CREST – 2

Carotid Revascularization

(Carotid Stenting or Endarterectomy)

versus

Intensive Medical Management

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MAYO CLINIC

- Why CREST-2?
- Why now?
- Can it done?
- How should the trial be performed?
- What will we learn?

Why CREST–2?

We all know medical treatments have improved since ACAS…

Articles

10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial

*Alison Halliday, Michael Harrison, Elizabeth Hayter, Xiangling Kong, Averil Mansfield, Joanna Marro, Hongchao Pan, Richard Peto, John Potter, Kazem Rahimi, Angela Rau, Steven Robertson, Jonathan Streifler, Dafydd Thomas, on behalf of the Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group**

Lancet 2010; 376: 1074–84

CREST-2

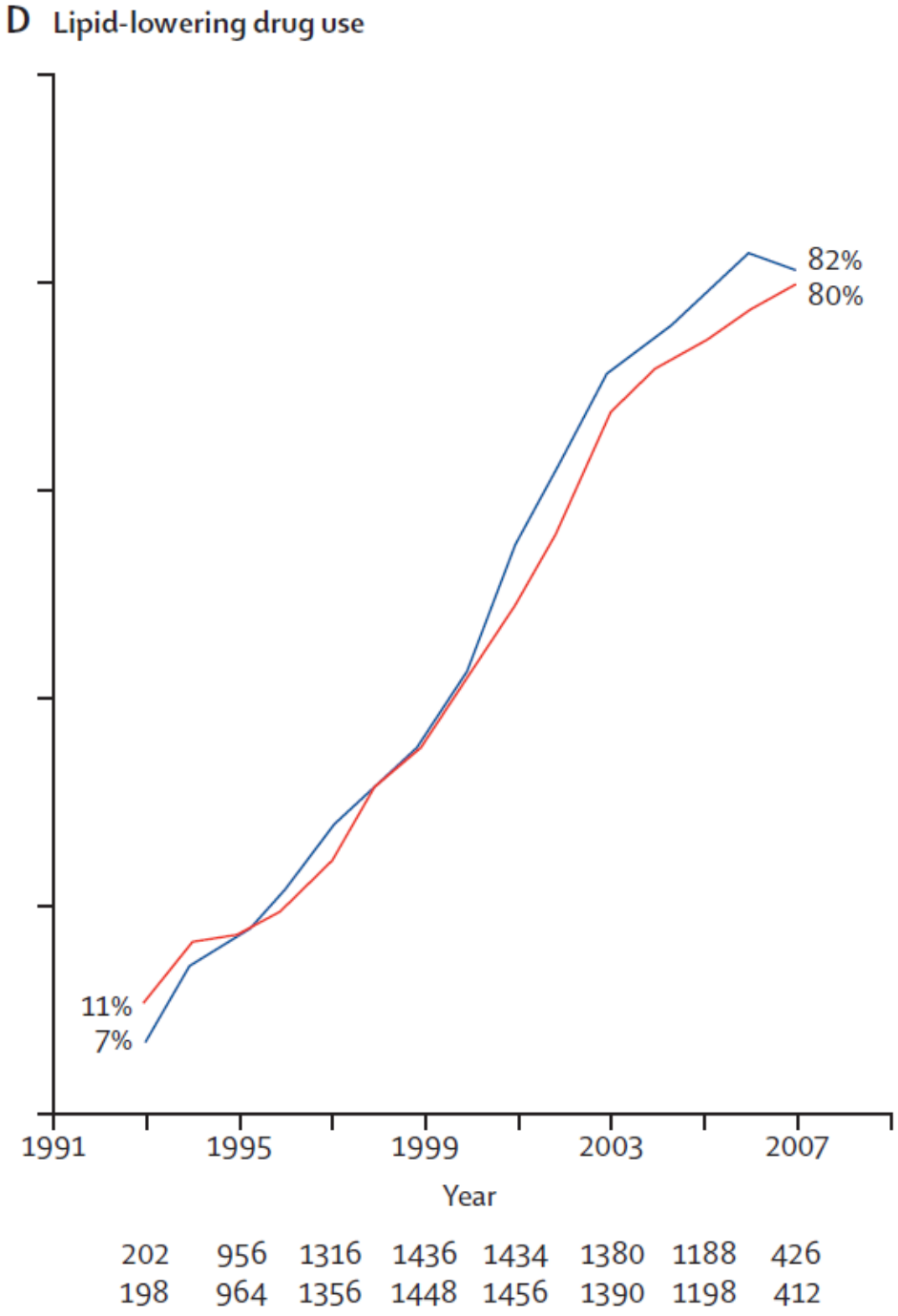
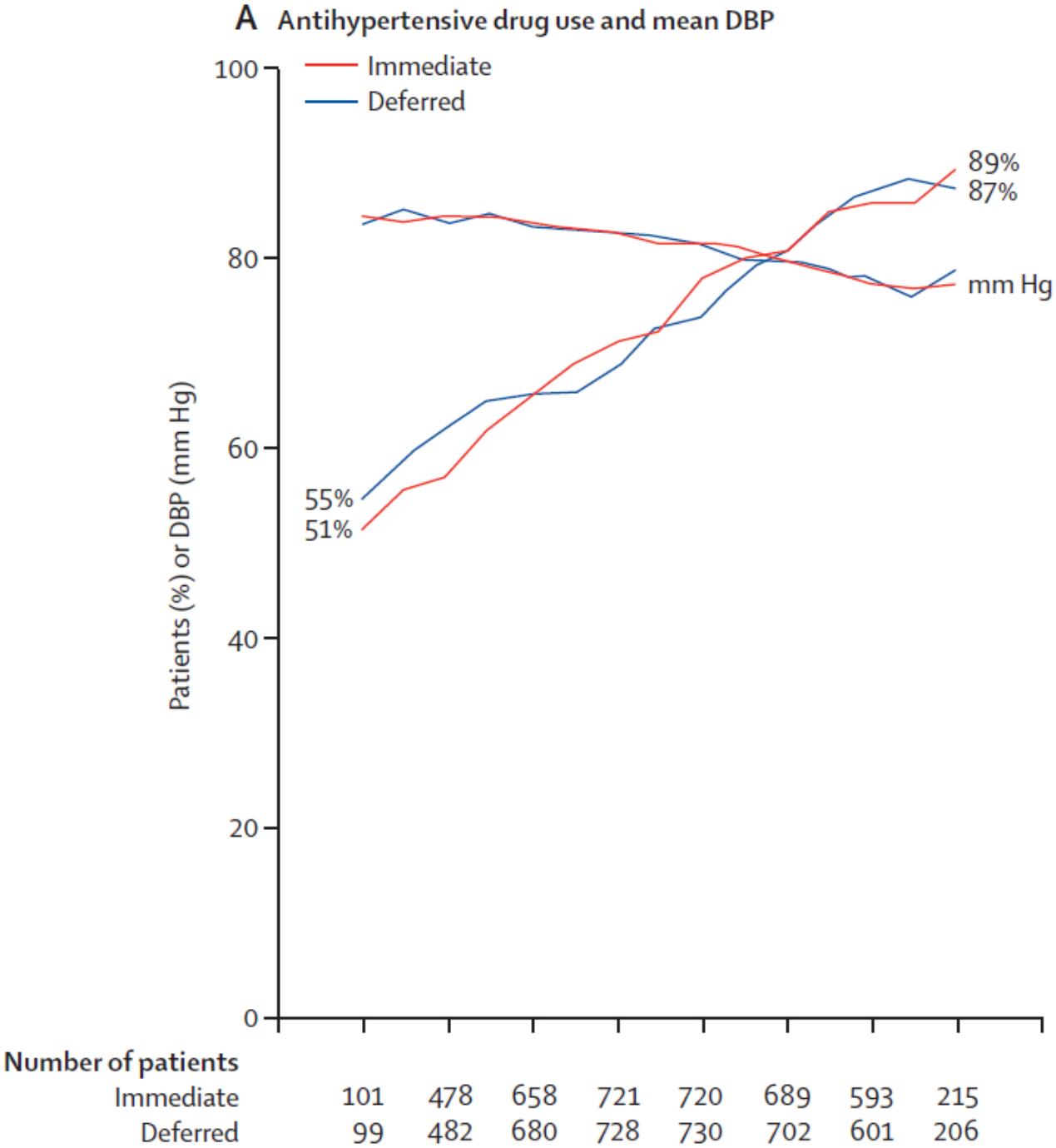
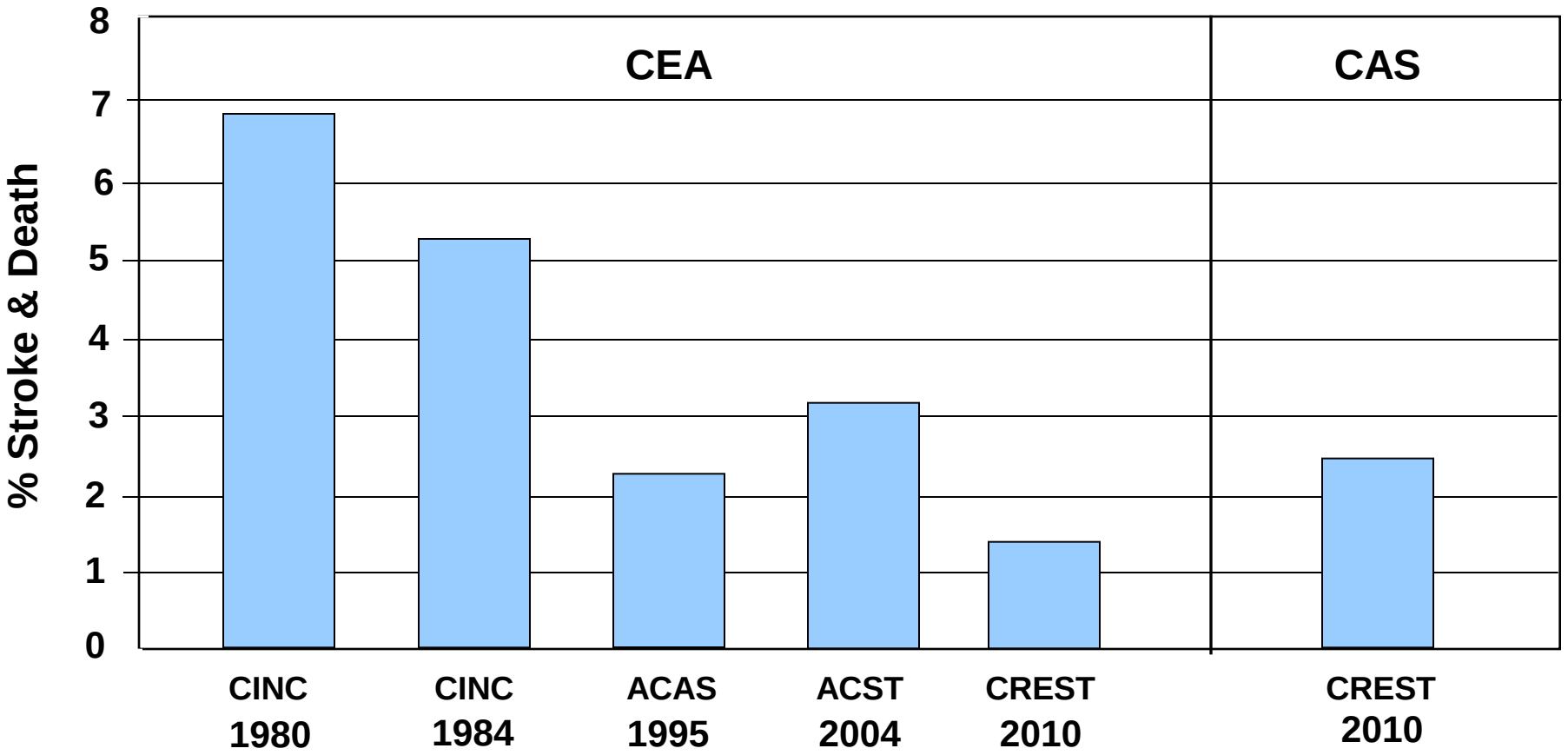


Figure 4: **Current use (at or after randomisation) of various medical treatments by year of follow-up and by original treatment allocation (to immediate or deferred CEA)**

CEA=carotid endarterectomy. DBP=diastolic blood pressure.


A Antihypertensive drug use and mean DBP
Immediate
Deferred
100
80
60
40
20
0
Patients (%) or DBP (mm Hg)
89%
87%
mm Hg
55%
51%
Number of patients
Immediate 101 478 658 721 720 689 593 215
Deferred 99 482 680 728 730 702 601 206

…CAS and CEA have also improved.



Periprocedural stroke and death rate. CINC denotes Cincinnati/Northern Kentucky.

Henry J. M. Barnett, MD, FRCPC, FACP

The NEW ENGLAND JOURNAL of MEDICINE

BENEFIT OF CAROTID ENDARTERECTOMY IN PATIENTS WITH SYMPTOMATIC MODERATE OR SEVERE STENOSIS

HENRY J.M. BARNETT, M.D., D. WAYNE TAYLOR, M.A., MICHAEL ELIASZIW, PH.D., ALLAN J. FOX, M.D., GARY G. FERGUSON, M.D., R. BRIAN HAYNES, M.D., RICHARD N. RANKIN, M.D., G. PATRICK CLAGETT, M.D., VLADIMIR C. HACHINSKI, M.D., DAVID L. SACKETT, M.D., KEVIN E. THORPE, M.MATH., AND HEATHER E. MELDRUM, B.A., FOR THE NORTH AMERICAN SYMPTOMATIC CAROTID ENDARTERECTOMY TRIAL COLLABORATORS*

Why now?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis

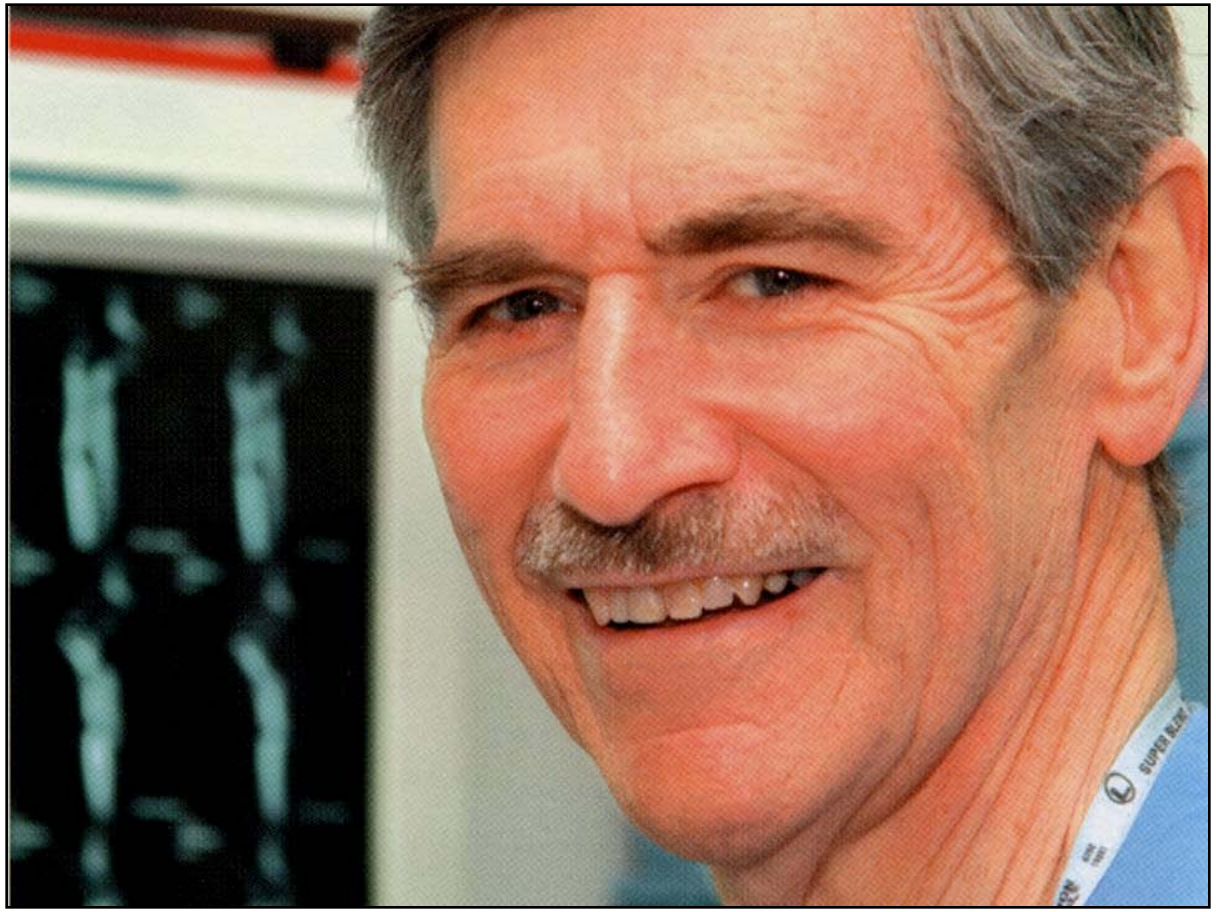
Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Colin P. Derdeyn, M.D., Tanya N. Turan, M.D., David Fiorella, M.D., Ph.D., Bethany F. Lane, R.N., L. Scott Janis, Ph.D., Helmi L. Lutsep, M.D., Stanley L. Barnwell, M.D., Ph.D., Michael F. Waters, M.D., Ph.D., Brian L. Hoh, M.D., J. Maurice Hourihane, M.D., Elad I. Levy, M.D., Andrei V. Alexandrov, M.D., Mark R. Harrigan, M.D., David Chiu, M.D., Richard P. Klucznik, M.D., Joni M. Clark, M.D., Cameron G. McDougall, M.D., Mark D. Johnson, M.D., G. Lee Pride, Jr., M.D., Michel T. Torbey, M.D., M.P.H., Osama O. Zaidat, M.D., Zoran Rumboldt, M.D., and Harry J. Cloft, M.D., Ph.D., for the SAMMPRIS Trial Investigators*

Risk Factor Treatment in SAMMPRIS

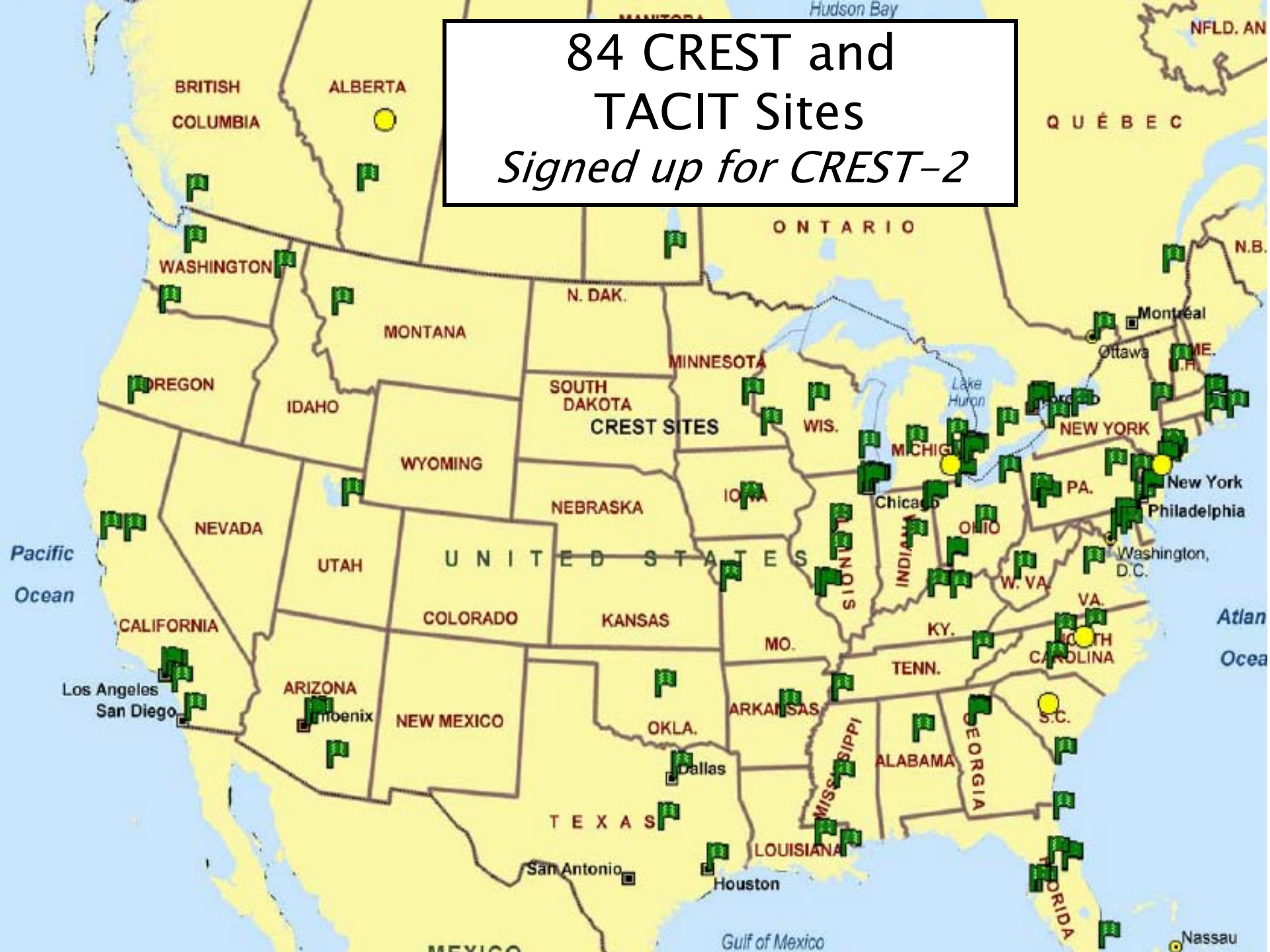
Clinical Factor		Baseline	4 Months	12 Months
Blood pressure	Systolic BP	145	134	131
Lipids	LDL	97	74	67
Glycated hemoglobin in diabetics	Level – %	8.1	7.7	7.4

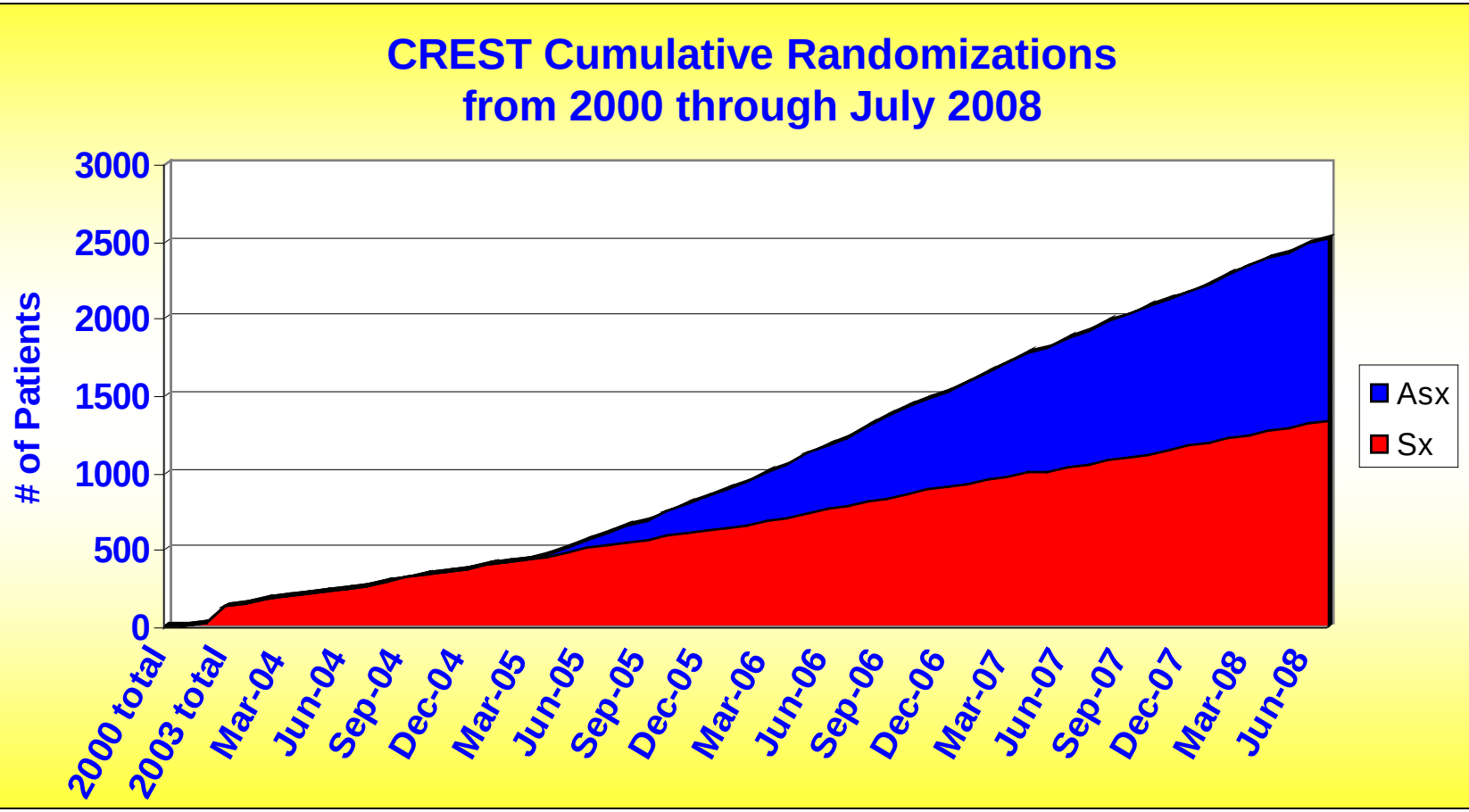
Can it be done?

Carotid Revascularization Endarterectomy vs Stenting Trial



Robert Hobson II MD, PI 1999-2007


84 CREST and
TACIT Sites
Signed up for CREST-2
CREST SITES
BRITISH COLUMBIA
ALBERTA
WASHINGTON
OREGON
CALIFORNIA
NEVADA
IDAHO
MONTANA
WYOMING
UTAH
ARIZONA
COLORADO
NEW MEXICO
N. DAK.
SOUTH DAKOTA
NEBRASKA
KANSAS
OKLA.
TEXAS
MINNESOTA
IOWA
MISSOURI
ARKANSAS
LOUISIANA
WIS.
ILLINOIS
MICHIGAN
INDIANA
OHIO
KY.
TENN.
MISSISSIPPI
ALABAMA
GEORGIA
FLORIDA
S.C.
N. CAROLINA
VA.
W. VA.
PA.
NEW YORK
ONTARIO
QUÉBEC
NFLD.
N.B.
ME.
Hudson Bay
Lake Huron
Montréal
Ottawa
New York
Philadelphia
Washington, D.C.
Chicago
Los Angeles
San Diego
Phoenix
Dallas
San Antonio
Houston
Nassau
Gulf of Mexico
Pacific Ocean
Atlan
Ocea


CREST Cumulative Randomizations
from 2000 through July 2008
# of Patients
3000
2500
2000
1500
1000
500
0
2000 total
2003 total
Mar-04
Jun-04
Sep-04
Dec-04
Mar-05
Jun-05
Sep-05
Dec-05
Mar-06
Jun-06
Sep-06
Dec-06
Mar-07
Jun-07
Sep-07
Dec-07
Mar-08
Jun-08
Asx
Sx

How should the trial be performed?

Key Design Elements

- Asymptomatic patients with high-grade carotid stenosis (≥ 70%).
- Two-arm trial, *in contrast to SPACE-2 which is having problems with enrolling into the CAS and CEA arms.*

Primary Aim

- To assess if contemporary **REVASCULARIZATION** – ***either CAS or CEA*** – …

- …provides an incremental benefit of 1.2% annual risk reduction over contemporary **MEDICAL**

Primary Outcome

- The primary outcome will be the classical composite of stroke or death within 30 days of enrollment or ipsilateral stroke up to 4-years thereafter.

Key Design Elements

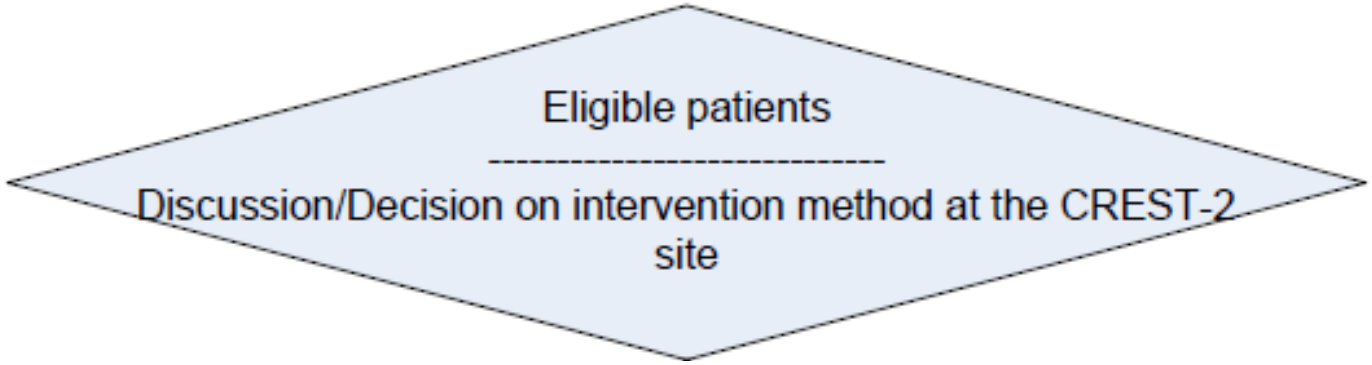
- Sample size 950 participants at approximately 70 centers.
- Statistical power will be ~ 90% to detect a 4.8% treatment difference (1.2% per year)

Innovative Design Elements

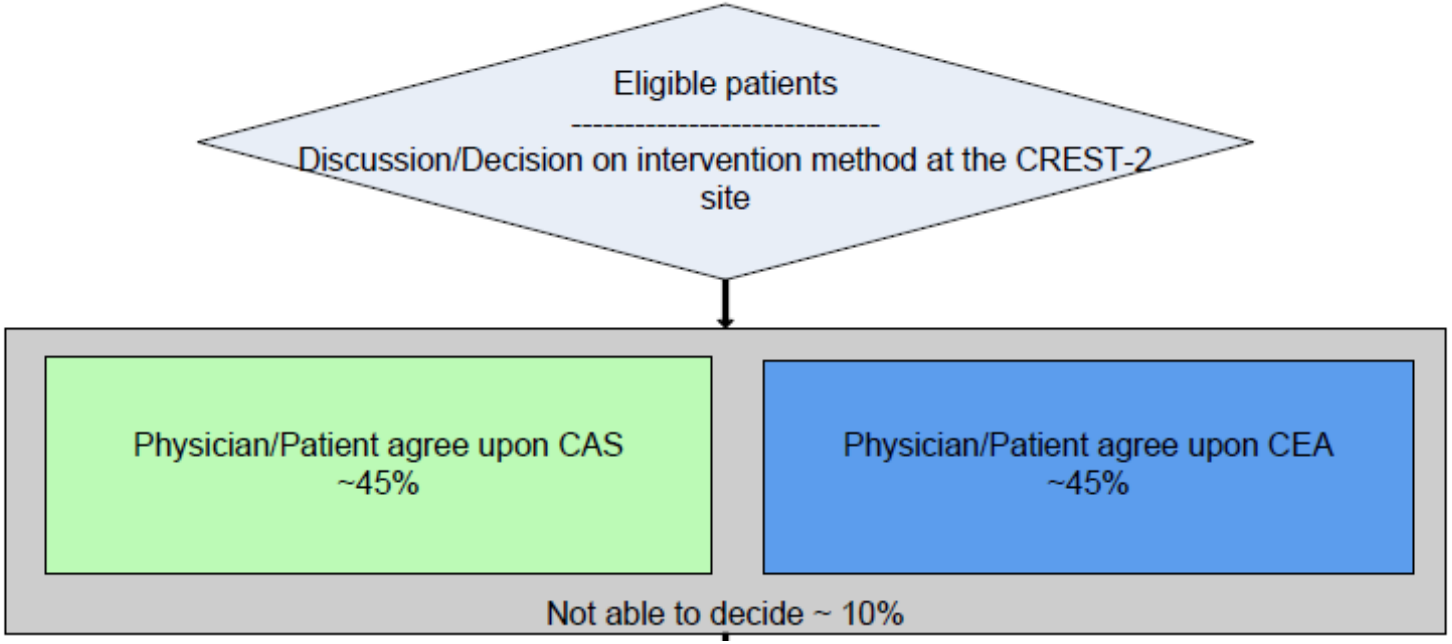
- SAMMPRIS Intensive Medical Management, *already demonstrated as feasible and highly effective*

- Randomization scheme that allows randomization to protect comparisons of ***CAS to MEDICAL*** and of ***CEA to MEDICAL***

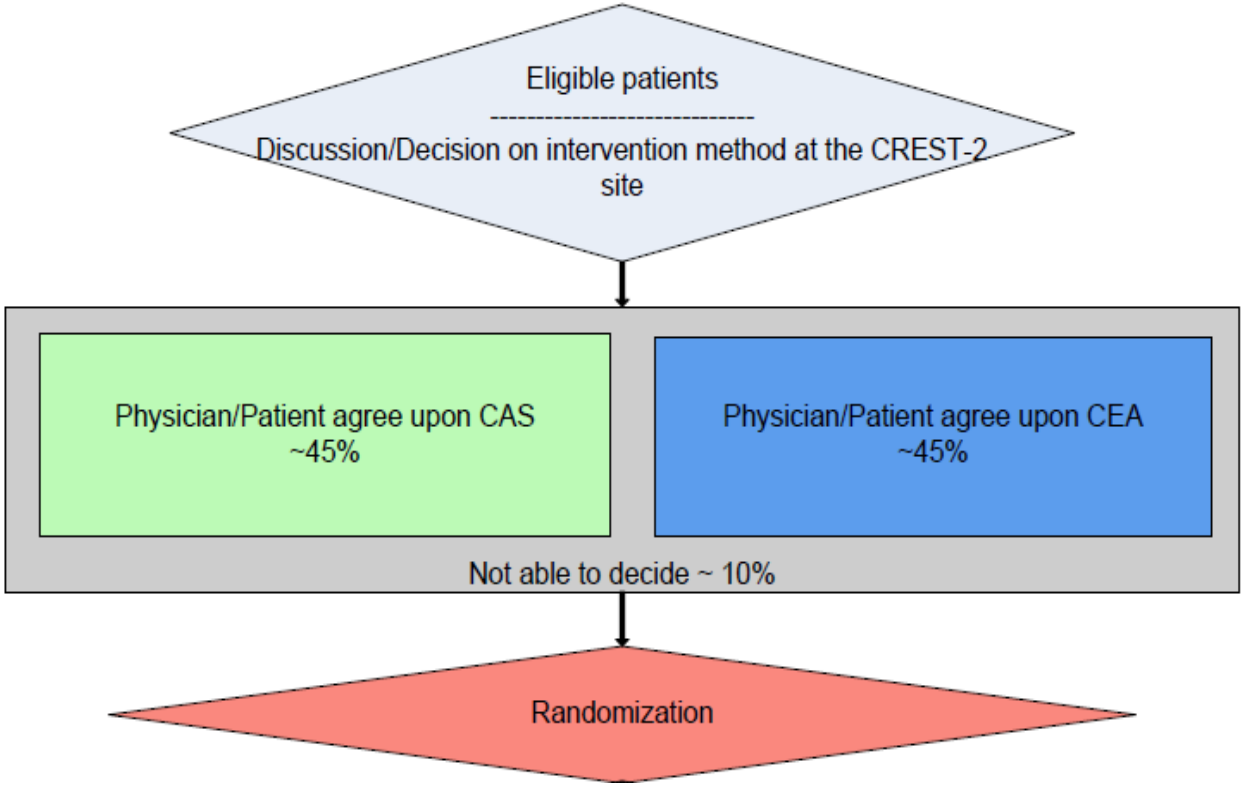
Randomization Scheme



Eligible patients will meet with CREST-2 teams regarding enrollment and choice of revascularization technique.

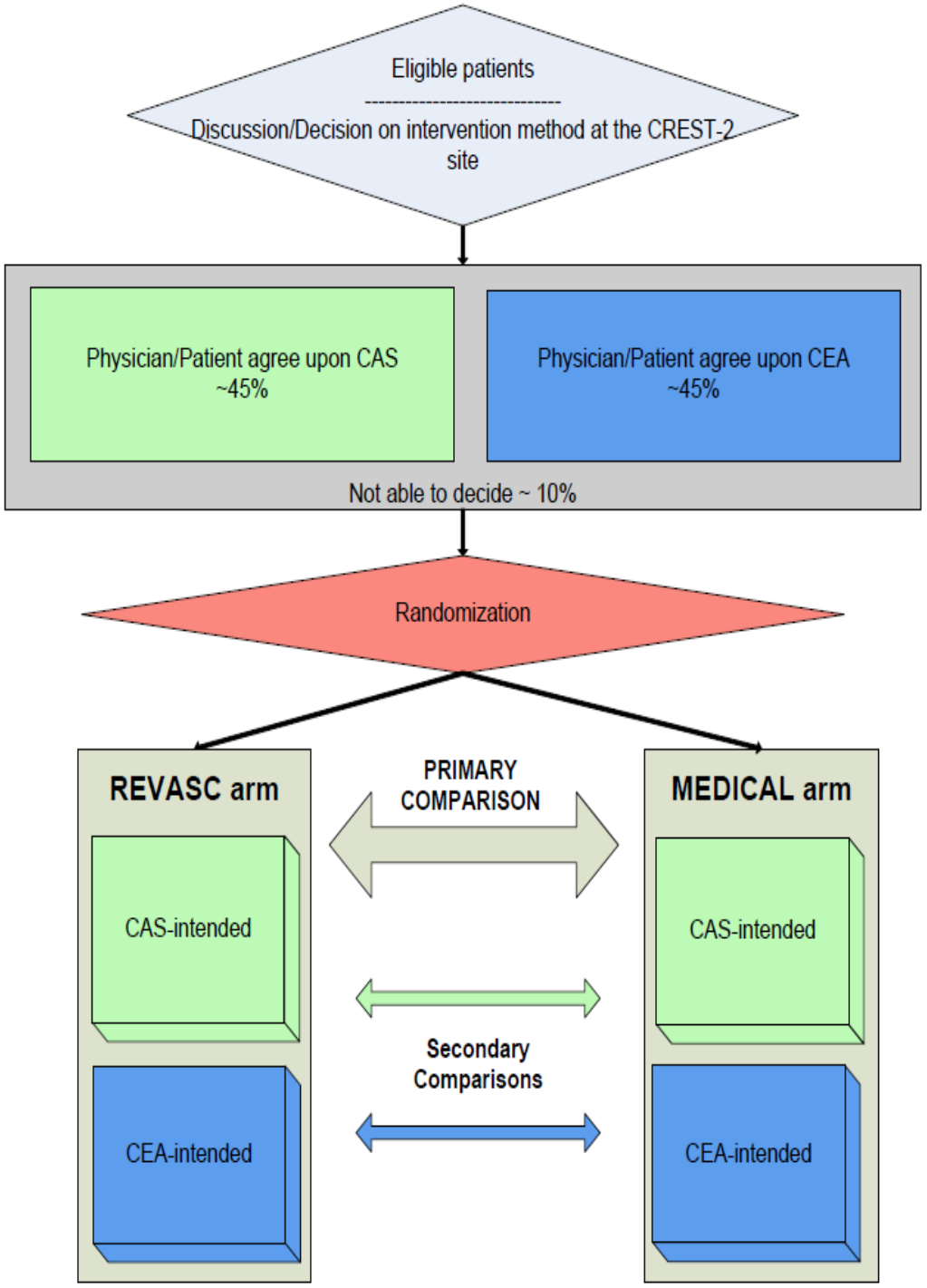


Prior to randomization, senior investigators estimate that 90% of patients intended for revascularization will be decided upon.



Patients will be randomized 1:1 to either intensive medical management (MEDICAL) or intensive medical management + revascularization (REVASC).

After randomization, the CAS and CEA groups imbedded in the REVASC and MEDICAL arms will allow randomized-protected comparisons of CEA-intended and CAS-intended patients to the MEDICAL patients.



Schedule of Events in CREST-2

Month	-1	0	1	4, 8	12, and every 4 months thereafter up to 4 years
Medical Hx	X	X	X	X	X
NIHSS	X		X	X	X
Ultrasound		X			X
Blood Pressure	X	X	X	X	X
Local/Core Lipids		X	X		X

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.

What will we learn?

Will answer a major public health question…

…and "working groups" to study

- **Plaque** characteristics as predictors of risk- *BK Lal, MD, University of Maryland*
- **MRI**- treatment differences- *Michael Hill, MD, University of Calgary*
- **Cognitive**- treatment differences- *David Knopman, MD, Mayo Clinic and Ronald Lazar, PhD, Columbia*
- **QOL and costs**- *David Cohen, MD,* Saint Luke's Mid America Heart and Vascular Institute
- **CMS and other databases** to enrich outcomes- *Judith Lichtman, PhD, Yale*
- **Hemodynamic changes** - by treatment and impact on outcomes- *Randy Marshall, MD, Columbia*

Thanks for your consideration.

Backup Slides

General Eligibility Criteria

- ≥ 35 years old.
- ≥ 70% stenosis.
- No Stroke or TIA within 180 days of randomization.
- Randomization to treatment group will apply to only one carotid artery.
- Carotid stenosis must be treatable with CEA, CAS, or both procedures.

General Eligibility Criteria

- To determine eligibility at screening:
  - DUS
  - CTA
  - MRA
  - CBA

CEA Exclusion Criteria

1. Serious adverse reaction to anesthesia.
2. Coronary artery disease with 2 or more proximal or major diseased arteries with ≥ 70% stenosis that have not, or cannot be revascularized.
3. Anatomical exclusions:
   - Radical neck dissection
   - Surgically inaccessible lesions
   - Adverse neck anatomy
   - Presence of tracheostomy stoma
   - Laryngeal nerve palsy contralateral to target vessel
   - Previous extracranial–intracranial or subclavian bypass procedure ipsilateral to target vessel
4. Known allergy to heparin or bivalirudin.

CAS Exclusion Criteria

1. Allergy to intravascular contrast dye.
2. Occlusive or critical ilio-femoral disease.
3. Severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries.
4. Type III, calcified aortic arch anatomy.
5. Qualitative characteristics of stenosis and stenosis-length of the carotid bifurcation (common carotid) and/or ipsilateral external carotid artery

CAS Exclusion Criteria

6. Angulation or tortuosity (≥ 90 degree) of the innominate and common carotid artery.

7. Severe angulation or tortuosity of the internal carotid artery.

8. Excessive circumferential calcification of the stenotic lesion .

9. Anatomic considerations such as tortuosity, arch anatomy, and calcification must be evaluated even more carefully in elderly subjects (≥ 70 years) in whom even modest elements of criteria 3 through 8 are considered exclusions for CAS in this study.

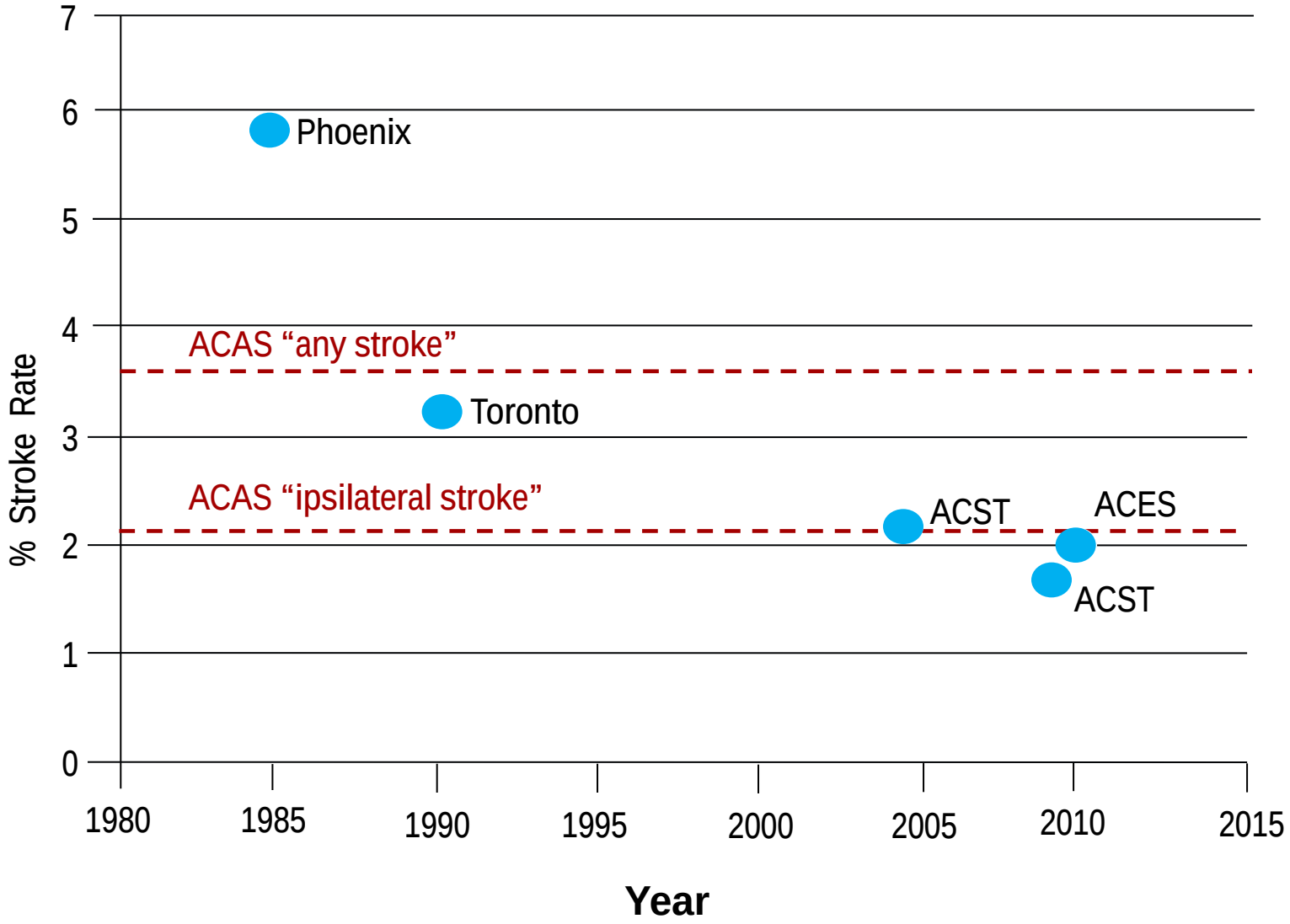
CAS Exclusion Criteria

10. "String sign" of the ipsilateral common or internal carotid artery.
11. Lesions >20 mm in length (normal appearing vessel to normal appearing vessel), sequential lesions, and narrow-mouth ulcers.
12. Target ICA vessel reference diameter <4.0 mm or >9.0 mm. Target ICA measurements may be made from angiography of the contralateral artery.
13. Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD).

CAS Exclusion Criteria

- In all circumstances where pre-CAS angiography displays unfavorable anatomy for stenting or the operator encounters difficulty in sheath placement or embolic protection device placement, the stenting procedure will be terminated and the patient directed to CEA.

- If the patient was originally high-risk for CEA and was being considered for CAS, that patient should cross over to the Medical group. In addition, should the angiography for CAS indicate <70% stenosis, the patient will cross over to the Medical group.


7
6
5
4
3
2
1
0
% Stroke Rate
Phoenix
ACAS “any stroke”
Toronto
ACAS “ipsilateral stroke”
ACST
ACES
ACST
1980
1985
1990
1995
2000
2005
2010
2015
Year

CREST-2

CREST-2 Study Organization Chart

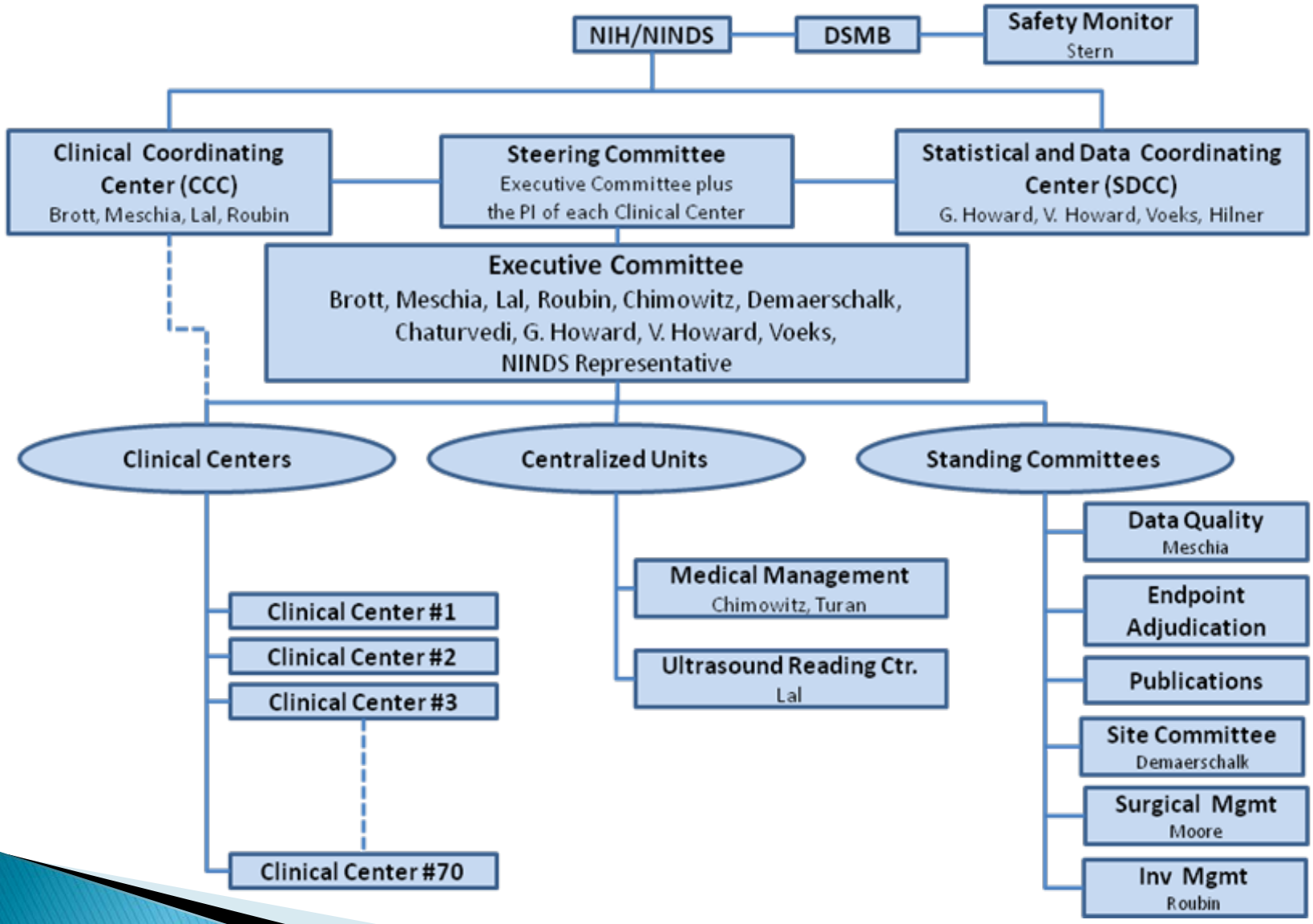


Table 3. Periprocedural Anti-thrombotic Therapy for all Carotid Stent Patients.				
Medication	**Pre-Procedure**	**Intra-Procedure**	**Post-Procedure**	**Post-Discharge**
Heparin*	PRN	Maintain ACT 250-300 sec.*	PRN**	None
Aspirin	325 mg p.o. b.i.d** (Begin 48 hours before)	None	325 mg† 1 to 2 tablets p.o. daily for 30 days	325 mg†,‡ 1 tablet p.o. daily thereafter
Clopidogrel	75 mg p.o. b.i.d. daily (Begin 48 hours before)	None	75 mg 1 tablet p.o. daily for 4 weeks	---
Ticlopidine (instead of Clopidogrel)	250 mg p.o. b.i.d. (Begin 48 hours before)	None	250 mg 1 to 2 tablets p.o. daily for 4 weeks	---

*Bivalirudin may be substituted for heparin. Use in accordance with manufacturer's instructions. ACT's are not collected when bivalirudin is used as the procedural anticoagulant. **Heparin may be given post-procedure as needed †May be substituted with 81 mg tablet if patient cannot tolerate 325 mg dosage. ‡After four weeks may be substituted with Aggrenox b.i.d. or clopidogrel.

Table 4. Schedule of Laboratory Tests Required for Intensive Medical Management

Laboratory Test	Scheduled	PRN
K+	• Baseline	• If on diuretic or ACE inhibitor: - 30 days after starting or changing dose - 4 and 12 months after starting either drug
Creatinine	• Baseline • Annually	• If on ACE inhibitor: - 30 days after starting or changing dose
Local Lipid	• Baseline (within 90 days prior to enrollment) • Annually	• If statin dose changed at 30 days: - Lipid profile at 60 days
AST/ALT	• Baseline • 30 day visit • 4 month visit • Annually	• If > 3x normal, repeat in 1 wk
CPK	• Baseline	• If patient develops symptoms of statin toxicity
HgA1c† (if diabetic)	• Baseline • At least twice a year	• If patient not meeting glycemic goals or if change in therapy - quarterly
Core Lipid Tests**	• Baseline (at enrollment) • 30 days	

** All tests may be performed at any qualified laboratory except for Core Lipid Tests. With the exception of the hemoglobin A1c, all tests should be ordered by study neurologist managing the patient's blood pressure and statin medications.*

*** Core Lipid Tests must be sent to Core Lipid Research Lab*

† Study neurologist should ensure that patient's primary care physician or diabetologist are following these ADA recommendations for evaluating the HgA1c.