# Expanded Indication for Abbott Vascular RX Acculink Carotid Stent System to Include Standard Surgical Risk Patients Based on Data from the CREST Study

FDA Review of P040012/S34

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# FDA Presentations

- Sadaf Toor
  Introduction
- Dr. Paul Chandeysson
  CREST Study Design
- Dr. Wolf Sapirstein
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# Introduction Outline

- Indications for Use
- Key Regulatory Milestones
- Device Background
- Discussion Points

# Currently Approved Indication (for high surgical risk patients)

- P040012 approved on August 30, 2004
- The RX Acculink Carotid Stent System, used in conjunction with Abbott Vascular's Accunet or Emboshield family of Embolic Protection Systems (EPS), is indicated for the treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below:

  1. Patients with neurological symptoms and ≥ 50% stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and ≥ 80% stenosis of the common or internal carotid artery by ultrasound or angiogram, AND

  2. Patients must have a reference vessel diameter within the range of 4.0mm and 9.0mm at the target lesion.

# Definition of High Surgical Risk

Patient is considered a non-surgical or a high risk surgical candidate based on the presence of any one or more of the following medical conditions:

a) Knowledge of two or more proximal or major diseased coronary arteries with ≥70% stenosis that have not, or cannot be revascularized

b) Ejection fraction <30% or New York Heart Association (NYHA) Functional Class III or higher

c) Unstable angina defined as rest angina with ECG changes

d) Currently on a list for major organ transplantation (i.e., heart, lung, liver, kidney) or is being evaluated for such

e) Malignancy or respiratory insufficiency limiting life expectancy to <5 years or FEV1 <30% (predicted)

f) Dialysis dependent renal failure

g) Uncontrolled diabetes defined as fasting glucose >400 mg/dl and ketones > +2

h) Concurrent requirement for any surgery requiring general anesthesia

# Definition of High Surgical Risk (cont.)

Patient may be considered a non-surgical candidate for CEA as a result of one or more anatomic conditions or features which preclude normal surgical access (a-f), or a high surgical risk defined as the presence of any one or more anatomic conditions that present an increased potential for adverse events (g-i).

a) Patient is status/post radiation treatment to the neck
b) Patient is status/post radical neck surgery
c) Surgically inaccessible lesions (i.e. lesions above level of C2)
d) Spinal immobility – inability to flex neck beyond neutral or kyphotic deformity
e) Symptomatic, well-delineated carotid artery dissection below the carotid siphon
f) Ostial lesion of LCCA/RCCA lesion below clavicle
g) Presence of tracheostomy stoma
h) Contralateral laryngeal nerve paralysis
i) Previous carotid endarterectomy, extracranial-intracranial or subclavian bypass procedure ipsilateral to the carotid stenosis

# Newly Proposed Indication (for standard surgical risk patients)

P040012/S34 proposes the addition of the following to the indications:

Standard Surgical Risk

The RX Acculink Carotid Stent System, used in conjunction with the Accunet Embolic Protection System (EPS), is indicated for the treatment of patients at standard risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below:

1. Patients with neurological symptoms and ≥ 70% stenosis of the common or internal carotid artery by ultrasound or ≥ 50% stenosis of the common or internal carotid artery by angiogram OR patients without neurological symptoms and ≥ 70% stenosis of the common or internal carotid artery by ultrasound or ≥ 60% stenosis of the common or internal carotid artery by angiogram, AND

2. Patients must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion.

# P040012/S34
# Key Regulatory Milestones

# May 11, 1999

- Guidant Corporation (acquired by Abbott Vascular in May 2006) initiated formal discussions with FDA regarding a clinical protocol and statistical analysis plan for the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST).

# July 19, 1999

- FDA and Guidant Corp. completed an Agreement Meeting regarding the CREST trial, which covered:
  - study hypotheses
  - primary and secondary endpoints
  - inclusion/exclusion criteria
  - statistical analysis model used to support broadening the Acculink Carotid Stent System indication

Binding on both FDA and the applicant and can only be changed:

- with the written agreement of the applicant OR
- when there is a substantial scientific issue essential to determining the safety or effectiveness of the device

# April 26, 2000

- FDA approved an Investigational Device Exemption (IDE) for the CREST trial (G000080)
  - Allowed enrollment of U.S. subjects in the study
  - Study protocol and statistical analyses were consistent with July 1999 agreement meeting

# March 20, 2003

- Sponsorship of the IDE for the CREST trial, along with the administrative responsibilities for the study, was transferred from Guidant Corporation to the University of Medicine and Dentistry of New Jersey

# January 12, 2005

- FDA approved modifications to the CREST protocol allowing the inclusion of subjects with asymptomatic carotid artery disease, in addition to the originally approved cohort of subjects with symptomatic disease.

  The modified protocol included restrictions on enrollment such that the final percentage of symptomatic subjects enrolled would be between 32% and 68%.
  - Necessary to ensure the validity of the proposed statistical analyses involving these populations

# December 21, 2005

- The July 19, 1999 agreement between FDA and Guidant was revised to incorporate the inclusion of asymptomatic subjects in the CREST trial.

  Reaffirmed:

  - the study hypotheses
  - primary and secondary endpoints
  - inclusion/exclusion criteria
  - statistical analysis model

  that would support expanding the indications for the Acculink Carotid Stent System to include patients with symptomatic and asymptomatic carotid artery stenosis who are not at high risk for adverse events from carotid endarterectomy.

# October 1, 2010

- FDA filed Panel-Track PMA Supplement P040012/S34
  - the subject of this Advisory Panel meeting
  - includes the previously agreed-upon analysis of the full pivotal study cohort of 2,502 randomized subjects from the CREST trial

# Device Background

- The submission contains no non-clinical testing
  - The design of the device remains the same as the currently approved device
- P040012 approved the Acculink (over-the-wire) and RX Acculink (rapid exchange) stent systems for the high-risk population
- The expanded indication is sought only for the RX version of the device
  - Acculink and RX Acculink differ only in their delivery system

# Primary Discussion Points

- Appropriateness of the indication
- Peri-procedural event rates
- Long-term outcomes
- Censored and crossover subjects
- Definition of MI
- Cranial nerve injury in CEA subjects
- Post-approval study considerations

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# CREST Study Design

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# Background on Stroke (from NINDS)

- More than 780,000 strokes in U.S. every year
- Third leading cause of death
- Leading cause of long-term disability
- Almost ¾ occur in people > 65 years
- Risk doubles each decade over 55 years

# Basic Elements of CREST

- Study objective
- Study design
- Study endpoints
- Additional analyses
- Patient population
- Patient treatment
- Patient follow-up

# Study Objective

- Show comparable results of the one-year primary endpoint between carotid artery stenting (CAS) and carotid endarterectomy (CEA) in the treatment of patients who have carotid artery stenosis and are at standard risk for surgery

# Study Design

CREST design consisted of 2 phases:

- A non-randomized lead-in phase for the training and credentialing of the CAS operators
  - Up to 20 patients per operator
  - Up to 119 centers in U.S. and 10 in Canada
- A prospective, multicenter, two-arm, concurrent, randomized clinical study comparing CAS vs. CEA
  - A non-inferiority hypothesis was used with a margin of 2.6%
  - A total of 2500 randomized patients was planned

# Primary Endpoint

- A 1-year composite of all-cause death, stroke, and myocardial infarction (MI) evaluated at 30 days after the index procedure, plus ipsilateral stroke evaluated between 31 days and 365 days

# Secondary Endpoints

- Primary endpoint stratified by patient symptomatic status
- A composite of death, stroke, and MI evaluated at 30 days
- Acute success evaluated using three different measures: device, procedure, and clinical success
- Target lesion revascularization at 12 months after the index procedure
- Access site complications requiring treatment
- Cranial nerve injury unresolved at 1 and 6 months after the index procedure

# Additional Analyses

- Poolability of symptomatic and asymptomatic patients
- Death, stroke and MI at 30 days plus ipsilateral stroke at 4 years after the index procedure
- Comparison of the event rates of the lead-in patients versus the randomized patients.
- “Recently asymptomatic” versus “Always asymptomatic” patients
- Male patients versus female patients
- Evaluation of the treated segment by ultrasound
- Multivariate analysis
- Analysis by octogenarian status

# Patient Population

- Initially, randomized patients had to be symptomatic. Later, asymptomatic patients were also randomized.
- The severity of the lesion depended on the imaging modality used and the symptomatic status of the patient.

# Primary Analysis Group

- For several reasons, different subgroups of the randomized population occurred.
- The primary analysis was done on the per-protocol patient subgroup for regulatory purposes.

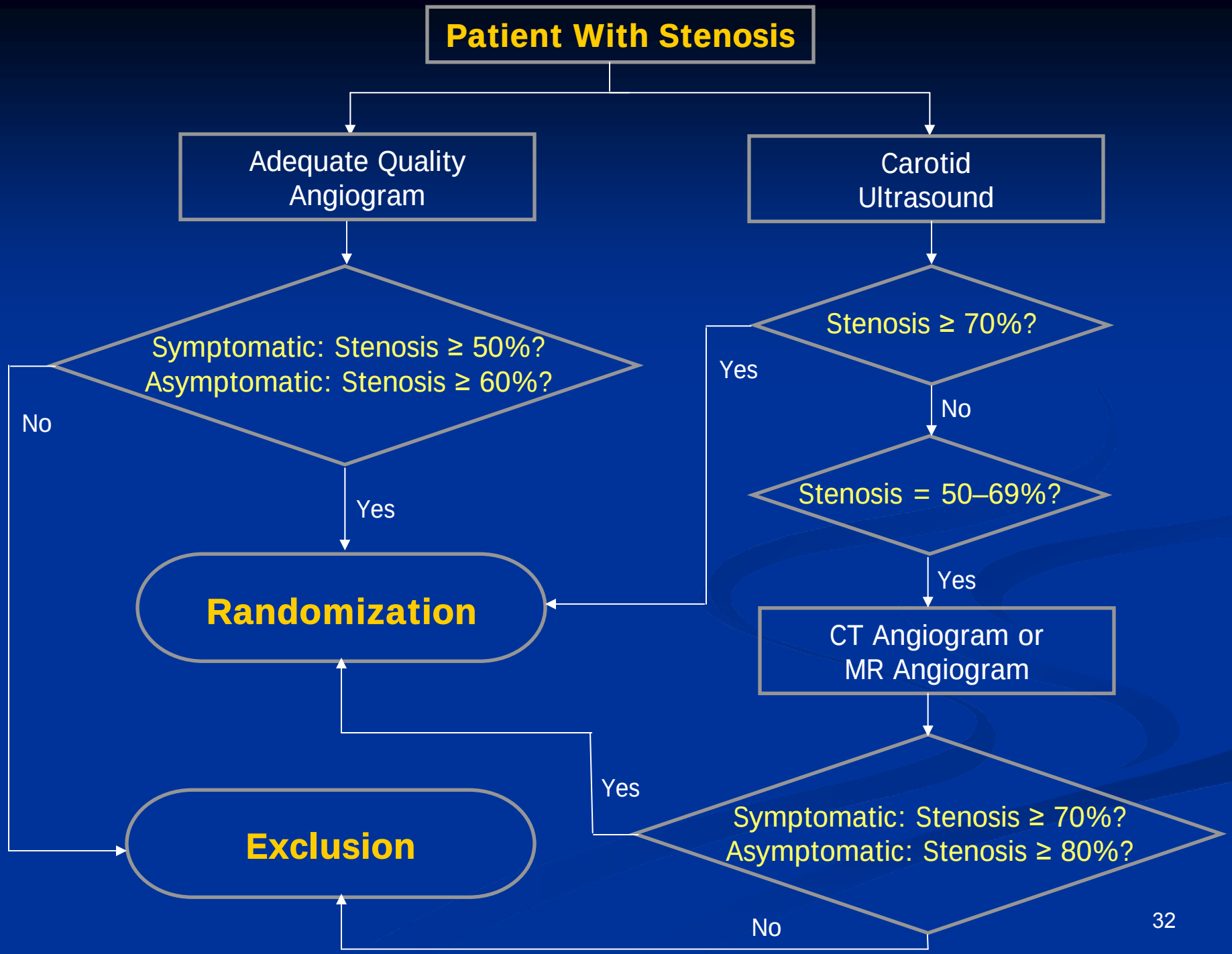
# Symptom Status

- Symptomatic patients had symptoms referable to the target lesion occurring within the 180 days preceding the baseline assessment. Symptoms include a non-disabling cerebral infarction, amaurosis fugax, or transient ischemic attack (TIA).

- Asymptomatic patients had no symptoms referable to the target lesion occurring within the 180 days prior to the baseline assessment.

# Required Lesion Severity

- Carotid arteriogram:
  - at least 50% for symptomatic patients, or
  - at least 60% for asymptomatic patients
- Carotid artery ultrasound examination:
  - at least 70%
- If the stenosis was 50% to 69% by sonography, a CT angiogram or MR angiogram:
  - at least 70% in symptomatic patients; or
  - at least 80% in asymptomatic patients


Patient With Stenosis
Adequate Quality Angiogram
Carotid Ultrasound
Symptomatic: Stenosis ≥ 50%?
Asymptomatic: Stenosis ≥ 60%?
No
Yes
Randomization
Exclusion
Stenosis ≥ 70%?
Yes
No
Stenosis = 50–69%?
Yes
CT Angiogram or MR Angiogram
Yes
Symptomatic: Stenosis ≥ 70%?
Asymptomatic: Stenosis ≥ 80%?
No

# Patient Treatment

- CAS
  - The Acculink Stent and the Accunet Embolic Protection System used per the Instructions for Use
  - Medications were heparin, ASA, clopidogrel, or others
- CEA
  - Performed as standard of practice of the surgeon
  - Medications were ASA, or others

# Patient Follow-up

- A neurological assessment was required 18 to 54 hours after the procedure in order to ensure the detection of early strokes.
- Follow-up visits at 30 days, 6 months, 12 months, and yearly thereafter.
- Telephone follow-up at 3 months, 9 months, 18 months, and yearly from that date.

# Summary

- The objective of CREST was to show comparable results of the primary endpoint for CAS and CEA in patients who have carotid artery stenosis and are at standard risk for adverse events from surgery.
- CREST was a large, multinational, clinical study with patients randomized 1:1 to CAS or CEA. CREST also includes a lead-in phase for training and credentialing of the CAS operators.
- The 1-year primary endpoint was a composite of death, stroke, and MI evaluated at 30 days after the index procedure, plus ipsilateral stroke evaluated between 31 days and 365 days. A non-inferiority hypothesis was used with blinded endpoint evaluation. Secondary endpoints were evaluated and additional analyses were done.

# Summary (cont.)

- To be randomized, patients originally had to be symptomatic from their carotid artery lesion. Later, asymptomatic patients were also randomized.
- The severity of the lesion needed for randomization depended on the imaging modality used and the symptomatic status of the patient.
- An early neurological assessment was required to assure the detection of early strokes. Follow-up visits were required at 30 days, 6 months, 12 months, and yearly thereafter. Telephone follow-up was scheduled between the follow-up visits.

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# CREST Study Clinical Results and Considerations

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# CREST

- Study hypothesis employed a Composite Primary Endpoint of specified adverse events analyzed at one year using the Per-Protocol population (2307 of 2502 enrolled)
- Statistical stratified analyses were undertaken for Pre-Specified Secondary Endpoints
- Additional analyses were conducted
  - for example, on impact of Demographic Characteristics
- (RX) Acculink Stent System was employed for CAS
  - Initially without the Accunet Embolic Protection System
  - Accunet system added when it became available
- CEA technique was surgeon's preference.

# Patient Demographics

- Difference in prior neurological events occurring in 2502 patients was significant only for Amaurosis Fugax.

| Event | CAS | CEA | Total | 95% CI |
|---|---|---|---|---|
| TIA (n/N) | 31.6% (390/1234) | 30.4% (367/1208) | 31.0% (757/2442) | -2.4, 4.9% |
| Amaurosis Fugax (n/N) | 14.6% (179/1223) | 17.0% (204/1202) | 15.8% (383/2425) | -5.2, 0.6% |
| Ipsilateral Stroke (n/N) | 85.4% (298/349) | 84.3% (279/331) | 84.9% (577/680) | -4.3, 6.5% |

- No clinically significant difference exists in Baseline Demographics and Medical History of study arms.

# Baseline Demographics

| | CAS N = 1262 | CEA N = 1240 | Total N = 2502 | Difference [95% CI] |
|---|---|---|---|---|
| **Age – Mean ± S.D.** | 68.9 ± 9.0 | 69.2 ± 8.8 | 69.1 ± 8.9 | -0.3 [- 1.0, 0.4] |
| **Median** | 69.1 | 70.0 | 69.7 | |
| **Range** | 39.8 – 96.2 | 40.7 – 91.5 | 39.8 – 96.2 | |
| **Male Gender** | 63.9% | 66.4% | 65.1% | -2.4 [-6.2%, 1.3%] |
| **Symptomatic** | 52.9% | 52.7% | 52.8% | 0.3% [-3.6%, 4.2%] |
| **Diabetes Mellitis** | 30.5% | 30.4% | 30.5% | 0.1% [-3.5%, 3.7%] |
| **Hypertension** | 85.8% | 86.1% | 85.9% | -0.3% [-3.0%, 2.5%] |
| **Coronary Artery Disease** | 42.5% | 36.1% | 39.5% | 6.4% [-15.5%, 28.3%] |
| **Dyslipidemia** | 82.9% | 85.8% | 84.4% | -2.9% [-5.7%, -0.0%] |
| **Smoking History** | 65.2% | 66.2% | 65.7% | -1.0% [-4.7%, 2.8%] |

# Study Endpoint Compliance

Primary Endpoint Evaluation (1 Year):

| | CAS | CEA |
|---|---|---|
| Eligible | 1131 | 1176 |
| Evaluated | 1085 (95.9%) | 1132 (96.3%) |
| Not evaluated | 46 (4.1%) | 44 (3.7%) |

Primary Endpoint Not Evaluated Due to:

| | CAS | CEA |
|---|---|---|
| Death | 18 (1.6%) | 12 (1.0%) |
| Withdrawal | 16 (1.4%) | 26 (2.2%) |
| Lost | 6 (0.5%) | 5 (0.4%) |
| Other | 6 (0.5%) | 1 (0.1%) |

# Primary Endpoint

- Death, stroke, and myocardial infarction (DSMI) peri-operatively (0 - 30 days), plus ipsilateral stroke 31 - 365 days post-procedure.

- Per-Protocol Analysis of Primary Endpoint:

| | CAS | CEA |
|---|---|---|
| N | 1131 | 1176 |
| Rate | 7.1% | 6.6% |
| Difference | 2.26% UCL | |

- Propensity Adjusted Per-Protocol Analysis of Primary Endpoint :

  Difference 2.41% UCL

- Non-Inferiority Delta for Primary Endpoint Comparison: **2.6%**

# Peri-Procedural Endpoint Components

| | CAS (N=1131) | CEA (N=1176) | Difference (UCL, NI margin) |
|---|---|---|---|
| DSMI | 65 (5.8%) | 60 (5.1%) | 2.2%, 2.3% |
| Death | 6 (0.5%) | 3 (0.3%) | |
| Stroke (All) | 46 (4.1%) | 22 (1.9%) | |
| Major | 10 (0.9%) | 5 (0.4%) | |
| Ipsilateral | 10 | 4 | |
| Minor | 36 (3.2%) | 18 (1.5%) | |
| Ipsilateral | 33 | 15 | |
| Myocardial Infarction | 22 (2.0%) | 40 (3.4%) | |
| Stroke and Death | 47 (4.3%) | 22 (1.9%) | |
| Major Stroke and Death | 12 (1.1%) | 5 (0.4%) | |

# Stroke Events

Minor stroke defined as lasting > 24 hours with NIHSS < 9 at 3 months

| | CAS (N = 1131) | CEA (N = 1176) |
|---|---|---|
| Peri-Procedural Stroke (0 - 30 Days): | | |
| Major | 10 (0.9%) | 5 (0.4%) |
| Minor | 36 (3.2%) | 18 (1.5%) |
| Total | 46 (4.1%) | 22 (1.9%) |
| | | |
| Late Ipsilateral Stroke (31 - 365 Days) | 19 (1.7%) | 18 (1.6%) |
| | | |
| Procedural Minor Strokes returning to baseline at 1 month | 17 (51.5%) | 7 (43.8%) |

# Procedural Myocardial Infarction

- MI definition: Biomarker and/or ischemic ECG/symptoms
  - (20 cases adjudicated by biomarkers only)

- Adjudication:
  - Based on all randomized subjects (N=2502)

| | CAS | CEA | Total |
|---|---|---|---|
| Definite | 15 | 24 | 39 |
| Possible | 10 | 18 | 28 |
| Total | 25 | 42 | 67 |

- Mortality Outcome of Peri-Procedural Myocardial Infarction:
  - 13 (19%) of 67 adjudicated cases died during a 4-year follow-up
    - 9 deaths in 39 Definite MI cases
    - 4 deaths in 28 Possible MI cases
  - 2 of all deaths specified as cardiac

# Primary Endpoint Results by Symptomatic Status

- Symptomatic definition: TIA, Amaurosis Fugax, Minor or Non-Disabling Stroke within 180 days of intervention

| | CAS | CEA | Difference (UCL) | N-I Margin |
|---|---|---|---|---|
| Symptomatic | 8.7% (N = 599) | 7.5% (N = 620) | 3.84% | 3.87% |
| Asymptomatic | 5.3% (N = 532) | 5.6% (N = 556) | 1.95% | 3.40% |

# Primary Endpoint Results by Age

| | Octogenarian | | Non-Octogenarian | |
|---|---|---|---|---|
| | CAS | CEA | CAS | CEA |
| N | 106 | 103 | 1025 | 1073 |
| 0 - 30 Day Events: | | | | |
| Death | 1 (0.9%) | 1 (1.0%) | 5 (0.5%) | 2 (0.2%) |
| MI | 2 (1.9%) | 7 (6.8%) | 20 (2.0%) | 33 (3.1%) |
| All Stroke and Death | 7 (6.6%) | 4 (3.9%) | 41 (4.0%) | 18 (1.7%) |
| Major Stroke and Death | 3 (2.8%) | 1 (1.0%) | 9 (0.9%) | 4 (0.4%) |
| 31 - 365 Day Events: | | | | |
| Ipsilateral Stroke | 5 (4.7%) | 2 (1.9%) | 14 (1.4%) | 16 (1.5%) |

# Pre-Stenting Angiographic Lesion Characteristics (Core Lab)

| | |
|---|---|
| Lesion Length: | |
| Data available (n/N; %) | 1029/1131 (82.4%) |
| Mean (mm) | 13.6 |
| Median (mm) | 12.9 |
| Range (mm) | 1.0 – 44.0 |
| Lesion Location Relative to Bulb (n; %): | |
| Contiguous | 686 (66.7%) |
| Remote | 254 (24.6%) |
| Both | 88 (8.6%) |
| Distance From Ostium: | |
| Mean (mm) | 2.0 |
| Range (mm) | 0.0 – 27.1 |

# Device Usage

- 2817 stents used
  - Exact number implanted is unclear
- Embolic protection devices used in 94.9% (1073/1131) of CAS cases
- Stent lengths used:
  - 20, 30, 40 mm

# Restenosis

- **Site Reported Ultrasound Review:**
  - Duplex evaluation of 1623 patients at 6-months and 1668 patients at 12 months
  - Samples drawn from Per-Protocol cohort

| **12-month results:** | **CAS** (N=834) | **CEA** (N=835) | **Difference** |
|---|---|---|---|
| Occluded | 0 | 4 (0.5%) | -0.5% |
| 70-99% | 30 (3.6%) | 22 (2.6%) | 1.0% |
| 50-69% | 130 (15.6%) | 107 (12.8%) | 2.8% |

| **1-Year Target Lesion Revascularization:**<br>Symptomatic: > 50% stenosis<br>Asymptomatic: > 80% stenosis | **CAS** | **CEA** |
|---|---|---|
| n | 10 | 12 |

| **Pre-operative 50-69% Stenosis:** | **CAS** (N=993) | **CEA** (N=1031) |
|---|---|---|
| n (%) | 113 (11.4%) | 108 (10.5%) |

# Acute Success

- CAS

| | |
|---|---|
| Device Delivery/Deployment/Retrieval Failure: | |
| Acculink Stent | 2 (0.2%) |
| Accunet EPD | 38 (3.4%) |
| Procedural Failure (Residual stenosis ≥50%) | 28 (2.5%) |
| Clinical Failure (AE & procedural failure) | 91 (8.1%) |

- CEA

| | |
|---|---|
| Procedural Failure (Neuro event, CNI day 0-1) | 75 (6.4%) |
| Clinical Failure (DSMI & procedural failure) | 120 (10.2%) |

# Cranial Nerve Injury

| | **As-Treated CEA** (N = 1246) |
|---|---|
| Cranial nerve injury (n; %) | 65 (5.2%) |
| Deficit persisting at 1 month (n; %) | 44 (3.5%) |
| Deficit persisting at 6 months (n; %) | 25 (2.0%) |
| Facial (lip droop) | 8 |
| Possible Vagus/RLN (Hoarseness) | 7 |
| Glossopharyngeal (Dysphagia) | 3 |
| Hypoglossal (tongue deviation) | 3 |
| Trigeminal (facial numbness) | 2 |
| Unknown | 2 |

# Gender Interaction

- Similar Gender distribution in study arms

| | CAS | CEA |
|---|---|---|
| % Male | 64.6% | 66.7% |
| n/N | 731/1131 | 784/1176 |

- Interaction between treatment and gender on primary endpoint:

| Variable | Coefficient (SE) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|
| CAS vs. CEA | 0.06 (0.26) | 1.06 (0.64, 1.76) | 0.82 |
| Male vs. Female | -0.19 (0.24) | 0.83 (0.52, 1.31) | 0.41 |
| Treat vs. Gender | 0.03 (0.33) | 1.03 (0.54, 1.97) | 0.92 |

# 4-Year Mortality

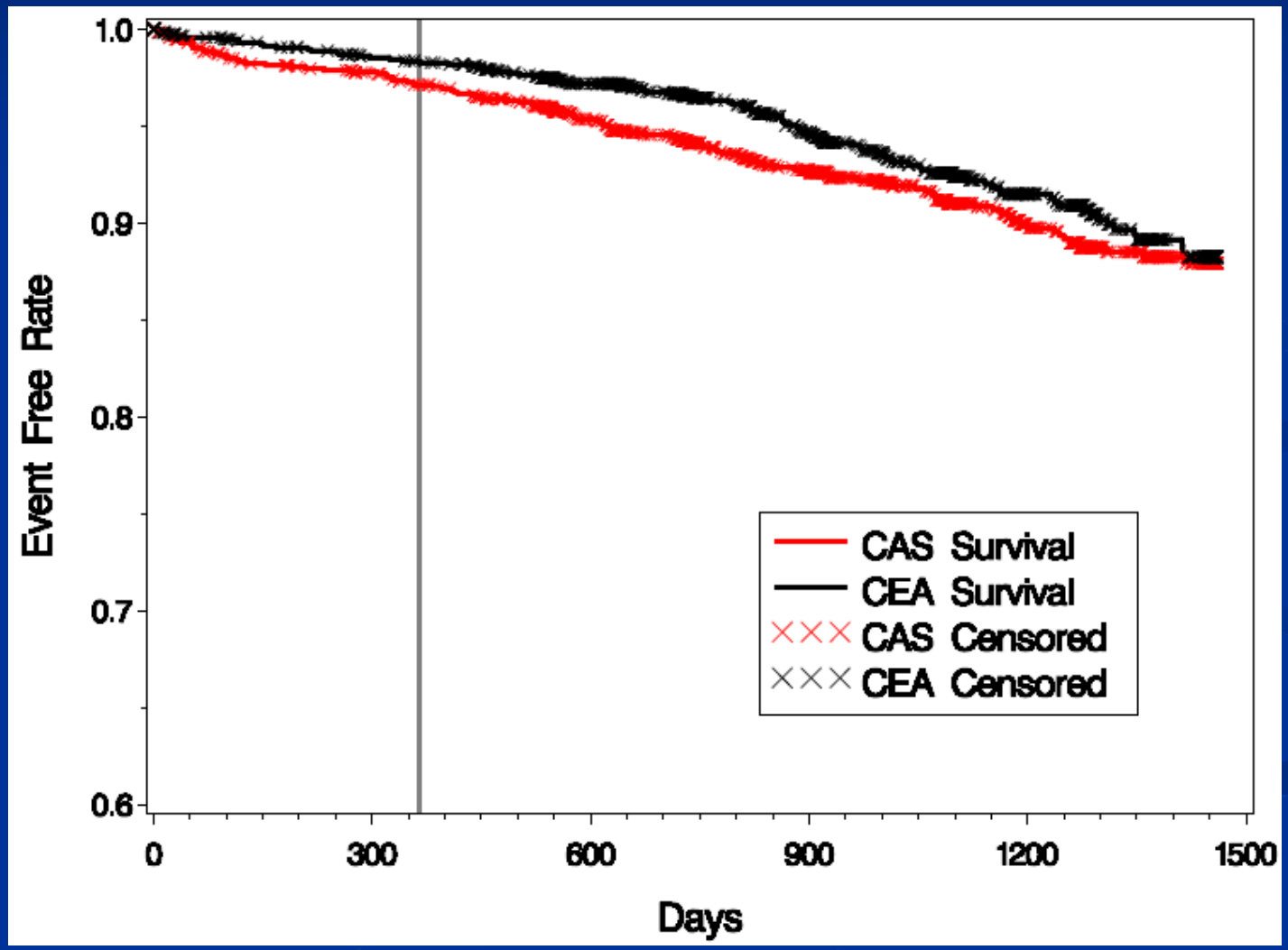
- Post Hoc Kaplan-Meier evaluation out to 4 years (median 3 years):

| | CAS | CEA |
|---|---|---|
| Onset Sample Size | 1131 | 1176 |
| 4-year Sample Size | 563 | 566 |

- 4-year Mortality:

| | CAS | CEA |
|---|---|---|
| n | 102 | 88 |
| Rate | 8.8% | 8.2% |
| HR | 1.08 | |

# Survival Curves – 4-Year Mortality



# Summary

- Study met the prespecified primary hypothesis for non-inferiority of CAS to CEA for the per-protocol analysis

- Study limitations:
  - Study design utilized criteria derived from studies in 1991 - 2004
  - Study conducted over 8 - 10 year period

- Additional analyses found that:
  - Stroke in CAS treated patients occurred twice as frequently as in the CEA arm
  - Stroke and death components of the primary endpoint occurred twice as frequently in the CAS than in the CEA patients
  - Restricted octogenarian enrollment precluded robust interpretation of higher event rates
  - CAS met non-inferiority criterion less strongly for symptomatic than asymptomatic patients

# Summary (cont.)

- Restenosis occurs with a similar incidence in CAS and CEA arms during an intermediate period of follow-up. The effect of and management of CAS restenosis are not well documented.
- The description of CAS treated lesions suggests that the available stents were suitable for treatment of localized stenosis rather than vessel disease.
- Stroke occurred significantly more frequently with CAS. NIHSS score used for categorizing strokes as minor or major serves only to predict recovery from disability.
- Procedural MI occurred more frequently in the CEA arm but did not significantly impact 4-year mortality.

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# CREST Study Statistical Conclusions and Considerations

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# Outline

- Endpoints and main statistical method
- Analysis populations
- Primary endpoint results
- Peri-procedural event results
- Results by symptomatic status
- Results by patient's age
- Summary

# Endpoints

- Primary endpoint:
  - Composite of Death, Stroke, and Myocardial Infarction (DSMI) in 30 days + ipsilateral stroke from day 31 to 365
- Peri-procedural endpoint:
  - Composite of DSMI in 30 days
- Endpoint events evaluated by the Stroke and the Myocardial Infarction Adjudication Committees (blinded to the assigned treatment)

# Main Analysis Method

- Event rates estimated by Kaplan-Meier method
- NI test performed using z test statistic

# Non-Inferiority Test

- Hypothesis

$$H_0: \pi_{CAS} \geq \pi_{CEA} + \delta$$
$$H_A: \pi_{CAS} < \pi_{CEA} + \delta$$

  - $\pi_{CAS}$: true event rate at 1-year for CAS
  - $\pi_{CEA}$: true event rate at 1-year for CEA
  - $\delta$: non-inferiority margin
    $\delta$ = 2.6% for primary endpoint; 2.3% for peri-procedural event

- $\alpha$ = 0.05 (one-sided)
- $\pi$ estimated using Kaplan-Meier method at the endpoint

# Analysis Populations

- Intent-To-Treat
  - Including most subjects who were enrolled and randomized
  - Analyzed in treatment groups to which they were randomized
- As-Treated
  - All subjects who actually received a treatment (regardless of the treatment assignment)
  - Analyzed in treatment groups to which they actually received
- Per-Protocol
  - All subjects who actually received the assigned treatment
  - A subset of the intent-to-treat

# Analysis Populations

| | CAS | CEA | Total |
|---|---|---|---|
| Intent-to-treat | 1259 | 1237 | 2496 |
| As Treated | 1151 | 1246 | 2397 |
| Per-protocol | 1131 | 1176 | 2307 |

# ITT vs. PP

- Proportion of PP / ITT
  - CAS – 89.8% (1131/1259)
  - CEA – 95.1% (1176/1237)

| Exclusion Category | Assigned to CAS | Assigned to CEA |
|---|---|---|
| Withdrew informed consent prior to procedure | 22 (1.7%) | 26 (2.1%) |
| No study procedure attempted | 28 (2.2%) | 23 (1.9%) |
| Crossover before procedure | 63 (5.0%) | 10 (0.8%) |
| Crossover after procedure attempted | 7 (0.6%) | 2 (0.1%) |
| Other | 8 (0.7%) | 0 (0.0%) |
| Total | 128 (10.2%) | 61 (4.9%) |

# Distribution of Baseline Covariates

- Distributions of baseline covariates between two arms are more likely to be similar in the ITT population, due to the randomization.

- Distributions of baseline covariates between two arms may be less similar in the PP population, due to patients in the exclusion categories.

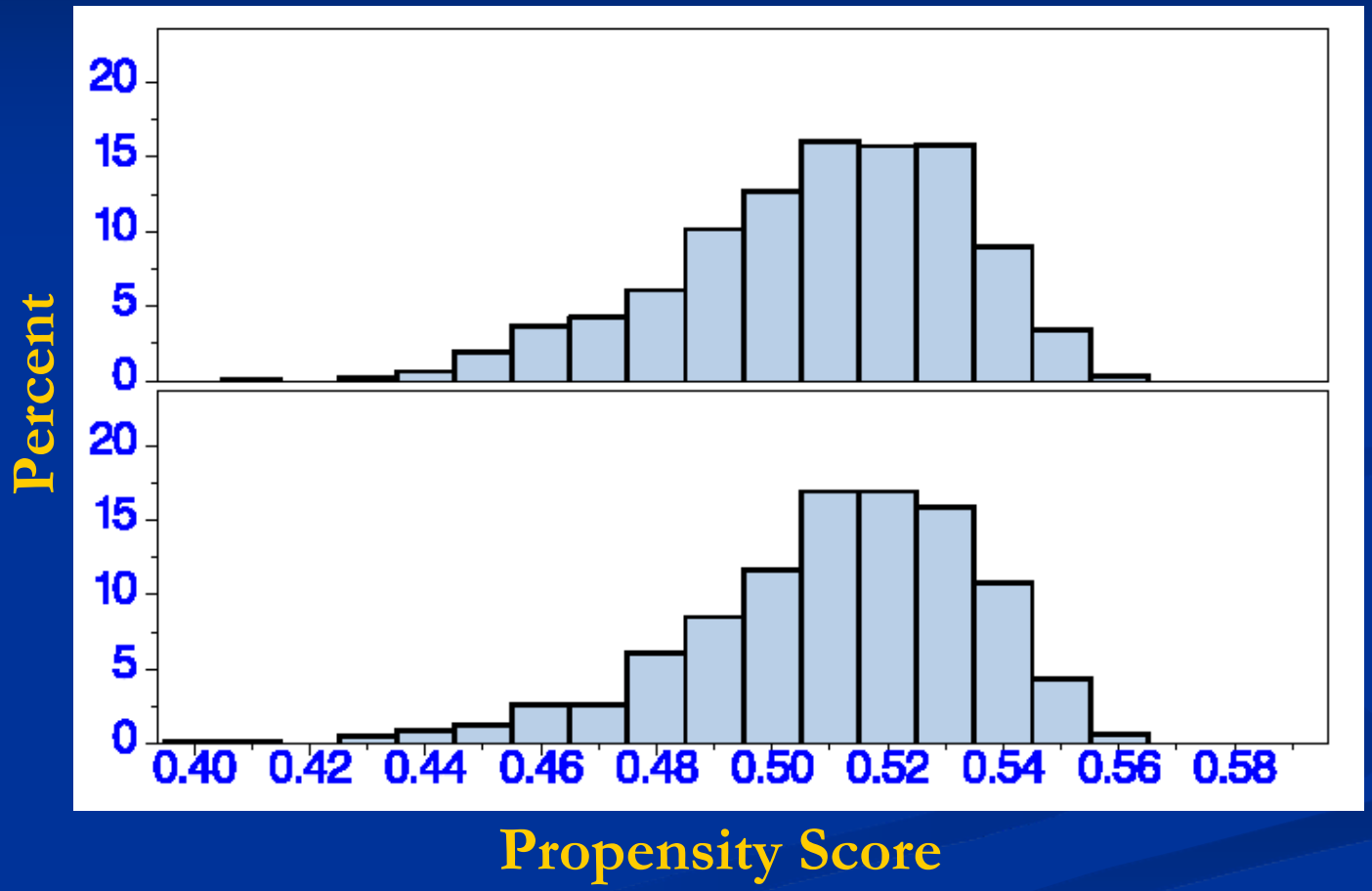
# Propensity Score Adjusted Analysis

- Propensity Score (PS):
  - Probability of treatment assignment conditional on observed baseline covariates
  - With same propensity score, treatment assignment not confounded with measured baseline covariates
- Pre-specified PS adjusted analysis:
  - PS are derived based on a logistic model
  - Each observation is weighted by its inverse propensity score of being in a certain arm
  - Weighted Kaplan-Meier estimate for each arm and associated standard error are then calculated

# Comparability of Propensity Scores

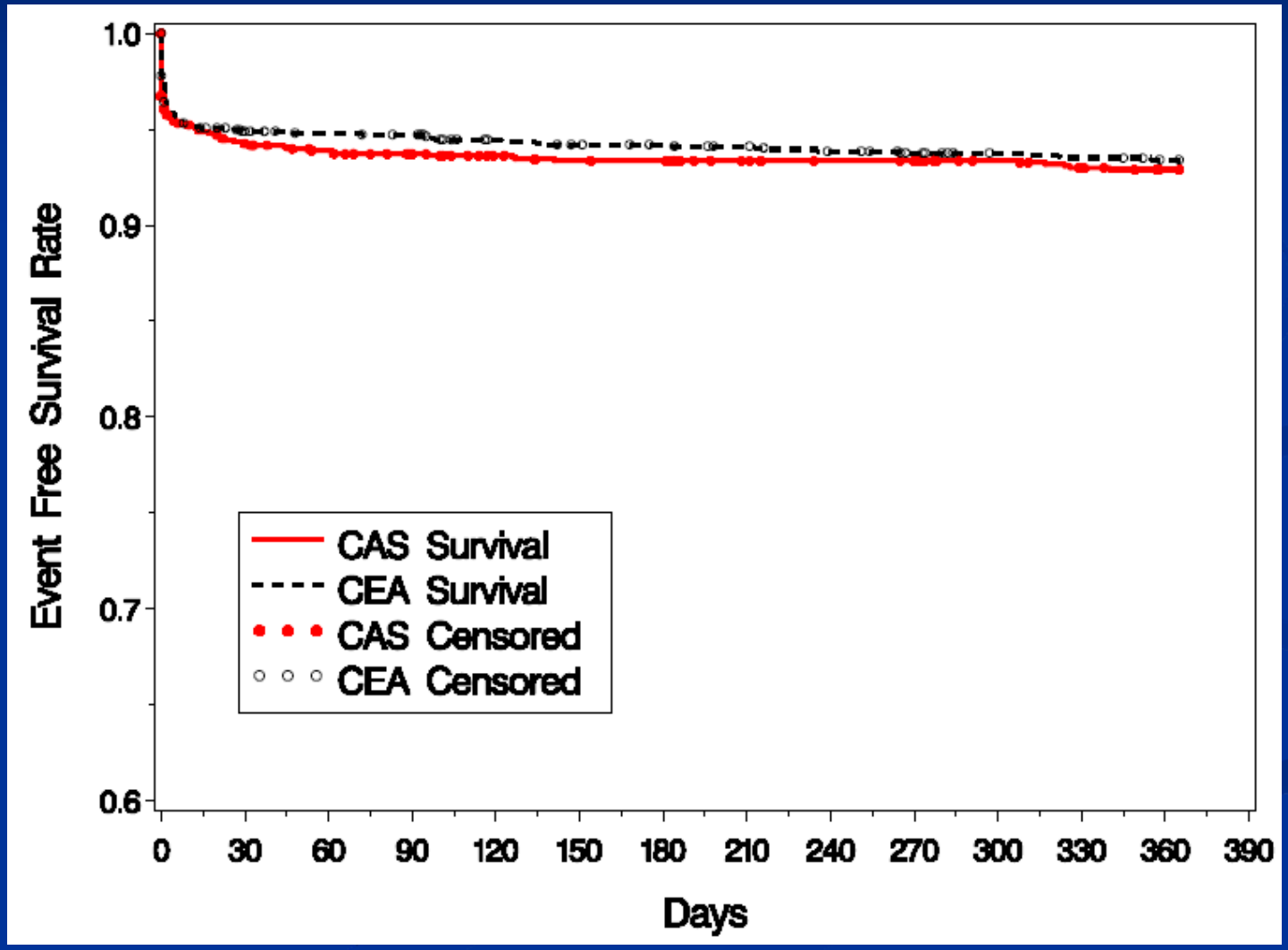
CAS

CEA



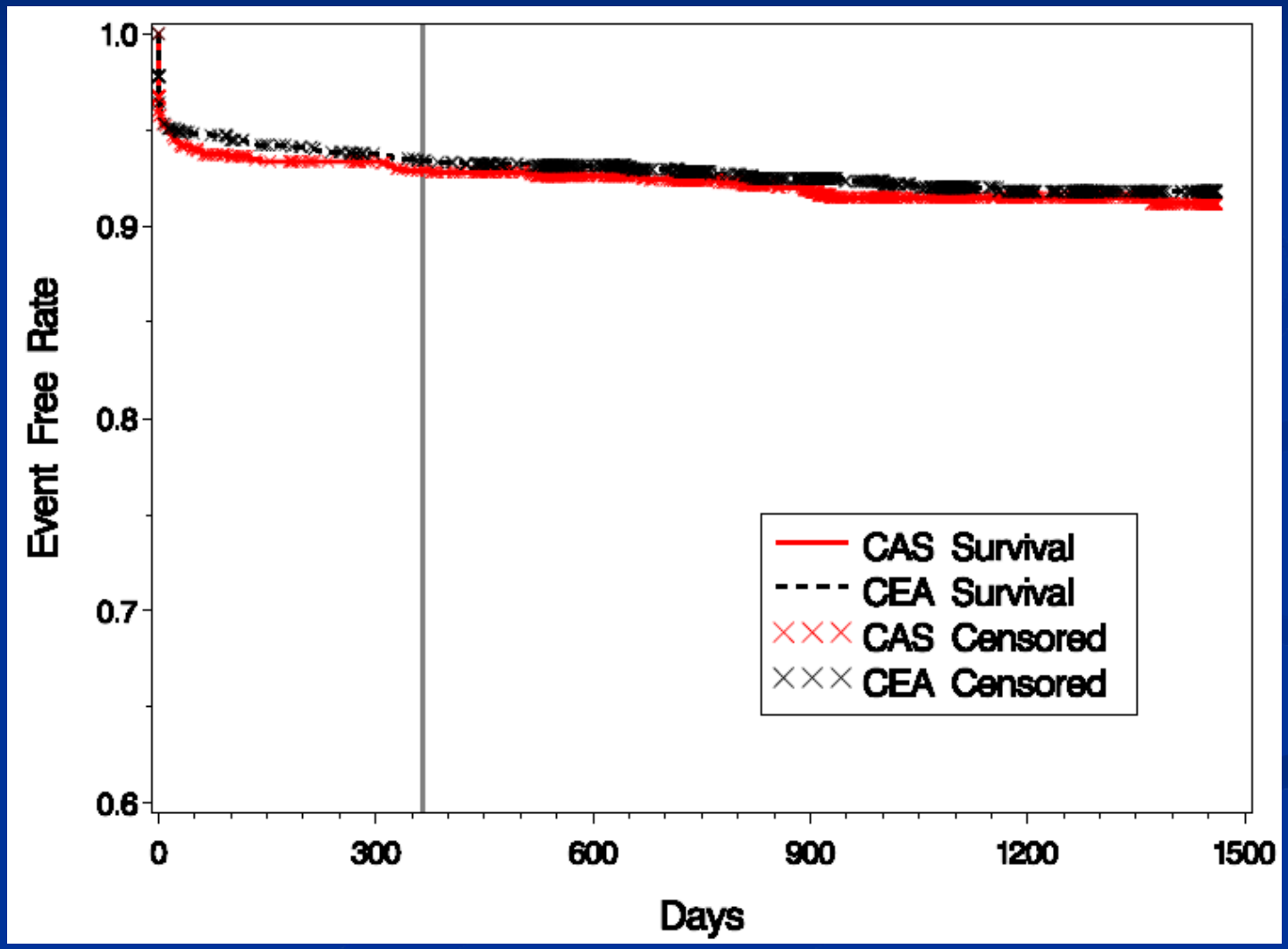
# Primary Endpoint Analysis

# Primary Endpoint
## KM Curves to 1 Year



# Primary Endpoint Events

## KM Curves to 4 Years



# Primary Endpoint Analysis

- NI test result (NI margin = 2.6%)

| | CAS Rate [N] | CEA Rate [N] | Difference (UB of 95% CI) | *p*-value |
|---|---|---|---|---|
| PP | 7.11% [1131] | 6.58% [1176] | 0.52% (2.26%) | 0.025 |
| PP (with PS adjustment) | 7.19% [1131] | 6.52% [1176] | 0.67% (2.41%) | 0.034 |
| ITT | 7.02% [1259] | 6.91% [1237] | 0.11% (1.80%) | 0.008 |

# Subjects Having Missing Value
## in ITT Population

- Subjects not observed any primary endpoint event nor completing the 1-year endpoint may be due to the following:
  - Death between 31 days and 1 year
  - Withdrawal from study
  - Lost to follow-up
- In ITT, # of subjects with missing value / Total # of subjects :

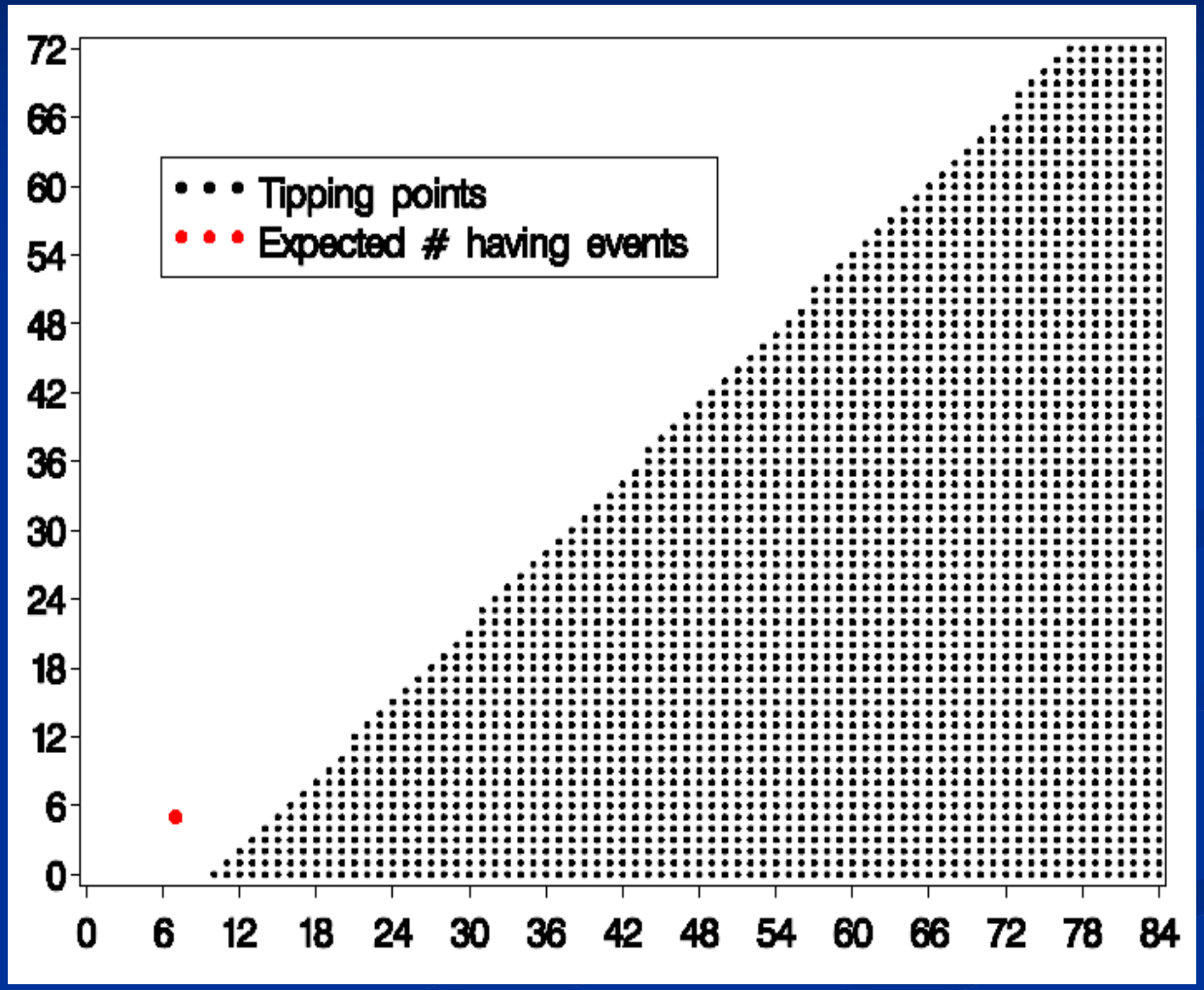
  CAS: 84/1259 (6.7%)  CEA: 72/1237 (5.8%)
- Kaplan-Meier estimate may be biased if
  - the pattern of censoring is not independent of the survival times, or
  - the survival rate of subjects who had missing value is not consistent with the rate in subjects remaining in the study.

# Primary Endpoint Analysis
## Tipping Point Analysis

- Among subjects who had missing value in each arm, some of them assumed to experience events
- Events imputed at the date of the last information available for these subjects
- NI Test conducted based on this imputation
- A tipping point identified if the case resulting in a change of conclusion

# Tipping Point Analysis

## Based on ITT Population

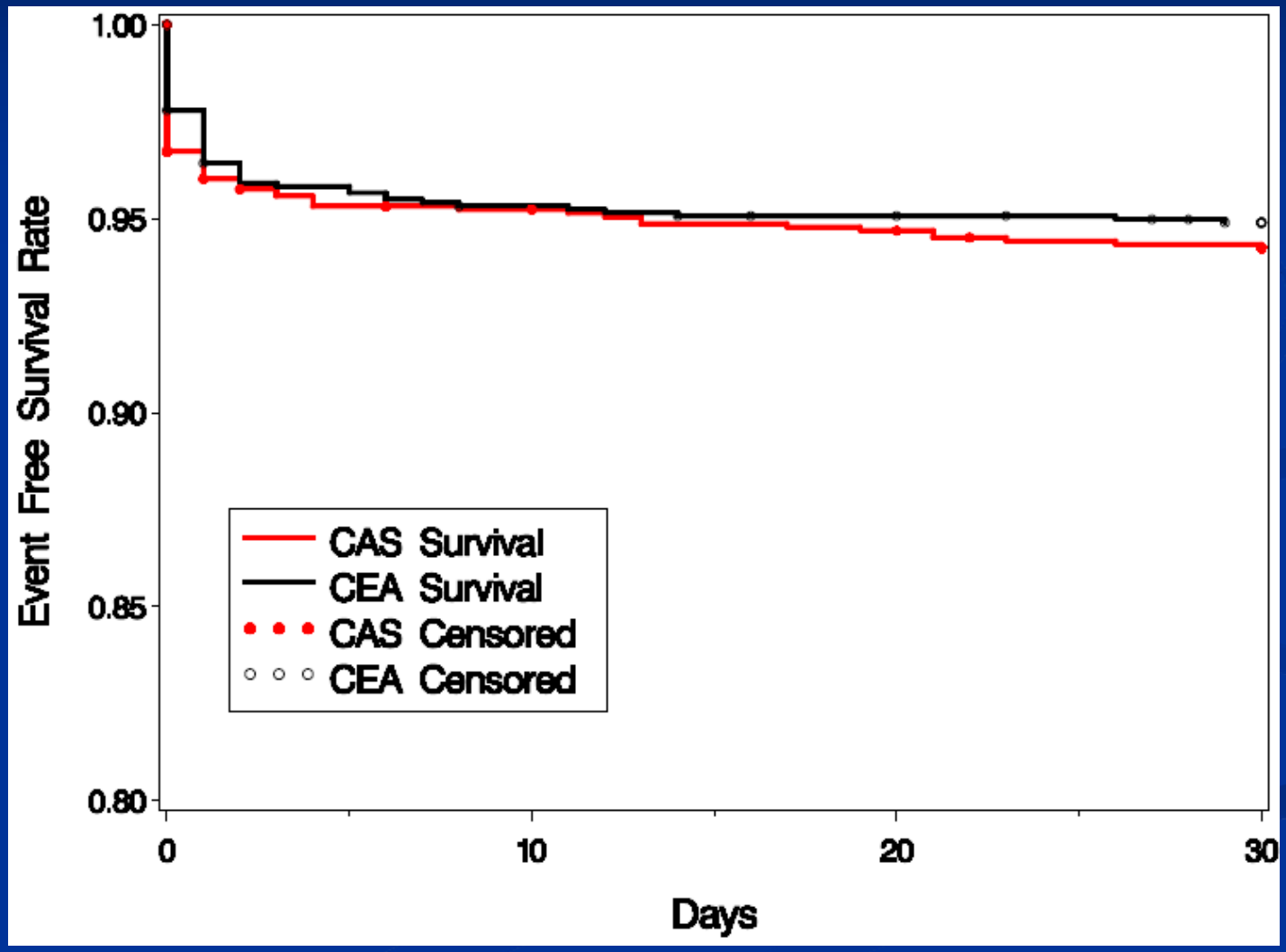



# of subjects with missing value having events in CEA

# of subjects with missing value having events in CAS

# Peri-Procedural Endpoint Analysis

# Peri-procedural Events K-M Curves



# Peri-procedural Events Analysis

- NI test result (NI margin = 2.3%)

| | CAS Rate [N] | CEA Rate [N] | Difference (UB of 95% CI) | *p*-value |
|---|---|---|---|---|
| PP | 5.75% [1131] | 5.10% [1176] | 0.65% (2.20%) | 0.040 |
| PP (with PS adjustment) | 5.80% [1131] | 5.00% [1176] | 0.80% (2.34%) | 0.055 |
| ITT | 5.77% [1259] | 5.47% [1237] | 0.30% (1.83%) | 0.016 |

# Subgroup Analysis by Symptomatic Status

# Symptomatic vs. Asymptomatic

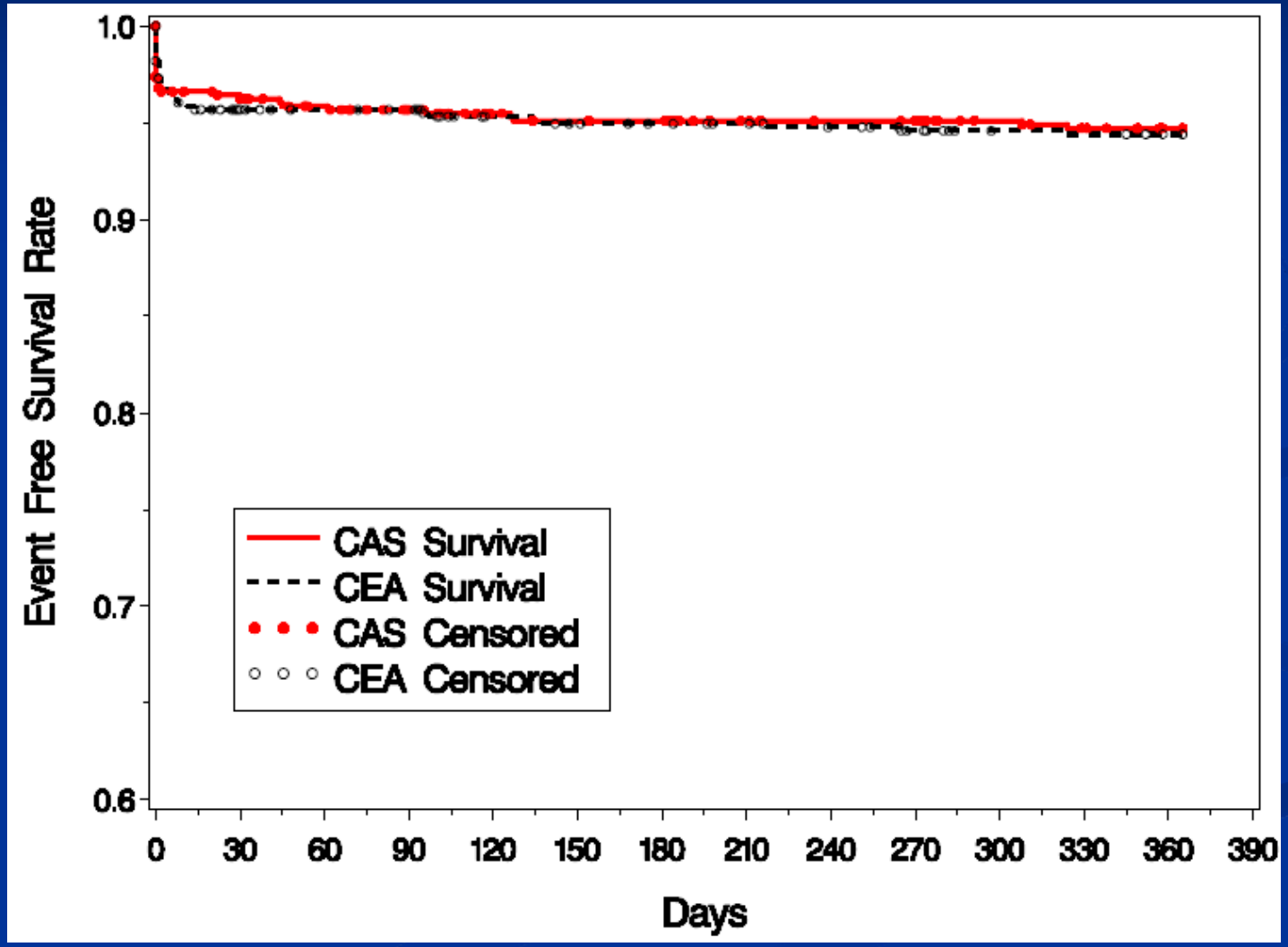
- CREST originally designed for symptomatic patients only
- Randomized within each group
- Pre-specified subgroup analysis
- 52.8% (1321/2502) of randomized subjects were symptomatic subjects

# Asymptomatic Patients

| Event(s) that a subject experienced | CAS [N=532] Count (%) | CEA [N=556] Count (%) |
|---|---|---|
| Within 30 days | | |
| Death | 1 (0.2) | 2 (0.4) |
| Stroke | 13 (2.5) | 7 (1.3) |
| Death and Stroke | 13 (2.5) | 7 (1.3) |
| MI | 9 (1.7) | 17 (3.1) |
| DSMI | 20 (3.8) | 24 (4.3) |
| At 1 year | | |
| Primary Endpoint | 28 (5.3) | 31 (5.6) |

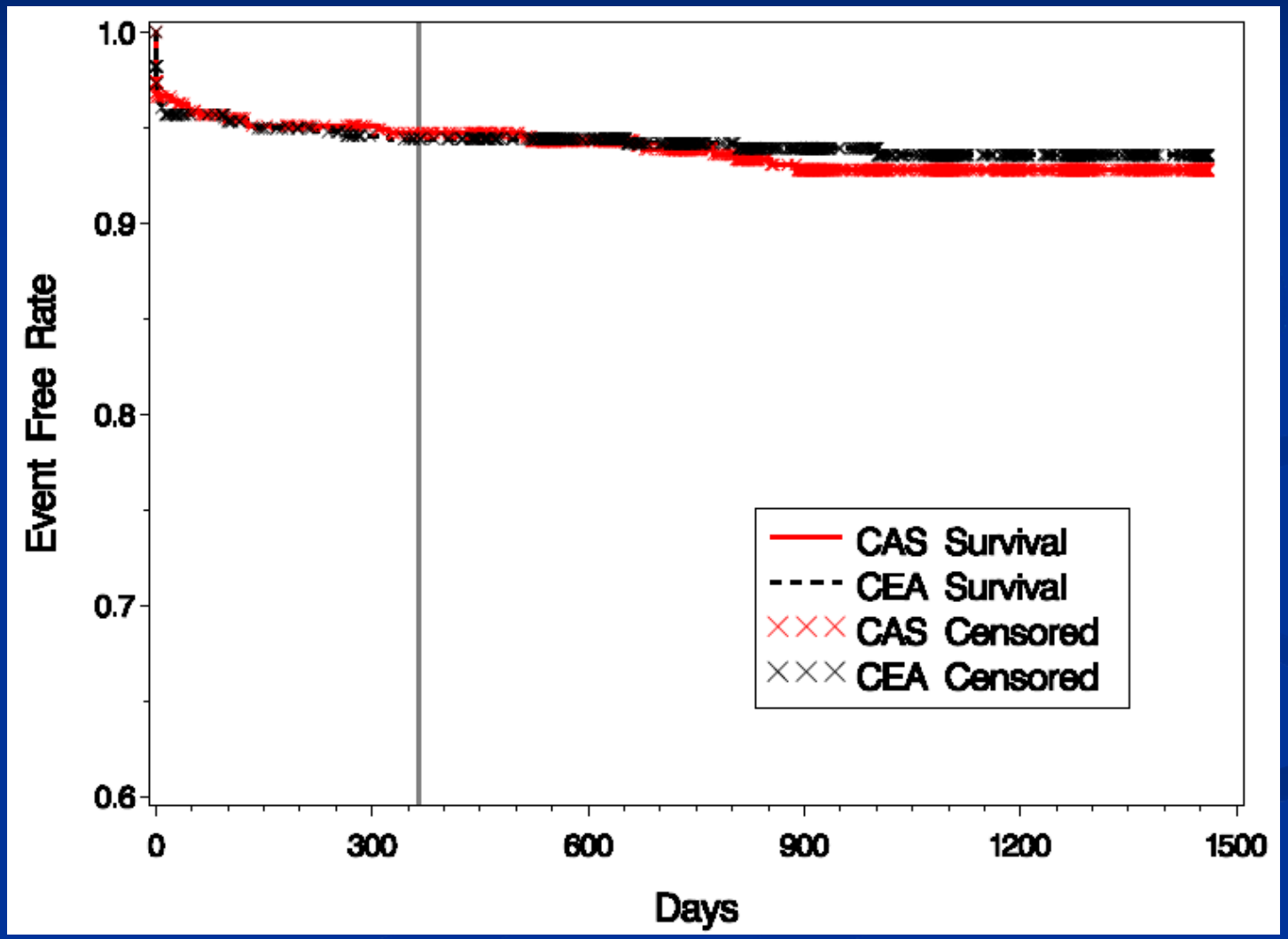
# Asymptomatic Patients

## K-M curves for primary endpoint event – up to 1 Year



# Asymptomatic Patients

## K-M curves for primary endpoint event – up to 4 Years

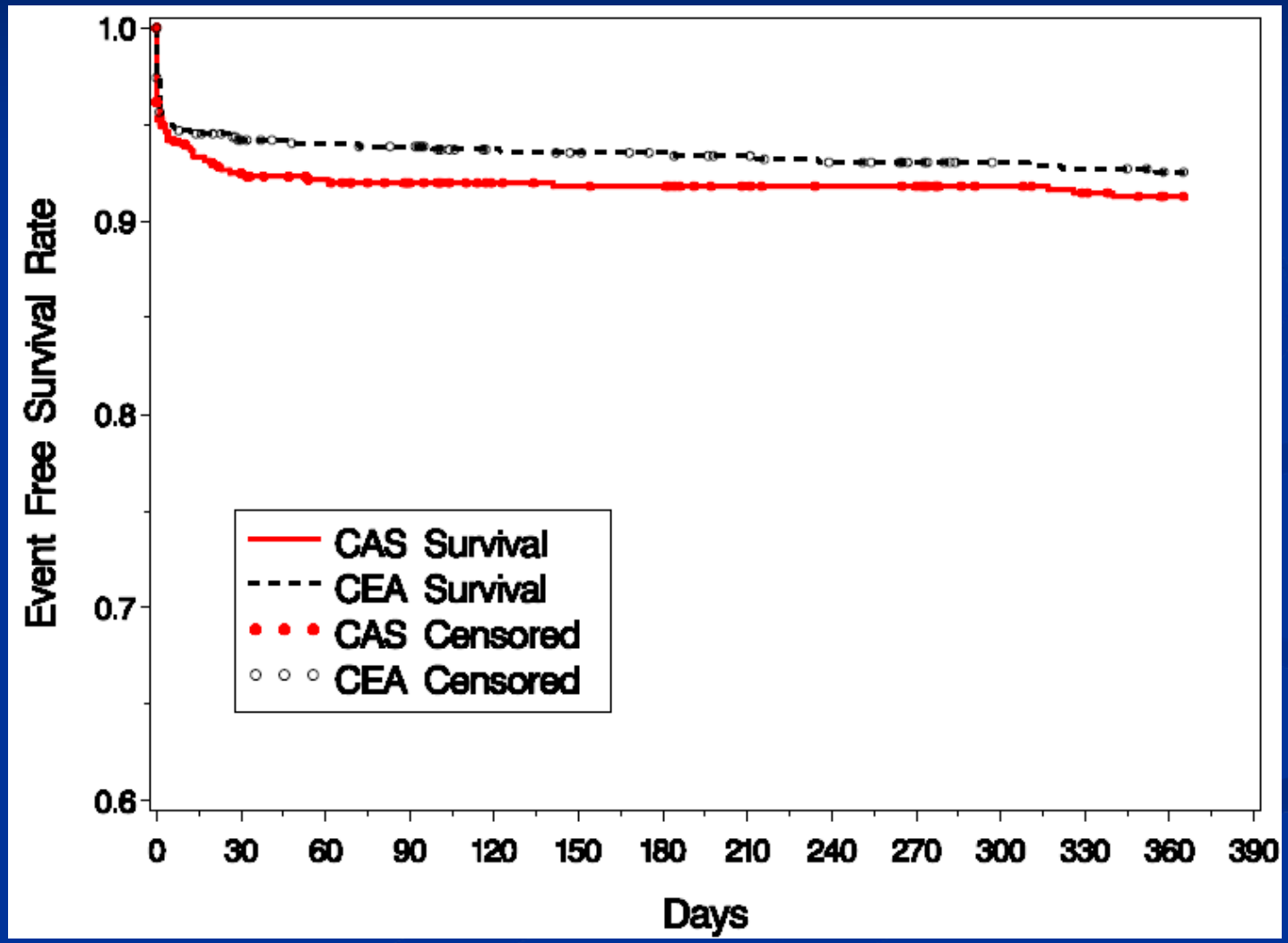


# Symptomatic Patients

| Event(s) that a subject experienced | CAS [N=599] Count (%) | CEA [N=620] Count (%) |
|---|---|---|
| Within 30 days | | |
| Death | 5 (0.8) | 1 (0.2) |
| Stroke | 33 (5.5) | 15 (2.4) |
| Death or Stroke | 35 (5.9) | 15 (2.4) |
| MI | 13 (2.2) | 23 (3.7) |
| DSMI | 45 (7.5) | 36 (5.8) |
| At 1 year | | |
| Primary Endpoint | 52 (8.7) | 46 (7.5) |

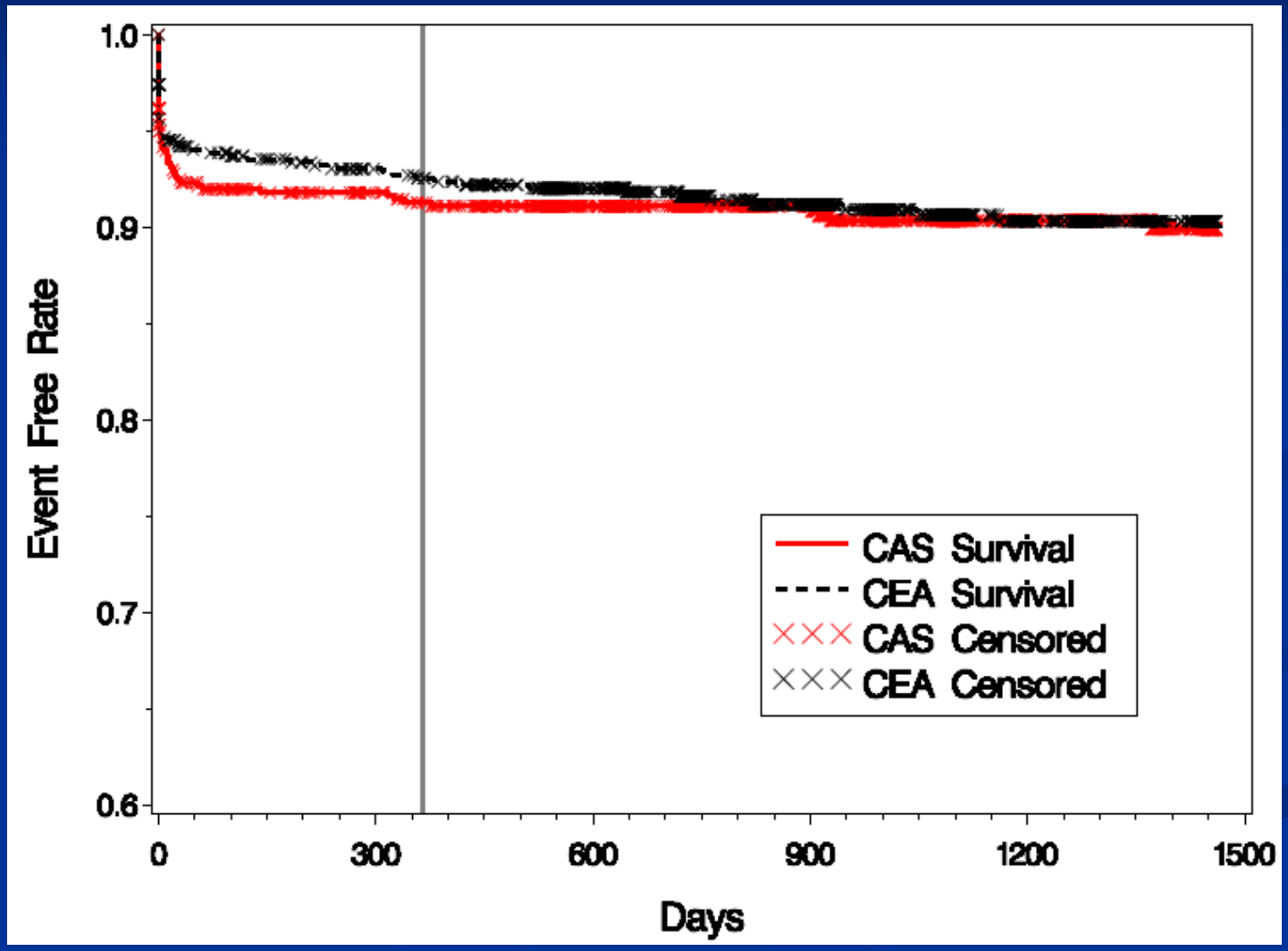
# Symptomatic Patients

## K-M curves for primary endpoint event – up to 1 Year



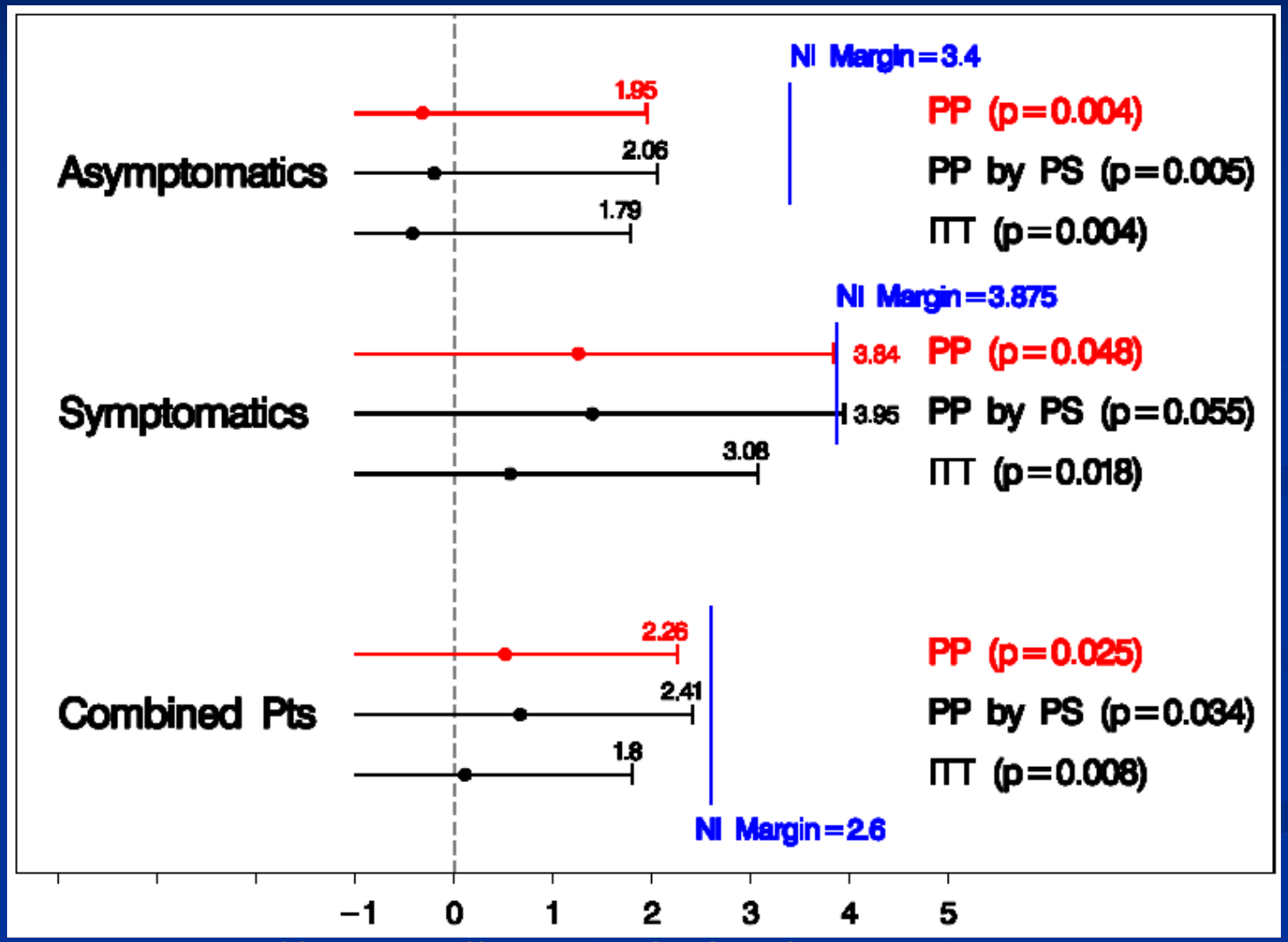
# Symptomatic Patients

## K-M curves for primary endpoint event – up to 4 Years



# Statistical Results by Subgroup

## Primary Endpoint of Rate Difference

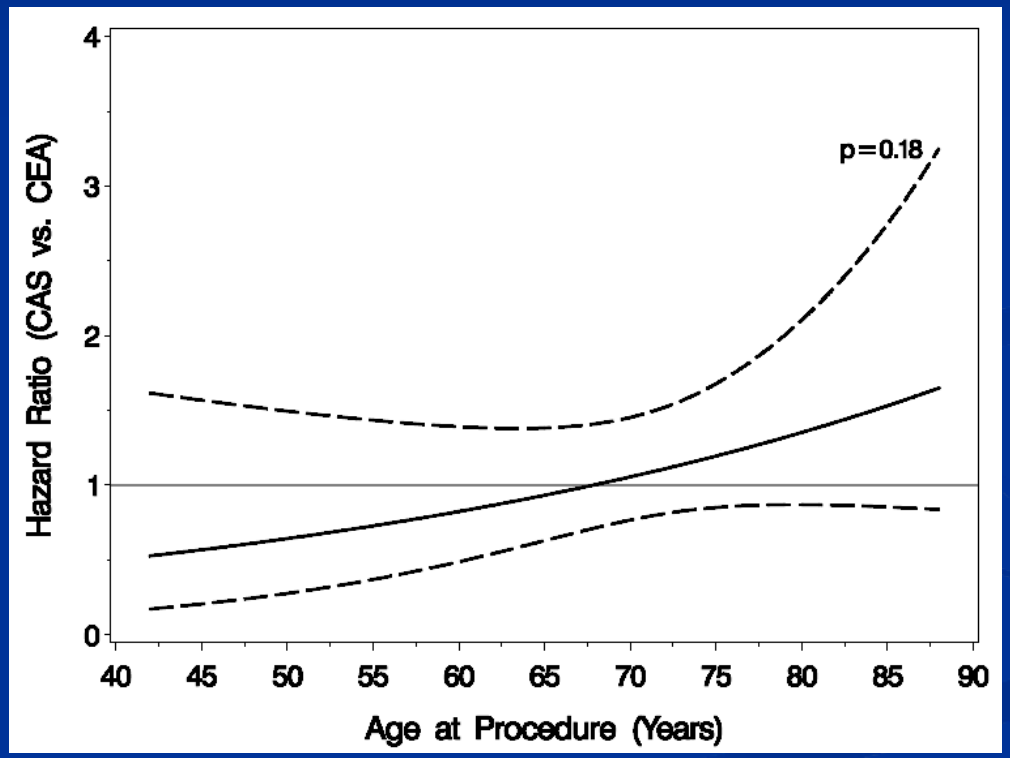



% Rate difference (CAS – CEA)

# Treatment Effect vs. Age

# Hazard Ratio vs. Patient's Age

- Hazard ratio for primary endpoint by age estimated from proportional hazards model, adjusted by symptomatic status and gender
- Based on PP population




Solid line : estimated HR by age at procedure
Dashed line: point-wise 95% confidence limits

# Summary

- The primary endpoint is met, if the statistical test result is unlikely to be changed due to subjects with missing value.
- Peri-procedural events
  - death and stroke rate in CAS about double the rate in CEA
  - MI rate in CAS lower than the rate in CEA
  - marginal evidence of non-inferiority of CAS to CEA
- By symptomatic status
  - Asymptomatics – there is evidence of non-inferiority of CAS to CEA at 1 year
  - Symptomatics – there is marginal evidence of non-inferiority of CAS to CEA at 1 year

# FDA Presentations

- Sadaf Toor
  Introduction
- Dr. Paul Chandeysson
  CREST study design
- Dr. Wolf Sapirstein
  CREST study clinical results and considerations
- Dr. Nelson Lu
  CREST study statistical conclusions and considerations
- Dr. Hesha Duggirala
  Post-approval study considerations
- Sadaf Toor
  Conclusions

# Post-Approval Study (PAS) Considerations

Hesha J. Duggirala, PhD
Division of Epidemiology
Office of Surveillance and Biometrics

# Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance.

# General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness

- Post-approval studies should <u>not</u> be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness

# Need for Post-Approval Studies

- Gather postmarket information
  - Long-term performance including effects of re-treatments and device changes
  - Real-world device performance (patients and clinicians)
  - Effectiveness of training programs
  - Sub-group performance
  - Outcomes of concern (safety and effectiveness)
- Account for Panel recommendations

# Post-Approval Study Components

- Fundamental study question or hypothesis
- Safety endpoints and methods of assessment
- Acute and chronic effectiveness endpoints and methods of assessment
- Duration of follow-up

# Important Postmarket Issues

- Risk of peri-procedural death and stroke in symptomatic and asymptomatic patients
  - Death and stroke rates from CREST CAS arm
    - 2.5% in asymptomatic
    - 5.9% in symptomatic
- Evaluation of additional long term follow-up to a real world population
- Learning curve issues associated with CAS*

* Smout J, et al. Int J Stroke. 2010 Dec;5(6):477-82.

# Outline for Proposed PAS

| | |
|---|---|
| Title | Carotid Artery Stenting Outcomes in the Standard Risk Population for Carotid Endarterectomy (“CANOPY” Study) |
| Study Design | Prospective, multi-center, non-randomized, single arm, post-approval study |
| Sample Size | Up to 350 clinical sites in the United States. At least 1200 sequentially-enrolled subjects |

# Outline for Proposed PAS (cont.)

| | |
|---|---|
| Study Hypothesis | $H_0$: Composite of death and stroke rate at 30 days plus ipsilateral stroke at 1 year<br>≥ 9.4% Objective Performance Goal (OPG)<br>$H_1$: Composite of death and stroke rate at 30 days plus ipsilateral stroke at 1 year<br>< 9.4% Objective Performance Goal (OPG) |
| Primary Endpoint | Evaluate the composite of death and stroke at 30 days plus ipsilateral stroke between day 31 and 1 year (365 days) |
| Secondary Endpoints | 1. Death and stroke at 3 years for symptomatic subjects<br>2. Death and stroke at 3 years for asymptomatic subjects |

# PAS Assessment

- Review team agrees with primary and secondary endpoints at 1 year and 3 years
- Review team would like to see sponsor enroll a separate cohort to evaluate peri-procedural event rates comparing symptomatic and asymptomatic patients
- Events associated with learning curve should be evaluated

# Panel Questions

- Please comment on appropriateness of a separate analysis at 30 days to evaluate peri-procedural death and stroke in symptomatic vs. asymptomatic patients

- Please comment on whether there is a need for the post-approval study to evaluate the learning curve for CAS operators and how this can be done

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  Conclusions

# Conclusions

- CREST met the pre-specified primary hypothesis
- The results indicate a higher death and stroke rate in the CAS arm vs. a higher rate of MI in the CEA arm
- Secondary analyses show higher peri-procedural event rates in octogenarian subjects in both CAS and CEA arms
- Non-inferiority of CAS to CEA is stronger for asymptomatic subjects vs. symptomatic subjects
- Potential sources of bias:
  - Censored subjects
  - Imbalance in number of crossovers between study arms

# Thank you