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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 Doctor's Trial, MRC-TPT, HOT, PPP, WHS, APTC, USPSTF, USPHS, ETDRS). Best Evidence (meta-analysis including all these trials, JAMA 2006;295:306-13): ASA 50-500mg/d over 6.4 years: ↓all CV events in M & F (NNTx1y=~2700); ↓MI in M (NNTx1y=~750; ↑ICH in M (NNHx1y=~5000); ↑major bleeding in M & F (NNHx1y=~2200). No other significant differences vs. placebo. WHS (NEJM 2005;352) showed ASA 100mg q2d ↓ ischemic stroke in healthy women >45y (RR 0.7; NNT 392x10y) and >65y (RR 0.7 NNT 93 x10y).
With CV risk factors: HPS [MI, CAD, diabetes, HTN] & no prior stroke/TIA: Simvastatin 40mg/d ↓ stroke: 27% RRR, 1.6% ARR, NNTx5.5y=63.
JUPITER [intermediate CV risk]: rosuvastatin 20mg/d ↓ stroke: HR 0.52, NNTx1.9y=270. **HOPE-STROKE** [CAD or risk factors & no prior stroke/TIA] (n=8284): Ramipiril 10mg/d x 5y--> placebo 4.2% / ramipril 2.9% (ARR 1.34%, RR~0.68, NNTx5y=75). Fatal strokes ↓ (ARR 0.6%, RRR 60%, NNTx5y=167), nondisabling strokes ↓ (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:a1840]

MODIFY RISK FACTORS: (ASA/AHA Primary & Secondary prevention guidelines. [Stroke 2010]
-**HTN:** 10/5 mm decrease in BP --> 30-40% ↓ in CVA rate. Diuretics & ACEI+diuretic are preferred.
-Control **diabetes** (stroke risk 1.8 - 4.0 x baseline) (not clear that tight control reduces risk: ACCORD, ADVANCE)
-Stop **smoking** (stroke risk 1.5 - 2.0 x baseline) (quitting ↓ risk by 30-40% in observational studies)
-Avoid heavy **alcohol** use (>40g ethanol in 24 hours ↑ risk of acute stoke by >5x). Variable evidence re: chronic use.
-Manage **hypercholesterolemia** - Statins: RR stroke ~0.8 [BMJ 2009;338:b2376, Br J Clin Pharmacol 2004;57:640-51]
Fibrates: no effect. [Lancet 2010; 375: 1875–84].
-Oral **contraceptives** (estrogen): CONTROVERSIAL. Meta-anal showed RR 2.75 overall, 2.0 with estradol <50 mcg, 4.53 with estradiol >50mcg/d, 2.78 for 50mcg/d. Age > or < 35 made no difference [JAMA 2000:284-72-78]; BUT all based on non-RCTs with severe methodologic limitations. Association may be nonexistent [Arch Intern Med 2004;164:741-7]
-Post menopausal HRT: estrogen+progestin: 1.8% vs 1.3% stroke risk @ 5.6y [HR 1.5, ARI 0.5%, NNH=200] [WHI, JAMA 2003;289:2673-84]. Similar for estrogen alone vs. placebo in WHI.
-Hyperhomocysteinemia - ↑ 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). CEA=carotid endarterectomy. CAS=carotid angioplasty & stenting.

Symptomatic? (recent [<6mos] ipsilateral)
- No → ACAS (JAMA 1995), ACST (Lancet 2004;363:1491-501), NEJM 358;15:1617-21. **CEA**: if >60% stenosis, surgical risk <3% and good 5-year survival prospects. Follow with ASA 75-100 mg/d lifelong. **Medical therapy**: if not getting surgery. All the usual CV risk reduction methods. ASA 75-100mg/d, avoid dual antiplatelets (MATCH, CHARISMA, ACCP 2008) **CAS**: value over medical therapy is unknown (e.g., CREST, ACT1) for these "low risk" patients.
- Yes → degree of stenosis (NASCET method)
  - <50% → No CEA/CAS. Optimal therapy unknown. Surgery worsens outcome (ECST, NASCET). Give antiplatelets + statin + manage atherosclerotic risk factors.
  - >50% → **CEA or CAS**. After CAS: ASA+Clopidogrel x at least 4 weeks (CREST). After CEA: ASA 50-100 mg/d prior to and lifelong (ACCP 2008).

Non-Rheumatic Atrial fibrillation
SPAF I-III, AFASAK , AFASAK2, BAATAF, CAFT, SPINAF, CAFA, SIFA, PATAF, MWNAF.

Mechanical heart valve(s)?
- No → paroxysmal → No stroke trials. Likely increased risk of stroke. Treat same as chronic, but consider % time in AF if possible. Statins may reduce AF recurrence rate (OR 0.39) vs. rate control. [JACC 2008;51:828-35]
- Yes → chronic or paroxysmal? → chronic → previous stroke/TIA associated with AF? (ie, cardioembolic stroke/TIA)
  - No → Choose preventative therapy based on annual stroke risk vs. bleeding risk + patient's values
  - Yes → **Atrial Fib + previous AF-associated stroke STROKE/TIA:**. RCTs are **EAFT, SIFA, RE-LY.** 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=13). 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. INR 2.5-4 not generally recommended or practiced in North America (use INR 2-3). SIFA (warfarin INR 2-3.5 vs. indobufen) x 1 year: warfarin not superior to indobufen. RE-LY included n=3623 with prior stroke/TIA: Both dabigatran doses had similar efficacy to warfarin; Major bleeding: D 110mg bid less than warfarin (RR 0.66); D 150 mg bid similar to warfarin (RR 1.01) [Lancet Neurol 2010; 9: 1157–63]. **These trials use odd interventions or comparators and/or show RRR similar in secondary prevention to primary prevention. Hence, use CHADS2 system rather than these trial results directly.**

Mechanical heart valve(s)
>1 MHV, previous thromboembolism, A.fib, CAD, anterior MI, hypercoagulable state, low EF, enlarged left atrium, left atrial thrombus?
- No → Mechanical **aortic** valve: Warfarin INR 2.5 (2-3)
  Mechanical **mitral** or aortic+mitral valve: Warfarin INR 3.0 (2.5-3.5). ADD aspirin 50-100mg if low risk of bleeding.
- Yes (highest risk) → Combination warfarin (INR 3.0) + ASA 75-100 mg/d (Turpie 1993). ↓ death+nonfatal embolism (9.9%/yr vs. 3.9%/yr) and ↓ mortality (7.4%/yr vs. 2.8%/yr); ↑ in major bleeds (8.5%/y vs. 6.6%/y - NS); ↑ overall bleeds (35%/y vs. 22%/y; p<0.05). Thus, use only in these highest risk patients and be cautious about bleeding.

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 recurent stroke @ 7 days: 11.5%, @ 30 days: 15%, @ 90 days: 18.5%. (BMJ 2004;328:326).
RRE-90 tool predicts 90-day recurrent rate http://www.nmr.mgh.harvard.edu/RRE/
ABCD2 not reliable CMAJ 2011. DOI:10.1503

Symptomatic intracranial stenosis? (>50% cerebral artery stenosis, angiographically confirmed)
- Yes → ASA preferred over warfarin. WASID (NEJM 2005;352:1305-16): ASA 650mg bid similar efficacy to warfarin INR2-3, less major bleeding, less death. Trial stopped early. Use ASA 50-325 mg/d (ASA/AHA).
- No → stroke/TIA suspected to be cardioembolic? (eg, HMCAS, pt in A.fib)
  - Yes → Mechanical heart valve(s)?
    - Yes (VERY high risk) → Combination warfarin (INR 3.0) + ASA 75-100 mg/d (Turpie 1993). ↓ death+nonfatal embolism (9.9%/yr vs. 3.9%/yr) and ↓ mortality (7.4%/yr vs. 2.8%/yr); ↑ in major bleeds (8.5%/y vs. 6.6%/y - NS); ↑ overall bleeds (35%/y vs. 22%/y; p<0.05). Thus, use only in these highest risk patients and be cautious about bleeding.
    - No → Recent anterior MI?
      - Yes → >33% will have intraventricular thrombus 2 weeks after anterior MI. RAMIPRIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5y=67), CV mortality (RR 0.78, NNTx5y=27) and overall mortality (RR 0.84, NNTx5y=56). (HOPE) **PLUS:** HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, & Ann Int Med 1998;128:89-95) **PLUS:** Warfarin INR 2-3 for at least 3 mos. (ASA/AHA 2010 Stroke 2ndary Prevention Guidelines). Based on meta-anlaysis of poor-quality trials, stroke OR 0.46 (Arch Intern Med 1992;152:2020-4]
      - No → **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, PRoFESS) 3. Add SR dipyridimole (ie, switch to Aggrenox) (ESPS-2, ESPRIT, PRoFESS) 4. Switch to warfarin (WARSS, ESPRIT) 5. Add clopidogrel? (CHARISMA, MATCH) 6. Increase ASA dose?

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

Anterior MI with mural thrombus or anterior wall akinesis
- Yes → >33% will have intraventricular thrombus 2 weeks after anterior MI. RAMIPRIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5y=67), CV mortality (RR 0.78, NNTx5y=27) and overall mortality (RR 0.84, NNTx5y=56). (HOPE) **PLUS:** HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, & Ann Int Med 1998;128:89-95) **PLUS:** Warfarin INR 2-3 for at least 3 mos. (ASA/AHA 2010 Stroke 2ndary Prevention Guidelines). Based on meta-anlaysis of poor-quality trials, stroke OR 0.46 (Arch Intern Med 1992;152:2020-4]
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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

-WASH (AmHJ 2004;148:157-64) showed warfarin or ASA no better than placebo for death+MI+stroke over 27mos (only placebo-controlled RCT). ASA recipients had MORE hospitalizations than placebo (NNH=7).
-WATCH (unpublished, 2004) showed no difference between warfarin, ASA, clopidogrel, with more hospitalizations in ASA group and more major bleeding with warfarin (vs. other 2 groups).
-WARCEF: warfarin not superior to aspirin (ICS 2012)

Overall, no clear evidence that either aspirin or warfarin are better than placebo, or that either is superior to the other.

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

previous thrombosis?
- No → Optimal therapy unkown. APASS/WARSS [JAMA 2004;291;576-84]: ASA and warfarin had same recurrence rate following cryptogenic stroke in aPL(+) subjects (~11%/yr) and no different from aPL(-) subjects. Nothing? 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 2ndary Prevention Guidelines: Warfarin INR 2-3. Also JAMA 2006;295:1050-1057. ACCP 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].

CHADS2 Risk Scoring System:
CHF/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)

online at www.sparctool.com with CHAD2DS-VASc & HAS-BLED

Score = 0? Score >0

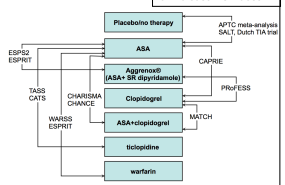
Age<65: "Lone a.fib": Annual stroke risk 1.3-1.4%. No treatment indicated. [ACCP 2008 guidelines recommend ASA 325mg/d, based on minimal evidence]
Age 65-75: SPAFIII re-analysis supports ASA 325 mg/d (stroke 1.1%/year). Also, SPAF II event rate 0.5%/yr in ASA group. No placebo arm in either trial. ACCP 2008 guidelines recommend Warfarin INR 2-3 or ASA 325mg/d.

Efficacy of ASA: [meta-analysis of 6 trials (AFASAK, ESPS-2, LASAF, UK-TIA, SPAF, EAFT)] ASA 325 mg/d: **RR 0.78**, vs. placebo. Fatal/nonfatal ischemic stroke: 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 patient's INDIVIDUALIZED chance of benefit using 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, NNH=222 x 1 year, ARI 0.45%/y) [BMJ 2000;321:1183-7]. Relative benefit of ASA ↓'s with age. [Stroke 2009;40:1410-1416].

Efficacy of Warfarin: [based on warfarin vs. placebo meta-analysis of primary prevention trials (AFASAK, SPINAF, SPAF I, CAFA, BAATAF) - Benavente et al. Cochrane Library 2000;2, 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%, RR 0.33, NNT 25). Confirmed in large *effectiveness* trial (JAMA 2003;290:2685-92). Calculate patient's INDIVIDUALIZED chance of benefit using RR + CHADS2 risk estimate. **Bleeding with Warfarin:** Overall major bleeding 2.4-2.8/y. 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, risks 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]: warfarin superior to ASA in >75 y/o's with no increased major bleeding. **Relative benefit of OAC does not ↓ with age. Absolute benefit ↑'s** [Stroke 2009;40:1410-1416]

Dabigatran [RE-LY] 150mg bid superior to warfarin RR 0.66 [0.53-0.82], similar major bleeding RR 0.93 (0.81-1.07). 110mg bid non-inferior to warfarin RR 0.91 (0.74-1.11), less major bleeding RR 0.80 (0.69-0.93). Similar pattern in pts with prior stroke/TIA [Lancet Neurol 2010; 9: 1157–63].
Rivaroxaban [ROCKET AF] 20mg superior to warfarin in primary analysis (on-treatment) stroke RR 0.79 (0.65-0.95). Non-inferior to warfarin in ITT analysis 0.88 (0.74-1.03). Similar major bleeding in both analyses 1.04 (0.90-1.20).
Apixaban:, ARISTOTLE (vs. warfarin) stroke HR 0.79 (0.66-0.95). Major bleeding in both analyses 0.69 (0.60-0.80).
Edoxaban: ENGAGE AF-TIMI 48 – stroke HR0.87 (0.73-1.04); major bleeding HR 0.8 (0.71-0.91)

Efficacy of ASA 75-100mg/d + clopidogrel 75mg/d [ACTIVE-A]: imputed efficacy vs. placebo: **RR 0.56**, (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 >1.



CHA2DS2-VASc [BMJ 2011;342:d124]:
-similar accuracy to CHADS2 (~77% based on c statistics). More accurate than CHADS2 if using the "3 group" (ie, score 0, 1, >1) approach (~88% vs. 80% accurate based on c statistics)
HAS-BLED [JACC 2011;57:173–80]:
-predictive accuracy no better than other prediction rules all of which are extremely poor. (55%-65% accurate based on c statistics). LR analysis shows not useful (Loewen & Dahri unpublished).
CHA2DS2-VASc & HAS-BLED are in SPARC tool at www.vhpharmsci.com/sparc

AHA/ASA recommends "antihypertensives" for all patients post-stroke (>24h post), regardless of presence of HTN.
PERINDOPRIL 4mg/d + Thiazide (PROGRESS): In normotensives post-stroke: ARR 4.8%, RRR 42%, NNTx4y=21. NOTE: Perindopril alone showed no benefit in normotensives.
?RAMIPRIL - although HOPE showed overall 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 (NNT=53 x 5y), fatal stroke HR 0.57 (NNT=143), hemorrhagic stroke HR 1.66 (NNH=107-no excess fatal hemorrhagic stroke).
?SIMVASTATIN 40mg/d (Heart Protection Study): Stroke endpoint: 27% RRR, 1.6% ARR, NNTx5.5y=63. *NOTE: HPS was PRIMARY prevention trial from stroke viewpoint. Only* n=1820 had prior stroke/TIA. In this group: 2.1% vs. 1.8% all vascular events over 5.5y (ARR 0.3%, RRR 14%, NNTx5.5y=309).
PLUS:
1. **ASA**: Typical evidence is SALT (ASA 75 mg/d vs placebo): NNT x 3y to prevent recurrent stroke/TIA=22. RR=0.82. APTC 2002 shows similar result with pool of 23,000 pts from 21 trials (mainly ASA): Recurrent nonfatal stroke/TIA over 26 mos: RRR=23%, ARR=2.5% NNT=40 OR=0.75. Mortality over 28 mos: RRR=12%, ARR=1.5% NNT=67. Dosage: 1300 mg/d=325 mg/d=30 mg/d w.r.t. efficacy and major nonfatal complications (Algra. Also APTC2002: no difference in efficacy between 75 and 1500mg/d). Thus, use 325 mg/d or less. (Dutch TIA trial, ESPS-2, SALT). **Bleeding**: 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) [BMJ 2000;321:1183-7).
ACCP 2012 recommends 75-100 mg/d.
2. **Dipyridamole SR 200 mg bid + ASA 50-75 mg/d** (e.g. Aggrenox®) (ESPS-2, ESPRIT). Meta-analysis: RR for primary outcome (vascular death+ischemic stroke+MI)=0.82 vs. ASA alone. Stroke: ESPS-2: 3% ARR vs ASA alone (NNTx2y=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. PRoFESS 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. **ACCP 2012 recommends this over aspirin alone.**
3. **Clopidogrel**: CAPRIE. Clopidogrel 75mg/d vs ASA 325mg/d starting >1 week after ischemic stroke. At 3y no difference in stroke recurrence. Overall benefit on combined recurrent stroke+MI+periph.art.dis. (NNT=196) 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 hospitaliz'n = 0.79 (clop 16.1% vs. ASA 18.5% per year, NNT x1 year = 42). Costs $83/month. PRoFESS 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. **ACCP 2012 recommends this over aspirin.**
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) overall, 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 + more major bleeding. CHANCE started ASA+clopidogrel within 24h of minor stroke/TIA. ASA+clop x 21d then clop alone to complete 90d was superior to ASA alone (8.2% vs. 11.7% recurrent stroke) with no excess 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;23:1723-7). Ticlop benefit:risk=31:1 (major strokes prevented per major complication caused vs. placebo) but based on much smaller N than ASA benefit:risk (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.

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/L drop in HgB, bleeding requiring transfusion of two or more units of blood, any intraocular, retroperitoneal, or intraarticular bleeding.

Other indications for stroke prophylaxis: (See *ACCP 2012 Antithrombotic Guidelines & AHA/ASA 2010 Stroke 2ndary Prevention Guidelines*)
1. Rheumatic Mitral valve disease + left atrial diameter >5.5cm: No therapy if L atrial diameter<5.5cm, assuming normal sinus rhythm. Warfarin INR 2-3 for secondary prevention.
2. Post-bioprosthetic valves [0.2% stroke risk/year if NSR]: Mitral: warfarin INR 2-3 x 3 months after insertion then ASA 75-100mg/d lifelong. Aortic: ASA 75-100mg/d only (no initial warfarin). Warfarin INR 2-3 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 50-100mg/d if PFO+stroke [AHA/ASA 2010, ACCP 2012, PICSS] No primary prevention trials. Warfarin INR 2-3 second-line. Efficacy of closure unknown.