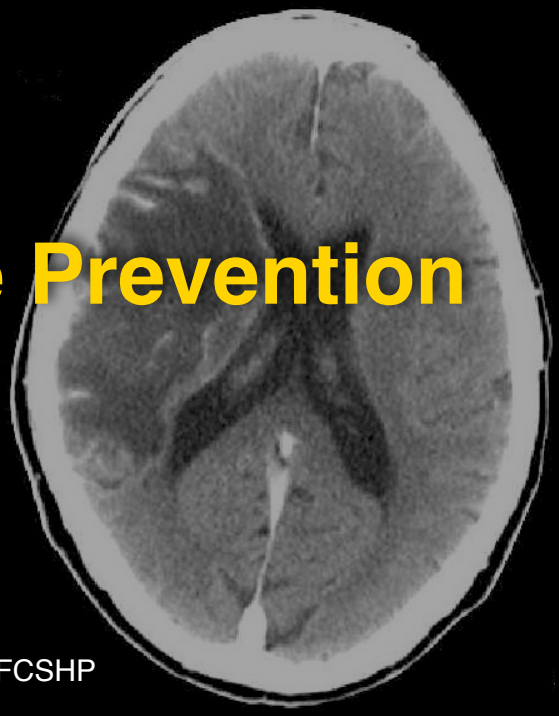
PHAR 451

Ischemic Stroke Prevention Therapeutics (non-AF)



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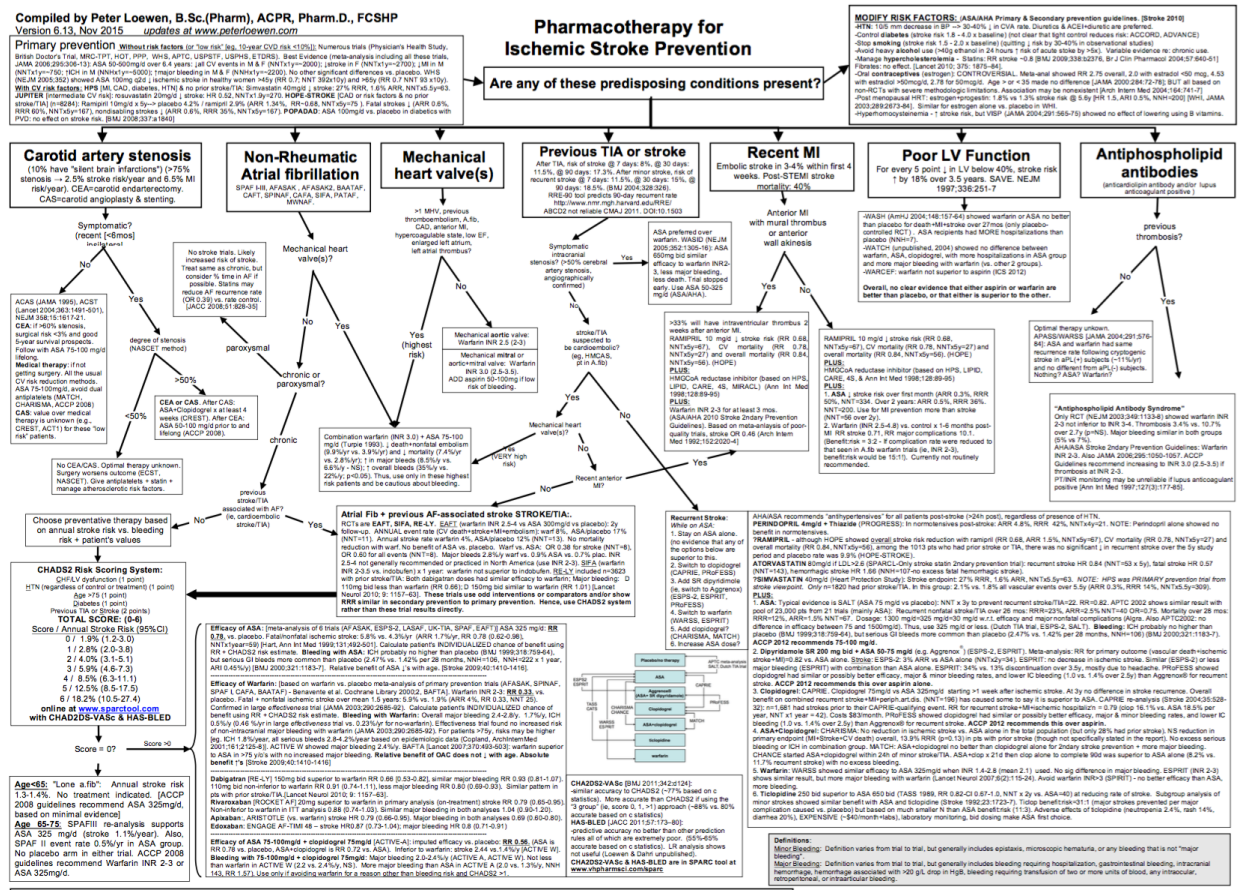
Vancouver General Hospital

Objective

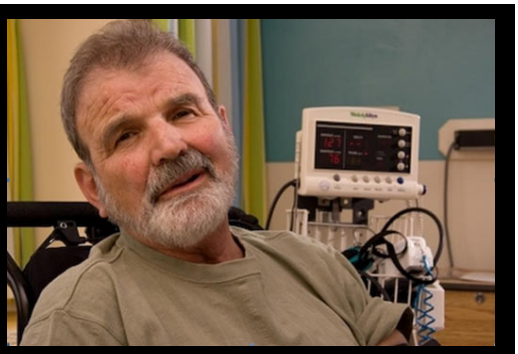
After the session, and upon personal reflection & study, students will be able to:

DESIGN and RATIONALIZE using EVIDENCE, a stroke prevention regimen in each of the following clinical scenarios:

- Primary Stroke Prevention
- Atrial Fibrillation
- Secondary Stroke Prevention

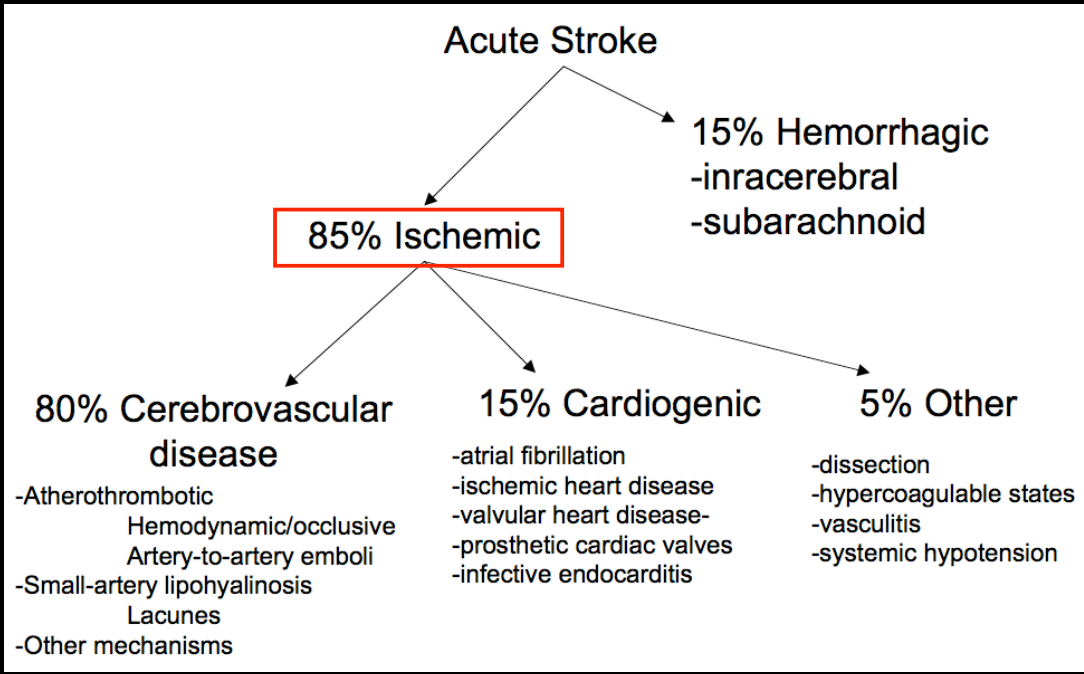


Case



- PY is a 73 y/o M who suffered an ischemic stroke 10 days ago (aphasia, L-sided weakness)
- PMH: HTN (~150/85)
- MPTA: HCTZ 25 mg/d
- O/E: no residual neurologic deficit
- CONSULT: What is the most appropriate therapy for secondary stroke prevention in this patient?

Stroke Subtypes



Primary/Secondary Prevention

Modifiable Stroke Risk Factors

- Control HTN
- Stop smoking
- Control hyperlipidemia
- Get physically active
- Manage obesity
- Avoid binge drinking
- Glycemic control in diabetes?

Stroke Risk Factors

- HTN (OR 2.64)
- cardiac causes [atrial fibrillation or flutter, previous myocardial infarction, rheumatic valvular disease, or prosthetic heart valve] (OR 2.38)
- smoking (OR 2.09)
- waist hip ratio (highest vs. lowest tertile OR 1.65)
- regular physical activity (OR 0.69)
- diabetes (1.36)
- alcohol intake (OR 1.51 for >30 drinks/month or binge)
- psychosocial stress (OR 1.3)
- depression (OR 1.35)

INTERSTROKE. Lancet 2010: 376; 112–23.

PRIMARY PREVENTION

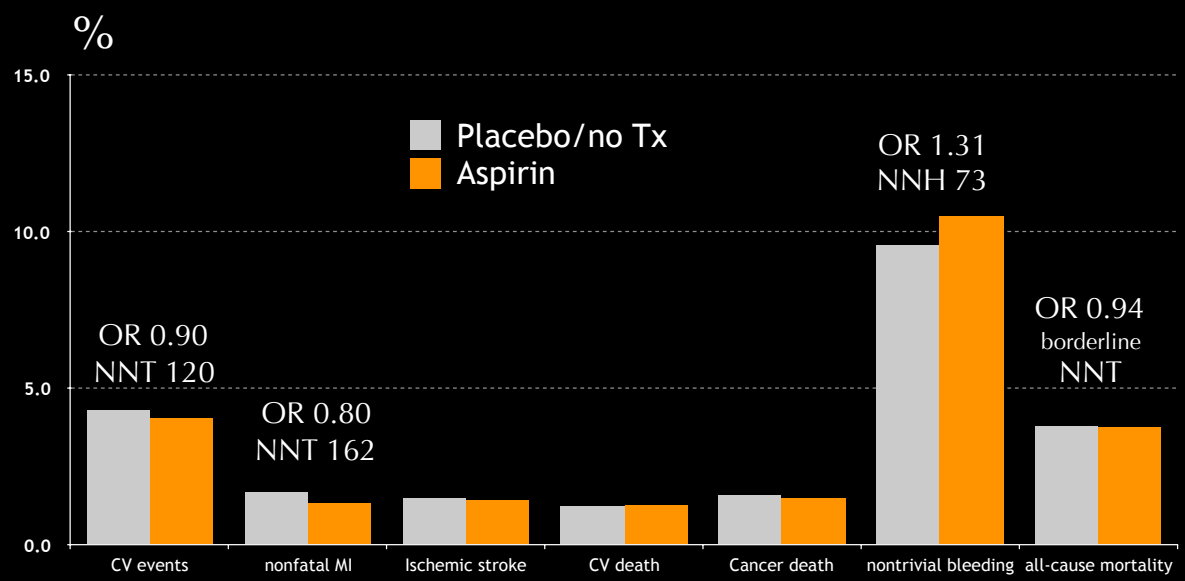
Stroke Primary Prevention

What we do	In whom	Why?
treat HTN	everyone	40% stroke RRR
ASA?	people who have a CV indication for ASA	Berger JS et al. JAMA 2006;295:306-13
ramipril (perindopril?)	high CV risk pts, regardless of HTN	HOPE (EUROPA?)
statin	pts at sufficiently high CV risk (e.g. >10% 10-year CV risk)	HPS, CARDS, ASCOT-LLA, JUPITER, LIPID

Primary Prevention

Aspirin: primary prevention

N=9 trials. N=102,621
ASA 75mg - 162 mg/d, mean 6.0 years followup.

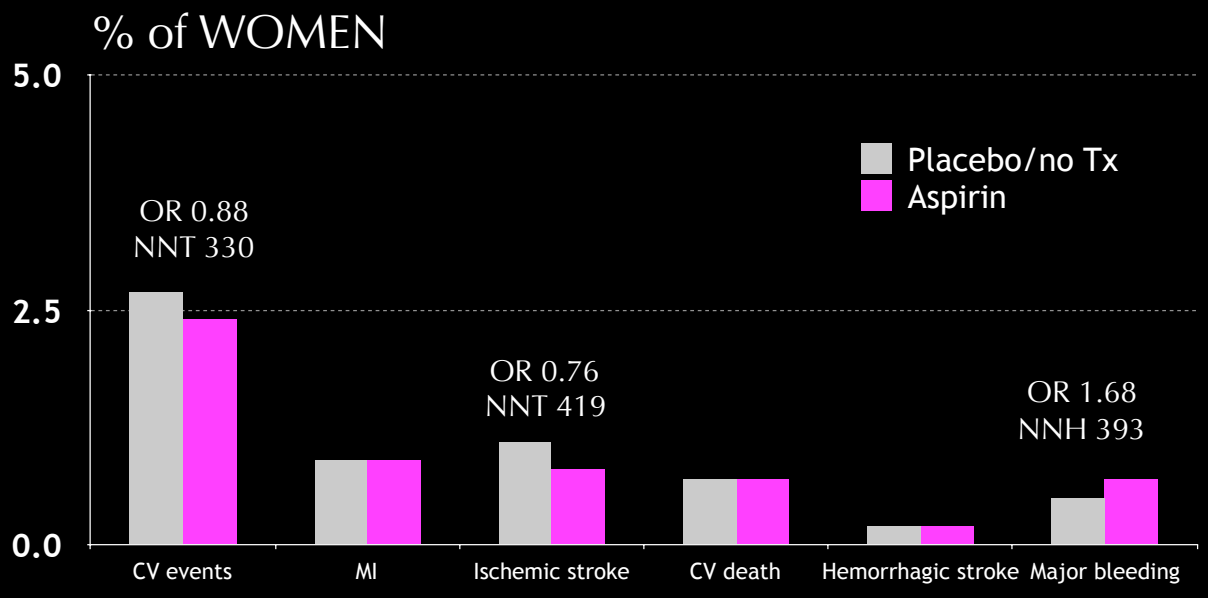


Seshasai SRK et al. Arch Intern Med 2012;9JAN

Primary Prevention

Aspirin: Effects by gender

N=6 trials. 51,342 women, 44,114 men.
ASA 75mg - 500 mg/d, mean 6.4 years followup.

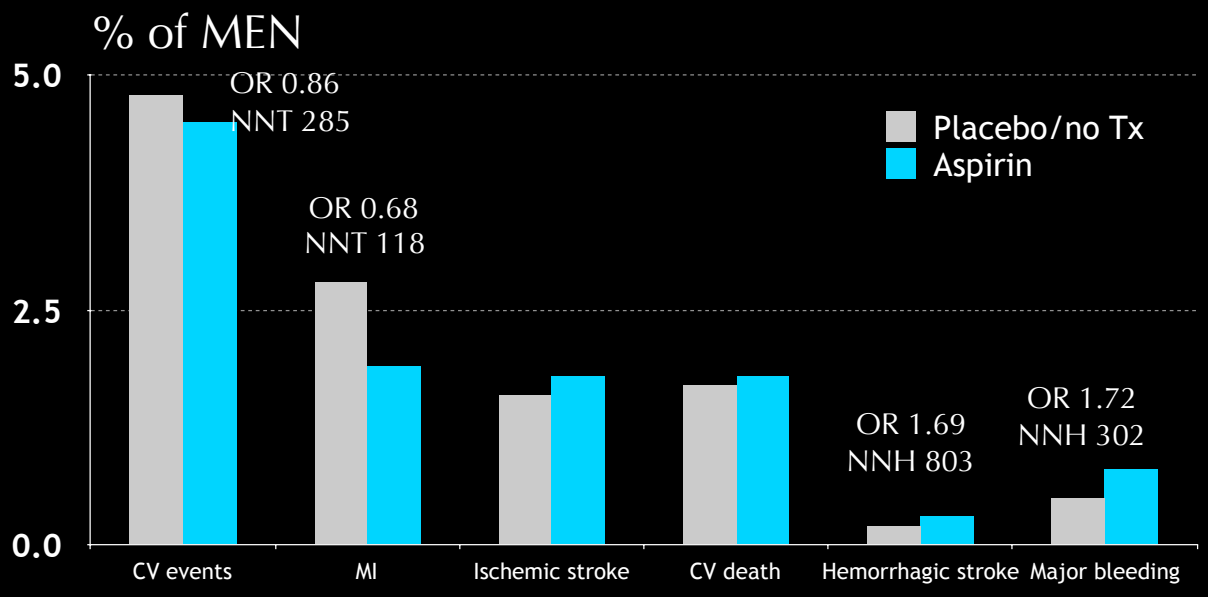


Berger JS et al. JAMA 2006;295:306-13

Primary Prevention

Aspirin: Effects by gender

N=6 trials. 51,342 women, 44,114 men.
ASA 50 - 500 mg/d, mean 6.4 years followup.



Berger JS et al. JAMA 2006;295:306-13

Primary Prevention

Aspirin for Primary Stroke Prevention Bottom Lines

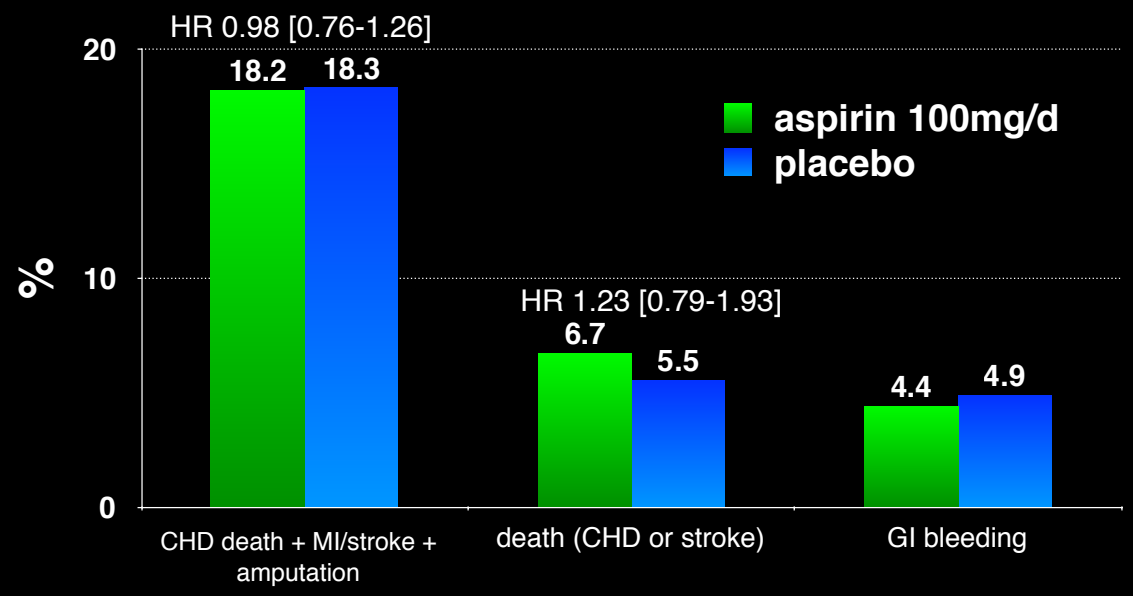
- Prevents overall CV events in low-risk males & females
  - Your patient has a 1 in ~2000 chance of benefit for every year they take aspirin
- Prevents stroke in females
  - Your patient has a 1 in ~2700 chance of benefit for every year they take aspirin
- Prevents MI in males
  - Your patient has a 1 in ~750 chance of benefit for every year they take aspirin
- Causes ICH in males
  - Your patient has a 1 in ~5000 chance of harm for every year they take aspirin
- Causes major bleeding in males & females
  - Your patient has a 1 in ~2200 chance of harm for every year they take aspirin

Berger JS et al. JAMA 2006;295:306-13

Primary Prevention

POPADAD

N=1276 Scots with DM1 or DM2, ABPI < 0.99 but no symptomatic CV disease. Median 6.7 years followup.

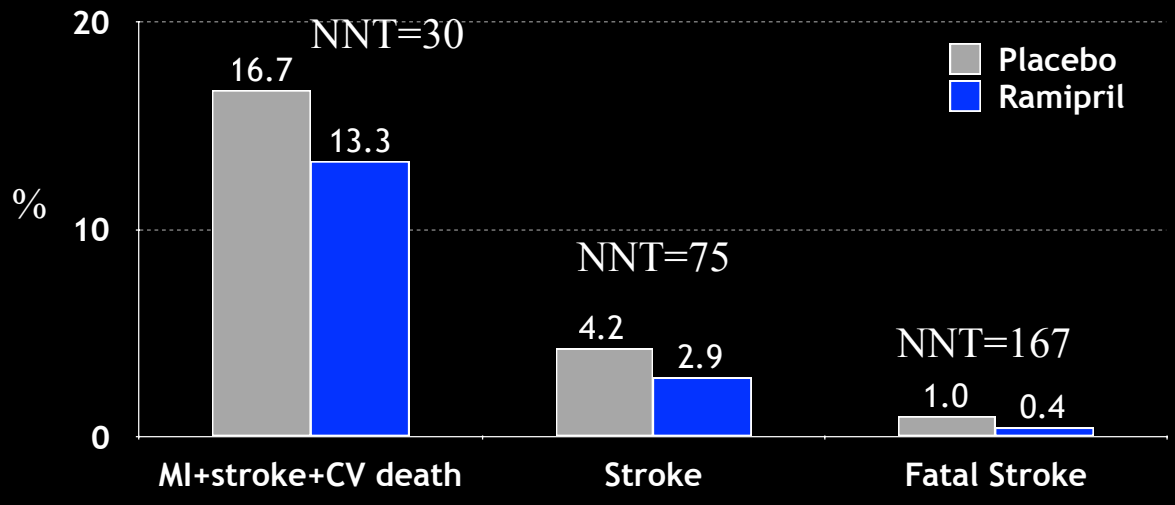


POPADAD. BMJ 2008;337:a1840

Primary Prevention

Ramipril – HOPE-STROKE

N=8284 pts with CAD, PVD, diabetes but no prior stroke/TIA treated x 4.5 years

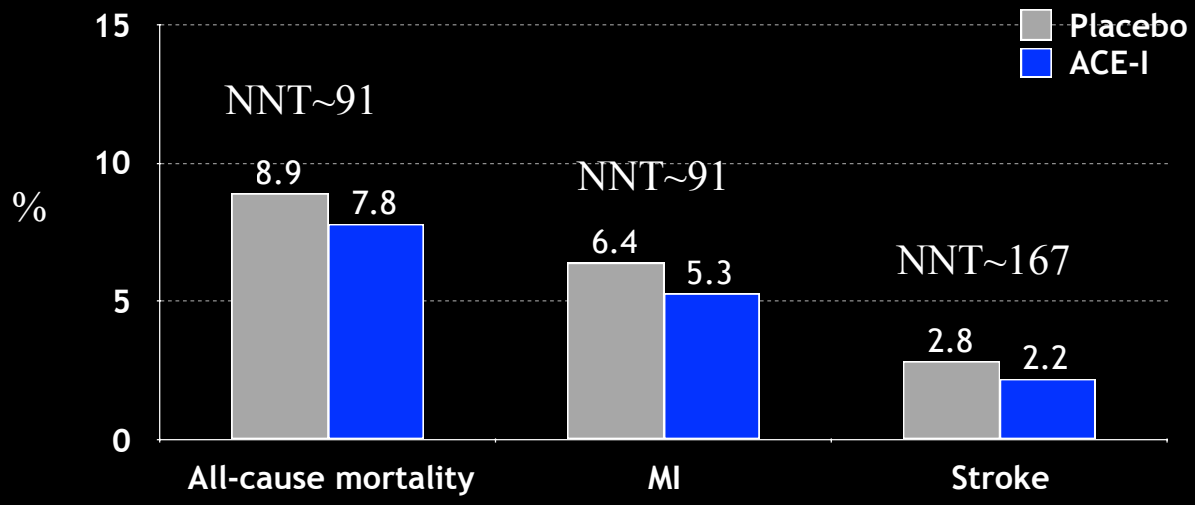


NEJM 2000;342;145-53 / BMJ 2002;324:1-5

Primary Prevention

All ACE-Is (R, T, & P)

N=3 trials (HOPE, PEACE, EUROPA - 29,805 pts) with CAD, PVD, diabetes but no prior stroke/TIA treated x 4.5 years



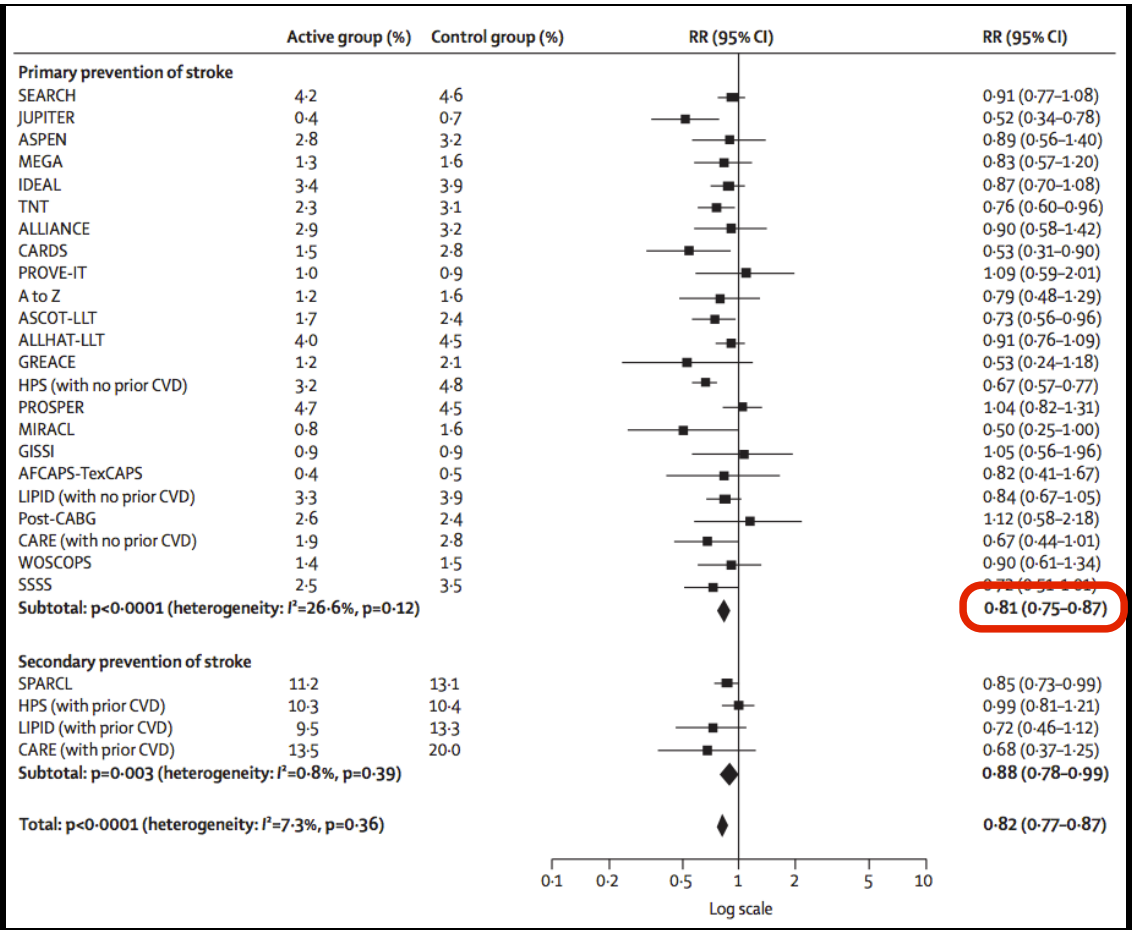
Lancet 2006; 368: 581-88

Overall Efficacy of Statins

	RRR	NNT x ~5 years
Major coronary events	~30%	1°: 67** 2°: 27
Stroke	~20%	1°: 202** 2°: 45*
All-cause mortality	10-17%	1°: 142** 2°: 48

Independent of gender, HTN, DM2, prior CAD, risk

ADAPTED FROM
Cheung et al. Br J Clin Pharmacol 2004;57:640-51
*SPARCL. Atorvastatin 80mg/d. NEJM 2006;355:549-59.
** Brugts et al. BMJ 2009;338:b2376.
Tonelli M, et al. CMAJ 2011. DOI:10.1503 /cmaj.101280



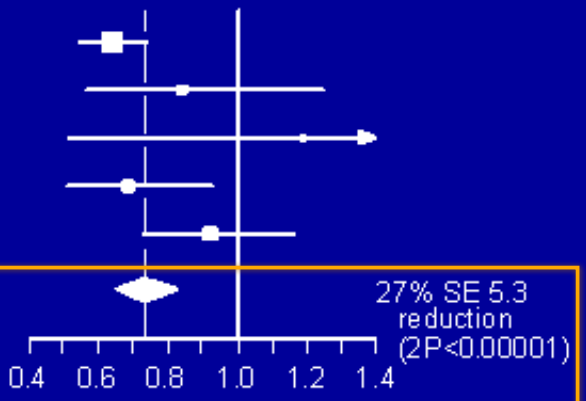
Amarenco & Labreuche. Lancet Neurol 2009; 8: 453–63

Primary Prevention

MRC/BHS Heart Protection Study

SIMVASTATIN: STROKE by AETIOLOGY

Stroke aetiology	STATIN (10269)	PLACEBO (10267)
Ischaemic	242	376
Haemorrhagic	45	53
Subarachnoid	12	10
Unknown	69	100
Unadjudicated	136	146
ALL STROKE	456 (4.4%)	613 (6.0%)



NNT x 5.5y=63

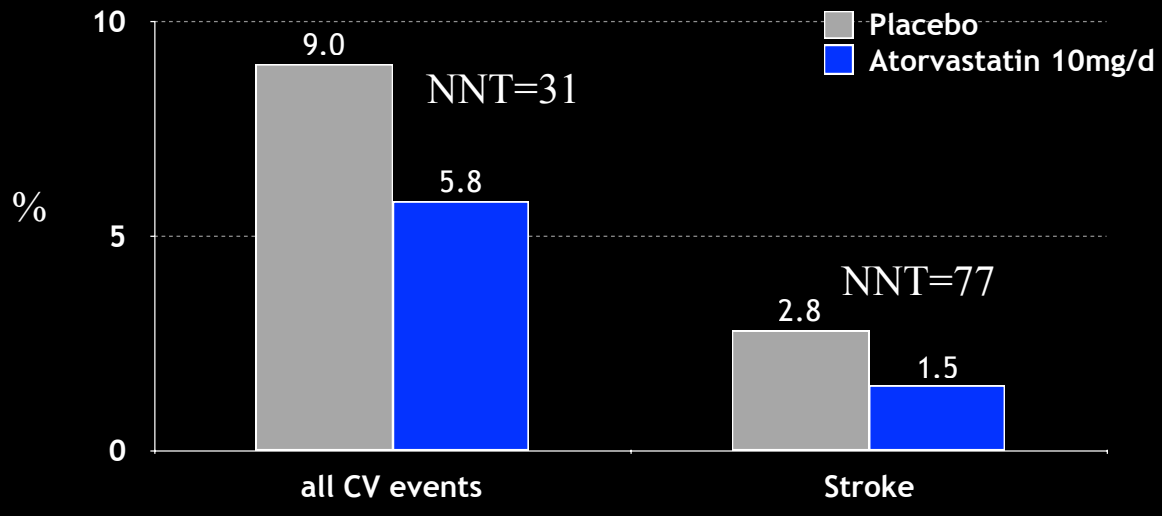
HPS. Lancet 2002;360:7-22

Primary Prevention

Atorvastatin - CARDS

N=2,838 DM2 pts with no CVD and normal cholesterol levels

Duration = 3.9 years



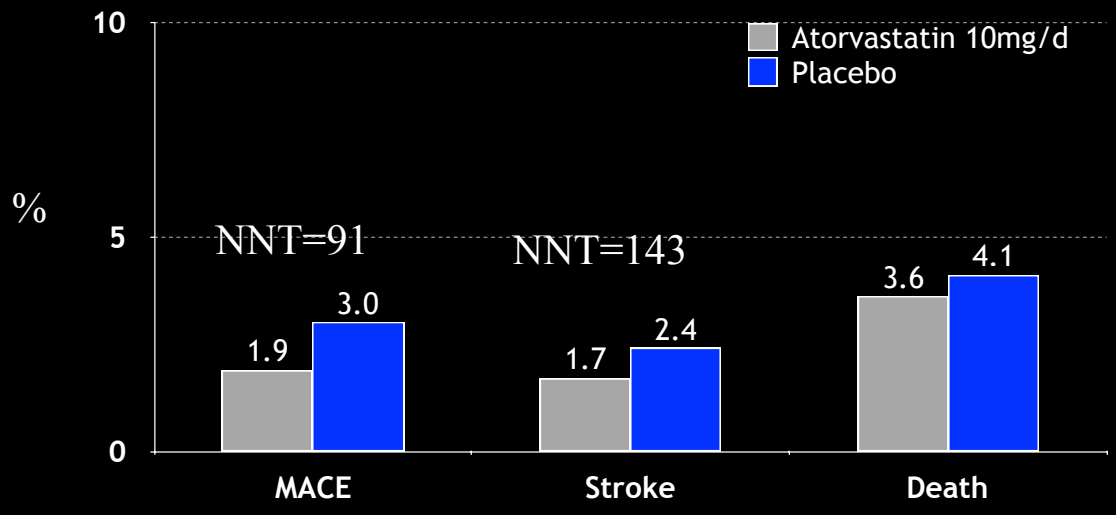
CARDS. Lancet 2004;364;685-96

Primary Prevention

Atorvastatin - ASCOT-LLA

N=10,305 hypertensives with ≥3 other CV risk factors,
Normal cholesterol, and NO CAD.

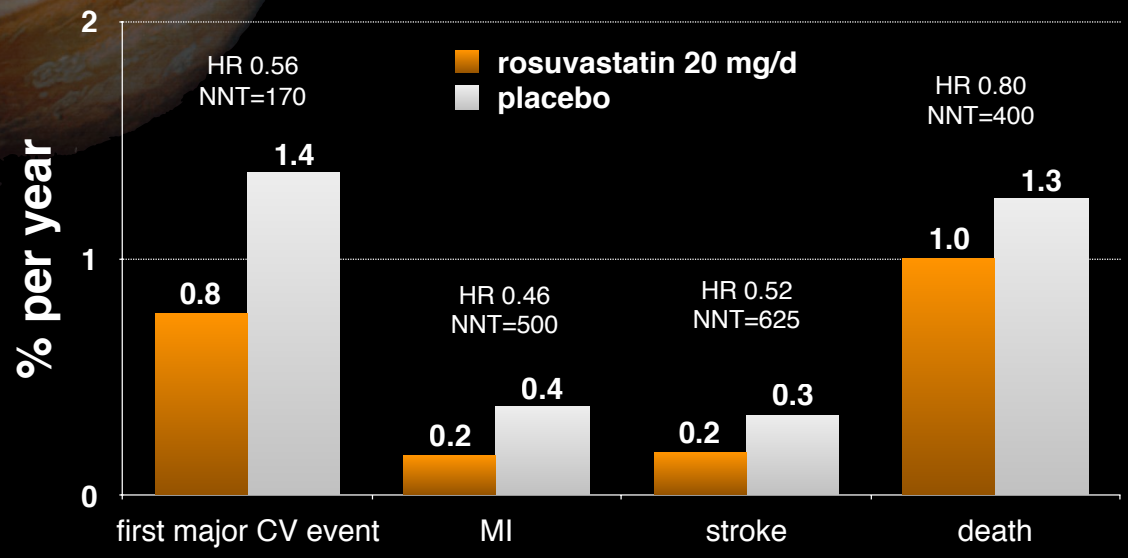
Duration = 3.3 years



ASCOT-LLA. Lancet 2003;361:1149-58

JUPITER

N=17,802 healthy people with normal LDL and CRP>2 mg/L.
Stopped after median 1.9y.

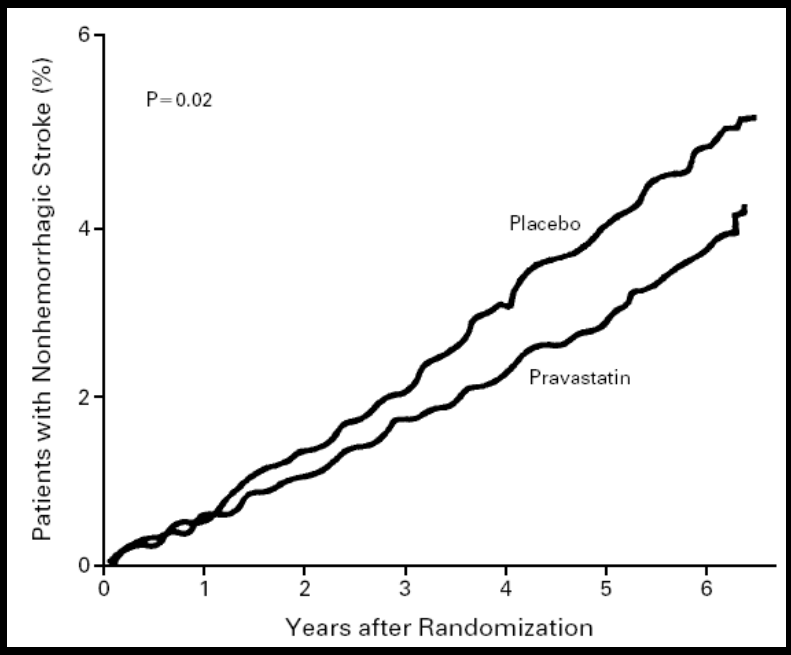


JUPITER. N Engl J Med 2008;359:2195-207

Primary Prevention

LIPID-STROKE: Pravastatin

N=9,000 pts post-MI treated with pravastatin 40mg/d

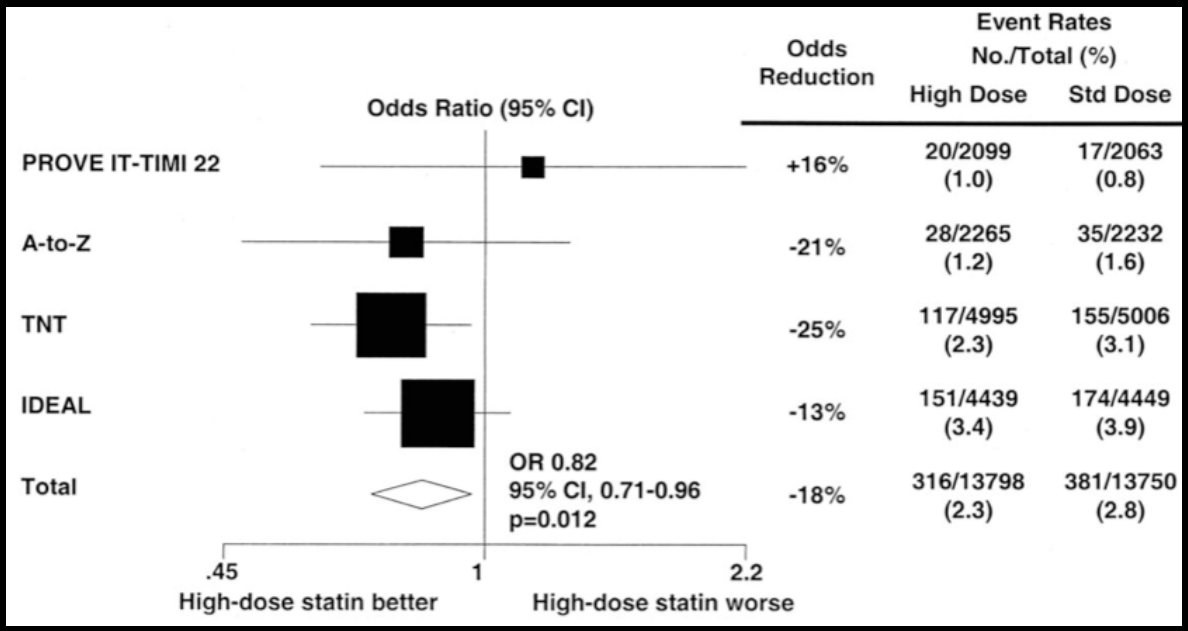


4.4%
3.4%
NNT x 6y: 100

White et al. NEJM 2000;343:317-26

"Intensive" Statin Therapy

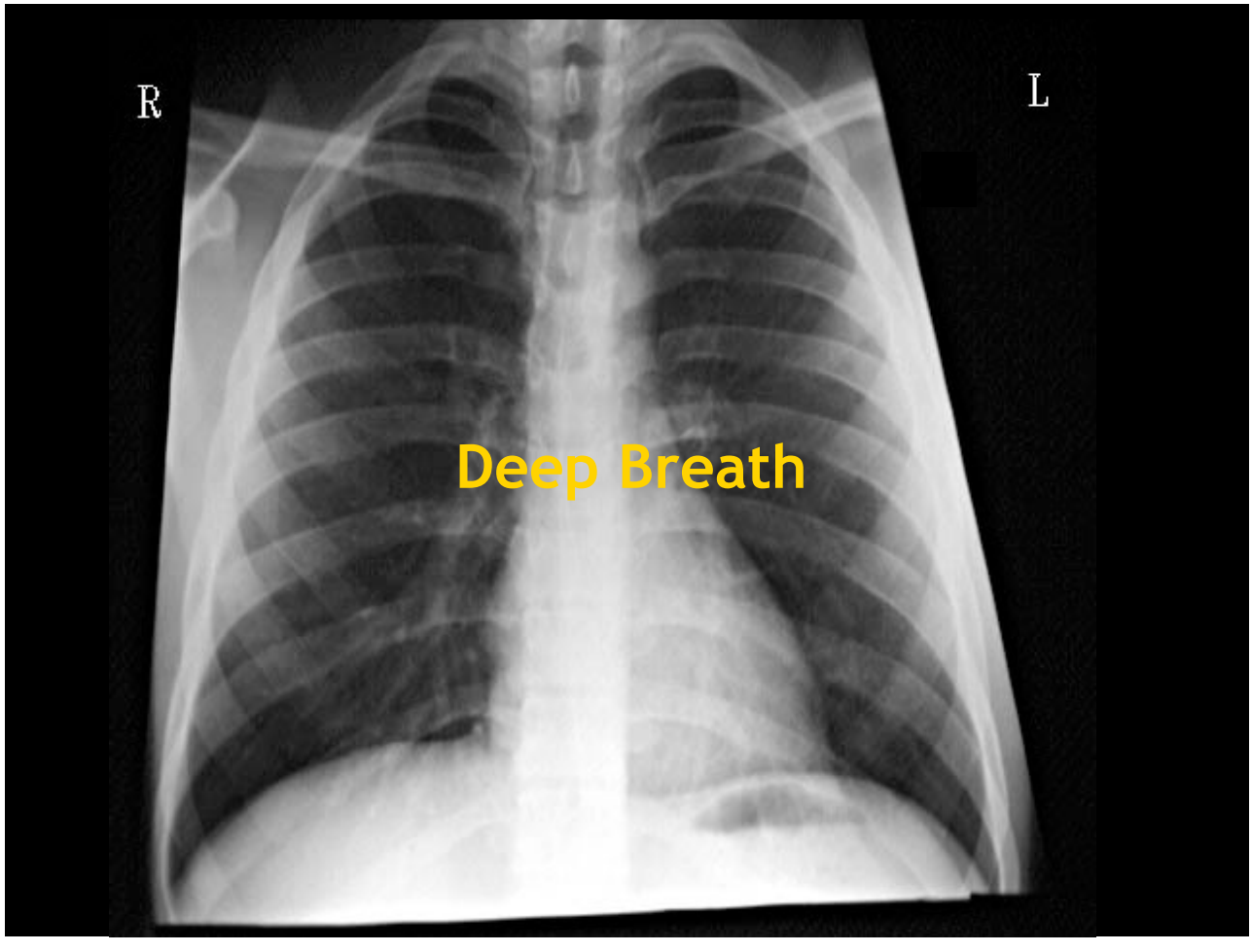
Stroke



Cannon et al. JACC 2006;48:438-45

Bottom line on primary prevention (non-AF)

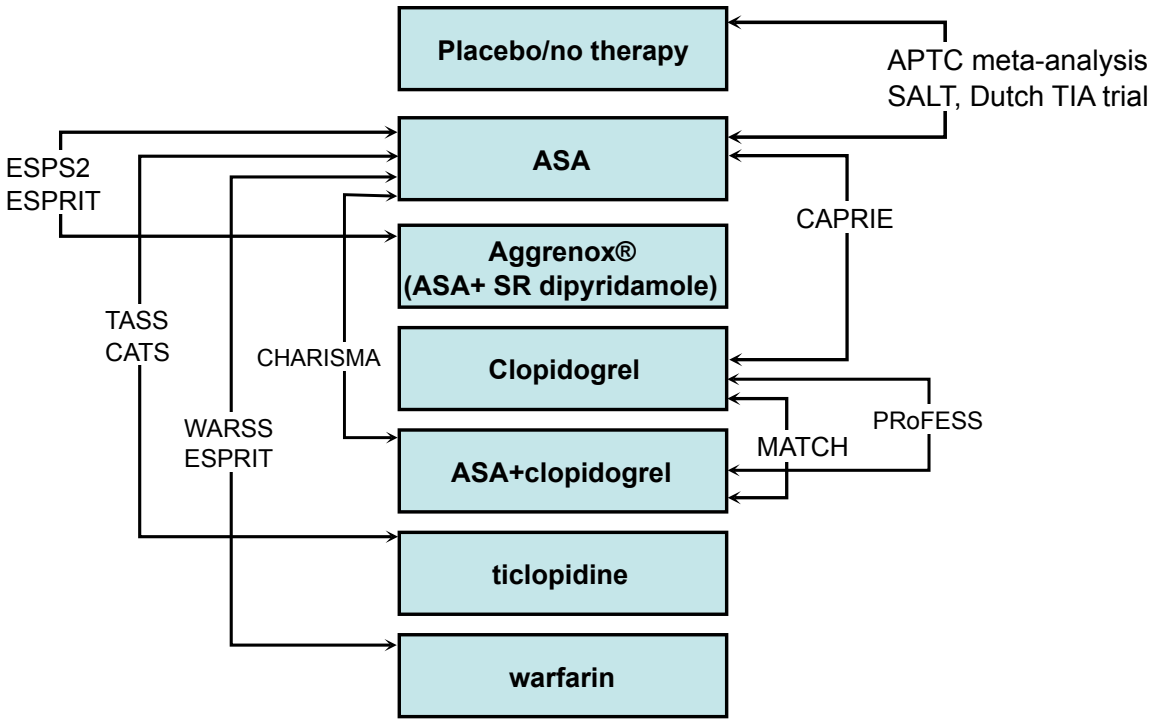
- Risk factor modification (especially HTN)
- Role for antithrombotic therapy?
- Ramipril in high risk pts (regardless of HTN)
  - Other ACE-Is? ARBs?: TRANSCEND, ONTARGET
- Statin (simva, prava, atorva) in high risk pts
  - especially those with CAD
  - regardless of baseline cholesterol levels



Stroke Secondary Prevention

What we do	In whom	Why?
treat HTN	everyone	40% stroke RRR
ASA	everyone	CAST, IST
clopidogrel	intolerant to ASA	CAPRIE
ASA+dipyridamole?	stroke on ASA or clopidogrel?	ESPS2
perindopril+indapamide (ramipril?)	ischemic stroke, regardless of HTN	PROGRESS (HOPE)
statin	all (non-AF) ischemic stroke patients	SPARCL, HPS

Antithrombotics for Secondary Stroke Prevention in NSR

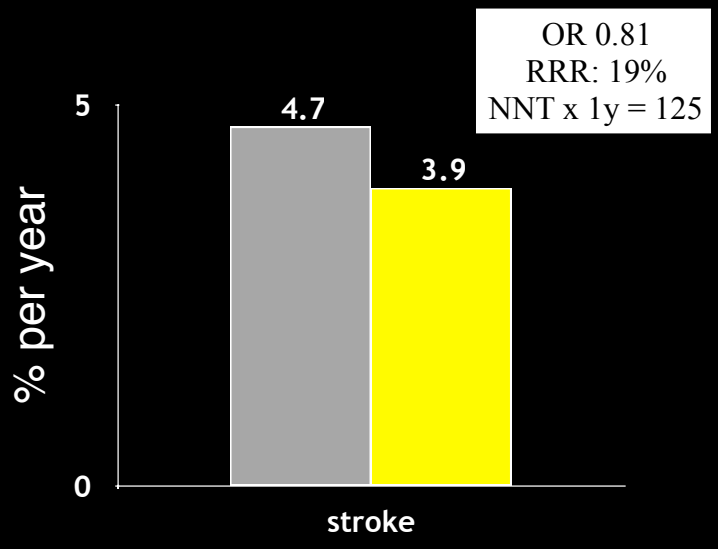


Antithrombotic Therapies

- The GOLD STANDARD:
  - ASA (ATTC 2009)
- Stuff that's BETTER than ASA:
  - ASA+Dipyridamole SR (ESPS-2, ESPRIT)
  - Ticlopidine (TASS)
- Stuff that's SIMILAR to ASA:
  - Clopidogrel (CAPRIE)
  - Warfarin (WARSS)
  - Clopidogrel + ASA (MATCH, CHARISMA)

Efficacy of ASA: The Gold Standard

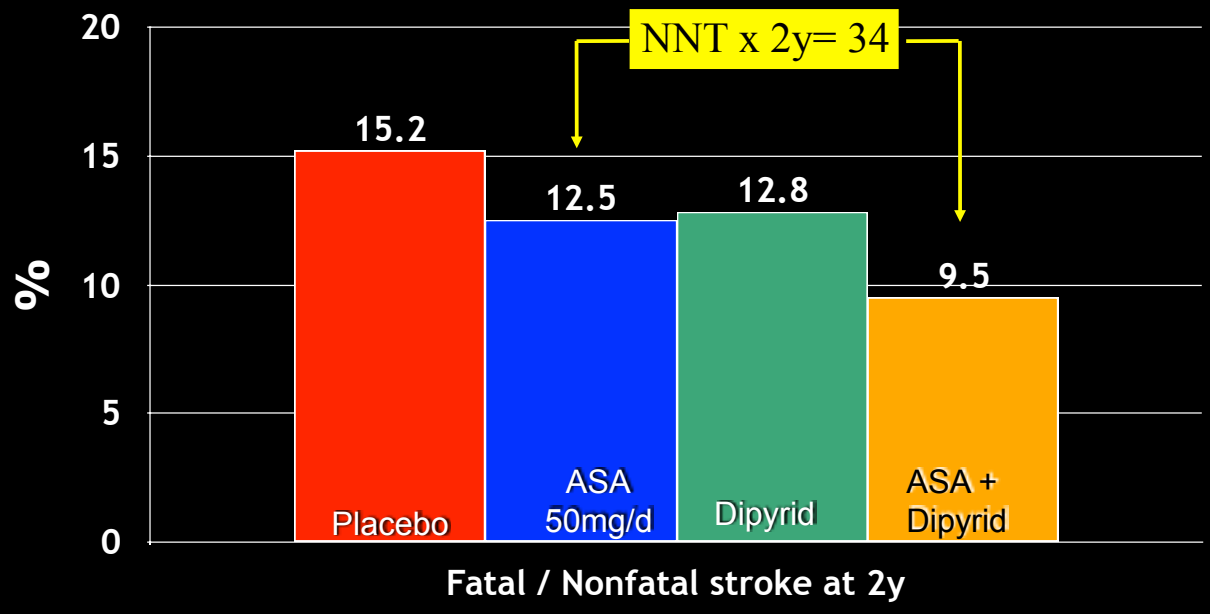
N=16 secondary prevention trials,43,000 person-years followup.



ATTC. Lancet 2009;373: 1849–60

Secondary Prevention

Stuff that's BETTER THAN aspirin: ASA + SR dipyridamole: ESPS-2



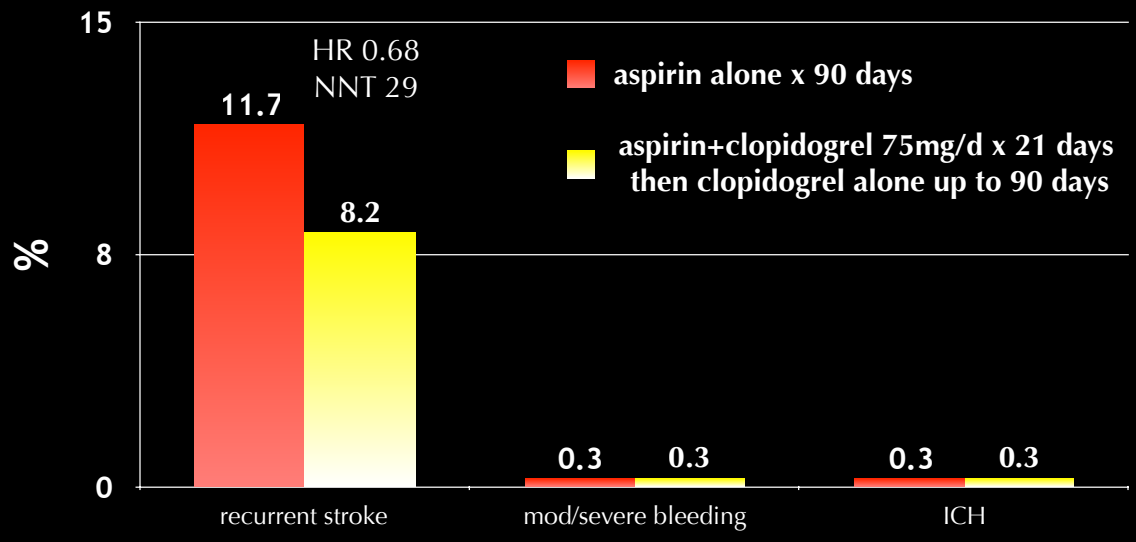
ESPS-2, Thromb Res 1998;92:S1-S6

Secondary Prevention

Stuff that's the better than aspirin Clopidogrel + ASA: CHANCE

N=5170 patients in China within 24h of minor ischemic stroke/TIA. All taking aspirin 75-300mg/d.

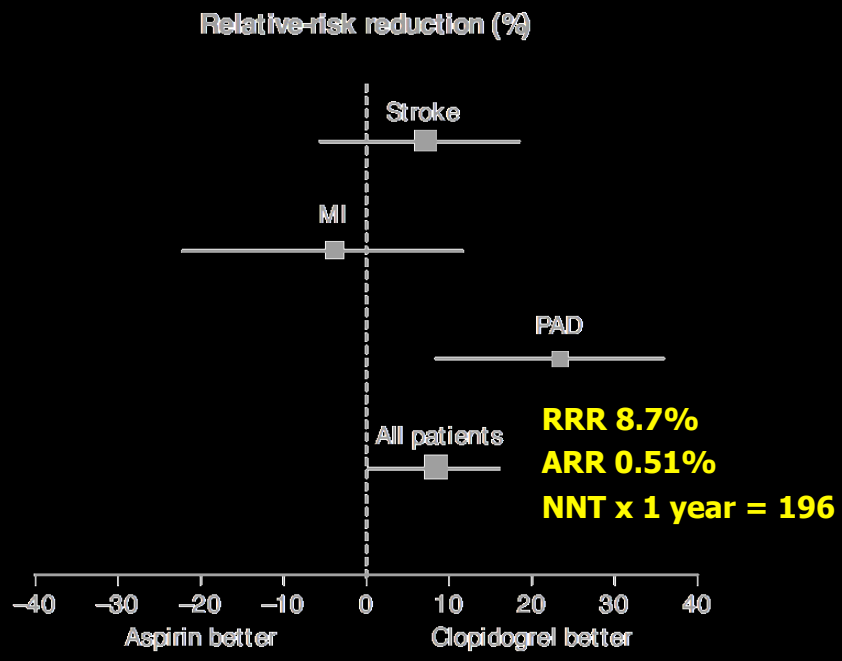
90 days followup.



CHANCE. New Engl J Med 2013;369:11–9.

Secondary Prevention

Stuff that's the SAME AS aspirin: Clopidogrel: CAPRIE

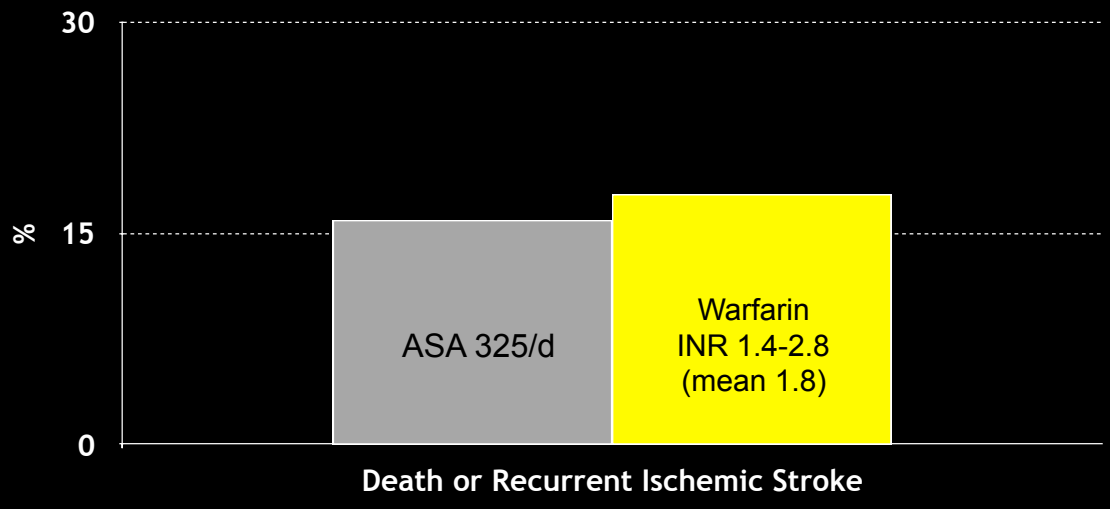


CAPRIE. Lancet 1996;348:1329-39

Secondary Prevention

Stuff that's the SAME AS aspirin: Warfarin: WARSS

N=2206 stroke survivors treated for 2 years.

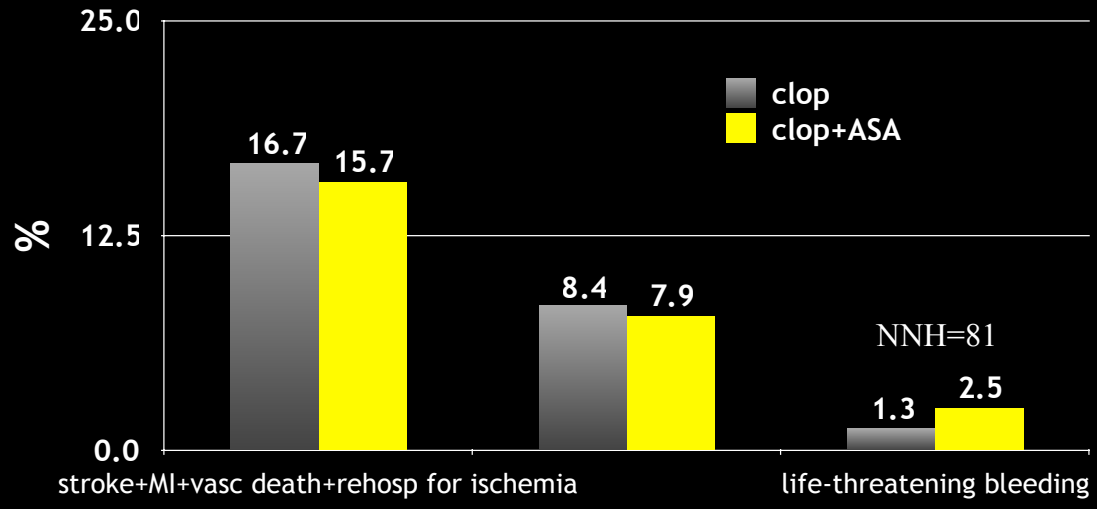


WARSS. NEJM 2001;345:1444-51

Secondary Prevention

Stuff that's the SAME AS aspirin Clopidogrel + ASA: MATCH

N=7,599 with recent ischemic stroke/TIA+1 additional risk factor + already on clopidogrel. Average follow-up 18 mos.



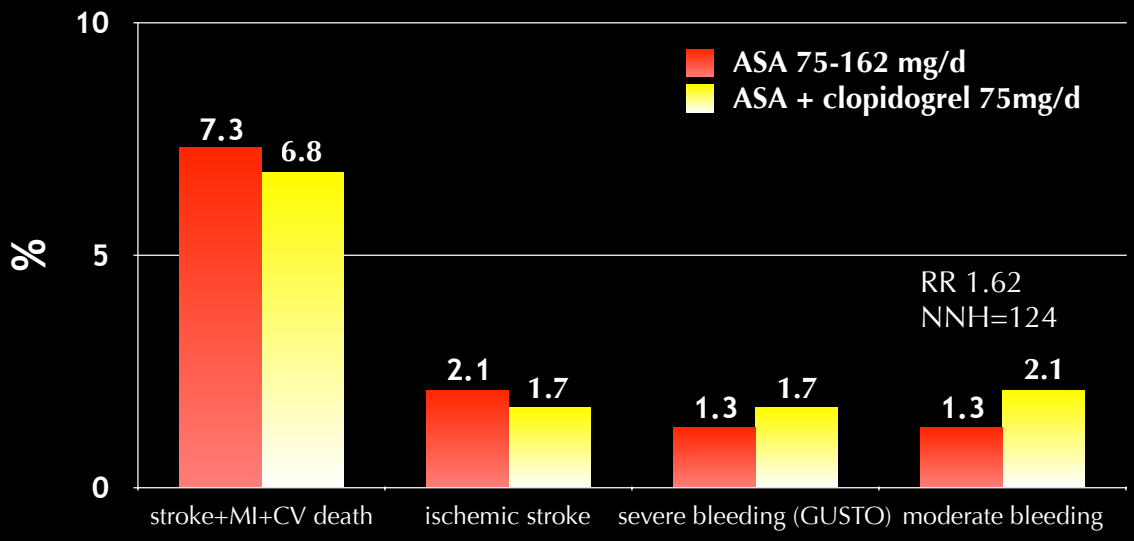
MATCH. Lancet 2004; 364: 331≷37

Primary/Secondary Prevention

Stuff that's the SAME AS aspirin Clopidogrel + ASA: CHARISMA

N=15,603 with prior ischemic stroke OR CAD OR PAD OR at high risk for CV events (2 major or 3 minor or 1 major + 2 minor risk factors).

Median 28 months followup



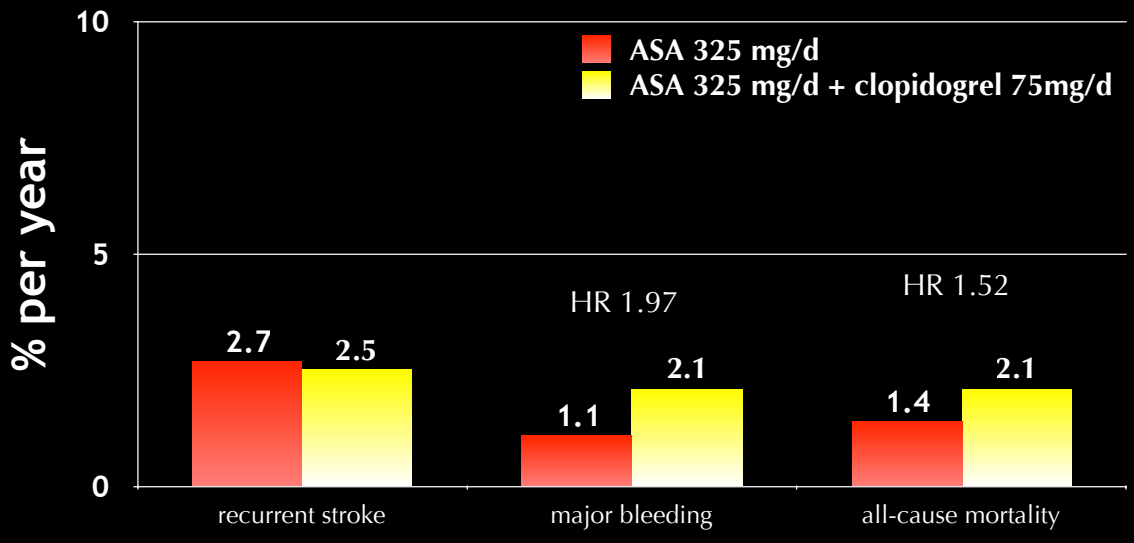
CHARISMA. NEJM 2006;354 (12MAR06)

Primary/Secondary Prevention

Stuff that's the SAME AS aspirin
Clopidogrel + ASA: SPS3

N=3020 patients with recent symptomatic lacunar infarcts identified by MRI.

Mean 3.4 years followup

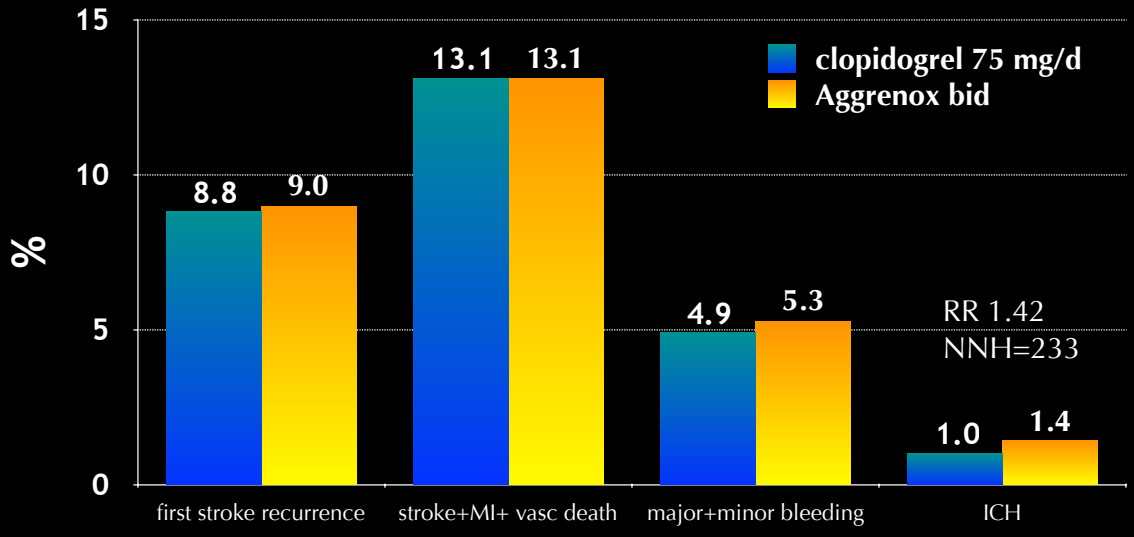


SPS3. N Engl J Med 2012;367:817-25.

Secondary Prevention

PRoFESS: Clopidogrel vs. Aggrenox

N=20,332 with prior ischemic stroke + >1 risk factor (DM2, HTN, Smoker, obesity, CAD, hyperlipidemia). Average follow-up 2.5y.

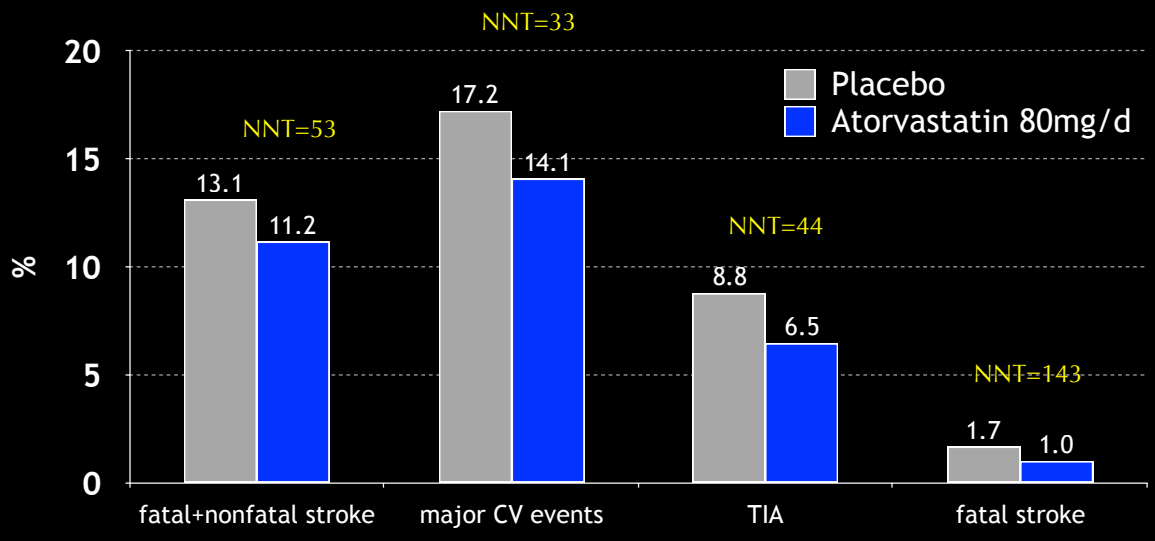


PRoFESS. NEJM 2008;359

Secondary Prevention

SPARCL: Atorvastatin

N=4731 pts with prior stroke/TIA, normal LDL, no CAD
Treated x 4.9 years

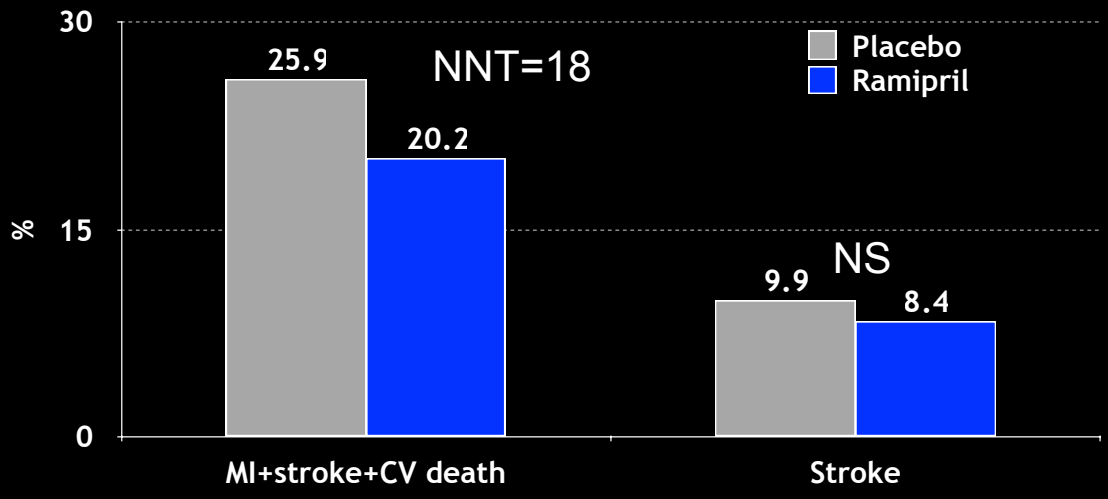


SPARCL. Lancet 2006;355:549-59

Secondary Prevention

HOPE: Ramipril

N=1013 pts with prior stroke/TIA treated x 4.5 years

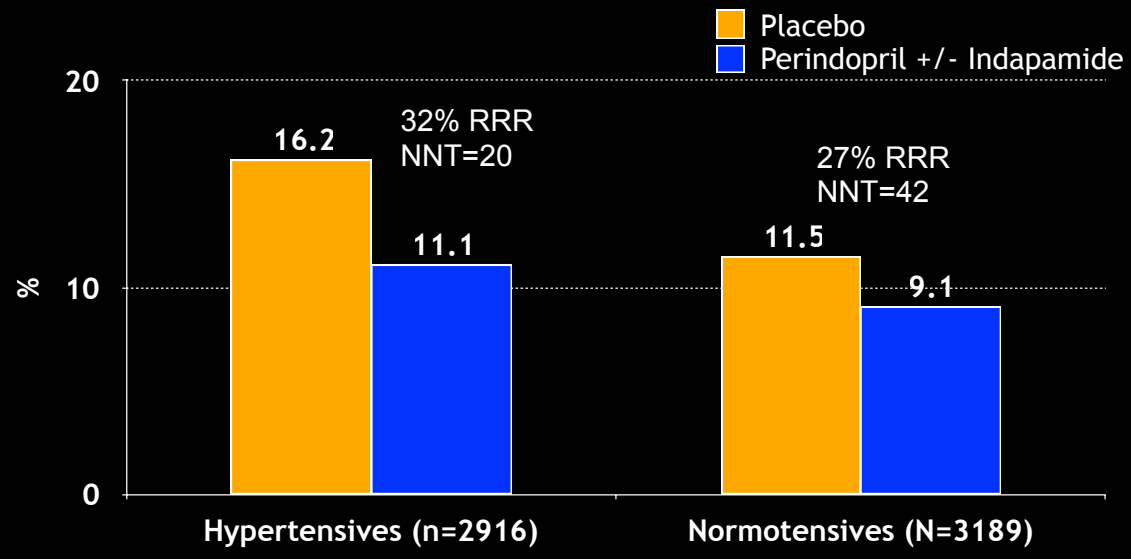


NEJM 2000;342;145-53
BMJ 2002;324:1-5

Secondary Prevention

Perindopril +/- Indapamide

N= 6105 stroke/TIA survivors treated x 4 years.

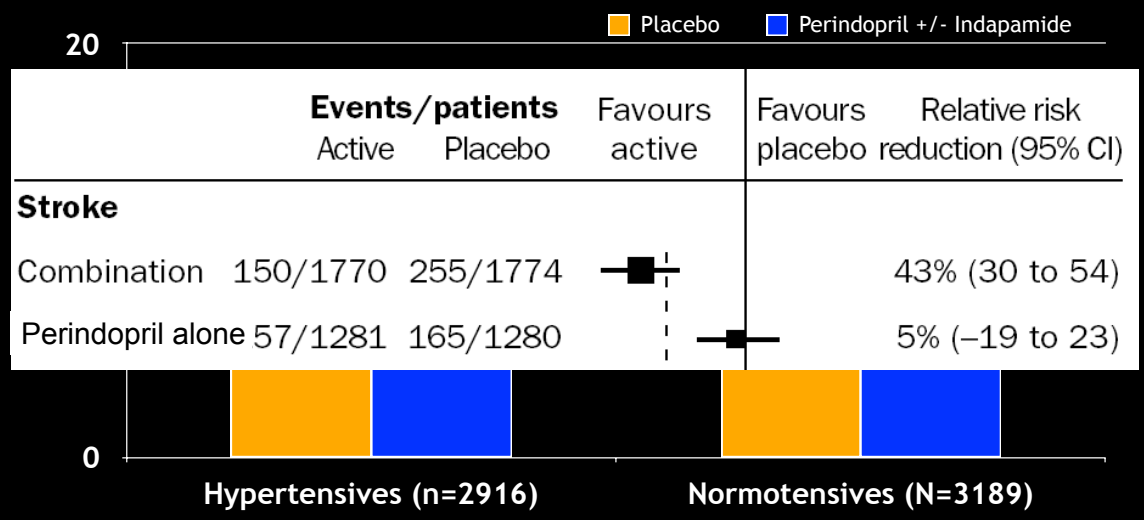


PROGRESS. Lancet 2001;358:1033-41

Secondary Prevention

Perindopril +/- Indapamide

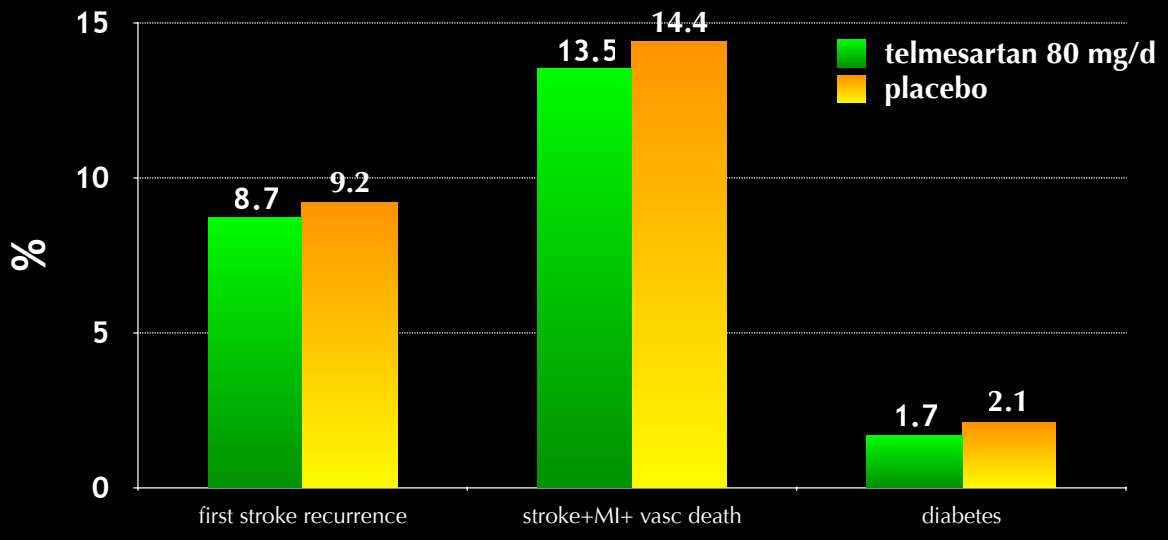
N= 6105 stroke/TIA survivors treated x 4 years.



PROGRESS. Lancet 2001;358:1033-41

ARBs: PRoFESS

N=20,332 with prior ischemic stroke + >1 risk factor (DM2, HTN, Smoker, obesity, CAD, hyperlipidemia). Average follow-up 2.5y.

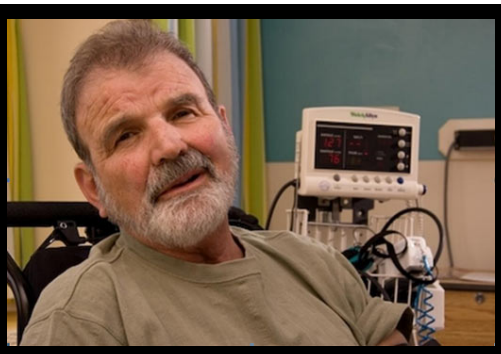


PRoFESS. NEJM 2008;359

Bottom line on secondary prevention in NSR

- Modify risk factors
- Antithrombotic Therapy
  - 1st line: ASA 80-325 mg/d
  - 2nd line: ASA+dipyridamole OR clopidogrel alone
  - 3rd line: ASA+clopidogrel ?
  - Anytime anticoagulation required: warfarin INR 2-3
- Ramipril or Perindopril+Thiazide, regardless of BP
- Atorvastatin (Other statins? Doses?)

Case



- PY is a 73 y/o M who suffered an ischemic stroke 10 days ago (aphasia, L-sided weakness)
- PMH: HTN (~150/85)
- MPTA: HCTZ 25 mg/d
- O/E: no residual neurologic deficit

- CONSULT: What is the most appropriate therapy for secondary stroke prevention in this patient?