Acute Ischemic Stroke and Chronic Carotid Artery Stenosis

Two Entities with Novel Approaches

Thomas G. Brott, M.D.

Session III: Systemic Arterial Disease – Chronic Coronary Disease, Stroke and Pulmonary Embolism

Friday, December 8, 2017

AMERICAN COLLEGE of CARDIOLOGY

Disclosure

- Relevant financial relationships

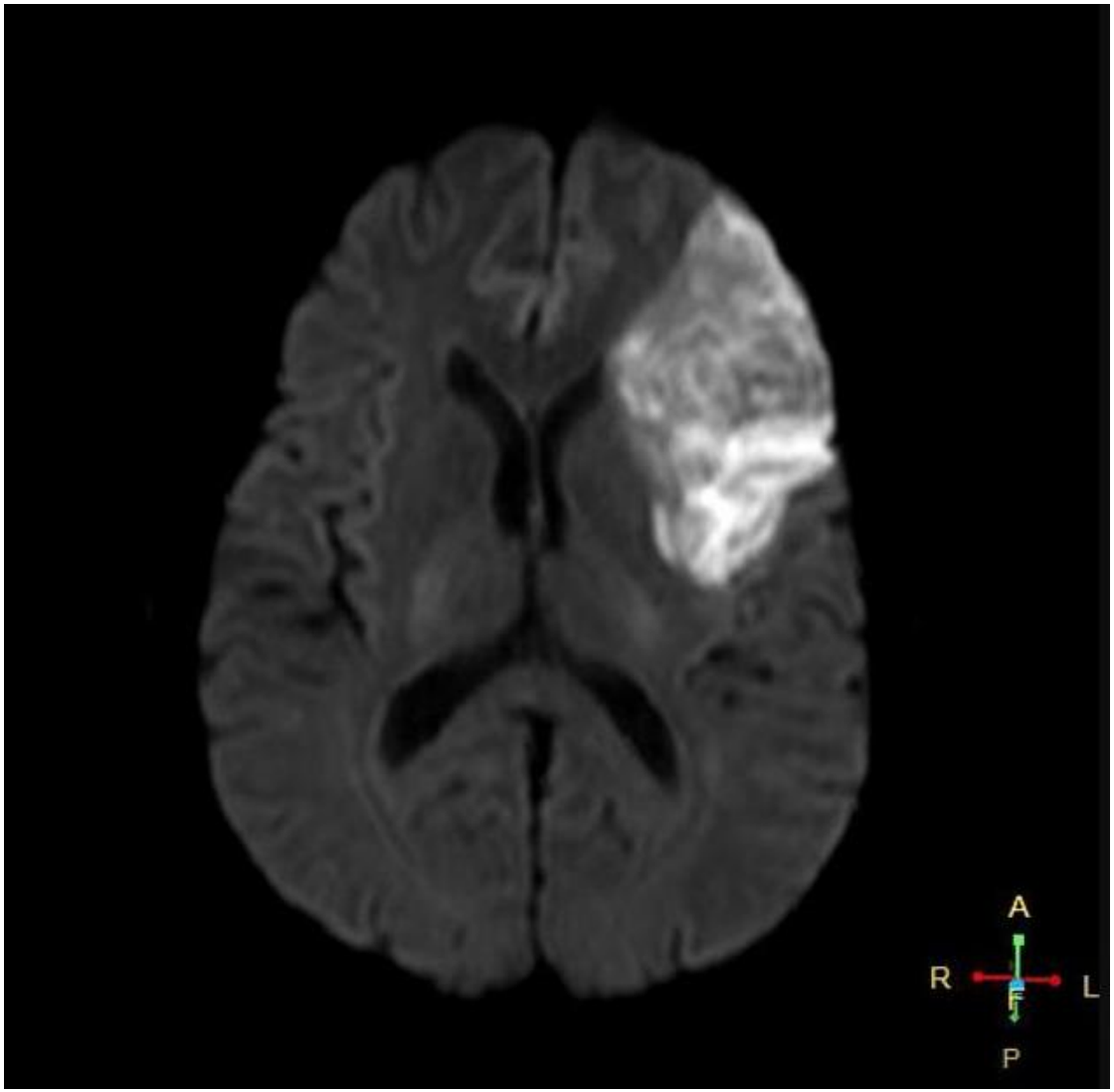
  None

- Off-label/investigational uses

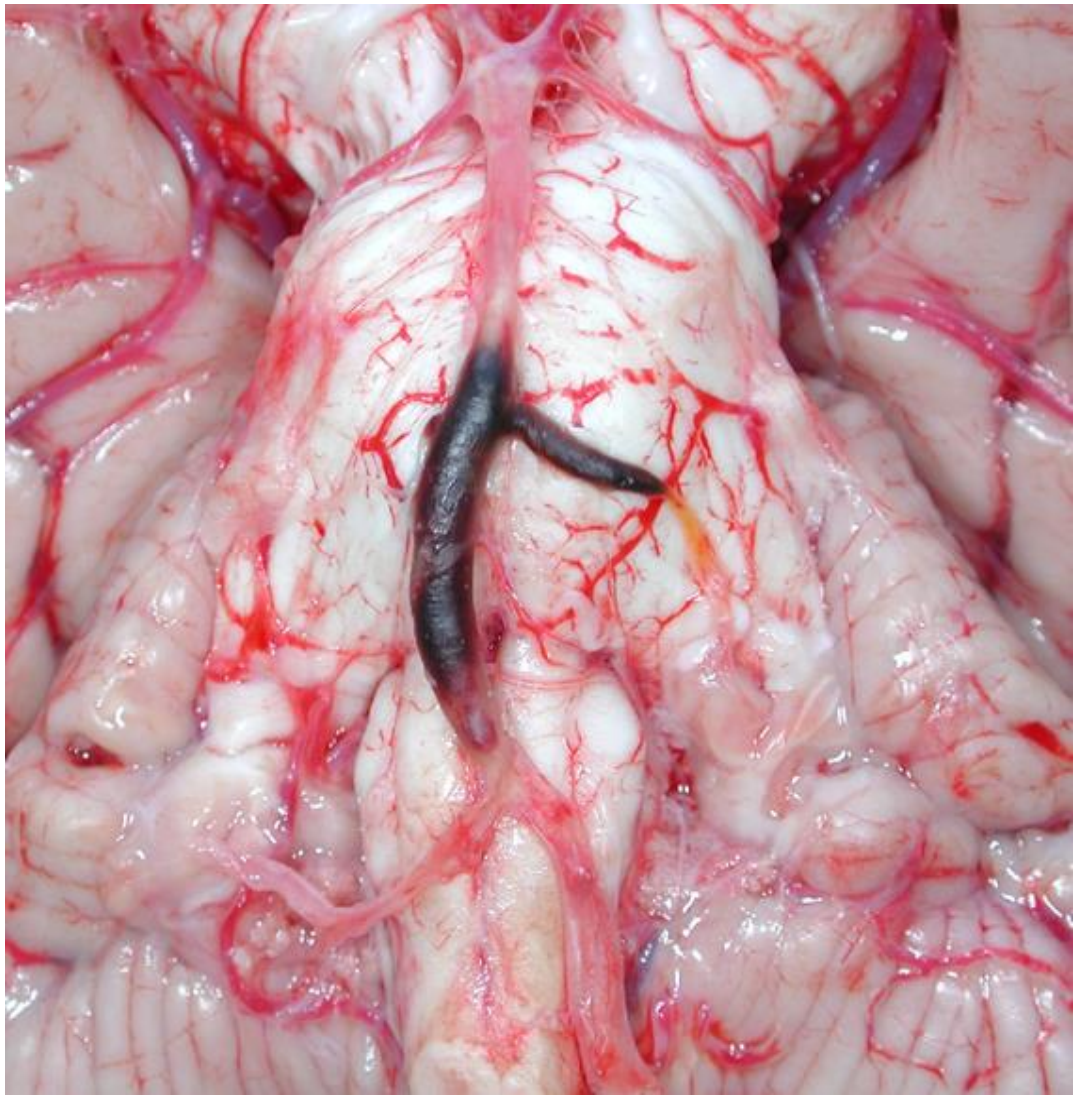
  None

911 Stroke

large vessel embolic infarct



Basilar Artery Embolus



The New England Journal of Medicine

Volume 333 DECEMBER 14, 1995 Number 24

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

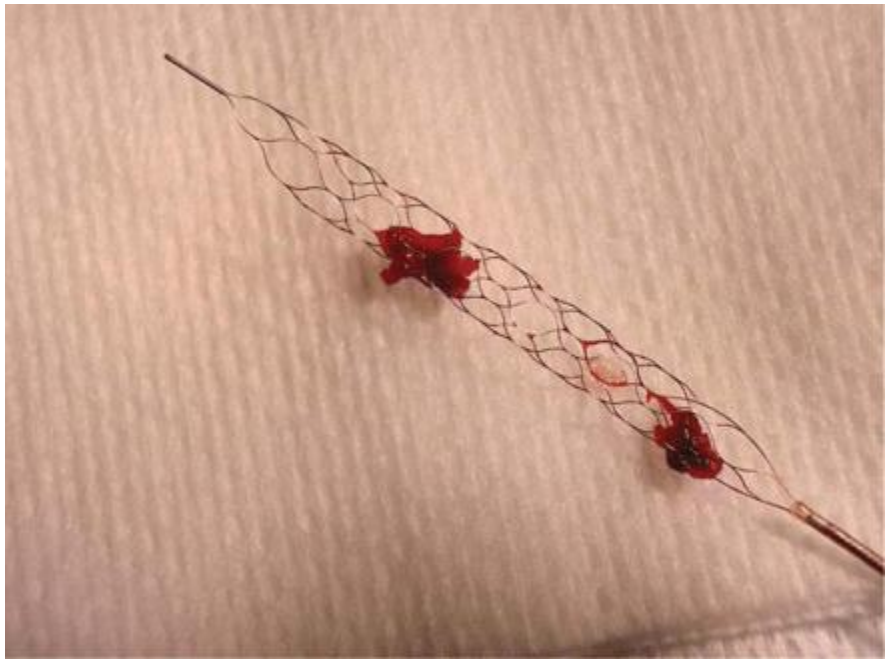
THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

Abstract *Background.* Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over base-line values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

Results. In part 1, there was no significant difference between the group given t-PA and that given placebo in the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo ($P<0.001$). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group ($P=0.30$).

Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)

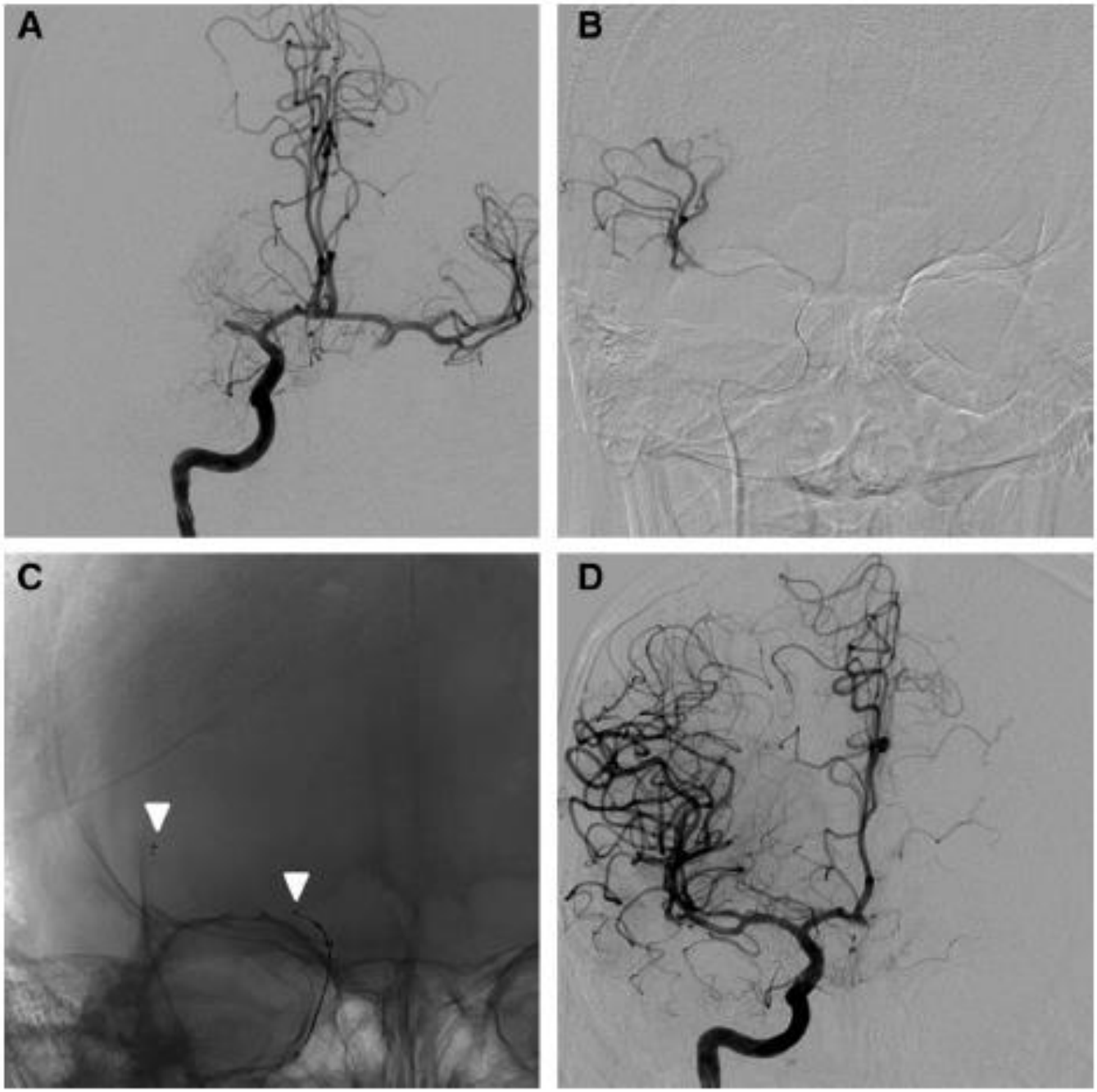


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

T.G. Jovin, A. Chamorro, E. Cobo, M.A. de Miquel, C.A. Molina, A. Rovira, L. San Román, J. Serena, S. Abilleira, M. Ribó, M. Millán, X. Urra, P. Cardona, E. López-Cancio, A. Tomasello, C. Castaño, J. Blasco, L. Aja, L. Dorado, H. Quesada, M. Rubiera, M. Hernández-Pérez, M. Goyal, A.M. Demchuk, R. von Kummer, M. Gallofré, and A. Dávalos, for the REVASCAT Trial Investigators*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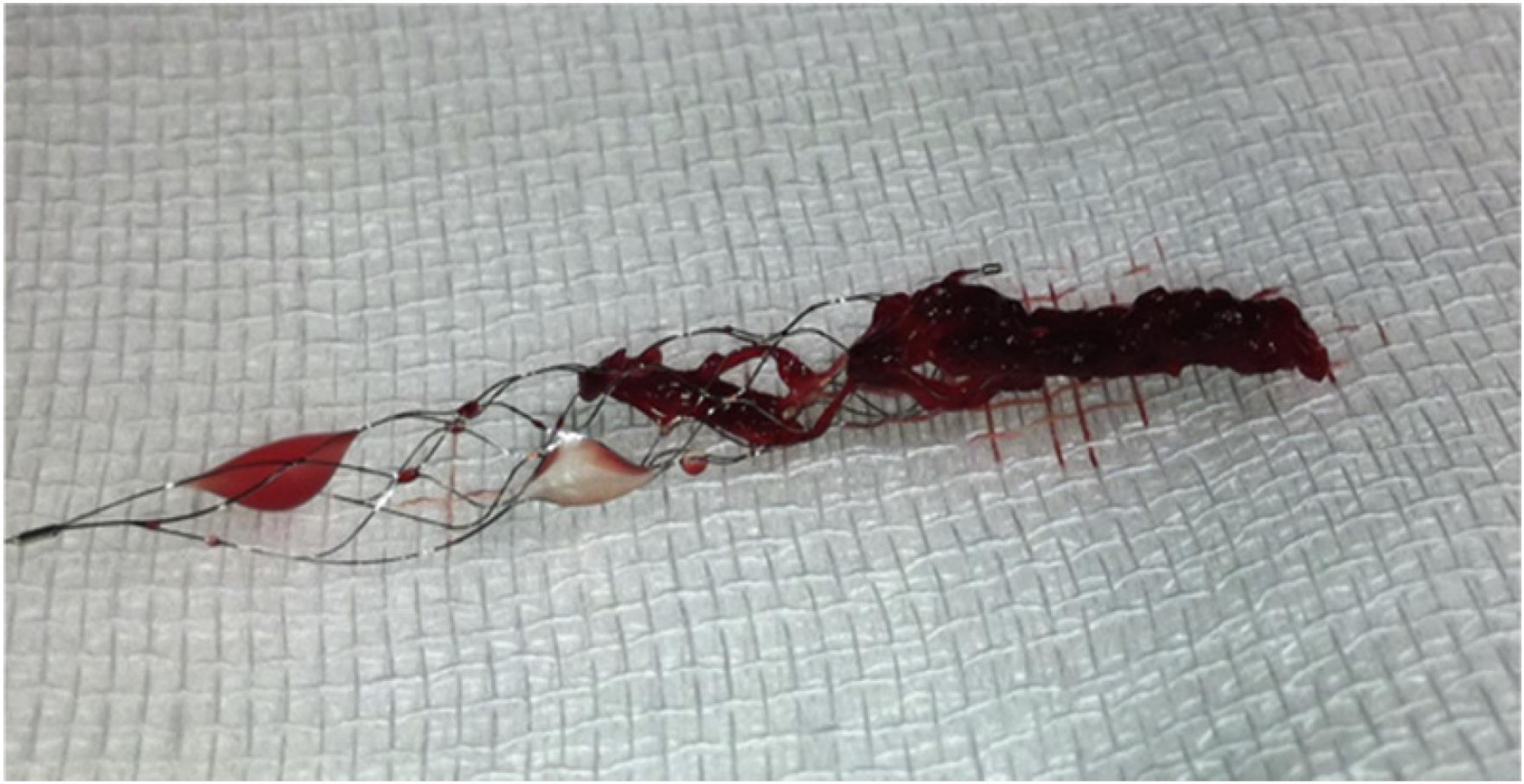

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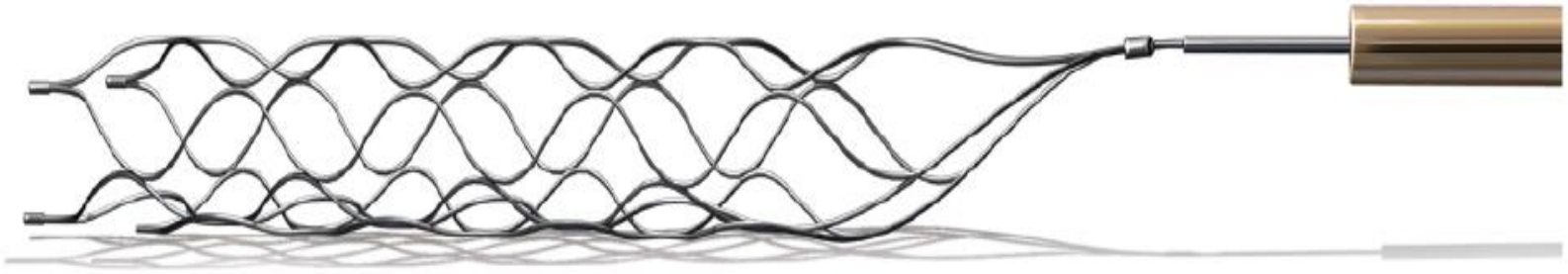

TREVO

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 1, 2015 VOL. 372 NO. 1

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

O.A. Berkhemer, P.S.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J.H. Wermer, M.A.A. van Walderveen, J. Staals, J. Hofmeijer, J.A. van Oostayen, G.J. Lycklama à Nijeholt, J. Boiten, P.A. Brouwer, B.J. Emmer, S.F. de Bruijn, L.C. van Dijk, L.J. Kappelle, R.H. Lo, E.J. van Dijk, J. de Vries, P.L.M. de Kort, W.J.J. van Rooij, J.S.P. van den Berg, B.A.A.M. van Hasselt, L.A.M. Aerden, R.J. Dallinga, M.C. Visser, J.C.J. Bot, P.C. Vroomen, O. Eshghi, T.H.C.M.L. Schreuder, R.J.J. Heijboer, K. Keizer, A.V. Tielbeek, H.M. den Hertog, D.G. Gerrits, R.M. van den Berg-Vos, G.B. Karas, E.W. Steyerberg, H.Z. Flach, H.A. Marquering, M.E.S. Sprengers, S.F.M. Jenniskens, L.F.M. Beenen, R. van den Berg, P.J. Koudstaal, W.H. van Zwam, Y.B.W.E.M. Roos, A. van der Lugt, R.J. van Oostenbrugge, C.B.L.M. Majoie, and D.W.J. Dippel, for the MR CLEAN Investigators*

Key features of MR CLEAN

- Usual care (89% IV tPA) vs endovascular
- Anterior circulation occlusion
- Treatment within 6 hours
- Retrievable stents used in 82%

Key features of MR CLEAN

- On F/U angiography, No Occlusion in 75% of intervention group vs. 33% of controls (OR=6.9, 95% CI 4.3-11).
- Mortality high in both groups, 21-22%
- Functional independence in 36% of the intervention group vs. 19% in controls (OR 2.2, 95% CI 1.4-3.4).

ACE 64

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JAMA | Original Investigation

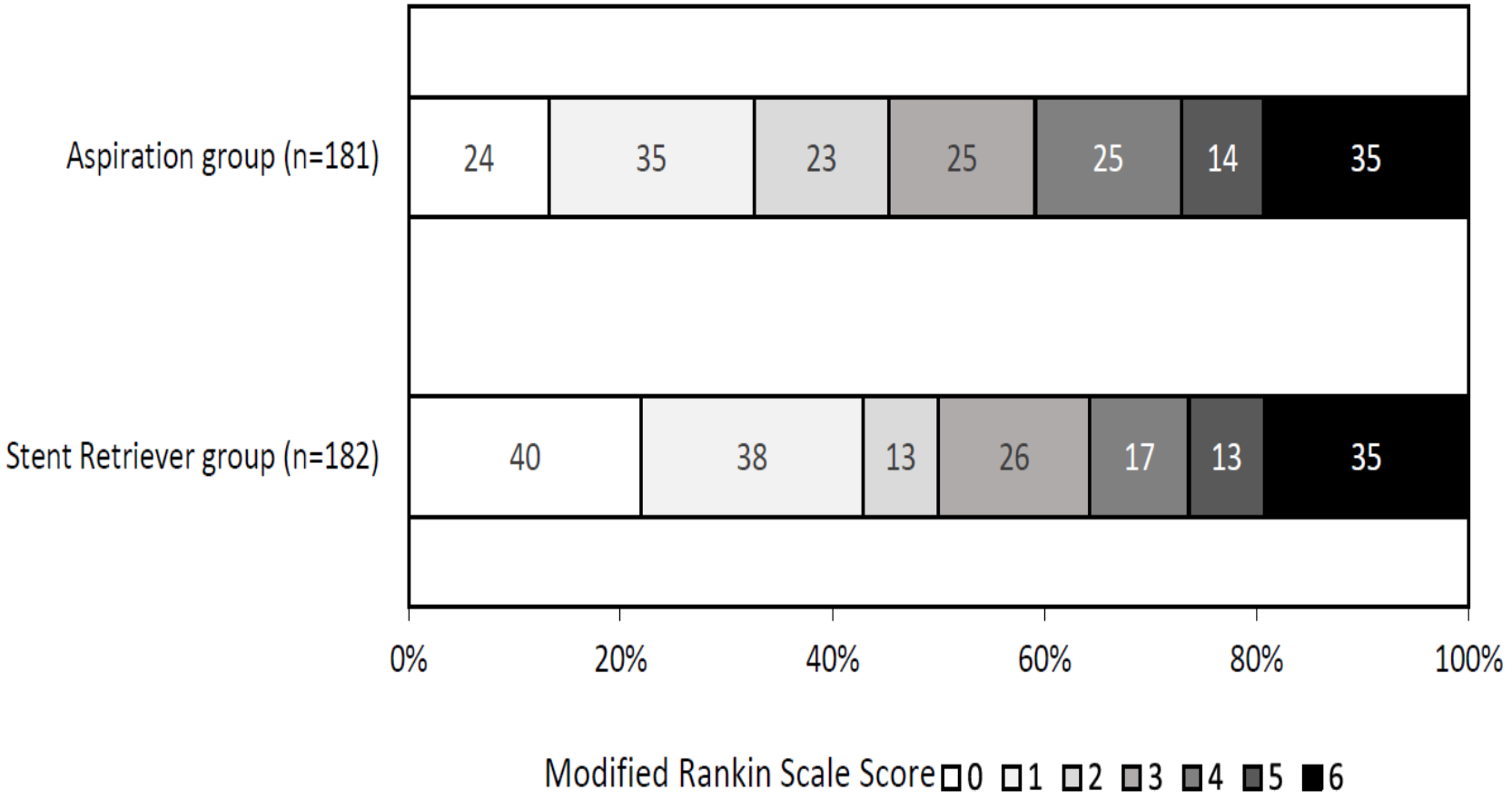
Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion

The ASTER Randomized Clinical Trial

Bertrand Lapergue, MD, PhD; Raphael Blanc, MD, MSc; Benjamin Gory, MD, PhD; Julien Labreuche, BST; Alain Duhamel, PhD; Gautier Marnat, MD; Suzana Saleme, MD; Vincent Costalat, MD, PhD; Serge Bracard, MD; Hubert Desal, MD, PhD; Mikael Mazighi, MD, PhD; Arturo Consoli, MD; Michel Piotin, MD, PhD; for the ASTER Trial Investigators

JAMA. 2017;318(5):443-452. doi:10.1001/jama.2017.9644

Functional Independence 59% vs 78%
p = 0.15



The DAWN Trial

The NEW ENGLAND JOURNAL of MEDICINE

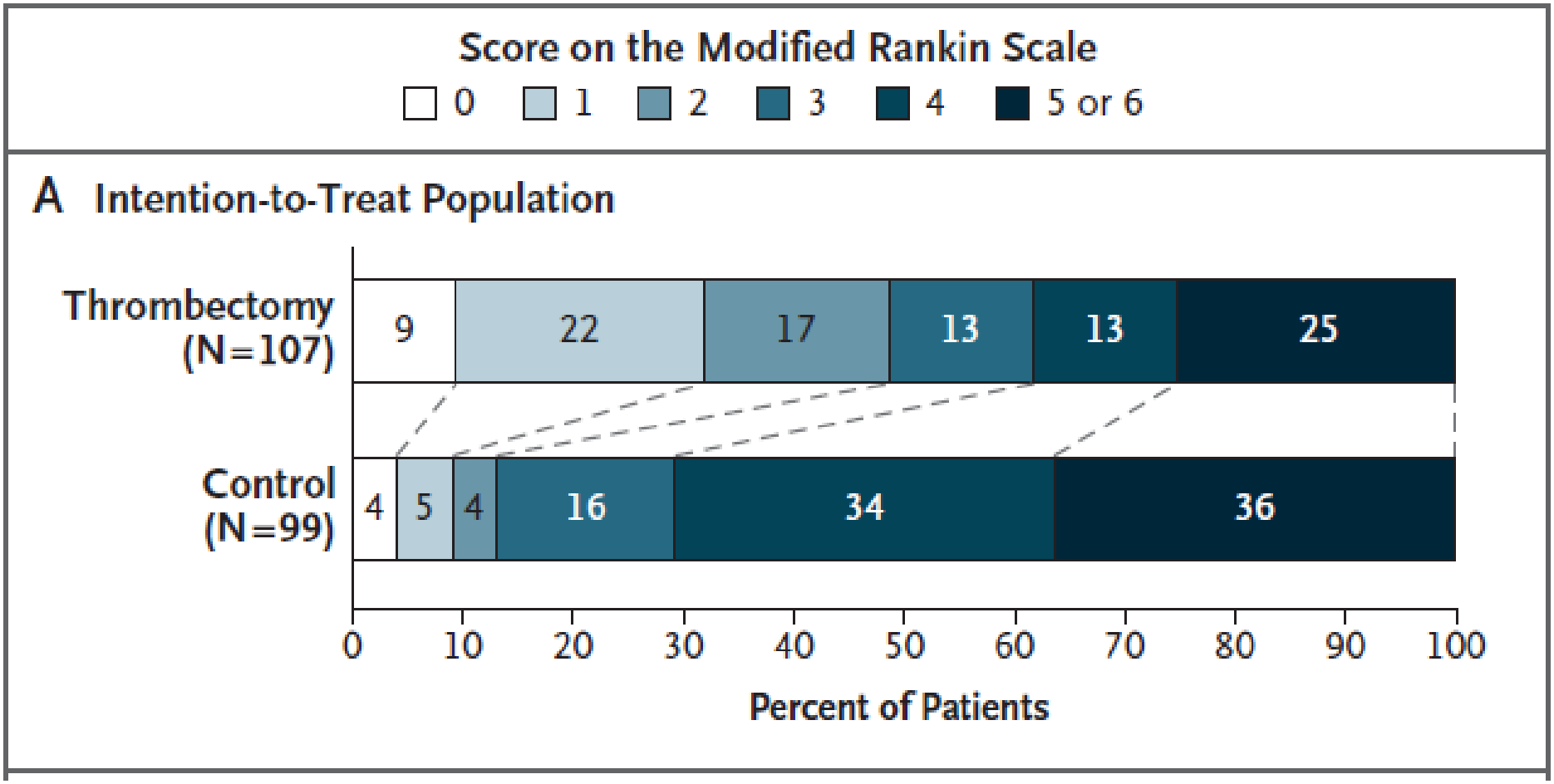
ORIGINAL ARTICLE

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva, D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan, E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira, B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu, F.R. Hellinger, L. Feng, J.F. Kirmani, D.K. Lopes, B.T. Jankowitz, M.R. Frankel, V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik, A.J. Furlan, M. Rubiera, A. Aghaebrahim, J.-M. Olivot, W.G. Tekle, R. Shields, T. Graves, R.J. Lewis, W.S. Smith, D.S. Liebeskind, J.L. Saver, and T.G. Jovin, for the DAWN Trial Investigators*

Key Points

- 206 patients, severe strokes (NIHSS median 17).
- M1 occlusion of middle cerebral artery in 78%.
- Time from last known to be well to randomization 12.2, 13.3 hours.
- Recanalization at 24 hours 77% vs 39%, $p<0.001$.
- Clinical outcomes improved though mortality still high.


Score on the Modified Rankin Scale
0
1
2
3
4
5 or 6
A Intention-to-Treat Population
Thrombectomy (N=107)
9
22
17
13
13
25
Control (N=99)
4
5
4
16
34
36
0
10
20
30
40
50
60
70
80
90
100
Percent of Patients

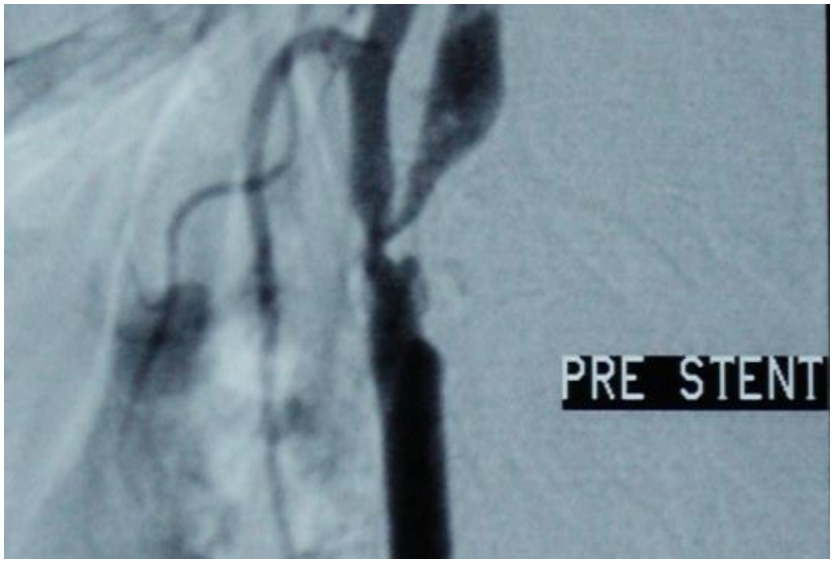
Technology and Logistics

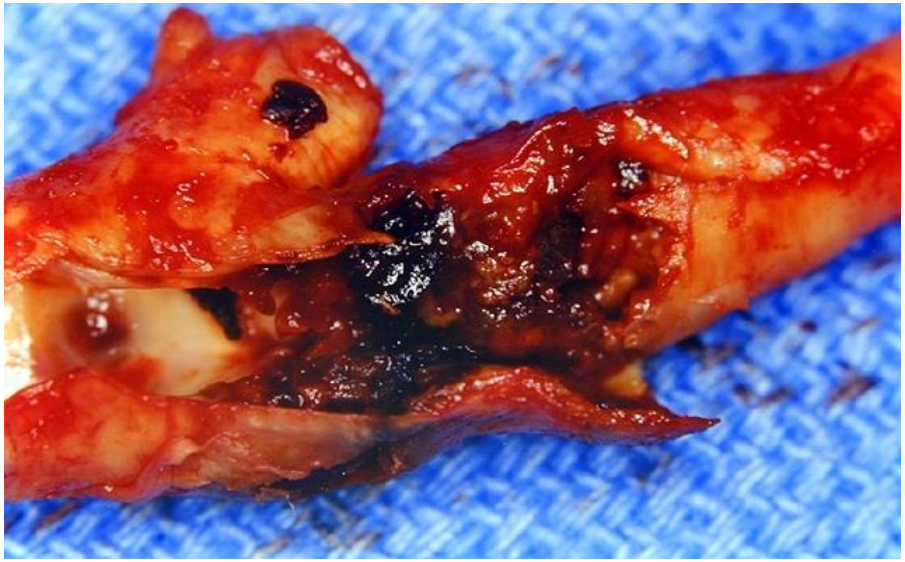
911 Stroke Treatment in 2017

- Emergency evaluation, including perfusion imaging when feasible. Time is Brain!
- Intravenous tPA if large vessel occlusion not seen.
- Endovascular intervention out to 6 hours for large vessel occlusion.
- Endovascular intervention out to 24 hours from onset
  - If mismatch detected, and if large, disabling infarct is not already present on CT.
  - With or without preceding IV alteplase.

Carotid Disease

– Associated with 5-8% of ischemic strokes in 2017, compared to 30% in 1980





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Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High-grade Carotid Stenosis

North American Symptomatic Carotid Endarterectomy Trial Collaborators

N Engl J Med 1991;325:445-53

THE LANCET

MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis

European Carotid Surgery Trialists' Collaborative Group

Lancet 1991;337:1235-43

JAMA Journal of the American Medical Association

Endarterectomy for Asymptomatic Carotid Artery Stenosis

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study

JAMA 1995;273:1421-1428

THE LANCET

Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial

MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group

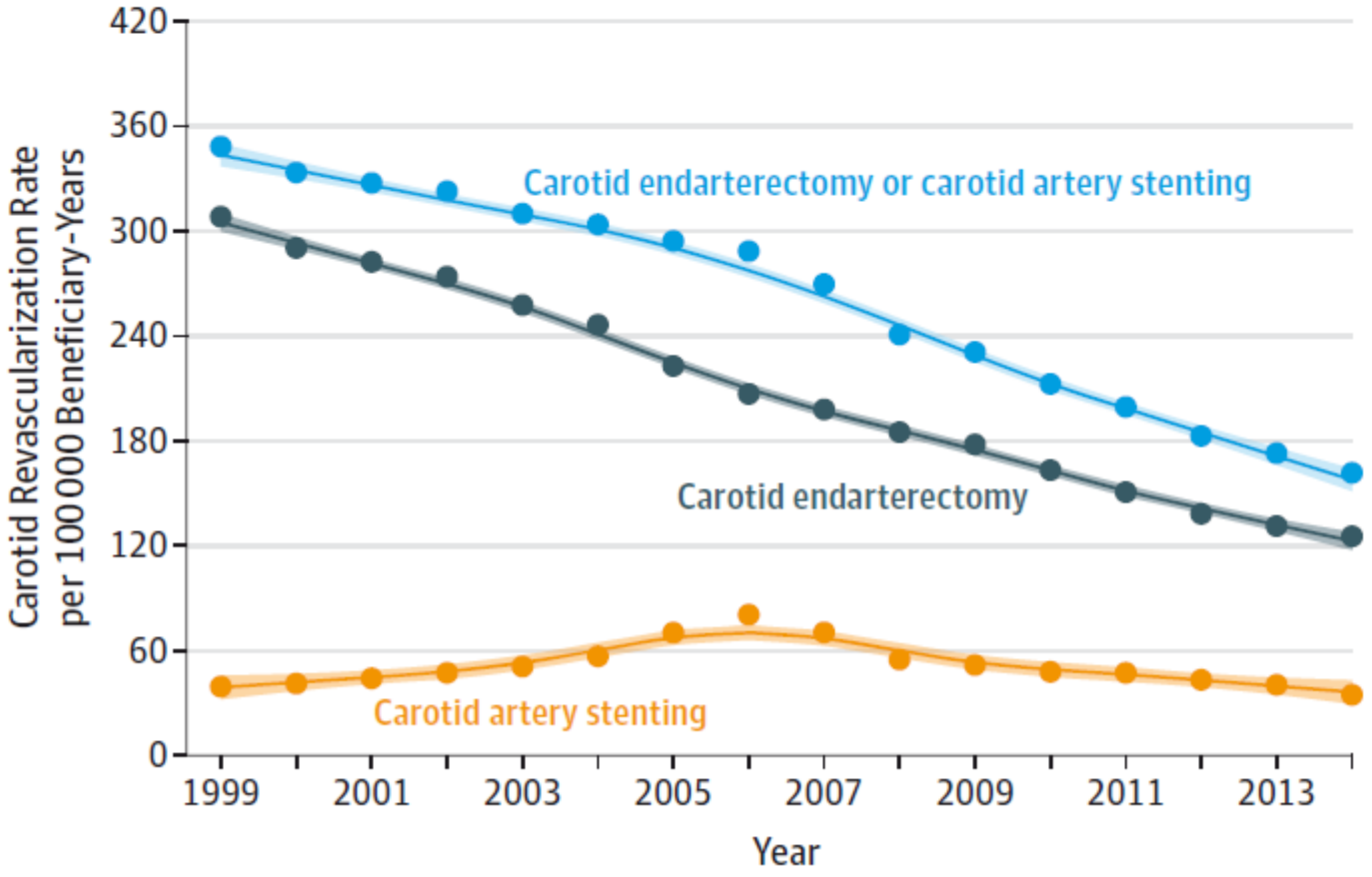
Lancet 2004;363:1491-502

JAMA | Original Investigation

Carotid Endarterectomy and Carotid Artery Stenting in the US Medicare Population, 1999-2014

Judith H. Lichtman, PhD; Michael R. Jones, MD; Erica C. Leifheit, PhD; Alice J. Sheffet, PhD; George Howard, DrPH; Brajesh K. Lal, MD; Virginia J. Howard, PhD; Yun Wang, PhD; Jeptha Curtis, MD; Thomas G. Brott, MD

Figure 1. National Carotid Revascularization Rates per 100 000 Beneficiary-Years From 1999 to 2014



CEA Outcomes

Outcome, % (95% CI)	1999	2014
In-hospital mortality	0.9 (0.9-1.0)	0.4 (0.4-0.5)
30-day stroke or death	1.6 (1.6-1.7)	1.1 (1.1-1.2)

CAS Outcomes

Outcome, % (95% CI)	1999	2014
In-hospital mortality	2.8 (2.6-3.0)	2.3 (2.1-2.5)
30-day stroke or death	4.7 (4.5-5.0)	4.8 (4.5-5.1)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

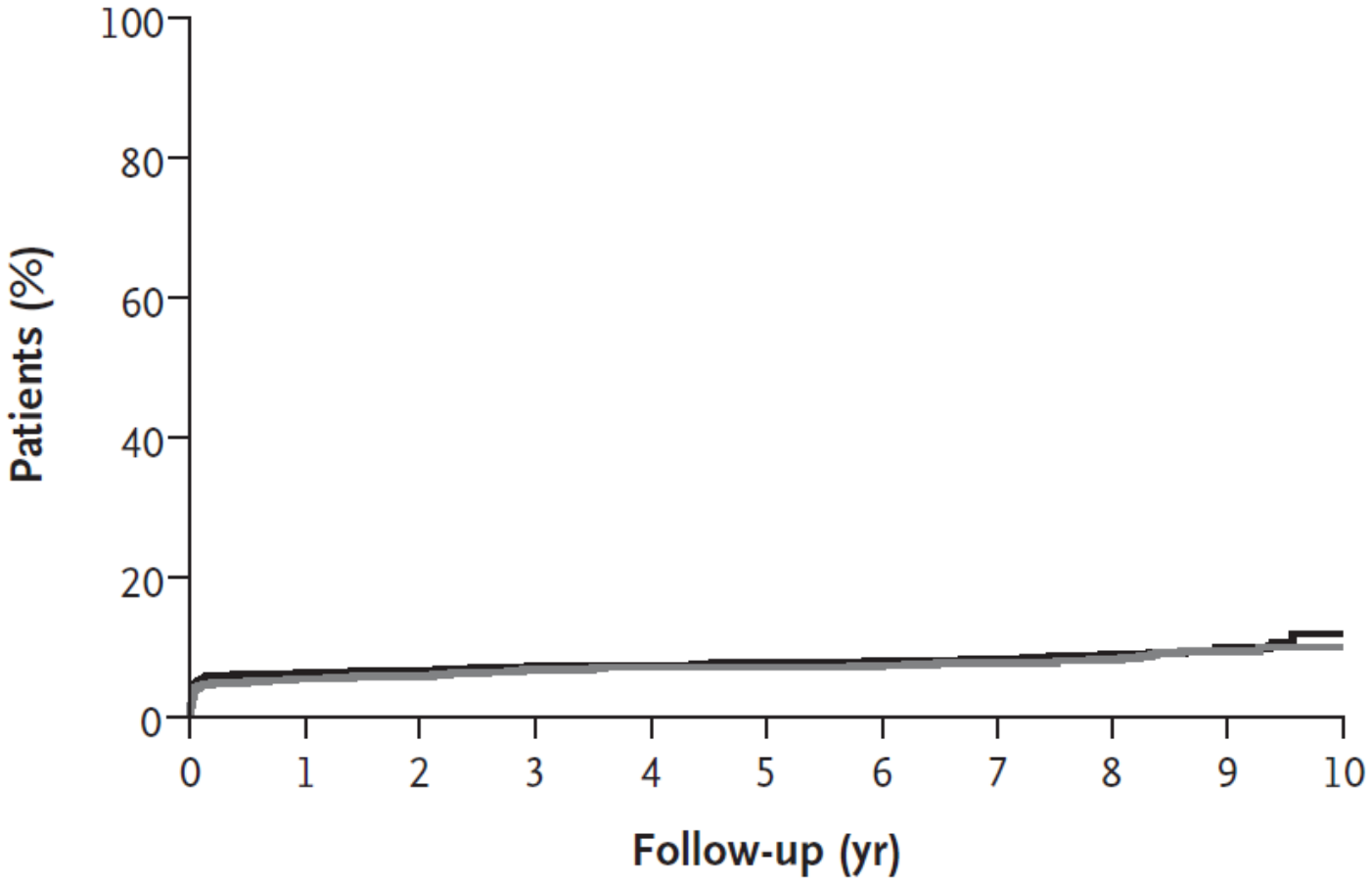
Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis

Thomas G. Brott, M.D., George Howard, Dr.P.H., Gary S. Roubin, M.D., Ph.D., James F. Meschia, M.D., Ariane Mackey, M.D., William Brooks, M.D., Wesley S. Moore, M.D., Michael D. Hill, M.D., Vito A. Mantese, M.D., Wayne M. Clark, M.D., Carlos H. Timaran, M.D., Donald Heck, M.D., Pierre P. Leimgruber, M.D., Alice J. Sheffet, Ph.D., Virginia J. Howard, Ph.D., Seemant Chaturvedi, M.D., Brajesh K. Lal, M.D., Jenifer H. Voeks, Ph.D., and Robert W. Hobson II, M.D.,* for the CREST Investigators†

Background

- 2502 symptomatic and asymptomatic patients randomized to CEA or CAS.
- ≥ 70% carotid stenosis.

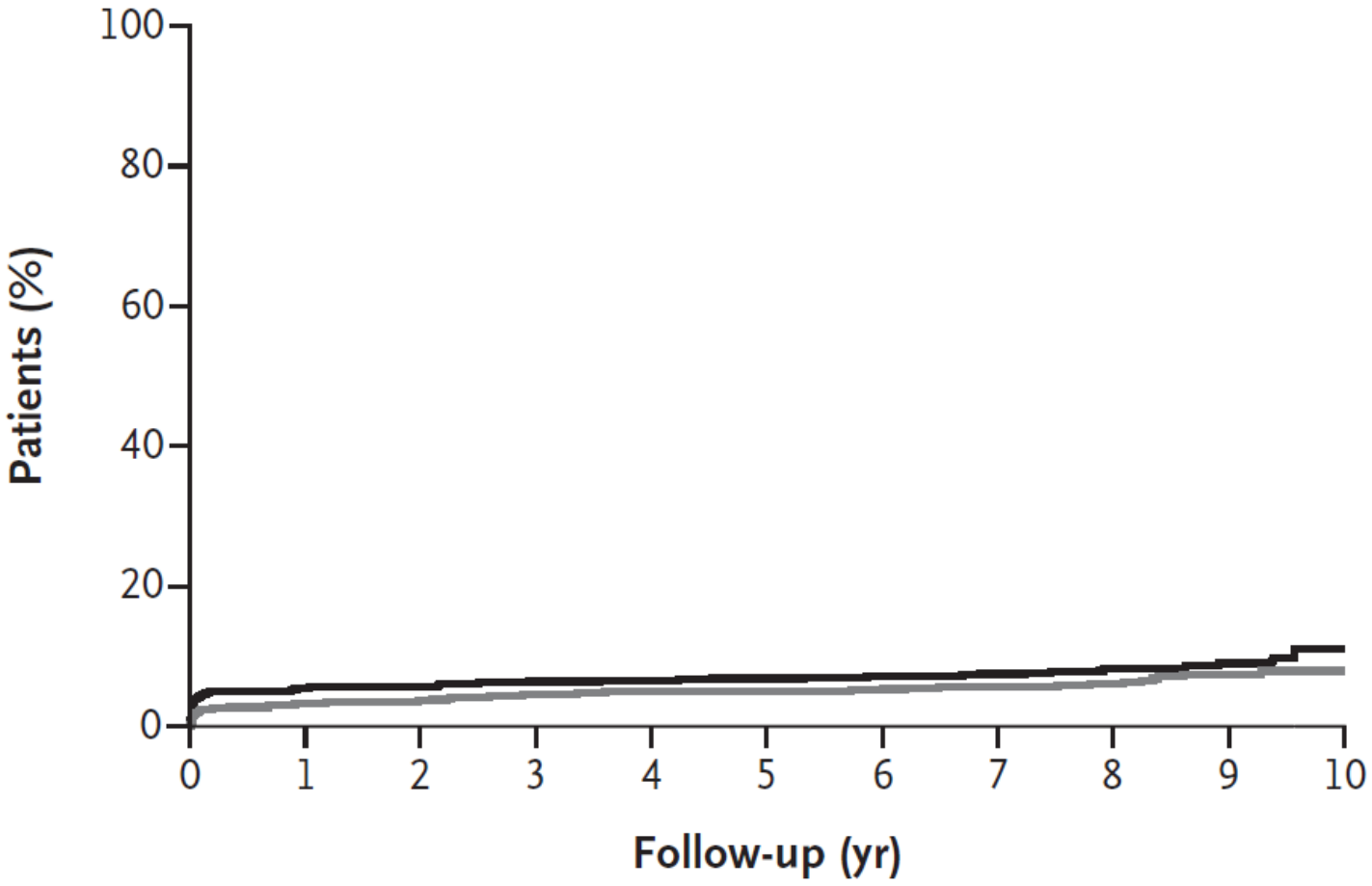
Primary Composite End Point



No. at Risk

Endarterectomy	1240	1104	1036	949	833	736	695	620	438	243	66
Stenting	1262	1103	1041	972	884	774	738	676	477	264	68

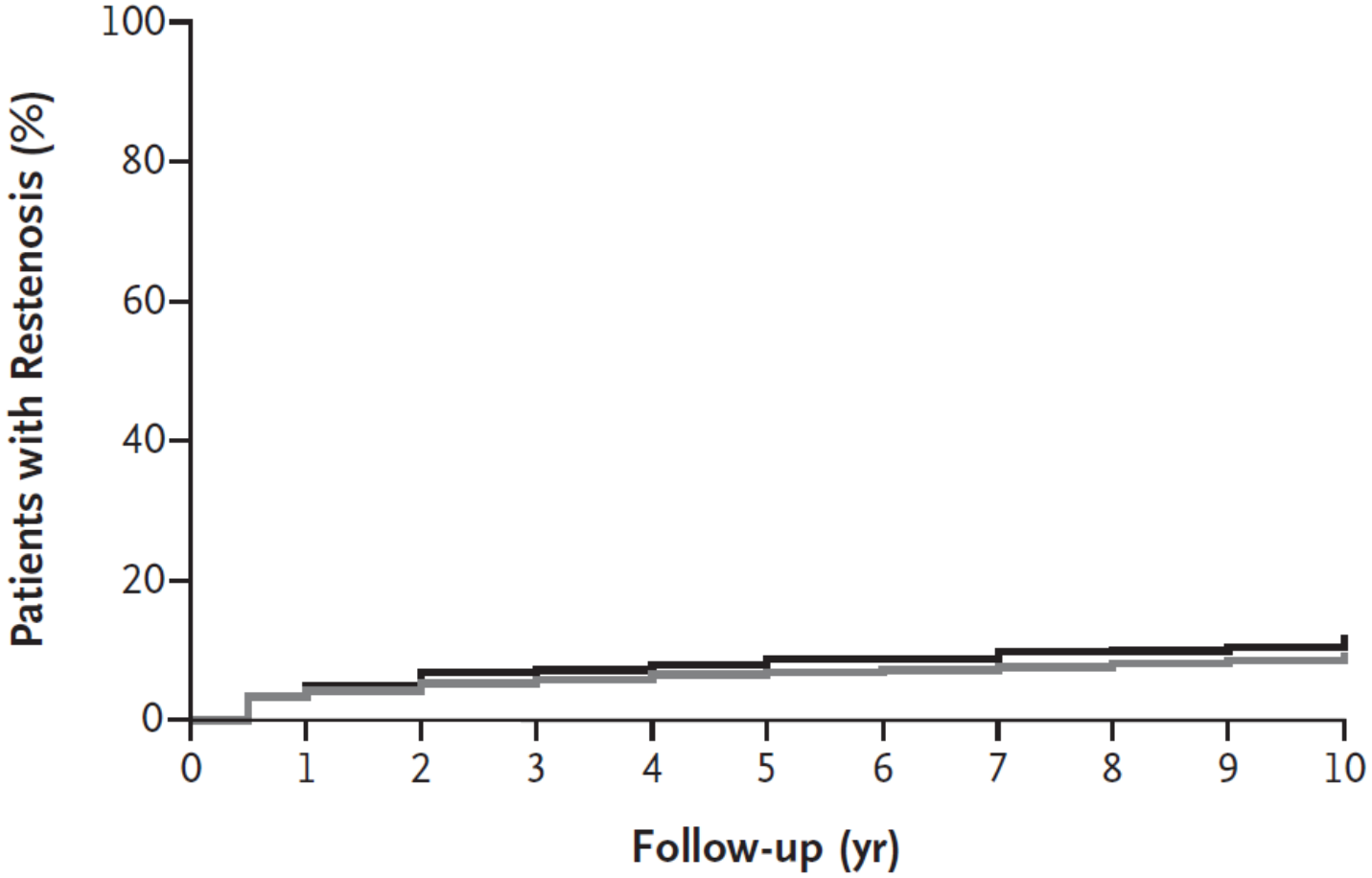
Stroke or Death



No. at Risk

Endarterectomy	1240	1127	1056	967	848	744	703	624	442	245	67
Stenting	1262	1111	1049	979	889	777	741	679	479	265	68

Estimated Rate of Restenosis



No. at Risk

Endarterectomy	1014	939	849	750	654	558	514	460	334	197	89
Stenting	1018	948	849	762	684	606	557	494	366	207	101

Postprocedural Long-term Stroke

		# Events	5 year %	10 year %
Asymptomatic	**CAS**	21	2.5	6.9
	CEA	20	2.7	5.6
Symptomatic	**CAS**	21	2.5	6.9
	CEA	21	2.7	5.6

Conclusions

- CAS and CEA are safe and durable
- Post-procedure, the rates of stroke are very low, less than 0.7% annually for asymptomatic and symptomatic patients.
- Restenosis is infrequent over 10 years, About 1% per year.

Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials

George Howard, Gary S Roubin, Olav Jansen, Jeroen Hendrikse Alison Halliday, Gustav Fraedrich, Hans-Henning Eckstein, David Calvet, Richard Bulbulia, Leo H Bonati, Jean-Pierre Becquemin, Ale Algra, Martin M Brown, Peter A Ringleb, Thomas G Brott, Jean-Louis Mas, on behalf of the Carotid Stenting Trialists' Collaboration

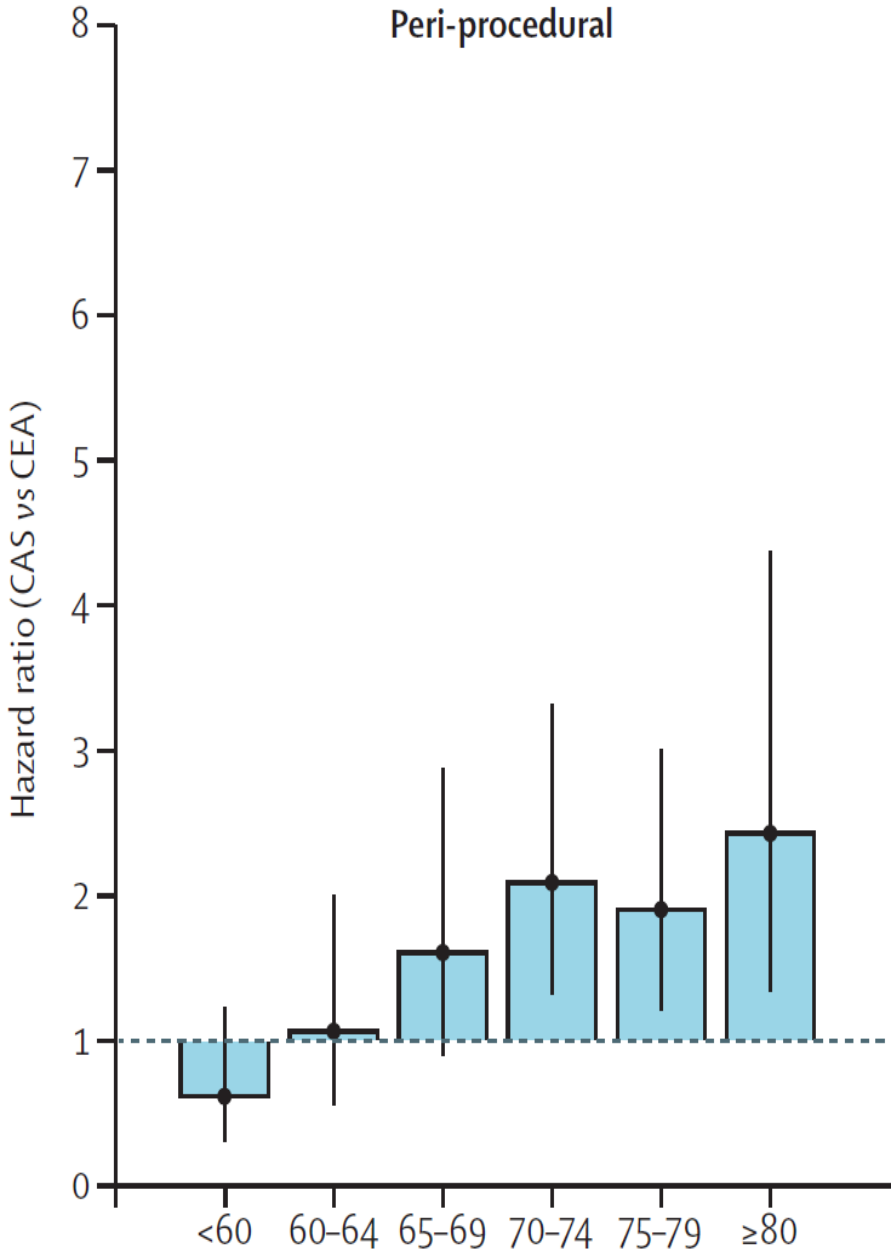


Figure 4: CAS versus CEA hazard ratio for events by age group

Symptomatic patients in 2017

- Endarterectomy or stenting for symptomatic patients with high degree of stenosis.
- CEA favored over Carotid Stenting for older symptomatics except possibly
  - For those age > 75 who have do not have tortuosity and
  - Who do not have evidence of lower “cerebral reserve” (excess white matter disease or silent infarcts by MRI, or known poor collaterals by imaging)

Asymptomatic patients in 2017

- Evidence for equipoise for stenting, surgery, and intensive medical management
- Guidelines favor CEA for stenosis >= 70%
- AHA/ACC Guidelines include Carotid Stenting as an acceptable alternative to CEA

The NEW ENGLAND JOURNAL of MEDICINE

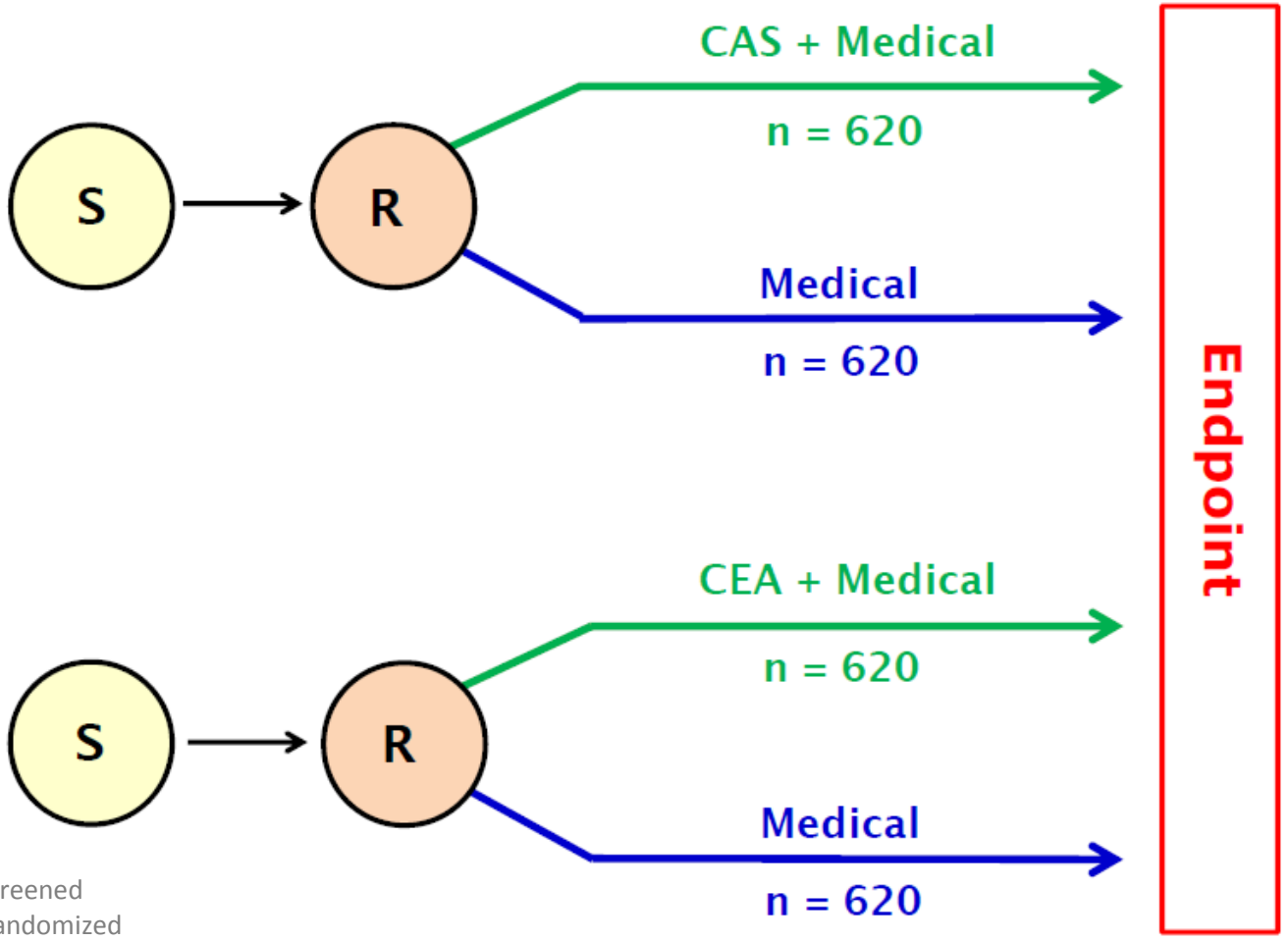
ESTABLISHED IN 1812 MARCH 17, 2016 VOL. 374 NO. 11

Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis

Kenneth Rosenfield, M.D., M.H.C.D.S., Jon S. Matsumura, M.D., Seemant Chaturvedi, M.D., Tom Riles, M.D., Gary M. Ansel, M.D., D. Chris Metzger, M.D., Lawrence Wechsler, M.D., Michael R. Jaff, D.O., and William Gray, M.D., for the ACT I Investigators*

www.crest2trial.org

CREST-2 Parallel Study Design



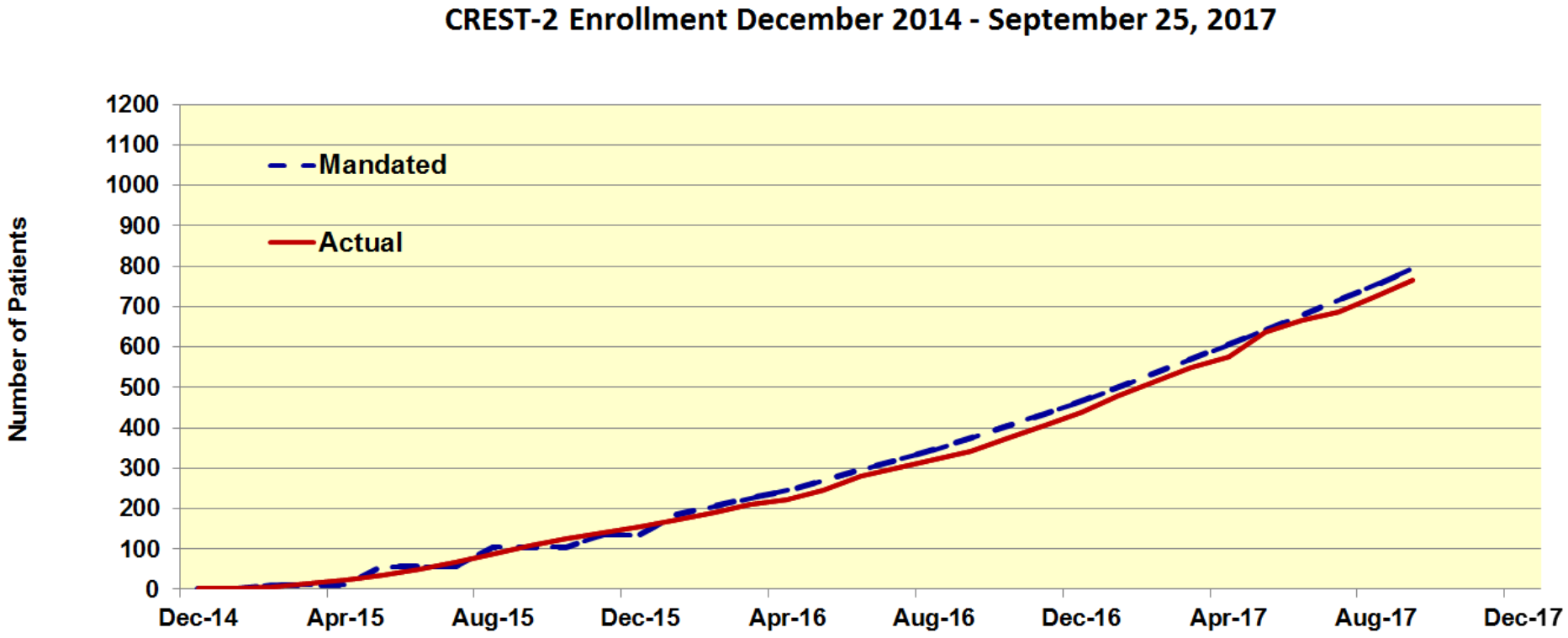
Endpoint = all stroke & death in first 30 days and ipsilateral stroke thereafter up to 4 years.

Primary Aims

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

- The treatment differences between intensive medical management and CEA
- The treatment differences between intensive medical management and CAS

Primary endpoint: any periprocedural stroke or death or ipsilateral ischemic stroke thereafter up to 4 years.


CREST-2 Enrollment December 2014 - September 25, 2017
Number of Patients
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Mandated
Actual
Dec-14
Apr-15
Aug-15
Dec-15
Apr-16
Aug-16
Dec-16
Apr-17
Aug-17
Dec-17

ACST-2 Time Line

Nov 2017	>2700 randomized
Dec 2019	Randomize 900 more patients
	Median follow-up of 5 years
Mid 2021	**ACST-2 report 5-year results**
	Procedural risks and early benefits
	IPD: CREST-1, ACT-1 + SPACE-2 (n=6000)
Mid 2025	**ACST-2 10-year results**
	Reliably compare durability of CEA vs CAS

Will ACST-2 be outdated?

ECST-2 Progress

- 32 centers enrolled
- 285 patients randomized to 15 Nov 2017
  - Number needed for MRI-based study = 320 with 2 years follow-up
- 110 included with MR plaque imaging
  - Number needed for MR plaque imaging analysis = 244 with 2 years follow-up
- New centers needed
- Please contact us on office@ecst2.com or via the website www.ecst2.com


Thanks for your attention