

Pharmacotherapy for Ischemic Stroke Prevention

MODIFY RISK FACTORS: (ASA/AHA Primary & Secondary prevention guidelines. [Stroke 2010]
HTN: 10.5 mm decrease in BP \rightarrow 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 stroke by >5x). Variable evidence re chronic use.
-Manage hypercholesterolemia - Statins: RR stroke -0.6 [BMJ 2009;339:2376-84, Br J Clin Pharmacol 2004;57:640-51]
Fibrates: no effect [Lancet 2010;375:1875-84].
-Oral contraceptives (estrogen): CONTRVERSIAL. Meta-analysis showed RR 2.75 overall. 2.0 with estradiol <50 mcg, 4.53 with estradiol >50mcg/d, 2.78 for 50mcg/d. Age > 40 or <35 made no difference [JAMA 2000;284:72-78]. BUT all based on non-RCTs with significant bias. Association may be inconsistent [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;286:73-84]. Similar for estrogen alone vs placebo in WHI.
-Hyperhomocysteinemia: ↓ stroke risk, but VISP [JAMA 2004;291:566-75] showed no effect of lowering using B vitamins.

Are any of these predisposing conditions present?

Carotid artery stenosis
(10% have "silent brain infarctions") (>75% stenosis \rightarrow 2.5% stroke risk/year and 6.5% MI risk/year). CEA=carotid endarterectomy. CAS=carotid angioplasty & stenting.

Non-Rheumatic Atrial fibrillation
SPAF III, AFASAK, AFASAK2, BAATAF, CAF, SPINAF, CAFSA, SIFA, PATAF, MNVAF.

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;328:326).
RRE-90 tool predicts 90 day recurrence rate <http://www.nmr.mgh.harvard.edu>
ABCD2 not reliable CMAJ 2011. DOI:10.1503

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? (recent <6mos)
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
Symptomatic (recent <6mos)
No
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
degree of stenosis (NASCET method)
>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).
<50%
No CEA/CAS. Optimal therapy unknown. Surgery worsens outcome (ECST, NASCET). Give antiplatelets + statin + manage atherosclerotic risk factors.

Mechanical heart valve(s)?
No
Bileaflet or Medtronic Hall tilting disc in aortic position: Warfarin INR 2.5 (2-3).
Tilting 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).
Yes (highest risk)
Combination warfarin (INR 3.0) + ASA 75-100 mg/d (Turpie 1993). ↓ death/nonfatal embolism (9.9% vs. 3.9%/yr) and ↓ mortality (7.4%/yr vs. 2.6%/yr) in major bleeds (8.5% vs. 6.6%/yr - NS). ↓ overall bleeds (35%/yr vs. 22%/yr; p<0.05). Thus, use only in these highest risk patients and be cautious about bleeding.

stroke/TIA suspected to be cardiac in origin? (eg. HCMAS, pt in A.fib)
Yes
ASA preferred over warfarin. WASID (NEJM 2005;352:1305-16). ASA 650mg bid similar efficacy to warfarin INR 2-3, less major bleeding, early death. Trial stopped early. Use ASA 50-325 mg/d (ASA/AHA).
No
stroke/TIA suspected to be cardiac in origin? (eg. HCMAS, pt in A.fib)
Yes
>33% will have intraventricular thrombus 2 weeks after anterior MI. RAMP1RIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5=67). CV mortality (NNTx5=27) and overall mortality (RR 0.64, NNTx5=56). (HOPE)
PLUS: HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, MIRACL) [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-analysis of poor-quality trials, stroke OR 0.46 [Arch Intern Med 1992;152:2020-4].

Anterior MI with mural thrombus or anterior wall akinesis
Yes
RAMP1RIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5=67). CV mortality (NNTx5=27) and overall mortality (RR 0.64, NNTx5=56). (HOPE)
PLUS: HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, MIRACL) [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-analysis of poor-quality trials, stroke OR 0.46 [Arch Intern Med 1992;152:2020-4].
No
stroke/TIA suspected to be cardiac in origin? (eg. HCMAS, pt in A.fib)
Yes
>33% will have intraventricular thrombus 2 weeks after anterior MI. RAMP1RIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5=67). CV mortality (NNTx5=27) and overall mortality (RR 0.64, NNTx5=56). (HOPE)
PLUS: HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, MIRACL) [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-analysis of poor-quality trials, stroke OR 0.46 [Arch Intern Med 1992;152:2020-4].

Recent anterior MI?
Yes
RAMP1RIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5=67). CV mortality (NNTx5=27) and overall mortality (RR 0.64, NNTx5=56). (HOPE)
PLUS: HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, MIRACL) [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-analysis of poor-quality trials, stroke OR 0.46 [Arch Intern Med 1992;152:2020-4].
No
stroke/TIA suspected to be cardiac in origin? (eg. HCMAS, pt in A.fib)
Yes
>33% will have intraventricular thrombus 2 weeks after anterior MI. RAMP1RIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5=67). CV mortality (NNTx5=27) and overall mortality (RR 0.64, NNTx5=56). (HOPE)
PLUS: HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, MIRACL) [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-analysis of poor-quality trials, stroke OR 0.46 [Arch Intern Med 1992;152:2020-4].

Antiphospholipid antibodies
previous thrombosis?
No
Optimal therapy unknown. APASS/WARRS [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].

Choose preventative therapy based on annual stroke risk vs. bleeding risk + patient's values
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.vpharmsci.com/sparc with CHADS2-VASc & HAS-BLED

paroxysmal
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%/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 2.3-5.5, vs. dabigatran) x 1 year: warfarin not superior to dabigatran. RE-LY included =3623 with prior stroke/TIA. Both dabigatran doses had similar efficacy to warfarin; Major bleeding: D 110mg bid less than warfarin (OR 0.66); D 150mg bid similar to warfarin (OR 1.01) [Lancet Neurol 2010;9:1157-63]. These trials use odd interventions or comparators and/or show RR similar in secondary prevention to primary prevention. Hence, use CHADS2 system rather than these trial results directly.

stroke/TIA suspected to be cardiac in origin? (eg. HCMAS, pt in A.fib)
Yes
>33% will have intraventricular thrombus 2 weeks after anterior MI. RAMP1RIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5=67). CV mortality (NNTx5=27) and overall mortality (RR 0.64, NNTx5=56). (HOPE)
PLUS: HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, MIRACL) [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-analysis of poor-quality trials, stroke OR 0.46 [Arch Intern Med 1992;152:2020-4].
No
stroke/TIA suspected to be cardiac in origin? (eg. HCMAS, pt in A.fib)
Yes
>33% will have intraventricular thrombus 2 weeks after anterior MI. RAMP1RIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5=67). CV mortality (NNTx5=27) and overall mortality (RR 0.64, NNTx5=56). (HOPE)
PLUS: HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, MIRACL) [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-analysis of poor-quality trials, stroke OR 0.46 [Arch Intern Med 1992;152:2020-4].

Recent anterior MI?
Yes
RAMP1RIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5=67). CV mortality (NNTx5=27) and overall mortality (RR 0.64, NNTx5=56). (HOPE)
PLUS: HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, MIRACL) [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-analysis of poor-quality trials, stroke OR 0.46 [Arch Intern Med 1992;152:2020-4].
No
stroke/TIA suspected to be cardiac in origin? (eg. HCMAS, pt in A.fib)
Yes
>33% will have intraventricular thrombus 2 weeks after anterior MI. RAMP1RIL 10 mg/d ↓ stroke risk (RR 0.68, NNTx5=67). CV mortality (NNTx5=27) and overall mortality (RR 0.64, NNTx5=56). (HOPE)
PLUS: HMGCoA reductase inhibitor (based on HPS, LIPID, CARE, 4S, MIRACL) [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-analysis of poor-quality trials, stroke OR 0.46 [Arch Intern Med 1992;152:2020-4].

Antiphospholipid antibodies
previous thrombosis?
No
Optimal therapy unknown. APASS/WARRS [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].

Antiphospholipid antibodies
previous thrombosis?
No
Optimal therapy unknown. APASS/WARRS [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].

Antiphospholipid antibodies
previous thrombosis?
No
Optimal therapy unknown. APASS/WARRS [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].

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 Warfarin: [based on warfarin vs. placebo meta-analysis of primary prevention trials (AFASAK, SPINAF, SPAF I, CAFSA, BAATAF) + Benavente et al. Cochrane Library 2000;2. BAATAF]. 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 patients' INDIVIDUALIZED chance of benefit using RR + CHADS2 risk estimate. Bleeding with Warfarin: Overall major bleeding 2.4-2.8%. 1.7%/yr, ICH 0.5%/yr (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 2.4-2.2%/year based on epidemiologic data (Cochran, Arch Intern Med 2001;161:1225-8)]. 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 1% [Stroke 2009;40:1410-1416].

Dabigatran [RE-LY] 150mg bid superior to warfarin INR 0.66 (5.0-3.82), 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 ITI 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 TIMI48 (pending).

Efficacy of ASA 75-100mg/d + clopidogrel 75mg/d [ACTIVE-A]: Imputed efficacy vs. placebo RR 0.56. 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. 1.7%, NNT 143, RR 1.57). Use only if avoiding warfarin for a reason other than bleeding risk and CHADS2 <1.

CHADS2-VASc [BMJ 2011;342:d124]: Similar accuracy to CHADS2 (<7% 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 & Dahl unpublished].
CHADS2-VASc & HAS-BLED are in SPARC tool at www.vpharmsci.com/sparc

CHADS2-VASc [BMJ 2011;342:d124]: Similar accuracy to CHADS2 (<7% 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 & Dahl unpublished].
CHADS2-VASc & HAS-BLED are in SPARC tool at www.vpharmsci.com/sparc

CHADS2-VASc [BMJ 2011;342:d124]: Similar accuracy to CHADS2 (<7% 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 & Dahl unpublished].
CHADS2-VASc & HAS-BLED are in SPARC tool at www.vpharmsci.com/sparc

Other indications for stroke prophylaxis: (See ACCP 2008 Antithrombotic Guidelines & AHA/ASA 2010 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. Warfarin INR 2-3 for secondary prevention.
2. Post-bioprosthetic valves [0.2% stroke risk/yr if NSR]. Mitral: warfarin INR 2-3 x 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 Afb [Ann Intern Med 2004;140:265-8]. ACCP guidelines recommend therapy as per Afb on theoretical and echocardiographic grounds. No efficacy data.
4. Patent Foramen Ovale (PFO): prevalence 34-46% in cryptogenic stroke patients. Aspirin if PFO+stroke [AHA/ASA 2010 Gdins, PICSS] No primary prevention trials. Unknown whether warfarin+aspirin. Efficacy of closure unknown.

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/dL drop in Hgb, bleeding requiring transfusion of two or more units of blood, any intracranial, retroperitoneal, or intraarticular bleeding.