

# CREST 2

Designed to Answer the Critical  
Questions About the Asymptomatic  
Carotid Patient.

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# Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

## **Affiliation/Financial Relationship**

- Royalty Income

## **Company**

- Cook Inc.
- Abbott Vascular Inc.

# CREST-2 *Primary Aims*

- CEA + medical management compared to medical management alone.
- CAS + medical management compared to medical management alone.
- In patients with  $\geq 70\%$  asymptomatic carotid stenosis.

# ≥ 70% Stenosis (Subject to review)

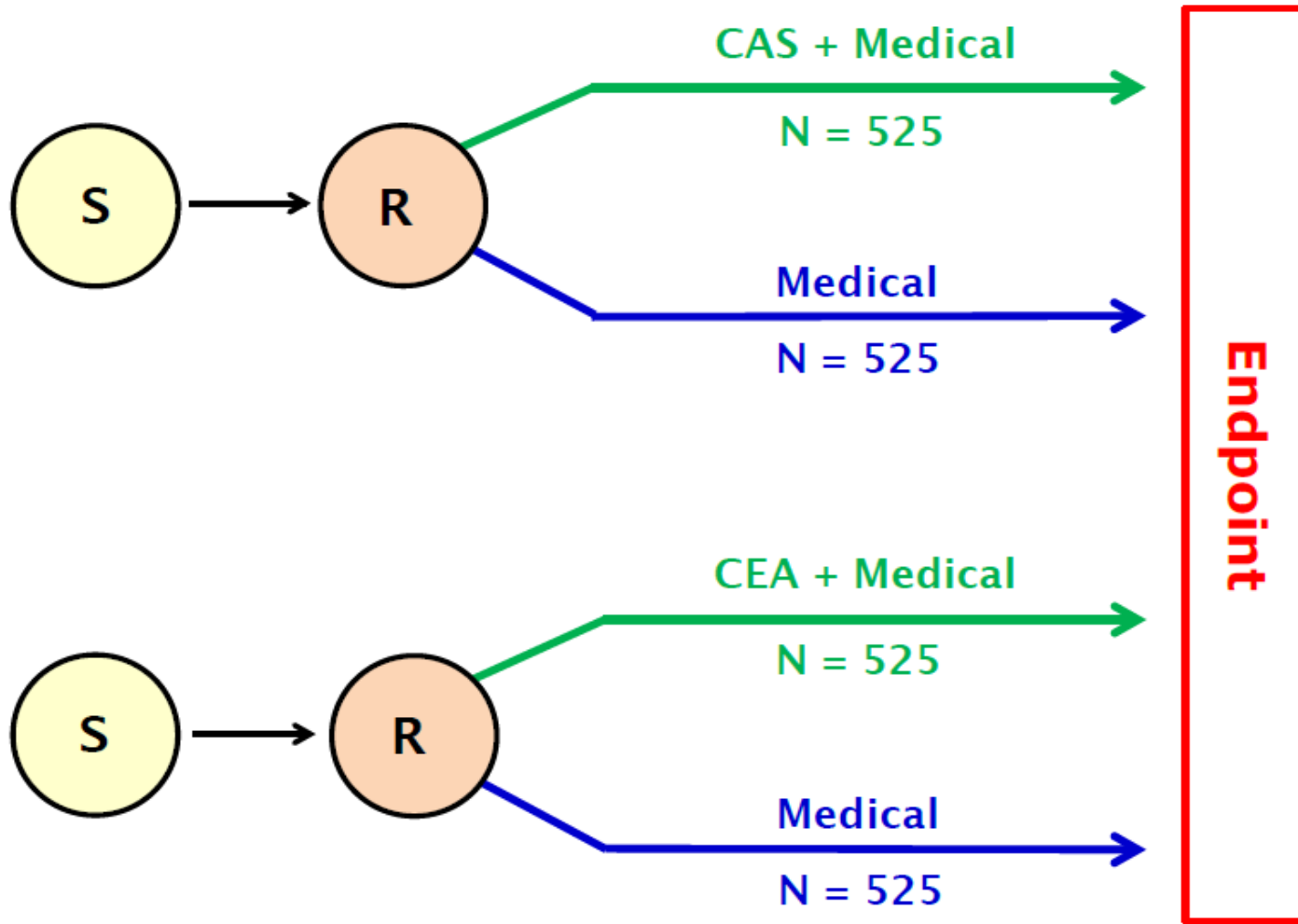
- PSV ≥ 230 cm/second plus EDV ≥ 100 cm/second
- PSV ≥ 230 cm/second plus  
ICC PSV/CCC PSV ≥ 4.0 DUS
- PSV ≥ 230 cm/second plus MRA, CTA

Need to lobby neurology PI's at your centers

## CREST-2 *Primary Outcome*

- Composite of stroke or death within 30 days of enrollment or ipsilateral stroke up to 4-years.

# CREST-2 Parallel Study Design (N = 1,050 in each trial)



Endpoints = stroke & death in first 30 days and ipsilateral stroke thereafter up to 4

# CREST-2 *Statistical Analysis*

- Intention-to-treat
- Non-inferiority
- 1% per year non-inferiority margin (4% at 4-years)
- 90% power for each of the parallel trials

# Selected *Protocol Summary* Bullets

- Observer-blinded endpoint.
- 5-year recruitment period.
- Length of follow-up out to 2-years after last patient is randomized.
- ~ 120 sites in North America (*and beyond?*)



# Which trial? Which procedure?

- For ages 50-74, no favored procedure as HR for Stroke and Death = 1.03, 95% CI, 0.44-2.44.
- For age < 50 years, CAS is the favored procedure.
- For age > 74 years, CEA is the favored procedure.

# *Selected CEA Exclusion Criteria*

- radical neck dissection
- surgically inaccessible lesions
- adverse neck anatomy that limits surgical exposure
- presence of tracheostomy stoma
- laryngeal nerve palsy contralateral to target vessel

# *Selected CAS Exclusion Criteria*

- Occlusive or critical ilio-femoral disease.
- Angiographic, CT, MR or ultrasound evidence of severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries.
- Type III, calcified aortic arch anatomy.
- Qualitative characteristics of stenosis and stenosis-length of the carotid of the carotid bifurcation (common carotid) and/or ipsilateral external carotid artery.
- Angulation or tortuosity ( $\geq 90$  degree).
- Severe angulation or tortuosity of the internal carotid artery.

- Excessive circumferential calcification of the stenotic lesion.
- **Mild tortuosity, arch anatomy, and lesion anatomy and calcification ,white matter disease will be exclusion criteria in elderly subjects ( $\geq 75$  years). ???**
- “String sign” of the ipsilateral common or internal carotid artery.
- **Lesions > 20 mm in length, sequential lesions, and narrow-mouth ulcers.**
- Target ICA vessel reference diameter < 4.0 mm or > 9.0 mm.
- Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD).

**Table 2. Table of Scheduled Events in CREST-2.**

Evaluation	Time										
	1	2	3	4,5	6	7,8	9	10,11	12	13,14	15
Visit number	-1	0	1	4,8	12	16,20	24	28,32	36	40,44	48
Month	-1	0	1	4,8	12	16,20	24	28,32	36	40,44	48
Informed Consent	X										
Demographics	X										
Medical History	X										
Interval Medical Hx		X	X	X	X	X	X	X	X	X	X
Stroke Questionnaire	X		X	X	X	X	X	X	X	X	X
Modified Rankin	X		X	X	X	X	X	X	X	X	X
NIHSS	X		X	X	X	X	X	X	X	X	X
<i>Cognitive Testing</i>		X	X		X		X		X		X
Ultrasound	X				X						
<i>CTA/MRA/CBA**</i>	X										
Blood Pressure		X	X	X	X	X	X	X	X	X	X
Creatinine		X			X		X		X		X
CPK		X									
Lipid panel		X			X		X		X		X
AST/ALT		X	X	X*	X		X		X		X
HgA1c (if DM)		X		X†		X†		X†		X†	
Smoking	X		X	X	X	X	X	X	X	X	X

Month -1 designates the screening visit.

Month 0 designates the baseline visit.

\*Month 4 visit only.

\*\*CBA indicates catheter-based angiogram.

† HgA1c to be completed once per quarter.

NOTE: For patients who undergo CAS and are prescribed ticlopidine, a complete blood count will be required at 2 weeks and 30 days per standard medical practice.

# CREST-2 *Medical Management*

## State of the Art

- Similar protocol to SAMMPRIS.
- Implemented by SAMMPRIS Team.
- Primary risk factor targets:
  - Systolic BP < 140 mmHg (< 130 mmHg for diabetics)
  - LDL < 70 mg/dl

# CREST-2 *Medical Management*

- Secondary risk factor targets:
  - Non-HDL cholesterol < 100 mg/dl
  - Hemoglobin A1c < 7.0%
  - Smoking cessation
  - Targeted weight management
  - > 30 min. of moderate exercise 3 x's/week

## CREST-2 *Credentialing of Investigators*

- Criteria for credentialing include:
  - Low complication rate
  - Use of standard techniques
  - Avoidance of erroneous techniques
  - **Submit 50 consecutive cases (CEA or CAS)**

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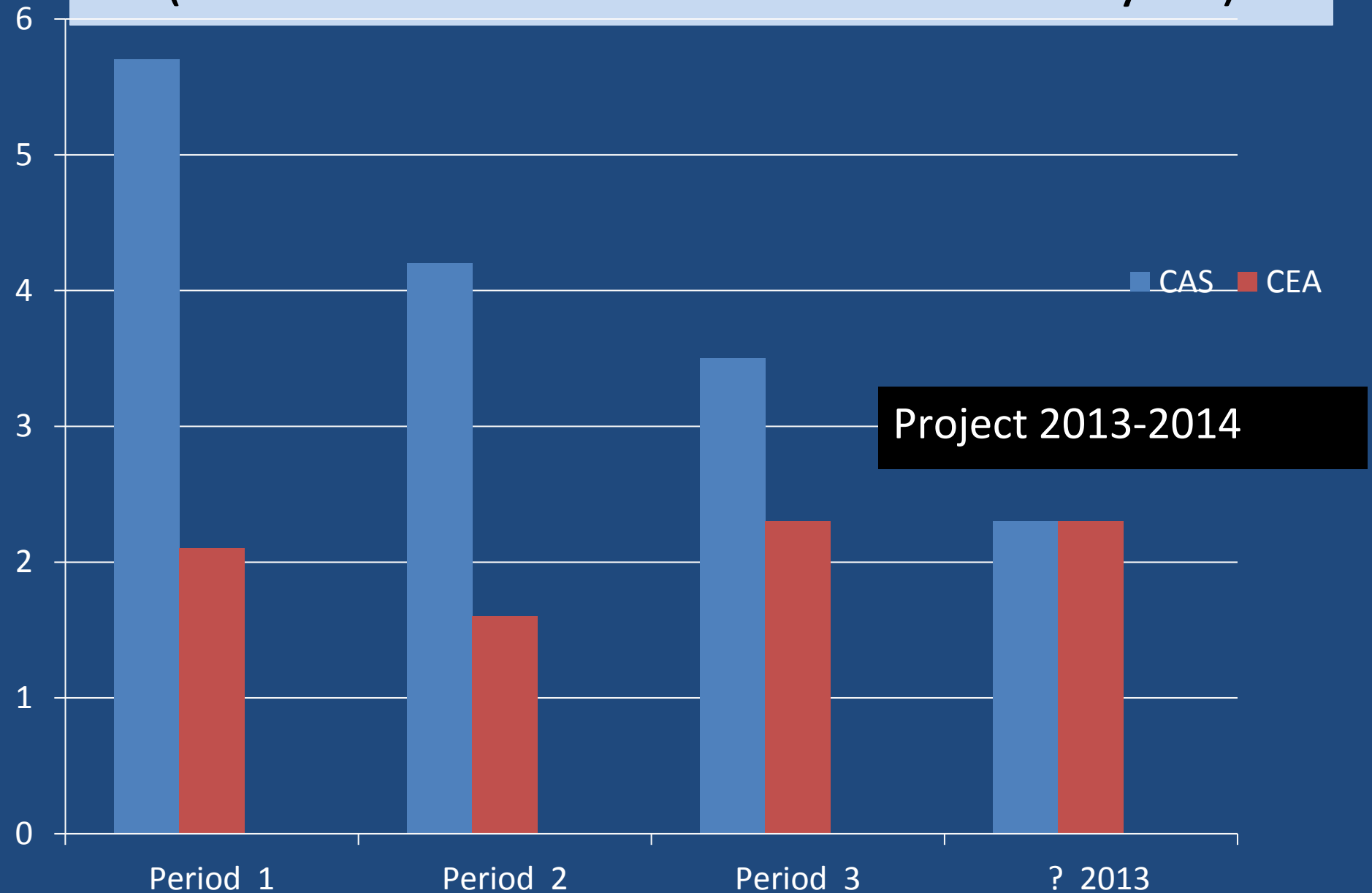
- **Experience of at least 30 procedures over the prior 12 months.**
- CEA and CAS must have been performed in asymptomatic patients with combined rate of stroke and death <3%.
- Can seek credentialing in either or both procedures.



Site #	Site (#)	Total	SX	ASX	#	enrolled patients that withdrew	Total Peri Strokes	Peri Stroke CAS	Peri Stroke CEA
296		125	105	20	19	15.2	2	1	1
179		111	56	55	10	9.0	4	3	1
499		101	74	27	5	5.0	7	3	4
293		89	82	7	9	10.1	8	4	4
292		79	31	48	11	13.9	2	2	
516		70	19	51	5	7.1	4	4	
346		66	21	45	3	4.5			
249		55	54	1	17	30.9	4	2	2
508		52	4	48	3	5.8	1	1	
340		48	36	12	6	12.5	1	1	
520		45	12	33	2	4.4	1	1	
32		44	17	27	15	34.1	2	1	1
57		44	28	16	10	22.7	1		1
374		43	22	21	1	2.3	1		1
222		41	40	1	2	4.9	2	1	1
344		40	27	13	1	2.5	2	2	
509		38	10	28	20	52.6			
297		34	7	27	5	14.7	1		1
42		33	28	5	17	51.5	1		1
223		33	13	20	9	27.3			
328		33	7	26	1	3.0			
107		30	6	24	7	23.3	2	1	1
407		30	6	24	9	30.0			
4		28	10	18	1	3.6			
100		28	9	19	2	7.1			
27		27	22	5	5	18.5			
28		27	23	4	4	14.8	1		1
44		26	26	0	16	61.5	1	1	
512		26	5	21	4	15.4			
295		25	18	7	5	20.0			
210		24	21	3	9	37.5			
339		24	13	11	7	29.2	1	1	
388		22	9	13	3	13.6			
497		22	12	10	2	9.1	2	2	
227		21	17	4	7	33.3			
355		21	0	21	2	9.5			
449		21	14	7	0	0.0			
505		21	18	3	4	19.0			
15		20	0	20	4	20.0			



# Temporal Trends in Outcomes in CREST (Stroke and Death – Per Protocol Analysis )



## CREST 2.

- I need help on the IMC to credential operators and monitor ongoing procedures for protocol patient selection and technical violations, introduction of new technology as it evolves and keeping the neurologists and surgeons” honest”.

**“Horatio” at the bridge!**

- Thank you.