

Pharmacotherapy for Ischemic Stroke Prevention

Are any of these predisposing conditions present?

Primary prevention without risk factors (or "low risk" [eg. 10-year CVD risk <10%]): Numerous trials (Physician's Health Study, British Doctors Trial, MRC-TPT, HOT, PPP, WHS, APTC, USPSTF, USPHS, EPHES). Best Evidence (meta-analysis including all these trials, JAMA 2006;295:306-314; ASA 50-500mg/d over 6.4 years; 1 all CV events in M & F (NNTx1y=2700); 1 stroke in F (NNTx1y=2700); 1 MI in M (NNTx1y=750); 1 ICH in M (NNTx1y=5000); 1 major bleeding in M & F (NNTx1y=2200). No other significant differences vs. placebo. WHS (NEJM 2005;352) showed ASA 100mg qd 1 ischemic stroke in healthy women >45y (RR 0.7; NNT 352/100y) and >65y (RR 0.7; NNT 93/100y).
With CV risk factors: HPS (MI, CAD, diabetes, HTN) in prior stroke/TIA: Simvastatin 40mg/d 1 stroke: 27% RRR, 1.8% ARR, NNTx5.5y=63. **JUPTER** (intermediate CV risk): rosuvastatin 20mg/d 1 stroke: 18% RRR, 1.2% ARR, NNTx1.9y=270. **HOPE-STROKE** (CAD or risk factors and no prior stroke/TIA) (n=8284): Ramipril 10mg/d x 5y -> placebo 4.2% / ramipril 2.5% (ARR 1.34%, RRR-0.68, NNTx5y=75). Fatal strokes 1 (ARR 0.6%, RRR 0.6%, NNTx5y=167), nonfatal strokes 1 (ARR 0.6%, RRR 35%, NNTx5y=167). **POPADAD**: ASA 100mg/d vs. placebo in diabetics with PVD: no effect on stroke risk [BMJ 2008;337:a1940]

MODIFY RISK FACTORS: (see also ASA/AHA 2ndary prevention guidelines. Stroke 2006;37:577-617)
-HTN (including ISH) (stroke risk 1.6-4x baseline) (5mm decrease in DBP -> 42% ↓ in CV rate)
-Control diabetes (stroke risk 1.8 - 4.0 x baseline) (not confirmed that tight control reduces risk)
-Stop smoking (stroke risk 1.5 - 2.0 x baseline) (quitting 1 yr risk by 30-40% in observational studies)
-Avoid heavy alcohol use (40g ethanol in 24 hours: 1 risk of acute stroke by 5x)
-Normalize hypercholesterolemia - HMCoCoAR-Ts: RRR stroke 0.76. All other interventions, no beneficial effect. (Corvol. Arch Intern Med 2003;163:669-76)
-Oral contraceptives (estrogen): CONTROVERSIAL. Meta-anal showed RR 2.75 overall, 2.0 with estradiol <50 mcg, 4.53 with estradiol >50mcg/100mg of ethinyl. Age > 35 made no difference [JAMA 2004;292:78-87]. BUT all based on case-control and cohort studies with severe methodologic limitations. Association may be nonexistent [Arch Intern Med 2004;164:741-7]
-Postmenopausal HRT: estrogen-progestin: 1.8% vs 1.3% stroke risk @ 5.6y [HR 1.5, ARI 0.5%, NNH=200] [WHI, JAMA 2002;286:273-84]. Similar for estrogen alone vs. placebo in WHI.
-Hyperhomocysteinemia - 1 stroke risk, but VISP (JAMA 2004;291:565-75) showed no effect of lowering using B vitamins.

Carotid artery stenosis
(10% have "silent brain infarctions") >75% stenosis -> 2.5% stroke risk/year and 6.5% MI risk/year

Non-Rheumatic Atrial fibrillation
SPAF, IAF, AFASAK, AFASAK2, BAATAF, CAFT, SPINAF, CAFSA, SIFA, PATAF, MWNAF.

Mechanical heart valve(s)
1 MHV, previous thromboembolism, A.fib, CAD, anterior MI, hypercoagulable state, low EF, enlarged left atrium, left atrial thrombus?

Previous TIA or stroke
After TIA, risk of stroke @ 7 days: 8%, @ 30 days: 11.5%, @ 90 days: 17.3%. After minor stroke, risk of recurrent stroke @ 7 days: 11.5%, @ 30 days: 15%, @ 90 days: 18.5%. (BMJ 2004;329:326)
RRE-90 tool predicts 90-day recurrent rate
http://www.nmr.mgh.harvard.edu/RRE/

Recent MI
Embolic stroke in 3-4% within first 4 weeks. Post-STEMI stroke mortality: 40%

Poor LV Function
For every 5 point ↓ in LV below 40%, stroke risk ↑ by 18% over 3.5 years. SAVE. NEJM 1997;336:251-7

Antiphospholipid antibodies
(anticardiolipin antibody and/or lupus anticoagulant positive)

Symptomatic? (anterior circulation TIA, stroke)
No: ACAS (JAMA 1995), ACST (Lancet 2004;363:1491-501), NEJM 358:15-16:17-21. Endarterectomy: if >60% stenosis, surgical risk <3% and good 5-year survival prospects. Follow with ASA 75-100 mg/d lifelong (ACCP 2008). Medical therapy: if not getting surgery. All the usual CV risk reduction methods. ASA 75-100mg/d, avoid dual antiplatelets (MATCH, CHARISMA, ACCP 2008). Stenting: not recommended outside clinical trials (e.g., CREST, ACT1) for these "low risk" patients.
Yes: degree of stenosis (NASCET method)
>50%: Endarterectomy + ASA 50-100 mg/d prior to and lifelong (ACCP 2008).
<50%: 7ASA-Clopid x7d superior to ASA alone in acute phase, while waiting for results (CARESS) non-clinical endpoints.
Optimal therapy unknown. Surgery worsens outcome (ECST, NASCET). Treat like TIA.

Mechanical heart valve(s)?
No: paroxysmal
Yes: chronic or paroxysmal?
Yes (highest risk): Bileaflet or Medtronic Hall tilting disc in aortic position: Warfarin INR 2.5 (2-3). Tilted disc or bileaflet in mitral position: Warfarin INR 3.0 (2.5-3.5). Caged ball or caged disc in any position: Warfarin INR 3.0 (2.5-3.5).
No: Combination warfarin (INR 2.5-3.5) + ASA 80-100 mg/d (Turpie 1993). 1 death/nonfatal embolism (9.9%/yr vs. 3.9%/yr) and 1 mortality (7.4%/yr vs. 2.6%/yr). 1 in major bleeds (5.5% vs. 2.2%; p<0.05). Thus, use only in these highest risk patients and be cautious about bleeding.

Symptomatic intracranial stenosis? (>50% cerebral artery stenosis, angiographically confirmed)
Yes: ASA preferred over warfarin. WASID (NEJM 2005;352:1305-16). NEJM 650mg bid similar efficacy to warfarin INR 2-3, less major bleeding, less death. Trial stopped early.
No: stroke/TIA suspected to be cardioembolic? (eg. HMCAS, pt in A.fib)
Yes: Mechanical heart valve(s)?
No: Recent anterior MI?
Yes: Recurrent Stroke: While on ASA: 1. Stay on ASA alone, (no evidence that any of the options below are superior to this). 2. Switch to clopidogrel (CAPRIE, PROGRESS). 3. Add SR dipyridamol (ie. switch to Aggrenox). 4. Switch to warfarin (WARSS, ESPRIT). 5. Add clopidogrel (CHARISMA, MATCH) 6. Increase ASA dose?

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Anterior MI with mural thrombus or anterior wall akinesis
Yes: RAMIPRIL 10 mg/d 1 stroke risk (RR 0.68, NNTx5y=67), CV mortality (RR 0.78, NNTx5y=27) and overall mortality (RR 0.84, NNTx5y=56). (HOPE)
No: >33% will have intraventricular thrombus 2 weeks after anterior MI. RAMIPRIL 10 mg/d 1 stroke risk (RR 0.68, NNTx5y=67), CV mortality (RR 0.78, NNTx5y=27) and overall mortality (RR 0.84, NNTx5y=56). (HOPE)
Yes: ASA + stroke risk over first month (ARR 0.3%, RRR 50%, NNT=334). Over 2 years: ARR 0.0%, RRR 36%, NNT=200. Use for MI prevention more than stroke (NNT=56 over 2y).
2. Warfarin (INR 2.5-4.8) vs. control x 1-6 months post-MI RRR stroke 0.71, RR major complications 10.1. (Benefit:RR = 3.2. If complication rate were reduced to that seen in A.fib warfarin trials (ie, INR 2-3), benefit:RR would be 15:1). Currently not routinely recommended.

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Antiphospholipid antibodies
previous thrombosis?
No: Optimal therapy unknown. APASS/WARSS [JAMA 2004;291:576-84]: ASA and warfarin had same recurrence rate following cryptogenic stroke in aPL(+) subjects (~11%/yr) and no difference from aPL(-) subjects. (Neither? ASA? Warfarin?)
Yes: "Antiphospholipid Antibody Syndrome" Only RCT (NEJM 2003;349:1133-8) showed warfarin INR 2-3 not inferior to INR 3-4. Thrombosis 3.4% vs. 10.7% over 2.7y (p=NS). Major bleeding similar in both groups (5% vs 7%).
AHA/ASA Stroke 2006 2ndary Prevention Guidelines: Warfarin INR 2-3. Also JAMA 2006;295:1050-1057. ACCP 2004 guidelines recommend increasing to INR 3.0 (2.5-3.5) if thrombosis at INR 2-3.
PT/INR monitoring may be unreliable if lupus anticoagulant positive [Ann Int Med 1997;127(3):177-85].

Choose preventative therapy based on annual stroke risk vs. bleeding risk + patient's values
CHA2DS2 Risk Scoring System:
QHr/LV dysfunction (1 point)
HTN (regardless of control or treatment) (1 point)
Age ≥75 (1 point)
Diabetes (1 point)
Previous TIA or Stroke (2 points)
TOTAL SCORE: (0-6)
Score / Annual Stroke Risk (95%CI)
0 / 1.9% (1.2-3.0)
1 / 2.8% (2.0-3.8)
2 / 4.0% (3.1-5.1)
3 / 5.9% (4.6-7.3)
4 / 8.5% (6.3-11.1)
5 / 12.5% (8.5-17.5)
6 / 18.2% (10.5-27.4)

Atrial Fib + previous AF-associated stroke STROKE/TIA: Warfarin INR 2-3 usually indicated.
Only RCTs are EAFT & SIFA. EAFT (warfarin INR 2.5-4 vs ASA 300mg/d vs placebo): 2y follow-up. ANNUAL event rate (CV death+stroke+MI+embolism): warf 8%. ASA/placebo 17% (NNT=11). Annual stroke rate warfarin 4%, ASA/placebo 12% (NNT=15). No mortality reduction with warf. No benefit of ASA vs. placebo. Warf vs. ASA: OR 0.38 for stroke (NNT=8), OR 0.60 for all events (NNT=8). Major bleeds 2.8%/y warf vs. 0.9% ASA vs. 0.7% plac. No 1 in ICH. Trial included many pts >70y (mean age 71). Used INR 2.5-4, but this is not generally recommended or practiced in North America (use INR 2.0-3.5). SIFA (warfarin INR 2.3-5 vs. indobufen) x 1 year. Warfarin superior to indobufen. Combined analysis (Stroke. 2005;36:914-915) shows warfarin superior to antiplatelets & causes excess extracranial bleeding. **These trials use odd interventions or comparators and don't permit INDIVIDUALIZATION of risk, so use CHADS2 system instead.**

Recurrent Stroke: While on ASA: 1. Stay on ASA alone, (no evidence that any of the options below are superior to this). 2. Switch to clopidogrel (CAPRIE, PROGRESS). 3. Add SR dipyridamol (ie. switch to Aggrenox). 4. Switch to warfarin (WARSS, ESPRIT). 5. Add clopidogrel (CHARISMA, MATCH) 6. Increase ASA dose?

PERINDOPRIL 4mg/d + Thiazide (PROGRESS): In normotensive post-stroke: ARR 4.8%, RRR 42%, NNTx4y=21. NOTE: Perindopril alone showed no benefit in normotensives.
FRAMIPRIL: although HOPE showed dxzral stroke risk reduction with ramipril (RR 0.68, ARR 1.5%, NNTx5y=67), CV mortality (RR 0.78, NNTx5y=27) and overall mortality (RR 0.84, NNTx5y=56), among the 1013 pts who had prior stroke or TIA, there was no significant ↑ in recurrent stroke over the 5y study period and placebo rate was 9.9% (HOPE-STROKE).
ATORVASTATIN 80mg/d if LDL>2.6 (SPARCL-Only stroke statin 2ndary prevention trial): recurrent stroke HR 0.84 (NNTx5y=34). ESPRIT: no decrease in ischemic stroke. Similar (ESPS-2) or less major bleeding (ESPRIT) with combination than ASA alone. ESPRIT: 34% vs. 13% discontinuation over 3.5y, mostly due to headache. PROGRESS showed clopidogrel had similar or possibly better efficacy, major & minor bleeding rates, and lower IC bleeding (1.0 vs. 1.4% over 2.5y) than Aggrenox® for recurrent stroke.
3. Clopidogrel: CAPRIE. Clopidogrel 75mg/d vs ASA 325mg/d starting >1 month after ischemic stroke. At 3y no difference in stroke recurrence. Overall benefit on combined recurrent stroke+MI+arr. dis. (NNT=198) has caused some to say it is superior to ASA. CAPRIE re-analysis (Stroke 2004;35:528-32): n=1,681 had strokes prior to their CAPRIE qualifying event. RR for recurrent stroke+MI+ischemic hospitalization = 0.79 (IOP 16.1% vs. ASA 18.5% per year, NNT 1x year = 42). Cost \$83/month. PROGRESS showed clopidogrel had similar or possibly better efficacy, major & minor bleeding rates, and lower IC bleeding (1.0 vs. 1.4% over 2.5y) than Aggrenox® for recurrent stroke.
4. ASA + Clopidogrel: CHARISMA: No reduction in ischemic stroke vs. ASA alone in the total population (but only 28% had prior stroke). NS reduction in primary endpoint (MI+Stroke+CV death), 13.9% RRR (p=0.13) in pts with prior stroke (though not specifically stated in the report). No excess serious bleeding or ICH in combination group. MATCH: ASA+clopidogrel no better than clopidogrel alone for 2ndary stroke prevention + major bleeding.
5. Warfarin: WARSS showed similar efficacy to ASA 325mg/d when INR 1.4-2.8 (mean 2.1). used. No sig difference in major bleeding. ESPRIT (INR 2-3) shows similar result, but more major bleeding with warfarin (Lancet Neurol 2007;6(2):115-24). Avoid warfarin INR>3 (SPIRIT) - no better efficacy than ASA, more bleeding.
6. Ticlopidine 250 bid superior to ASA 650 bid (TASS 1989, RR 0.82 CI 0.67-1.0, NNT x 2y vs. ASA=40) at reducing rate of stroke. Subgroup analysis of minor strokes showed similar benefit with ASA and ticlopidine (Stroke 1992;33:723-7). Ticlopidine superior for major strokes prevented by major complication caused by placebo (but based on small number) than ASA benefit (11.3). Adverse effects of ticlopidine (neutropenia 2.4%, rash 14%, diarrhea 20%), EXPENSIVE (~\$40/month+labs), laboratory monitoring, bid dosing make ASA first choice.

Score = 0? Score >0?
Age <65: "Lone a.fib": Annual stroke risk 1.3-1.4%. No treatment indicated. [ACCP 2004 guidelines recommend ASA 325mg/d, based on minimal evidence]
Age 65-75: SPAF/III re-analysis supports ASA 325 mg/d (stroke 1.1%/year). Also, SPAF II event rate 0.5%/yr in ASA group. No placebo arm in either trial. ACCP 2004 guidelines recommend Warfarin INR 2-3 or ASA 325mg/d.

Effect of ASA: [based on ASA vs. placebo meta-analysis of 6 trials (AFASAK, ESPS-2, LASAF, UK-TIA, SPAF, EAFT)] ASA 325 mg/d vs. placebo. Fatal & nonfatal ischemic stroke over mean 1.5 years: 5.8% vs. 4.3%/yr (ARR 1.7%/yr, RR 0.78 [0.62-0.98], NNTx1year=59) (Hart, Ann Int Med 1999;131:492-501). Calculate patients' INDIVIDUALIZED chance of benefit from RR + CHADS2 risk estimate.
Bleeding with ASA: ICH probably no higher than placebo (BMJ 1999;318:759-64), but serious GI bleeds more common than placebo (2.47% vs. 1.42% per 28 months, NNH=106, NNHx22 x 1 year, ARI 0.45%/y) [BMJ 2000;321:1183-7]. Relative benefit of ASA vs. placebo meta-analysis of 1410-1416].
Effect of Warfarin: based on warfarin vs. placebo meta-analysis of primary prevention trials (AFASAK, SPINAF, SPAF I, CAFSA, BAATAF) - Benavente et al. Cochrane Library 2002, BAFTA, Warfarin INR 2-3. RR 0.33 vs. placebo. Fatal & nonfatal ischemic stroke over mean 1.5 years: 5.9% vs. 1.9% (ARR 4%, RRR 33%, NNT 25). Confirmed in large effectiveness trial (JAMA 2003;290:2685-92). Calculate patients' INDIVIDUALIZED chance of benefit from RR + CHADS2 risk estimate.
Bleeding with Warfarin: Overall major bleeding 2.4-2.8y. 1.7%/y, ICH 0.5%/y (0.46 %/yr in large effectiveness trial vs. 0.23%/yr for no-warfarin). Effectiveness trial found no increased risk of non-intracranial major bleeding with warfarin (JAMA 2003;290:2685-92). For patients >75y, risk may be higher (eg. ICH 1.8%/year, all serious bleeds 2.8-4.2%/year based on epidemiologic data [Copland, ArchInternMed 2001;161:2125-8]). ACTIVE W showed major bleeding 2.4%/y. BAFTA (Lancet 2007;370:493-503) confirms warfarin's superiority over ASA in >75y/o's without increased major bleeding risk.
Relative benefit of OAC does not ↓ with age. Absolute benefit ↑ [Stroke 2009;40:1410-1416]

Oral DTIs: Dabigatran 110 or 150 mg bid. RELY [NEJM 2009;361] shows non-inferior/superior stroke/embolism efficacy vs. warfarin (110mg bid RR 0.91 [0.74-1.1]; 150mg bid RR 0.66 [0.53-0.82]), much less ICH (RR 0.30), similar or less major bleeding (110mg bid RR 0.80 [0.69-0.93]; 150mg bid RR 0.93 [0.81-1.07]). Rivaroxaban: ROCKET AF pending. Apixaban: ARISTOTLE, AVERRONES pending. Edoxaban: ENGAGE AF-TIMI48 pending.

Effect of ASA 75-100mg/d + clopidogrel 75mg/d [ACTIVE-A]: imputed efficacy vs. placebo: RR 0.66, (ASA is RR 0.78 vs. placebo, ASA+clopidogrel is RR 0.72 vs. ASA). Inferior to warfarin: stroke 2.44 vs. 1.4%/y [ACTIVE W].
Bleeding with 75-100mg/d + clopidogrel 75mg/d: Major bleeding 2.0-2.4%/y (ACTIVE A, ACTIVE W). Not less than warfarin in ACTIVE W (2.2 vs. 2.4%/y, NS). More major bleeding than ASA in ACTIVE A (2.0 vs. 1.3%/y, NNH 143, RR 1.57). Use only if avoiding warfarin for a reason other than bleeding risk and CHADS2 score >1.

Other indications for stroke prophylaxis: (See **ACCP 2008 Antithrombotic Guidelines** & **AHA/ASA 2006 Stroke 2ndary Prevention Guidelines**)
1. Rheumatic Mitral valve disease + left atrial diameter >5.5cm: Warfarin INR 2-3. No therapy if L atrial diameter <5.5cm, assuming normal sinus rhythm.
2. Post-infective mitral regurgitation: warfarin INR 2-3 + 3 months after infection followed by ASA 50-100mg/d lifelong. Aortic: ASA 50-100mg/d only (no initial warfarin). Warfarin alone if another indication for warfarin.
3. Atrial flutter. Some evidence of higher stroke risk than Afib [Ann Intern Med 2004;140:265-8]. ACCP guidelines recommend therapy as per Afib on theoretical and echocardiographic grounds. No efficacy data.
4. Patent Foramen Ovale (PFO): prevalence 34-46% in cryptogenic stroke patients. Aspirin or warfarin if PFO/stroke [AHA/ASA 2006 Gdlns, PICSS] No primary prevention trials. Surgical closure if >1 stroke.

Definitions:
Minor bleeding: Definition varies from trial to trial, but generally includes epistaxis, microscopic hematuria, or any bleeding that is not "major bleeding".
Major bleeding: Definition varies from trial to trial, but generally includes bleeding requiring hospitalization, gastrointestinal bleeding, intracranial hemorrhage, hemorrhage associated with >20 g/d drop in Hgb, bleeding requiring transfusion of two or more units of blood, any intraocular, retroperitoneal, or intraauricular bleeding.

References
-AHA/ASA 2006 Stroke 2ndary Prevention Guidelines. Stroke 2006;37:577-617.
-ESPAF: AHA/ASA 2006 Stroke Primary Prevention Guidelines. Stroke 2006;online May4.
-ACCP Antithrombotic Therapy Guidelines: Chest 2004;126(3).
-PICSS Circulation 2002;105:2625-2631
-COPAGEN Study (AFASAK) - Lancet 1989;1:1175-9.
-CAPRIE - Circulation 1991;84:527-39
-SPAF II - Lancet 1994;343:678-81
-SPAF III - Lancet 1996;348:337-40
-SPAF III reanalysis - JAMA 1998;279:161-1273-7
-Turpie Trial - Lancet 2000;352:924-9
-TASS - NEJM 1989;321:501-7
-CATS - Lancet 1993;339:1989
-Canadian Cooperative Study - NEJM 1978;299:53-9
-WARSS - Circulation 2005;111:2233-40.
-EAFT - Lancet 1993;342:1255-62.
-SIFA - Stroke 1997;28(6):1015-21.
-ACT 2002 - BMJ 2002;324:71-66
-SALT - Lancet 1991;338:1345-9
-SPIRIT - Ann Neurol 1991;24(6):857-65
-ESPS-2: Thromb Res 1998;82:51-56
-ESPRIT - Lancet 2006;367:1665-75
-CAPRIE - Lancet 1996;348:1323-39
-Dutch TIA Trial - NEJM 1991;325:1261-6
-Algra, J. Neurology Neurosurg Psychol 1996;60:197.
-SPARCL - NEJM 2006;355:549-59.
-CHARISMA - NEJM 2006;359:986-95
-HOPE-STROKE: BMJ 2002;324:1-5.
-WARSS: NEJM 2001;345:1444-51.
-CHADS2 - Lancet 2001;285:2984-70.
-HPS - Lancet 2002;360:7-22.
-USPSTF: AnnInternMed 2002;136:161-172
-PROGRESS - Lancet 2001;358:1033-41.
-CHARISMA - NEJM 2006;354(12M0AR06)
-MATCH - Lancet 2004;364:331-7
-ESPS-2: Thromb Res 1998;82:51-56
-JUPIITER - NEJM 2008;359:2195-2207
-ACTIVE A: NEJM 2009;360(2APR09)
-ACTIVE W: Lancet 2006;367:1903-12