StrokeNet and CREST-2

June 3, 2014

NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

CREST-2 Protocol Summary

(we need your RCC and your satellite centers)

Carotid Revascularization for Primary Prevention of Stroke (CREST-2)

- Two parallel multi-center randomized, observer blinded endpoint trials
- Clinical Coordinating Center
  Mayo Clinic Florida
- Statistical and Data Coordinating Center
  University of Alabama at Birmingham

CREST-2

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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

Secondary Aims

- Differences in cognitive function, intensive medical management compared to CEA and to CAS at 4 years of follow-up.
- Differences in major stroke events at 4-years.
- Are differences in primary outcomes affected by patient age, sex, severity of carotid stenosis, risk factor level, and duration of asymptomatic period.

Sources of patients

Referrals from Primary Care Doctors

Your Own Clinic: Asymptomatic Patients being Followed long-term

Patients with a Carotid Bruit

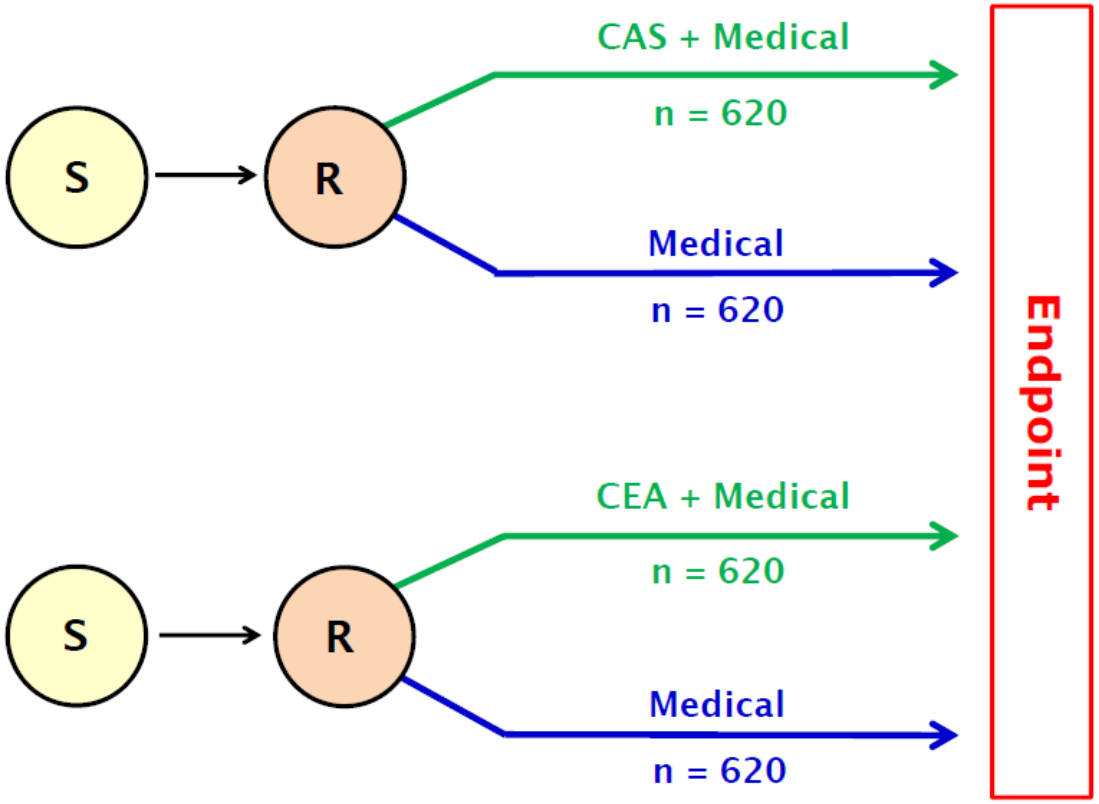
Patients with Symptomatic Contralateral Carotid Stenosis

Patients with Atherosclerosis in other Vascular Beds
- Coronary Artery
- Renal Artery
- Mesenteric Arteries
- Lower Extremity (PAD)

≥70% Stenosis

- PSV ≥ 230 cm/second on DUS plus one of the following:
  - 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

Which Trial?
Which Procedure?



Which Trial?
Which Procedure?

Based on data from CREST:

- For ages 50-74, no favored procedure
- For ages <50 years, CAS is the favored procedure
- For ages >74 years, CEA is the favored procedure
- BUT, in CREST asymptomatic patients had few events, so there were wide confidence interval
- **So choice of CEA or CAS cannot, and is not, mandated in CREST-2**
- Individual patient characteristics and preferences may supersede guidelines based upon patient age

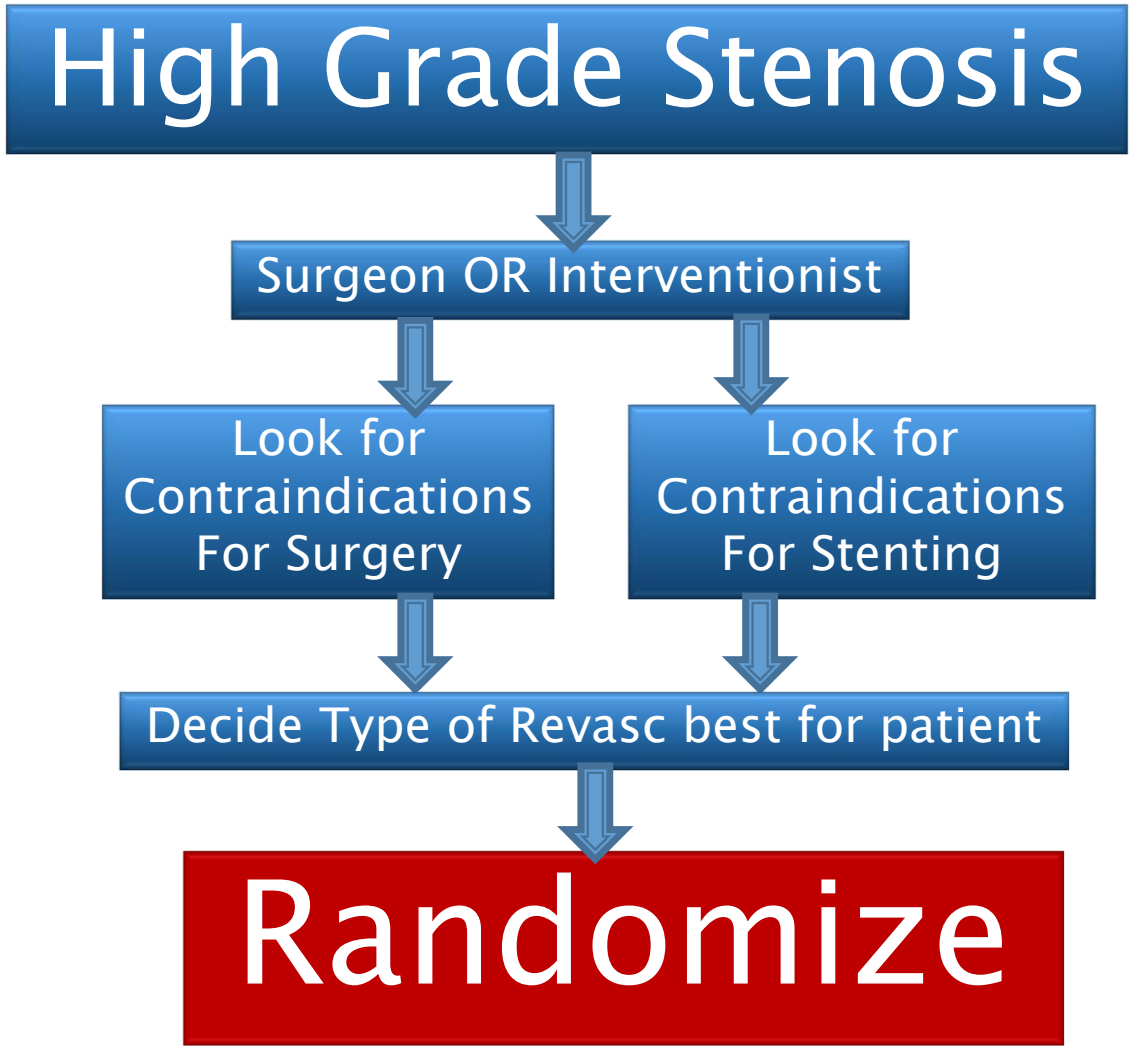
CAS Credentialing

- Potential investigators submit 25 recent cases for thorough review by the Interventional Management Committee (IMC).
- IMC has developed an SOP for the approval process based upon recent vs. total volume and experience in CREST-1
- As of June 1, conditionally approved 22 investigators pending submission of additional cases. Approved only 1 investigator without requirement of additional cases.

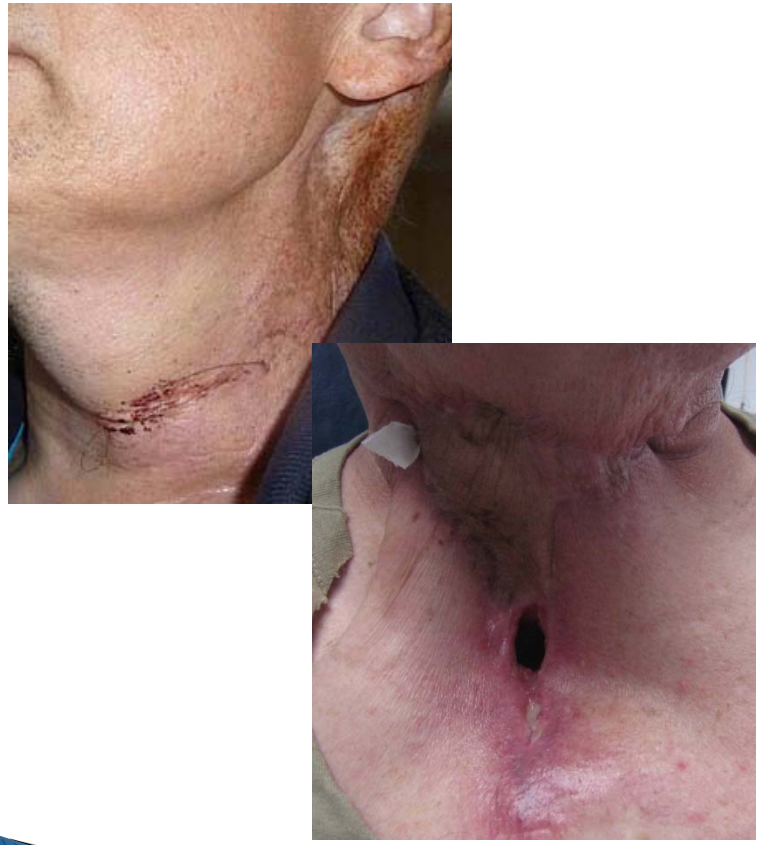
CAS Companion Registry

- CMS re-imbursement.
- Utilizes pre-existing SVS and ACC Registries, currently for high risk symptomatics.
- Patient Eligiblity: standard risk symptomatic and asymtomatic patients with >= 70% stenosis and other smaller subsets.
- Interventionists Eligibility: > 50 cases and > 8 cases in the last two years.

What Will Happen when a Carotid Patient comes to Clinic

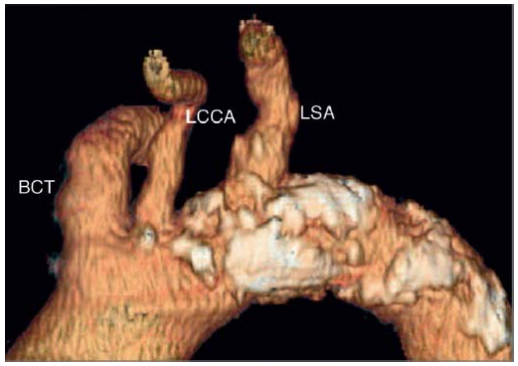


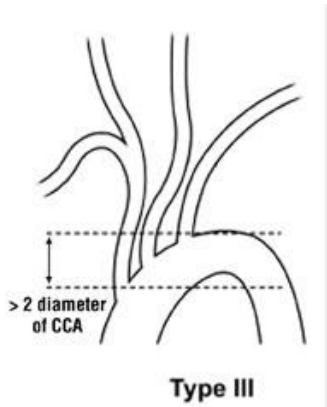
Selected CEA Exclusions
Generally needs a good history & physical



- Radical neck dissection
- Surgically inaccessible lesions
- Adverse neck anatomy that limits surgical exposure
- Presence of tracheostomy stoma
- Laryngeal nerve palsy contralateral to target vessel

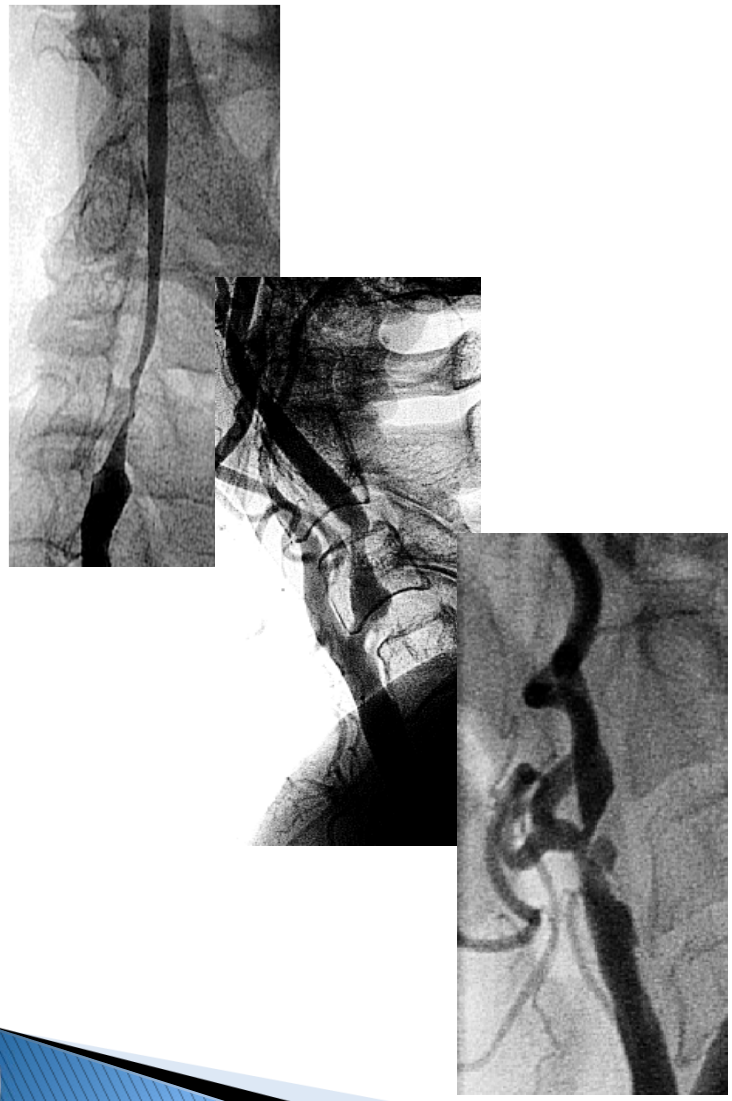
Selected CAS Exclusions
Generally needs a good CTA or MRA





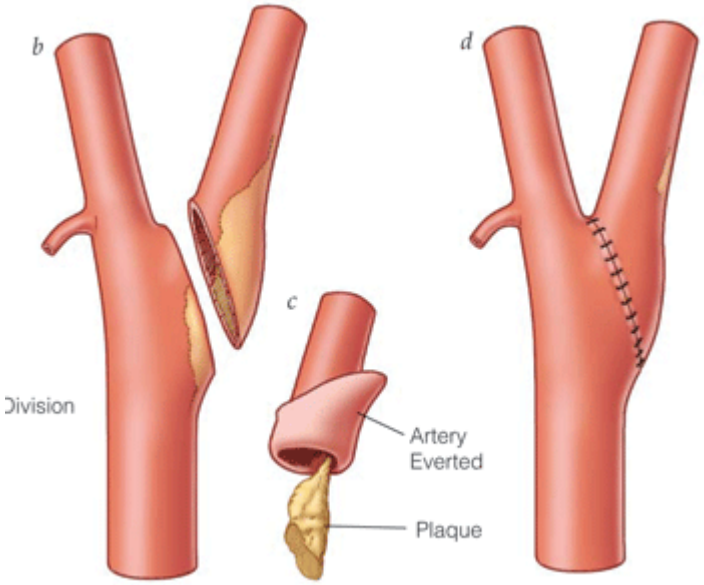
- Severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries
- Type III, calcified aortic arch anatomy
- Angulation or tortuosity (≥90°) of the innominate, common or internal carotid artery

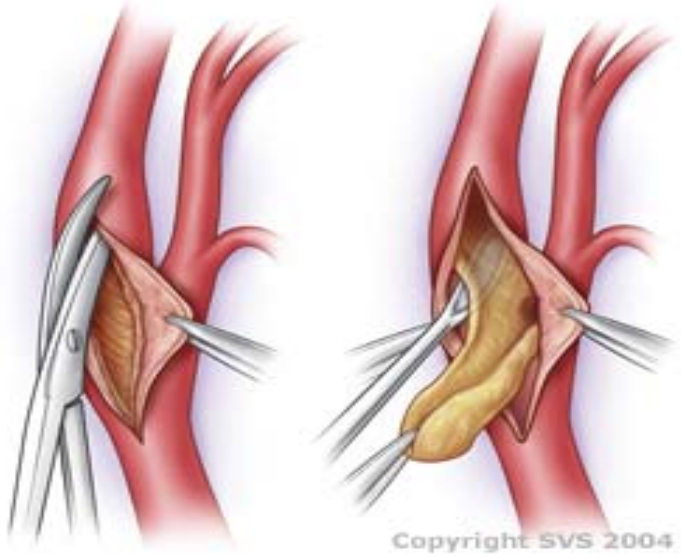
Selected CAS Exclusions



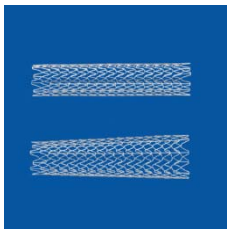
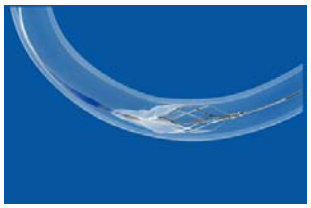
- Excessive or circumferential calcification of the stenotic lesion
- Lesions >20 mm in length, sequential lesions, and narrow-mouth ulcers
- Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD)

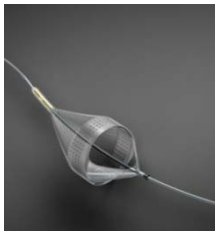
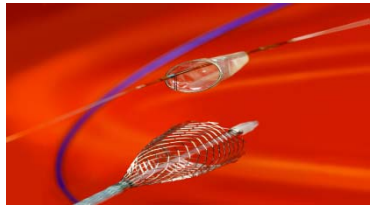
JUST LIKE CREST
This is not a ONE-CEA Trial





UNLIKE CREST
This is not a ONE-CAS Trial


Company Name	Stent	Embolic Protection Device
Abbott	Acculink	RX Accunet OR Emboshield Nav6
	Xact Stent	Emboshield Nav6
Boston Scientific	Carotid Wallstent	FilterWire EZ
Medtronic		MOMA Proximal Cerebral Protection Device

Medical Management

- 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
  - Managed by the study neurologist
  - Target systolic blood pressure <140 mmHg
  - Target LDL <70 mg/dl.

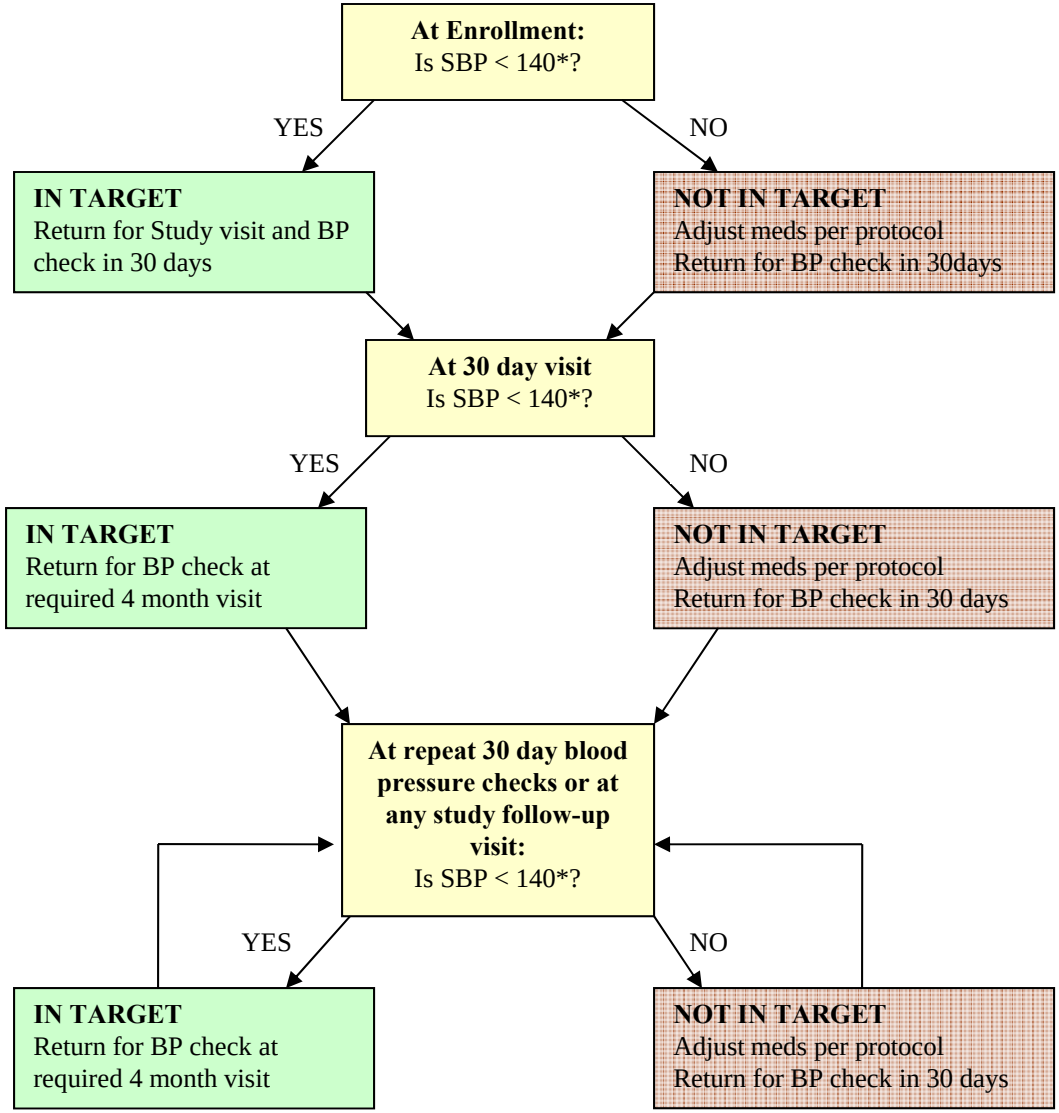
Medical Management

- 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)

BP Management Algorithm



Managing LDL

At enrollment:

1. **If LDL ≥ 70, start Atorvastatin 40* mg** (if not already on a statin) *OR* increase dose of patient's current statin, *OR* switch from current statin to Atorvastatin
2. If LDL < 70, leave on current statin at current dose
3. Send Baseline AST/ALT & CK (if not done already)

LDL values within 90 days of enrollment are acceptable

***starting dose 20 mg in Asians**
Do NOT start Atorvastatin if:
-patient has documented allergy to Atorvastatin *OR*
-estimated creatinine clearance < 30 mL/min

CAS and CEA patients: Extra dose of Atorvastatin 80 mg or maximum dose of patient's current statin night before procedure

Next visit at day 30

If enrollment LDL ≥ 70 recheck LDL at 30 days:

- If LDL < 70, no change

-**If LDL still ≥ 70, increase Atorvastatin to 80 mg** (40 mg in Asians) *OR* increase dose of patient's other statin to maximum dose.

Managing LDL

At the 4 month visit:

- If the 30 day LDL was ≥ 70, send Lab for LDL. **If LDL still ≥ 70 and at 80 mg per day of atorvastatin or equivalent dose of other statin, assess compliance. If patient compliant, email MUSC for advice**

At the annual visits:

-Send Lab for LDL: **If ≥ 70, and at 80 mg per day of atorvastatin or equivalent dose of other statin, assess compliance. If patient compliant, email MUSC for advice**

INTERxVENT

- Lifestyle management and cardiovascular disease risk reduction program.
- Provides individualized risk factor counseling telephone sessions at regular intervals:
  - twice a month for 12 weeks.
  - monthly thereafter.

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? *(Cognitive function may be a surrogate for TIA and/or asymptomatic brain injury).*

- Computer-aided telephonic assessment by team at University of Alabama.

Current Finances

(potential modification based upon StrokeNet support already in place has not yet been addressed)

- Each site will be provided a $2000 start-up fee
- Per patient compensation assumes all protocol required imaging and laboratory tests are standard of care and billable to the patient and/or their insurance.
- Sites will be compensated based upon submitted CRFs in the following installments:
  - Enrollment/baseline = $2,000
  - Every protocol-driven follow-up visit thereafter: $700
  - Total compensation per patient (assuming patients complete all visits for 4 years) = $9,000 (higher than the $6,000 limit published in the FOA for StrokeNet)

StrokeNet Central IRB

- CREST-2 will utilize the cIRB of StrokeNet.
- Regulatory documents will be maintained in WebDCU™.
- The CCC is establishing the initial approval and will do modifications to add on centers as reliance agreements between the cIRB and local IRBs are established.

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QUESTIONS?

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