

CREST-2 Update

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www.crest2trial.org

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CREST-2 Parallel Study Design

1 Patient Screened



Men and women who:

- > 34 years old
- > 70% carotid stenosis
- Lack other serious medical complications

2 Randomized



- Stenting *
- Medical Management
- Endarterectomy
- Medical Management

*1,240 in each Trial

3 Endpoint

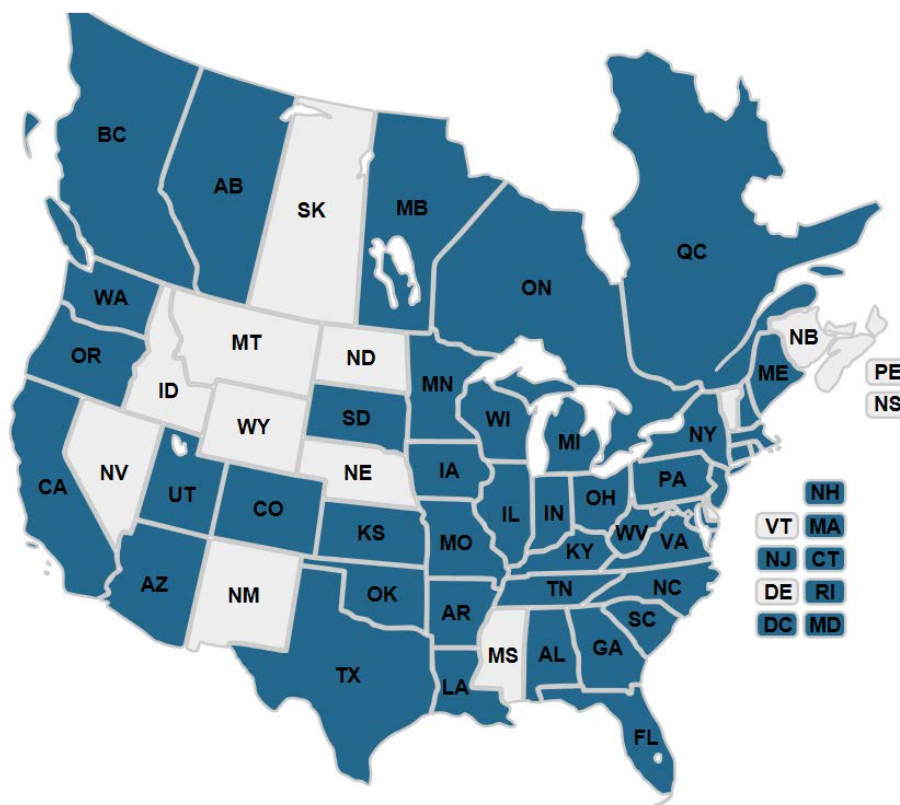


Any stroke or death within 44 days of randomization or ipsilateral ischemic stroke thereafter up to 4 years.

Map of CREST-2 Study Center Locations

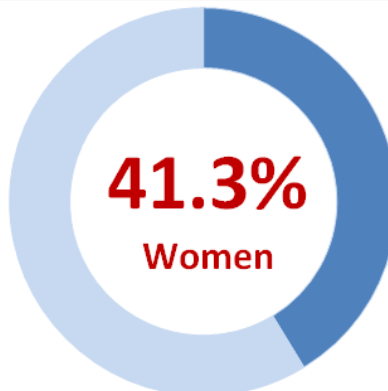
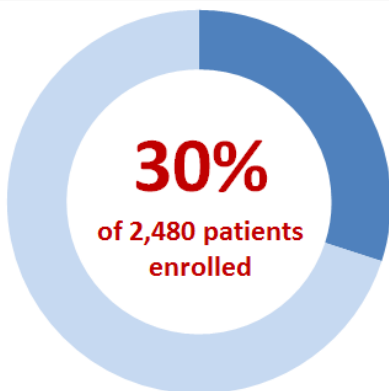
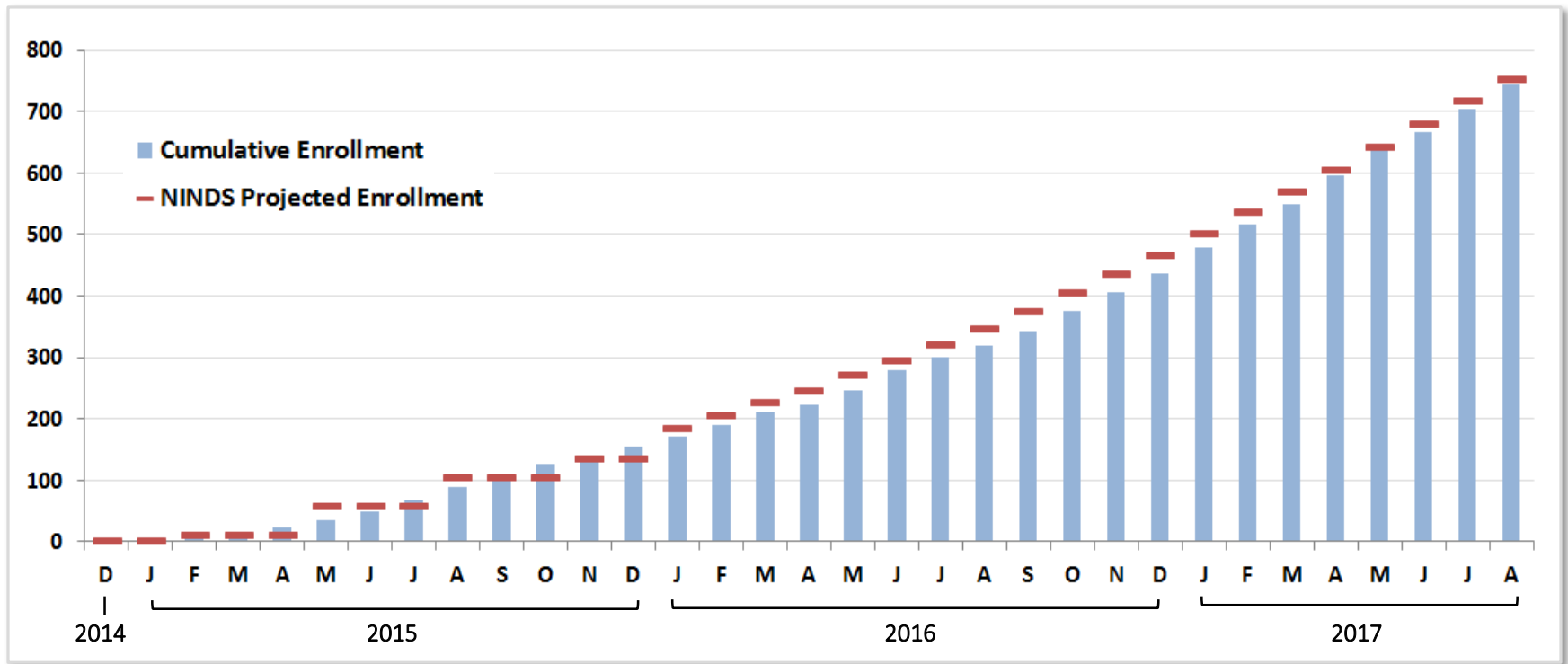
113 CREST-2 Centers have enrolled **743** of 2,480 CREST-2 Participants

365 CEA Trial; **378** CAS Trial



As of 09/05/2017

CREST-2 Enrollment



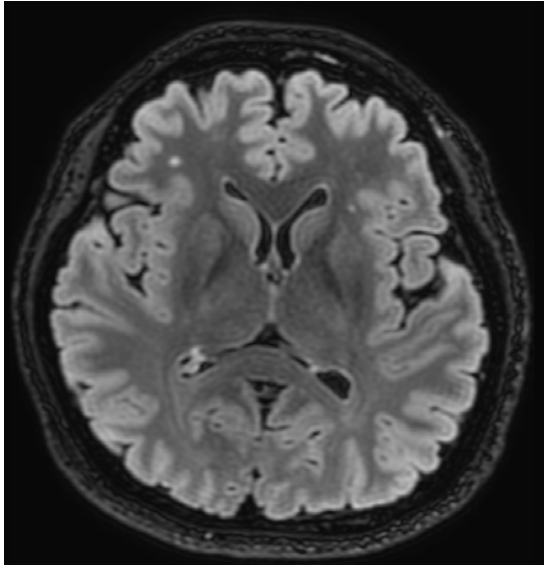
StrokeNet vs. Non-StrokeNet Recruitment

- StrokeNet:
 - 168 patients have been recruited in 814 clinic months
 - average of 0.21 patients per clinic per month
- Non-StrokeNet:
 - 574 patients have been recruited in 1,914 clinic months
 - average of 0.30 patients per clinic per month
- Recruitment in the StrokeNet sites is about 30% slower than the Non-StrokeNet sites
- In the past year, Non-StrokeNet sites have recruited 308 patients in 1,018 clinic-months (average, 0.30), while StrokeNet sites have recruited 115 patients in 490 clinic-months (average, 0.23)

CREST-2 Protocol Version 4.4 Amendments

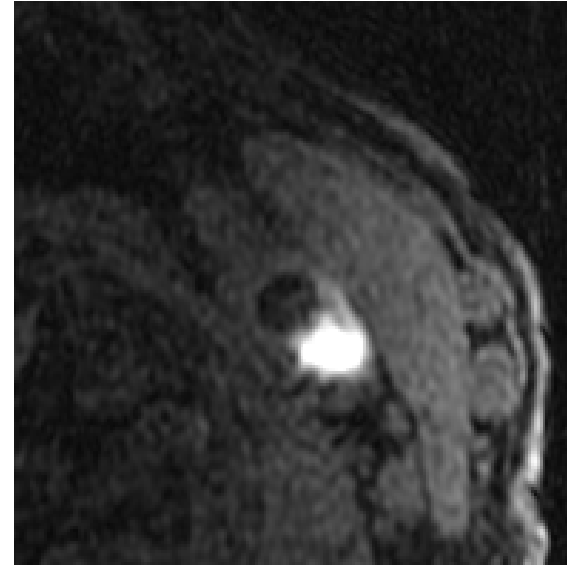
- Addition of alirocumab
- Addition of prasugrel
- Removal of ticlopidine
- Addition of MR Imaging:
 - Carotid plaque imaging at the time of entry into the study and exit from the study (*patients randomized to medical management*)
 - Structural brain imaging at exit from the study (*all patients*)

CREST-2 Magnetic Resonance Imaging



Structural Brain Imaging

- High resolution sagittal T1
- Axial T2 FLAIR
- Diffusion weighted with ADC map
- 3D time-of-flight MR angiogram
- MR Perfusion for blood flow quantification
- Gradient echo imaging



Carotid Plaque Imaging

- 3D time-of-flight carotid MR angiogram
- Coronal T1 MPRAGE for carotid hemorrhage
- 3D T1 pre- and post-contrast for carotid lipid core

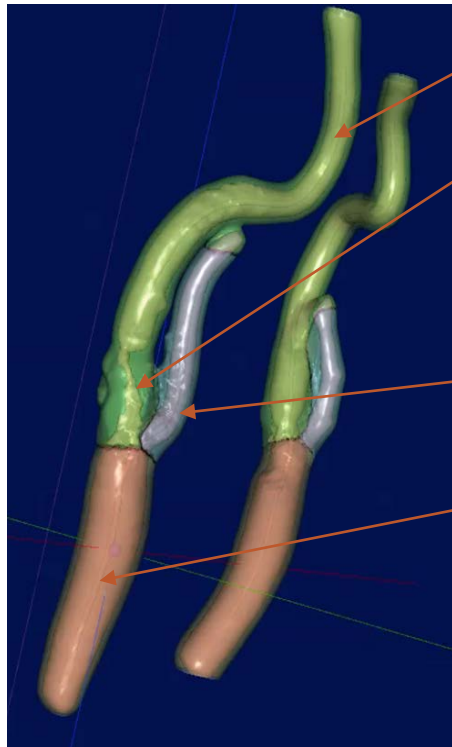
CREST-2: An “Image-rich Environment”

CREST-2 Vascular Imaging Core Facility

University of Maryland

| Imaging study type | Number received |
|---|---------------------------|
| Carotid ultrasounds for CREST-2 sonographer certification | 604 |
| Carotid ultrasounds at CREST-2 enrollment/follow-up | 862 |
| Catheter based angiograms | 72 |
| Computed tomography angiograms | 66 |
| Magnetic resonance angiograms | 21 |
| Magnetic resonance imaging – brain | 26 |
| 748 patients enrolled in CREST-2 | 1,651 image-sets received |

Plaque geometry and morphology assessment : An opportunity in CREST-2



Right internal carotid artery

Plaque geometry

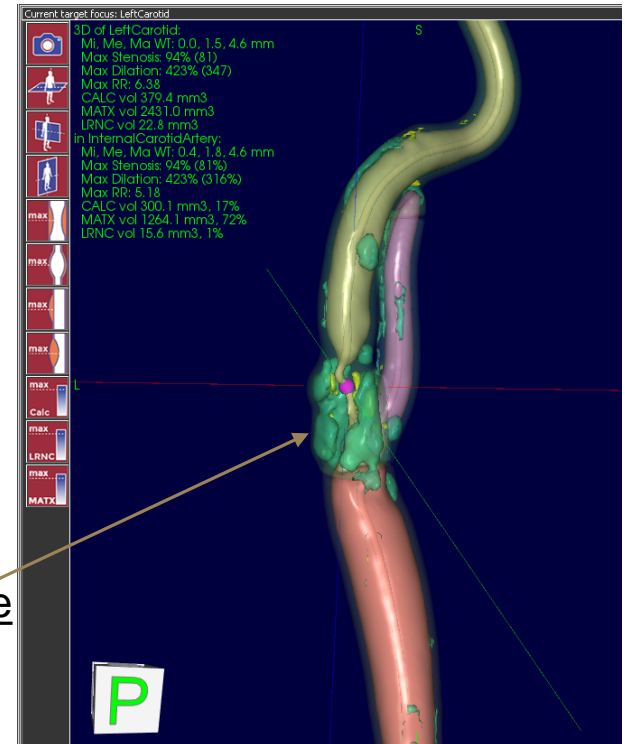
- 94% stenosis
- Least luminal diameter 0.4 mm
- Plaque volume 1579.8 mm³

Right external carotid artery

Right common carotid artery

Virtual histology analysis of plaque

- Calcium 300.1 mm³ (17%)
- Connective tissue matrix 1264.1 mm³ (72%)
- Lipid/necrotic core 15.6 mm³ (1%)
- Hemorrhage 0 mm³ (0%)



CREST-2 Protocol Version 4.4 Amendment

- Increase the total number of CREST-2 sites from 120 to 150
- Add international sites beyond Canada
- Provide remuneration to patients for supplemental BP recheck visits when outside of target

Control of Vascular Risk Factors at Baseline in CREST-2

Rationale: Asymptomatic carotid stenosis is commonly seen in medical practice. CREST-2 is a pair of concurrent two-arm multi-site randomized trials of intensive medical management versus intensive medical management in combination with revascularization by endarterectomy or stenting. It is not known how often patients entering the trials have opportunities for further risk factor reduction at study entry and whether these opportunities vary across trial centers.

Methods: Baseline data on 683 patients from 109 clinical sites were used for these analyses. We determined the rates of control at baseline for systolic blood pressure (SBP), defined as <140 mmHg (or ≥ 140 with >15 mmHg orthostatic drop), and low density lipoprotein (LDL), defined as <70 mg/dl. We then tested differences in these baseline control rates by site-related characteristics, including site type, StrokeNet site vs. not, specialty of site Principal Investigator (PI), type of hospital, central vs local IRB, type of research team and whether site is enrolling in one or both trials. P-value <0.05 was considered significant.

Results: At baseline, the mean SBP was 140.4 ± 20.5 mmHg, but only 62% of participants were in target. The mean LDL at baseline was 83.7 ± 36.9 mg/dl, with 42% in target. None of the site characteristics were associated with a higher level of control for SBP at baseline. The only characteristic associated with having a higher level of LDL control was sites enrolling in only the CAS trial (57%) compared to those enrolling in the CEA only (24%) or in both trials (42%) ($p=0.02$).

Conclusions: Opportunities to improve on risk factors are common among CREST-2 participants, but site characteristics did not predict the likelihood of being at goal for SBP, while sites enrolling in only the CAS trial had a higher level of LDL control.

Relationship Between Risk Factor Control and Physician Specialty in the CREST-2 Trial

| 105 sites (# sites) | # pts with LDL values | % in target for last LDL | p- value | # pts with SBP values | % in target for last SBP | p- value |
|---|--------------------------------|-----------------------------------|-------------|--------------------------------|-----------------------------------|-------------|
| Total | 608 | 62 | | 613 | 84 | |
| | | | | | | |
| PI specialty | | | | | | |
| Cardiology (29) | 224 | 66 | 0.30 | 226 | 84 | 0.98 |
| Interv.Radiol/Neuroradiol (5) | 47 | 62 | | 48 | 83 | |
| Neurology (30) | 124 | 60 | | 124 | 85 | |
| Neurosurgery (8) | 35 | 71 | | 35 | 80 | |
| Vascular Surgery (33) | 178 | 57 | | 180 | 83 | |
| | | | | | | |
| MMP specialty* | | | | | | |
| Cardiology (47) | 306 | 65 | 0.06 | 311 | 83 | 0.84 |
| Internal Medicine (5) | 22 | 73 | | 22 | 77 | |
| Neurology (46) | 236 | 60 | | 236 | 84 | |
| Vascular Surgery (6) | 43 | 47 | | 43 | 86 | |
| *only 1 site with 1 patient had an MMP as a neurosurgeon. That person was excluded from the analysis of MMP | | | | | | |

Questions & Discussion