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MULTIDISCIPLINARY EUROPEAN
ENDOVASCULAR THERAPY

Best Medical has improved: but how much and will BMT be good enough to replace repair?

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Disclosure

Isabelle Van Herzeele has the following potential conflicts of interest to report:

☑ Consulting

Silk Road Medical, Sunnyvale, CA, USA

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Medtronic Academia, Tolochenaz, Swiss

Silk Road Medical, Sunnyvale, CA, USA

Why is the management of asymptomatic carotid disease so controversial?

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A. Ross Naylor *

Who Benefits Most from Intervention for Asymptomatic Carotid Stenosis: Patients or Professionals?

A.R. Naylor [a,*], P.A. Gaines [b], P.M. Rothwell [c]

From the Editors

The Story of Anybody, Somebody, Nobody and Everybody

A.R. Naylor, MD [a,*], J.-B. Ricco, MD, PhD [b]

Carotid Intervention Is It Warranted in Asymptomatic Individuals if Risk Factors Are Aggressively Managed?

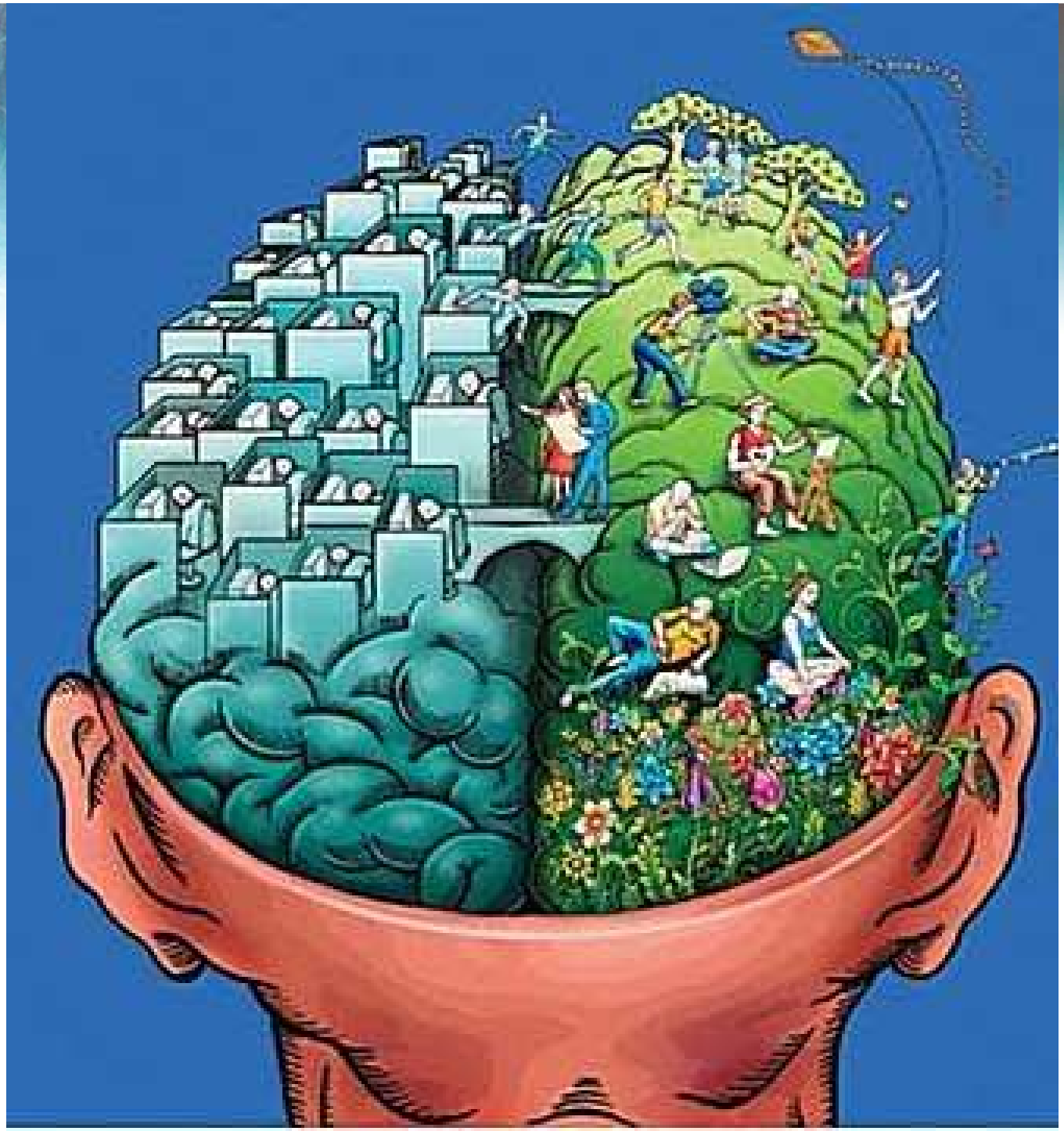
Katherine Pahigiannis, PhD;
Petra Kaufmann, MD; Walter Koroshetz, MD

Carotid Stenting—Why Treating an Artery May Not Treat the Patient

Mark J. Alberts, MD

Revascularization of asymptomatic carotid stenosis is not appropriate in patients on dialysis

Theodore H. Yuo, MD, MS, Joseph Sidaoui, MD, Luke K. Marone, MD, Michel S. Makaroun, MD, and Rabih A. Chaer, MD, MS, *Pittsburgh, Pa*



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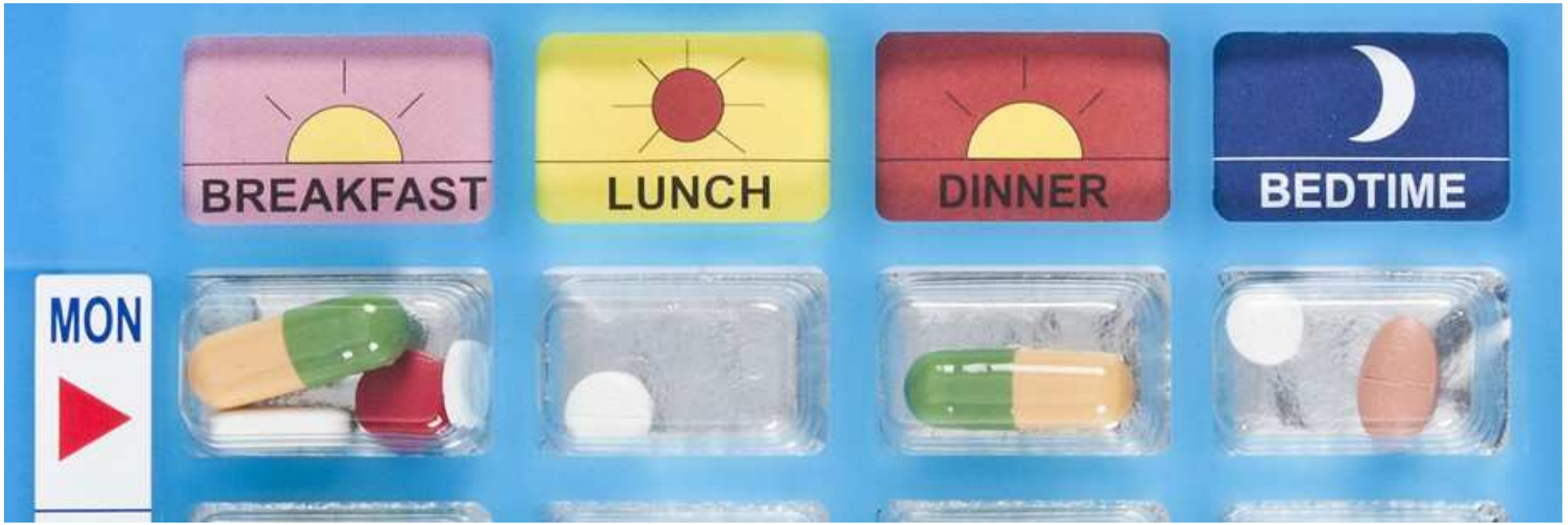
BEST MEDICAL TREATMENT?



ANTIPLATELETS

Symptomatic carotid disease

- Antiplatelet Trialists Collaboration

  ASA (75-150 mg) ***20-25% RR reduction of tromboembolic stroke***

  BMJ 2002; 324: 71-86
- CARESS ASA + clopidogrel ↓ microemboli
  Circulation 2005; 111: 2233-40
- CHANCE ASA + clopidogrel for 21 days after initial TIA
  - N= 5170 – China
  - Stroke 8.2% vs. 11.7% - HR 0.68 95% CI 0.57-0.81
    NEJM 2013; 369: 11-9
- + clopidogrel – day before surgery ↓ microemboli
  Circulation 2004; 109: 1476-81
- ASA +dipyridamole, clopidogrel, trifusal …
  Stroke 2008; 39: 1638-46, Lancet 2006; 367: 1665-73

Disease	Treatment	RRR %	ARR % per year	NNT to avoid 1 event per year
Non-cardioembolic ischaemic stroke or TIA	aspirin / PCB	13	1.0	100
	aspirin + DIP / PCB	28	1.9	53
	aspirin + DIP / aspirin	18	1.0	104
	Clop / PCB	23	1.6	62
	Clop / aspirin	10	0.6	166
Atrial fibrillation (primary prevention)	warfarin / PCB	62	2.7	37
	aspirin / PCB	22	1.5	67
Atrial fibrillation (secondary prevention)	warfarin / PCB	67	8	13
	aspirin / PCB	21	2.5	40

ESO Guidelines 2008

ANTIPLATELETS

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Asymptomatic carotid stenosis

- Meta-analysis : ↓ coronary or cardiovasc events – no reduction in stroke
  Ann Intern Med 1995: 123: 649-55
- US Preventive Task Force - ASA in high risk patients ≥ 3% per 5 years
  Stroke 2011; 42: 517-84
- CHARISMA
  - ASA vs. ASA + clopidogrel – ***no*** benefit in asympt carotid artery disease (>70%)

INTENSIVE STATIN THERAPY

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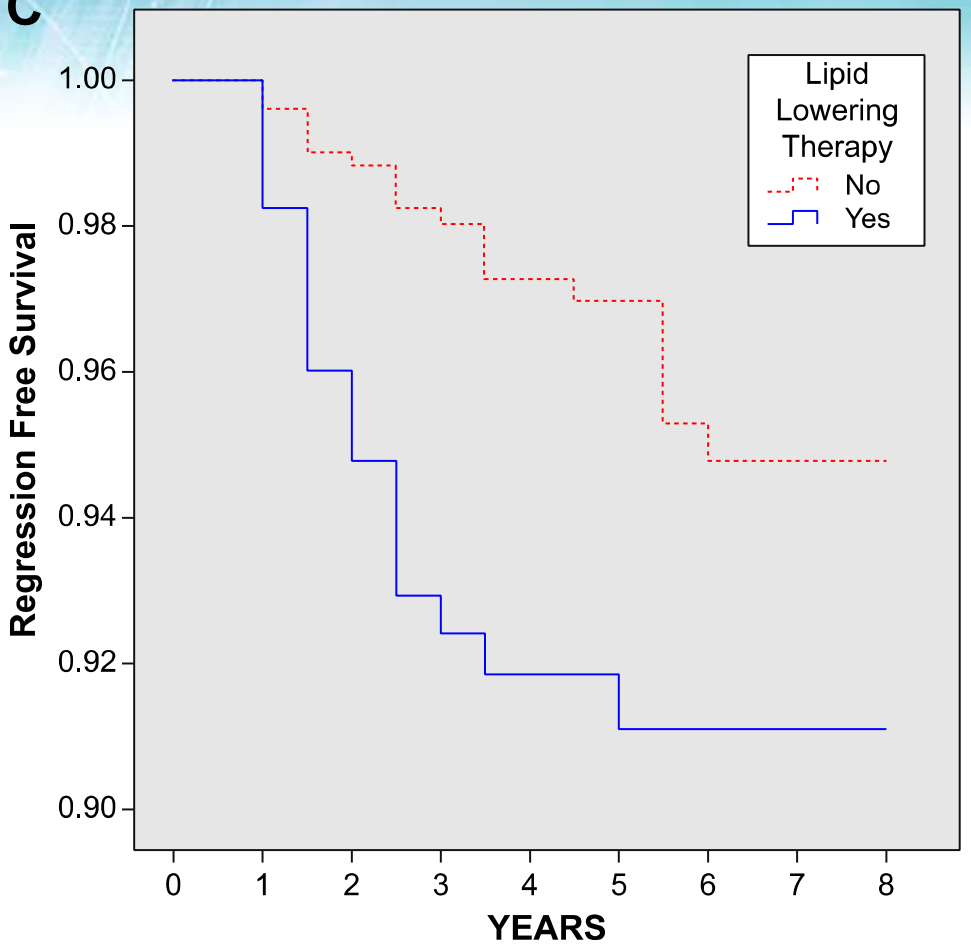
- **Heart Protection Study** Simvastatin 40 mg OD vs. placebo
  Lancet 2002; 360: 7-22
  - All patients N= 20 536 (CHD, TIA/Stroke, CEA)
  - 25% reduction in stroke, 30% reduction in ischemic stroke
- **SPARCL trial** Atorvastatin 80 mg OD or placebo
  NEJM 2006; 355: 549-59
  - N= 4731 (recent stroke or TIA < 6 months)
  - 33% reduction in any stroke

  Stroke 2008; 39: 3297-302
  - N= 1007 (known carotid stenosis) –***ARR of stroke = 1% per year –*** NNT= 20 over 5 years
- Meta-analysis
  Each 10% reduction in LDL chol – reduction stroke risk by 15.6%
  J Vasc Surg 2007; 46: 373-86
- Intensive statin treatment + ***Ezetimibe - reduction in plaque area***
  Stroke 2012; 43: 1153-55

  to be confirmed by ***IMPROVE-IT trial***

ACSRS Study: Impact of statins

C



Numbers at risk				
Lipid lowering therapy				
No	704	420	262	117
Yes	276	175	112	56

J Vasc Surg 2014; 59: 956-67

Best Medical Treatment

- ***Medical***
  - DIABETIC CONTROL – no significant stroke reduction
    - UK prospective diabetic study *Circulation 1999; 99: 461-2*
    - ACCORD *NEJM 2008; 358: 2545-59*
    - ADVANCE *NEJM 2008; 358: 2560-72*

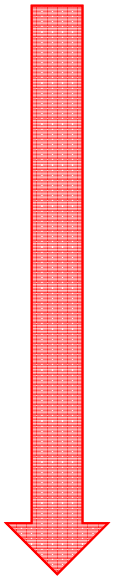
  - ANTI-HYPERTENSIVES ***30-40% reduction in stroke***
    - PROGRESS perindopril (TIA/Stroke) 30% stroke reduction *Lancet.* 2001;358:1033–41
    - ***Ideal antihypertensive agent ???***
      Thiazides, ACE inhibitors, beta-blockers
      HOPE, CAPPP, PATS, LIFE, ALLHAT, Veterans Administration Cooperation Study Group Trial
- ***Life style***
  - Smoking cessation *smoking doubles risk of ischemic stroke*
    BMJ 1989; 298: 789-94
  - Lifestyle modification
    - Moderate exercise
    - Mediterranean Diet (healthy incl. fish, fruit, vegetables, fibers)
      Northern Manhattan Study – ↓ composite outcome of ischemic stroke, MI and vascular death
      Am J Clin Nutr 2011; 94: 1458-64

Clinical condition	Treatment	RRR %	ARR % per year	NNT to avoid 1 event per year
General population with increased blood pressure	Antihypertensive	42	0.4	250
General population with increased vascular risk	ACE-Inhibitor	22	0.65	154
Post-stroke / TIA with increased blood pressure	Antihypertensive	31	2.2	45
Post-stroke / TIA with normal blood pressure	ACE-inhibitor ± diuretic	24	0.85	118
Post-stroke / TIA	Statins	16	0.44	230
	Smoking cessation	33	2.3	43

ESO Guidelines 2008

IMPROVEMENT OF BMT

TRIAL	year published	study years	5 year rate of 'any' stroke	5 year rate of 'ipsilateral' stroke
ACAS	1995	1-5	17.5% (3.5%pa)	11.0% (2.2%pa)
ACST	2004	1-5	11.8% (2.4%pa)	5.3% (1.1%pa)
ACST	2010	6-10	7.2% (1.4% pa)	3.6% (0.7%pa)



EJVES 2009; 37: 625-32
The Surgeon 2015; 34-43

Changes in risk factor profile of patients recruited to carotid endarterectomy trials over 20 years

Risk factor	ECST (1988-1994)	ICSS (2001-2008)	
Current smoker	53%	23%	P<0.05
Mean cholesterol	6.4 mmol/L	5.3 mmol/L	P<0.005

	30-day death/stroke after CEA	Stroke Rate including 30-day death/stroke		strokes prevented per 1000 CEAs	unnecessary CEAs per 1000 CEAs
		CEA	BMT		
ACAS[11] 5 yrs	2.3%	5.1%	11.0%	59@5y	941 (94%)
	Modeled at 0.0%*	2.8%	11.0%	82@5y	918 (92%)
ACST[12] 5 yrs	2.8%	6.4%	11.8%	53@5y	947 (95%)
	Modeled at 0.0%*	3.5%	11.8%	83@5y	917 (92%)
ACST[13] 10 yrs	2.8%	13.4%	17.9%	46@10y	954 (95%)
	Modeled at 0.0%*	10.5%	17.9%	74@10y	926 (93%)

The benefits were calculated using the procedural risks observed in the constituent trial. They were then remodelled assuming a 0% procedural risk to see whether this significantly increased the number of strokes prevented.

The Surgeon 2015; 34-43

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BMT GOOD ENOUGH TO REPLACE REPAIR (CEA OR CAS)?

TIMELY INITIATION OF BMT

Symptomatic disease

EXPRESS study = Effect of urgent treatment of TIA and minor stroke on early recurrent stroke

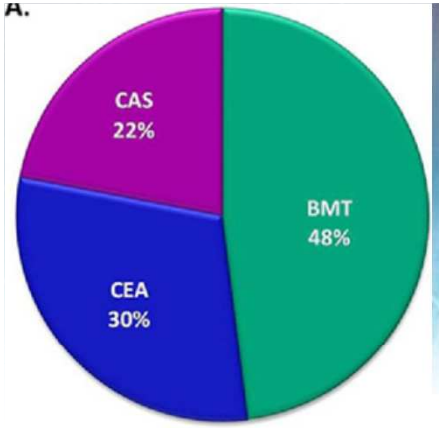
- GP initiates BMT

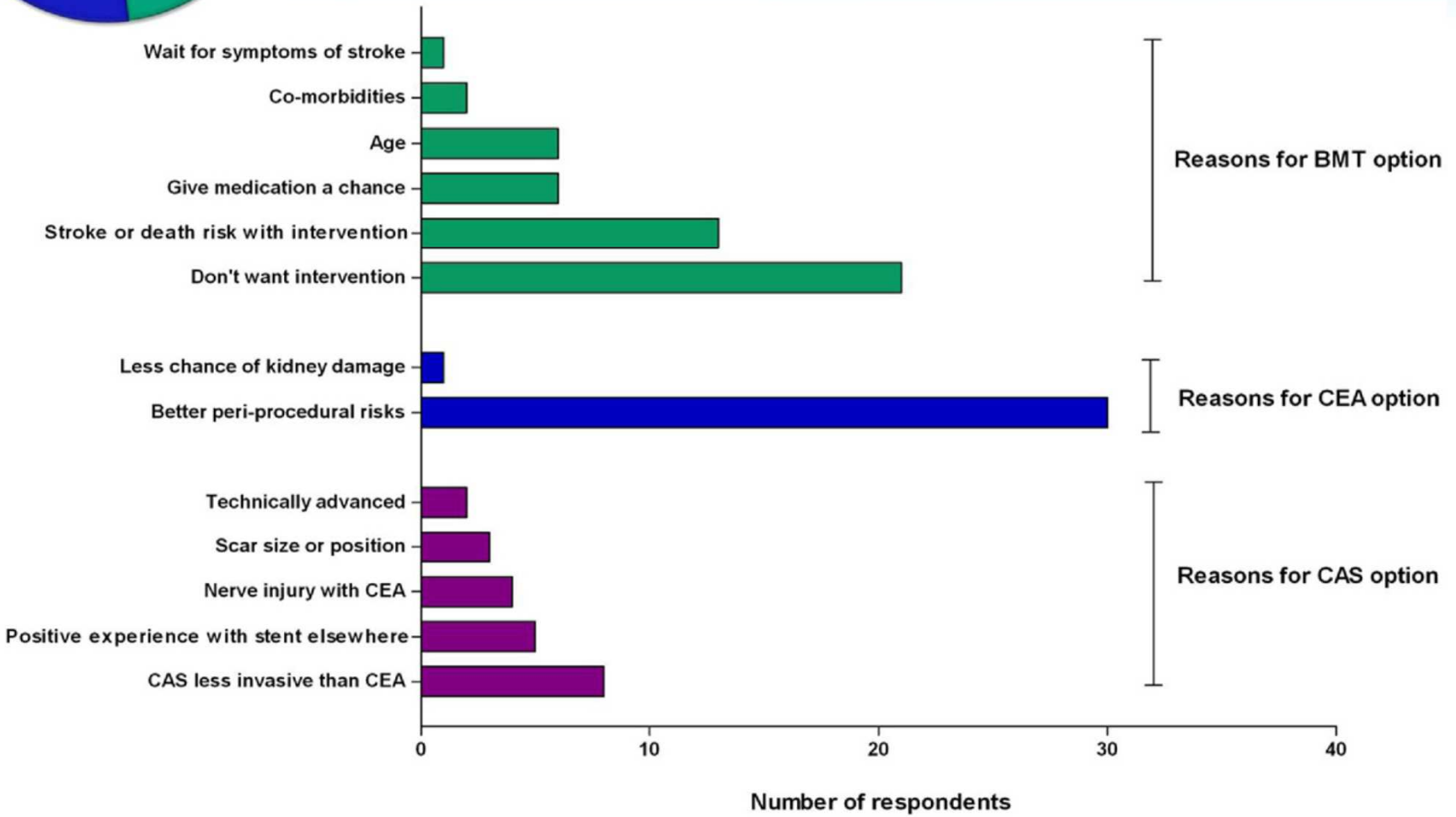
versus

- Outpatient clinic – BMT initiated
- 10% vs. 2% (p= 0.0001) risk of stroke within 90 days

Lancet 2007; 370: 1432-42

WHAT DOES THE PATIENT WANT?





J Vasc Surg 2011; 53: 1466-72

PATIENT COMPLIANCE

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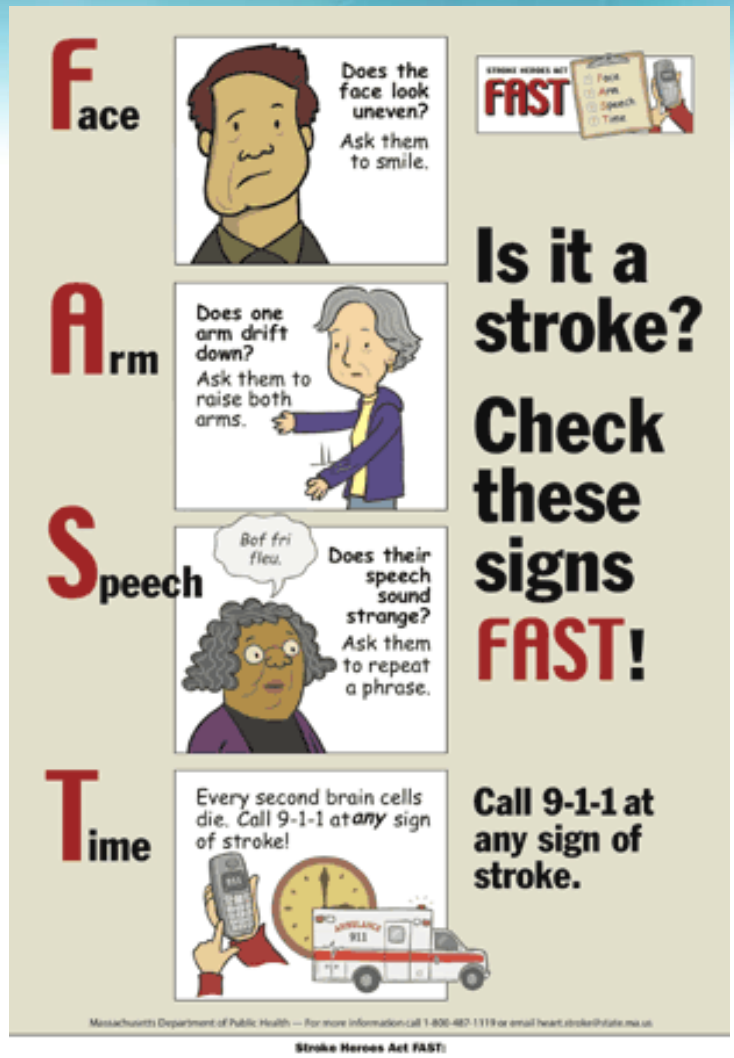
- 50% - 80%
  - Forgetfulness
  - Being away from home
  - Drug shortage

  Arch Pharm Res 2011; 34: 1143-52

  EJVES 2015; 49: 366-74
- Better compliance in acute than in chronic conditions

  NEJM 2005; 353: 487-97
- Patient Education
- In clinical trials 43- 78%
  - More access to clinicians



BMT in ACST II

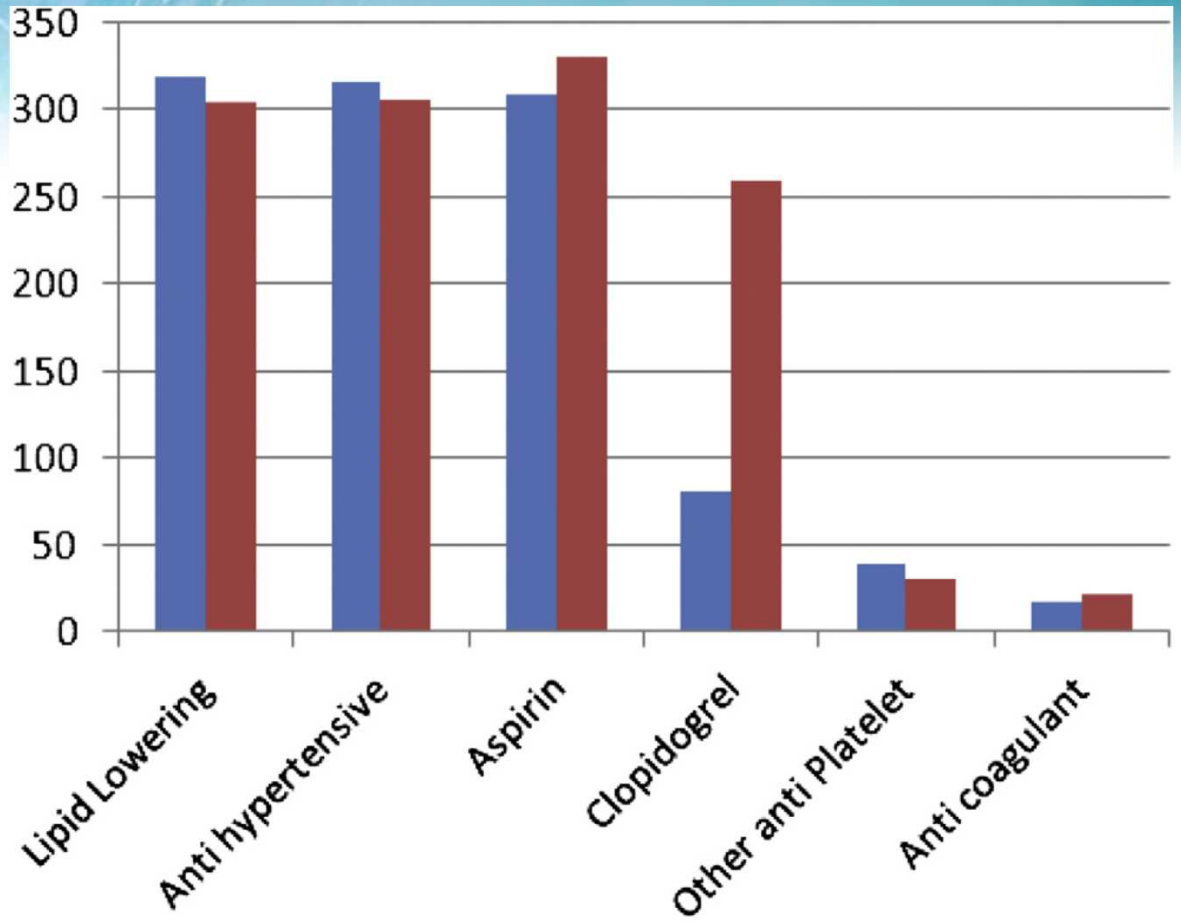


Figure 1. Current therapy at 1-month follow-up. Blue = carotid endarterectomy; red = carotid artery stenting.

EJVES 2014; 46 (5): 500-18

WHAT HAPPENS AROUND THE WORLD?

Treatment of asymptomatic significant carotid artery stenosis

- USA 90%
- Italy 70%
- Hungary and Switzerland 40%
- UK, Finland, Sweden and Norway 15-20%
- Denmark 0%

J Vasc Surg 2008; 48: 1442-50

EJVES 2012; 44: 11-7

*…. Enthusiasm of revascularization is driven by the worst nightmare of clinicians that a patient with a known carotid artery stenosis on BMT experiences a disabling stroke and that "**they should have done more**"…*

STOP !!!

Mortality Risk after CAS

among Medicare Beneficiaries

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Original Investigation

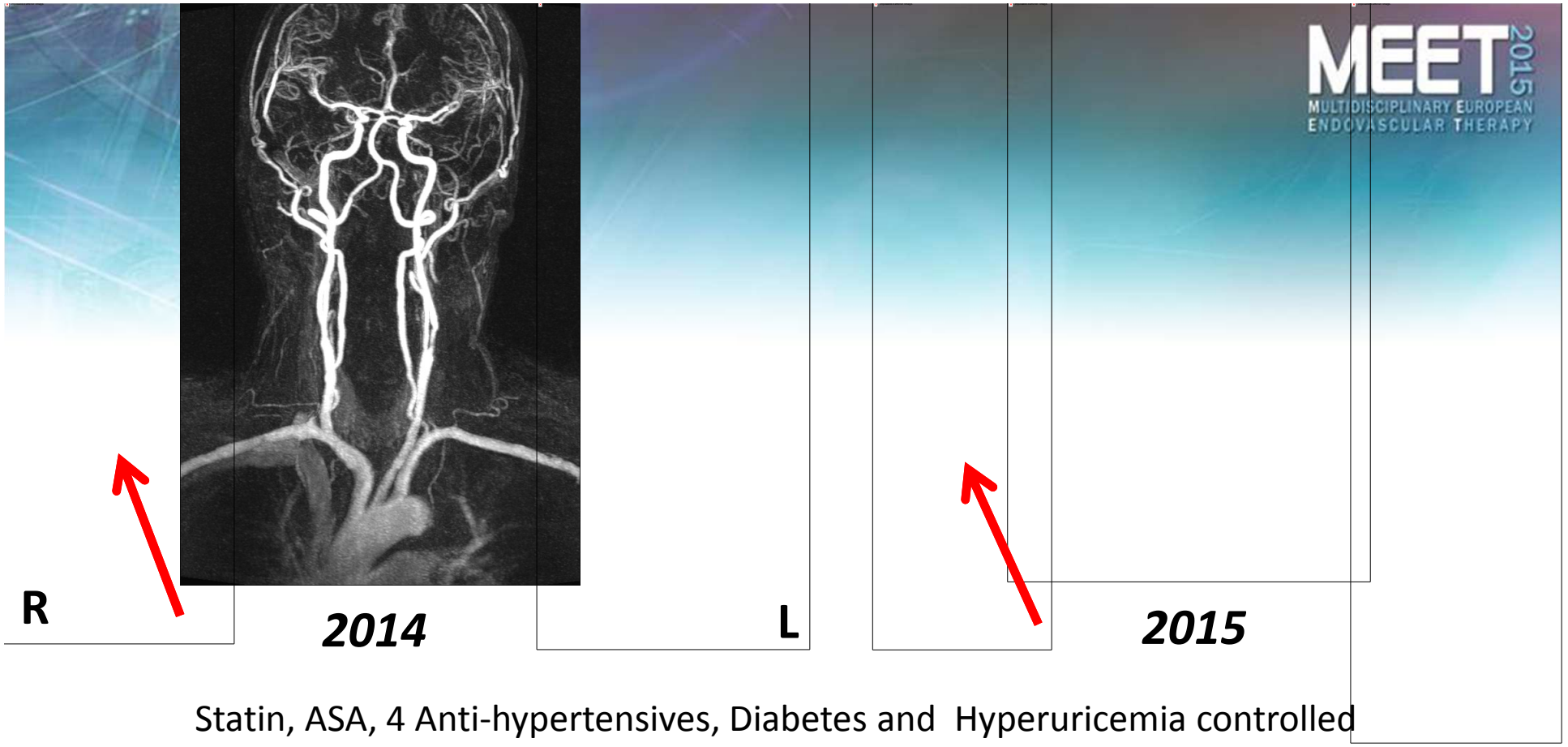
Outcomes After Carotid Artery Stenting in Medicare Beneficiaries, 2005 to 2009

N = 22 000

Variable	No.	Asymptomatic	
		Periprocedural Period	After the Periprocedural Period
Overall	11 839	1.2 (0.9-0.1)	27.7 (26.4-28.9)
Patient Characteristics			
Age, y			
66-69	2122	0.6 (0.3-1.0)	18.1 (15.6-20.7)
70-74	2928	0.7 (0.4-1.0)	23.1 (20.5-25.6)
75-79	3186	1.2 (0.8-1.6)	28.4 (25.7-31.1)
≥80	3603	1.4 (1.0-1.8)	36.8 (34.2-39.2)

JAMA Neurol 2015; 72(3): 276-86

JAMA Neurol 2015; 72(3): 263-4



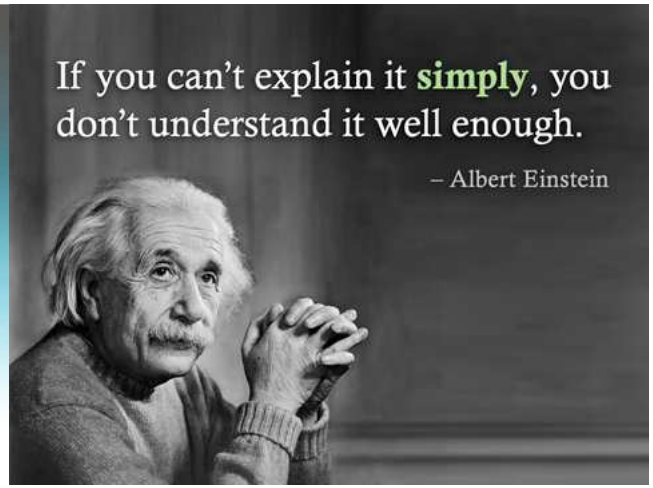
Statin, ASA, 4 Anti-hypertensives, Diabetes and Hyperuricemia controlled

Progression of asymptomatic carotid stenosis despite optimal medical therapy.

At the 5-year of follow-up, OMT failed to prevent carotid disease ***progression*** or development of ***ipsilateral symptoms*** in ***45%*** of patients with AMCAS.

Conrad MF et al. J Vasc Surg. 2013 Jul;58(1):128-35

Asymptomatic
carotid artery stenosis
Identify high-risk



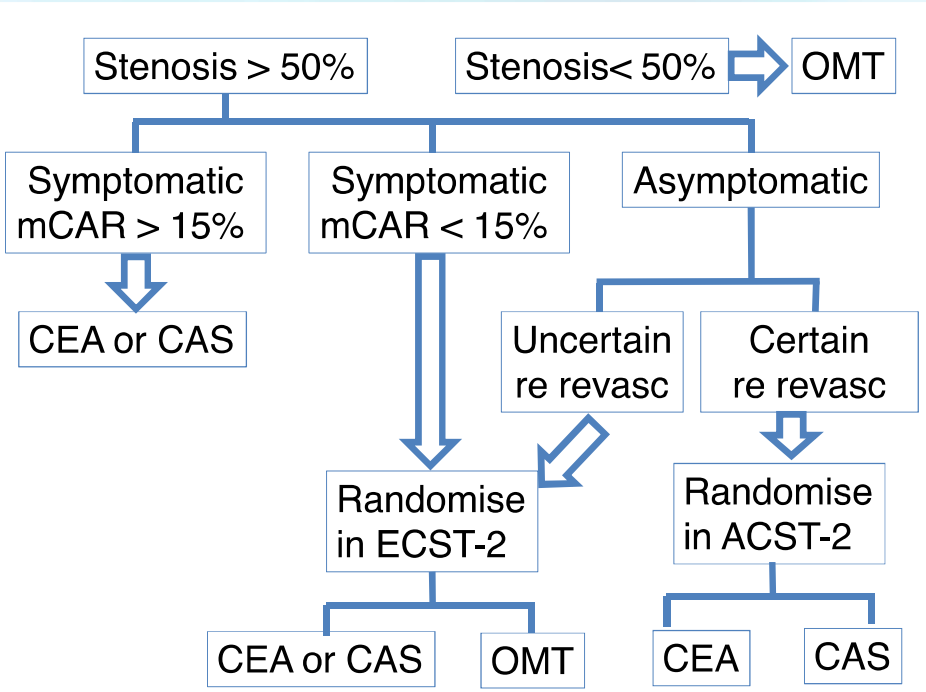
- History of contralateral stroke or TIA - *HR 3*
- Baseline degree of stenosis - *weak predictor*
- Microemboli on TCD ≥ 2 embolic signals/ hour
- Unstable carotid plaque
  - US – plaque echolucency, ulceration, rupture - ACSRS study
  - MRI – intraplaque hemorrhage, luminal thrombus
- Reduced Cerebral Blood Flow Reserve
- Silent embolic infarcts brain CT or MRI *double stroke risk*
- Progression in severity of asymptomatic carotid stenosis despite BMT – *double ipsilateral stroke risk 2%*

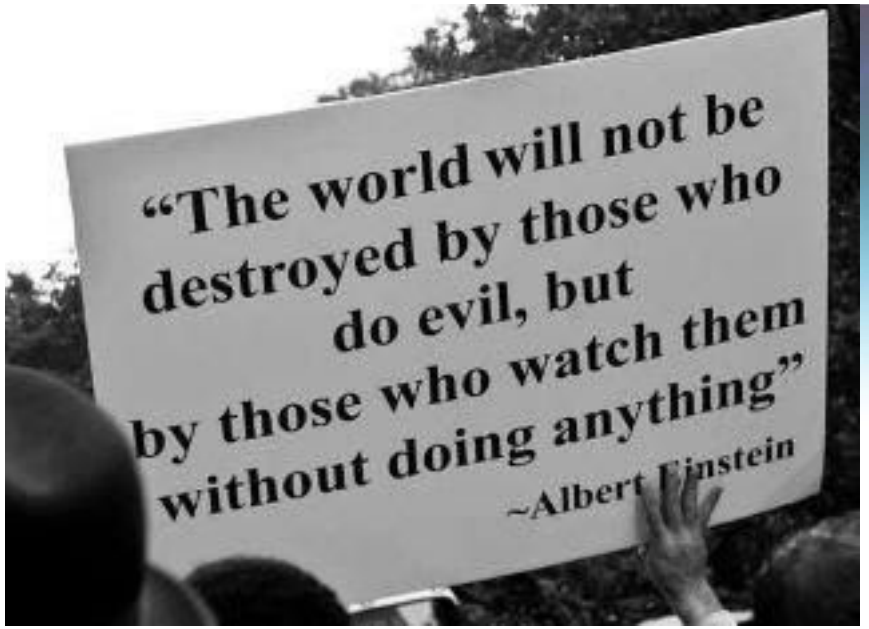
Stroke 2013; 2955-6
Stroke 2014; 3720-4

Trials awaited

- AMTEC = BMT vs. BMT+CEA (atorvastatin, asa, losartan, amlodipine) Aggressive Medical Treatment Evaluation for asymptomatic carotid stenosis
  Completed (N=400)
- *Compass trial* = rivoroxaban +ASA vs. rivoroxaban (Bayer)
  Cardiovascular OutcoMes for People Using Anticoagulation StrategieS
  Enrolling
- ACT 1 = 3 CAS vs. 1 CEA asympt carotid (Abbott) – Halted (business decision)
- SPACE 2= 3 to 2 arm strategy BMT+CAS vs. BMT+ CEA asympt carotid – Halted Jan 2015 (>500)
- *ACST 2*= CAS vs. CEA asympt carotid (enrolled 1849/3600)
- *CREST 2*= BMT vs. BMT+CEA; BMT vs. BMT+CAS (enrolled 36/2480)
- *ECST 2* = sympt or asympt moderate or severe carotid stenosis at low or intermediate risk of future stroke (CAR score) – BMT (deferred CEA) vs. BMT + CEA (CAS) -(enrolled 81/2000)

ECST-2 en ACST-2





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- BMT has improved
  - Initiate and control BMT
- ***At present*** BMT will ***NOT*** replace carotid treatment
  - Interdisciplinary teams
    - Treat symptomatic carotid disease early
    - Treat asymptomatic carotid stenosis selectively
  - WE must participate in RCT