SUMMARY of SAFETY and EFFECTIVENESS DATA

MEDTRONIC FREESTYLE® AORTIC ROOT BIOPROSTHESIS

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P970031

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1. General Information

Device Generic Name: ..... Replacement Heart Valve

Device Trade Name: ..... Medtronic FREESTYLE® Aortic Root Bioprosthesis

Applicant's Name and Address: ..... Medtronic Heart Valves, Inc.
7000 Central Avenue NE
Minneapolis, MN 55432

PMA Application Number: P970031

Date of Panel Recommendation: ..... September 15, 1997

Date of Notice of Approval to the Applicant: ... November 26, 1997

2. Indications For Use

The Medtronic FREESTYLE® Aortic Root Bioprosthesis (hereafter called the Medtronic FREESTYLE® Bioprosthesis), is indicated for the replacement of malfunctioning native or prosthetic aortic valves with the option of aortic root replacement.

No clinical data are available which evaluate the long-term impact of the AOA treatment in patients.

3. Contraindications

No contraindications for use of this device are known.

4. Warnings and Precautions

4.1 Warnings

- FOR SINGLE USE ONLY.
- DO NOT RESTERILIZE the valve by any method. Exposure of the bioprosthesis and container to irradiation, steam, ethylene oxide or other chemical sterilants will render the bioprosthesis unfit for use.
- Accelerated deterioration due to calcific degeneration of bioprosthesis may occur in:
  - ◊ children, adolescents, or young adults;
  - ◊ patients with altered calcium metabolism (e.g., chronic renal failure, hyperparathyroidism).

4.2 Precautions

- Implanting physicians must be familiar with the techniques for implanting an unstented bioprosthesis. These techniques are similar to those required for allograft implantation.
- *In vitro* testing of the Medtronic FREESTYLE® Bioprosthesis has only been performed in less compliant simulated aorta comparable to the aorta of middle aged or older patients. Data from clinical or *in vitro* testing are not available from more compliant simulated aorta comparable to the aorta of a young adult.
- Limited implant experience is available for the 19mm bioprosthesis implanted with the root-inclusion technique (none), and with the full-root technique (nine patients); and for the 21mm bioprosthesis implanted with the root-inclusion technique (four patients) (see Section 10, Summary of Clinical Studies).

Precautions Prior to Use

Do not use the Medtronic FREESTYLE® Bioprosthesis:

◊ if the tamper evident seal is broken;

◊ if the glutaraldehyde storage solution does not completely cover the bioprosthesis;

◊ if the bioprosthesis has been exposed to freezing or has had prolonged exposure to heat as indicated by the temperature indicators provided in the packaging;

◊ if the bioprosthesis is damaged.

Precautions During Use

◊ Do not expose the bioprosthesis to storage solutions other than the storage solution in which it was shipped, the sterile isotonic saline solution used during the rinsing procedure, or the sterile isotonic saline used to irrigate the bioprosthesis.

◊ Do not allow the tissue of the bioprosthesis to dry. Continuous submersion or irrigation is required.

◊ Do not add antibiotics to either the storage or the rinse solution. Do not apply antibiotics to the bioprosthesis.

◊ Do not lacerate the leaflet tissue. If a valve is damaged, the valve must be explanted and replaced.

◊ Do not evert the valve. Eversion will damage valve tissue.

◊ Passage of a catheter through any bioprosthesis may damage the valve and is, therefore, not recommended.

◊ Trim suture end close to the knot to prevent abrasion of leaflet tissue.

5. Device Description

The Medtronic FREESTYLE® Bioprosthesis, Model 995, is comprised of a porcine aortic root preserved by collagen crosslinking in a buffered 0.2% glutaraldehyde solution. During fixation, a 40 mmHg hydrostatic pressure is applied to the root with a zero pressure differential across the valve leaflets. The preserved aortic root has a thin, single layer of polyester fabric covering the myocardium and the inflow circumference of the bioprosthesis. All stitching is done with polyester suture. The Medtronic FREESTYLE® Bioprosthesis is supplied sterile in a buffered 0.2% glutaraldehyde solution. The Medtronic FREESTYLE® Bioprosthesis is designed for the aortic position only and is available in the following implantation diameters: 19 mm, 21 mm, 23 mm, 25 mm and 27 mm. The function of a stentless bioprosthetic valve is sensitive to surgical implant technique. The Medtronic FREESTYLE® Bioprosthesis is packaged as a single device that is modified at operation for insertion with one of three techniques to replace the native valve leaflets with the subcoronary technique, to replace the entire valve mechanism with the root-inclusion technique, or to replace the entire valve mechanism as well as the aortic root with the full-root technique.

6. Alternative Practices and Procedures

The alternative to the Medtronic FREESTYLE® Bioprosthesis is surgical replacement of the malfunctioning aortic valve with a homograft, mechanical prosthetic valve, or a stented bioprosthetic valve for which there is an approved premarket approval application (PMA). The choice of replacement valve depends on an assessment of patient factors which include age, preoperative condition, anatomy and the patient's ability to tolerate long-term anticoagulant therapy.

Other forms of treatment may include the use of cardiac drug therapy.

7. Marketing History

Commercial distribution of the Medtronic FREESTYLE® Bioprosthesis outside the U.S. began in January 1996. Currently the device is distributed in the following countries: Argentina, Austria, Australia, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Israel, Italy, The Netherlands, New Zealand, Norway, South Africa, Spain, Sweden, Switzerland, United Kingdom.

The Medtronic FREESTYLE® Bioprosthesis has not been withdrawn from marketing for any reason relating to the safety and/or the effectiveness of the device.

8. Adverse Effects of the Device on Health

A prospective non-randomized multicenter international study evaluated the Medtronic FREESTYLE® Bioprosthesis with patient follow-up out to three years. A total of 882 patients received the bioprosthesis. Patients were monitored throughout the entire postoperative period for possible adverse events. The cumulative follow-up was 1246 patient-years with a mean follow-up of 17 months (SD = 12 months, range = 0 to 42 months).

8.1 Observed Adverse Events - Subcoronary Technique

A total of 640 Medtronic FREESTYLE® Bioprostheses were implanted with the subcoronary technique in 640 patients at 15 centers. Nine of the 640 patients were excluded from the data summary of adverse events for the following reasons: five patients had their bioprosthesis removed and replaced with another prosthesis during the initial surgery due to difficulty sizing a small aortic root, high mean gradient, or patient prosthesis mismatch; and four patients had either a pre-existing or concomitant implant of a mitral valve prosthesis. The adverse event rates were based on 631 bioprostheses implanted in 631 patients. The cumulative follow-up was 913 patient-years with a mean follow-up of 17 months (SD = 11 months, range = 0 to 42 months).

Table 1. Observed Adverse Events for the Subcoronary Technique

All patients analyzed, N = 631, Cumulative follow-up = 913 patient-years

	Early Events [1]		Late Events		Actuarial Freedom by Kaplan-Meier (%)	
	N	% of Patients	N	% / Patient-Year [2]	1 Year (95% CI)	3 Years (95% CI)
All Deaths	31	4.9%	31	3.6%	91.6% [89.0% - 94.2%]	85.9% [77.5% - 94.3%]
Bioprosthesis-Related or Unexplained	4	0.6%	9	1.0%	97.9% [96.5% - 99.3%]	97.5% [93.5% - 100.0%]
Study Bioprosthesis-Related AEs						
Thromboembolism [3]	14	2.2%	13	1.5%	95.6% [93.6% - 97.6%]	94.6% [88.8% - 100.0%]
Permanent Neurological Event	11	1.7%	6	0.7%	97.3% [95.8% - 98.8%]	96.6% [91.9% - 100.0%]
Transient Neurological Ebent	3	0.5%	6	0.7%	98.5% [97.3% - 99.7%]	98.2% [94.7% - 100.0%]
Bioprosthetic Thrombosis	0	0.0%	1	0.1%	99.8% [99.4% - 100.0%]	99.8% [98.6% - 100.0%]
Structural Deterioration [4]	0	0.0%	0	0.0%	100.0% [99.1% - 100.0%]	100.0% [93.7% - 100.0%]
Nonstructural Dysfunction [4]	0	0.0%	0	0.0%	100.0% [99.1% - 100.0%]	100.0% [93.7% - 100.0%]
Major Antithromboembolic-Related Hemorrhage	10	1.6%	7	0.8%	97.0% [95.4% - 98.6%]	97.0% [92.6% - 100.0%]

	Early Events [1]		Late Events		Actuarial Freedom by Kaplan-Meier (%)	
	N	% of Patients	N	% / Patient-Year [2]	1 Year (95% CI)	3 Years (95% CI)
Primary Paravalvular Leak	3	0.5%	8	0.9%	98.6% [97.5% - 99.7%]	97.6% [93.6% - 100.0%]
Endocarditis	2	0.3%	8	0.9%	98.5% [97.3% - 99.7%]	97.9% [94.2% - 100.0%]
Primary Hemolysis [4]	0	0.0%	0	0.0%	100.0% [99.1% - 100.0%]	100.0% [93.7% - 100.0%]
Reoperation	0	0.0%	7	0.8%	98.9% [97.9% - 99.9%]	98.6% [95.6% - 100.0%]
Explant	0	0.0%	6	0.7%	99.0% [98.0% - 100.0%]	98.7% [95.8% - 100.0%]

NOTES:
AEs = Adverse Events
1. Hospital or 30 day event for death or 30 day event for adverse events.
2. Calculations were based on 864 late patient-years.
3. One late event was peripheral arterial embolus.
4. The number of patients remaining at risk at one year (N = 415) and three years (N = 57) was used for N in the calculations of the lower confidence limits for the actuarial estimates. The calculation methods are those described in the following note.

Note: Adverse event rates were calculated as the percentage of patients for early events. For late adverse events, the linearized rates (%/patient-year) were calculated. For time to first event (early or late), actuarial rates using Kaplan-Meier method and confidence intervals were calculated. For adverse events with no occurrences, the lower two-sided 95% confidence limits for the Kaplan-Meier estimates were calculated as (1 - maximum risk), where (1 - maximum risk) is equal to $(0.025)^{1/N}$. If there was no censoring, N would be the total sample size. Since there was censoring, the number of patients remaining at risk at one and three years was used for N. Using the number of patients remaining at risk ignores the experience of all the patients who were censored before the relevant time points and, therefore, overestimates the maximum risk.

8.2 Observed Adverse Events - Full-Root Technique

A total of 159 Medtronic FREESTYLE® Bioprostheses were implanted with the full-root technique in 159 paients at 14 centers. Two of the 159 patients were excluded from the data summary of adverse events for the following reasons: two patients had either a pre-existing or concomitant implant of a mitral valve prosthesis.

The adverse event rates were based on 157 bioprostheses implanted in 157 patients. The cumulative follow-up was 189 patient-years with a mean follow-up of 14 months (SD = 13 months, range = 0 to 38 months).

Table 2. ***Observed Adverse Events for the Full-Root Technique***

All patients analyzed, N = 157, Cumulative follow-up = 189 patient-years

	Early Events [1]		Late Events		Actuarial Freedom by Kaplan-Meier (%)	
	N	% of Patients	N	% / Patient-Year [2]	1 Year (95% CI)	3 Years (95% CI)
All Deaths	22	14.0%	8	4.5%	79.8% [72.0% - 87.6%]	78.5% [62.5% - 94.5%]
Bioprosthesis-Related or Unexplained	1	0.6%	4	2.2%	96.3% [92.3% - 100.0%]	94.7% [85.1% - 100.0%]
Study Bioprosthesis-Related AEs						
Thromboembolism [3]	5	3.2%	6	3.4%	93.3% [87.9% - 98.7%]	90.1% [76.2% - 100.0%]
Permanent Neurological Event	2	1.3%	3	1.75	96.6% [92.7% - 100.0%]	95.0% [85.4% - 100.0%]

	Early Events [1]		Late Events		Actuarial Freedom by Kaplan-Meier (%)	
	N	% of Patients	N	% / Patient-Year [2]	1 Year (95% CI)	3 Years (95% CI)
Transient Neurological Ebent	2	1.3%	3	1.7%	96.3% [92.2% - 100.0%]	94.7% [84.3% - 100.0%]
Bioprosthetic Thrombosis	0	0.0%	0	0.0%	100.0% [95.5% - 100.0%]	100.0% [83.2% - 100.0%]
Structural Deterioration [4]	0	0.0%	0	0.0%	100.0% [95.5% - 100.0%]	100.0% [83.2% - 100.0%]
Nonstructural Dysfunction [4]	0	0.0%	0	0.0%	100.0% [95.5% - 100.0%]	100.0% [83.2% - 100.0%]
Major Antithromboembolic-Related Hemorrhage	2	1.3%	1	0.6%	97.7% [94.4% - 100.0%]	97.7% [91.0% - 100.0%]
Primary Paravalvular Leak	1	0.6%	0	0.0%	99.2% [97.3% - 100.0%]	99.2% [95.3% - 100.0%]
Endocarditis	0	0.0%	0	0.0%	100.0% [95.5% - 100.0%]	100.0% [83.2% - 100.0%]
Primary Hemolysis [4]	0	0.0%	0	0.0%	100.0% [95.5% - 100.0%]	100.0% [83.2% - 100.0%]
Reoperation	0	0.0%	0	0.0%	100.0% [95.5% - 100.0%]	100.0% [83.2% - 100.0%]
Explant	0	0.0%	0	0.0%	100.0% [95.5% - 100.0%]	100.0% [83.2% - 100.0%]

NOTES:
AEs = Adverse Events

1. Hospital or 30 day event for death or 30 day event for adverse events.
2. Calculations were based on 179 late patient-years.
3. One late event was peripheral arterial embolus.
4. The number of patients remaining at risk at one year (N = 81) and three years (N = 20) was used for N in the calculations of the lower confidence limits for the actuarial estimates. The calculation methods are those described in the note following Table 1.

8.3 Observed Adverse Events - Root-Inclusion Technique

A total of 83 Medtronic FREESTYLE® Bioprostheses were implanted with the root-inclusion technique in 83 patients at 14 centers. Three of the 83 patients were excluded from the data summary of adverse events for the following reasons: three patients had their bioprosthesis removed and replaced with another prosthesis during the initial surgery due to a leaflet tear during suturing, difficulty seating and orienting the coronaries, or a paravalvular leak.

The adverse event rates were based on 80 bioprostheses implanted in 80 patients. The cumulative follow-up was 139 patient-years with a mean follow-up of 21 months (SD = 13 months, range = 0 to 39 months).

Table 3. Observed Adverse Events for the Root-Inclusion Technique

All patients analyzed, N = 80, Cumulative follow-up = 139 patient-years

	Early Events [1]		Late Events		Actuarial Freedom by Kaplan-Meier (%)	
	N	% of Patients	N	% / Patient-Year [2]	1 Year (95% CI)	3 Years (95% CI)
All Deaths	4	5.0%	5	3.8%	88.8% [80.9% - 96.7%]	87.0% [72.5% - 100.0%]
Bioprosthesis-Related or Unexplained	3	3.8%	3	2.3%	91.5% [84.4% - 98.6%]	91.5% [79.2% - 100.0%]
Study Bioprosthesis-Related AEs						
Thromboembolism [3]	3	3.8%	7	5.3%	91.3% [83.8% - 98.8%]	87.2% [70.2% - 100.0%]
Permanent Neurological Event	0	0.0%	2	1.5%	98.3% [95.0% - 100.0%]	96.3% [87.3% - 100.0%]

	Early Events [1]		Late Events		Actuarial Freedom by Kaplan-Meier (%)	
	N	% of Patients	N	% / Patient-Year [2]	1 Year (95% CI)	3 Years (95% CI)
Transient Neurological Event	3	3.8%	5	3.8%	93.0% [86.1% - 99.9%]	87.6% [71.5% - 100.0%]
Bioprosthetic Thrombosis	0	0.0%	0	0.0%	100.0% [93.5% - 100.0%]	100.0% [81.5% - 100.0%]
Structural Deterioration [4]	0	0.0%	0	0.0%	100.0% [93.5% - 100.0%]	100.0% [81.5% - 100.0%]
Nonstructural Dysfunction [4]	0	0.0%	0	0.0%	100.0% [93.5% - 100.0%]	100.0% [81.5% - 100.0%]
Major Antithromboembolic-Related Hemorrhage	2	2.5%	0	0.0%	97.4% [93.2% - 100.0%]	97.4% [90.1% - 100.0%]
Primary Paravalvular Leak	2	2.5%	0	0.0%	97.4% [93.2% - 100.0%]	97.4% [90.1% - 100.0%]
Endocarditis	1	1.3%	1	0.8%	96.9% [92.4% - 100.0%]	96.9% [89.0% - 100.0%]
Primary Hemolysis [4]	0	0.0%	0	0.0%	100.0% [93.5% - 100.0%]	100.0% [81.5% - 100.0%]
Reoperation	2	2.5%	2	1.5%	94.4% [88.5% - 100.0%]	94.4% [84.1% - 100.0%]
Explant	2	2.5%	2	1.5%	94.4% [88.5% - 100.0%]	94.4% [84.1% - 100.0%]

NOTES:
AEs = Adverse Events
1. Hospital or 30 day event for death or 30 day event for adverse events.
2. Calculations were based on 179 late patient-years.
3. One late event was peripheral arterial embolus.
4. The number of patients remaining at risk at one year (N = 81) and three years (N = 20) was used for N in the calculations of the lower confidence limits for the actuarial estimates. The calculation methods are those described in the note following Table 1.

8.4 Potential Adverse Events

Adverse events potentially associated with the use of bioprosthetic heart valves (in alphabetical order) include:

- cardiac dysrhythmias
- endocarditis
- hemorrhage, anticoagulant/antiplatelet-related
- nonstructural dysfunction (pannus, suture, inappropriate sizing, or other)
- thromboembolism
- death
- hemolysis
- leak, transvalvular or paravalvular
- structural deterioration (calcification, leaflet tear, or other)
- valve thrombosis

9. Summaries of Pre-clinical Studies

9.1 Bench Testing

9.1.1 Biocompatibility, Immunology and Toxicology Studies

Biocompatibility tests were performed on alpha amino oleic acid (AOA) and glutaraldehyde tanned porcine tissue treated with AOA. All samples used in these tests were subjected to the maximum number of resterilization cycles (2X) with the exception of the testing of the AOA compound.

The biocompatibility of the AOA compound and the AOA treated Medtronic FREESTYLE® Bioprosthesis were assessed by determining it's influence on: the inflammatory response, cytotoxicity, hemolysis, mutagenicity (Ames genotoxicity), USP rabbit pyrogenicity, systemic toxicity, intracutaneous toxicity, sensitization (Kligman guinea pig), and thrombogenicity. The approach used for the biocompatibility assessment of the Medtronic FREESTYLE® Bioprosthesis is consistent with the intent of the Biological

Evaluation of Medical Devices Memorandum (G95-1) issued by FDA on May 1, 1995. The results of the biocompatibility studies performed support the biocompatibility of the Medtronic FREESTYLE® Bioprosthesis.

A health risk assessment was done to assess the amount of the glutaraldehyde that leaches out over time from the tissue. All tests were negative, and the amount of glutaraldehyde leaching out was 0.069 mg/l, which peaked at 4 hours, and was less than the 20.5 mg/l used in the acute toxicity test. The applicant did not conduct carcinogenicity, subchronic, chronic or reproductive toxicity testing because glutaraldehyde tanned porcine tissue has a long history of use, the device does not contact soft tissue, and no leachable components were detected during acute testing.

9.1.2 Hydrodynamic Performance

9.1.2.1 Test Chamber Development

Test chamber development for the *in vitro* evaluation of the Medtronic FREESTYLE® Bioprosthesis took into consideration that the aortic valve in it's natural state does not have a fixed shape and can only be described at a given time in the cardiac cycle such as mid-systole or mid-diastole. Another consideration was that the aorta expands quite easily at low internal pressure but stiffens at higher pressures to prevent ballooning.

In order to produce simulated aortas of consistent, repeatable geometry and dimensions, steel compression molds were produced. Model aortas were constructed from silicone rubber formulated to produce the desired compliance for the *in vitro* tests, and cured until the molded part was stabilized. Dimensions were patterned from data available through published clinical literature. The geometry of the model aorta was based on the normal human adult aorta rather than a diseased aorta, since the geometry of the diseased aorta varies with the type and extent of the disease.

Hydrodynamic performance testing was conducted on Medtronic FREESTYLE® Bioprostheses mounted in these compliant test chambers. Table 4 is a summary of the hydrodynamic performance testing.

Table 4. ***Summary of Hydrodynamic Performance Testing***

Test	Number of Samples: Freestyle	Number of Samples Control: Model 242	Pass/Fail Criteria	Results
Steady State Flow Pressure Drop	15 (3 of each size) for each implant technique (full-root, root inclusion, subcoronary)	4 (3 size 31mm, 1 size 19mm)	Pressure Drop to be ≤ the Control valve	Pass
Pulsatile Flow Pressure Drop	15 (3 of each size) for each implant technique (full-root, root inclusion, subcoronary)	4 (3 size 31mm, 1 size 19mm)	Pressure Drop to be ≤ the Control valve.	Pass
Pulsatile Flow Regurgitation (Regurgitant Volume)	15 (3 of each size) for each implant technique (full-root, root inclusion, subcoronary)	4 (3 size 31mm, 1 size 19mm)	Regurgitant Volume to be ≤ to Control valve of equivalent flow area.	Pass
Dynamic Regurgitation (Leakage Volume vs Back Pressure)	15 (3 of each size) for each implant technique (full-root, root inclusion, subcoronary)	4 (3 size 31mm, 1 size 19mm)	Leakage Volume to be ≤ to Control valve of equivalent flow area.	Pass
In-Vitro Doppler Ultrasound	3 for each implant technique (full-root, root inclusion, subcoronary) size 19mm, 23mm, and 27mm	N/A	Assessment: Determine if the Bernoulli equation $\Delta P = 4(V_2^2 - V_1^2)$ may be used to assess peak and mean pressure gradients	Bernoulli equation works well within the experimental error (5%).
Flow Visualization (Color Doppler Flow Mapping)	1 (27mm)	N/A	Qualitatively visualize leaflet motion and downstream flow fields.	Flow accelerates uniformly through the valve with a uniform flat profile downstream. No appearance of a jet with steep velocity gradients.
Accelerated Wear tested at room temperature, in sterile/filtered saline, at 1450 RPM, peak closed valve pressure drop = 110± 5mmHg	52 (3 of each size 19mm through 25mm) (6 27mm)-full root, (3 of each size) subcoronary, root inclusion (3 Non-AOA treated, two 19mm; one 23mm)-	4 (size 31mm)	Wear (as defined by abrasion, tears, holes, coaptation, Delamination and other characteristics) to be ≤ the Control valve.	Pass. Observed Wear- No valve failures for either Freestyle or control. Wear patterns were similar to control wear. Most Frequent wear- 1.wear abrasion caused by contact to fraying aortic sutures; 2. surface abrasion; 3. holes, resulting from abrasion; 4. tears resulting from abrasion.

9.1.2.2 Steady State Flow Pressure Drop

Steady state flow testing to examine pressure drop as a function of flow rate was performed on each size of the Medtronic FREESTYLE® Bioprosthesis (19 mm, 21 mm, 23 mm, 25 mm & 27 mm. The aortic Hancock Standard valve (31 mm & 19 mm) was used as a control.

FULL ROOT CONFIGURATION

The results demonstrated that the steady state flow mean pressure drop across the Medtronic FREESTYLE® Bioprosthesis in all sizes was lower than the pressure drop across the 19 mm Hancock Standard control valve. In addition, the mean steady state flow pressure drop across the 25 mm and 27 mm Medtronic FREESTYLE® Bioprostheses was lower than the mean pressure drop across the 31 mm Hancock Standard control valve.

ROOT INCLUSION AND SUBCORONARY CONFIGURATIONS

The results demonstrated that the steady state flow mean pressure drop across the Medtronic FREESTYLE® Bioprosthesis, in sizes 25 mm and 27 mm, was lower than the mean pressure drop across the 31 mm Hancock Standard control valve.

9.1.2.3 Pulsatile Flow Pressure Drop

Pulsatile flow pressure drop testing was completed on each size of the Medtronic FREESTYLE® Bioprosthesis (19 mm, 21 mm, 23 mm 25 mm & 27 mm). The aortic Hancock Standard valve (31 mm & 19 mm) was used as a control. Testing was performed at a cardiac output range of 2.5 to 7.5 L/min, and a pulse rate of 70 beats per minute (bpm), with systole accounting for approximately 35% of the simulated cardiac cycle.

FULL ROOT CONFIGURATION

The results demonstrated that the pulsatile flow mean pressure drop across the Medtronic FREESTYLE® Bioprosthesis in all sizes was lower than the pressure drop across the 19 mm Hancock standard control valve. In addition, the mean pressure drop across the Medtronic FREESTYLE® Bioprosthesis, in sizes 25 mm and 27 mm, was lower than the mean pressure drop across the 31 mm Hancock Standard control valve.

ROOT INCLUSION AND SUBCORONARY CONFIGURATIONS

The results demonstrated that the pulsatile flow mean pressure drop across the 25 mm and 27 mm sized Medtronic FREESTYLE® Bioprosthesis was lower than the mean pressure drop across the 31 mm Hancock Standard control valve.

9.1.2.4 Pulsatile Flow Regurgitation

Pulsatile flow regurgitation was completed on each size of the Medtronic FREESTYLE® Bioprosthesis (19 mm, 21 mm, 23 mm 25 mm & 27 mm). The aortic Hancock Standard valve (31 mm & 19 mm) was used as a control. Testing was performed at 5.0 L/min and a pulse rate of 70 beats per minute (bpm), with systole accounting for approximately 35% of the simulated cardiac cycle. Regurgitant volume versus back pressure (closing pressures applied to the valve) data were obtained at back pressures (mean arterial pressure) of 90, 110, 130 and 150 mmHg.

FULL ROOT CONFIGURATION

- ***Total Regurgitant Volume***: The pulsatile flow regurgitation data demonstrates that the total regurgitant volume for the Medtronic FREESTYLE® Bioprosthesis and the Hancock Standard control valve was less than 7 ml/beat.

- *Closing Volume*: The pulsatile flow regurgitation data demonstrates that the closing volume was less than 4 ml/beat for the Medtronic FREESTYLE® Bioprosthesis and the Hancock Standard control valve.
- *Leakage Volume*: The pulsatile flow regurgitation data demonstrates that the leakage volume was less than 4 ml/beat for the Medtronic FREESTYLE® Bioprosthesis and the Hancock Standard control valve.

ROOT INCLUSION AND SUBCORONARY CONFIGURATIONS

- *Total Regurgitant Volume*: The pulsatile flow regurgitation data demonstrates that the total regurgitant volume for the Medtronic FREESTYLE® Bioprosthesis and the Hancock Standard control valve was less than 8 ml/beat.
- *Closing Volume*: The pulsatile flow regurgitation data demonstrates that the closing volume was less than 4 ml/beat for the Medtronic FREESTYLE® Bioprosthesis and the Hancock Standard control valve.
- *Leakage Volume*: The pulsatile flow regurgitation data demonstrates that the leakage volume was less than 4 ml/beat for the Medtronic FREESTYLE® Bioprosthesis and the Hancock Standard control valve.

9.1.2.5 Dynamic Regurgitation

Pulsatile flow regurgitant volume versus beat rate (dynamic regurgitation) testing was completed on each size of the Medtronic FREESTYLE® Bioprosthesis (19 mm, 21 mm, 23 mm 25 mm & 27 mm) configured for the full root technique. The aortic Hancock Standard valve (31 mm & 19 mm) was used as a control. Testing was performed using a simulated heart rate of 50, 70 and 100 beats per minute (bpm), with systole accounting for approximately 35% of the simulated cardiac cycle, and a cardiac output of 5.0 L/min. The valves were tested at a back pressure (mean arterial pressure) of 90 mmHg.

The results demonstrated that the mean total Regurgitant volume was less than 7 ml/beat for the Medtronic FREESTYLE® Bioprosthesis and the Hancock Standard control valve.

9.1.2.6 In Vitro Doppler Ultrasound

In Vitro Doppler Ultrasound was used to determine if the Bernoulli relationship, $\Delta P = 4(V_2^2 - V_1^2)$, may be used to noninvasively assess pressure gradients in patients implanted with a Medtronic FREESTYLE® Bioprosthesis using the full root, root inclusion and subcoronary technique. Three Medtronic FREESTYLE® Bioprostheses, 19mm, 23mm, and 27mm were used for each technique. The study was conducted at cardiac outputs in the range of 2.5 to 8.0 L/min., at a pulse rate of 70 bpm, with systolic duration of 280 to 320 msec (35% of the simulated cardiac cycle). Mean aortic pressure was 90 to 100 mmHg and mean left atrial pressure was 5 to 10 mmHg. An aqueous solution of saline with a viscosity of 1.0 cP was used as a blood analog fluid at a temperature of 22° C, with 1-2 % cornstarch particles added to the fluid to act a acoustic scatterers.

For the ultrasound Doppler, the root mean square velocities and the mean systolic pressure drops at 30mm and 100mm distal locations indicate that the Bernoulli equation works well within experimental error (within 5%) with the Medtronic FREESTYLE® Bioprosthesis using the full root, root inclusion and subcoronary technique.

9.1.2.7 Flow Visualization

Color Doppler Flow Mapping (CDFM) was utilized to qualitatively visualize the downstream flow field of a 27 mm Medtronic FREESTYLE® Bioprosthesis in all configurations. The 27 mm sized valve was chosen since it was the largest annulus size. The study was conducted at a heart rate of 70 bpm, systolic

duration of approximately 280 msec (35% of the simulated cardiac cycle), mean aortic pressure of 100 mmHg, and cardiac outputs of approximately 3.0 and 5.0 L/min.

The study showed good opening of the valve leaflets by CDFM, M-mode and 2D echo. The flow accelerated uniformly through the valve and appeared to have a uniform flat profile downstream of the prosthesis. There was no appearance of a jet with steep velocity gradients, as has been observed with stented porcine bioprostheses. The flow visualization study demonstrated that the Medtronic FREESTYLE® Bioprosthesis utilizing the full root technique has a more uniform and less turbulent flow field when compared to stented porcine bioprostheses.

9.1.3 Structural Performance (Accelerated Wear)

9.1.3.1 Accelerated Wear

Accelerated wear testing was performed on Shelhigh accelerator testers. Wear was defined as abrasion, tears, holes, coaptation, delamination, and other characteristics, and should be less than that of the control valve. A peak closed-valve pressure drop of 110 ± 5 mmHg was maintained. Each valve was visually examined and photographed prior to initiation of the test. All valves were tested for a minimum of 200 x 10^6 cycles with visual examination and photographs taken at every 20 X 10^6 cycles. Test parameters were monitored on a routine basis.

All of the Medtronic FREESTYLE® Bioprostheses (AOA and nonAOA treated) demonstrated normal functioning as exhibited by proper opening and closing along with the maintenance of a closed valve pressure drop throughout the 200 X 10^6 cycles. All observed tissue wear anomalies were determined to be artifactual of the test fixture and environment.

FULL ROOT CONFIGURATION

Accelerated wear testing was completed on 18 Medtronic FREESTYLE® Bioprostheses (3 per size: 19 mm, 21 mm 23 mm & 25 mm; 6 per size: 27 mm) treated with AOA and 3 non-AOA treated FREESTYLE® Bioprostheses (2 per size: 19 mm and 1 per size: 23 mm). Three (3) aortic Standard Hancock valves (size 31 mm) were used as controls. Tester speed and stroke volume were adjusted to allow typical leaflet excursion (full opening and closing) during cardiac cycling with the tester speed eventually being established at 1310 rpm.

ROOT INCLUSION & SUBCORONARY CONFIGURATIONS

Accelerated wear testing was completed on three (3) Medtronic FREESTYLE® Bioprostheses of each size (19 mm, 21 mm 23 mm, 25 mm & 27 mm) and configuration for a total of 30 valves. One (1) aortic Standard Hancock (size 31 mm) valve was used as a control. Tester speed and stroke volume were adjusted to allow typical leaflet excursion (full opening and closing) during cardiac cycling with the tester speed being established at 1450 rpm.

9.1.3.2 Accelerated Wear - Hydrodynamic Assessment

Pulsatile flow pressure drop and valvular regurgitation were assessed on the accelerated wear test valves and control valves. The test and control valves were the same as those described for the accelerated wear configurations.

Pulsatile flow pressure drop was performed at a cardiac output range of 2.5 to 7.5 L/min, and a pulse rate of 70 beats per minute (bpm), with systole accounting for approximately 35% of the simulated cardiac cycle. Pulsatile flow regurgitant volume tests were performed at 5.0 L/min and a pulse rate of 70 bpm. Regurgitant volume versus back pressure data were obtained at back pressures of 80, 100, 120, 140 and 160 mmHg. Hydrodynamic assessment occurred at the pretest, 60 X 10^6, 120 X 10^6 and 200 X 10^6 cycle intervals of the accelerated wear testing.

FULL ROOT CONFIGURATION

The pulsatile flow pressure drop and total regurgitant volume in some valves were significantly lower after durability cycling (accelerated wear) than before cycling. The difference for all valves, except one outlier (19 mm Medtronic FREESTYLE® Bioprosthesis; pre to 2000 X 10^6 difference equals 2.2 mmHg), was found to be within the test system accuracy (±1 mmHg and ±1ml/beat).

ROOT INCLUSION AND SUBCORONARY CONFIGURATIONS

The pulsatile flow pressure drop and total regurgitant volume in most valves were found to be unaffected by accelerated wear cycling which means that the observed differences were found to be within the accuracy of the test system (±1 mmHg and 1± ml/beat). Some valves, during the course of the accelerated wear testing, did exhibit changes in hydrodynamic performance (i.e., increase in total regurgitant volume). Artifactual related damage to the valves along with the rigidity of the test apparatus were found to be contributing causes to the altered hydrodynamic performance of the device.

9.2 Animal Studies

Two *in-vivo* animal studies (acute and chronic) were performed on the Medtronic FREESTYLE® Bioprosthesis. The first was a short-term implant (acute) study in the adult sheep model which was designed to evaluate the hemodynamic efficacy and surgical handling characteristics of the device. The short term study involved implantation of 6 bioprostheses (size 19 mm) in mature sheep. Five of the 6 animals were sacrificed between 6 to 10 weeks post-implant and the sixth animal was sacrificed 16 months post implant. The results of the short term (acute) sheep implantation study demonstrated the following surgical handling characteristics of the Medtronic FREESTYLE® Bioprosthesis:

- comparable to aortic root replacement using an allograft valve;
- accurate sizing was critical;
- coronary artery implantation was without difficulty; and
- cloth reinforcement of the proximal orifice prevented dehiscence.

Hemodynamically, the transvalvular pressure gradient for the 19 mm Medtronic FREESTYLE® Bioprosthesis was found to be comparable to the small mean differential pressures noted clinically with 19 mm aortic homografts. Explant pathology findings described for valves implanted in the short-term study are similar to those reported following studies of implantation in juvenile sheep; however, no leaflet calcification was noted. Hematocrit and hemoglobin values were noted to be normal at the time of explant.

The second study was a long-term implant (chronic) study which was performed in juvenile sheep in an effort to determine the effect of AOA as a potential antimineralization treatment. A total of 16 Medtronic FREESTYLE® Bioprostheses (7 AOA Treated and 9 NonAOA Treated) were implanted as an apico-aortic bypass graft for a 20 week period. Three Hancock, Model 105, size 18mm valved conduits, were used as controls to assess the potential of the animal model to mineralize a commercially available standard high pressure-fixed porcine bioprosthesis. The results of the study showed a significant difference ($p<0.0002$) in leaflet calcium for AOA-treated valves when compared to the non-AOA treated valves. Although little to no mineralization of treated leaflets was observed, the aortic wall segment of the treated and control valves was found to be focally calcified.

In addition to the sheep studies, a series of subdermal rat implant studies were performed, utilizing treated (AOA) and non-treated samples. The implant duration was 1, 2, 3, and 4 months. For the period of time studied, the AOA treated samples contained significantly less calcium (mg of calcium/mg dry tissue) than the untreated.

9.3 Sterilization

The Medtronic FREESTYLE® Bioprosthesis is sterilized in a 0.2% buffered glutaraldehyde solution with placement of the packaged valve assembly into an incubator for terminal sterilization at 38°C - 42°C for 20 -22 hours. After completion of terminal sterilization the product is held in quarantine until sterility is verified in accordance with process specifications. Annual requalification of the sterilization process is performed.

9.4 Shelf Life

The shelf life for the Medtronic FREESTYLE® Bioprosthesis underwent qualification testing to ensure that both package and product integrity had been maintained after aging to three years. The package integrity samples were exposed to accelerated aging to three years; whereas, the product integrity samples underwent real time aging to a minimum of three years.

9.4.1 Package Integrity

Package integrity was assessed by testing the sterile barrier of the Medtronic FREESTYLE® Bioprosthesis. The testing included a vacuum leak test (60 aged samples), lid removal torque test (60 aged samples/30 non-aged samples), solution volume check test (60 aged samples), and a microbial challenge (37 test samples, 2 positive controls, 1 negative control). All test samples were subjected to a worst-case processing condition for sterilization of 3 cycles (maximum manufacturing specification of two cycles plus one additional cycle) and environmental stress conditioning as well as having undergone a shipping and handling test prior to performance of the sterile barrier tests.

9.4.2 Product Integrity

The product integrity portion of the shelf life assessment consisted of a battery of tests which were designed to affirm the functionality of the valve through the examination of multiple aspects of valve performance and structure. The qualification included the following tests: shrink temperature (10 aged samples, 10 non-aged samples), collagen content (enzyme susceptibility) (10 aged samples, 10 non-aged samples, 10 fresh controls), moisture content (10 aged samples, 10 non-aged samples), hydrodynamic performance (3 aged test valves 19/23/27 mm, 1 non-aged control), biaxial mechanical (7 aged valves, 7 non-aged valves), histological evaluation (3 aged valves 19/23/27 mm, 1 non-aged control), storage solution pH (15 samples), and glutaraldehyde percentage (15 samples). All 3 year real time aged samples had been sterilized two times (maximum allowed per manufacturing specification) and underwent environmental stress conditioning before the product integrity assessment was performed.

The pre-established criteria for the package and product integrity testing were found to have been met. Thus, the Medtronic FREESTYLE® Bioprosthesis is considered to be qualified for a three year shelf life.

10.0 Summary of Clinical Studies

10.1 Objectives

The primary objectives of the study were to evaluate the effectiveness, safety, and clinical performance of the Medtronic FREESTYLE® Bioprosthesis in patients requiring isolated aortic heart valve replacement. Specifically, improvement in coronary function as measured by NYHA classification at baseline and follow-up; and, improvement in hemodynamic performance, in terms of mean pressure gradient, effective orifice area (EOA), cardiac output and prosthesis regurgitation. The study compared the implantation and short- and mid-term performance of the Medtronic FREESTYLE® Bioprosthesis with the published literature on tissue valves, which serves as a source of benchmarks for evaluating efficacy in terms of mean pressure gradient and regurgitation, and EOA. FDA reviewed the published literature and approved three

articles which contained results directly comparable to the Medtronic FREESTYLE® Bioprosthesis for mean pressure gradient and regurgitation.

Objective performance criteria were used to evaluate safety in terms of adverse events: thromboembolism, valve thrombosis, hemorrhage, paravalvular leak, endocarditis, hemolysis, valve deterioration, and valve dysfunction. In addition to mortality data, reoperation and explant data were also collected.

10.2 Study Design

From 1992 to 1997, a prospective non-randomized international study evaluated the Medtronic FREESTYLE® Bioprosthesis at 21 centers with patient follow-up out to three years. A total of 882 patients received the bioprosthesis using three implant techniques: the subcoronary cohort included 640 patients; the full-root cohort included 159 patients; and, the root-inclusion cohort included 83 patients.

10.2.1 Inclusion Criteria

Patients who were diagnosed as having sufficient symptoms to warrant isolated replacement of their natural aortic valve or root, or previously implanted prosthetic or bioprosthetic aortic valve were eligible to enter the study. An isolated procedure was defined as one in which only the aortic valve (or root) was replaced, with the three remaining valves being the native valves. Concomitant procedures (other than valve replacement) were permitted.

10.2.2 Exclusion Criteria

Patients who required concomitant valve replacement or who already had a pre-existing prosthetic valve in another position were excluded from enrollment in the study.

10.2.3 Data Collection

Patients were evaluated preoperatively, within 30 days post-operatively, at 3 and 6 months, and annually. Patients were monitored throughout the postoperative period for possible adverse events. The cumulative follow-up was 1246 patient-years with a mean follow-up of 17 months (SD = 12 months, range = 0 to 42 months). Table 5 describes patient follow-up by implant technique and valve size.

Table 5. Number of Patients by Duration of Follow-up and Implant Technique

All patients implanted, approved sizes, N = 882

Implant Technique	Duration of follow-up (years)				
	0	1	2	3	3.5
	Number of patients by technique by year				
Total	882	552	348	96	1
Subcoronary	640	416	255	58	1
Full-Root	159	81	48	20	0
Root-Inclusion	83	55	45	18	0
Size	Number of patients by size by year				
19mm	36	22	12	4	0
21mm	149	91	57	13	0
23mm	250	156	99	26	1
25mm	236	153	99	31	0
27mm	212	130	81	22	0

10.3 Analysis for Gender Bias

Study inclusion and exclusion criteria were designed and the study carried out to avoid gender bias in patient enrollment. Of all patients enrolled, 335 of 631 (53%) were male. This proportion of males (335/296 = 1.1) is consistent with the male to female incidence of patients presenting for valve replacement in the US and Canada.

Based on risk factors analyses, the underlying distribution of complications did not vary by gender. Comparing EOA, mean and peak systolic gradient, and cardiac index between females and males, there was no statistically significant difference in hemodynamic performance based on gender. Hence, the results presented in the following analyses are representative for both men and women.

10.4 Description of Patients

The subcoronary cohort included 640 patients implanted with the bioprosthesis. Five patients had perioperative explants and 4 patients had multiple prostheses (mitral valve), and were not included in the analysis. Of the remaining 631 patients, 335 were men and 296 were women. Cumulative follow-up was 913 patient-years with mean follow-up of 1.4 years per patient (SD = 0.9 years, range = 0 to 3.5 years. Table 6 presents patient characteristics for the subcoronary technique.

Table 6. Patient Characteristics: Subcoronary Technique; All patients analyzed, N = 631

Age at implant in years (mean ± SD, N [min, max]	71 ± 8, 631 [32,91]
Gender (% male / % female)	53% / 47%
Etiology	
Stenosis - percent of patients with stenosis alone [%(number in subgroup / N)]	43% (272 / 631)
Insufficiency - percent of patients with insufficiency alone [%(number in subgroup / N)]	6% (39 / 631)
Mixed - percent of patients with stenosis and insufficiency [%(number in subgroup / N)]	50% (318 /631)
Other [1] - percent of patients with etiology other than stenosis or insufficiency [%(number in subgroup / N)]	0% (2/631)

[1] One patient had incidental replacement of a previously implanted prosthesis and one patient had endocarditis without lesion.

The full-root cohort included 159 patients implanted with the bioprosthesis. Two patients had multiple implants (mitral valve) and were not included in the analysis. Of the remaining 157 patients, 80 were male and 77 were female. Cumulative follow-up was 189 patient-years with mean follow-up of 1.2 years per patient (SD = 1.1 years, range = 0 to 3.2 years). Table 7 presents patient characteristics for the full-root technique.

Table 7. Patient Characteristics: Full-Root Technique; All patients analyzed, N = 157

Age at implant in years (mean ± SD, N [min, max]	70 ± 8, 157 [38,87]
Gender (% male / % female)	51% / 49%
Etiology	
Stenosis - percent of patients with stenosis alone [%(number in subgroup / N)]	31% (49 / 157)
Insufficiency - percent of patients with insufficiency alone [%(number in subgroup / N)]	21% (33 / 157)
Mixed - percent of patients with stenosis and insufficiency [%(number in subgroup / N)]	47% (74 /157)
Other [1] - percent of patients with etiology other than stenosis or insufficiency [%(number in subgroup / N)]	1% (1/157)

[1] One patient had a dissecting ascending aortic aneurysm.

The root-inclusion cohort included 83 patients implanted with the bioprosthesis. Three patients had perioperative explants and were excluded from the analysis. Of the remaining 80 patients, 58 were male and 22 were female. Cumulative follow-up was 139 patient-years with mean follow-up of 1.7 years per patient (SD = 1.1 years, range = 0 to 3.3 years). Table 8 presents patient characteristics for the root-inclusion technique.

Table 8. Patient Characteristics: Root-Inclusion Technique; All patients analyzed, N = 80

Age at implant in years (mean ± SD, N [min, max]	69 ± 9, 80 [40, 90]
Gender (% male / % female)	73% / 28%
Etiology	
Stenosis - percent of patients with stenosis alone [%(number in subgroup / N)]	41% (33 / 80)
Insufficiency - percent of patients with insufficiency alone [%(number in subgroup / N)]	11% (9 / 80)
Mixed - percent of patients with stenosis and insufficiency [%(number in subgroup / N)]	48% (38 /80)

10.4 Data Analyses

10.4.1 Functional NYHA

At baseline, 75% of the 631Subcoronary patients were NYHA Classes III and IV. At one year follow-up, 8 patients were in Classes III and IV, or 2% of the 454 patients evaluated at one year. For the 157 Full-Root Technique patients, 78% were in Classes III and IV at baseline; none of the 87 patients evaluated at one year were in Classes III and IV. For the 80 Root-Inclusion Technique patients, 69% were in Classes III and IV at baseline; None of the 54 patients evaluated at one year were in Classes III and IV. These results by implant technique are presented in tables 9, 10 and 11.

Table 9. Effectiveness Outcomes, Functional NYHA: Subcoronary Technique

All patients analyzed: N = 631, mean ± SD (number), percent (numerator / N)

Endpoint	Preoperative	3 - 6 Months	One Year
Functional NYHA	2.9 ± 0.6 (631)	1.2 ± 0.5 (525)	1.2 ± 0.5 (454)
I - % of patients in NYHA class I	2% (14 / 631)	80% (419 / 525)	84% (380 / 454)
II - % of patients in NYHA class II	20% (129 / 631)	18% (96 / 525)	14% (64 / 454)
III - % of patients in NYHA class III	61% (400 / 631)	2% (10 / 525)	2% (8 / 454)
IV - % of patients in NYHA class IV	14% (88 / 631)	0% (0 / 525)	0% (2 / 454)

Table 10. Effectiveness Outcomes, Functional NYHA: Full-Root Technique

All patients analyzed: N = 157, mean ± SD (number), percent (numerator / N)

Endpoint	Preoperative	3 - 6 Months	One Year
Functional NYHA	2.9 ± 0.7 (155)	1.1 ± 0.2 (114)	1.1 ± 0.3 (87)
I - % of patients in NYHA class I	1% (2 / 155)	94% (107 / 114)	91% (79 / 87)
II - % of patients in NYHA class II	20% (31 / 155)	6% (7 / 114)	9% (8 / 87)
III - % of patients in NYHA class III	61% (95 / 155)	0% (0 / 114)	0% (0 / 87)
IV - % of patients in NYHA class IV	17% (27 / 155)	0% (0 / 114)	0% (0 / 87)

Table 11. Effectiveness Outcomes, Functional NYHA: Root-Inclusion Technique

All patients analyzed: N = 80, mean ± SD (number), percent (numerator / N)

Endpoint	Preoperative	3 - 6 Months	One Year
Functional NYHA	2.7 ± 0.6 (80)	1.2 ± 0.6 (60)	1.1 ± 0.3 (54)
I - % of patients in NYHA class I	5% (4 / 80)	87% (52 / 60)	91% (49 / 54)
II - % of patients in NYHA class II	26% (21 / 80)	10% (6 / 60)	9% (5 / 54)
III - % of patients in NYHA class III	68% (54 / 80)	3% (2 / 60)	0% (0 / 54)
IV - % of patients in NYHA class IV	1% (1 / 80)	0% (0 / 60)	0% (0 / 54)

10.4.2 Hemodynamics, Valvular Regurgitation

The published literature reports 63.4% of patients (2 articles) with no regurgitation postoperatively during the first month or "in-hospital"; 38% of patients (1 article) with no regurgitation at 1 year; and, 7.3% of patients (1 article) with moderate to severe regurgitation at 1 year (or the last evaluation, or within 1 to 81 months). The results for the Medtronic FREESTYLE® Bioprosthesis by implant technique are presented in tables 12, 13 and 14, and indicate that for all implant techniques, valve leakage was trivial or mild and did not increase in severity over time.

Table 12. Effectiveness Outcomes, Hemodynamics, Valvular Regurgitation: Subcoronary Technique

All patients analyzed: N = 631, mean ± SD (number), percent (numerator / N)

Endpoint	< 30 Days	3 - 6 Months	One Year
Valvular Regurgitation [1]	0.3 ± 0.4 (552)	0.3 ± 0.5 (523)	0.3 ± 0.4 (456)
0% of patients with no Rg.	65% (358/ 552)	62% (326 / 523)	65% (296 / 456)
< 1+ % of patients with < mild Rg.	15% (82 / 552)	17% (87 / 523)	20% (92 / 456)
1+ % of patients with mild Rg.	20% (108 / 552)	19% (101 / 523)	13% (61 / 456)
2+ % of patients with mod Rg.	1% (3 / 552)	2% (8 / 523)	1% (5 / 456)
3+ / 4+% of patients with mod/severe Rg.	0% (1 / 552)	0% (1 / 523)	0% (2 / 456)

Rg. = Regurgitation

[1] The data reflect regurgitation noted at all locations combined. Data coded as "trivial/mild" were included in the category "< 1+, < mild regurgitation." Data in the category "< 1+ " were coded as "0.5" for the calculation of mean ± SD.

Table 13. Effectiveness Outcomes, Hemodynamics, Valvular Regurgitation: Full-Root Technique

All patients analyzed: N = 157, mean ± SD (number), percent (numerator / N)

Endpoint	< 30 Days	3 - 6 Months	One Year
Valvular Regurgitation [1]	0.1 ± 0.3 (131)	0.1 ± 0.3 (113)	0.1 ± 0.2 (90)
0% of patients with no Rg.	86% (113/ 131)	87% (98 / 113)	87% (78 / 90)
< 1+ % of patients with < mild Rg.	8% (10 / 131)	8% (9 / 113)	11% (10 / 90)
1+ % of patients with mild Rg.	5% (7 / 131)	4% (5 / 113)	2% (2 / 90)
2+ % of patients with mod Rg.	1% (1 / 131)	1% (1 / 113)	0% (0 / 90)
3+ / 4+% of patients with mod/severe Rg.	0% (0 / 131)	0% (0 / 113)	0% (0 / 90)

Rg. = Regurgitation

[1] See footnote for Table 12.

Table 14. Effectiveness Outcomes, Hemodynamics, Valvular Regurgitation: Root-Inclusion Technique

All patients analyzed: N = 80, mean ± SD (number), percent (numerator / N)

Endpoint	< 30 Days	3 - 6 Months	One Year
Valvular Regurgitation [1]	0.2 ± 0.4 (75)	0.1 ± 0.3 (63)	0.2 ± 0.3 (51)
0% of patients with no Rg.	77% (58/ 75)	79% (50 / 63)	76% (39 / 51)
< 1+ % of patients with < mild Rg.	15% (11 / 75)	14% (9 / 63)	16% (8 / 51)
1+ % of patients with mild Rg.	5% (4 / 75)	6% (4 / 63)	8% (4 / 51)
2+ % of patients with mod Rg.	3% (2 / 75)	0% (0 / 63)	0% (0 / 51)
3+ / 4+% of patients with mod/severe Rg.	0% (0 / 75)	0% (0 / 63)	0% (0 / 51)

Rg. = Regurgitation
[1] See footnote for Table 12.

10.4.3 Hemodynamics, Mean Pressure Gradient

The FDA selected literature articles report 77% of patients (1 article) with a mean gradient < 10 mm Hg postoperatively for stented valves. The results for the Medtronic FREESTYLE® Bioprosthesis by implant technique are presented in tables 15, 16, and 17, and indicate improved gradients over time for all implant techniques and most valve sizes within a technique, nearing physiologic values at one year.

Table 15. Effectiveness Outcomes, Hemodynamics, Mean Pressure Gradient: Subcoronary Technique

All patients analyzed: N = 631, number in subgroup/N, mean ± SD [min, max]

Endpoint	< 30 Days	3 - 6 Months	One Year
Mean Pressure Gradient (mmHg)			
19mm	19/27, 17.6 ± 7.6 [8.0, 42.0]	19/27, 12.0 ± 5.7 [2.0, 23.0]	18/27, 11.7 ± 4.7 [5.0, 19.0]
21mm	100/117, 14.6 ± 8.1 [1.0, 48.0]	91/117, 9.0 ± 6.2 [1.0, 47.0]	83/117, 9.8 ± 7.4 [0.8, 51.0]
23mm	165/191, 12.9 ± 6.9 [2.0, 39.0]	156/191, 8.9 ± 5.9 [1.0, 35.0]	138/191, 8.8 ± 6.8 [0.0, 57.0]
25mm	145/167, 9.1 ± 4.6 [1.0, 28.0]	146/167, 5.5 ± 3.3 [1.0, 19.0]	119/167, 5.1 ± 3.3 [0.0, 18.0]
27mm	112/129, 7.3 ± 4.1 [1.0, 22.0]	110/129, 5.0 ± 3.7 [1.0, 30.0]	92/129, 4.4 ± 2.9 [0.7, 13.0]

Table 16. Effectiveness Outcomes, Hemodynamics, Mean Pressure Gradient: Full-Root Technique

All patients analyzed: N = 157, number in subgroup/N, mean ± SD [min, max]

Endpoint	< 30 Days	3 - 6 Months	One Year
Mean Pressure Gradient (mmHg)			
19mm	7/7, 11.9 ± 6.0 [6.0, 23.0]	7/7, 13.4 ± 6.7 [7.0, 27.0]	5/7, 16.8 ± 7.4 [9.0, 27.1]
21mm	14/21, 7.8 ± 3.4 [2.0, 14.0]	12/21, 7.6 ± 3.5 [2.0, 14.0]	9/21, 7.2 ± 4.0 [3.0, 14.0]
23mm	20/32, 6.8 ± 3.8 [0.9, 13.0]	20/32, 5.4 ± 3.4 [1.0, 12.0]	13/32, 7.1 ± 3.7 [1.6, 14.0]
25mm	31/35, 4.9 ± 2.9 [1.0, 12.0]	29/35, 4.2 ± 2.9 [1.0, 12.0]	23/35, 4.5 ± 3.4 [1.0, 17.0]
27mm	59/62, 4.4 ± 3.4 [1.0, 20.0]	46/62, 3.8 ± 2.9 [0.7, 15.0]	38/62, 3.2 ± 1.8 [1.0, 8.0]

Table 17. Effectiveness Outcomes, Hemodynamics, Mean Pressure Gradient: Root-Inclusion Technique

All patients analyzed: N = 80, number in subgroup/N, mean ± SD [min, max]

Endpoint	< 30 Days	3 - 6 Months	One Year
Mean Pressure Gradient (mmHg)			
21mm	4/5, 12.3 ± 7.0 [3.0, 20.0]	3/5, 8.0 ± 2.6 [6.0, 11.0]	2/5, 9.0 ± 1.4 [8.0, 10.0]
23mm	21/25, 13.8 ± 10.7 [2.0, 52.0]	17/25, 10.3 ± 12.1 [2.0, 54.0]	14/25, 8.7 ± 8.8 [2.0, 36.0]
25mm	29/30, 9.6 ± 6.7 [2.0, 28.0]	25/30, 8.2 ± 6.7 [2.0, 29.0]	17/30, 7.6 ± 6.8 [2.0, 29.0]
27mm	19/20, 6.4 ± 3.4 [2.0, 14.0]	18/20, 4.4 ± 2.4 [1.0, 8.0]	15/20, 3.7 ± 2.2 [1.0, 8.0]

10.4.4 Hemodynamics, Effective Orifice Area

The results for the Medtronic FREESTYLE® Bioprosthesis by implant technique are presented in tables 18, 19, and 20, and indicate improved effective orifice area over time for all implant techniques and most valve sizes within a technique, when compared to stented valves in FDA selected literature articles, and emphasize a low flow impediment.

Table 18. Effectiveness Outcomes, Hemodynamics, Effective Orifice Area: Subcoronary Technique

All patients analyzed: N = 631, number in subgroup/N, mean ± SD [min, max]

Endpoint	< 30 Days	3 - 6 Months	One Year
Mean Pressure Gradient (mmHg)			
19mm	19/27, 0.9 ± 0.2 [0.5, 1.4]	19/27, 1.1 ± 0.3 [0.6, 1.7]	18/27, 1.1 ± 0.3 [0.7, 1.7]
21mm	97/117, 1.3 ± 0.4 [0.5, 2.4]	91/117, 1.5 ± 0.5 [0.8, 4.3]	82/117, 1.4 ± 0.4 [0.4, 3.1]
23mm	160/191, 1.4 ± 0.5 [0.5, 3.7]	154/191, 1.7 ± 0.5 [0.6, 3.6]	137/191, 1.7 ± 0.5 [0.8, 3.9]
25mm	143/167, 1.8 ± 0.6 [0.4, 3.9]	146/167, 2.0 ± 0.5 [0.9, 3.5]	119/167, 2.0 ± 0.5 [0.8, 3.5]
27mm	110/129, 2.2 ± 0.7 [0.8, 5.1]	109/129, 2.4 ± 0.6 [1.2, 4.1]	92/129, 2.5 ± 0.7 [1.3, 4.4]

Table 19. Effectiveness Outcomes, Hemodynamics, Effective Orifice Area: Full-Root Technique

All patients analyzed: N = 157, number in subgroup/N, mean ± SD [min, max]

Endpoint	< 30 Days	3 - 6 Months	One Year
Mean Pressure Gradient (mmHg)			
19mm	7/7, 1.3 ± 0.4 [0.5, 1.7]	7/7, 1.1 ± 0.3 [0.6, 1.5]	5/7, 1.0 ± 0.1 [0.9, 1.1]
21mm	14/21, 1.5 ± 0.6 [0.9, 3.3]	12/21, 1.7 ± 0.4 [1.2, 2.3]	9/21, 1.4 ± 0.3 [1.1, 1.9]
23mm	19/32, 1.7 ± 0.4 [0.7, 2.4]	19/32, 1.8 ± 0.5 [1.2, 3.0]	13/32, 2.0 ± 0.5 [1.5, 3.3]
25mm	31/35, 2.1 ± 0.6 [1.1, 3.8]	29/35, 2.1 ± 0.5 [1.1, 3.8]	24/35, 2.2 ± 0.6 [1.3, 3.5]
27mm	59/62, 2.1 ± 0.6 [1.1, 4.0]	46/62, 2.3 ± 0.5 [1.3, 3.3]	37/62, 2.4 ± 0.7 [1.3, 4.3]

Table 20. Effectiveness Outcomes, Hemodynamics, Effective Orifice Area: Root-Inclusion Technique

All patients analyzed: N = 80, number in subgroup/N, mean ± SD [min, max]

Endpoint	< 30 Days	3 - 6 Months	One Year
Mean Pressure Gradient (mmHg)			
21mm	4/5, 1.6 ± 0.8 [1.0, 2.8]	2/5, 1.4 ± 0.2 [1.3, 1.5]	2/5, 1.0 ± 0.1 [0.9, 1.2]
23mm	21/25, 1.6 ± 0.6 [0.8, 3.0]	16/25, 1.8 ± 0.5 [0.9, 3.0]	14/25, 1.9 ± 0.4 [1.1, 3.1]
25mm	29/30, 1.9 ± 0.8 [0.9, 3.4]	22/30, 2.2 ± 0.8 [1.2, 3.8]	17/30, 2.2 ± 0.8 [1.0, 3.6]
27mm	19/20, 2.4 ± 0.7 [1.4, 4.0]	18/20, 2.7 ± 0.7 [1.8, 4.7]	15/20, 3.0 ± 0.9 [1.7, 5.0]

11. Conclusions Drawn from Studies

The *in vivo* and *in vitro* performance testing for biocompatibility, immunogenicity, toxicity, steady and pulsatile flow pressure drop, pulsatile and dynamic regurgitation, flow visualization, and accelerated wear/hydrodynamic assessment demonstrates that the Medtronic FREESTYLE® Bioprosthesis meets specifications, performs comparably to the aortic Hancock Standard control valve, and suggests that this device is suitable for long-term implant.

The acute and chronic animal studies in sheep demonstrated that hemodynamic performance and handling were similar to allograft valves, and that the AOA treatment reduced the extent of leaflet calcification when compared to non-AOA treated valves, and commercially available porcine valves. However, inhibition of aortic wall mineralization was not observed. A short-term subdermal implant study (0 - 4 months) in rats using AOA-treated and non-treated valves demonstrated that the AOA-treated samples contained less calcium than the untreated. Calcification of the aortic wall is a concern for the bioprostheses implanted by the root-inclusion and full-root techniques. Since the animal studies did not determine the likelihood and effect of aortic wall calcification, further clinical evaluation is necessary.

The results of the clinical studies submitted in the PMA suggest that the performance of the Medtronic FREESTYLE® Bioprosthesis using the Subcoronary Technique (n = 640 patients) is comparable to stented valve prostheses. A similar assessment cannot be made for the Full-Root Technique (n = 159 patients) or the Root-Inclusion Technique (n = 83 patients) as there were fewer patients implanted using these techniques. However, the clinical experience with the Full-Root and Root-Inclusion Techniques is considered sufficient because the bioprosthesis is provided as a single configuration that the implant team modifies to the desired configuration, and to match the patient's anatomy, prior to insertion by one of the three implant techniques. The labeling will state that there is limited data for the Full-Root Technique in the 19mm, 21mm and 23mm sizes and the Root-Inclusion Technique in the 19mm and 21mm sizes.

This short term study did not reveal calcification of the aortic wall, however, this becomes a concern after longer implant duration. Further clinical evaluation will be necessary to address this issue. The labeling will state that no clinical data are available which evaluate the long-term impact of the AOA treatment in patients.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

13. Panel Recommendations

The panel recommended to approve all sizes and configurations of the device with the following conditions: a post approval study shall be conducted to assess hemodynamic performance to at least 8 years, with

annual clinical assessment which should include NYHA classification, anticoagulant and antiplatelet drugs used, and murmur assessment, with a focus on thromboembolic complications (correlated with age), reoperation, and explant analysis. Physician training was also stipulated, as were labeling refinements to the warnings.

14. FDA Decision

FDA agreed with the recommendations of the Panel, and recommended approval of the 19, 21, 23, 25, and 27 mm sizes for the subcoronary, full-root and root inclusion implant techniques. The conditions of approval include two post-approval studies: one to assess long-term bioprosthesis performance for a period of 10 years in 100 patients currently implanted with the bioprosthesis, with aggressive follow-up for safety and effectiveness outcomes using the IDE protocol or an alternate protocol agreed to by FDA; and, a study involving new patients to assess valve-related death, explant, and re-operation, using the tracking database or other appropriate method of determining the implant population (denominator). The focus of these studies is failure mode and calcification to provide the data necessary for future labeling updates. The third condition of approval asked for additional bench testing of the device in a compliant chamber in an attempt to predict performance in younger patients. The applicant agreed to these three conditions and further agreed to implement a physician training program and to modify the labeling as suggested by FDA. FDA issued an approval order on November 26, 1997. The applicant's manufacturing facility was inspected and was found to be in compliance with the device Good Manufacturing Practice regulations.

15. Approval Specifications

Directions for use: See the labeling.

Hazards to health from use of the device: See indications, contraindications, warnings, precautions and adverse events in the labeling.

Postapproval requirements and restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at http://www.fda.gov/cdrh/pmapage.html.