Update on the Status of CREST2: Problems and Progress When Will We Have Answers How Definitive Will They Be?

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Disclosures
No Conflicts

- NIH: Co-PI CREST 2
- NIH: PI Vascular Imaging Core Facility (VIC)
- NIH/CMS/FDA: PI National Carotid Repository (C2R)
- NIH: PI Dental Carotid Cognitive Study (DCCS)
- VA Merit: PI Cognitive Impairment in Carotid Disease (ACCOF-2)
- VA Merit: PI Flow mediated thrombus resolution in DVT (EFFORT)
- MIPS/SBIR: PI Development of novel diagnostic markers for PAD

Two Concurrent Two-arm Trials

Primary endpoint: periprocedural stroke or death plus ipsilateral ischemic stroke up to 4 years

Lal BK, Meschia J, Brott TG et al. Semin Vasc Surg 2017

Problem #1:
In an environment of low stenting activity nationwide, how do you credential high-quality interventionalists?

Interventional Management Committee
- 383 Total applications
- 12 Not Approved
- 371 (97%) Approved

Surgical Management Committee
- 332 Total Applications
- 9 Denied
- 119 Conditionally Approved
- 160 (48.2%) Approved

As of October 2018

CREST-2 Registry (C2R) 2015

- Objectives
  - Rapid initiation and completion of enrollment in CREST-2
  - That CAS is performed by adequately experienced operators within the CREST-2 trial and the companion registry

Ph: Lal BK, Co-PI Rosenfield K
Symptomatic 44.1%  
Asymptomatic- Primary atherosclerosis 38.2%  
Asymptomatic- Restenosis 17.7%  
30-day stroke and death 2.51%  
Access site complications 3.4%  
Dysrrhythmia 0.7%  

Lal BK et al, Int Stroke Conf 2018

102 meetings; 8311 cases reviewed  
Median of applicants:  
• 130 cases (IQR 75 to 266)  
Median experience of approved:  
• 211 cases (IQR 100 to 350)  
Factors associated with approval (multivariate analysis)  
• Number of cases performed per month (p<0.0001)  
• Specialty was not a factor


How do you achieve a target enrollment of women (50%) and minorities (15%) when no other carotid trial has ever come even close to those numbers?

Demaerschalk B et al. Stroke 2017

Is “asymptomatic” carotid stenosis associated with cognitive impairment?

PI- Lal BK, Co-PI-Brott TG, 2018
“Asymptomatic” carotid stenosis and cognitive impairment

50% had at least 2 domains impaired
80% of those with impaired perfusion had at least 1 domain impaired

Lal BK et al, Am Acad of Neurology 2016
Lal BK et al, J Vasc Surg 2018

Problem #4:
How can you lose this golden opportunity to search for subsets of patients at an inordinately high risk for stroke?

CREST-H (Hemodynamics) 2017
- Goal: To determine whether patients with cerebral hemodynamic impairment ("flow failure") and cognitive impairment benefit from revascularization
- Enrollment goal: 500 patients
- Additional testing: MRI perfusion scan

Lal BK et al, Am Acad of Neurology 2016
Lal BK et al, J Vasc Surg 2018

Goal: To determine whether patients with cerebral hemodynamic impairment ("flow failure") and cognitive impairment benefit from revascularization
- Enrollment goal: 500 patients
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Pl-Marshall R, Co-PI- Lazar R

Problem #5:
How do we incorporate new technology and new procedures into a “flexible” trial requiring several years to complete?

CREST-M (Imaging) 2018
- Goal: To determine whether carotid plaque disruption may be influenced by biomechanical forces acting in combination with morphological changes occurring within the plaque
- Enrollment goal: 500 patients
- Additional testing: Carotid MRA, ultrasound cine-loop, Brain MRI

Pl-Lal BK, Co-PI-Huston J
Huston J et al, AJNR 2016
Lal BK et al, J Vasc Surg 2017

CREST-T (TCAR) 2019
- Randomized trial nested within C2R
- To determine: Differences in clinical outcomes between TCAR versus CEA and CAS
- Eligible patients: Symptomatic carotid stenosis (standard risk)

Lal BK and Chaloner et al, Am Acad of Neurology 2016
Lal BK et al, Am Acad of Neurology 2016
Lal BK et al, J Vasc Surg 2018
Huston J et al, J Vasc Surg 2017
Creer J et al, J Vasc Surg 2018
Meschia J et al, J Vasc Surg 2018
Brott TG et al, J Vasc Surg 2018

Pl-Lal BK, Co-PIs Meschia J & Brott TG
CREST family of studies
Will they be the final answer?
It is the last chance in many years to get a contemporary answer.