MAYO CLINIC

SVIN: *Update on CREST-2 Trial*

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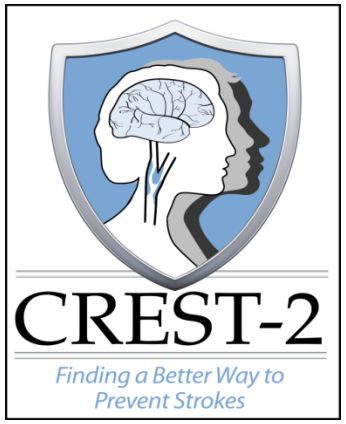
Disclosures

- Edwards Lifesciences Corporation – Consultant
- Daiichi-Sankyo – Honorarium

Outline

- CREST-2 Research Plan
- FDA
- NINDS
- CMS
- CED
- Input from audience



Intensive Medical Management

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compared to

Carotid Endarterectomy or Carotid Stenting *plus* Intensive Medical Management

Grant # U01 NS080168 – Clinical Coordinating
Grant # U01 NS080165 – Statistical and Data Management

Background

- ~ 140,000 carotid revascularizations (CEA and CAS) yearly in the US.

- Annual US costs for CEA ~ $21 Billion
  - CAS costs are comparable on a per case basis.

"Do the benefits of these two procedures persist?"

Background

- For 1181 asymptomatic CREST patients, the primary endpoint was similar in CAS compared to CEA (5.6% vs. 4.9%).
- Perioperative stroke and death rates were low, within the AHA Guideline-recommended range of < 3% for asymptomatic patients (2.5% for CAS and 1.4% for CEA).

"RCT needed to compare CAS and CEA to intensive medical management."

Primary Aims

In patients with ≥ 70% asymptomatic stenosis, to assess:

- The treatment differences between medical management and **CEA**.
- The treatment differences between medical management and **CAS**.

Asymptomatic

- No stroke or stroke-like symptoms ipsilateral to the stenosis within 180 days of randomization.

≥ 70% Stenosis

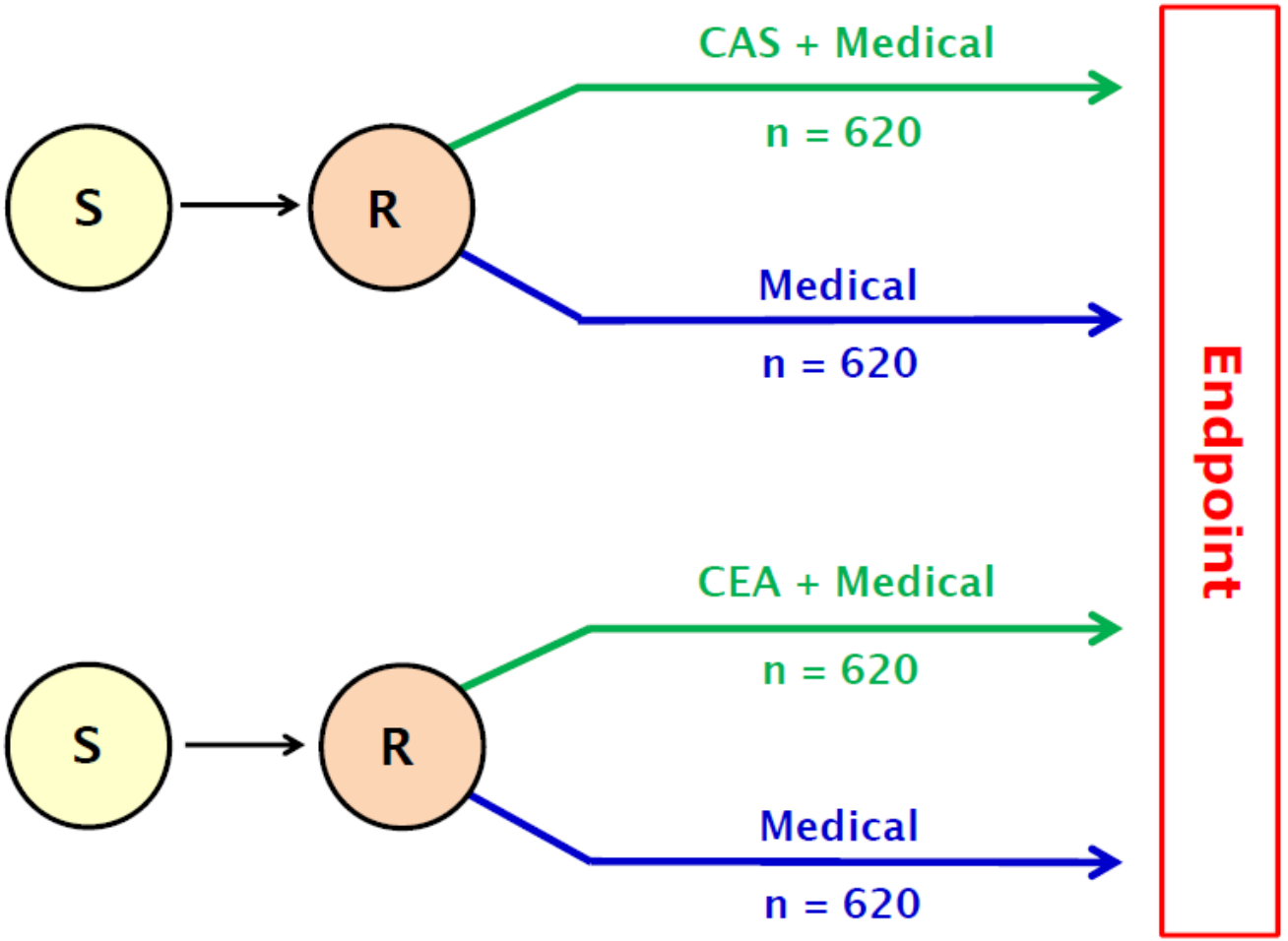
- PSV ≥ 230 cm/second on DUS **and:**
  - EDV ≥ 100 cm/second on DUS, or
  - ICC PSV/CCC PSV ≥ 4.0 on DUS, or
  - ≥ 70% stenosis on MR angiogram, or
  - ≥ 70% stenosis on CT angiogram.

Primary Outcome

- Composite of all stroke and death within 30 days of randomization and ipsilateral stroke thereafter up to 4 years.

CREST-2 Parallel Study Design

(n = 1,240 in each trial)



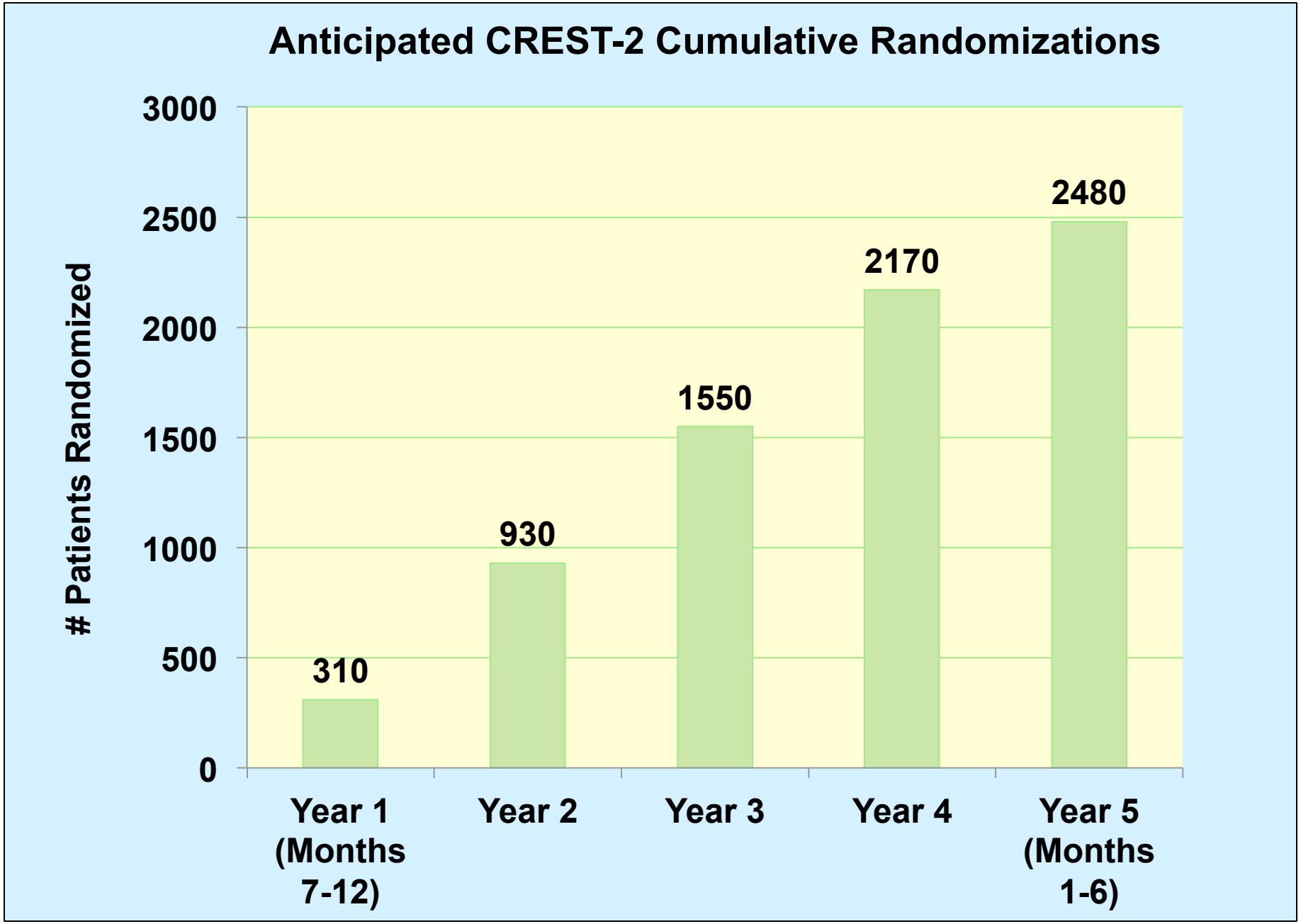
Endpoint = all stroke & death in first 30 days and ipsilateral stroke thereafter up to 4 years.

Primary Statistical Analysis

- Intention-to-treat.
- Superiority assessment of differences in event rate at 4-years.
- 85% power to detect differences in either trial:
  - 3.6% CEA/CAS versus 8.4% medical (1.2% per year)
  - 3.6% CEA/CAS versus 0.8% medical

Protocol

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


Anticipated CREST-2 Cumulative Randomizations
Patients Randomized
3000
2500
2000
1500
1000
500
0
310
930
1550
2170
2480
Year 1 (Months 7-12)
Year 2
Year 3
Year 4
Year 5 (Months 1-6)

Which trial? Which procedure?

Based on data from CREST:

- For ages 50-74, no favored procedure as HR for Stroke and Death = 1.03, 95% CI, 0.44 to 2.44.
- For ages < 50 years, CAS is the favored procedure.
- For ages > 74 years, CEA is the favored procedure.
- Caveat: in CREST, asymptomatic patients had few events, and so there were **wide confidence intervals** about the point estimates comparing CEA and CAS.
- Accordingly, **choice of CEA or CAS cannot be mandated** -- individual patient characteristics and preferences may supersede guidelines based upon patient age.

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

- Severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries.
- Type III, calcified aortic arch anatomy.
- Angulation or tortuosity (≥ 90°) of the innominate and common carotid artery.
- Excessive or circumferential calcification of the stenotic lesion.
- Lesions > 20 mm in length, sequential lesions, and narrow-mouth ulcers.
- Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD).

CREST-2 Schedule of Events															
Evaluation	**Time**														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
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	X	X	X	X
Stroke Questionnaire	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Modified Rankin	X		X	X	X	X	X	X	X	X	X	X	X	X	X
NIHSS	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive Testing		X	X			X			X			X			X
Ultrasound	X					X									
CTA/MRA/CBA**	X														
Blood Pressure		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Medical Management:
SAMMPRIS model and Team

- Patients in both trials will take aspirin 325 mg/ day for the entire follow-up period (CAS patients will also take clopidogrel per protocol).

- Primary risk factors (systolic blood pressure and LDL) will be managed by the study neurologist according to predefined protocols targeting a systolic blood pressure < 140 mmHg (< 130 mmHg if diabetic) and LDL < 70.

Medical Management

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

Covered Medications

- Antiplatelet agents
  (clopidogrel)

- Anti-hypertensive Rx
  (one drug from each major class will be made available: diuretic, ACE inhibitor, potassium-sparing diuretic, angiotensin receptor blocker, beta blocker, vasodilator, central alpha agonist, long-acting calcium channel antagonist)

- Statin
  (atorvastatin)

Cognitive Outcome

- Is the change of cognitive function from baseline to 48 months no worse among those in the MEDICAL cohort compared to the CEA/ CAS cohorts?
- Is the change of cognitive function a surrogate for TIAs or small DWI infarcts?

Credentialing

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

Credentialing

- 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.

Interventional Management Committee

Draft Roster

- Thomas G. Brott, MD – ExOfficio
- James Meschia, MD
- Gary S. Roubin, MD, PhD – Chair
- William Gray, MD
- Ricardo Hanel, MD
- Kenneth Rosenfield, MD

Surgical Management Committee

Draft Roster

- Thomas G. Brott, MD – ExOfficio
- Wesley S. Moore, MD – Chair
- B.K. Lal, MD
- Two CREST-2 site investigators who rotate on 2-year basis

Site Selection Committee

Draft Roster

- Thomas G. Brott, MD – ExOfficio
- Bart Demaerschalk, MD – Chair
- Virginia Howard, PhD
- Frank Veith, MD
- Nils Wahlgen, MD

New Technology/Techniques

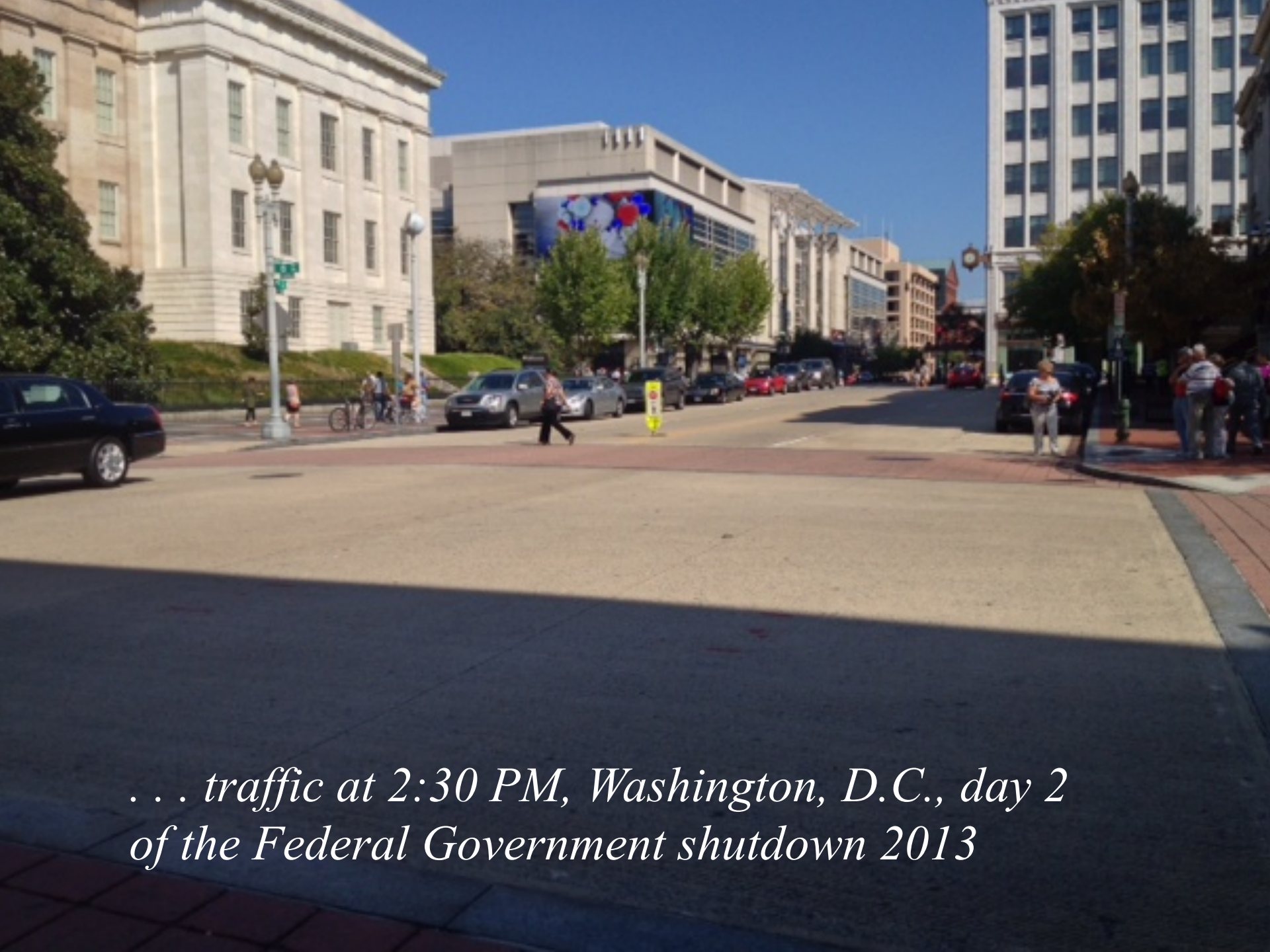
- Ideally, we should incorporate advances into the protocol as they become feasible, and when the data available support safety and effectiveness.

  Potential examples include:

  - Proximal occlusion with flow reversal as an embolic protection strategy independent of type of stent
  - Mini incision CEA
  - Filtered stents
  - Hybrid stents (combined open and closed cell designs)

Conclusion

- CEA, CAS, and medical treatments have all improved since ACAS and ACST.
- CREST-2 will test these 3 options for patients with asymptomatic carotid artery disease.
- The results will change practice for the coming decade.



. . . traffic at 2:30 PM, Washington, D.C., day 2 of the Federal Government shutdown 2013

FDA

- IDE application submitted 9/25
- Abbott: Acculink and Xact stents
- Boston Scientific: Wallstent
- Medtronic: MoMA
- Opportunity to mix and match
- Up to $5M to maintain IDE at 120 ctrs

NINDS

- NOGA (Notice of Grant Award) cannot be issued until the IDE is approved
- *(and when NINDS has the dollars?)*

CMS

- CAS for conventional risk patients is not re-imbursed
- CREST-2 interventionist-leadership concerned with decline in operator experience
- CED (Coverage under Evidence Development) – *hybrid RCT/registry*

CED

- CMS, NINDS, FDA, AHRQ, FDA, Industry, physician stake-holders engaged
- *"…with the goal of crefully expanding coverage for stenting in a way that supports CREST-2…The aim is for the coverage decision to be open for reconsideration by the end of the year"*

Sean Tunis, Center for Medical Technology Policy, October 26, 2013

CED: *points of contention*

- Asymptomatics and symptomatics?
- High risk too?
- CREST-2 eligibles outside CREST-2?
- If yes, how many?
- Oversight

Input from audience

- Load of atorvastatin for CEA ?
- Load of atorvastatin and clopidogrel for CAS?

Input from audience

- LA peak systolic velocity ≥230 cm/second on DUS,
- **plus** confirmatory findings of an end diastolic velocity of ≥100 cm/second **or** internal carotid/common carotid ratio of PSV ≥4.0 on DUS **or** ≥70% stenosis observed on MRA or on CTA will be required, or
- **Or**, conventional angiography documenting ≥ 70% stenosis.

Thanks

to our CREST partners…and to those who will be participating in CREST-2

- CONTACTS:

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