Survival free from target vessel failure (death, Q wave myocardial infaction, or target vessel revascularization) at 9 months estimated using Kaplan-Meier methods.
Major Adverse Cardiac Events (MACE): Death, Q wave MI, emergent CABG, target lesion CABG or TL-PTCA.
Primary endpoint: Death, Q wave MI, emergent CABG, target lesion revascularization, or subacute closure within 30 days of the index procedure.
Vascular complications: Any vascular complication requiring surgical repair.

11. CONCLUSIONS DRAWN FROM THE STUDIES

The results of the preclinical testing and the Resistant Lesion Registry, along with the safety information obtained in the Global Randomized Trial, provide valid scientific evidence and reasonable assurance that the Cutting Balloon™ is safe and effective when used in a manner consistent with the product labeling.

12. PANEL RECOMMENDATIONS

A Circulatory System Device Panel meeting was held on March 4, 1996, to discuss approval of the device for the treatment of Type A and B coronary artery lesions. At that time only the acute results from a subset of patients in the GRT were available for review. The Panel recommended not approvable based on the need for completion of the GRT and suggested that the Cutting Balloon might benefit the population of patients with balloon resistant lesions.

Based on a review of the March 4, 1996, Panel proceedings, and the clinical data provided in the PMA, it was determined that a second Panel meeting was not necessary for review of this device.

13. FDA DECISION

The applicant's manufacturing facility was inspected and was found to be in compliance with the Good Manufacturing Practices (GMP) regulation (21 CFR, Part 820).

The FDA issued an approval order on APR 18 2000.

14. APPROVAL SPECIFICATIONS

Directions for Use: See labeling.

Hazards to Health from Use of the Device: See INDICATIONS, CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, and ADVERSE EVENTS in the labeling.

Post-approval Requirements and Restrictions: See Approval Order.

LABELING

Questions:
Call Interventional Technologies Customer Service Department at (800) 545-1901.

© Copyright 2000 Interventional Technologies Inc. All rights reserved. Cutting Balloon, Atherotome and Atherotomy are trademarks of Interventional Technologies Inc. Teflon is a registered trademark of E.I. Dupont de Nemours Inc.

Protected under one or more of the following U.S. patents: 4273128,5196024, 5209799,5226887, 5320634, 5334401, and 5336234. Other U.S. and international patents pending. Prices, specifications and model availability are subject to change without notice.

P/N 1883
04/27/00

Interventional Technologies
engineering solutions

3574 Ruffin Road
San Diego, California 92123
(800) 545-1901
(858) 268-4488
Fax (858) 541-2858

The Cutting Balloon™ Instructions For Use

Caution

US Law restricts this device to sale by or on the order of a physician.

Device Description:
The Cutting Balloon consists of a non-compliant balloon with 3 or 4 atherotomes™ (microsurgical blades) mounted longitudinally on its outer surface. When the Cutting Balloon is inflated, the atherotomes score the plaque, creating initiation sites for crack propagation. This process referred to as atherotomy®, allows dilatation of the target lesion with less pressure.

The Cutting Balloon catheter shaft consists of two lumens. The outer lumen is used to inflate and deflate the balloon. The inner lumen permits the passage of a PTCA guidewire to aid placement of the Cutting Balloon. At the proximal end of the catheter is a Y-connector with standard luer fittings.

Intended Use / Indications:
The Cutting Balloon is indicated for dilatation of stenoses in coronary arteries for the purpose of improving myocardial perfusion in those circumstances where a high pressure balloon resistant lèsion is encountered. In addition, the target lesion should possess the following characteristics: discrete (≤15 mm in length) or tubular (10 to 20 mm in length); with a reference vessel diameter ranging from 2.0 mm to 4.0 mm; readily accessible to the device; light to moderate tortuosity of proximal vessel segment, non-angulated lesion segment (<45°), smooth angiographic contour; and absence of angiographically-visible thrombus and/or calcification.

Contraindications:
- Coronary artery spasm in the absence of a significant stenosis.

Warnings:
- This device is intended for one time use only. Do *not* resterilize and/or reuse it, as this can potentially result in compromised device performance and increased risk of inappropriate sterilization and cross contamination.

- Atherotomy, because of its mechanism of action, may pose a greater risk of perforation than that observed with conventional PTCA. Oversizing increases the risk of perforation. To reduce the potential for vessel damage the inflated diameter of the Cutting Balloon should approximate a 1.1:1 ratio of the diameter of the vessel just proximal and distal to the stenosis.

- Atherotomy in patients who are not acceptable candidates for coronary artery bypass surgery requires careful consideration, including possible hemodynamic support during atherotomy, as treatment of this patient population carries special risk.

- When the catheter is exposed to the vascular system, it should be manipulated while under high-quality fluoroscopic observation. Do not advance or retract the catheter unless the balloon is fully deflated under vacuum. If resistance is met during manipulation, determine the cause of the resistance before proceeding.

- Balloon pressure should not exceed the rated burst pressure. The rated burst pressure is based on the results of *in vitro* testing. At least 99.9% of the balloons, (with a 95% confidence) will not burst at or below their rated burst pressure. Use of a pressure monitoring device is recommended to prevent over pressurization.

- Atherotomy should only be performed at hospitals where emergency coronary artery bypass graft surgery can be quickly performed in the event of a potentially injurious or life-threatening complication.

- Use only the recommended balloon inflation medium (e.g.- contrast medium). Never use air or any gaseous medium to inflate the balloon.

- Use the catheter prior to the "Use Before" date specified on the package.

Precautions:

- Prior to atherotomy, the catheter should be examined to verify functionality and ensure that its size and shape are suitable for the specific procedure for which it is to be used.

- The Cutting Balloon should be used only by physicians who have received the appropriate training by Interventional Technologies Inc.

- During the Cutting Balloon procedure, appropriate anticoagulant and coronary vasodilator therapy should be provided to the patient. Anticoagulant therapy should be continued for a period of time after the procedure to be determined by the physician.

- Do not over-tighten the hemostatic connector around the shaft of the Cutting Balloon. Otherwise, constriction of the inflation/deflation lumen may occur, resulting in increased inflation/deflation time.

- The Cutting Balloon is not designed for, and therefore, cannot be used to monitor *in vivo* arterial pressures.

Adverse Events

Observed Adverse Events

The Adverse Events reported in this section were those observed in two clinical investigations: the Resistant Lesion Registry (RLR), which demonstrated the ability of the Cutting Balloon to dilate lesions in a series of patients whose lesions could not be dilated with conventional balloon angioplasty; and the Global

b. Repeat coronary arteriography to confirm successful result.

c. Dispose of entire Cutting Balloon. *For single use only.*

Storage:

The Cutting Balloon should be handled with care and stored in an area with good ventilation under conditions which protect it from extremes of temperature and humidity. Cartons containing this item should be protected from liquids and should be stacked in a manner to avoid crushing. Proper stock rotation should be accomplished.

Shelf Life:

The Cutting Balloon is supplied sterile and will remain so as long as the package is unopened and undamaged. The recommended shelf life for this product is printed on the product label. Interventional Technologies does not make provisions for reprocessing or replacing outdated products.

References:

The physician should consult recent literature on current medical practice on balloon dilatation, such as that published by ACC/AHA.

Bertrand OF., et al. Management of Resistant Coronary Lesions by the Cutting Balloon: Initial Experience. Cathet Cardiovasc Diagn 1997;41:179-184.

Interventional Technologies Inc. (Interventional) warrants that each component of this system has been manufactured, packaged and tested with reasonable care and will be free from defects in workmanship and materials. Interventional will not be liable for any incidental, special or consequential loss, damage or expense direct or indirect, from the use of this product. Interventional's sole obligation shall be to repair or replace, at its option, any device that we feel was defective at the time of shipment if notice thereof is received before the device's expiration date indicated on the package. Buyer assumes all liability, whether arising on warranty, contract, negligence or otherwise, from the handling, possession, use or misuse of the product. Because Interventional has no control over the operation, inspection, maintenance or use of its products after sale and has no control over the selection of patients, *This warranty is expressly in lieu of any other express or implied warranty of merchantability or fitness for any particular purpose, and of any other obligation on the part of the seller.* The remedies set forth in this Warranty and Limitations shall be the exclusive remedy available to any person. No Agent, employee or representative of Interventional has any authority to change any of the foregoing or assume or bind Interventional to any additional liability or responsibility in connection with this device.

the balloon. Do not inflate balloon.

g. After negative prep is accomplished, withdraw full negative on the syringe and shut stopcock off to the balloon and remove syringe.

h. Prepare an inflation device with 5 cc of undiluted contrast media. Attach inflation device to stopcock. Purge stopcock by flushing 2cc of contrast media through the middle port.

i. Turn stopcock lever toward middle port and immediately withdraw inflation device plunger to full vacuum and lock.

j. Remove the blue protective sheath from the catheter tip with a gentle, straight motion. Do not use a twisting motion. Do not manipulate the balloon.

k. Insert a .014 inch coronary guidewire through the Cutting Balloon guidewire lumen. Retract distal end of guidewire into the distal tip of Cutting Balloon.

l. Insert Cutting Balloon into the guiding catheter through fully-opened hemostasis valve. Once balloon has passed through the hemostasis valve's "O-ring", tighten hemostasis valve to minimize back-bleeding.

2. **Cutting Balloon Positioning:**
   a. Position the Cutting Balloon, under fluoroscopy, proximal to the first curve of the guiding catheter (a 96 cm marker is provided for easy reference for use with conventional PTCA guiding catheters). Advance guidewire across target lesion and position tip in distal vessel.

   b. Advance Cutting Balloon over the guidewire and position balloon within lesion so that the lesion is centered between the radiopaque markers of the Cutting Balloon.

3. **Cutting Balloon Inflation:**
   a. Under fluoroscopy, slowly inflate the Cutting Balloon (1 atm/ 5sec) until balloon indentation is no longer visible or to a minimum of 6 atm. Do not inflate the Cutting Balloon above 10 atm.

   b. When using the Cutting Balloon on long lesion segments (≤20mm), the distal portion(s) of the target lesion should be treated first. Then, overlapping dilatation of the proximal lesion segment may be performed. However, ***do not perform repeat dilatation of the same lesion segment.***

4. **Cutting Balloon Removal:**
   a. Deflate the Cutting Balloon by applying vacuum with inflation/deflation device. Maintain vacuum on the Cutting Balloon and verify deflation with fluoroscopy. Withdraw Cutting Balloon into the guiding catheter.

Randomized Trial (GRT), a multi-centered, randomized trial designed to compare the Cutting Balloon with conventional angioplasty. Twenty-nine patients were entered into the RLR and a total of 1245 patients were randomized in the GRT; 622 to the Cutting Balloon arm and 623 to the PTCA arm. Seven patients (5 in the Cutting Balloon arm and 2 in the PTCA arm) were deregistered after randomization but before receiving the assigned treatment. Therefore, there were 1238 evaluable patients in the GRT.

In the RLR, dissection was the only in-lab complication recorded. Dissections occurred 14 times: six times prior to Cutting Balloon treatment; two times after Cutting Balloon treatment; and six times as part of the post-Cutting Balloon adjunctive treatment.

One patient death from a cardiac arrest and acute pulmonary edema occurred in the RLR 24-48 hrs post-procedure. This patient was treated for a mid-RCA lesion with a series of four inflations with a PTCA balloon catheter, followed by a single inflation with the Cutting Balloon. A dissection was noted following use of the Cutting Balloon. Adjunctive treatment included two inflations with a second PTCA balloon catheter followed by placement of a stent.

The major adverse events occurring in the GRT are listed in Table 1.

There were eight deaths among the patients randomized to the Cutting Balloon arm. Two deaths occurring during the procedure involved perforations. In the first case, the perforation was associated with contrast extravasation and a Grade F dissection which was treated with balloon angioplasty and one stent. QCA reported TIMI 3 flow with a 35% residual stenosis and persistent contrast extravasation at the end of the procedure. Tamponade developed and the patient died during surgery. An intramyocardial hematoma was identified. In the second case, the coronary artery ruptured at the Cutting Balloon site and the patient developed ventricular fibrillation. The patient was resuscitated and treated emergently for tamponade, but expired following CABG. In both of these cases, the Cutting Balloon was oversized. The balloon:artery ratio, as determined by QCA, was 1.25:1 and 1.8:1, respectively.

A perforation also occurred in the death of another patient who was randomized to the Cutting Balloon arm, but treated with a PTCA balloon because of a failure to cross the lesion with the Cutting Balloon. This patient died 105 days post-procedure due to complications of a CABG performed at that time.

One patient died within an hour of the procedure from a presumed re-occlusion.

A fifth patient died at 130 days post-procedure from a reported heart attack. Two deaths occurred following exacerbation of a pre-existing chronic obstructive pulmonary disease and respiratory failure (20 days), and emergency surgery for an abdominal aortic aneurysm (50 days). The

remaining death was reported as the result of respiratory failure caused by chronic obstructive pulmonary disease.

Perforation was observed in five cases, all in the Cutting Balloon arm. As described above, in two of these cases the patient died acutely. Perforations were treated with PTCA, a stent or both.

Table 1 - GRT Major Adverse Events Occurring Within 270 Days (1238 Patients)

Adverse Event	*Cutting Balloon**	*Conventional Balloon**	*Difference [95% CI]†*
MACE‡	13.6% (84/617)	15.1% (94/621)	-1.5% [-5.4%, 2.4%]
Death	1.3% (8/617)	0.3% (2/621)	1.0% [0.0%, 2.0%]
MI	4.7% (29/617)	2.4% (18/621)	1.8% [-0.3%, 3.9%]
Q Wave MI	1.5% (9/617)	1.1% (7/621)	0.3% [-0.9%, 1.6%]
Non-Q Wave MI	3.2% (20/617)	1.3% (11/621)	1.5% [-0.3%, 3.2%]
Emergent CABG	1.0% (6/617)	1.0% (6/621)	0% [-2.3%, 1.7%]
TLR§	11.7% (72/617)	14.8% (92/621)	-3.1% [-6.9%, 0.6%]
CABG (per pt.)	1.5% (9/617)	2.1% (13/621)	-0.6% [-2.1%, 0.8%]
PTCA (per pt.)	10.5% (65/617)	12.7% (79/621)	-2.2% [-5.8%, 1.4%]
Subacute Closure	1.3% (8/617)	1.6% (10/621)	-0.3% [-1.5%, 3.0%]
Bleeding Complications	0.3% (2/617)	0.0% (0/621)	0.3% [-1.9%, 0.7%]
Vascular Complications¶	0.3% (2/617)	0.2% (1/621)	0.1% [-1.9%, 1.0%]
Clinical Perforations	0.8% (5/617)	0.0% (0/621)	0.8% [-0.4%, 2.3%]

*Numbers are % (counts/sample size)
†Difference = S_{CB}-S_{PTCA} SE_{Diff}=sqrt[SE_{CB}^2+SE_{PTCA}^2] CI=Diff±1.96*SE_{Diff}
‡Major Adverse Cardiac Events (MACE): Death, Q Wave MI, emergent CABG, target lesion CABG or TL-PTCA
§Target lesion revascularization (TLR) at 9 months: any "clinically driven" PTCA (TL-PTCA) or bypass surgery (TL-CABG) performed on the target lesion after documentation of recurrent angina and/or evidence of myocardial ischemia by stress testing.
¶Vascular complications: Any vascular complication requiring surgical repair.

Potential Adverse Events

Potential adverse events include, but are not limited to, the following:

- Death
- Acute myocardial infarction
- Total occlusion of the coronary artery or bypass graft
- Coronary vessel dissection, perforation, rupture, or injury
- Aneurysm

List of Additional Supplies:

In addition to the Cutting Balloon, the following supplies should be prepared for use:

- .014" coronary guidewire (with Teflon® as a component of its coating);
- Large-lumen 8 Fr. or 9 Fr. guide catheter;
- Heparinized saline solution;
- Radiopaque contrast medium;
- Infusion manifold/apparatus;
- Pressure-indicating inflation/deflation device;
- Appropriately-sized vessel introducer;
- Other supplies and medications per local protocols.

Directions for Use:

All equipment to be used for the procedure, including the Cutting Balloon, should be examined carefully to verify functionality. Inspection prior to use should verify that the catheter has not been damaged in shipment and that it is ready to be used. The Cutting Balloon should be prepared and tested following the directions provided below prior to insertion into the body.

1. Cutting Balloon Preparation

Sizing the Cutting Balloon to the reference artery is extremely important for a successful dilation. Oversizing the balloon increases the risk of perforation. To reduce the potential for vessel damage, the inflated diameter of the Cutting Balloon should approximate a ratio of 1.1:1 in relation to the average diameter of the reference coronary artery.

Caution:

This is a wet negative prep procedure. Customary balloon preparation methods do not apply. These steps must be followed exactly.

a. Using sterile technique, remove the Cutting Balloon from its package and place onto sterile field. Remove the Cutting Balloon from its protective ring. Do not remove the blue protective sheath from the catheter tip.

b. Flush the guidewire lumen of the Cutting Balloon with heparinized saline.

c. Connect a three-way stopcock to the balloon port (Luer hub). Attach a 20cc syringe with full-strength contrast to the opposite port of the stopcock.

d. Shut stopcock port off to the balloon and purge air out of 20 cc syringe and stopcock.

e. Holding the syringe vertically above the Cutting Balloon, open stopcock to the balloon and draw a full vacuum stroke on the syringe. Pause long enough for air bubbles to flow into the syringe. Then allow the syringe to go forward slowly and contrast to enter the "Y" connector.

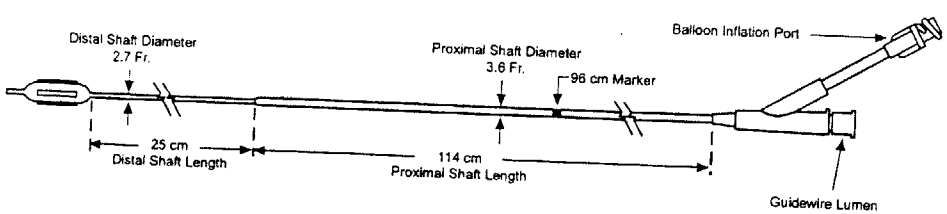
f. Draw back another full vacuum stroke on the syringe. Observe for a large volume of air coming from the balloon. If this does not occur, repeat prior steps. Always maintain negative pressure on

Specifications:

Model Number	Inflated Profile (mm) (E — Fig 1)	Deflated Profile	Number of Atherotomes	Atherotomes Length (mm) † (F — Fig 1)
B120010	2.00	.041"	3	10
B122510	2.25	.041"	3	10
B125010	2.50	.041"	3	10
B127510	2.75	.041"	3	10
B130010	3.00	.041"	3	10
B132510	3.25	.041"	3	10
B135010	3.50	.044"	4	10
B137510	3.75	.044"	4	10
B140010	4.00	.046"	4	10
B120015	2.00	.041"	3	15
B122515	2.25	.041"	3	15
B125015	2.50	.041"	3	15
B127515	2.75	.041"	3	15
B130015	3.00	.041"	3	15
B132515	3.25	.041"	3	15
B135015	3.50	.044"	4	15
B137515	3.75	.044"	4	15
B140015	4.00	.046"	4	15

†Balloon working length = atherotome length.

Figure 2



- Restenosis of the dilated vessel
- Unstable angina
- Embolism
- Arrhythmias, including ventricular fibrillation
- Hypo/hypertension
- Coronary artery spasm
- Hemorrhage or hematoma
- Arteriovenous fistula
- Drug reactions, allergic reactions to contrast medium
- Infection.

Observed Device Malfunctions

There were no cutting Balloon malfunctions in the RLR.

A total of 15 Cutting Balloon malfunctions were recorded in the GRT. Two devices failed to inflate. Thirteen cases of balloon leak or rupture were reported: 9 with the first inflation and 4 with the second inflation.

CLINICAL STUDIES:

Resistant Lesion Registry (RLR)

The Resistant Lesion Registry (RLR) contains registry data on 30 lesions in 29 patients. All patients were enrolled at a single site between November 1996 and November 1999.

Study Endpoints

The primary endpoint was acute lesion success defined as a reduction in lumen narrowing of at least 20%. The secondary endpoint was procedural success. Procedural success was defined as lesion success, a final residual stenosis of ≤50% after all devices are used and no major adverse events (MACE, defined as death, CABG, or non-fatal MI).

Study Population

The RLR patients were selected for treatment on the basis of failed conventional angioplasty, defined as failure to reduce the lumen diameter narrowing by >20% and the final residual stenosis ≥50% with PTCA balloon inflation pressures > 10 atmospheres. The demographics, risk factors and prior history of these patients are shown in Table 2.

Table 2 - Demographics, Risk Factors and Prior Procedures.

Demographics:	
%Male	69% (20/29)
Age	65 ± 8.4
Angina Class (CCS)	2.8 ± 0.8
Risk Factors:	
Diabetes	14% (4/28)
Smoking	39% (11/28)
HB Pressure	29% (8/28)
Hyperlipidemia	48% (13/27)
Prior Procedures:	
MI	33% (9/27)
CABG	22% (6/27)
PTCA	22% (6/27)

Methods

Patient data were obtained prospectively on 6 patients under a formal clinical protocol and retrospectively on 23 patients. For both prospective and retrospective patient

groups, conventional balloon angioplasty was used as the initial treatment in all but two cases. In these two cases the Cutting Balloon was used as the first treatment for dilatation of an unprotected left main, a vessel known to be resistant to PTCA dilatation. Physician discretion was used to further decrease the residual stenosis with additional adjunctive devices following treatment with the Cutting Balloon.

Results

Of the 29 patients entered into the RLR, balloon resistant lesions were treated in 26 native vessels and 4 saphenous vein grafts (SVGs). Patients were treated with a sequence of devices including the Cutting Balloon. The Cutting Balloon was usually used as the second (14 cases) or third (10 cases) device in each treatment sequence. In three cases, the Cutting Balloon failed to cross the lesion on the initial attempt. Successful crossing was achieved with the second attempt (2 cases) following an additional crossing with a PTCA balloon. In the third case there were no further attempts to cross the lesion.

In most cases, the Cutting Balloon was inflated once (78%, 25/32); while the number of inflations with the PTCA catheter, prior to the Cutting Balloon, varied from 1 (31%, 14/45), 2 (36%, 16/45), 3 (18%, 8/45) to ≥4 (16%, 7/45) inflations. Inflation pressures ranged from 8-16 atmospheres for the Cutting Balloon and 4-25 atmospheres for the PTCA catheters. The average inflation pressure for the Cutting Balloon was significantly less than the average pressure used for the PTCA catheters [9.3±1.8 atm (n=32) versus 15.4±3.6 atm (n = 45), $p < 0.0001$].

The principal safety and efficacy results of the RLR are shown in Table 3. The primary and secondary endpoints, used for the prospectively enrolled patients, were also applied to the patients enrolled retrospectively.

Individualization of Treatment

Avoid use in patients whose lesions possess the following characteristics: reference coronary artery diameter of less than 2.0 mm; diffuse (>20 mm in length); total obstruction (occlusion); heavy calcification; excessive tortuosity of proximal vessel segment; moderate to extreme angulation of target lesion segment (≥45°); inaccessible to the device; thrombus present.

Appropriate sizing of the Cutting Balloon is extremely important. Do not exceed a balloon:artery ratio of 1.1 to 1.

Delivery failures are likely to be more frequent with the Cutting Balloon than with conventional PTCA. This occurs for two reasons. First, the Cutting Balloon has a larger profile than a conventional PTCA catheter of the same nominal inflated diameter. Second, the materials of construction prevent the Cutting Balloon from being as flexible as a conventional balloon.

If you intend to use a 15 mm device, but suspect that you may have difficulty in reaching the lesion because of tortuosity, consider using a 10 mm device with tandem inflations.

Specifications

Maximum Recommended Guidewire Diameter	Distal Balloon Tip Length (A — Fig 1)	Radiopaque Marker Width (B — Fig 1)	Distance Between Radiographic Markers & Atherotomes (C — Fig 1)	Working Atherotome Height (D — Fig 1)	Nominal Inflation Pressure	Rated Burst Pressure (RBP)
0.014"	.25 cm	.050" (1.3 mm)	.023" (,6 mm)	.005" - .007"	6 atm	10 atm

Figure 1

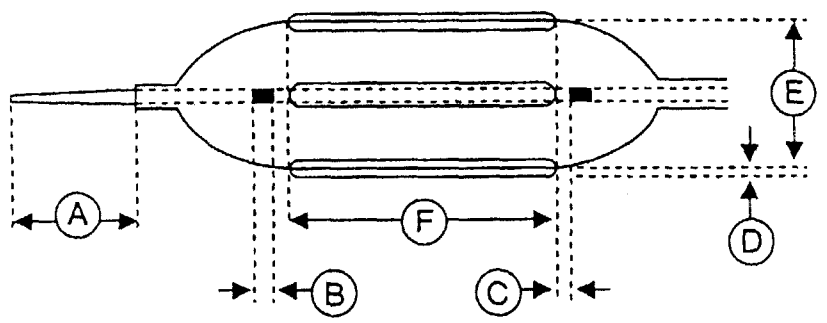


Table 4 - Principal Effectiveness and Safety Results (Intent-to-Treat)
All Randomized Lesions Treated (1238 Patients, 1385 Lesions)

Efficacy Measures (per lesion)	Cutting Balloon (N=689)	PTCA (N=696)	Relative Risk [95% C.I.]	Difference [95% C.I.]
Lesion Success	95.5% (642/672)	96.5% (668/692)	0.99 [0.97,1.01]	-1.0% [-3.1%,1.1%]
Device Success	77.7% (473/609)	77.8% (460/617)	1.00 [0.94,1.06]	-0.1% [-4.8%,4.5%]
Procedure Success	92.9% (566/609)	94.7% (584/617)	0.98 [0.95,1.01]	1.0% [-1.1%,3.1%]
MLD after Device (mm) Range (min,max)	2.05±0.52 (672) (0.00, 4.14)	2.13±0.53 (692) (0.00, 4.07)	N/A	-0.08 [-0.14,-0.03]
%DS after Device Range (min, max)	29%±14% (672) (-13%, 100%)	27%±13% (692) (-12%, 100%)	N/A	1.6% [0.1%,3.0%]
MLD after 6 months (mm) Range (min,max)	1.63±0.62 (551) (0.00, 3.44)	1.65±0.61 (559) (0.00, 3.40)	N/A	-0.02 [-0.10,0.05]
%DS after 6 months Range (min, max)	42%±19 (551) (-11%, 100%)	42%±19% (559) (-4%, 100%)	N/A	0.1% [-2%,2%]
Restenosis Rate at 6 months	31.4% (173/551)	30.4% (170/559)	1.03 [0.87,1.23]	1.0% [-4.5%,6.4%]
TLR-free at 9 months*	89.3%	86.1%	1.04 [1.00,1.08]	3.2% [-0.3%,6.7%]
TVR-free at 9 months†	88.5%	84.6%	1.05 [1.00,1.09]	3.9% [0.3%,7.5%]
TVF-free at 9 months‡	86.9%	84.8%	1.03 [0.98,1.07]	2.2% [-1.7%,6.1%]
Safety Measures and Other Clinical Events (per patient)	**(N=617)**	**(N=621)**	**Relative Risk [95% C.I.]**	**Difference [95% C.I.]**
MACE ≤ 30 days	3.7% (23/617)	2.7% (17/621)	1.36 [0.74,2.52]	1.0% [-1.0%,3.0%]
MACE> 30 days	10.0% (62/617)	12.9% (80/621)	0.78 [0.57,1.06]	-2.8% [-6.4%,0.7%]
Perforations	0.8% (5/617)	0% (0/621)	N/A	0.8% [-0.4%, 2.3%]
Vascular Complications	0.3% (2/617)	0.2% (1/621)	2.01 [0.19,21.11]	0.2% [-0.4%,0.7%]

Numbers are % (counts/sample size) or Mean ± 1 SD. CI = Confidence interval.
Survival estimates by Kaplan-Meier method; Standard Error estimates by Greenwood formula.
Relative Risk = S_{CB}/S_{PTCA} SE_{RR}= sqrt[$(SE_{CB}/S_{CB})^2$ +$(SE_{PTCA}/S_{PTCA})^2$] CI=RR*exp(1.96*SE_{RR})
Difference = S_{CB}-S_{PTCA} SE_{Diff}= sqrt[SE_{CB}^2 + SE_{PTCA}^2] CI=Diff±1.96*SE_{Diff}
Lesion success: Lesion success was defined as the achievement of a final residual diameter stenosis of <50% (by QCA core laboratory) using any percutaneous method.
Device success: Achievement of a final residual diameter stenosis of <50% (by QCA core laboratory) in the absence of unplanned coronary stenting, randomized treatment failure or crossover.
Procedure success: Achievement of a final residual diameter stenosis of <50% (by QCA core laboratory) in the absence of : In-Hospital MACE or target lesion revascularization within 7 days after the index procedure.
* - TLR-free: Survival free from target lesion revascularization at 9 months estimated using Kaplan-Meier methods.
† - TVR-free: Survival free from target vessel revascularization at 9 months estimated using Kaplan-Meier methods.
‡ - TVF-free: Survival free from target vessel failure (death, Q wave myocardial infaction, or target vessel revascularization) at 9 months estimated using Kaplan-Meier methods.
Major Adverse Cardiac Events (MACE): Death, Q wave MI, emergent CABG, target lesion CABG or TL-PTCA.
Primary endpoint: Death, Q wave MI, emergent CABG, target lesion revascularization, or subacute closure within 30 days of the index procedure.
Vascular complications: Any vascular complication requiring surgical repair.

Table 3 - Principal Effectiveness and Safety Results Resistant Lesion Registry
(n= 29 patients, 30 lesions)

Effective Measures:	**Cutting Balloon %, (n/N), [95% CI]**
Acute Lesion Success	78% (18/23) [56%, 93%]
Procedural Success	74% (17/23) [52%, 90%]
%DS - Initial	73% (30) [70%, 77%]
Post PTCA	51% (17) [44%, 59%]
Post CB	36% (22) [28%, 45%]
Final	16% (30) [8%, 23%]
Safety Measures:	
MACE	3% (1/30) [1%, 10%]
Dissection, Prior to Cutting Balloon	20% (6/30) [8%, 39%]
Dissection, Cutting Balloon + Adjunctive Use	12% (8/30) [12%, 47%]

Global Randomized Trial (GRT)

The Global Randomized Trial (GRT) was a multi-centered, randomized trial designed to compare the Cutting Balloon with conventional angioplasty. Patient enrollment in the GRT occurred between June 1994, and November 1996, at 31 centers in the US, Canada, France, Belgium and the Netherlands. Of the 1245 patients enrolled, 622 were assigned to the Cutting Balloon arm and 623 to the PTCA arm. Seven patients (5 in the Cutting Balloon and 2 in the PTCA arm) were deregistered after randomization but before receiving the assigned treatment. Deregistration occurred for the following reasons: resolution of the stenosis between the prior angiogram and the index procedure (3 cases), the presence of calcification requiring atherectomy (1 case), and failing to meet the inclusion criteria (3 cases).

Study Endpoints

The primary endpoint was angiographic restenosis at 6 months. Secondary endpoints included TLR and MACE at 9 months. A clinical events committee blinded to treatment assignment adjudicated all major clinical events.

Study Population

Patients, between the ages of 25 and 75 years, with atherosclerotic coronary artery disease were eligible for enrollment in the GRT if they were suitable candidates for coronary artery bypass graft surgery and the target lesions were *de novo* Type A or B lesions in native arteries without total obstructions or visible thrombus, and were accessible to the Cutting Balloon.

Methods

Patients were prospectively randomized to treatment with either the Cutting Balloon or PTCA. Access to the target lesion was gained through the femoral artery approach. The reference vessel diameter (located just proximal to the target lesion) was measured by quantitative angiography.

Selection of the Cutting Balloon with the appropriately sized balloon diameter was based on the reference vessel diameter. If necessary, tandem dilatations were allowed for lesion lengths ≤ 20 mm. Oversizing of the balloon was not recommended in the PTCA arm.

The protocol allowed for a single inflation of the CB up to 8 atmospheres for a maximum of 90 seconds. Subsequent dilatation(s) with a PTCA balloon were allowed only if the residual stenosis was > 40%. In the PTCA arm, the inflation times and pressures were left to the discretion of the investigator. Serial inflations with a single balloon, or subsequent inflations with increased diameter PTCA balloons were allowed to achieve a ≥20% reduction in stenosis and a ≤50% residual stenosis. Multiple violations of the procedural protocol were reported in the CB arm [33% (212/617) of the Cutting Balloon subjects were not treated per protocol].

Clinical follow-up was performed at 6 weeks, 6 months and 9 months. Baseline quantitative coronary angiography (QCA) was performed pre-procedure, following device use, and after the final treatment in all patients. Follow-up quantitative coronary angiography at 6 months was required in all patients. Anti-coagulation included aspirin 325 mg/day throughout the study.

Results

The acute and 6 month angiographic and clinical results demonstrated that the Cutting Balloon was similar to PTCA with respect to Procedure Success (defined as achievement of <50% residual diameter stenosis and freedom from in-hospital major adverse cardiac events [MACE, defined as death, Q wave MI, emergent coronary artery bypass surgery, or repeat target lesion revascularization]), 30-Day incidence of MACE, and Angiographic Restenosis (defined as >50% minimum lumen diameter stenosis at follow-up angiography). The principal safety and efficacy results are shown in Table 4.