Secondary Stroke Prevention

Dr Iftekhar Ahmed MD FAAN

Research Medical Center

Kansas City MO

Stroke Secondry prevention

- Describe CVA subtypes
- Identify CVA Risk Factors
- Identify Signs & Symptoms of Acute Stroke
- Describe management strategies for CVA subtypes
- Describe outcomes of secondary prevention trials
  - Antiplatelets
  - Combo therapies
  - Warfarin & anticoagulants
  - Statins
  - Blood Pressure Control

  - **The Bottom Line!**

Stroke signs

1. Sudden one-sided weakness, numbness, or paralysis of face, arm or leg.
2. Sudden blurry or ↓ vision.
3. Sudden difficulty speaking or understanding simple statements.
4. Sudden dizzy, loss of balance or coordination.
5. Sudden severe, unexplainable headache – "worst …

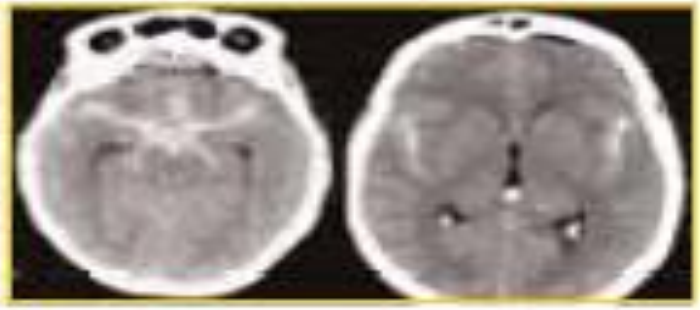
Type Of Strokes

Stroke Subtypes

Hemorrhagic Stroke (17%)

Intracerebral Hemorrhage (59%)

Subarachnoid Hemorrhage (41%)



Ischemic Stroke (83%)

Atherothrombotic Cerebrovascular Disease (20%)

Cryptogenic (30%)

Lacunar (25%) Small vessel disease

Embolism (20%)

Albers GW, et al. *Chest*. 1998;114:683S-698S. Rosamond WD, et al. *Stroke*. 1999;30:736-743.

Risk Factors

- Non-Modifiable Risk Factors

Secondary Stroke prevention

Age (Doubling rate each decade > 55 y.o.)	Prior CVA	FHx
Race (Blacks/Hispanics > Whites)	Low Birth Weight (RR ~2) (Wt < 2.5kg vs > 4 kg)	Male

Modifiable Risk Factors

- **Hypertension**
  - The Biggest Risk Factor!
  - ~ 28-38% Risk Reduction with Treatment

Hypertension

- Acute Phase CVA If TPA To be Administered All Pt Systolic BP Under 185
- Acute phase CVA No TPA Than Hydrate patient make Euvolemic
- A. Acute phase CVA If Chronically Hypertensive Systolic BP Permissive HTN 200+-
- In Normotensive Slow decrease to 140 systolic.
- For Chronic BP control 140-160 range all patients.
- Maintain MABP >100 {MABP=CPP+ICP}
- Reperfusion Achieved Assure Euvolemia SBP 160-170 MABP AT80-100
- Continued Recovery SBP 140
- CPP = MAP- ICP OR JVP which ever is greater

Modifiable risk Factors

Ischemic Heart Disease (IHD)

- CAD, CHF, LVH
- Major Risk Factor

Risk factors

- CHADS-2 model
- score from 0 to 6, based on:
  - CHF = 1
  - High BP = 1
  - Age > 75y.o. = 1
  - Diabetes = 1
  - Stroke Hx = 2

Contd

- Yearly risk of stroke due to AFib based on **CHADS-2 Score:**

0 - 1.9%

1 - 2.8%

2 - 4.0%

3 - 5.9%

4 - 8.5%

5 - 12.5%

6 - 18.2%

Modifiable risk factors

- **Smoking**
  - 50% Risk Reduction w/i 1 yr
  - Baseline > 5 yrs
  - Major Risk Factor!

Risk Factors

- **Diabetes**
  - Major Risk Factor!
  - BP Control is KEY
  - Mortality benefit with statins
  - * No evidence that tight sugar control reduces risk of CVA
  - > 140 increase morbidity by 7-10%

contd

- **Dyslipidemia**
  - 25-30% Risk Reduction with statin use

Contd

- **Physical Inactivity**
- **Heavy Alcohol use**
  - > 5 drinks /day
- **Obesity**

Contd

- **High Dose Estrogen**
  - > 50 mcg /day

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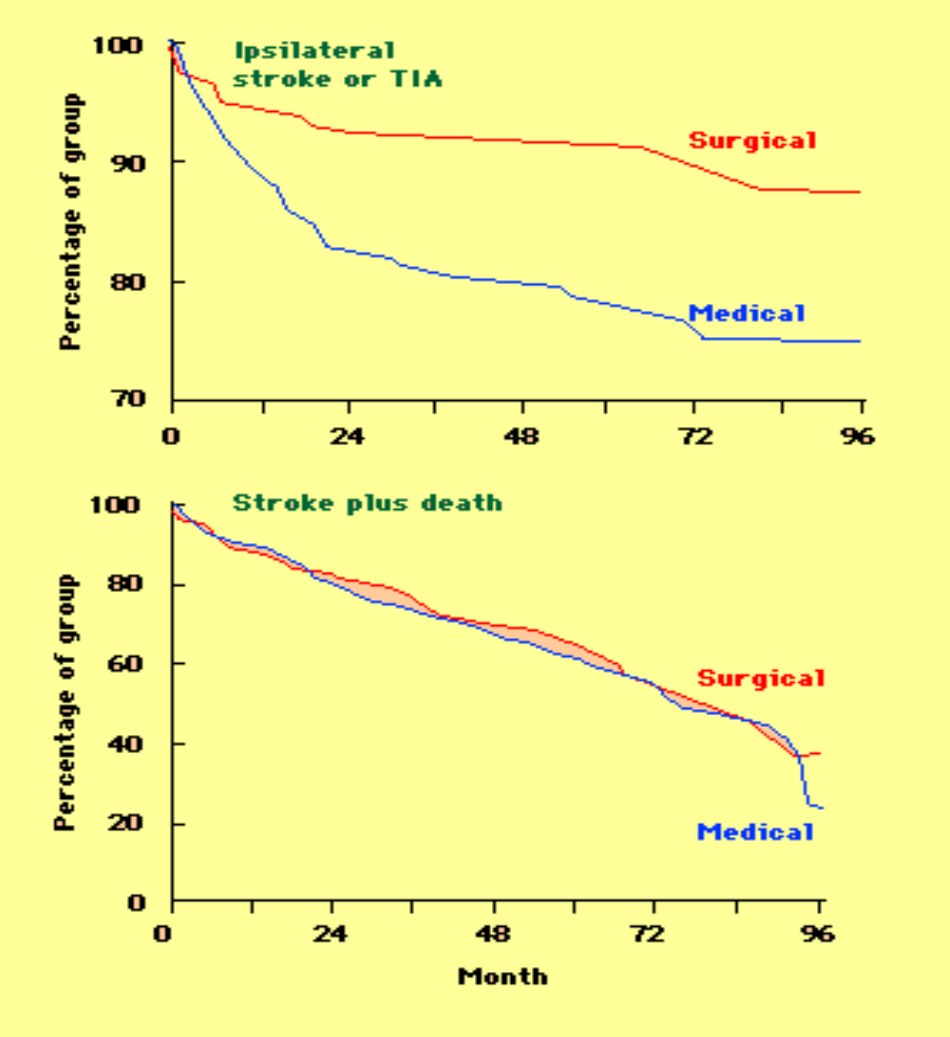
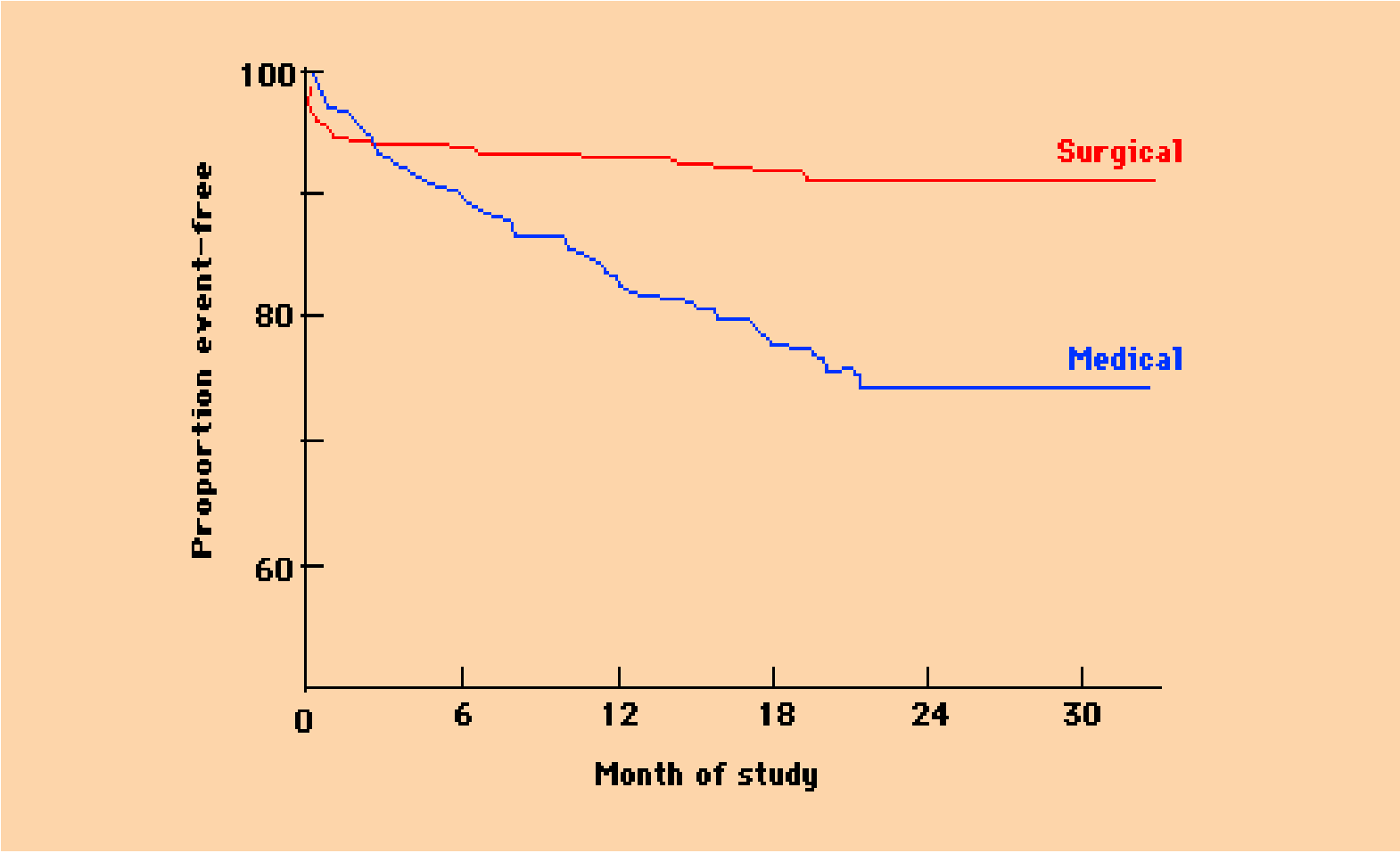
- **Asymptomatic Carotid Stenosis**
  - 50% Risk Reduction with endarterectomy

Veterans Administration Cooperative trial



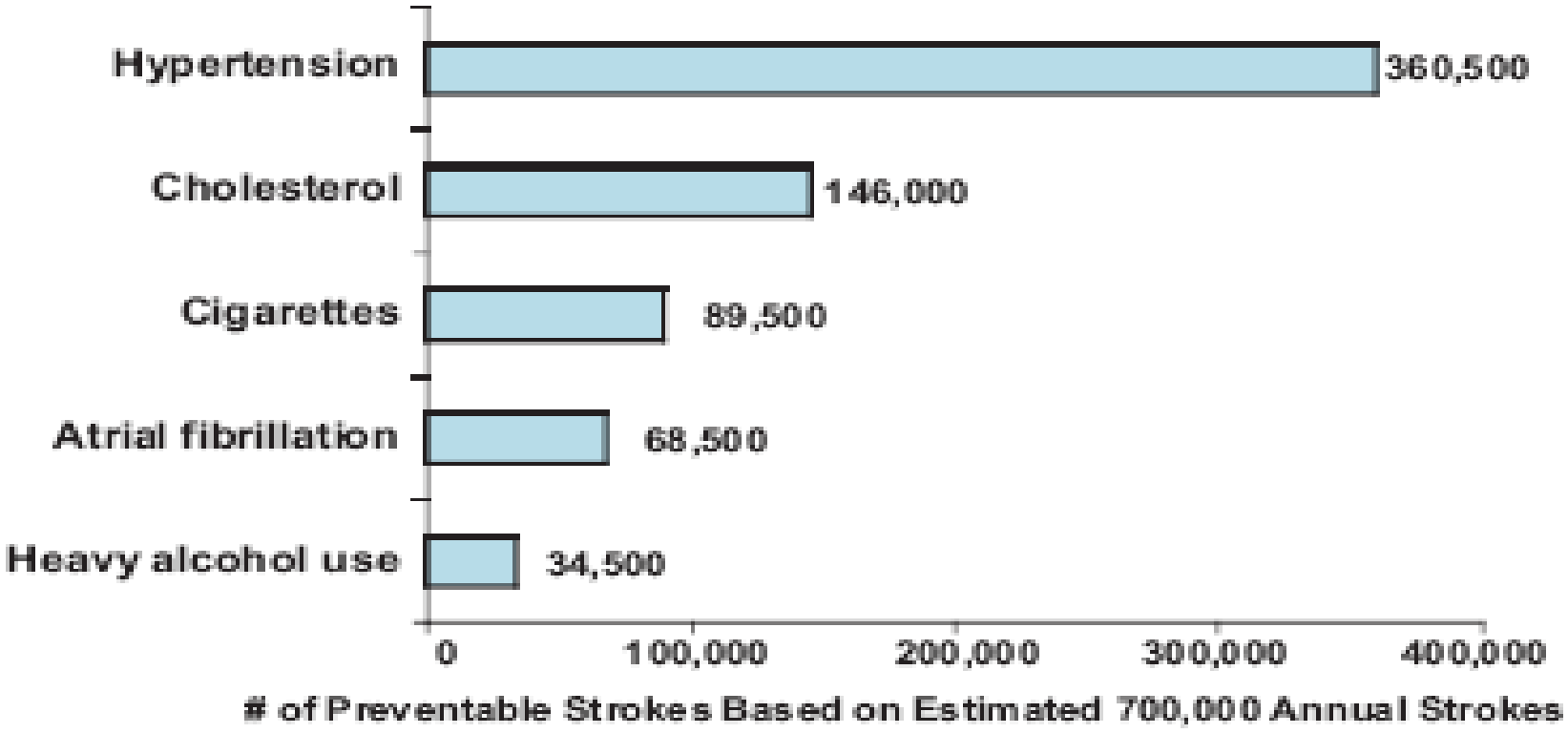
Carotid endarterectomy reduces stroke, but not endpoint of stroke and death, in asymptomatic men Medical versus surgical (carotid endarterectomy) therapy in 444 men with asymptomatic carotid stenosis ≥50 percent. Top panel: Carotid endarterectomy reduced the four year incidence of ipsilateral stroke or TIA compared to medical therapy (8 versus 20.6 percent, P<0.001). Bottom panel: There was no difference between the two groups in the incidence of stroke and death (41 versus 44 percent) (lower panel). (Redrawn from Hobson, RW, Weiss, DG, Fields, WS, et al, N Engl J Med 1993; 328:221.)

The cumulative risk of any ipsilateral stroke at two years was 26% in the 331 medical patients and 9% in the 328 surgical patients -an absolute risk reduction 17%



Secondry Prevention

How Many US Strokes Can Be Prevented by Risk Factor Control?



Gorelick PB. *Arch Neurol.* 1995;52:347-355.

Medical Therapies

- Anti-platelets
  - ASA
  - Clopidogrel
  - Combo Strategies
    - Clopidogrel + ASA
    - ASA + ER-Dipyridamole (Aggrenox™)
  - Ticagrelor
  - Prasugrel

Anti-coagulants

Anti-dyslipidemics (Statins)

Anti-hypertensives

contd

- ~23% RRR ASA over placebo
- NNT ~ 50-100 for 1 year to prevent any vascular event.
  - at a dose range of 50-325mg ASA
- NNH ~ 1 to 2 major extra-cranial bleeds per 1000 people

- **Antiplatelet Trialists**
  - large meta-analysis (~70% ASA trials)
  - ASA 75-150mg - beneficial in all high risk patients except for those with hemorrhagic stroke.
  - No added benefit of ASA 500 – 1300 mg
  - BMJ 2002;324:71-86

contd

- **CAST/IST Trials**
  - ASA w/i 48h of CVA
  - Combined analysis - significant reduction of 9 fewer deaths or nonfatal strokes per 1000 treated patients w/ ASA (160-325 mg/d)
  - Absolute risk reduction **(ARR) = 0.9%;**
  - Number needed to treat **(NNT) = 111**
  - BMJ 1988; 296:313-16

contd

- **SALT** Trial – ASA 75mg vs placebo
  - **Bottom line** - Low dose ASA significantly reduces risk of stroke and death in patients with ischemic stroke when used for ~ 32 months
  - **ARR = 4.6%**
  - **NNT = 22**
  - Lancet 1991;338:1345-9

contd

- Antiplatelets
  - Small differences in efficacy or toxicity, dictate that cost will drive selection.
  - = ASA
  - Combination therapy where indicated
- Anticoagulants
  - Small differences in efficacy
  - Important unknowns in toxicity w/ newer agents
    - (age effects, renal dysfunction, lack of antidotes)
  - Use warfarin except for carefully selected patients with *significant* compliance barriers due to the inconvenience of INR testing.

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- Ischemic CVA – Aggrenox or Plavix or ASA
  - If can't tolerate one, change therapy
  - If ASA allergy – clopidogrel 75mg qd
- Cardioembolic CVA – Warfarin (INR 2-3)
  - Good CrCL and poor INR control – consider Apixaban
- Hemorrhagic CVA
  - If ischemic or cardioembolic transformation:
    - treat as above
  - If primary hemorrhage – usually due to HTN
    - Add ASA once acute bleed resolved (primary prevention of ischemic event)

Contd

- Ticagrelor – no improvement vs clopidogrel and possible increase in harm in stroke patients
  - PLATO study
- Prasugrel – possible improvement vs clopidogrel in ACS, but more intracranial bleeding.
  - esp. in pts with previous stroke!
  - TRITON-TIMI 38 study

contd

Agent	Monotherapy	Combo w/ ASA
ASA	ASA ~23% RRR > placebo NNT ~ 50-100 x1 year to prevent any vascular event. (50-325mg) (CAST, IST, SALT, Dutch-TIA trials)	--
Ticlopidine	Superior to ASA (CATS & TASS trials)	unknown
Clopidogrel	Equivalent to ASA (*extremely* small absolute improvement per CAPRIE trial)	Possible improvement for 1st 21 days post CVA (CHANCE trial) No benefit long term (CHARISMA, MATCH trials)
Aggrenox®	*Superior* to ASA (ESPRIT & ESPS2 trials), but *Equivalent* to Clopidogrel (PRoFESS trial) whaa?	--

Secondry Stroke Prevention

Outcome	ASA-ERDP (n = 10,181) # (%)	Clopidogrel (n = 10,151) # (%)	Hazard Ratio for ASA-ERDP (95% CI)
Major hemorrhagic event	419 (4.1)	365 (3.6)	1.15 (1.00–1.32)
Life-threatening	128 (1.3)	116 (1.1)	
Non-life-threatening	291 (2.9)	249 (2.5)	
Hemorrhagic event (minor or major)	535 (5.3)	494 (4.9)	1.08 (0.96–1.22)
Intracranial hemorrhage	147 (1.4)	103 (1.0)	**1.42 (1.11–1.83)**
Hemorrhagic stroke	**90 (0.9)**	**55 (0.5)**	
Fatal	28 (0.3)	29 (0.3)	
Nonfatal	**62 (0.6)**	**26 (0.3)**	
Intraocular hemorrhage	22 (0.2)	22 (0.2)	
Nonstroke intracranial hemorrhage	**35 (0.3)**	**26 (0.3)**	

Secondry Stroke prevention

Outcome	ASA–ERDP 10,055 (100.0) # (%)	Clopidogrel (n= 10,040 (100.0) # (%)
Adverse events leading to discontinuation	1,650 (16.4)	1,069 (10.6)
Headache	593 (5.9)	87 (0.9)
Vomiting	158 (1.6)	37 (0.4)
Nausea	155 (1.5)	58 (0.6)
Dizziness	134 (1.3)	52 (0.5)
Atrial fibrillation	122 (1.2)	143 (1.4)
Diarrhea	102 (1.0)	42 (0.4)
Hypotension	54 (0.5)	35 (0.3)

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3) Cost

- **ASA**

Pennies! 4) Convenience

- **ASA**
  - 75-325mg once daily
- **Clopidogrel**
  - 75mg once daily
- **Aggrenox®**
  - 200/25mg **BID** po

- **Clopidogrel**
  - ~ $95/mo
  - LU code for ASA intolerance only
- **Aggrenox®**
  - ~ $61/mo
  - LU code for CVA

Contd

Agent	Cost	Convenience
Warfarin	~ $40/mo (with INR monitoring)	QD po INR q3d – q1mo (ODB covered)
Dabigatran	$110/mo	BID po (ODB w/ LU code 431 for AFib)
Rivaroxaban	$100/mo	QD with food (ODB w/ LU codes for Afib or VTE)
Apixaban	$140/mo	BID po (ODB w/ LU code 448 for Afib)

Contd

- **Warfarin**
- Vitamin K antagonist Rivaro**xa**ban
- Factor **Xa** inhibitorRivaro**xa**ban
  - Factor **Xa** inhibitor
- Api**xa**ban
  - Factor **Xa** inhibitor(clotting factors 2,7,9,10, protein C & S)
- **Dabigatran**
  - Direct thrombin inhibitor (factor 2)

Secondry Stroke Prevention

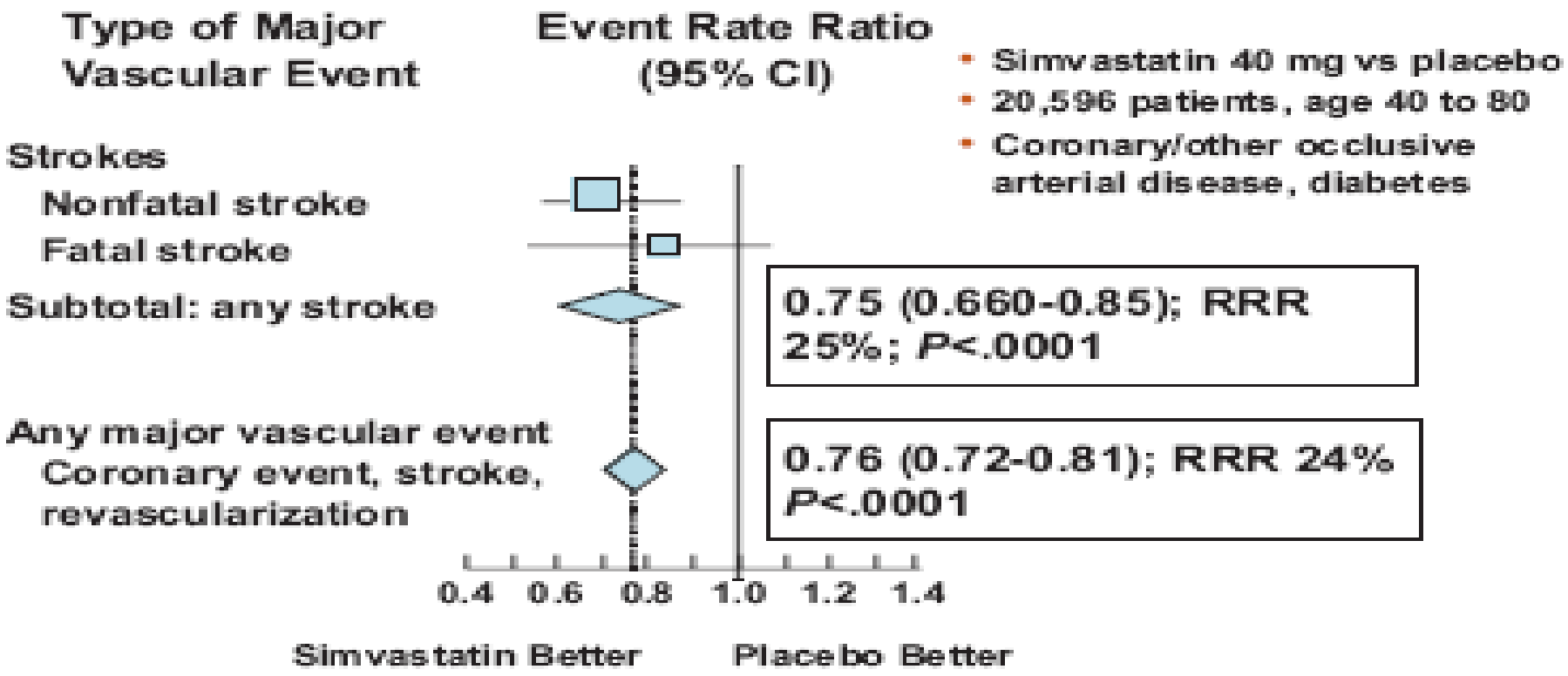
Anticoagulation in Non-valvular[22] AFib

Rx FILES

	COUMADIN / Warfarin	PRADAXA / Dabigatran[150mg]	XARELTO / Rivaroxaban	ELIQUIS / Apixaban
Stroke/Embolism	✓[1]	✓ ✓?[2]	✓?[3]	✓ ✓?[4]
ICH	✗	✓[5]	✓[6]	✓[7]
Major GI Bleed	✓	✗[8]	✗[9]	✓[10]
Major Bleed	✓	✓[11]	✓[12]	✓✓[13]
Manage Bleed	✓[14]	✗ ✗	✗?	✗?
MI	✓	✗?[15]	- ?	- ?
DC Rate /Dyspepsia	-	✗[16] /↑ GI	-	✓
Low renal fx CrCl	✓ ✓[17]	CI<30	CI<30	CI<15 Trial CI<25
Cost $40-110-140/mo	✓ ✓[18]	✗	✗	✗ ✗
Half life Pros/Cons[19]	Dosing frequency, impact of missed dose, bleed management			
Monitoring[20]	Need for/ability to monitor INR has pros & cons.			
Certainty vs Un-[21]	✓ ✓	✗	✗	✗

contd

Effects of Simvastatin on First Stroke



Adapted from Heart Protection Study Collaborative Group. *Lancet*. 2004;363:757-767.

contd

- **HPS trial – 20,596 high risk pts**
- Simvastatin 40mg vs placebo
- Stroke - 4.3% vs 5.7% (RRR 25%)
- **Significant regardless of age or cholesterol level!**
- Lancet 2002; 360: 23-33

Summary

- Cardioembolic CVA
  - Statin, ACEinh (since likely has CHD)
  - B-blockers (CHD, also for rate control)
- Ischemic CVA
  - Statin; ACEinh and/or diuretic
- Hemorrhagic CVA
  - If primary bleed - BP control!
  - If transformation – treat as ischemic CVA once bleed resolves

Summary

- BP reduction is key!
  - **Aggressive reduction**
- Up to 28% reduction of second CVA
  - Up to 40-50% reduction in first CVA!
- ACEinh or Thiazides – 1st among equals?
  - Some evidence as well for ARBs
- Strongly consider ACEinh + diuretic combo
- Thank You