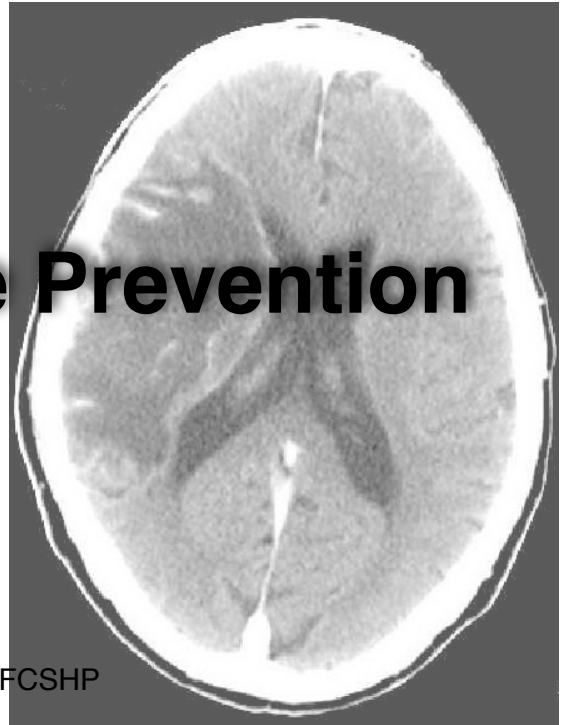


PHAR 451

Ischemic Stroke Prevention

Therapeutics

(non-AF)



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University of British Columbia
Vancouver General Hospital

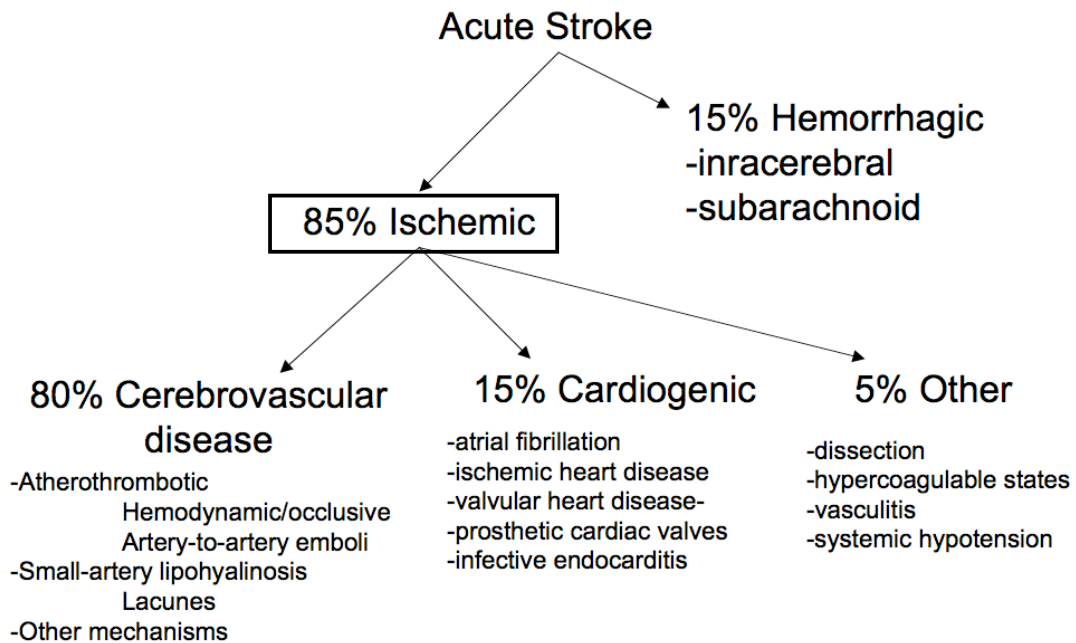
Objective

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

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

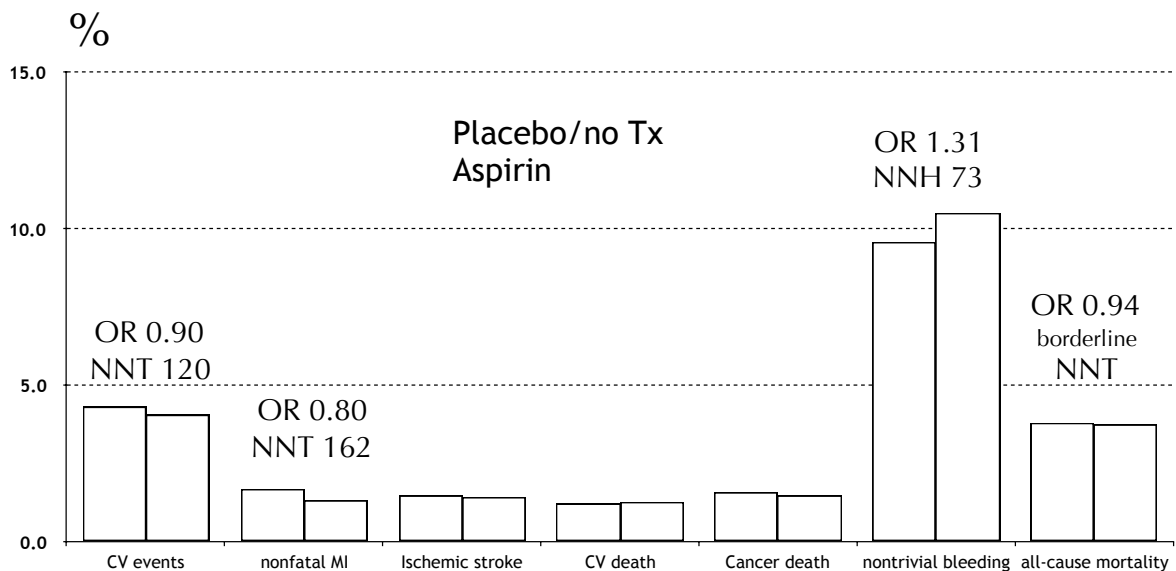
What we do	In whom	Why?
treat HTN	everyone	40% stroke RRR
ASA?	people who have a CV indication for ASA	Berger JS et al. JAMA 2006;295:306-13
ramipril (perindopril?)	high CV risk pts, regardless of HTN	HOPE (EUROPA?)
statin	pts at sufficiently high CV risk (e.g. >10% 10-year CV risk)	HPS, CARDS, ASCOT-LLA,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

Primary Prevention

Aspirin: primary prevention

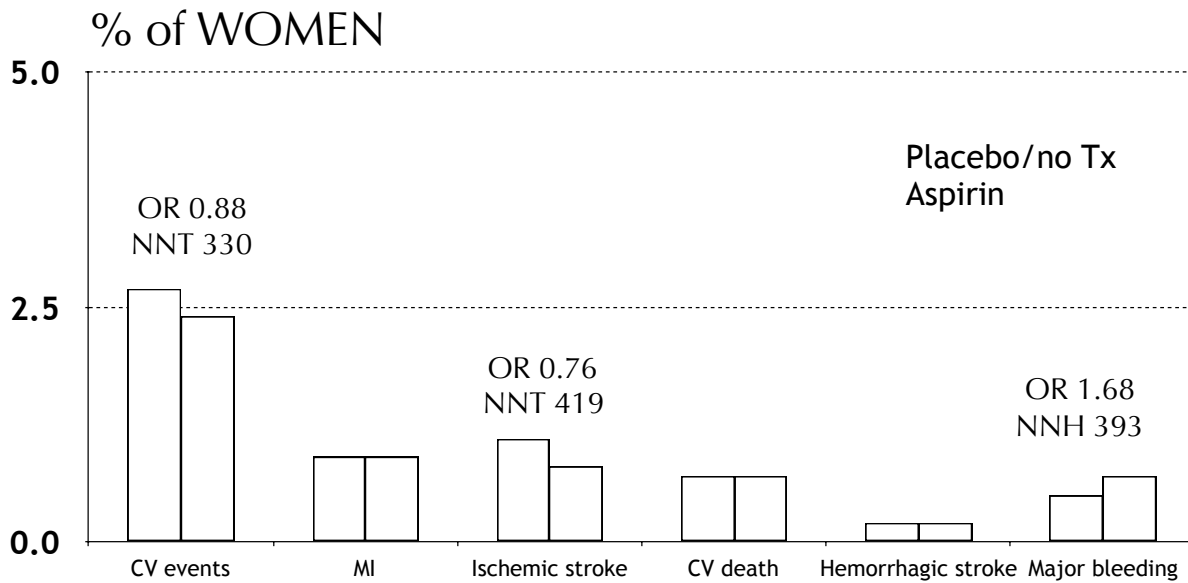
N=9 trials. N=102,621

ASA 75mg - 162 mg/d, mean 6.0 years followup.



Aspirin: Effects by gender

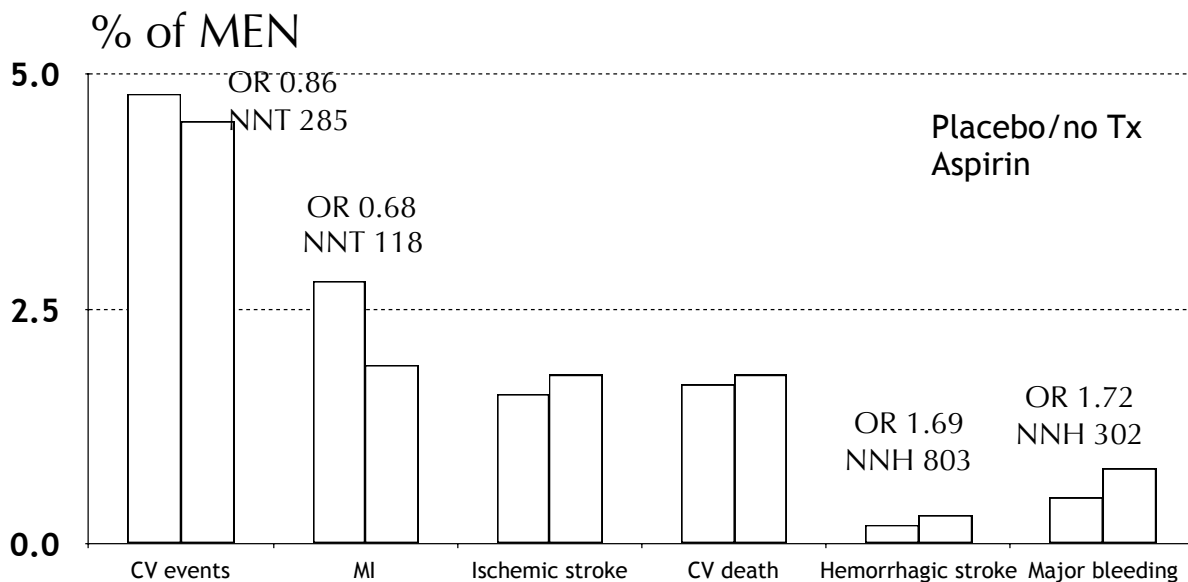
N=6 trials. 51,342 women, 44,114 men.
ASA 75mg - 500 mg/d, mean 6.4 years followup.



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

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

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

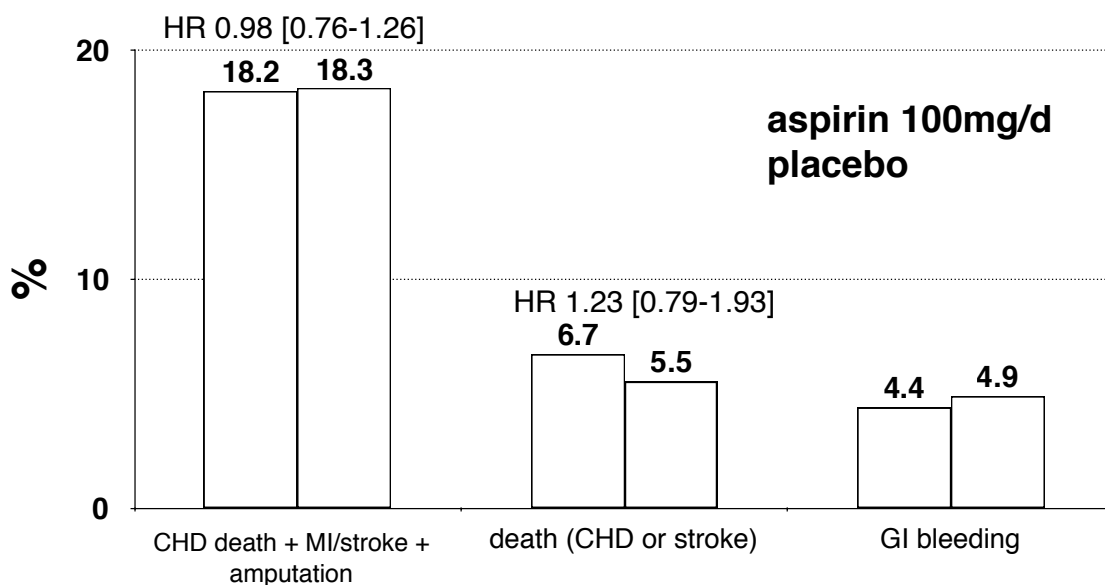
Causes major bleeding in males & females

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

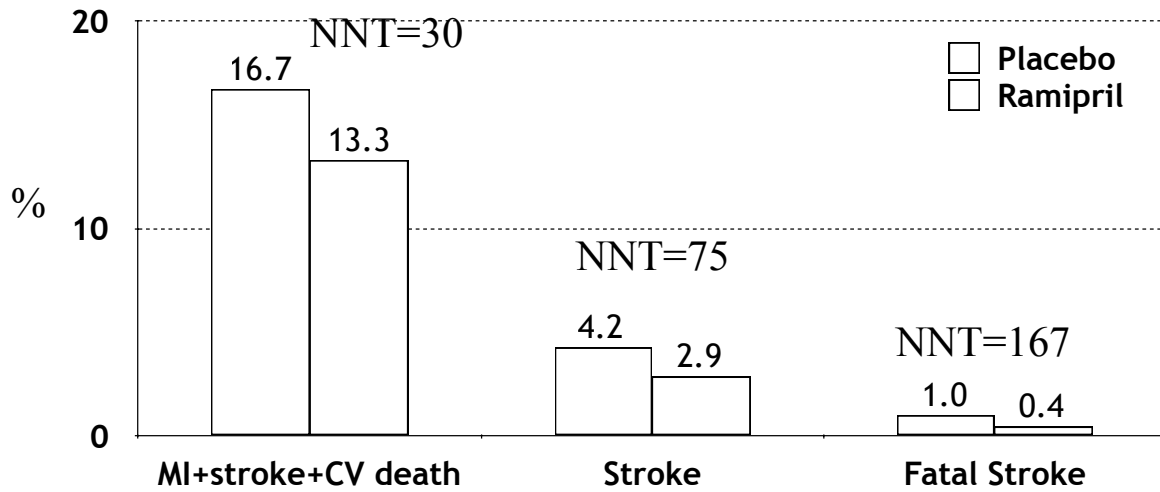
POPADAD

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



Ramipril - HOPE-STROKE

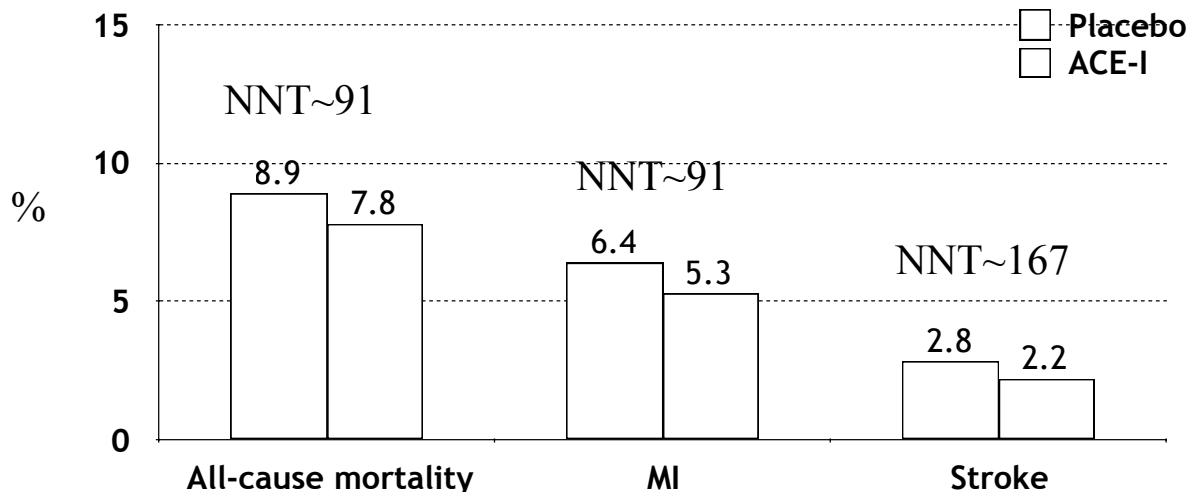
N=8284 pts with CAD, PVD, diabetes but no prior stroke/TIA treated x 4.5 years



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

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



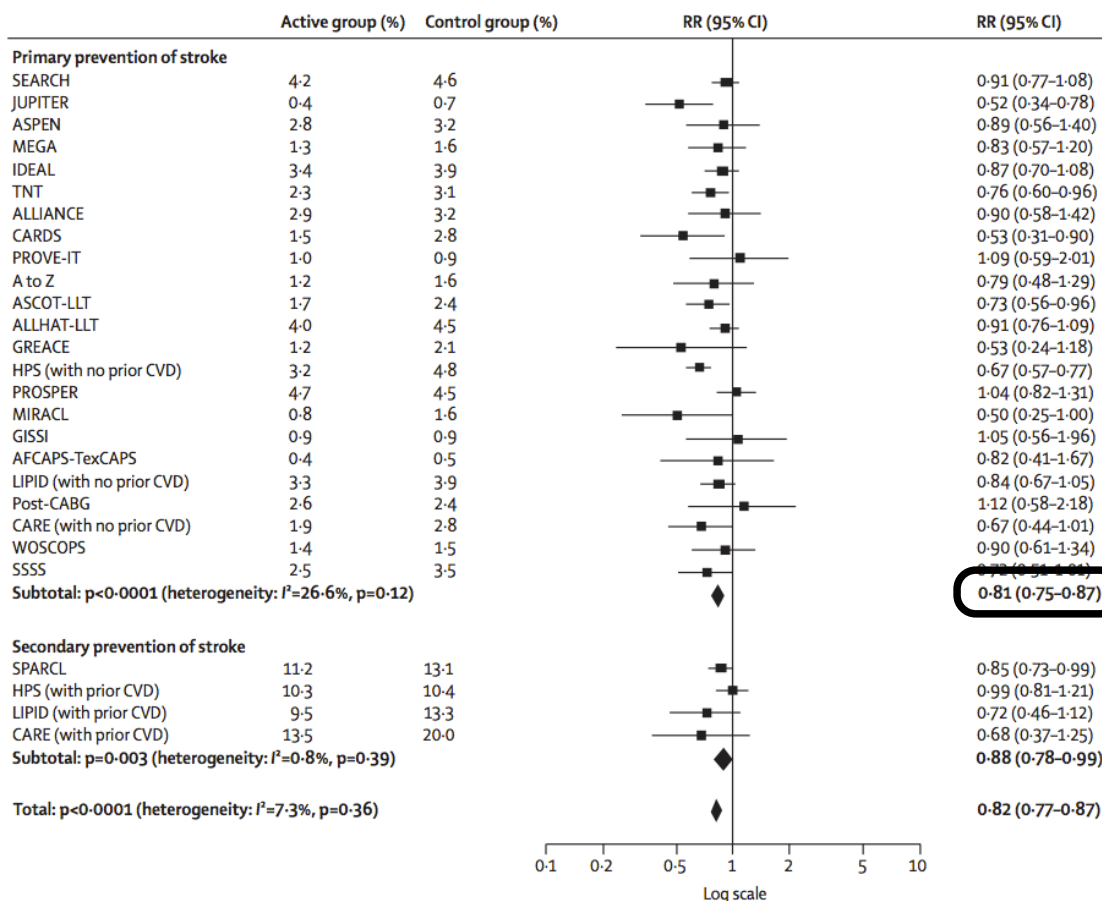
Lancet 2006; 368: 581-88

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

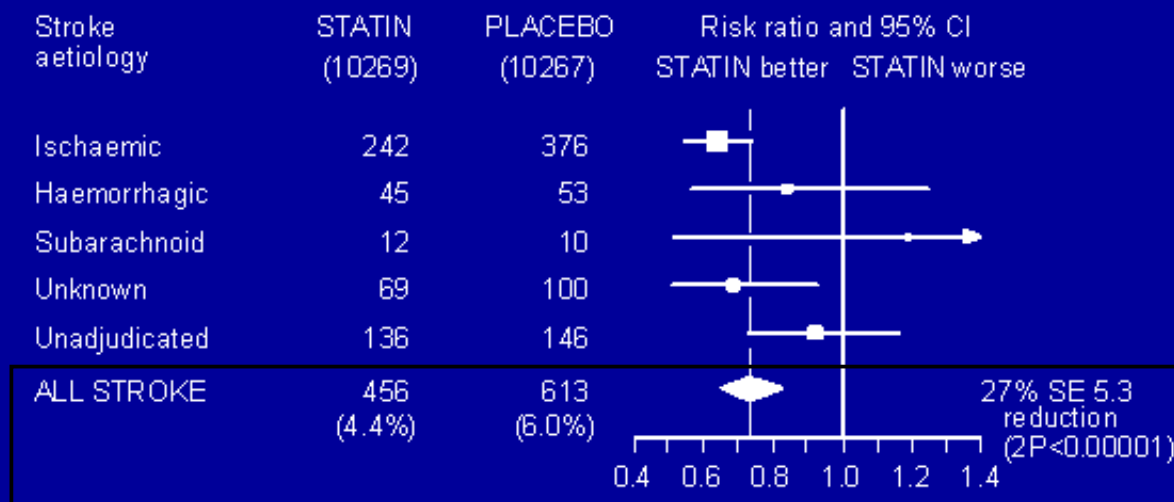
↑
Independent of
gender, HTN, DM2,
prior CAD, risk

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



MRC/BHS Heart Protection Study

SIMVASTATIN: STROKE by AETIOLOGY



NNT x 5.5y=63

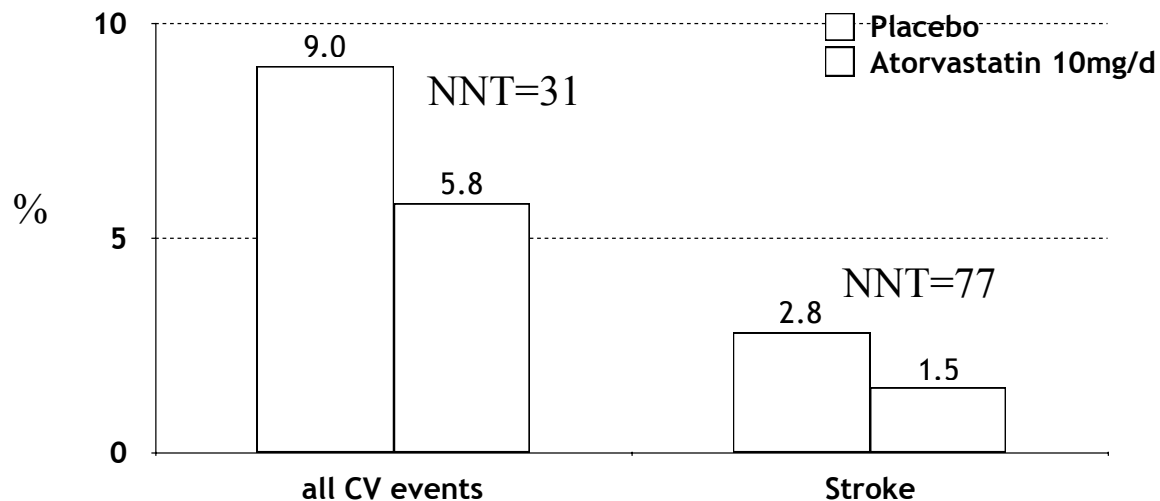
HPS

HPS. Lancet 2002;360:7-22

Atorvastatin - CARDS

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

Duration = 3.9 years

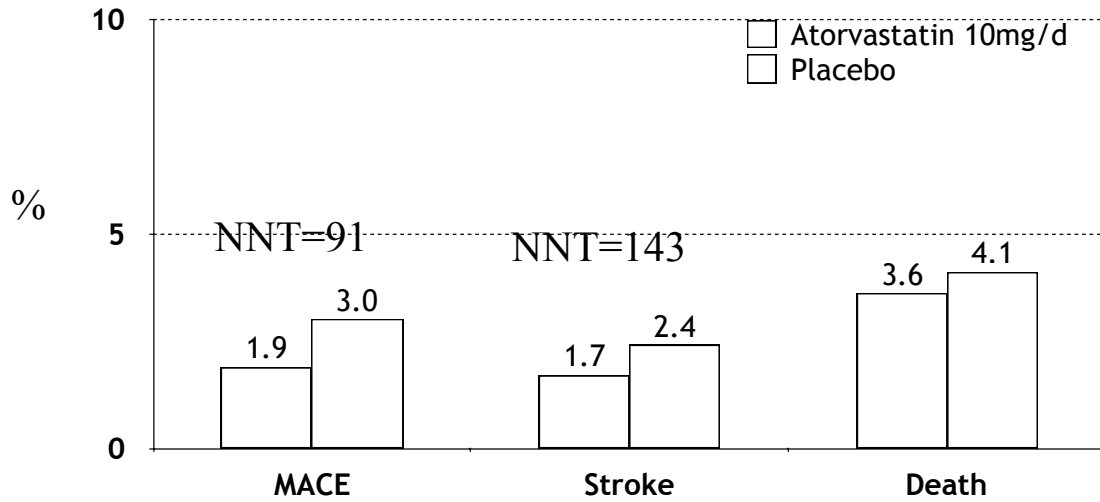


CARDS. Lancet 2004;364;685-96

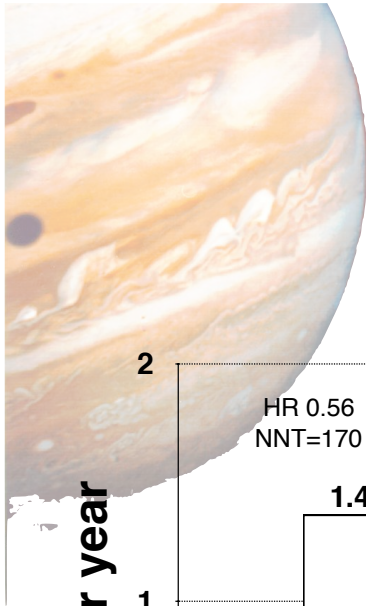
Atorvastatin - ASCOT-LLA

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

Duration = 3.3 years

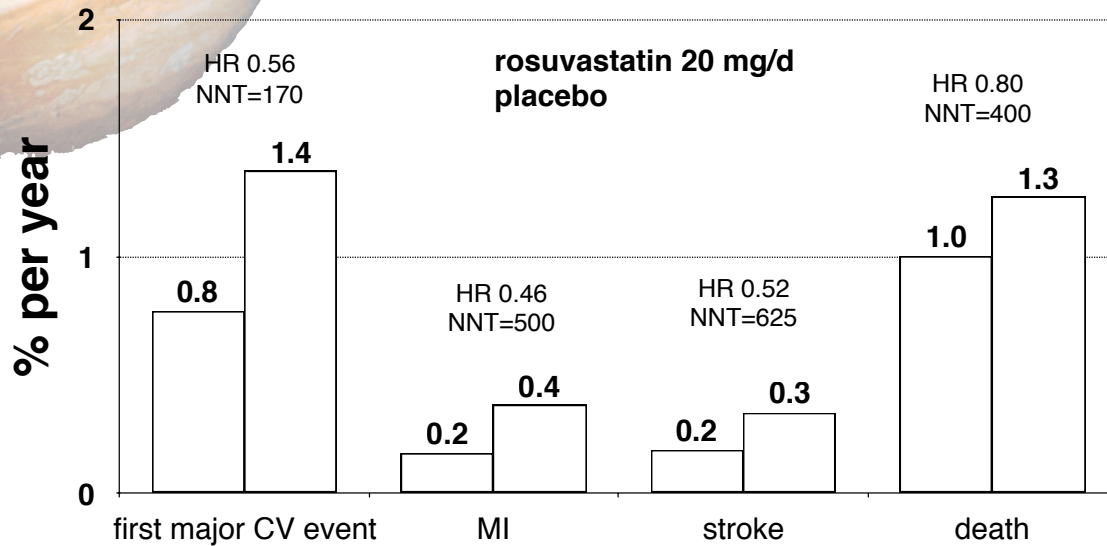


ASCOT-LLA. Lancet 2003;361:1149-58



JUPITER

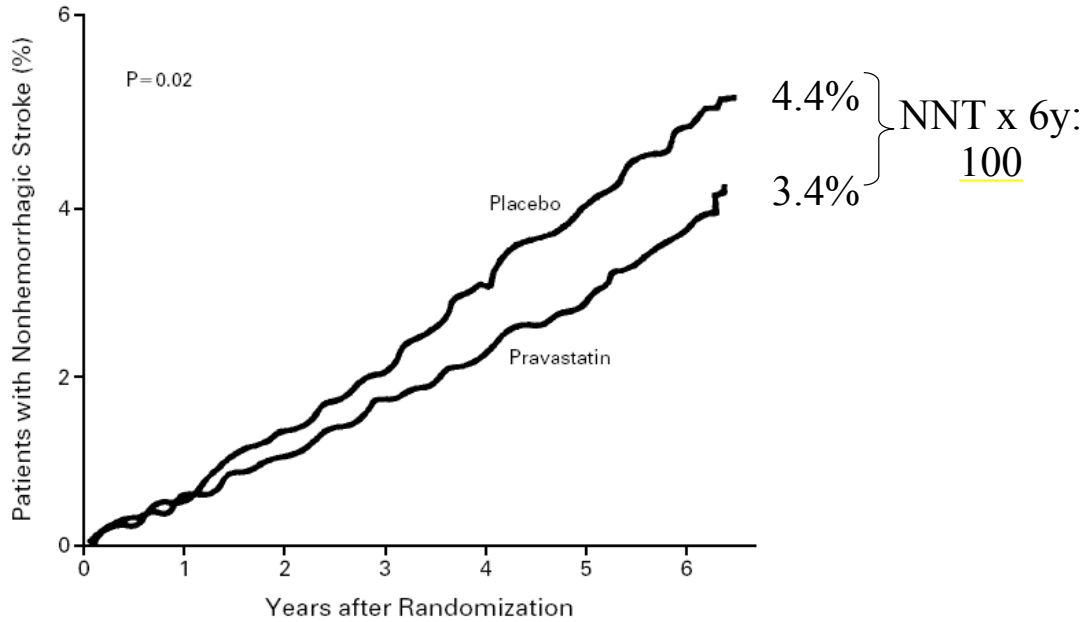
N=17,802 healthy people with normal LDL and CRP>2 mg/L. Stopped after median 1.9y.



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

LIPID-STROKE: Pravastatin

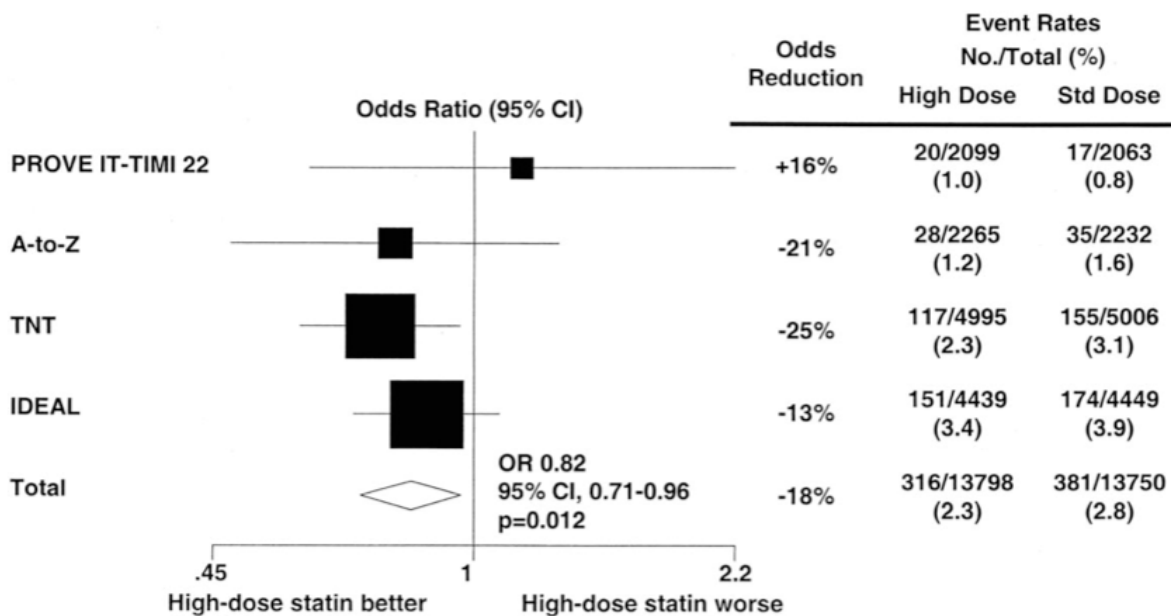
N=9,000 pts post-MI treated with pravastatin 40mg/d



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)

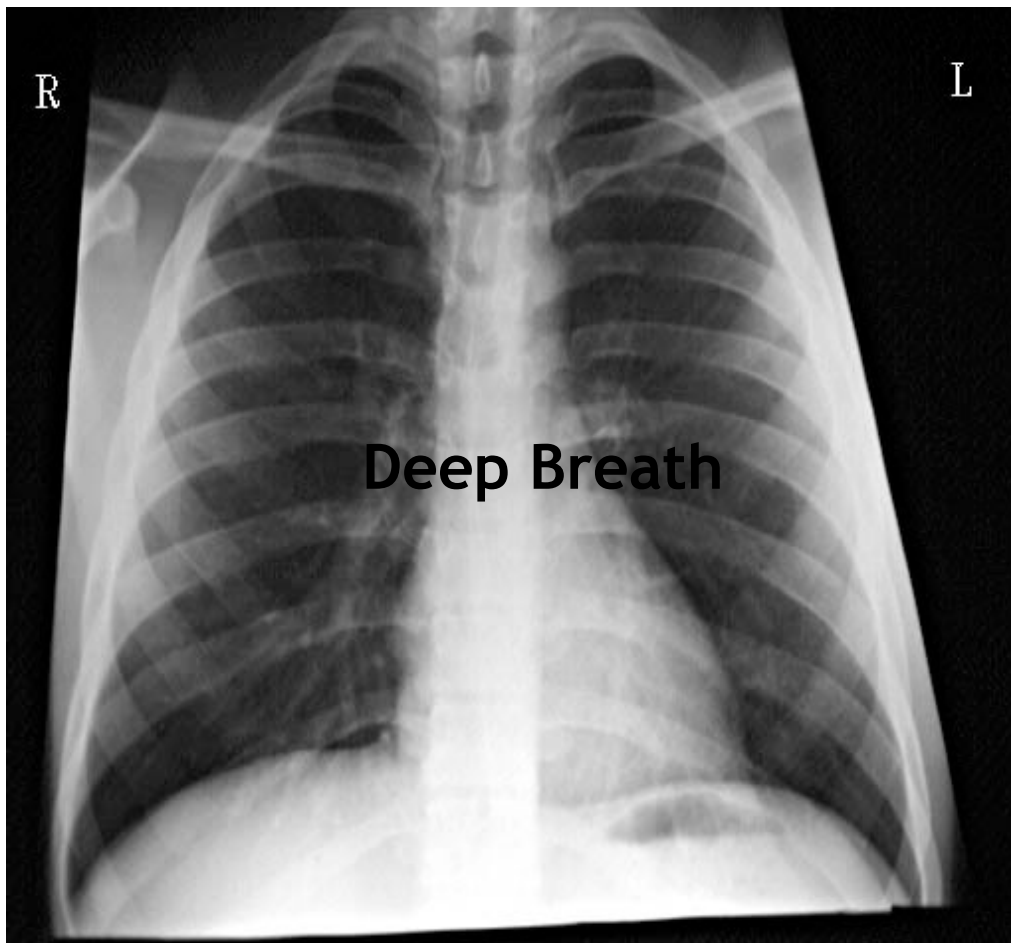
Role for antithrombotic therapy?

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

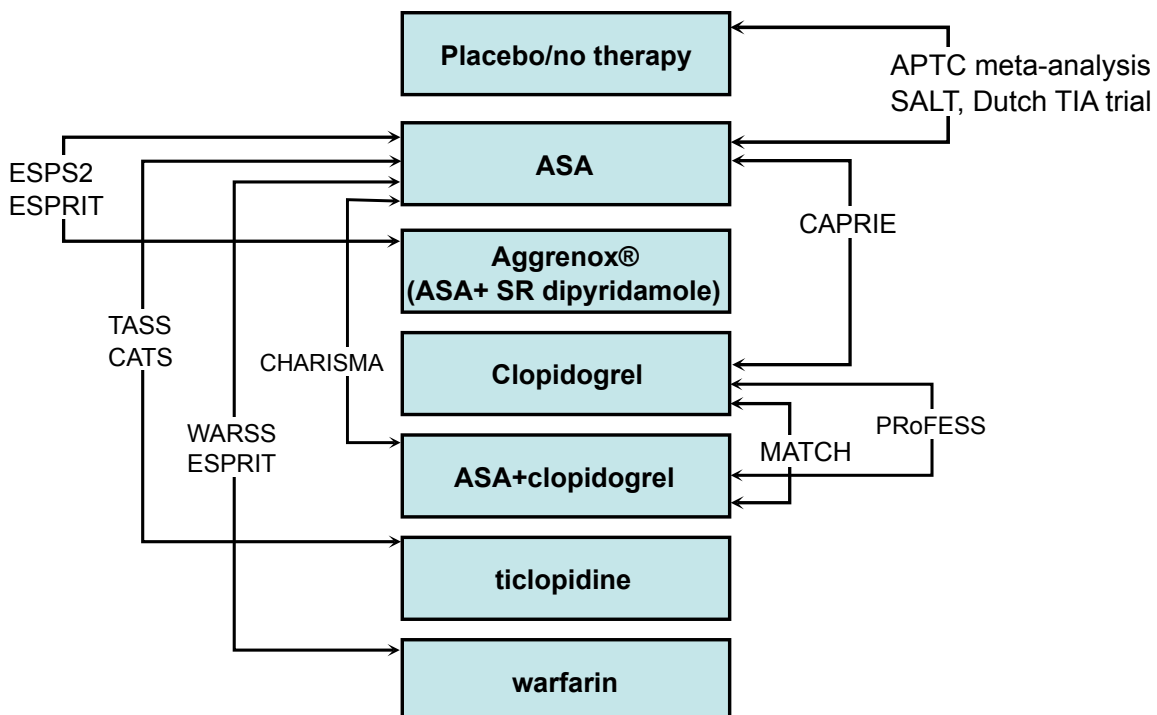
regardless of baseline cholesterol levels



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:

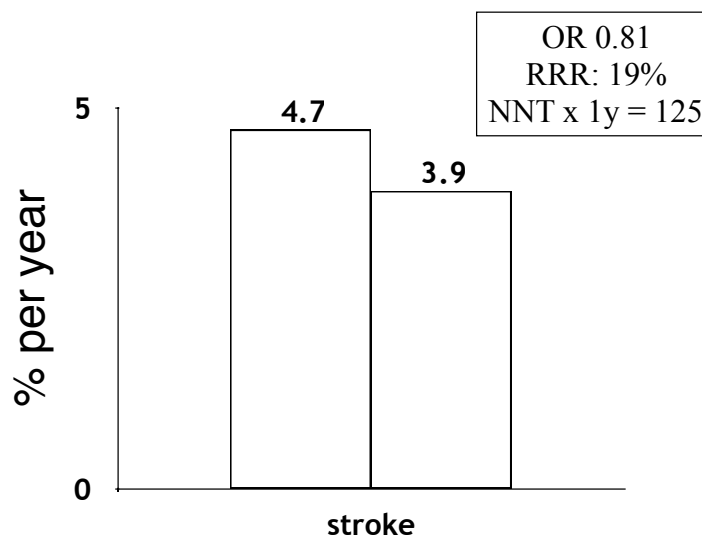
Clopidogrel (CAPRIE)

Warfarin (WARSS)

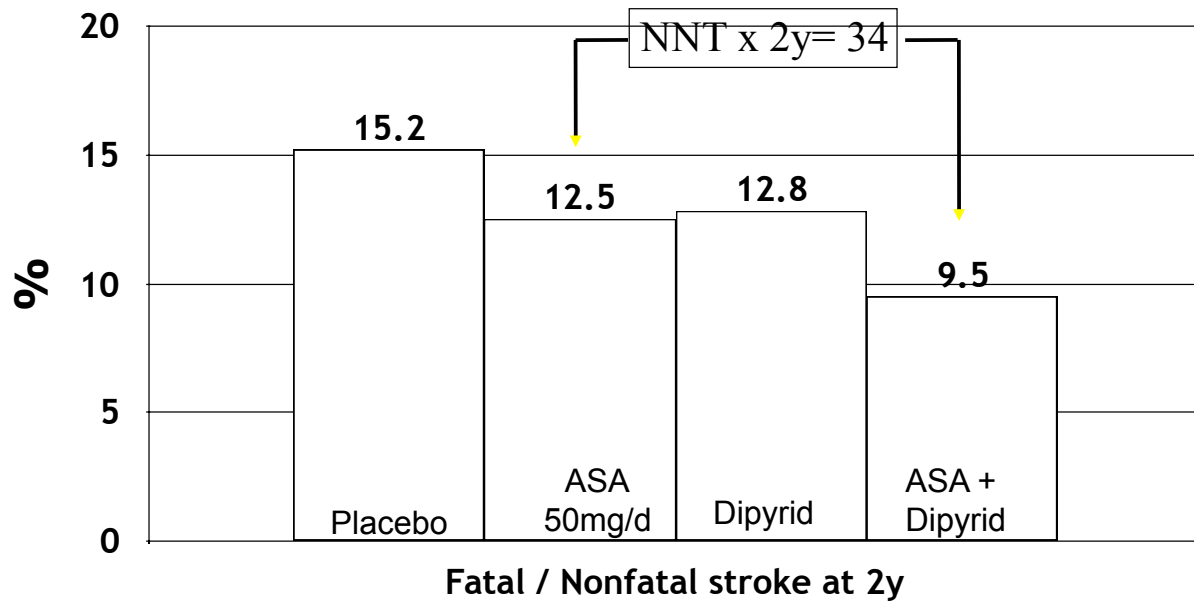
Clopidogrel + ASA (MATCH, CHARISMA)

Efficacy of ASA: The Gold Standard

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



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

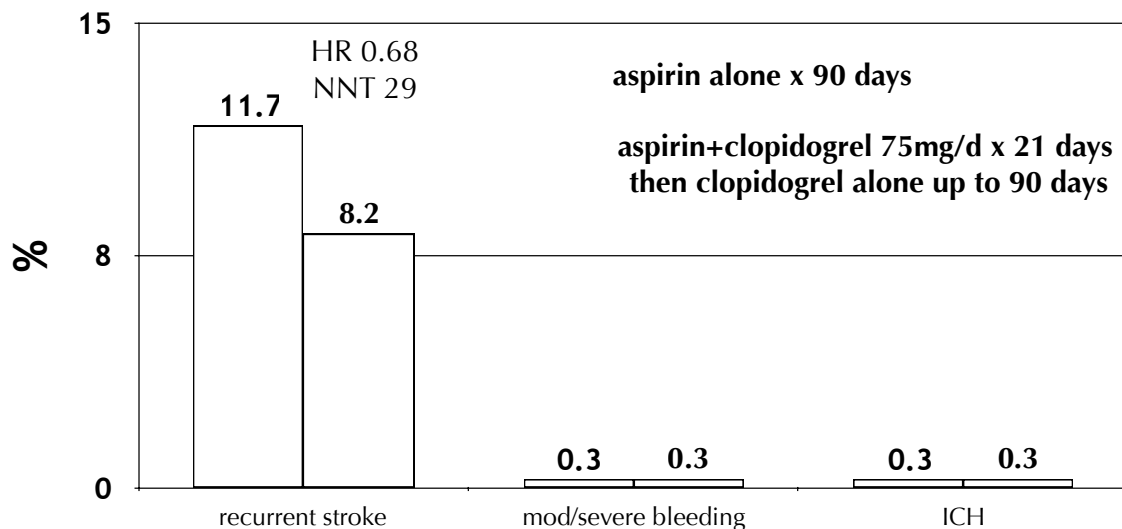


ESPS-2, Thromb Res 1998;92:S1-S6

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

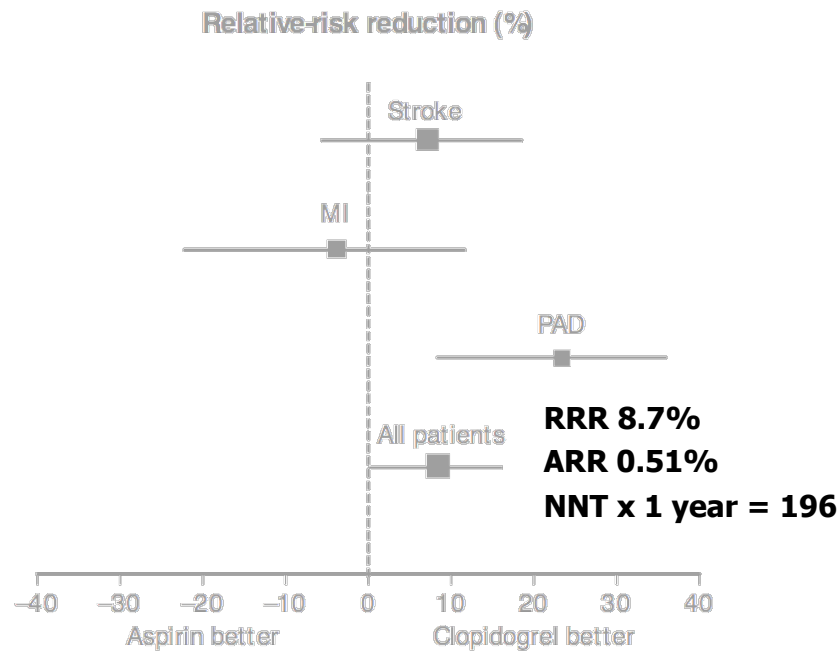
N=5170 patients in China within 24h of minor ischemic stroke/TIA. All taking aspirin 75-300mg/d.

90 days followup.



CHANCE. New Engl J Med 2013;369:11-9.

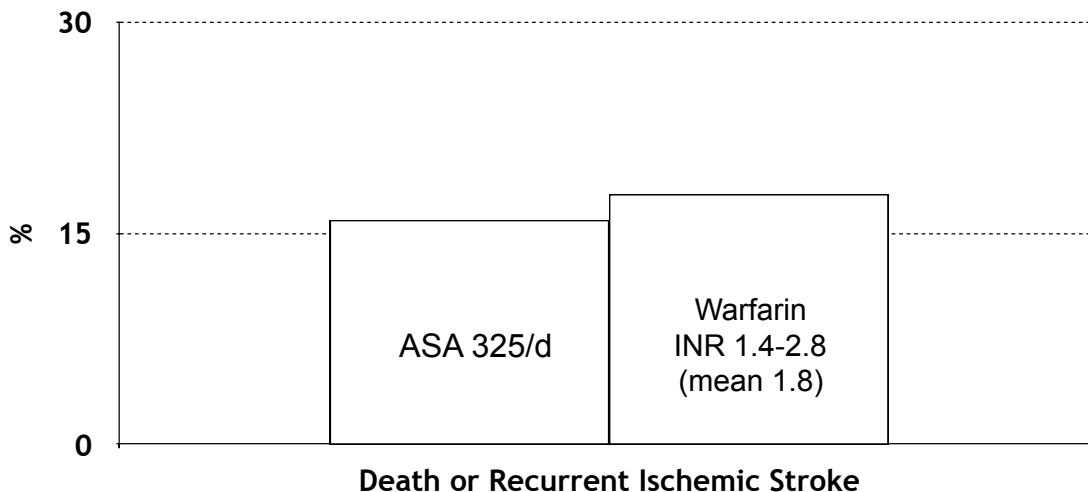
Stuff that's the SAME AS aspirin: Clopidogrel: CAPRIE



CAPRIE. Lancet 1996;348:1329-39

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

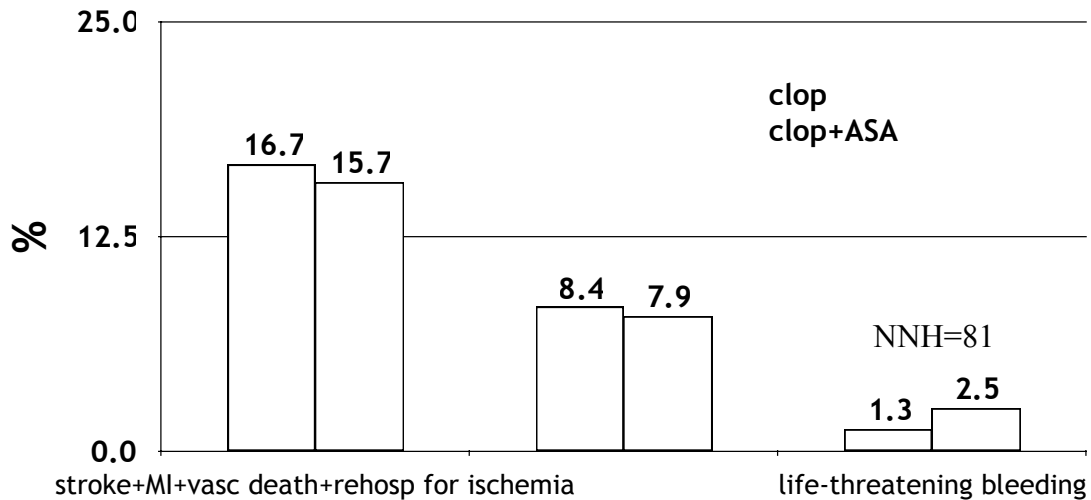
N=2206 stroke survivors treated for 2 years.



WARSS. NEJM 2001;345:1444-51

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.

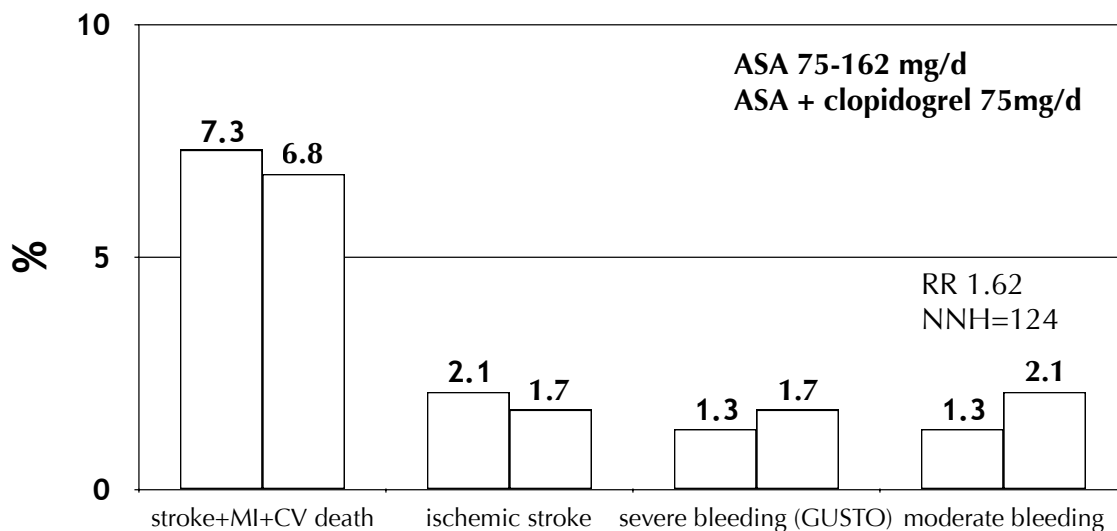


MATCH. Lancet 2004; 364: 331-37

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



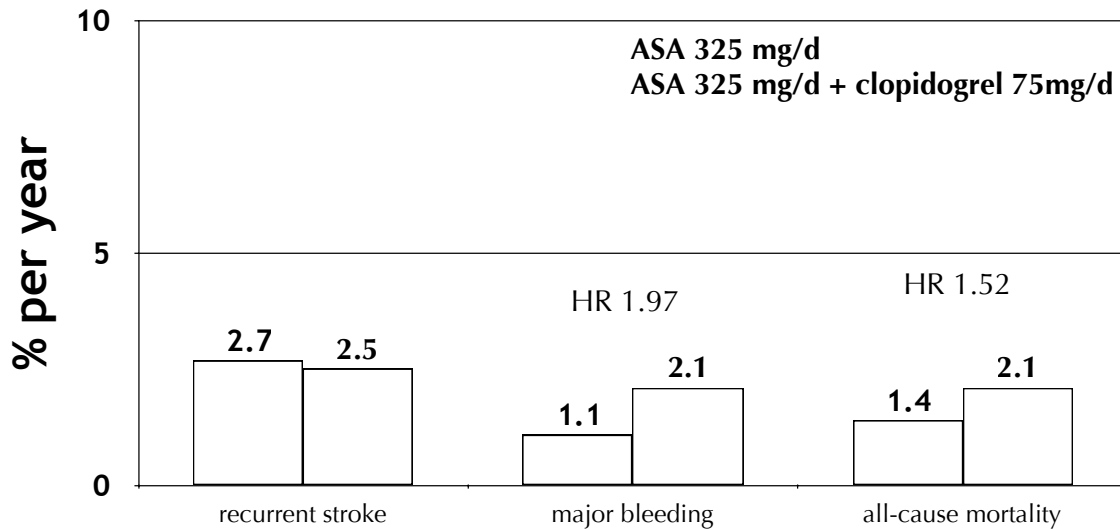
CHARISMA. NEJM 2006;354 (12MAR06)

Stuff that's the SAME AS aspirin

Clopidogrel + ASA: SPS3

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

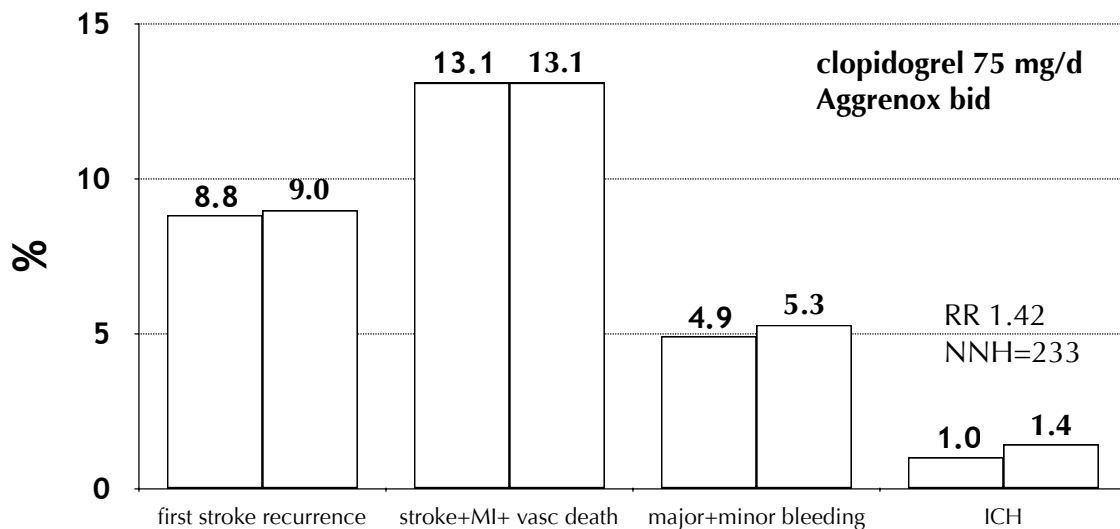
Mean 3.4 years followup



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

PRoFESS: Clopidogrel vs. Aggrenox

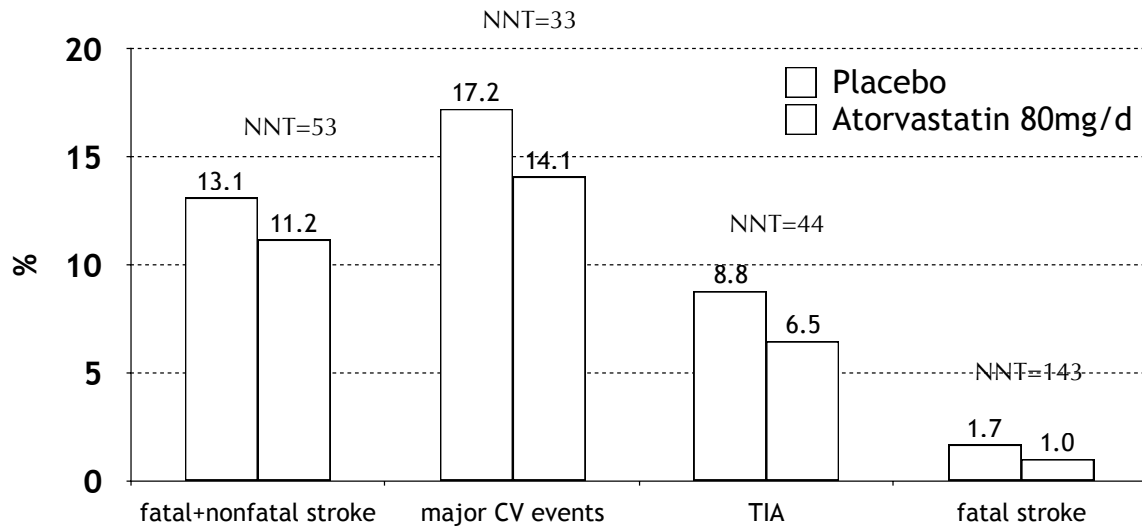
N=20,332 with prior ischemic stroke + >1 risk factor (DM2, HTN, Smoker, obesity, CAD, hyperlipidemia). Average follow-up 2.5y.



PRoFESS. NEJM 2008;359

SPARCL: Atorvastatin

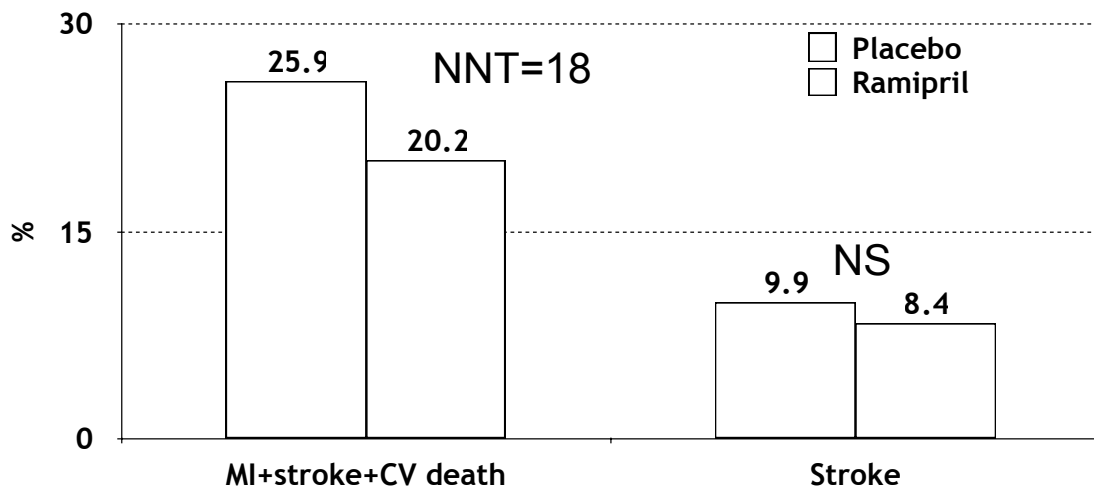
N=4731 pts with prior stroke/TIA, normal LDL, no CAD
Treated x 4.9 years



SPARCL. Lancet 2006;355:549-59

HOPE: Ramipril

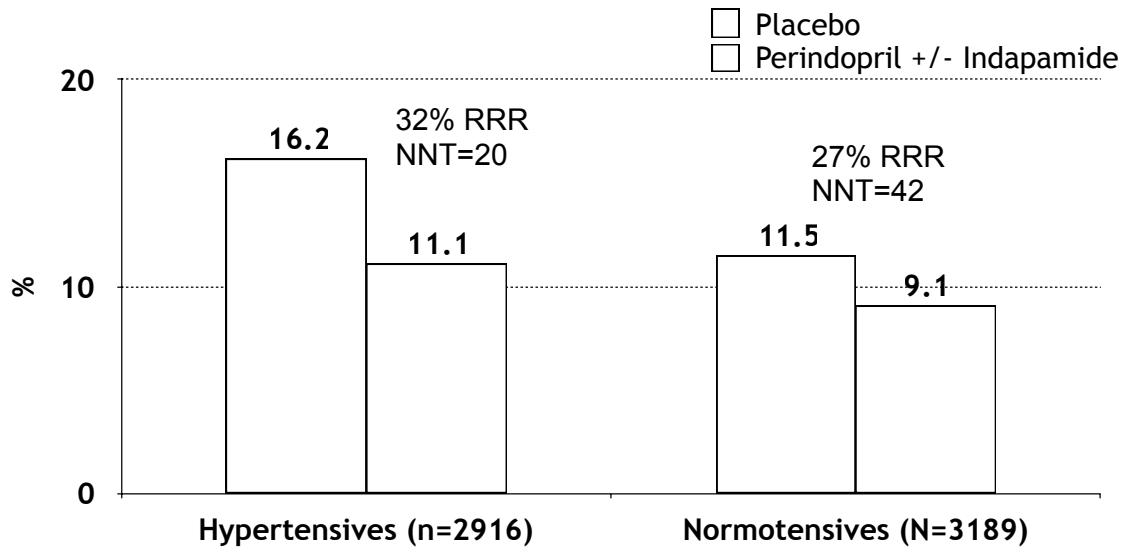
N=1013 pts with prior stroke/TIA treated x 4.5 years



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

Perindopril +/- Indapamide

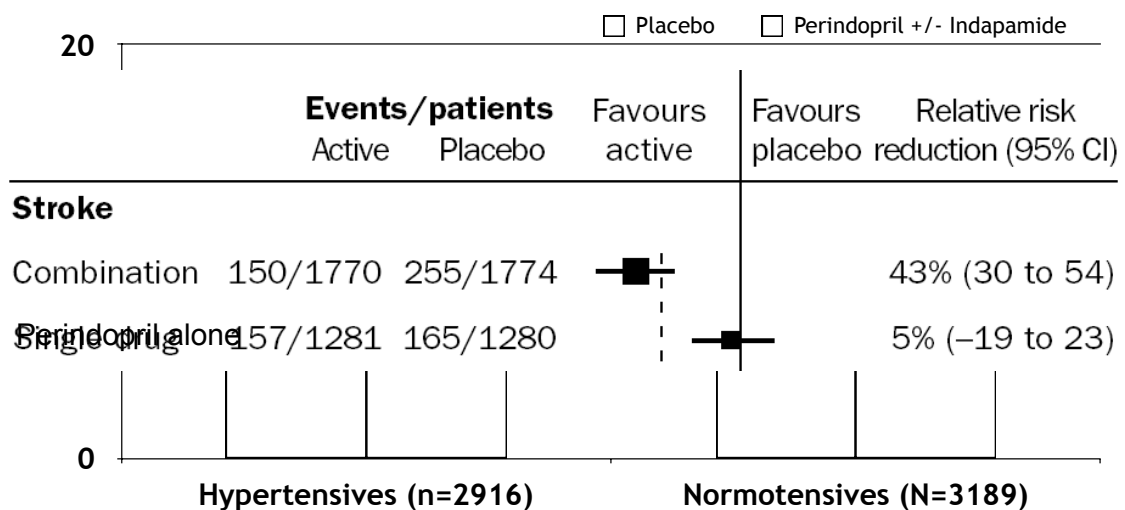
N= 6105 stroke/TIA survivors treated x 4 years.



PROGRESS. Lancet 2001;358:1033-41

Perindopril +/- Indapamide

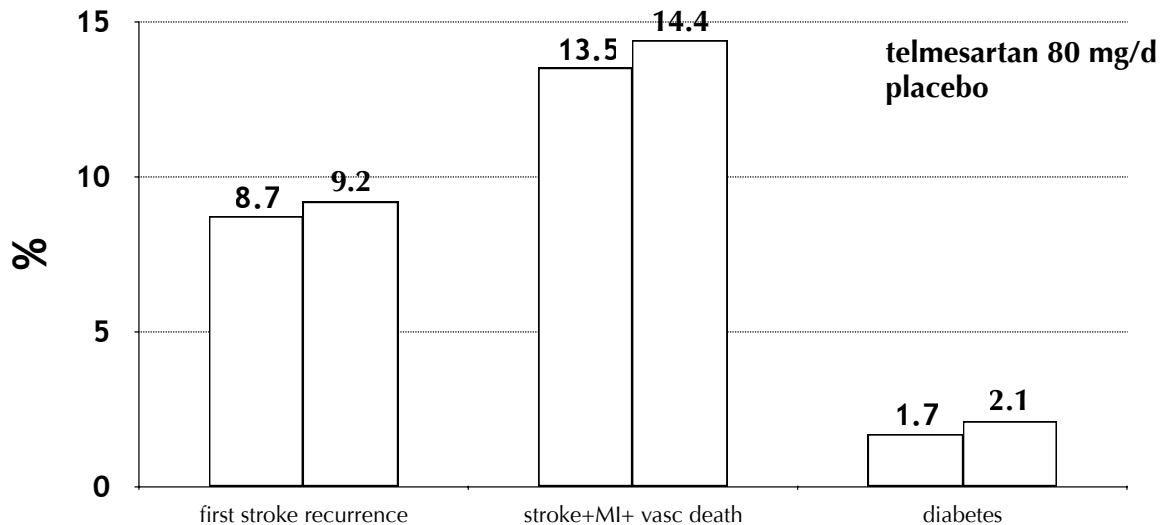
N= 6105 stroke/TIA survivors treated x 4 years.



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?

