



*Stenting and Angioplasty with
Protection in Patients at High Risk
for Endarterectomy
(The SAPPHIRE Study)*

AHA Scientific Sessions

November 19, 2002



Presented By Dr. Jay S. Yadav on Behalf of the Sapphire Investigators

<u>Institution</u>	<u>Principal Investigator(s)</u>	<u>Randomized Patients</u>	<u>Registry Patients</u>
The Cleveland Clinic	Patrick Whitlow, MD	90	56
Shadyside Hospital	Mark Wholey, MD	12	62
Prairie Cardiovascular	Greg Mishkel, MD	42	26
St. Luke's Medical Center	Tanvir Bajwa, MD / Arvind Ahuja MD	28	31
St. Luke's Medical Towers	Neil Strickman, MD	28	24
Midwest Cardiology Research Foundation	Gary Ansel, MD	16	31
St. Elizabeth's Hospital	Ken Rosenfield, MD / Robert Shainfield / Peter Soukas, MD	10	17
Union Memorial	Frank Criado, MD	0	25
Fountain Valley / Hoag Hospital	Subbarao Myla, MD	3	20
The Heart Institute of Spokane	Rod Raabe, MD	7	13
North Central Heart Institute	Michael Bacharach, MD	14	4
Kaiser Permanente	Robert Hye, MD	9	8
Miami Cardiac & Vascular Institute	Barry Katzen, MD	5	11
Hahnemann Hospital	Dan McCormick, MD	7	7
Cardiovascular Institute of the South	David Allie, MD / Craig Walker MD	0	13
Washington Adventist	Fayaz Shawl, MD	1	12



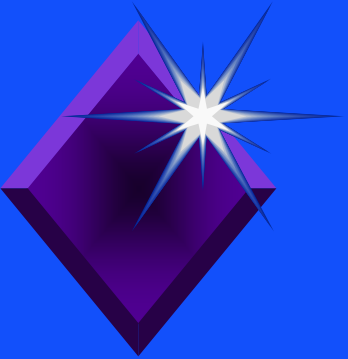
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of the Sapphire Investigators***

<u>Institution</u>	<u>Principal Investigator</u>	<u>Randomized Patients</u>	<u>Registry Patients</u>
Mission Hospital	John Belville, MD	3	10
Comprehensive Stroke Center	Souheil Saddekni, MD / Ming Liu, MD / Camilo Gomez, MD	7	5
St. Luke's Medical Center	Richard Heuser, MD	9	1
St. Joseph's Medical Center	Madyoon Hooman, MD	7	2
Greenville Hospital	Timothy Sullivan, MD/Bruce Gray, MD	0	9
Lenox Hill Hospital	Gary Roubin, MD	0	9
St. Frances Hospital	George Petrossian, MD	0	5
Swedish Hospital	William Gray, MD	3	1
Millard Filmore	L. Hopkins, M.D.	0	5
Cardiovascular Research Foundation of Louisiana	P. Michael Davis, MD	3	4
Oschner Clinic	Stephen Ramee, MD	1	2
Abbott Northwestern Hospital	Mark Myers, MD / David Tubman, MD	1	1
Montefiore Medical Center	Takao Ohki, MD	0	1



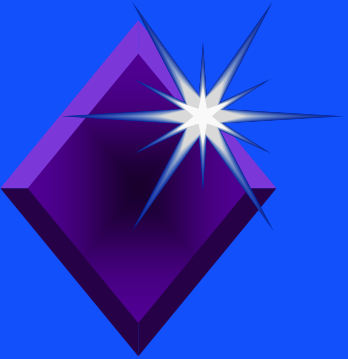
Study Overview

- ◆ **Randomized, multi-center trial comparing stenting with protection to endarterectomy in high surgical risk patients**
- ◆ **Non-randomized patients entered a stent or surgical registry**
- ◆ **Cordis PRECISE Nitinol Stent System and the ANGIOGUARD XP distal protection device**
- ◆ **29 investigational sites**



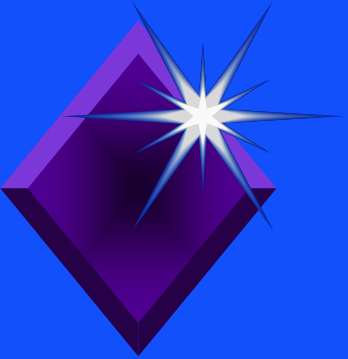
Executive Committee

- ◆ Jay S. Yadav, MD Cardiology
- ◆ Mark Wholey, MD Radiology
- ◆ Barry Katzen, MD Radiology
- ◆ Kenneth Ouriel, MD Vascular Surgery
- ◆ Pierre Fayad, MD Neurology



Data Analysis

- ◆ **Data Management:** Harvard Clinical Research Institute (HCRI)
CEC
DSMB
- ◆ **QCA Core Lab:** Jeff Popma (Brigham & Womens)
- ◆ **Ultrasound Core Lab:** Mike Jaff (VasCore)
- ◆ **Economic Analysis:** David Cohen (HCRI)
- ◆ **Analysis of Filters:** Renu Virmani (AFIP)
- ◆ **Sponsor:** Cordis Corporation



Surgical Experience

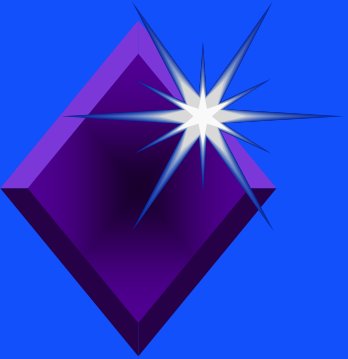
◆ Median Annual CEAs : 30 (15-100)

◆ MeanComplication Rates:

Stroke: 1.0%

Death: 1.0%

MI: 1.0%



Interventionalist Experience

◆ Median Carotid Stents: 64 (20-700)

◆ Mean Complication Rates for Stent Procedures:

Stroke: 2.0%

Death: 0.0%

MI: 0.0%

TIA: 2.0%



SAPPHIRE

$\geq 50\%$ Stenosis Sx

$\geq 80\%$ Stenosis Asx

One or More Comorbidity Criteria

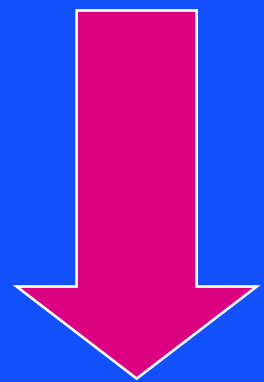
Physician Team: Neurologist, Surgeon, Interventionalist

CONSENSUS

SURGICAL
REFUSAL



STENT
REGISTRY
409



RANDOMIZED
307

Stenting=156

CEA=151

INTERVENTIONAL
REFUSAL



SURGICAL
REGISTRY
7



Study Overview (continued)

Followup:

- ◆ 30-days
- ◆ 6 months
- ◆ 1 year
- ◆ 2 years
- ◆ 3 Years



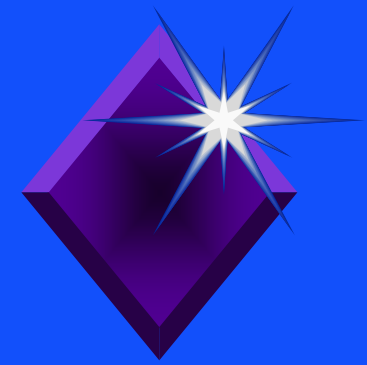
Primary Endpoints

- ◆ **Death, any Stroke, and MI at 30-days post- procedure**
- ◆ **30 day MACE plus Death and Ipsilateral Stroke between 31-days and 12-months post-procedure**



Key Secondary Endpoints

- ◆ **Patency (<50% restenosis)**
 - ◆ By Ultrasound at 48 hrs., at 6 months, 1, 2, and 3 years post-procedure
- ◆ **Disabling stroke @ 30-days and 6 months**
- ◆ **Composite of Major Adverse Clinical Events**
 - ◆ @ 6 month, 1 year, 2 year, and 3 years
- ◆ **Safety assessment of the ANGIOGUARD XP**



Tertiary Endpoints

- ◆ **Quality-of-Life**
- ◆ **Economic analysis**



Device Specifications

ANGIOGUARD™

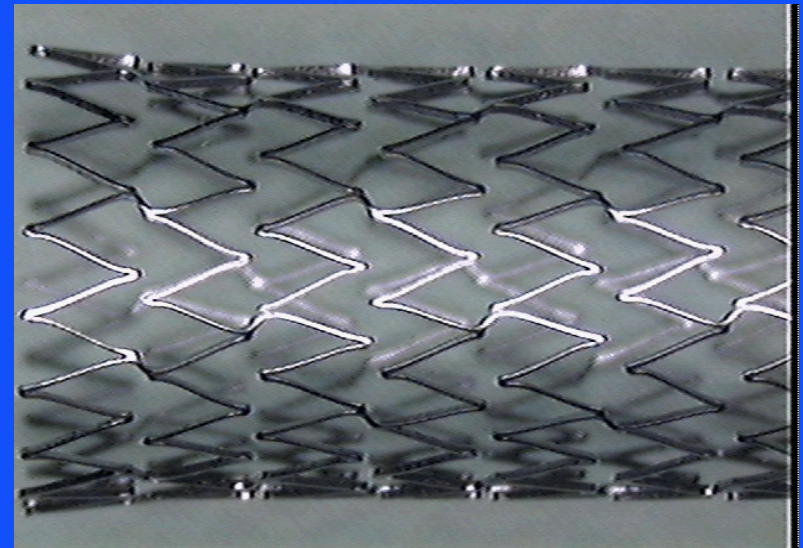


Inventor
of Device

.014" Emboli Prevention Guidewire

Filter pore size 100 microns

PRECISE™



Nitinol Self-Expanding Stent

5.5 & 6 French Delivery System



Key Inclusion Criteria

- ◆ **Symptomatic $\geq 50\%$ stenosis by US or angiogram**
- ◆ **Asymptomatic $\geq 80\%$ stenosis by US or angiogram**
 - ◆ **Stratification for symptomatic and asymptomatic patients**
- ◆ **Native Common or Internal Carotid Artery**
- ◆ **Consensus agreement by multidisciplinary team**
 - ◆ **Surgeon, Consulting Neurologist, Interventionalist**



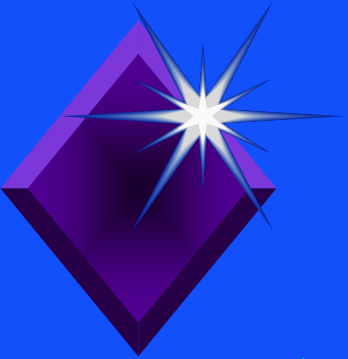
Key Inclusion Criteria (Continued)

- ◆ **Patients must have one or more of the following conditions that place them at increased surgical risk:**
 - **congestive heart failure (class III/IV) and/or known severe left ventricular dysfunction LVEF <30%**
 - **open heart surgery needed within six weeks**
 - **recent MI (>24 hrs. and <4 weeks)**
 - **unstable angina (CCS class III/IV)**



Key Inclusion Criteria (continued)

- **severe pulmonary disease**
- **contralateral carotid occlusion**
- **contralateral laryngeal nerve palsy**
- **radiation therapy to neck**
- **previous CEA with recurrent stenosis**
- **high cervical ICA lesions or CCA lesions below the clavicle**
- **severe tandem lesions**
- **age greater than 80 years**



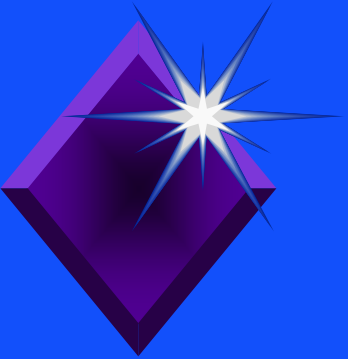
Key Exclusion Criteria

- ◆ **Acute ischemic neurologic stroke or past 48 hrs.**
- ◆ **Total occlusion of the target carotid artery**
- ◆ **Percutaneous or surgical interventions planned within 30 days of the index procedure**
- ◆ **Ostial lesions of the common carotid**



Screening and Baseline Period

- ◆ **Detailed Neurological Exam**
- ◆ **MRI or CT scan**
- ◆ **Quality of Life assessment**
- ◆ **Screening log at each site of all pts evaluated for carotid revascularization**



Medications

Stent Patients:

Pre-Procedure:

- ◆ Aspirin (72 Hours Prior)
- ◆ Ticlopidine or Clopidogrel at least 24 hrs. prior to the procedure

Intraprocedural:

- ◆ Heparin 3,000-5,000 units, ACT 300

Post Procedure:

- ◆ Ticlopidine or Clopidogrel for 2 weeks
- ◆ ASA (325 mg q.d.) indefinitely

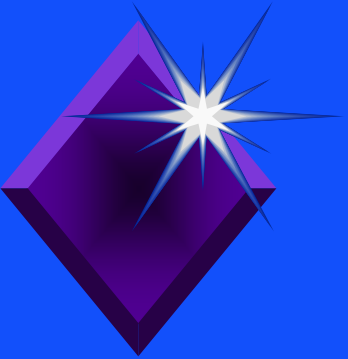
CEA Patients:

Pre-Procedure:

- ◆ Aspirin (325 mg q.d.) beginning at least 72 hrs. prior to the procedure

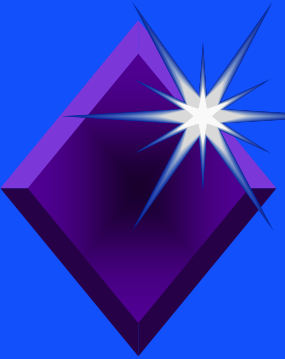
Post-Procedure:

- ◆ Aspirin (325 mg q.d.) indefinitely



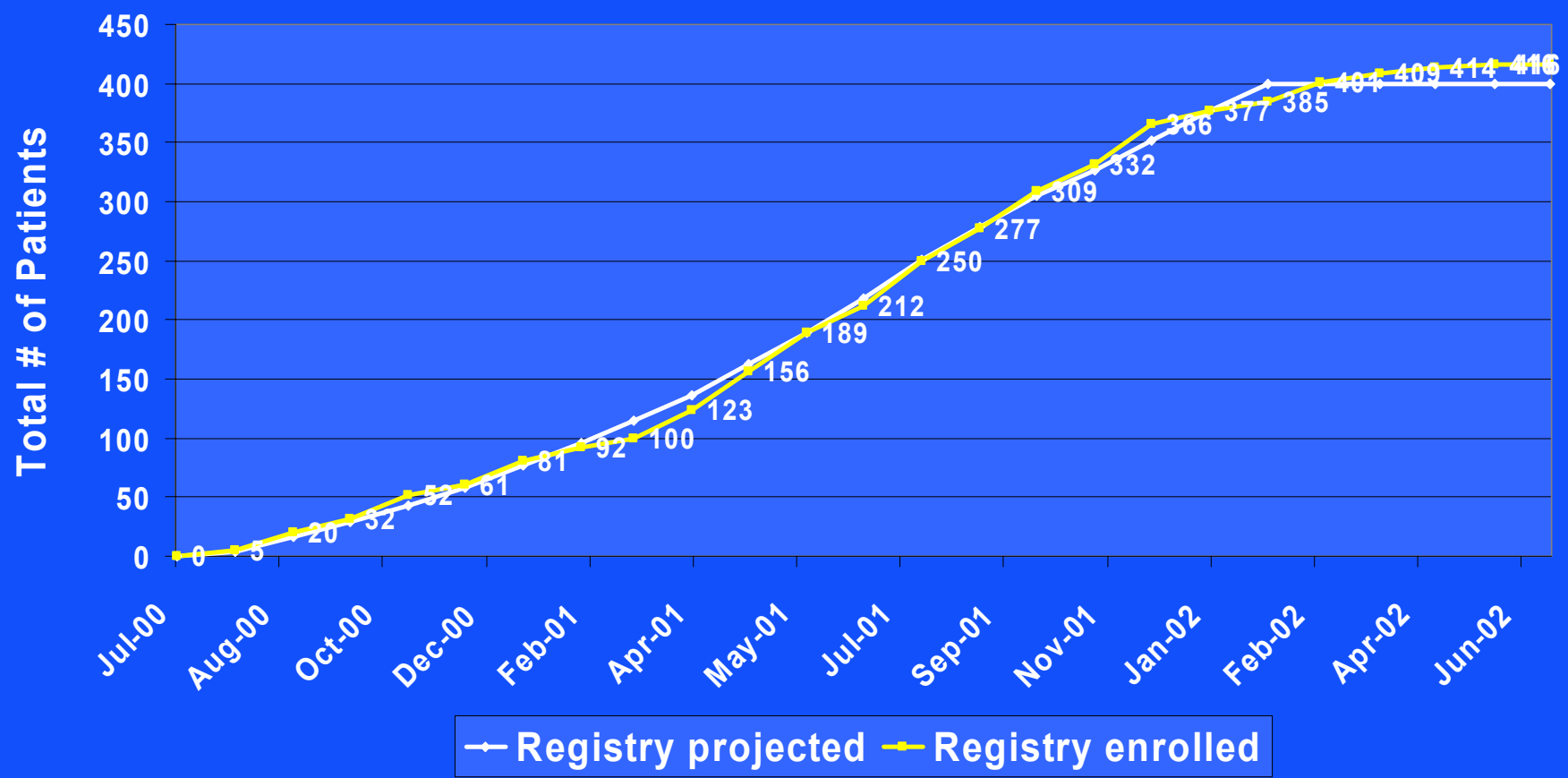
Status of Patient Entry

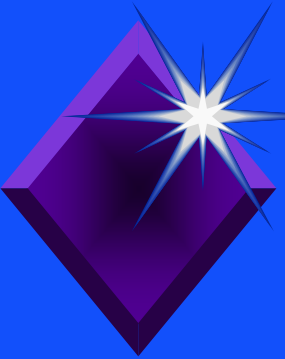
- ◆ **Total of 723 patients enrolled in trial:**
 - ◆ **Registry Arm Completed February 2002:**
 - ◆ Registry Stent Patients: 409
 - ◆ Registry CEA Patients: 7
 - ◆ **Randomized Arm Stopped June 2002:**
 - ◆ Randomized Stent Patients: 156
 - ◆ Randomized CEA Patients: 151



Sapphire Registry Subjects

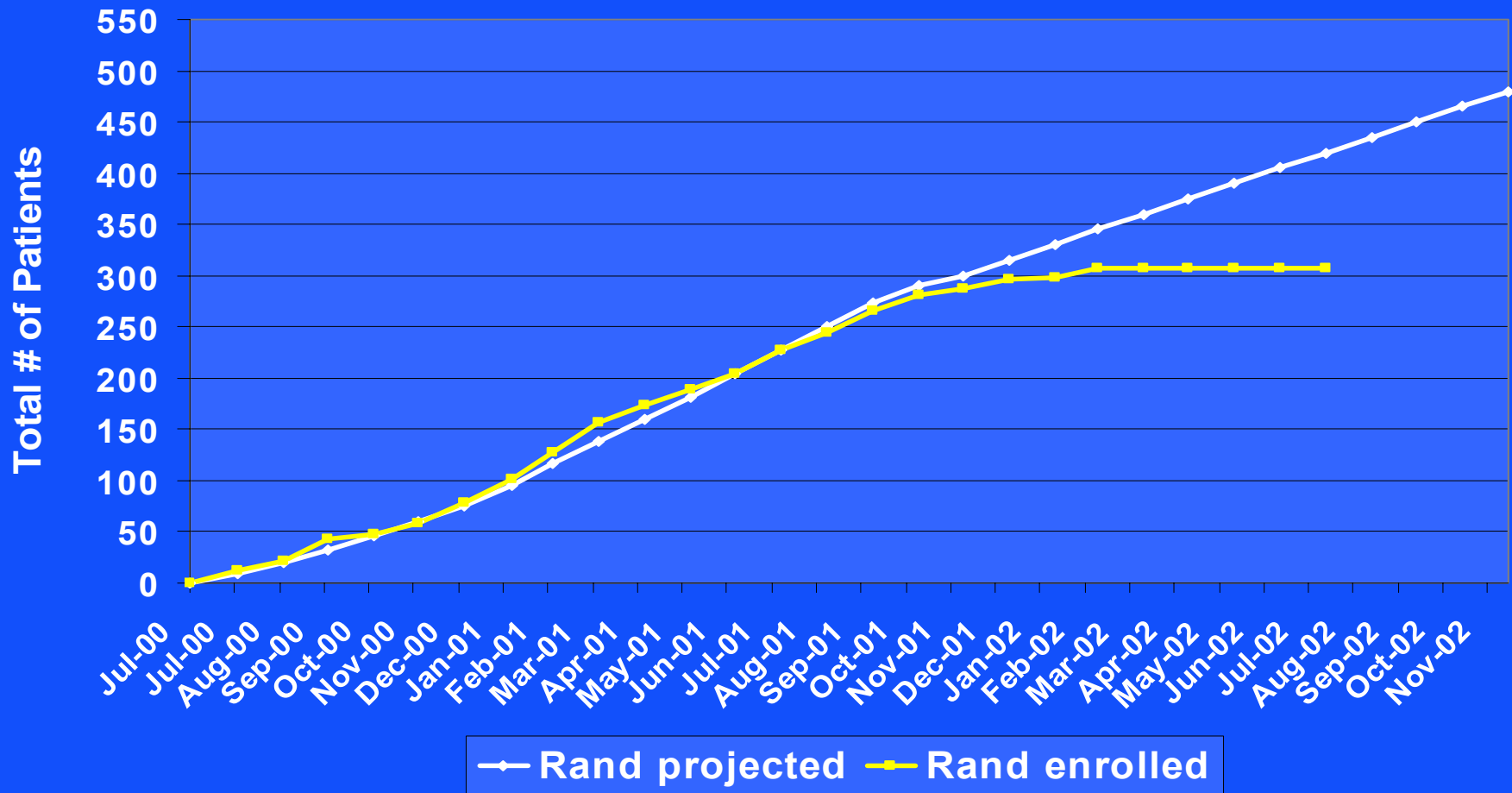
Rate of Enrollment

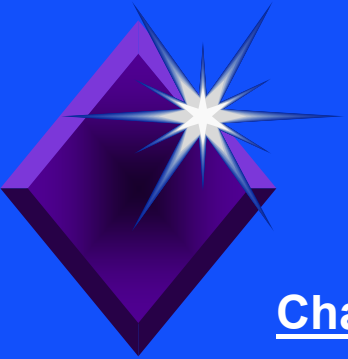




Sapphire Randomized Subjects

Rate of Enrollment






Randomized Patients

Demographic Characteristics

<u>Characteristic</u>	<u>Randomized Stent</u>	<u>Randomized CEA</u>	<u>p Value</u>
Mean Age	72.5	72.6	0.94
% Symptomatic	31.6%	28.5%	0.61
% Male	67.3%	68.5%	0.90
Coronary Artery Disease	84.7%	73.5%	0.03*
Previous Q or Non-Q MI	29.4%	35.3%	0.31
Previous CABG	42.9%	31.0%	0.04*
Previous PTCA	34.0%	24.3%	0.09
CCS III or IV	25.0%	17.2%	0.29

* Significant Difference



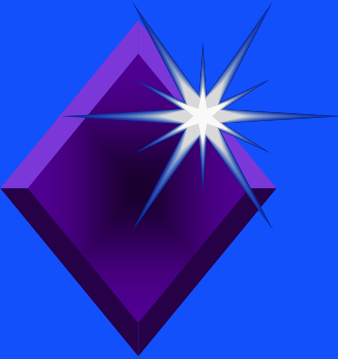
Randomized Patients

Demographic Characteristics (cont.)

<u>Characteristic</u>	<u>Randomized Stent</u>	<u>Randomized CEA</u>	<u>p Value</u>
Clinical CHF	18.1%	18.0%	>0.99
History of Stroke	25.3%	26.0%	>0.99
History of TIA	29.6%	32.9%	0.61
Prior CEA	29.9%	23.3%	0.23
COPD	18.4%	10.3%	0.07
History of Hypertension	85.6%	85.6%	>0.99
Diabetes Mellitus	23.8%	26.9%	0.59
History Dyslipidemia	79.2%	77.9%	0.89

Stent Registry

Demographic Characteristics



Mean Age	71.5
% Male	64.7%
Coronary Artery Disease	68.8%
Previous Q or Non-Q MI	33.1%
Previous CABG	31.2%
Previous PTCA (Coronary)	21.1%
CCS III or IV	32.8%



Stent Registry

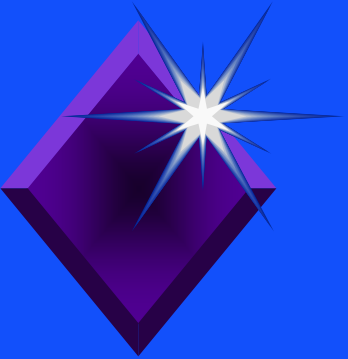
Demographic Characteristics (cont.)

Clinical CHF	18.1%
History of Stroke	31.5%
History of TIA	34.4%
COPD	18.1%
History of Hypertension	84.4%
Diabetes Mellitus	30.8%
History Dyslipidemia	73.6%



High Risk Characteristics of Patients Randomized vs Patients Enrolled in Stent Registry (Significantly Different Parameters Only)

	<u>All Randomized Patients (N=307)</u>	<u>Stent Registry Patients (N=408)</u>	<u>p Value</u>
Post Radiation Treatment	7.1%	17.2%	0.001
Previous CEA, Recurrent Stenosis	24.5%	40.8%	<0.001
High Cervical ICA Lesions	6.3%	16.7%	<0.001
CCA Lesions Below the Clavicle	0.0%	3.9%	0.003
Patients Having >1 High Risk Criteria	24.6%	36.5%	0.004



Acute Procedural Success

◆ **Device Success:** (residual stenosis of <30%)

◆ **Randomized Stent:** 91.2%

◆ **Registry Stent:** 91.3%

◆ **ANGIOGUARD Success:** (Successful delivery and retrieval of the ANGIOGUARD Device)

◆ **Randomized Stent:** 98.6%

◆ **Registry Stent:** 98.4%

Randomized Patients

30-Day Events

Events

Stent (156 pts)
[95% CI]

CEA (151 pts)
[95% CI]

p Value

Death:	0.6% [-0.6%,1.9%]	2.0%[-0.2%,4.2%]	0.36
Stroke:	3.8% [0.8%,6.9%]	5.3% [1.7%,8.9%]	0.59
Major Ipsilateral:	0.0%	1.3%	0.24
Major Non-Ipsilateral:	0.6%	0.7%	>0.99
Minor Ipsilateral:	3.2%	3.3%	>0.99
Minor Non-Ipsilateral:	0.6%	0.0%	>0.99
MI (Q or NQ)	2.6% [0.1%,5.0%]	7.3% [3.1%,11.4%]	0.07
Q-Wave MI	0.0%	1.3%	0.24
Non-Q Wave MI	2.6%	6.0%	0.16
Death/Stroke:	4.5% [1.2%,7.7%]	6.6% [2.7%,10.6%]	0.46
Death/Stroke/MI	5.8%[2.1%,9.4%]	12.6%[7.3%,17.9%]	0.047



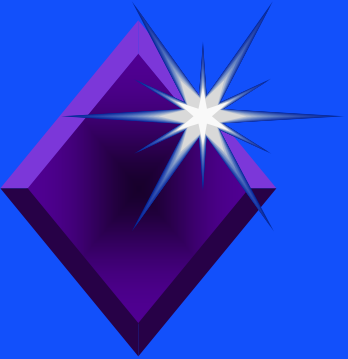
Randomized Symptomatic Patients 30-Day Events

<u>Event</u>	<u>Stent (48 pts)</u> <u>[95% CI]</u>	<u>CEA (39 pts)</u> <u>[95% CI]</u>	<u>p Value</u>
Death:	0.0% [- , -]	5.1% [-1.8%,12.1%]	0.20
Stroke:	2.1% [-2.0%,6.1%]	7.7% [-0.7%,16.1%]	0.32
Major Ipsilateral:	0.0%	0.0%	---
Major Non-Ipsilateral:	0.0%	2.6%	0.45
Minor Ipsilateral:	2.1%	5.1%	0.58
Minor Non-Ipsilateral:	0.0%	0.0%	---
MI (Q or NQ):	2.1% [-2.0%,6.1%]	5.1% [-1.8%,12.1%]	0.58
Q-Wave MI	0.0%	0.0%	---
Non-Q Wave MI	2.1%	5.1%	0.58
Death/Stroke:	2.1% [-2.0%,6.1%]	10.3% [0.7%,19.8%]	0.17
Death/Stroke/MI:	4.2% [-1.5%,9.8%]	15.4% [4.1%,26.7]	0.13



Randomized Asymptomatic Patients 30-Day Events

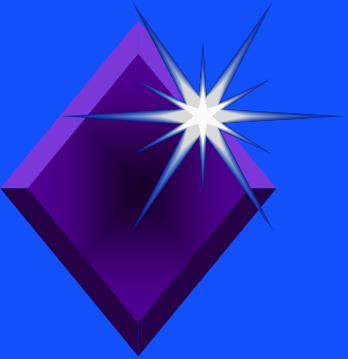
<u>Events</u>	<u>Stent (104 pts)</u> <u>[95% CI]</u>	<u>CEA (98 pts)</u> <u>[95% CI]</u>	<u>p Value</u>
Death:	1.0% [-0.9%,2.8%]	1.0% [-1.0%,3.0%]	>0.99
Stroke:	4.8% [0.7%,8.9%]	5.1% [0.7%,9.5%]	>0.99
Major Ipsilateral:	0.0%	2.0%	0.23
Major Non-Ipsilateral:	1.0%	0.0%	>0.99
Minor Ipsilateral:	3.8%	3.1%	>0.99
Minor Non-Ipsilateral:	1.0%	0.0%	>0.99
MI (Q or NQ):	2.9% [-0.3%,6.1%]	7.1% [2.0%,12.2%]	0.20
Q-Wave MI	0.0%	2.0%	0.23
Non-Q Wave MI	2.9%	5.1%	0.49
Death/Stroke:	5.8% [1.3%,10.3%]	6.1% [1.4%,10.9%]	>0.99
Death/Stroke/MI:	6.7% [1.9%,11.5%]	11.2% [5.0%,17.5%]	0.33



Stent Registry Patients

30-Day Events

<u>Event</u>	<u>Stent Registry</u> (408 pts)	<u>95% CI</u>
Death:	2.5%	[1.0%, 4.0%]
Stroke:	5.6%	[3.4%, 7.9%]
Major Ipsilateral:	2.9%	
Major Non-Ipsilateral	0.2%	
Minor Ipsilateral	2.2%	
Minor Non-Ipsilateral	0.5%	
MI (Q or NQ):	1.7%	[0.5%, 3.0%]
Q Wave MI	0.0%	
Non-Q Wave MI	1.7%	
Death/Stroke:	6.9%	[4.4%,9.3%]
Death/Stroke/MI:	7.8%	[5.2%, 10.5%]



CEA Registry Patients

30-Day Events

<u>Event</u>	<u>CEA Registry</u> (N = 7)
Death:	0.0%
Stroke:	0.0%
Major Ipsilateral:	0.0%
Major Non-Ipsilateral	0.0%
Minor Ipsilateral	0.0%
Minor Non-Ipsilateral	0.0%
MI (Q or NQ):	14.3%
Q Wave MI	0.0%
Non-Q Wave MI	14.3%
Death/Stroke:	0.0%
Death/Stroke/MI:	14.7%



30-Day MACE Rates In/Out of Hospital

<u>MACE</u>	<u>Randomized Stent (N=156)</u>	<u>Randomized CEA (N=151)</u>	<u>p Value</u>
In-hospital	4.5%	10.6%	0.051
Out-of hospital	1.3%	2.0%	0.68

	<u>Stent Registry</u>
In-Hospital	3.9%
Out-of Hospital	3.9%

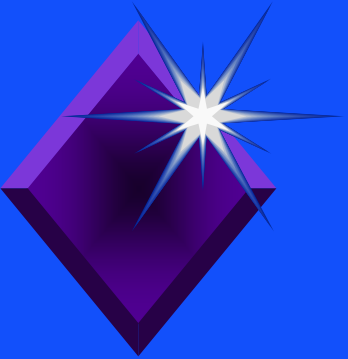


Randomized Patients

30-Day Events

<u>Events</u>	<u>Stent</u> (156 pts)	<u>CEA</u> (151 pts)	<u>p Value</u>
TIA's:	3.8%	2.0%	0.50
Major Bleeding:	8.3%	10.6%	0.56
Cranial Nerve Injury:	0.0%	5.3%	<0.01*

* Significant Difference



Stent Registry Patients

30-Day Events

<u>Events</u>	<u>408 pts</u>
TIA's:	5.4%
Major Bleeding:	11.5%
Cranial Nerve Injury:	0.0%



Preliminary Conclusions

- ◆ **First Randomized Study Comparing Carotid Stenting With Emboli Protection to Surgery**
 - ◆ Only High Risk Study With Randomization
 - ◆ Surgical Registry Defined by the Surgeons
- ◆ **MACE Includes MI Unlike Previous CEA Trials**
- ◆ **Provides Surgical Complication Rate For a Large Group of Patients That Were Excluded From Previous Cea Trials**
- ◆ **High Technical Success Rate for Distal Protection Technology Used in Carotid Stenting**



Preliminary Conclusions

- ◆ Significantly Lower 30 Day MACE for Stenting With EPD Than for CEA
 - ◆ Favorable Trend for Stenting in All Categories:
 - ◆ Asx and Sx
 - ◆ Mi, Stroke and Death
 - ◆ In-hospital and Out-of-hospital
- ◆ Long Term Event Rates Pending