Primary Prevention of Stroke: present and future

Montreal, QC
Friday, September 11, 2015

James Meschia, MD
Mayo Clinic, Jacksonville, FL

SSVQ
Société des sciences vasculaires du Québec

Primary Prevention of Stroke: present and future

Objectives

- Summarize the recommendations regarding traditional and emerging risk factors of stroke and their treatment
- Cognition as a cerebrovascular outcome
- Locate the stakes of the study CREST-2

Physical Inactivity

- Healthy adults should perform at least moderate- to vigorous-intensity aerobic physical activity at least **40 min** per day for at least **3 to 4 days** per week

Diet and Nutrition

- **Reduced intake of sodium** and **increased intake of potassium** as indicated in the US Dietary Guidelines for Americans are recommended to lower BP
- A DASH-style diet, which emphasizes **fruits, vegetables, and low-fat dairy products and reduced saturated fat,** is recommended to lower BP
- A diet that is rich in fruits and vegetables and thereby high in potassium is beneficial and **may lower the risk of stroke**

Dyslipidemia

- In addition to therapeutic lifestyle changes, treatment with and **HMG coenzyme-A reductase inhibitor (statin)** medication is recommended for the primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for cardiovascular events as recommended in the 2013 “ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults”

Cigarette smoking

- **Counseling, in combination with drug therapy** using nicotine replacement, bupropion, or varenicline, is recommended for active smokers to assist in quitting smoking
- **Abstention from cigarette smoking** is recommended for patients who have never smoked on the basis of epidemiological studies showing a consistent and overwhelming relationship between smoking and both ischemic stroke and SAH

Hypertension

- Regular **BP screening** and appropriate **treatment of patients with hypertension , including lifestyle modification and pharmacological therapy**, are recommended
- **Annual screening for high BP** and health promoting **lifestyle modification** are recommended for patients with **prehypertension**
- Patients who have hypertension should be treated with **antihypertensive drugs to a target BP of <140/90 mm Hg**
- **Successful reduction of BP** is more important in reducing stroke risk than the choice of a specific agent
- **Self-measured BP monitoring** is recommended to improve BP control

Alcohol consumption

- **Reduction or elimination of alcohol consumption** in heavy drinkers through established screening and counseling strategies is recommended
- For individuals who choose to drink alcohol, **consumption of ≤2 drinks per day for men and ≤1 drink per day for non-pregnant women** might be reasonable (Class IIb)

Migraine

- **Smoking cessation** should be strongly recommended in **women with migraine headaches with aura**
- **Alternatives to OCs**, especially those containing estrogen, might be considered in **women with active migraine headaches with aura (Class IIb)**
- **Closure of PFO is not indicated for preventing stroke in patients with migraine (Class III)**

Atrial fibrillation

- For patients **with valvular AF at high risk for stroke**, defined as a CHA2DS2-VASc score ≥2 and acceptably low risk for hemorrhagic complications, **long-term oral anticoagulant therapy with warfarin at a target INR of 2.0-3.0** is recommended
- For patients with **non-valvular AF**, a CHA2DS2-VASc score of ≥2, and acceptably low risk for hemorrhagic complications, **oral anticoagulants** are recommended. Options include warfarin, dabigatran, apixaban, and rivaroxaban.

Antiplatelet agents and aspirin

- **Aspirin is not useful for preventing a first stroke in low-risk individuals (Class III)**
- **Aspirin is not useful for preventing a first stroke in people with diabetes mellitus in the absence of other high-risk conditions (Class III)**
- The use of **aspirin for cardiovascular prophylaxis** is reasonable **for people whose risk is sufficiently high (10-year risk >10%)** for the benefits to outweigh the risks associated with treatment **(Class IIa)**

Sleep-disordered breathing

- Because of its association with stroke risk**, screening for sleep apnea** through a detailed history, including structured questionnaires, physical examination, and polysomnography may be considered (Class IIb)
- Treatment of sleep apnea to reduce the risk of stroke **may be reasonable, although its effectiveness for primary prevention of stroke is unknown (Class IIb)**

Obesity and body fat distribution

- Among overweight **(BMI 25 to 29)** and obese **(BMI >30)** individuals, **weight reduction is recommended for lowering BP**
- Among overweight and obese individuals, **weight reduction is recommended for reducing the risk of stroke**.

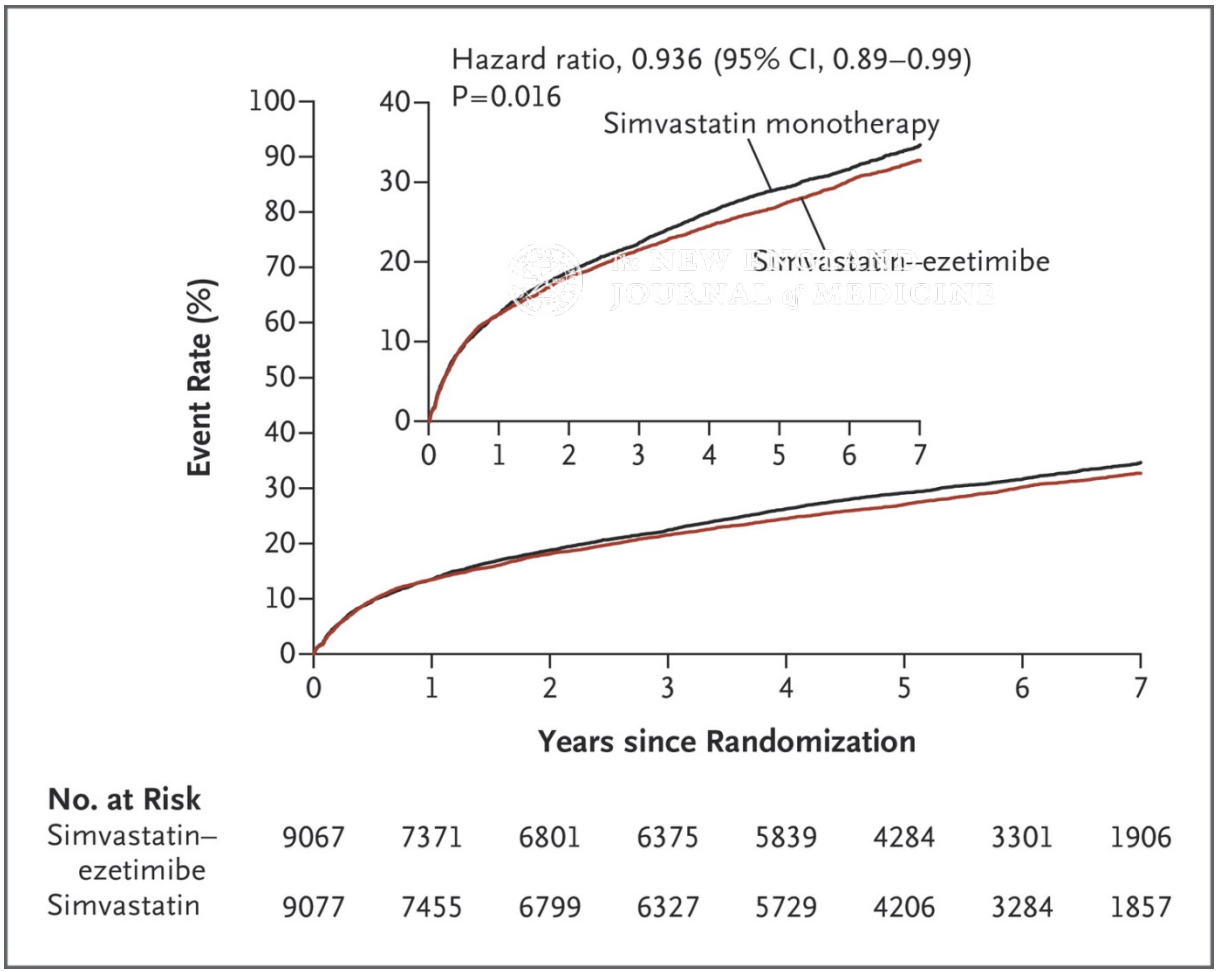
Diabetes mellitus

- Control of **BP to a target <140/90 mm Hg** is recommended in patients with **type 1 or type 2 diabetes** mellitus
- Treatment of adults with diabetes mellitus with a statin, especially those with additional risk factors, is recommended to lower risk of first stroke

Asymptomatic carotid stenosis

- Patients with asymptomatic carotid stenosis should be prescribed **daily aspirin and a statin**
- In patients who are to undergo **CEA**, **aspirin** is recommended **perioperatively and postoperatively** unless contraindicated
- It is reasonable to **consider** performing **CEA in asymptomatic patients who have >70% stenosis of ICA if risk of post-operative stroke, MI, and death is <3% (Class IIa)**

Prevention of composite: CV death, nonfatal MI, unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke

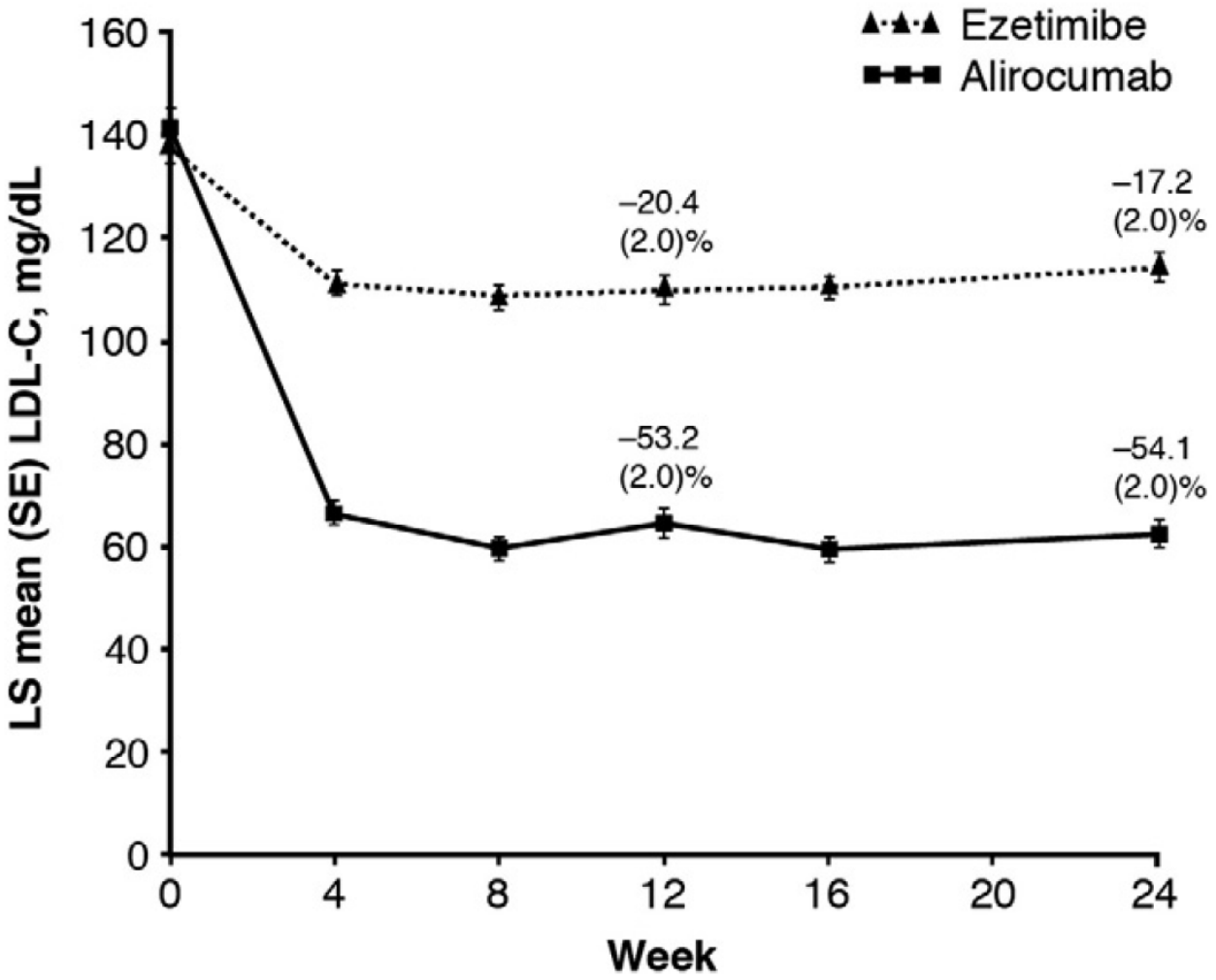


Cannon CP et al. N Engl J Med 2015;372:2387–2397

Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial

Eli M. Roth [a,*], Marja-Riitta Taskinen [b], Henry N. Ginsberg [c], John J.P. Kastelein [d], Helen M. Colhoun [e], Jennifer G. Robinson [f], Laurence Merlet [g], Robert Pordy [h], Marie T. Baccara-Dinet [i]

International Journal of Cardiology 176 (2014) 55–61



LDL-C levels (mg/dl) versus study time point (on-treatment analysis).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D.,

- Assessed safety of 5 mg IV idarucizumab in patients with serious bleeding or in need of urgent procedure who were taking dabigatran
- 90 patients, median age 76.5 years
- Reversal assessed using dilute thrombin time or ecarin clotting time
- The drug normalized the tests within minutes

maximum percentage reversal was 100% (95% confidence interval, 100 to 100). Idarucizumab normalized the test results in 88 to 98% of the patients, an effect that was evident within minutes. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients. Among 35 patients in group A who could be assessed, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 patients in group B who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.

CONCLUSIONS

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes. (Funded by Boehringer Ingelheim; RE-VERSE AD ClinicalTrials.gov number, NCT02104947.)

Mun, NT, Hong Kong (C.-W.K.). Address reprint requests to Dr. Pollack at Thomas Jefferson University, Scott Memorial Library, 1020 Walnut St., Rm. 616, Philadelphia, PA 19107, or at charles.pollack@jefferson.edu.

This article was published on June 22, 2015, at NEJM.org.

N Engl J Med 2015;373:511-20.
DOI: 10.1056/NEJMoa1502000

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BRAIN
A JOURNAL OF NEUROLOGY
BRAIN 2015: 138; 761–771

Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly

Prashanthi Vemuri,[1] Timothy G. Lesnick,[2] Scott A. Przybelski,[2] David S. Knopman,[3] Greg M. Preboske,[1] Kejal Kantarci,[1] Mekala R. Raman,[3] Mary M. Machulda,[4] Michelle M. Mielke,[2] Val J. Lowe,[1] Matthew L. Senjem,[1] Jeffrey L. Gunter,[1] Walter A. Rocca,[2,3] Rosebud O. Roberts,[2] Ronald C. Petersen[3] and Clifford R. Jack Jr[1]

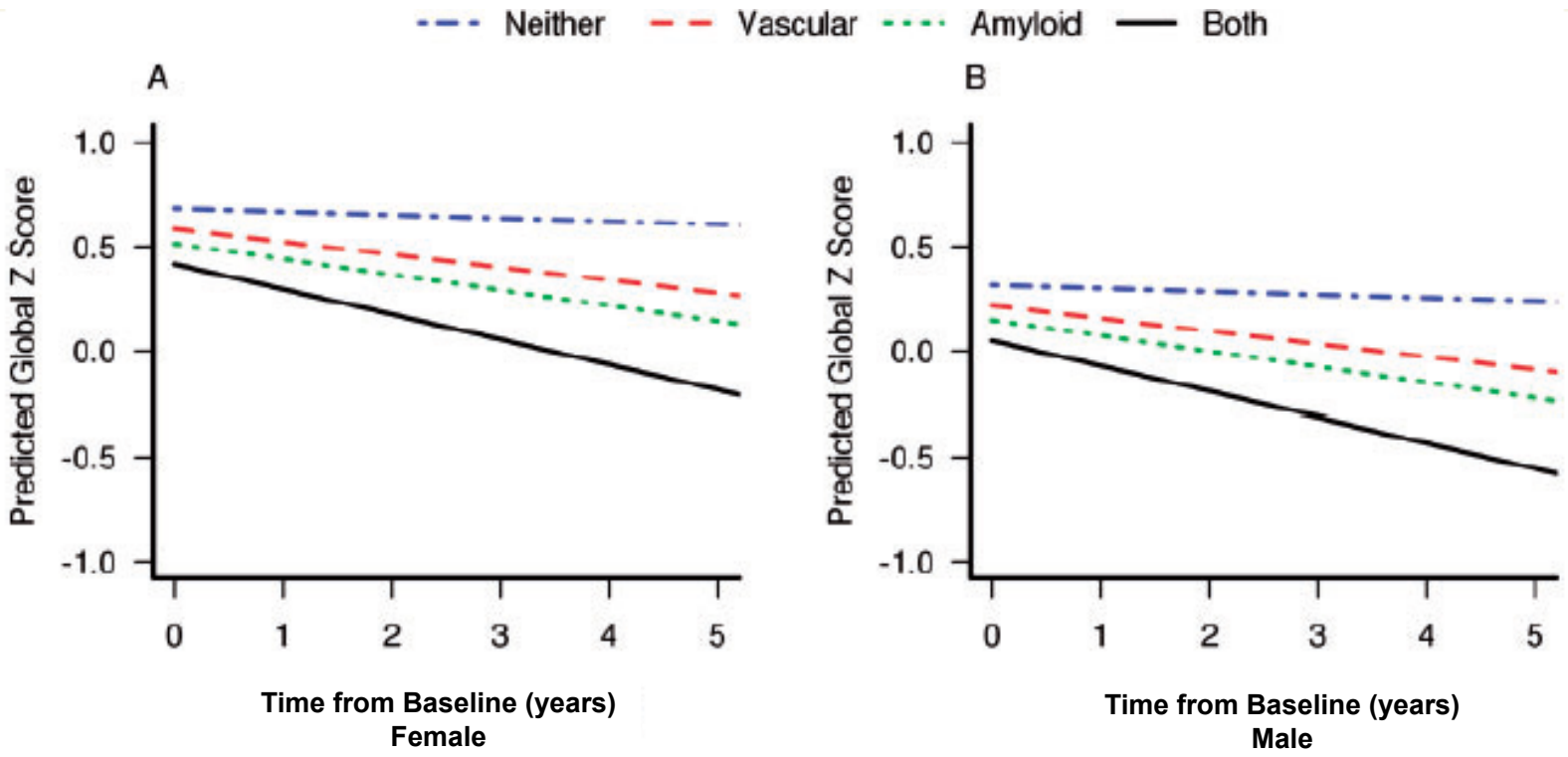


Figure 2 Decrease in predicted cognitive scores with pathway in female (A) and male (B) subjects.

NEUROLOGY®

Cerebral hemodynamics and cognitive performance in bilateral asymptomatic carotid stenosis

Clotilde Balucani, MD
Giovanna Viticchi, MD
Lorenzo Falsetti, MD

ABSTRACT

Objectives: To evaluate cognitive performance in subjects with bilateral asymptomatic carotid stenosis (B-ACS) compared to subjects with unilateral ACS and to subjects with no carotid steno-

- 333 patients with bilateral, unilateral and no asymptomatic carotid stenosis had cognitive testing and TCD-based breath-holding index testing
- Subjects with bilateral and unilateral ACS were more likely to have cognitive dysfunction
- Link between cognitive and hemodynamic impairment

patients with ACS are poorly understood. The impaired cerebral hemodynamic status resulting from chronic hypoperfusion may contribute to the development of cognitive dysfunction.[9,11] Contralateral ACS is a predictor of progression of internal carotid artery (ICA) stenosis[12] reflecting a more severe and diffuse atherosclerotic disease. Cognitive performance in bilateral ACS (B-ACS) and its relationship with the cerebral hemodynamic status has not been systematically evaluated.

JAMA®
The Journal of the American Medical Association

JAMA. 2011;306:1983-92

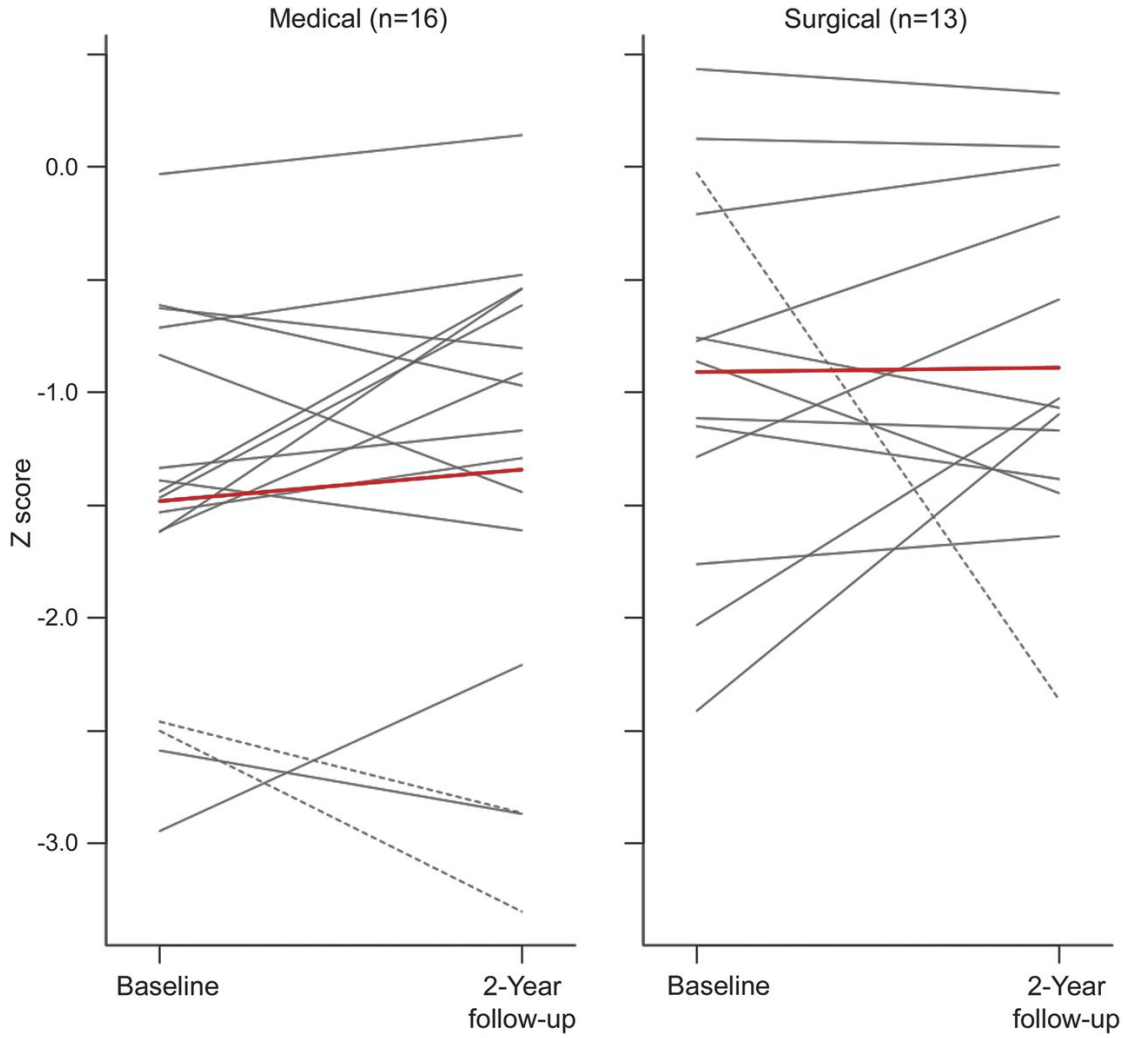
ORIGINAL CONTRIBUTION

Extracranial-Intracranial Bypass Surgery for Stroke Prevention in Hemodynamic Cerebral Ischemia

The Carotid Occlusion Surgery Study Randomized Trial

- 195 patients with recent symptomatic ICA occlusion and increased OEF on PET were randomized to STA-MCA bypass or not.
- Primary endpoint = stroke & death < 30 days + ipsi stroke thereafter.
- Stopped for futility (21.0% vs. 22.7%).
- RECON = cognitive substudy of 41 patients.
- Surgery did not improve cognitive 2-year outcomes.
- Of the 26 patients with no stroke in follow-up showed greater cognitive improvement with lesser OEF impairment.

Individual composite cognitive change scores by treatment group. Dashed lines indicate patients with contralateral stroke during the follow-up period.



Randolph S. Marshall et al. Neurology 2014;82:744-751

AMERICAN ACADEMY OF NEUROLOGY

THE LANCET

Lancet 2015; 385: 529-38

Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial

Leo H Bonati, Joanna Dobson, Roland L Featherstone, Jörg Ederle, H Bart van der Worp, Gert J de Borst, Willem P Th M Mali, Jonathan D Beard,

- No difference in 5-year risk of fatal or disabling stroke (6.4% vs. 6.5%).
- Any stroke was more frequent in the CAS group (15.2% vs. 9.4%).
- Distribution of 1- and 5-year MRS scores was not significant.

Interpretation Long-term functional outcome and risk of fatal or disabling stroke are similar for stenting and endarterectomy for symptomatic carotid stenosis.

Funding Medical Research Council, Stroke Association, Sanofi-Synthélabo, European Union.

London, UK (J Dobson MSc); Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus (H B van der Worp PhD), Department of Vascular Surgery (G J de Borst PhD), and Department of Radiology

NEUROLOGY®

Cognition after carotid endarterectomy or stenting

A. Altinbas, MD
M.J.E. van Zandvoort, PhD
E. van den Berg, PhD
L.M. Jongen, MD, PhD
A. Algra, MD, PhD
F.L. Moll, MD, PhD
P.J. Nederkoorn, MD, PhD
W.P.T.M. Mali, MD, PhD
L.H. Bonati, MD
M.M. Brown, MD, FRCP
L.J. Kappelle, MD, PhD
H.B. van der Worp, MD, PhD

Address correspondence and reprint requests to Dr. Aysun Altinbas, Department of

- 2-Center substudy of ICSS.
- N = 140 baseline and 120 at 6-month.
- DWI before and 3-days after revascularization.
- New ischemic lesions were twice as common in CAS vs. CEA (p = 0.041).
- Non-significant decrease in cognitive sumscore in CAS vs. CEA.

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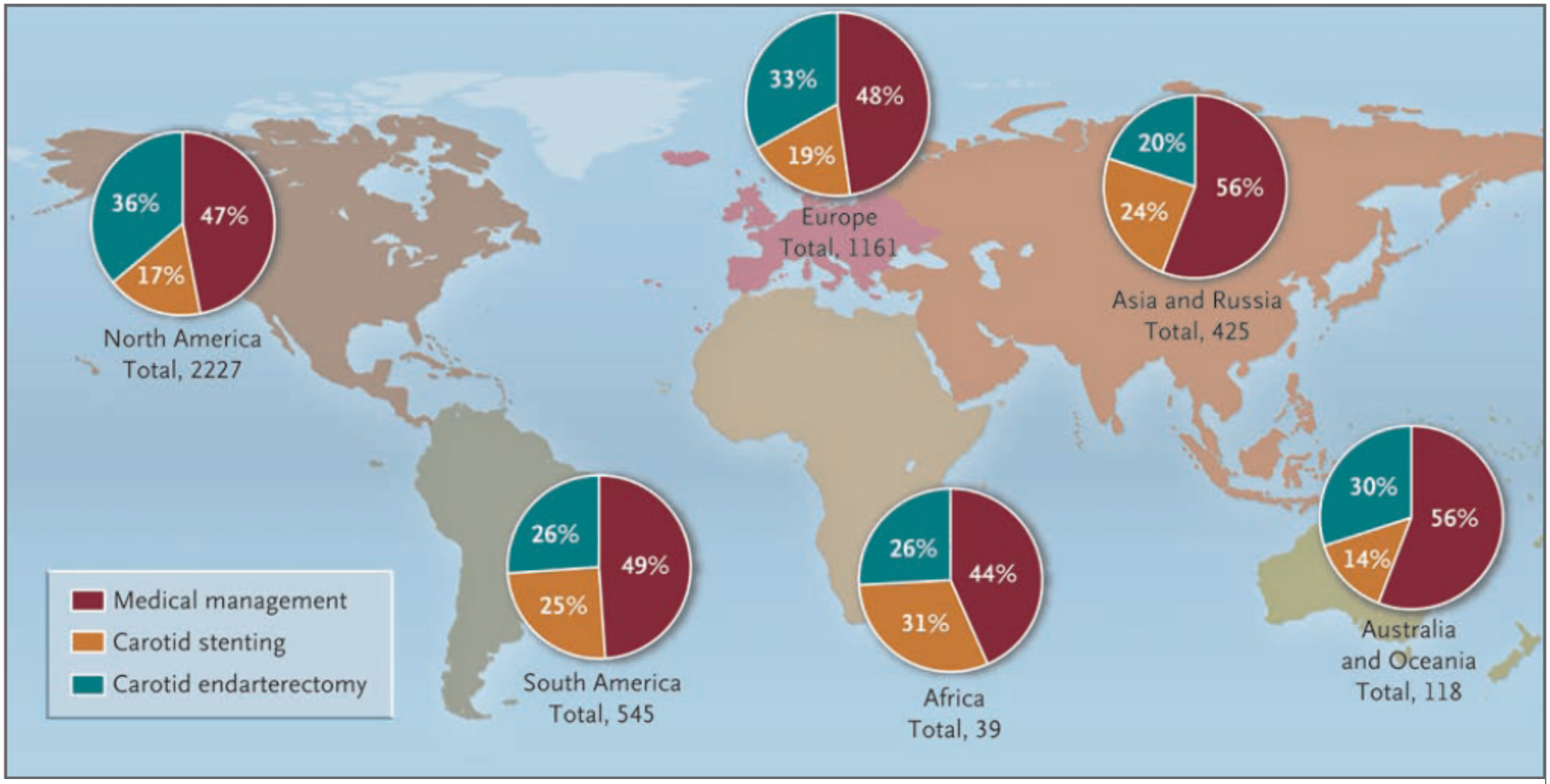
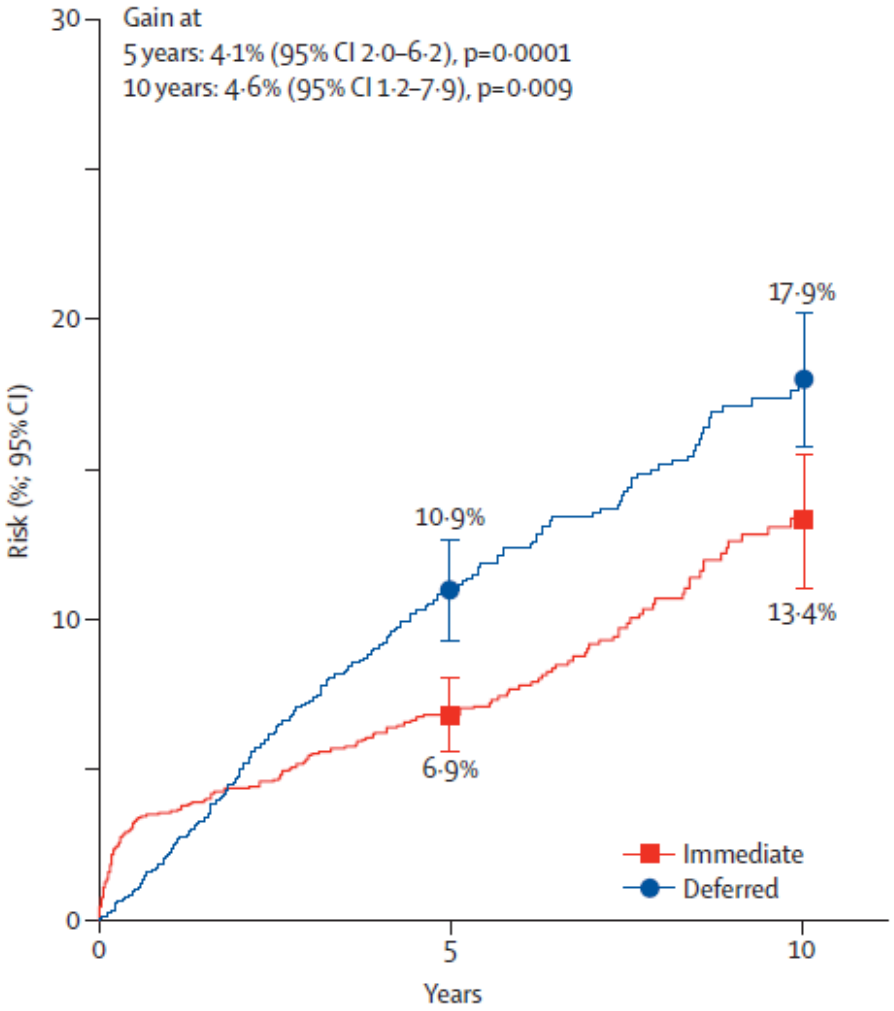
- Locate the stakes of the study “CREST-2”

How would you manage a non-smoker with 70-80% RICA stenosis, irregular plaque, and 20% stenosis of LICA?





Perioperative events/CEAs (%)+other events

	Years 0–5	Years 5–10	
	44/1509 (2·9%)+56	0/23 (0·0%)+43	Immediate
	14/360 (3·9%)+140	2/87 (2·3%)+48	Deferred

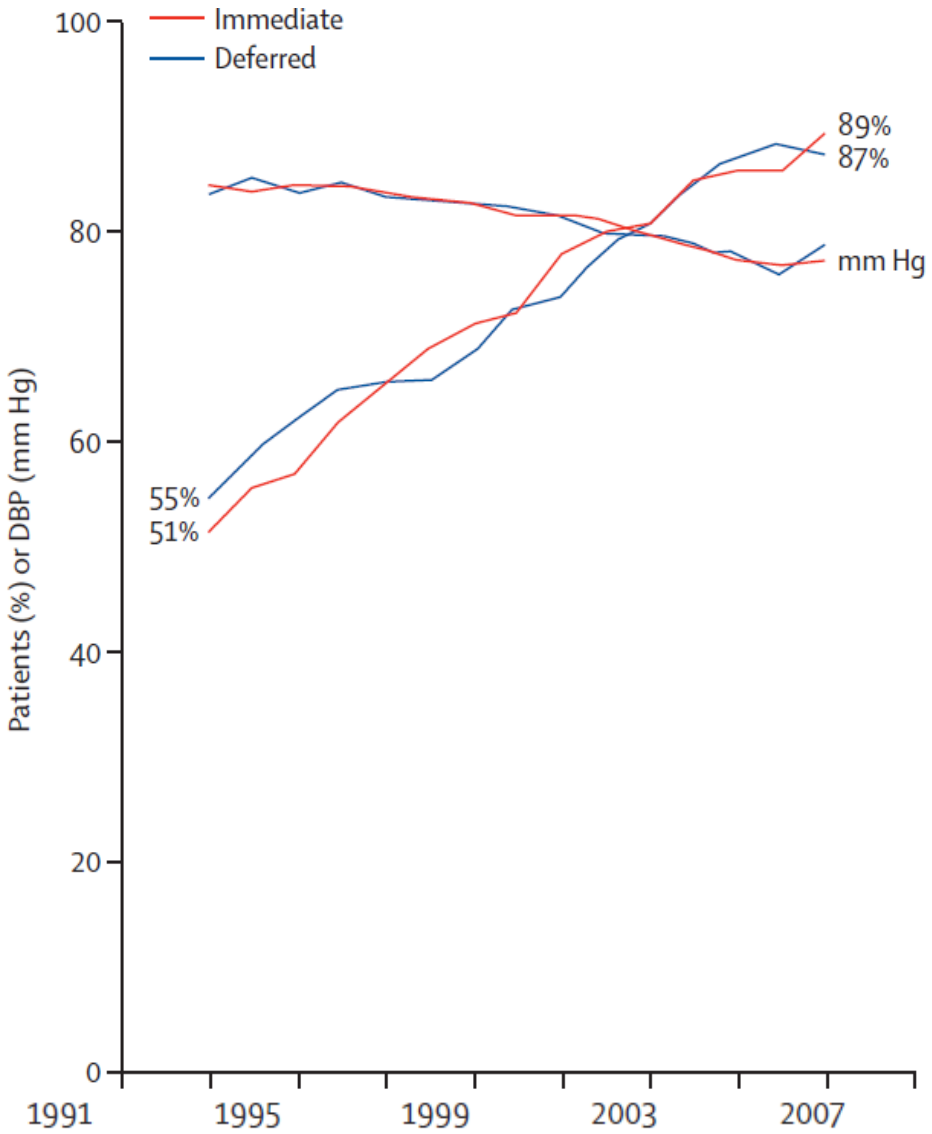
Number at risk

Immediate	1560	1003	293
Deferred	1560	981	281

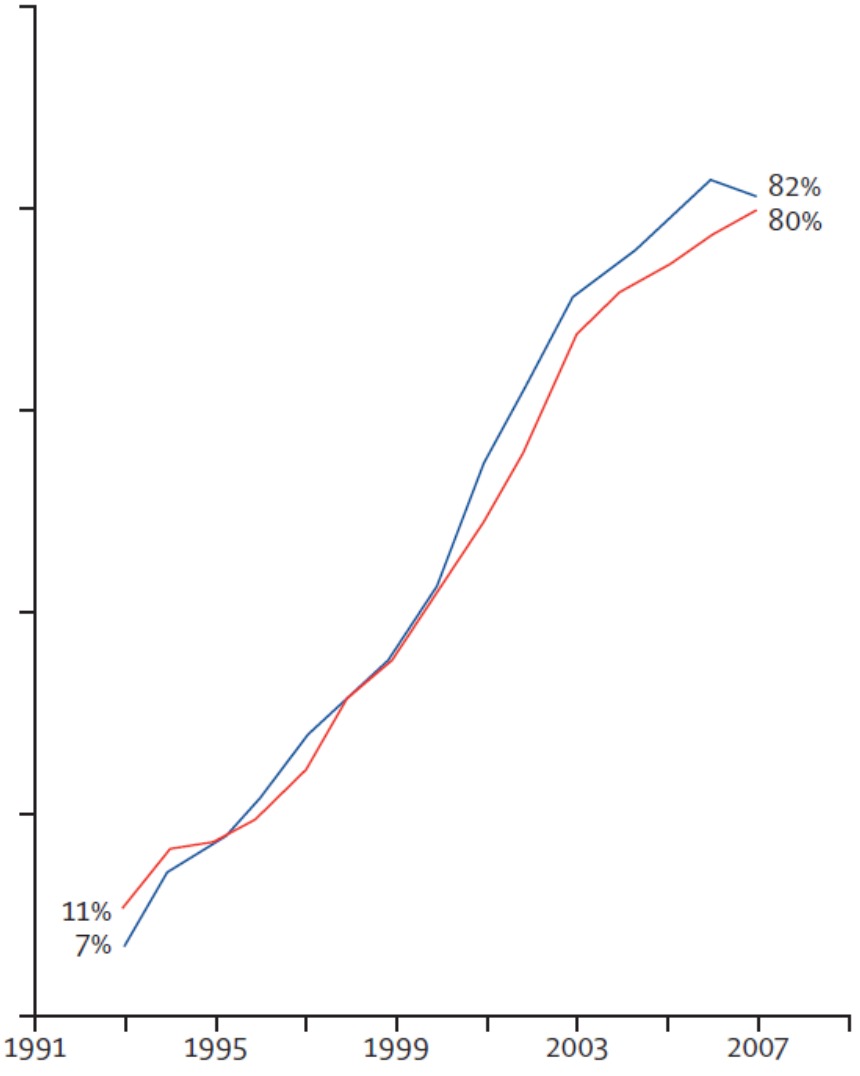
Any stroke or perioperative death

Medical Management in ACST

Antihypertensive drug use & mean DBP



Lipid-lowering drug use



Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial

Colin P Derdeyn, Marc I Chimowitz*, Michael J Lynn, David Fiorella, Tanya N Turan, L Scott Janis, Jean Montgomery, Azhar Nizam, Bethany F Lane, Helmi L Lutsep, Stanley L Barnwell, Michael F Waters, Brian L Hoh, J Maurice Hourihane, Elad I Levy, Andrei V Alexandrov, Mark R Harrigan, David Chiu, Richard P Klucznik, Joni M Clark, Cameron G McDougall, Mark D Johnson, G Lee Pride Jr, John R Lynch, Osama O Zaidat, Zoran Rumboldt, Harry J Cloft, for the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators†*

- Stopped early at 451 patients (764 planned)
- 32.4 months median follow-up
- Primary endpoint = stroke and death within 30 days + target artery ischemic stroke thereafter
- Absolute differences in primary endpoint were 7.1% at 1 year, 6.5% at 2 years and 9.0% at 3 years

Findings During a median follow-up of 32·4 months, 34 (15%) of 227 patients in the medical group and 52 (23%) of 224 patients in the stenting group had a primary endpoint event. The cumulative probability of the primary endpoints was smaller in the medical group versus the percutaneous transluminal angioplasty and stenting (PTAS) group (p=0·0252). Beyond 30 days, 21 (10%) of 210 patients in the medical group and 19 (10%) of 191 patients in the stenting group had a primary endpoint. The absolute differences in the primary endpoint rates between the two groups were 7·1% at year 1 (95% CI 0·2 to 13·8%; p=0·0428), 6·5% at year 2 (–0·5 to 13·5%; p=0·07) and 9·0% at year 3 (1·5 to 16·5%; p=0·0193). The occurrence of the following adverse events was higher in the PTAS group than in the medical group: any stroke (59 [26%] of 224 patients *vs* 42 [19%] of 227 patients; p=0·0468) and major haemorrhage (29 [13%] of 224 patients *vs* 10 [4%] of 227 patients; p=0·0009).

Interpretation The early benefit of aggressive medical management over stenting with the Wingspan stent for high-risk patients with intracranial stenosis persists over extended follow-up. Our findings lend support to the use of aggressive medical management rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis.

NEUROLOGY®

VIEWS & REVIEWS

Published Ahead of Print on June 26, 2015 as 10.1212/WNL.0000000000001781

Temporal trends in safety of carotid endarterectomy in asymptomatic patients

Systematic review

Alex B. Munster, BSc
Angelo J. Franchini, MSc
Mahim I. Qureshi, MA, MRCS
Ankur Thapar, MRCS, PhD
Alun H. Davies, DM, FRCS

Figure 3 Temporal trends in 30-day perioperative death incidence in clinical trials

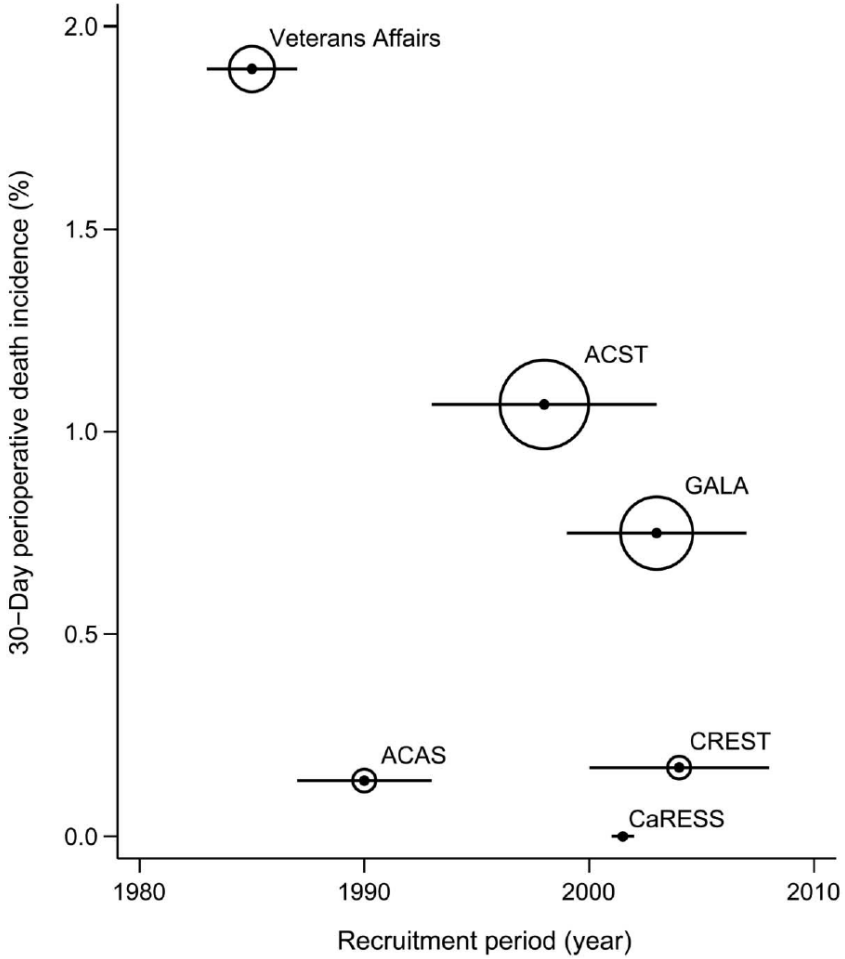
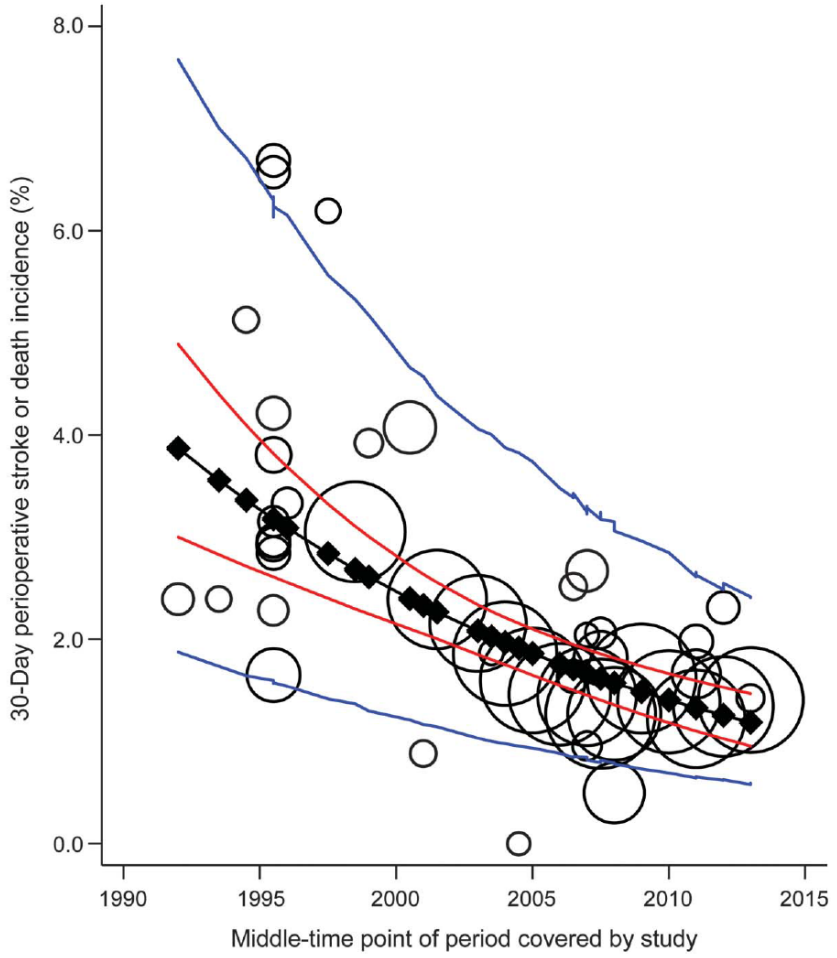


Figure 4 Temporal trends in 30-day perioperative stroke or death incidence in clinical registries



CREST-2 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

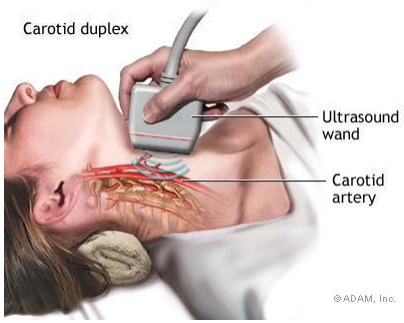
Primary endpoint: proportion of patients who experienced any stroke or death within 44 days of randomization or ipsilateral ischemic stroke thereafter up to 4 years.

CREST-2 Secondary Aims

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

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

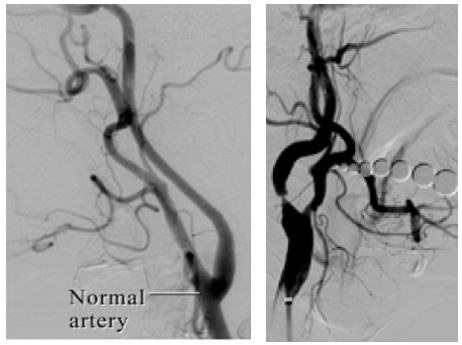
Definitions for ≥70% Stenosis



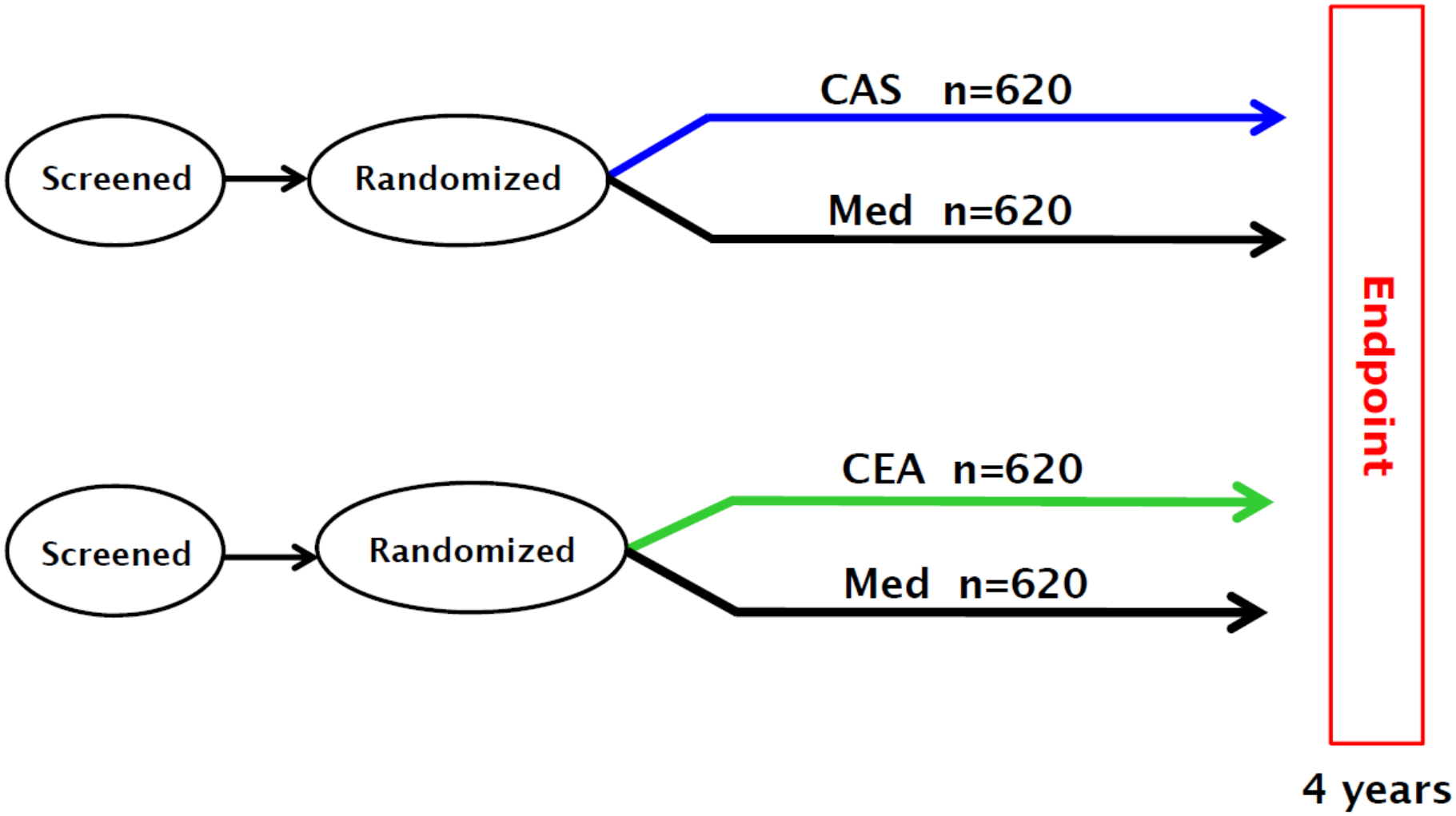
Peak systolic velocity ≥230 cm/sec on Duplex ultrasound plus

At least one of the following:

- End diastolic velocity ≥100 cm/sec or
- IC/CC peak systolic velocity ratio ≥4.0
- ≥70% stenosis on MR angiogram or
- ≥70% stenosis on CT angiogram



Allocation to treatment group is done by clinical judgement followed by randomization



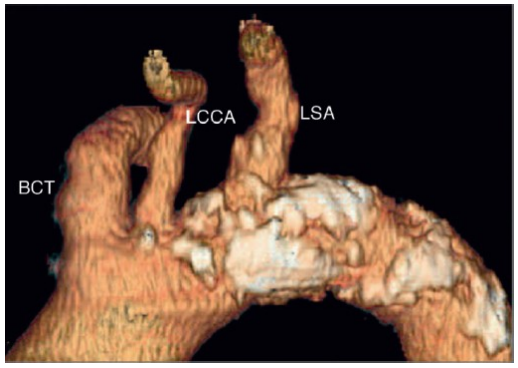
Selected CEA Exclusions in CREST-2

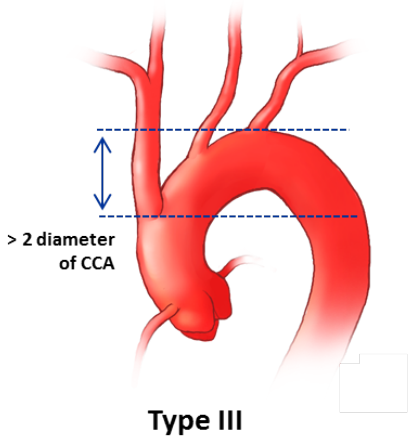
Neck dissection

Tracheostomy stoma

- Radical neck dissection
- Surgically inaccessible lesions
- Neck anatomy limiting surgical exposure
- Tracheostomy stoma
- Laryngeal nerve palsy contralateral to target vessel

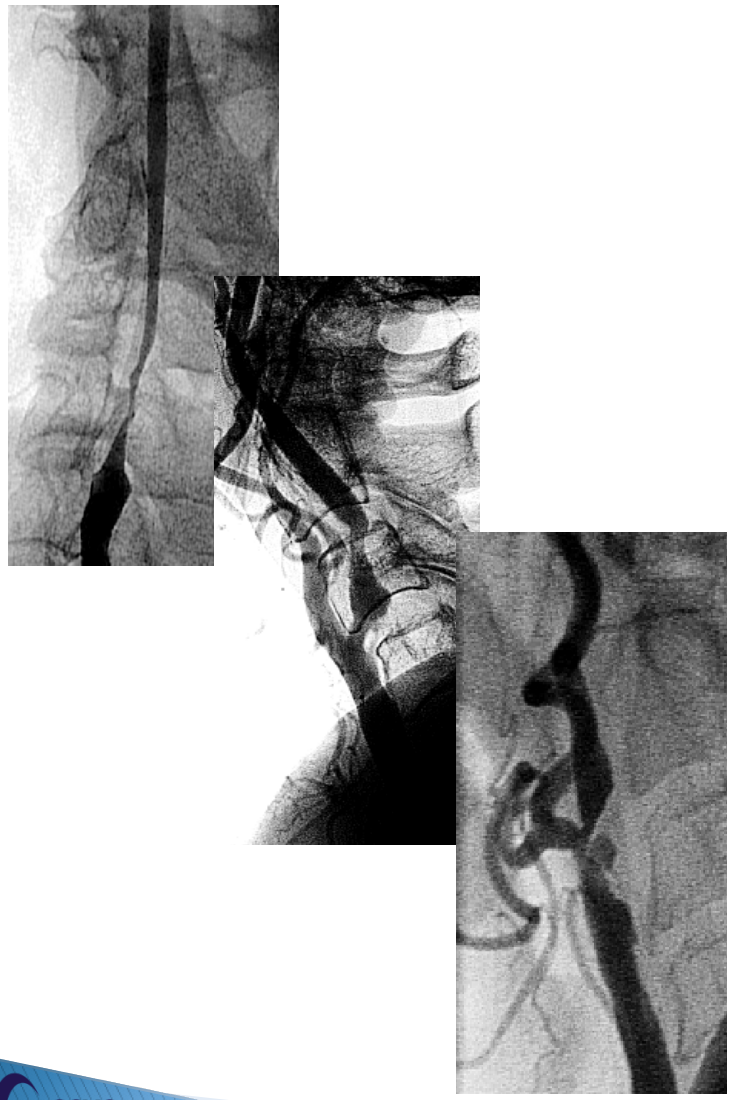
Selected CAS Exclusions in CREST-2





- 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 in CREST-2



- Excessive or circumferential calcification of the stenotic lesion
- Lesions >30 mm in length, sequential lesions, and narrow-mouth ulcers
- Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD)

CREST-2 Medical Management

Patients in both trials will take aspirin 325mg/d for the entire follow-up period (CAS patients will be on dual antiplatelet therapy for 1 month post-procedure).

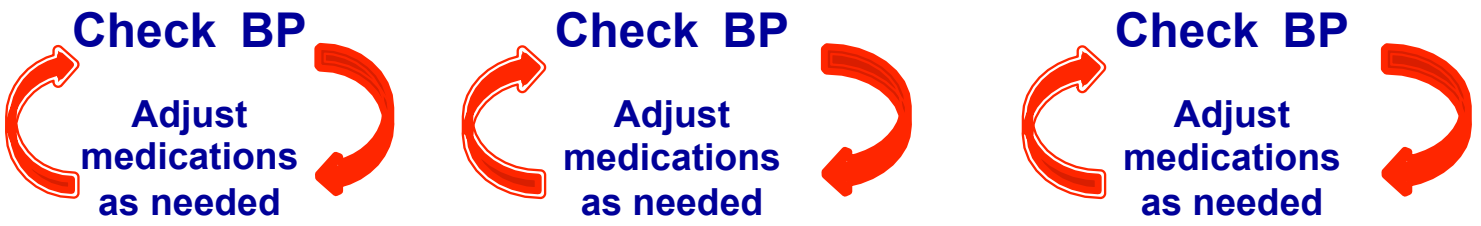
Primary Risk Factor Targets

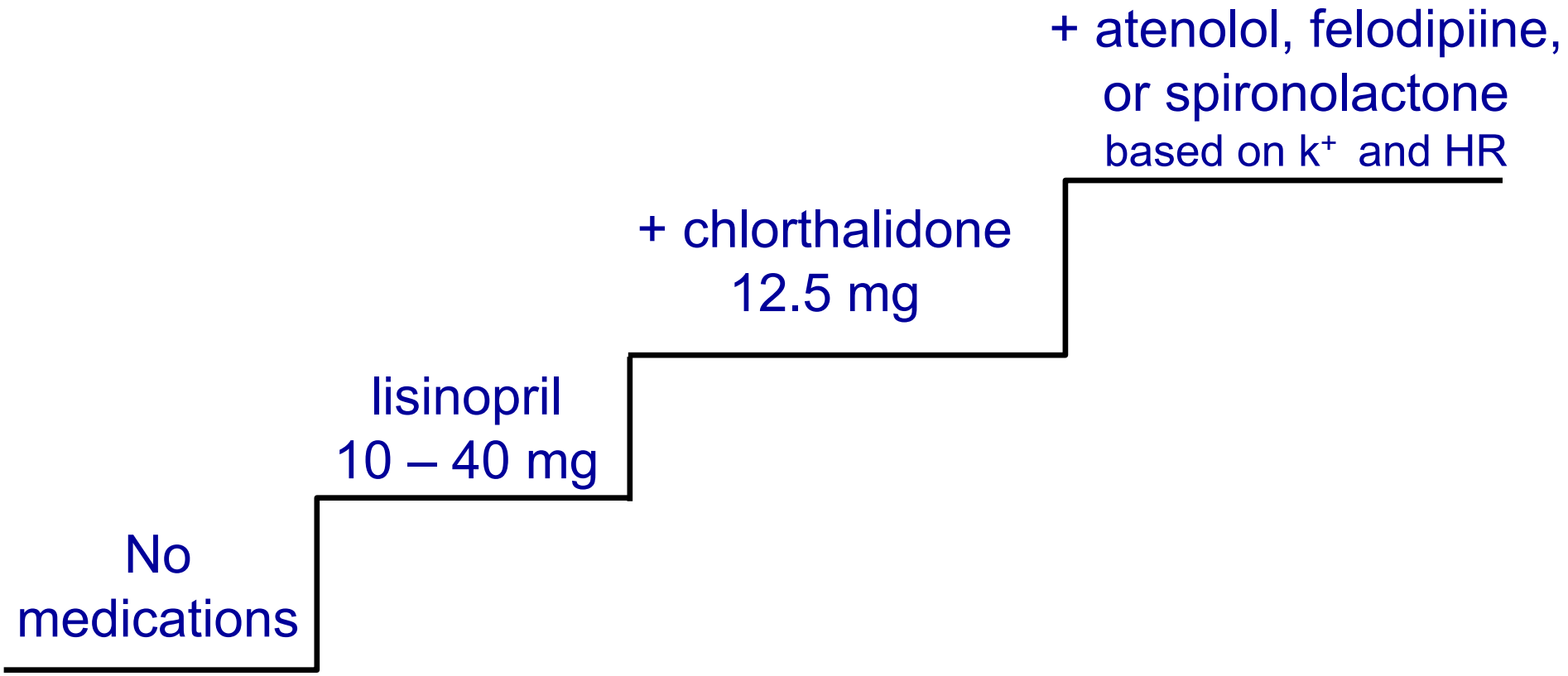
- Systolic BP <140 mm Hg
- LDL cholesterol <70 mg/dl

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

BP Management Algorithm





Lifestyle Coaching in CREST-2

- Lifestyle management is being done by INTERVENT.
- Incorporates SAMMPRIS targets and national guidelines.
- Provides individualized risk factor counseling telephone sessions at regular intervals:
  - Months 1 to 3: 2 per month.
  - Months 4 to 12: 1 per quarter.
  - Months 12 to close: 2 per year.
- Case Managers at INTERVENT call center, Savannah, GA.

Cognitive Testing in CREST-2

- Word list learning
- Word list learning (recall)
- Animal learning
- SF-12
- Letter fluency
- Digit span (forward and backward)
- CES-D-4 Depression scale

Brain Imaging for Possible Stroke Endpoints

- Sites advised to evaluate all patients with possible stroke or TIA endpoint with brain MRI unless contraindicated, in which case CT is acceptable.
- Brain imaging should be done as close to symptom onset as possible, preferably within the first 2-7 days.
- Brain imaging should be completed even if symptoms resolve within 24 hours.
- Stroke evaluation should also include an NIH Stroke Scale.

THE LANCET

Challenges in evaluating surgical innovation

Patrick L. Ergina, MD, Jonathan A. Cook, PhD, Jane M. Blazeby, MD, Isabelle Boutron, MD, Pierre-Alain Clavien, MD, Bamaby C. Reeves, DPhil, Christoph M. Seiler, MD, for the Balliol Collaboration

Lancet 2009; 374: 1089-96

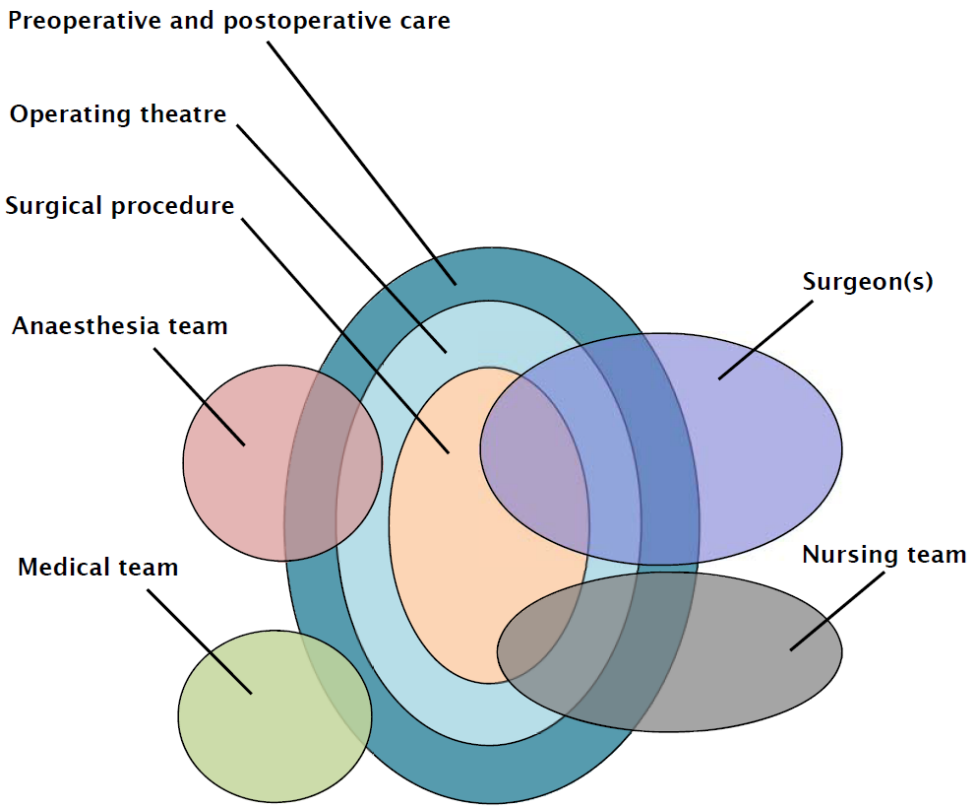
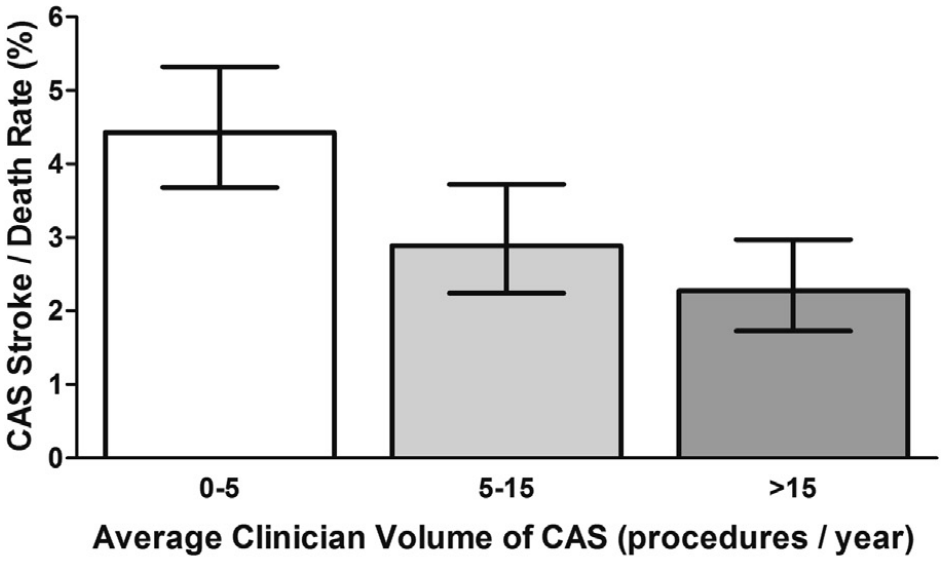


Figure. Complexity of a surgical intervention



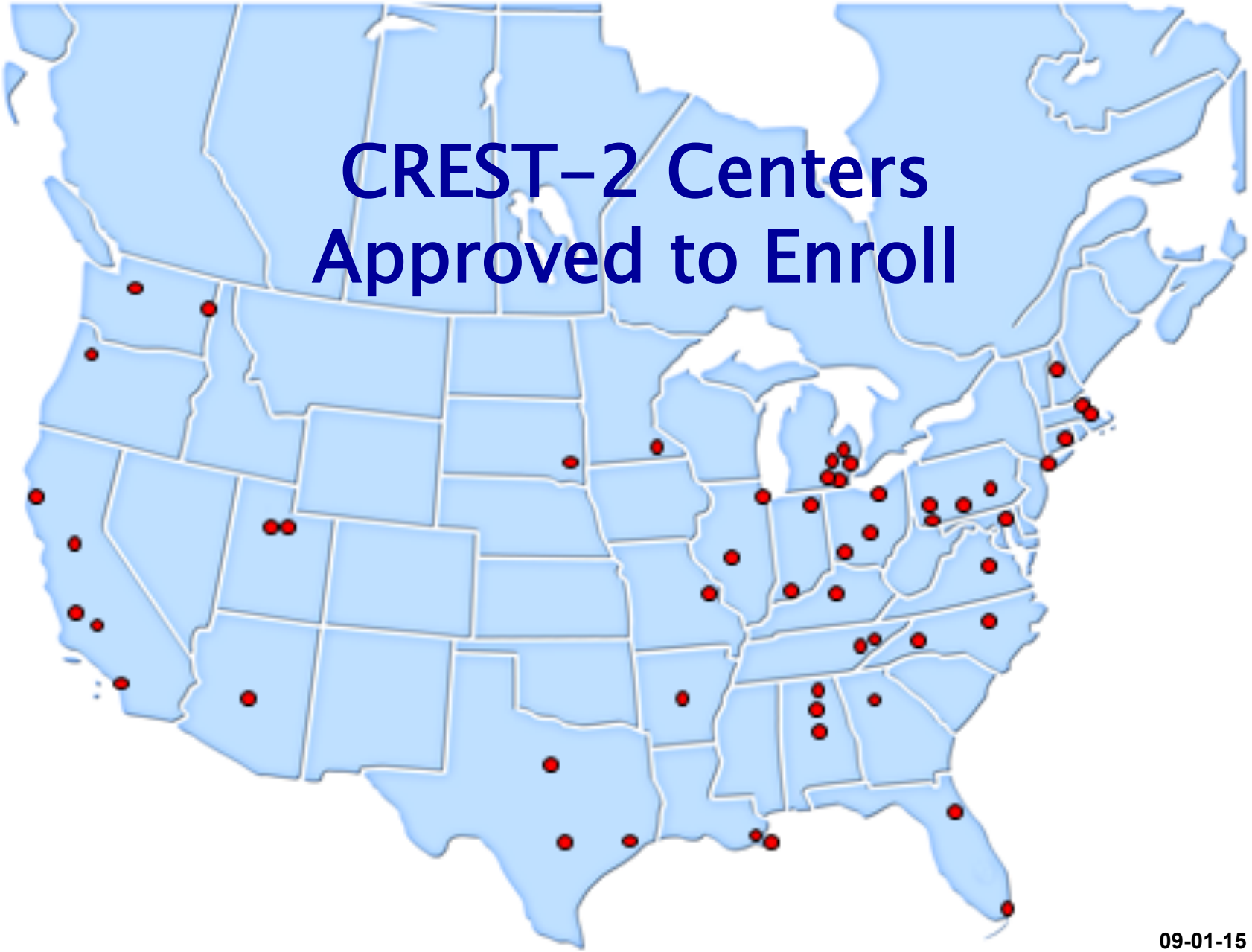
Journal of Vascular Surgery®

Low rates of complications for carotid artery stenting are associated with a high clinician volume of carotid artery stenting and aortic endografting but not with a high volume of percutaneous coronary interventions

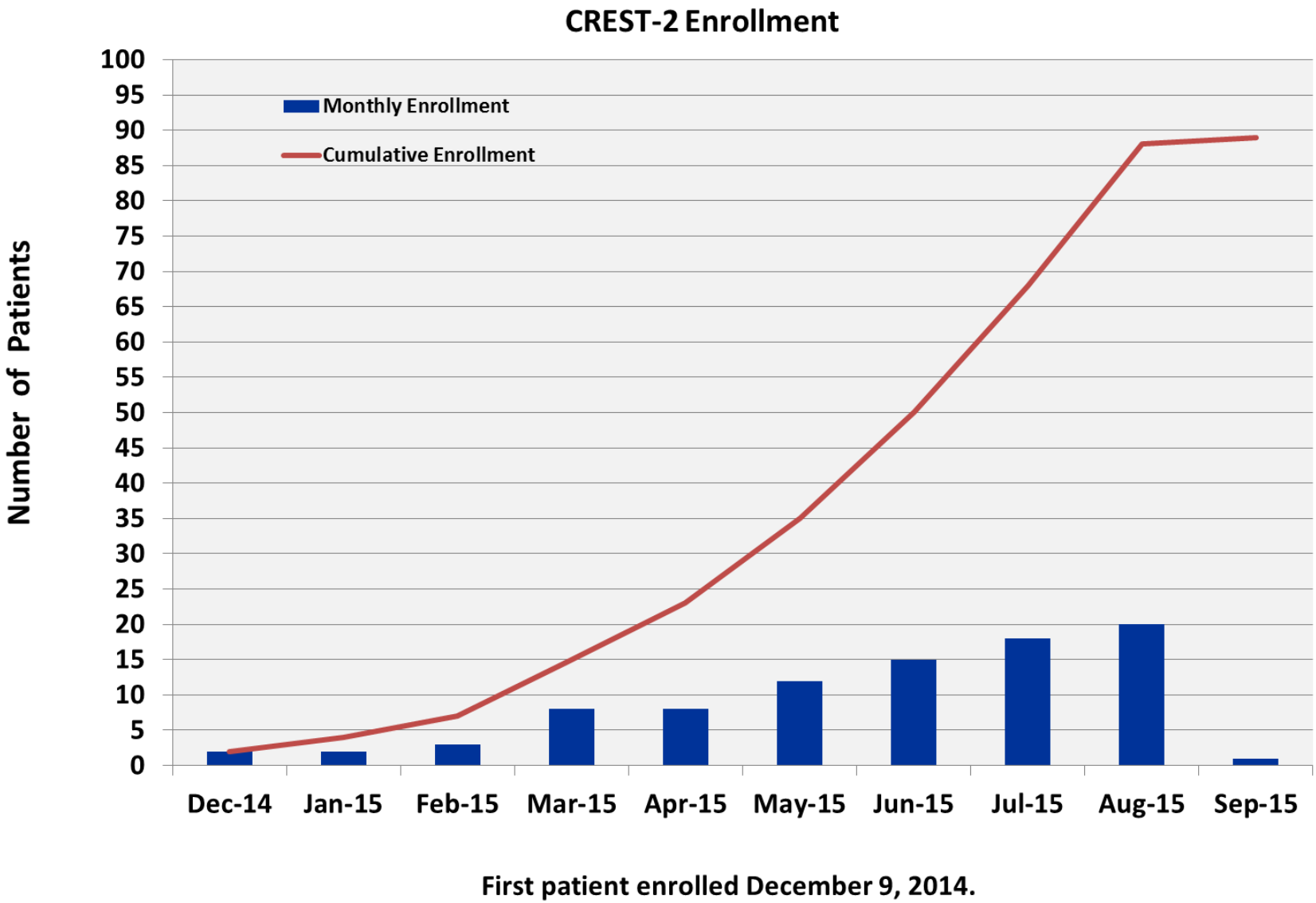
J. Gregory Modrall, MD, Jayer Chung, MD, Melissa L. Kirkwood, MD, M. Shadman Baig, MD, Shirling X. Tsai, MD, Carlos H. Timaran, MD, R. James Valentine, MD, and Eric B. Rosero, MD, MS, Dallas, Tex

J Vasc Surg 2014;60:70-6

CREST-2 Centers Approved to Enroll



09-01-15



First patient enrolled December 9, 2014.

Summary

- Numerous clearly proven lifestyle, medical and surgical interventions reduce risk of stroke
- Cognitive impairment may be a rough surrogate for stroke prevention, but may also need to be seen as a goal of vascular disease prevention in and of itself
- CREST-2 is an actively recruiting trial of revascularization for primary prevention of stroke and prevention of progressive cognitive impairment in patients with high-grade asymptomatic carotid stenosis