

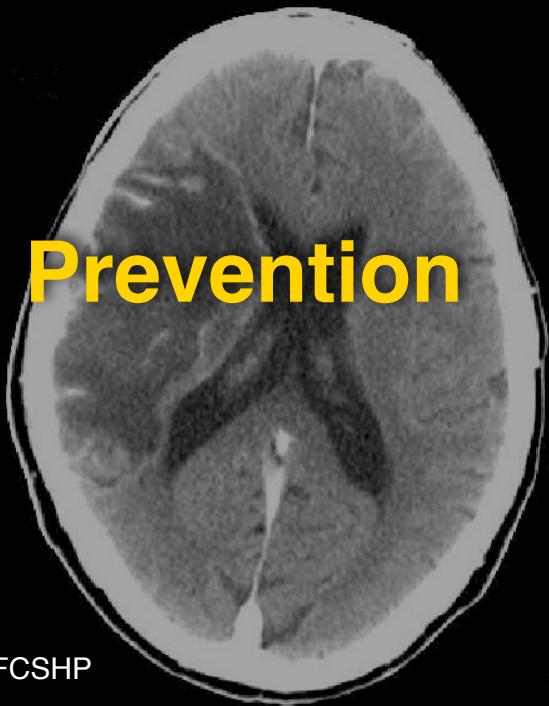
# **PHAR 451**

# **Ischemic Stroke Prevention**

# **Therapeutics**

# **(non-AF)**

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Vancouver General Hospital



## **Objective**

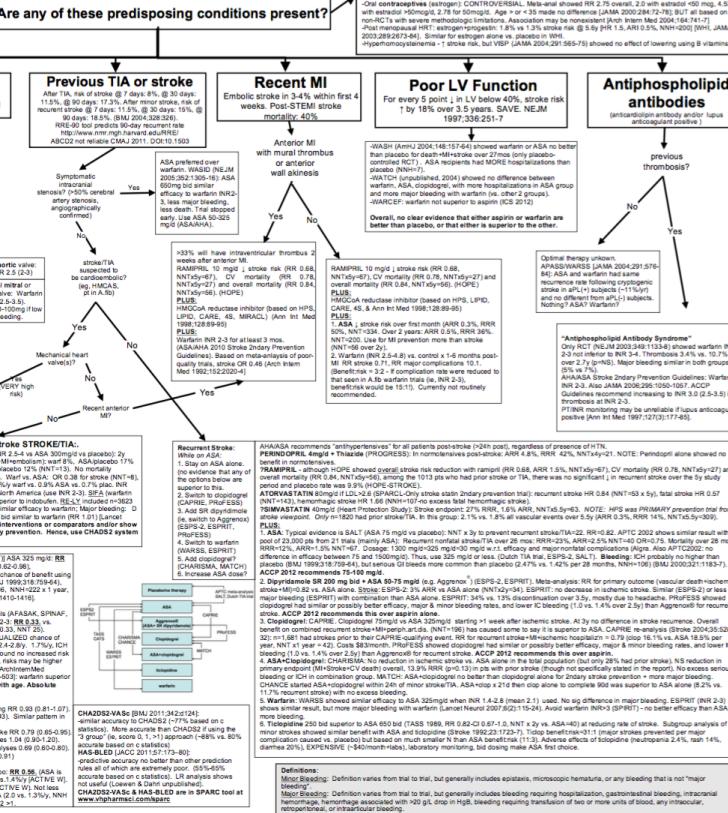
After the session, and upon personal reflection & study, students will be able to:

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

- Primary Stroke Prevention
- Atrial Fibrillation
- Secondary Stroke Prevention

**Primary prevention warfarin vs. aspirin** (for "low risk" vs. "higher risk") Numerous trials in Primary Prevention Study, Brunn-Dorfer's Trial, MRC-1971, HOT, PPHT, WHS, APTC, USPSTF, USPHS, ETRDS. Best Evidence (meta-analysis) including all these trials, JAMA 2008;298(306-13): ASA 50-50mg/d over 6.4 years,  $\geq$ 2 CV events in NNT<sub>10</sub>=7 (vs. 70/21 = 1M in HOT). In HOT, ASA 50-50mg/d was better than warfarin (RR 0.7, NNT 39/21=10) and HPS (RR 0.7, NNT 93/21=1). In WHS, ASA 50-50mg/d was better than warfarin (RR 0.7, NNT 39/21=10) and HPS (RR 0.7, NNT 93/21=1). In JUPITER (Intermediate CV risk); rosuvastatin 20mg/d + stroke RR 0.2, NN<sub>10</sub>=72 (vs. 1M). **HOPE**-STROKE CAD risk factors & prior stroke? (n=8681) Ramipril 10mg/d + placebo 4.2% (ramipril 1.2%, HOPE-DB) NN<sub>10</sub>=88, NN<sub>100</sub>=10. Prior stroke ↓ (HR 0.96, 95% CI 0.91-1.01, P=0.001), prior history of stroke ↓ (HR 0.95, 95% CI 0.91-0.99, P=0.046), HPS 30%, NN<sub>100</sub>=10. **PARADIGM**: ASA 50mg/d vs. placebo in patients with diabetes with PVOD: no effect on stroke risk, JAMA 2008;299(1):849.

## Pharmacotherapy for Ischemic Stroke Prevention



**Carotid artery stenosis**  
(10% have silent infarctions) ( $\geq$ 75% stenosis → 2.5% stroke/year and 8.5% MI/year). CEAN=carotid endarterectomy, CAS=carotid angioplasty & stenting.

**Symptomatic (recent <6mos):**  
No → ASA/CAS (JAMA 1995; ACST (Lancet 2004;363:1481-501), NEJM 358:15-1617-21, CAS: 10-year survival 75% vs. 50% surgery risk  $\times$  10% and good surgical results. Carotid Endarterectomy with ASA 75-100 mg/d lifetime. Medical Therapy: If not grafted, all the usual CV risk reduction. ASA 75-100mg/d, avoid aspirin (ASA 75-100 mg/d, CHAMPS, ACCIP, 2008). CAS over need of immediate reoperation (e.g., CREST, ACT) for these "low risk" patterns.

No → ASA/CAS (Optimal therapy unknown. Surgery worsens outcome (EST), but may reduce risk of stroke + manage atherosclerotic risk factors).

Yes → degree of stenosis (NASCET method):  $<50\%$  → paroxysmal;  $\geq 50\%$  → chronic or paroxysmal? CEA or CAS. After CAS, asymptomatic for at least 4 weeks (CREST). After CEA, asymptomatic for 2 years (ACCIP 2008).

Choose preventive therapy based on annual stroke risk vs. bleeding risk + patient's preference.

**CHADS2 Risk Scoring System:** CHADS (1 point): HTN (regardless of control or treatment) (1 point). Diabetes (1 point). Previous stroke or TIA (1 point). Total Score: (0-4)

**Score = Annual Stroke Risk (%)**

0 / 7.0%	0.2%	1.2%
1 / 2.8%	0.2%	0.3%
2 / 4.0%	0.3%	1.5%
3 / 5.9%	0.4%	4.7%
4 / 8.8%	0.5%	7.7%
5 / 12.5%	0.6%	15.7%
6 / 18.2%	0.7%	18.7%

with CHADS2+VALE + HAS-BLED  
Score = 0.7 → Score > 0

**Age $\geq$ 65: "Lone a-fib":** Annual stroke risk 1.3-1.4%, warfarin indicated (ACCP 2008). Guidelines recommend ASA 325mg/d, based on minimal evidence.

**Age  $\geq$ 75: SPAFF** re-analysis supports ASA 75-100 mg/d over warfarin (RR 0.8, SPAF II event rate 0.59% vs. ASA group). No placebo arm in either trial. ACCP 2008 guidelines recommend Warfarin INR 2-3 or ASA 325mg/d.

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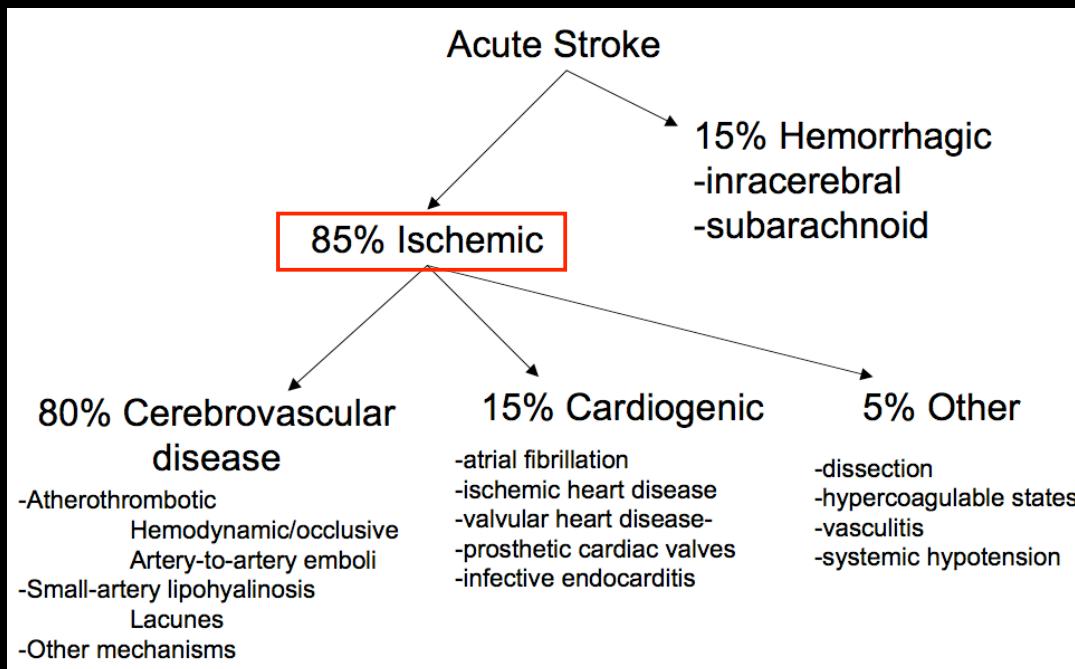
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# Stroke Subtypes



## *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.

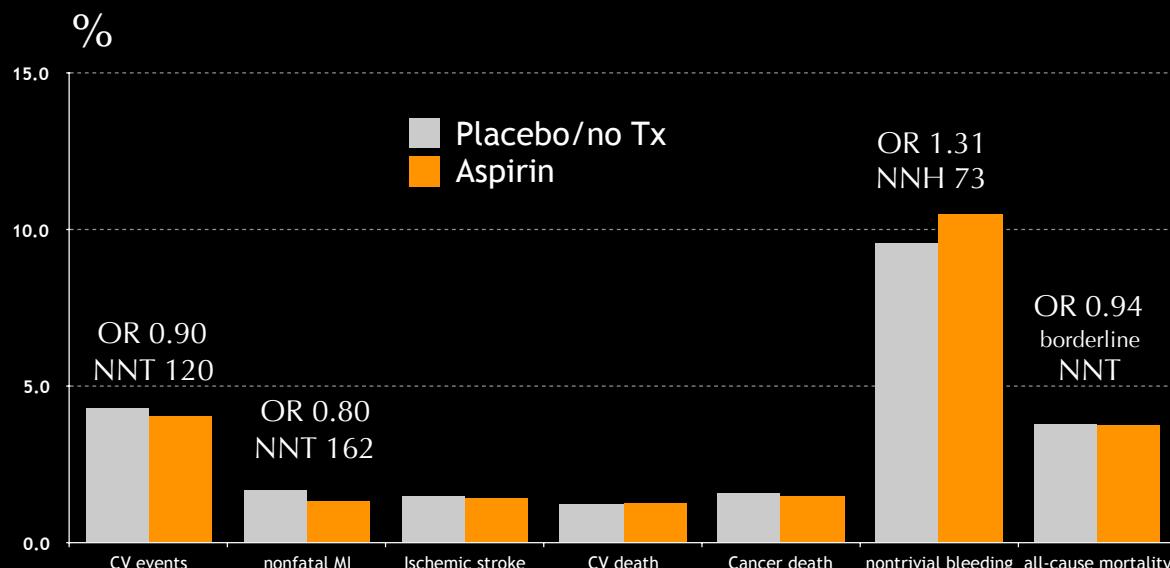
## **PRIMARY PREVENTION**

# 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

## Aspirin: primary prevention Primary Prevention

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



## *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.

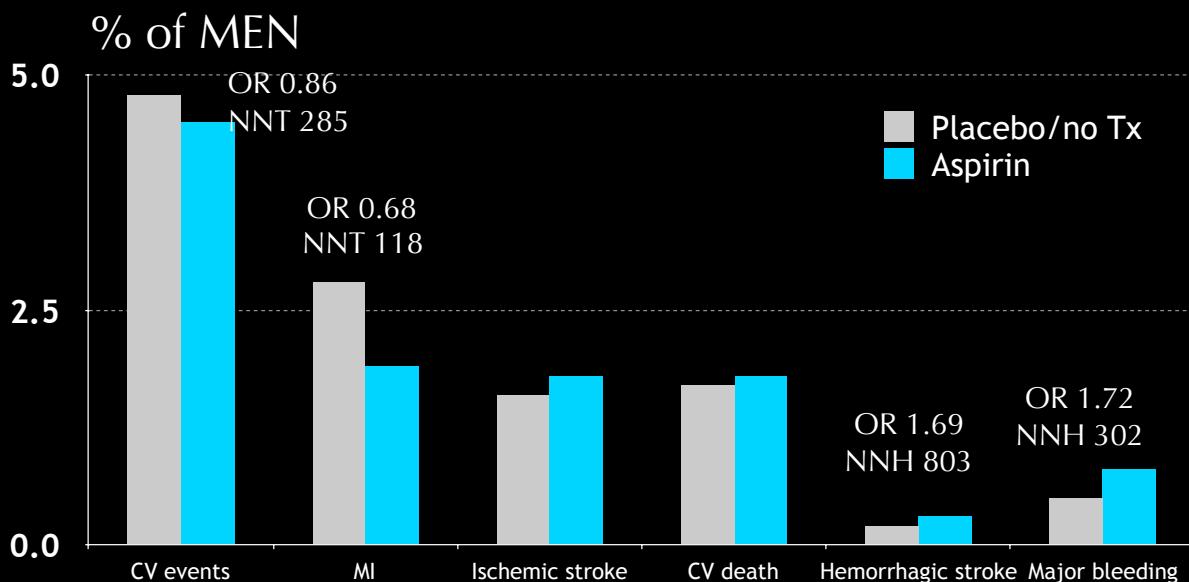


Berger JS et al. JAMA 2006;295:306-13

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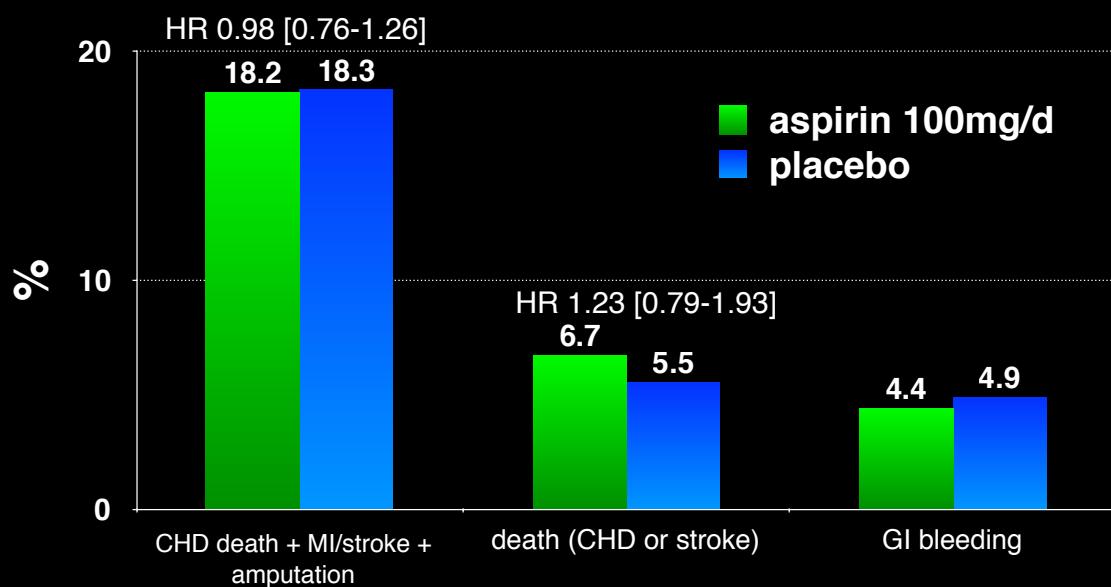
# Aspirin for Primary Stroke Prevention Bottom Lines

- 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

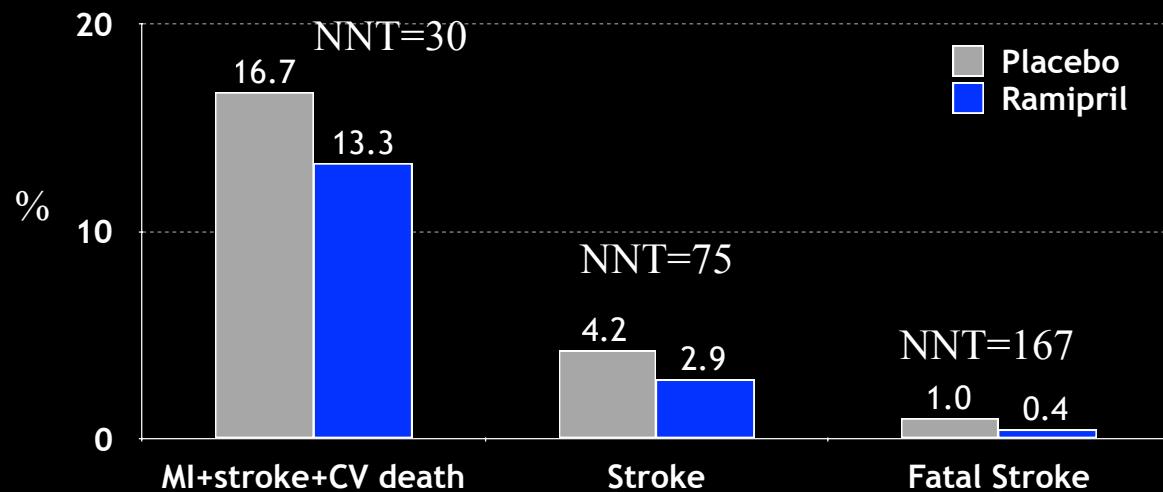
N=1276 Scots with DM1 or DM2, ABPI < 0.99 but no symptomatic CV disease. Median 6.7 years followup.



## Primary Prevention

### Ramipril - HOPE-STROKE

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

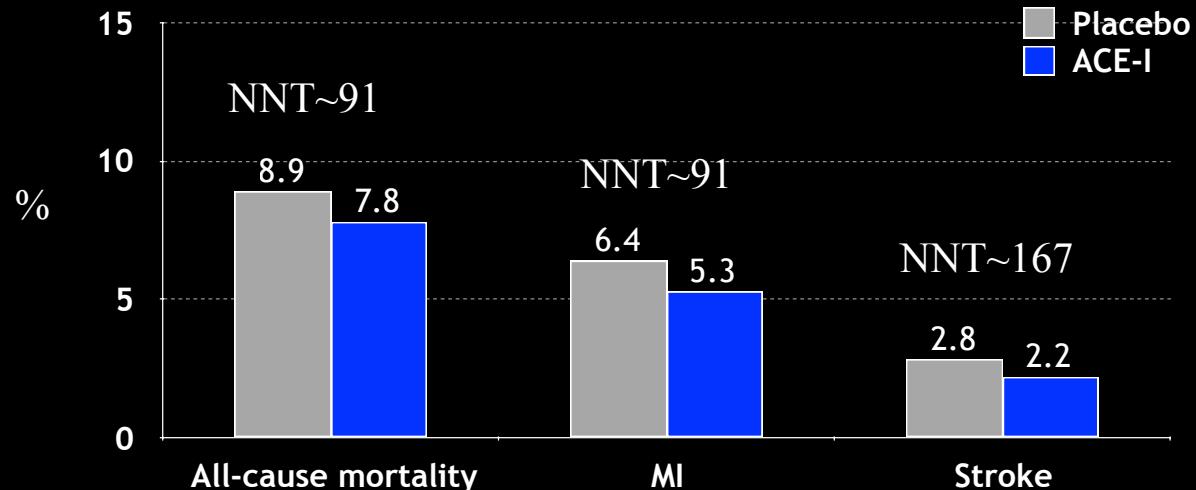


NEJM 2000;342:145-53 / BMJ 2002;324:1-5

## Primary Prevention

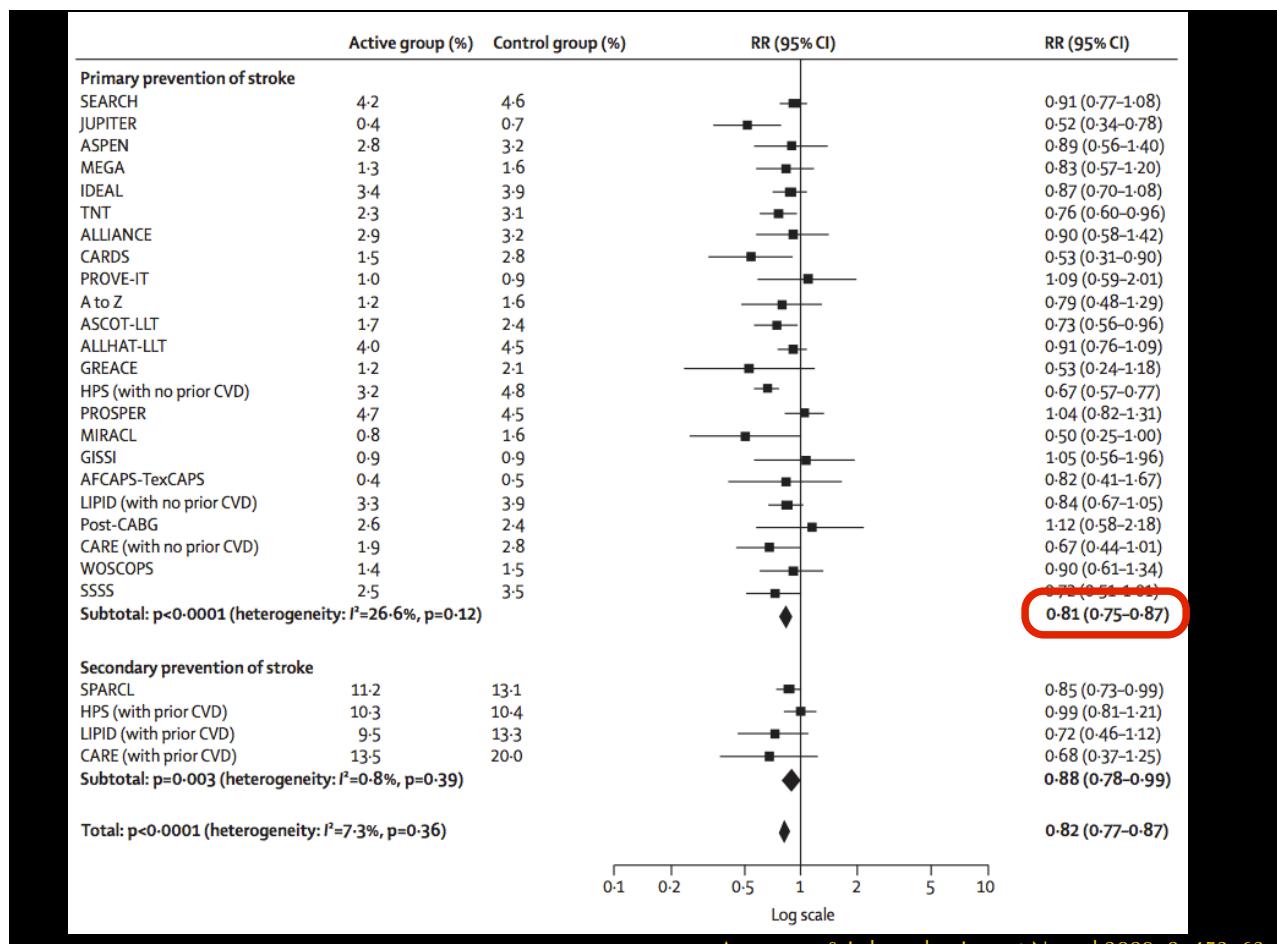
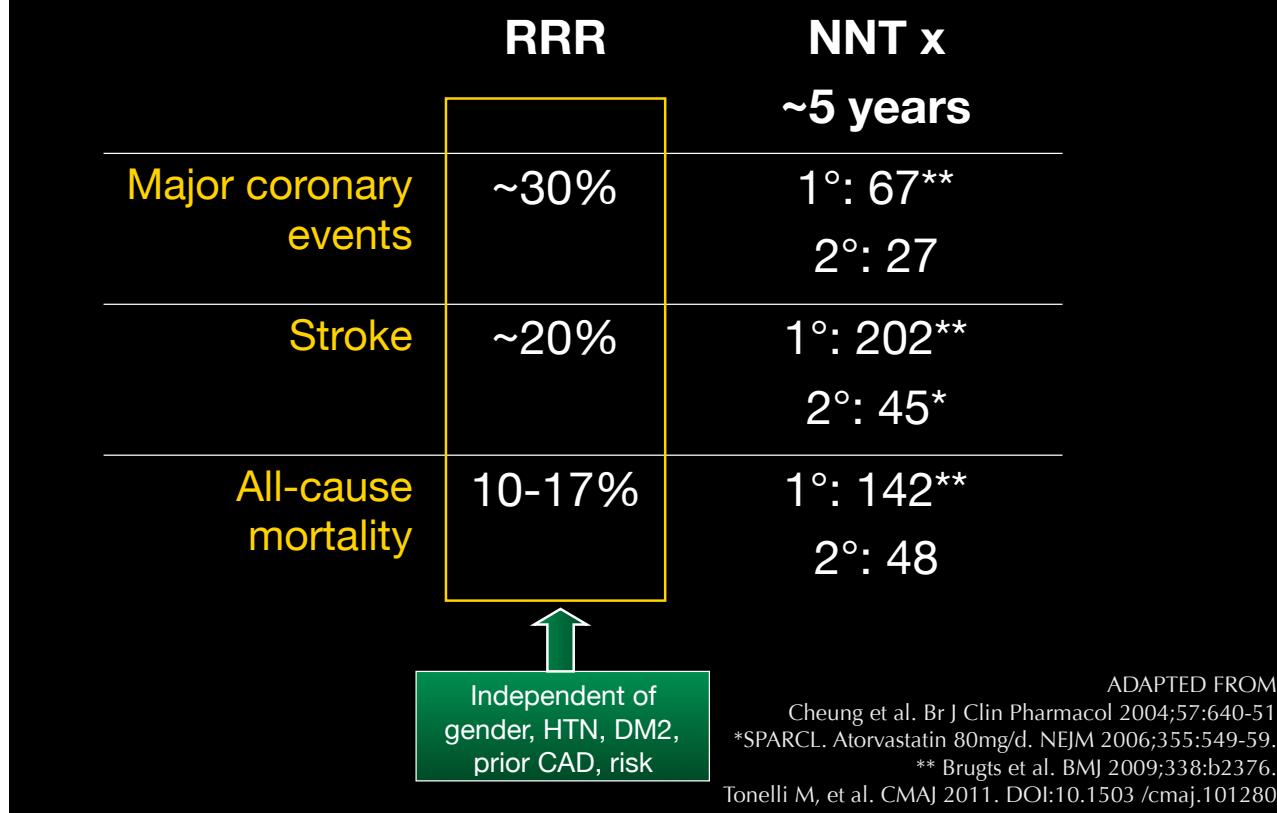
### All ACE-Is (R, T, & P)

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



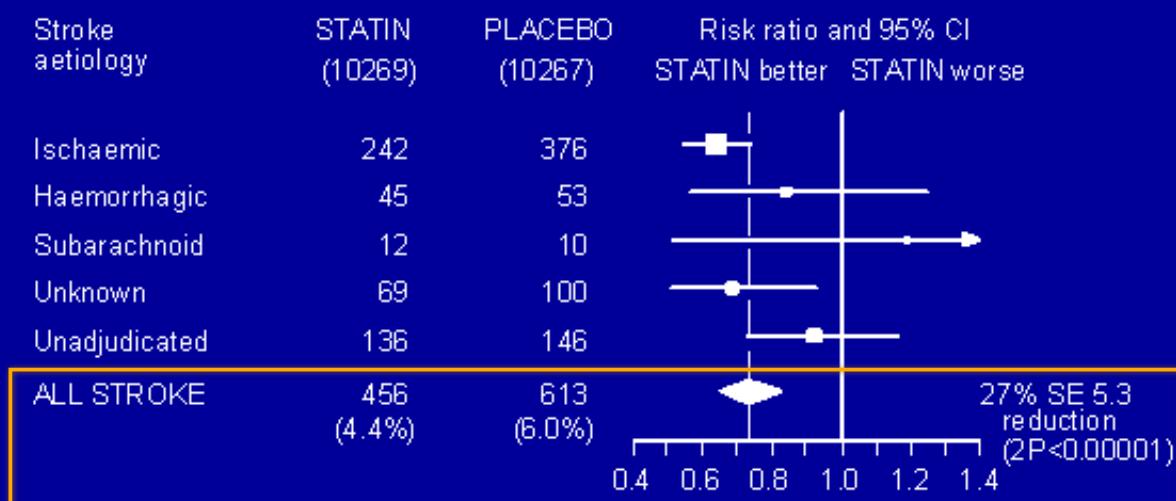
Lancet 2006; 368: 581-88

# Overall Efficacy of Statins



# MRC/BHS Heart Protection Study

## SIMVASTATIN: STROKE by AETIOLOGY



NNT x 5.5y=63

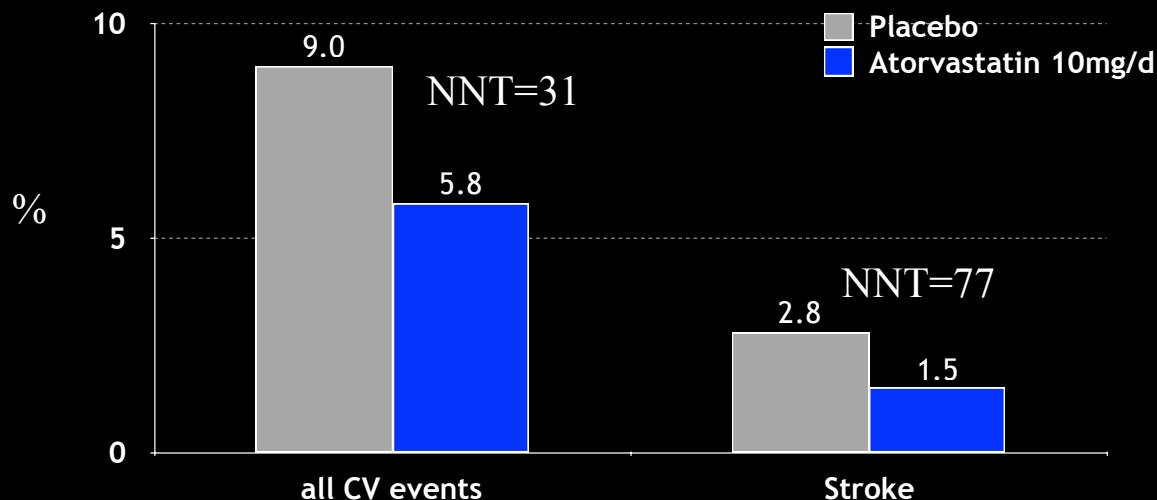
*hps*

HPS. Lancet 2002;360:7-22

## Atorvastatin - CARDS

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

Duration = 3.9 years



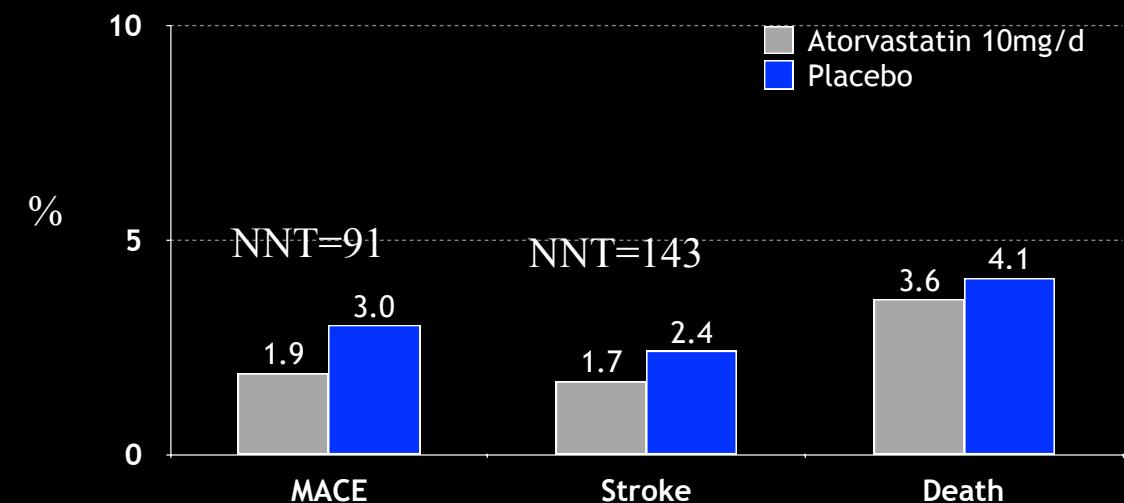
CARDS. Lancet 2004;364:685-96

*Primary Prevention*

## Atorvastatin - ASCOT-LLA

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

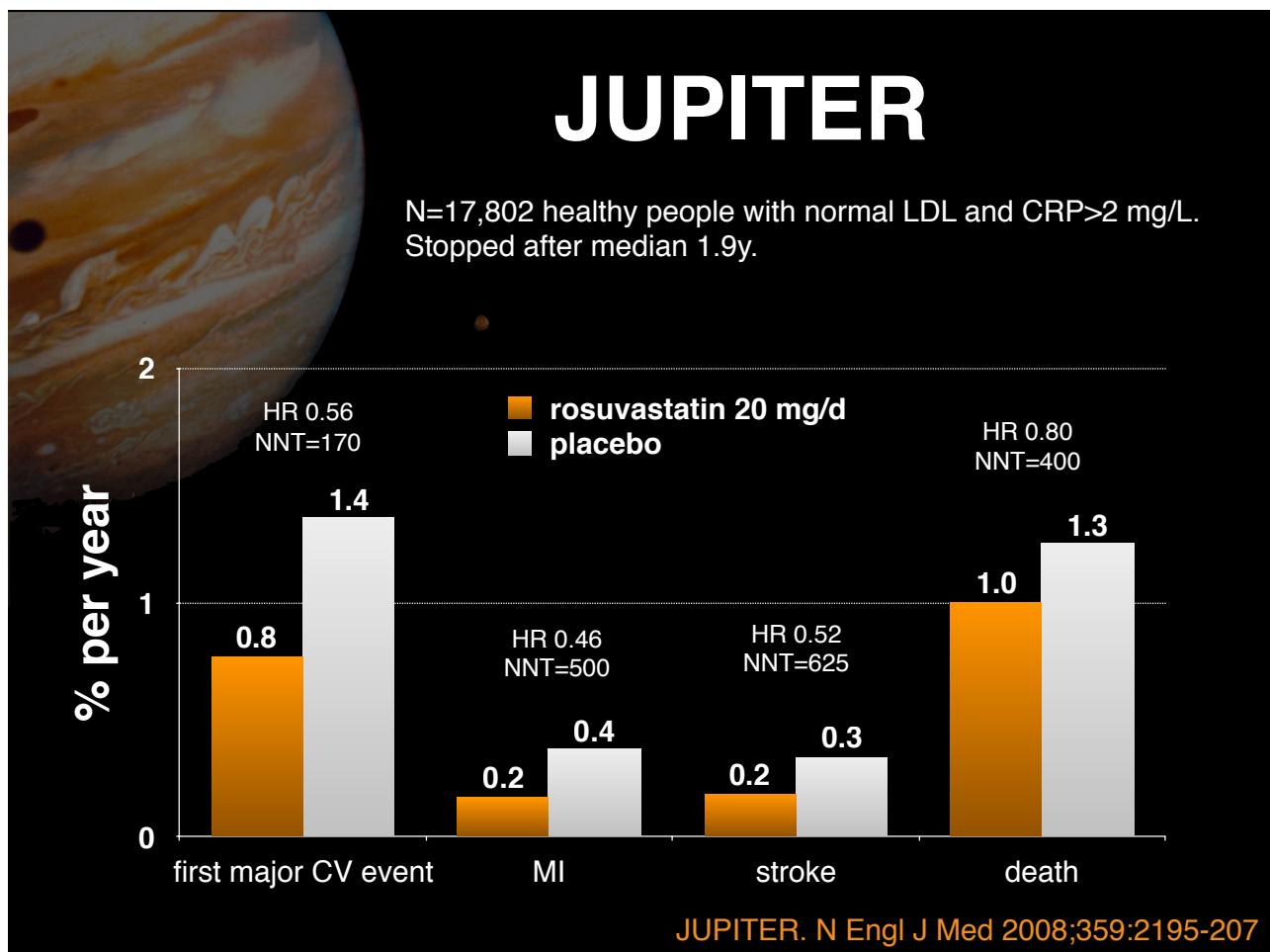
Duration = 3.3 years



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

## JUPITER

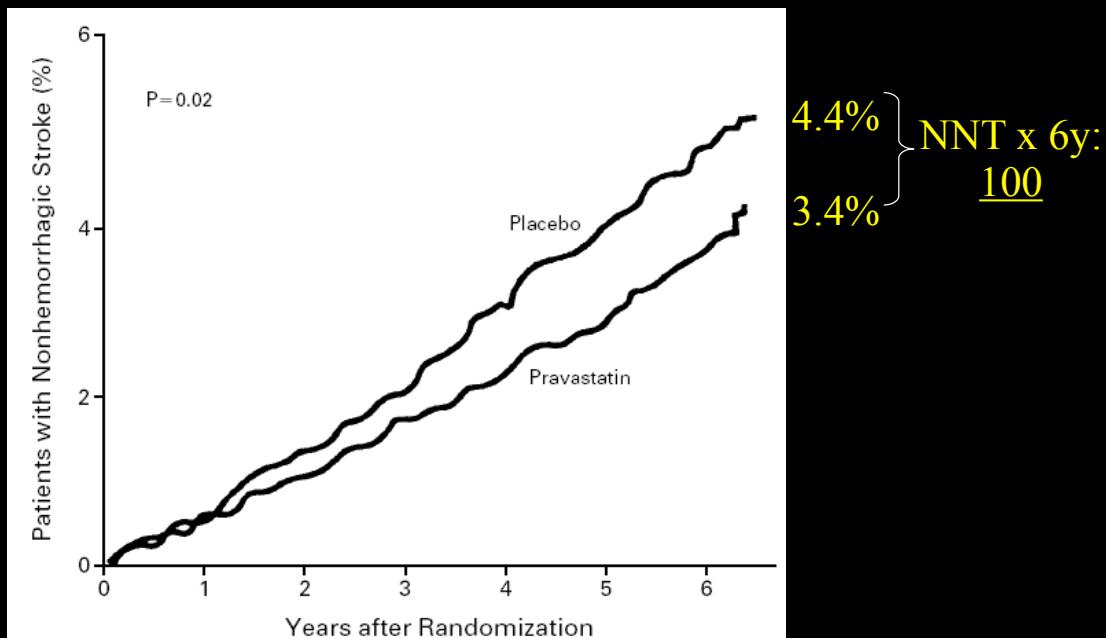
N=17,802 healthy people with normal LDL and CRP>2 mg/L.  
Stopped after median 1.9y.



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

# LIPID-STROKE: Pravastatin

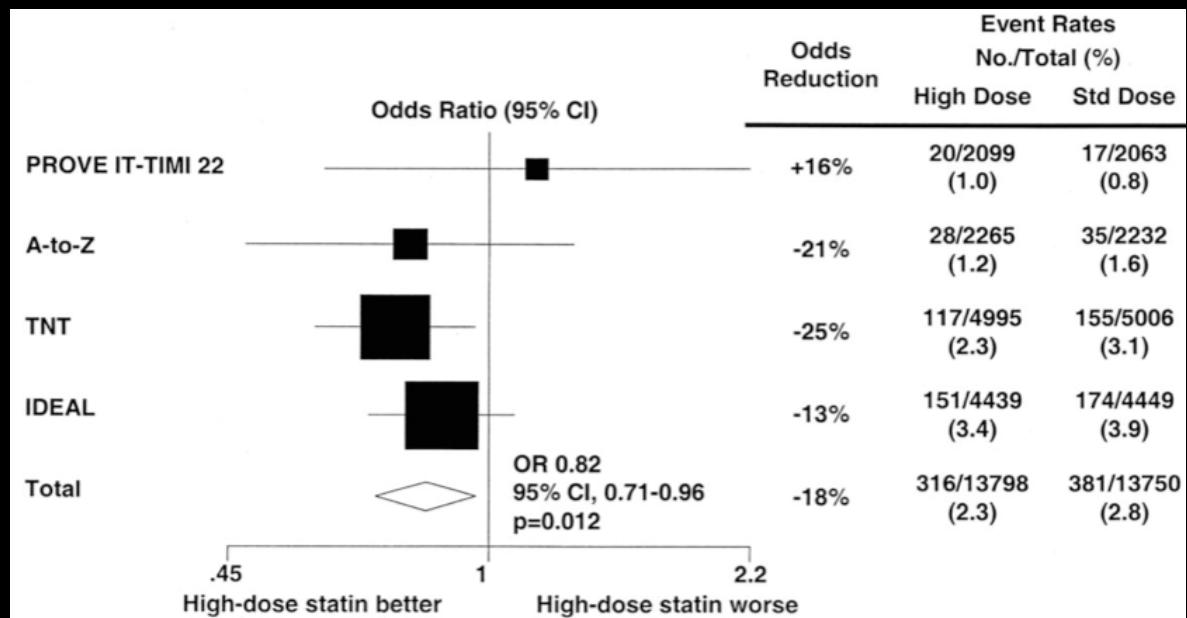
N=9,000 pts post-MI treated with pravastatin 40mg/d



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

## “Intensive” Statin Therapy

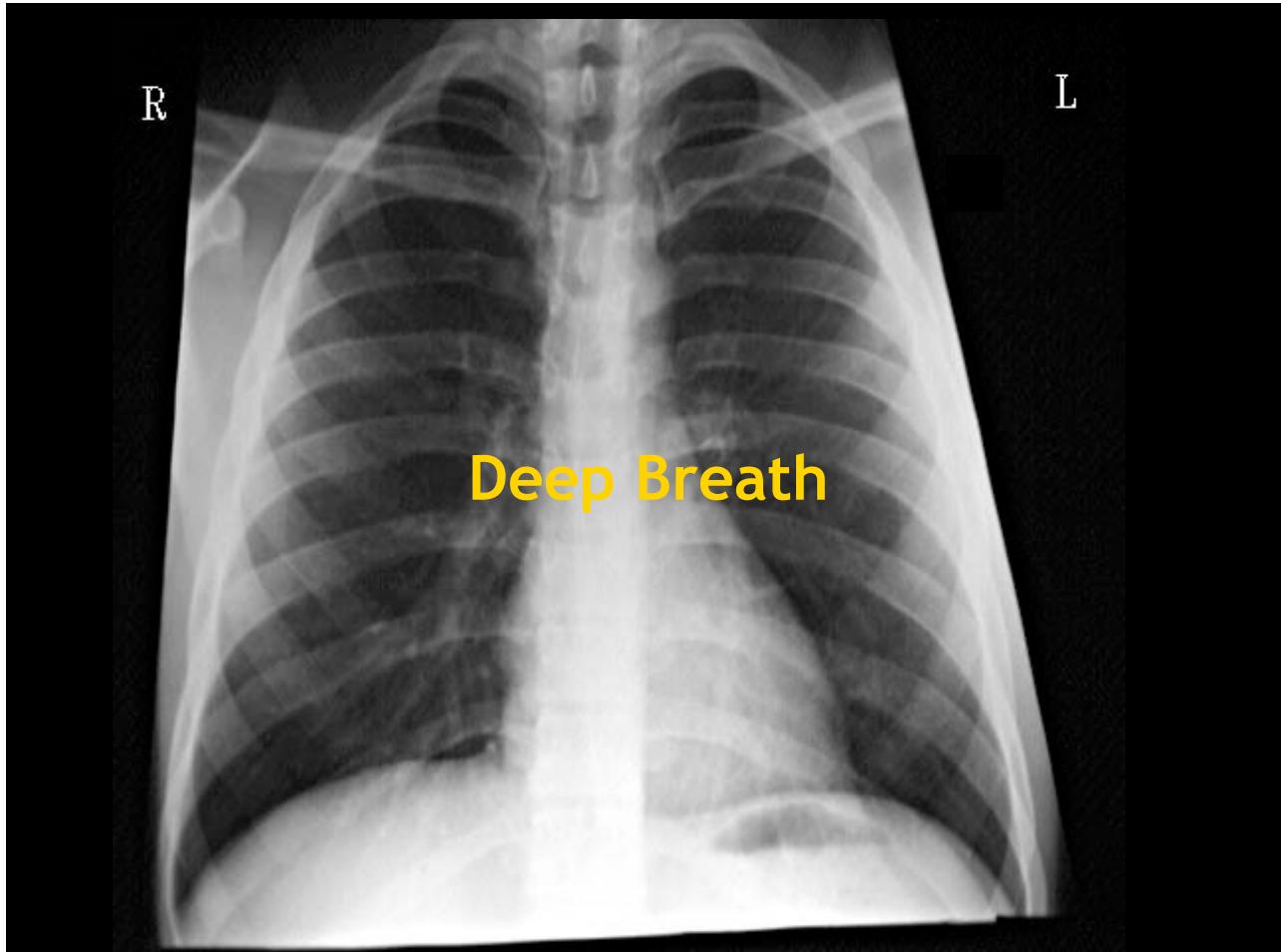
### Stroke



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

## **Bottom line on primary prevention (non-AF)**

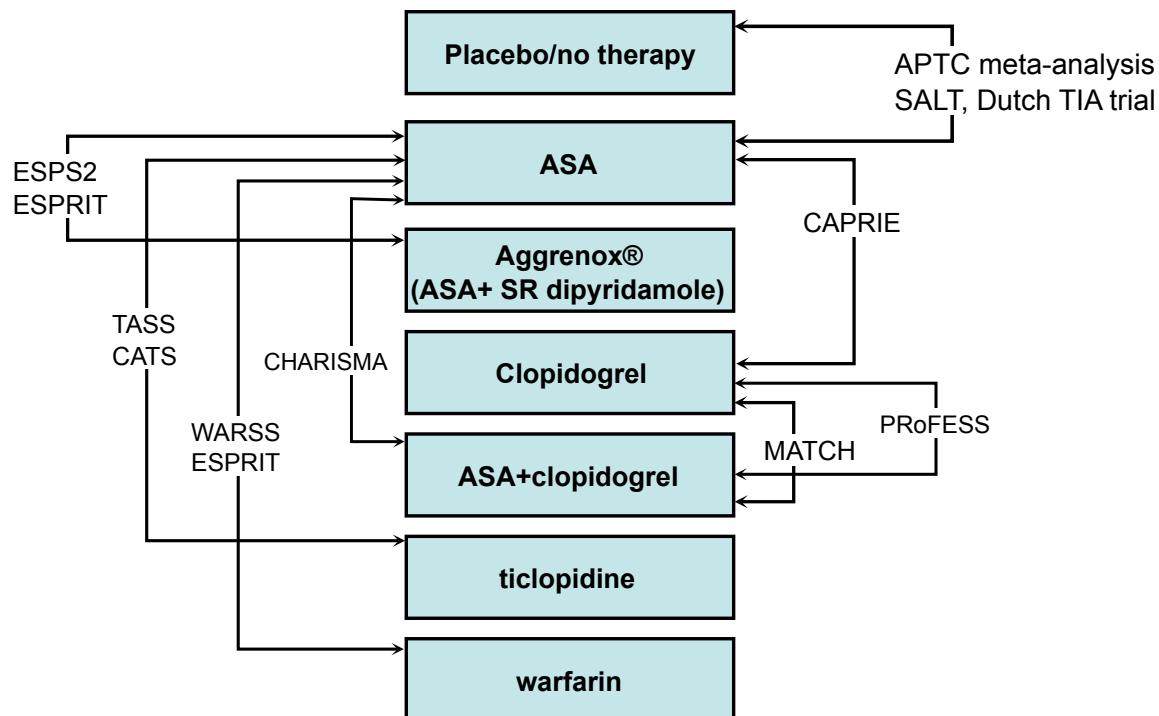
- Risk factor modification (especially HTN)
- Role for antithrombotic therapy?
- Ramipril in high risk pts (regardless of HTN)
  - Other ACE-Is? ARBs?: TRANSCEND, ONTARGET
- Statin (simva, prava, atorva) in high risk pts
  - especially those with CAD
  - regardless of baseline cholesterol levels



# 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

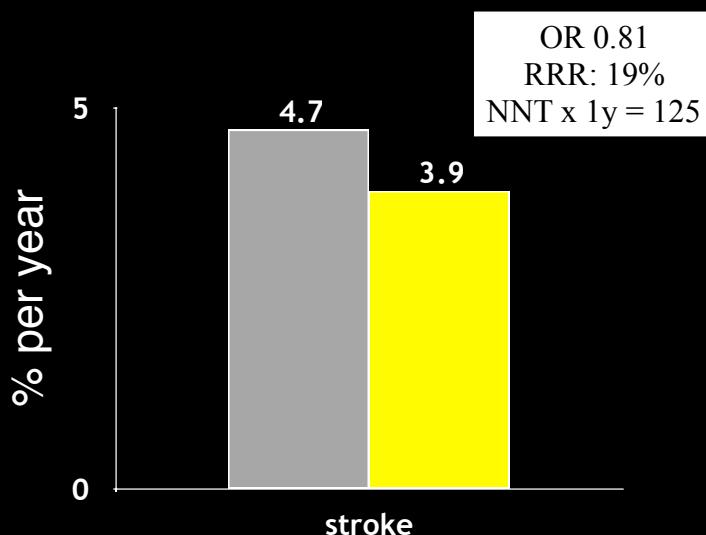


## Antithrombotic Therapies

- 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)

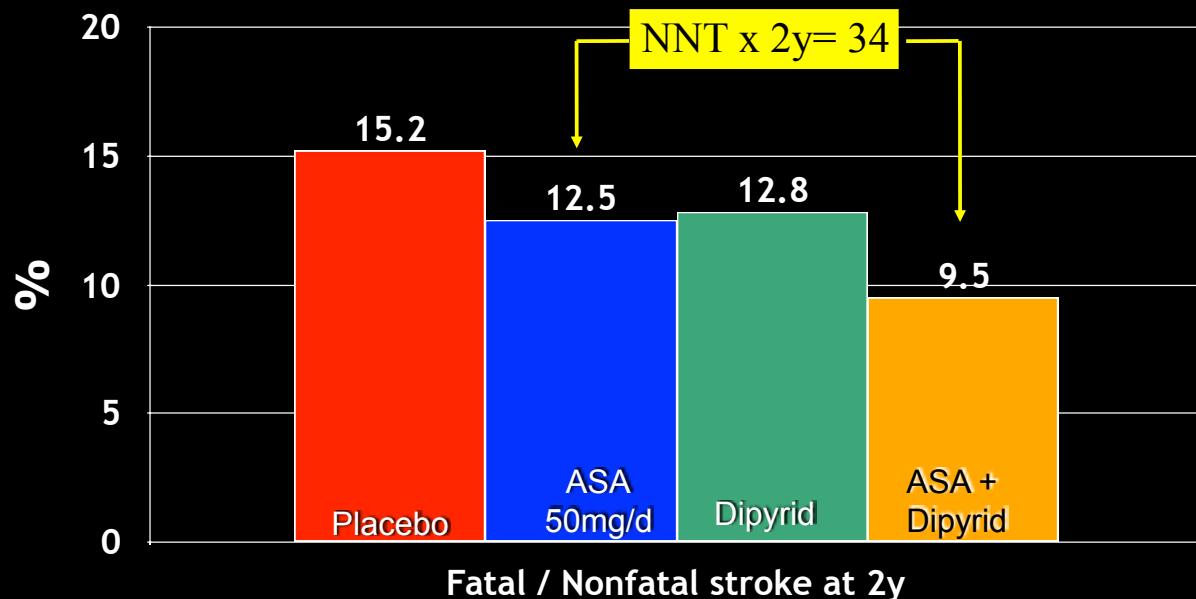
## Efficacy of ASA: The Gold Standard

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



## Secondary Prevention

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



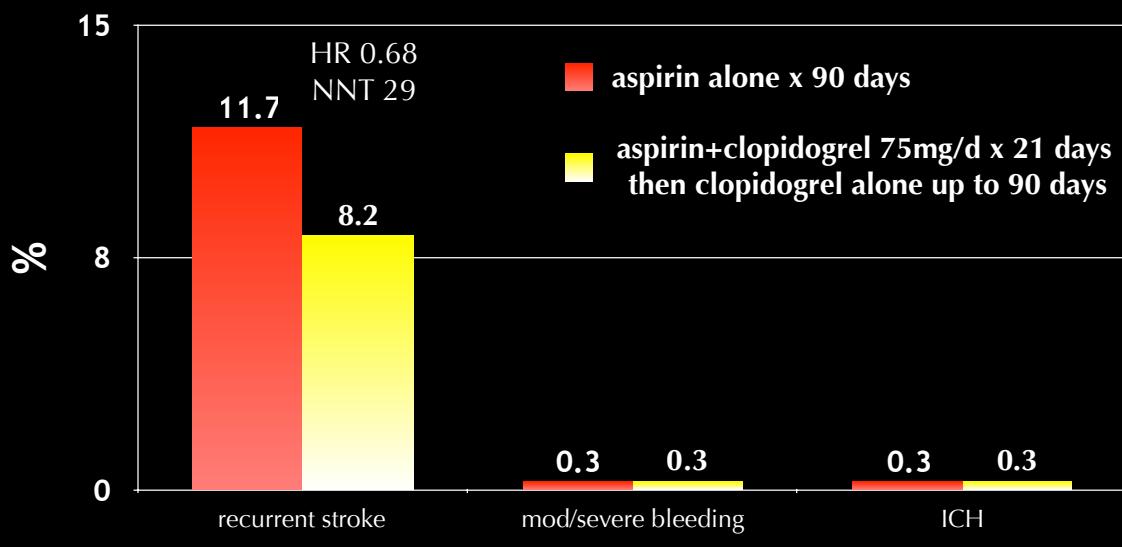
ESPS-2, Thromb Res 1998;92:S1-S6

## Secondary Prevention

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

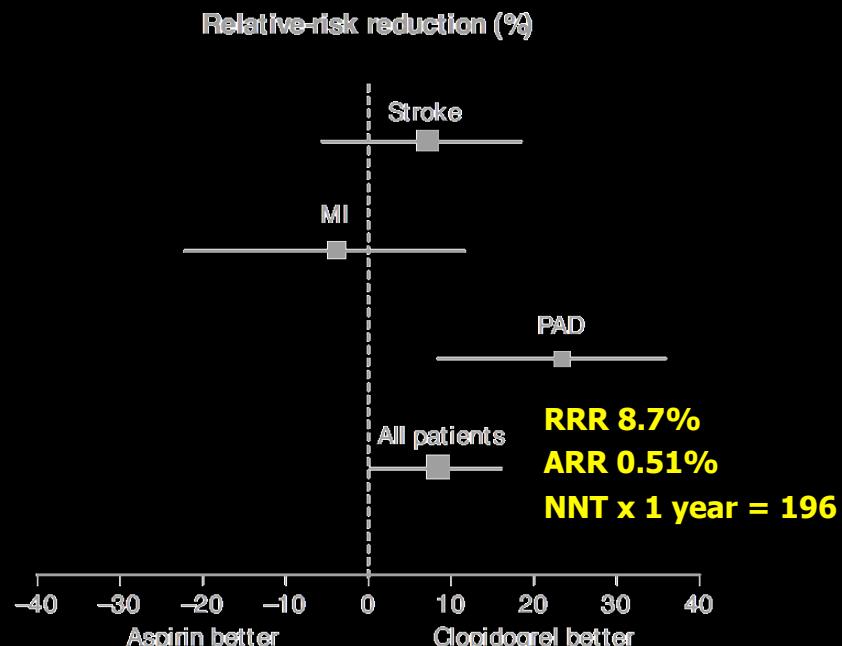
N=5170 patients in China within 24h of minor ischemic stroke/TIA. All taking aspirin 75-300mg/d.

90 days followup.



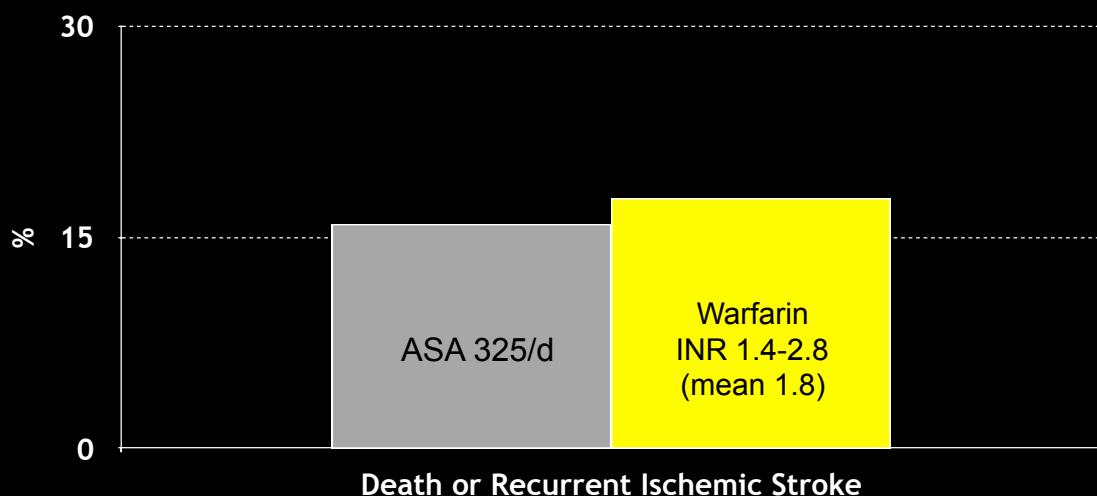
CHANCE. New Engl J Med 2013;369:11–9.

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



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

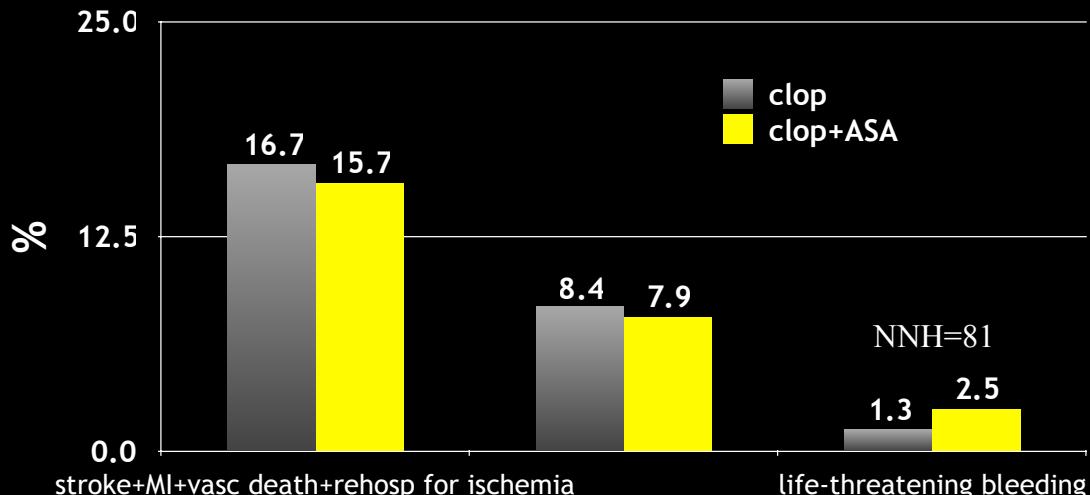
N=2206 stroke survivors treated for 2 years.



## 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.



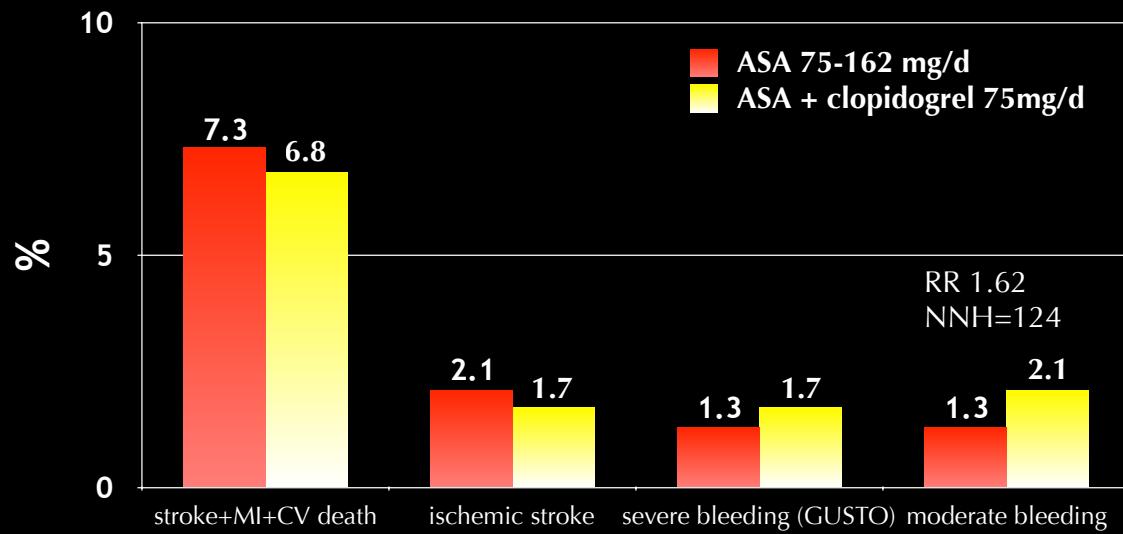
MATCH. Lancet 2004; 364: 331-337

## 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



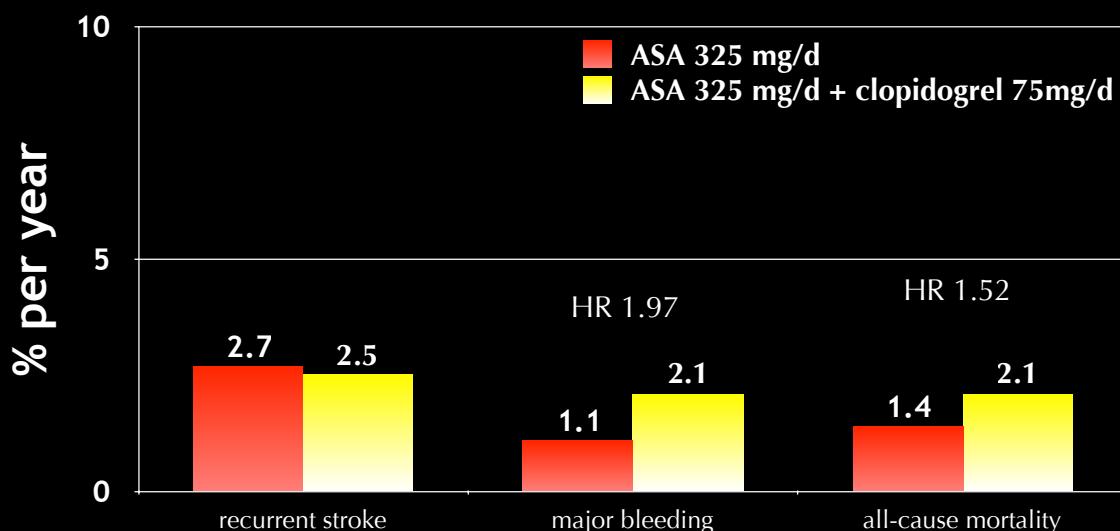
CHARISMA. NEJM 2006;354 (12MAR06)

*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

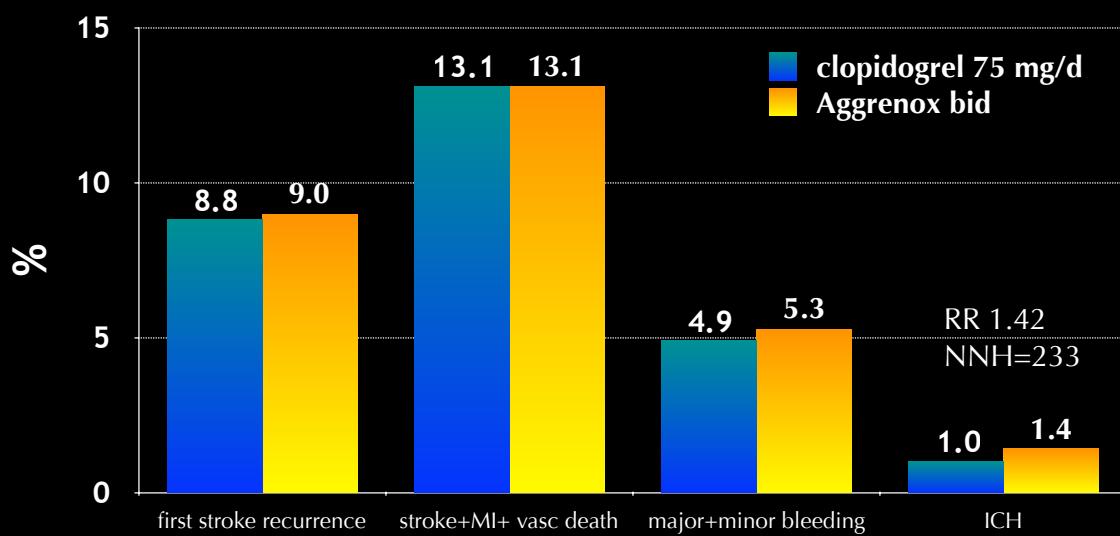


SPS3. N Engl J Med 2012;367:817-25.

*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.

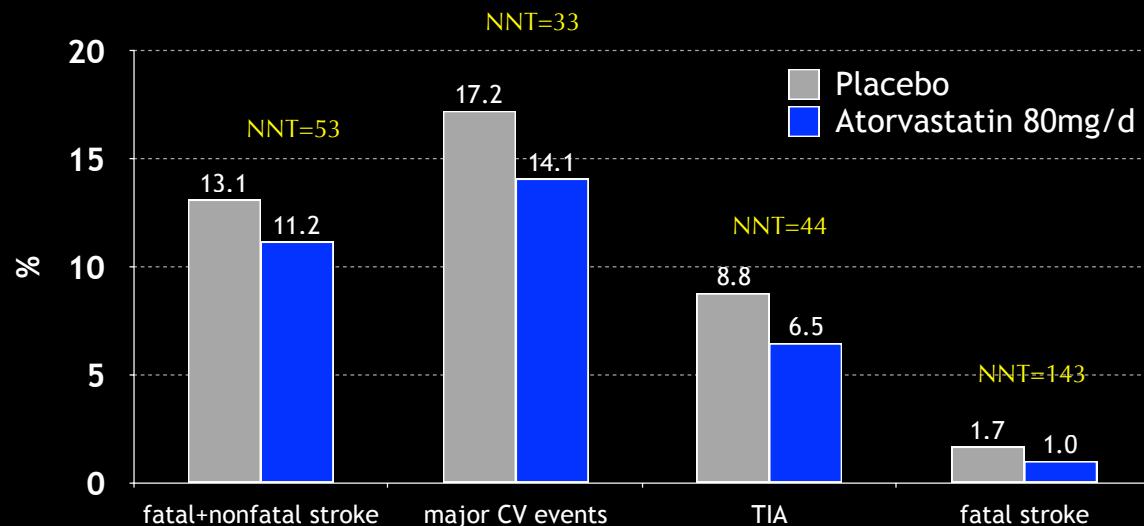


PRoFESS. NEJM 2008;359

## Secondary Prevention

### SPARCL: Atorvastatin

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

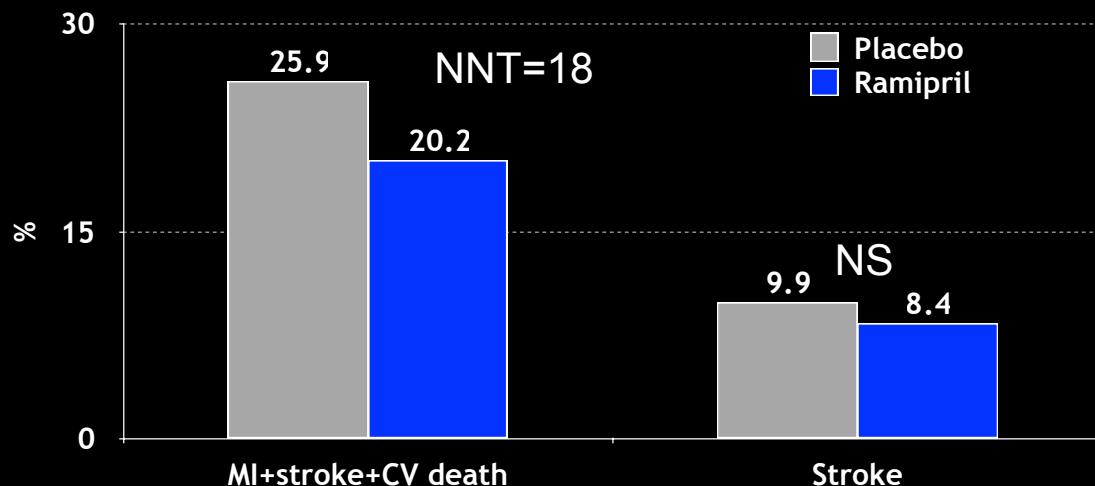


SPARCL. Lancet 2006;355:549-59

## Secondary Prevention

### HOPE: Ramipril

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

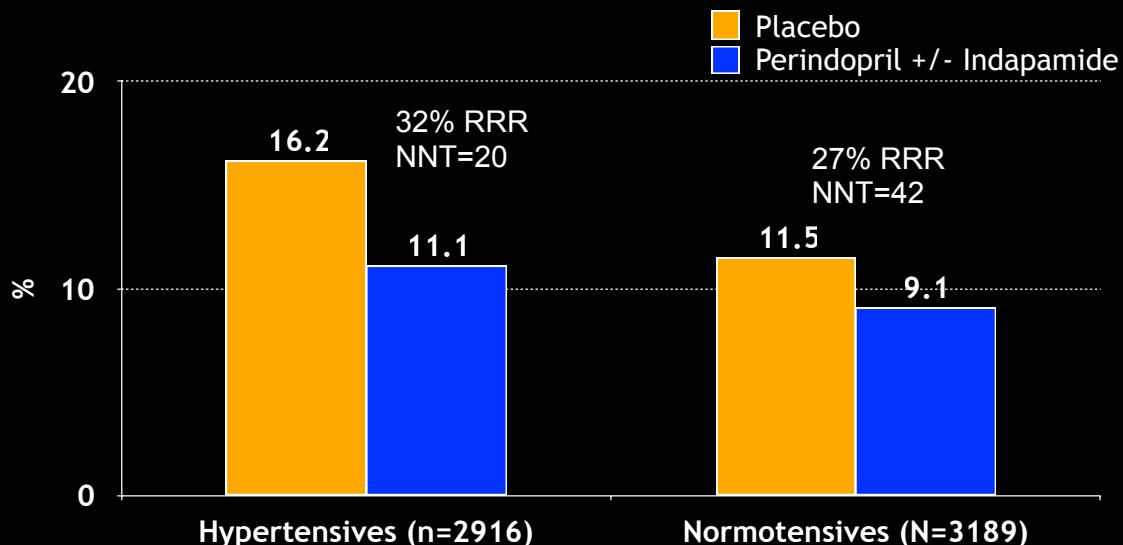


NEJM 2000;342:145-53  
BMJ 2002;324:1-5

## Secondary Prevention

### Perindopril +/- Indapamide

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

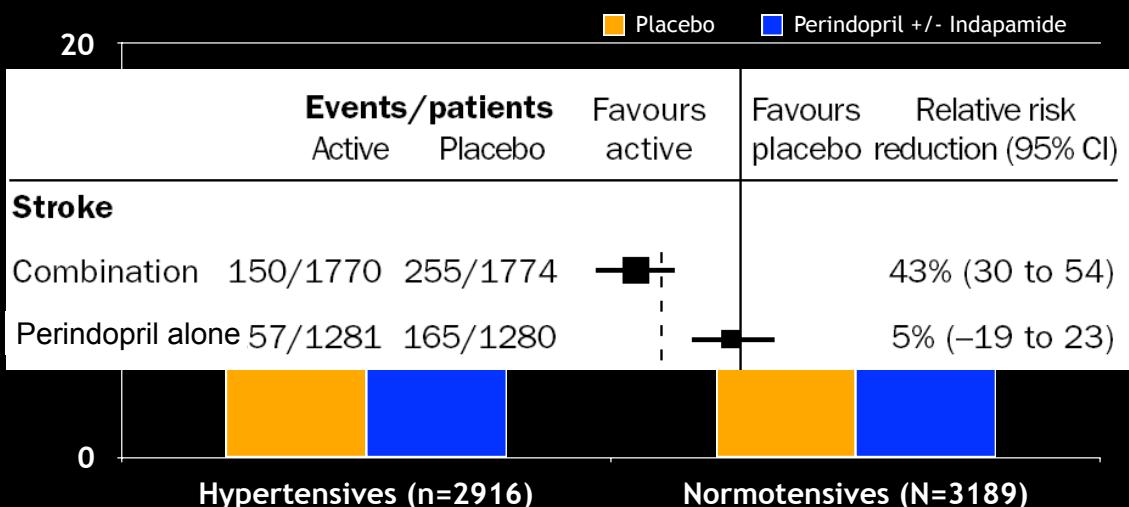


PROGRESS. Lancet 2001;358:1033-41

## Secondary Prevention

### Perindopril +/- Indapamide

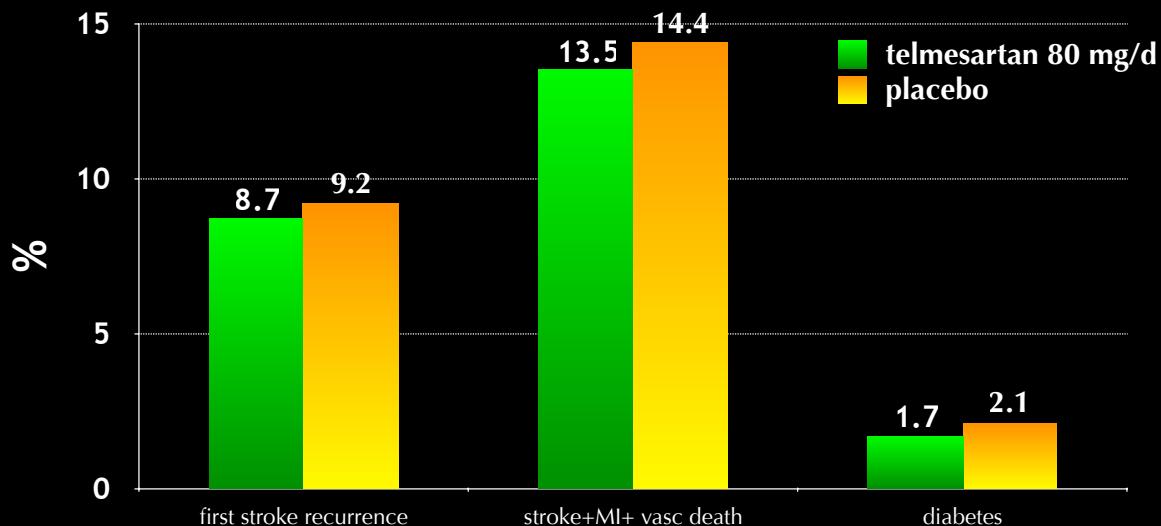
N= 6105 stroke/TIA survivors treated x 4 years.



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?

