ORAL ANTIPLATELET & ANTITHROMBOTIC AGENTS

Prepared by: B. Jensen, S. Downey, L. Regier - **www.RxFiles.ca**

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Generic/ TRADE (Strength & forms)	INDICATIONS	ADVERSE EFFECTS	COMMENTS/ CONTRAINDICATIONS (CI) / MONITOR (M)	DOSE $ /30 Day
Acetylsalicylic acid (ASA) –irreversibly inhibit COX-1 to ↓ thromboxane production; resistance to antiplatelet effect occurs in 5-10% of pts with stable coronary disease NEJM May 02				
Aspirin/ASA C/D OTC **ENTROPHEN**/Generics 150✗⊗ & 650✗⊗mg supp OTC 80✗▼,325✗▼mg regular tab OTC 81✗▼,162✗⊗,325▼,500✗⊗,650▼, 975✗⊗mg EC tab OTC (Note: only **325 & 650mg EC** tabs **covered** on Sask. formulary) 325✗⊗,650✗⊗mg EC caplet OTC	**Primary MI Prevention** [7] **only if:** (consider ASA if 10yr CAD risk ≥10% AHA 2002 [19]) ◆ **diabetes** >40yr old ADA 2004 39 ◆ **>50 yrs AND…≥ 1 risk factor**: smoking, ↑ BP, ↑ cholesterol, history of young parental infarct ,albuminuria ◆**no contraindication to ASA** (**NNT=175** 3.8yr to prevent 1 major CV event in treated hypertensive pts HOT) **Secondary Prevention** to ↓ MI, stoke or death in: Acute Coronary Syndrome **ACS** Coronary Artery Disease **CAD** Cerebral Vascular Disease **CVD** Angioplasty Coronary Artery Bypass Surgery (**NNT=22** 2.6yr to prevent 1 stroke or death in post TIA/stroke pts SALT; Meta-analysis[2]:16%→12.9%**NNT=33**) **ASA Combination Treatment Options:** but combo ASA&clopidogrel ↑bleeding MATCH 1) **ASA + Dipyridamole** for recurrent stroke 2) **ASA + Clopidogrel** x 4-52 weeks for post coronary stenting; CABG for non-STE ACS x ~1yr 3) **ASA 80mg + Warfarin (INR 2-3)** for recurrent systemic embolism in mitral valve stenosis/regurgitation; mitral mechanical valve; aortic mechanical valve & atrial fibrillation 4) **ASA 80mg + Warfarin (INR 2.5-3.5)** for mechanical valve with recurrent systemic embolism or other cardiac risk	**GI upset ~ 5%** Fatigue, rash 4.6% CAPRIE Muscle weakness **Any GI bleed 2.7%** CAPRIE **Severe GI bleed 0.7%** Leuko/thrombocytopenia rarely <1% Renal: can ↓ renal fx esp. if CrCl < 30ml/min	◆**Drug of choice in many pts** (20% ↓ in relative risk) ◆80/81mg tabs ↑ expense; can use ¼ x 325mg ◆>80mg not more efficacious but ↑ SE bleeding ◆chew EC tab if need rapid onset of action ◆**Options to ASA in STROKE prevention (no options clearly offer more benefit vs risk):** ◆do nothing if options are contraindicated ◆AGGRENOX (Chest'04→ maybe drug of choice) ◆PLAVIX or (TICLID not recommended) ◆ASA + PLAVIX but combo ↑bleeding MATCH NNH=77 1.5yr ◆↑dose of ASA(?≤325mg/d if on ~80mg/d) ◆in select pts mortality benefit shown by using other therapies (eg. thiazides, ACEIs & statins). **CI**: Bleeding disorders, allergy & possibly asthma **M**: CBC if indicated ASA 50-325mg od Chest 2004 ,Primary Prevention 75-162mg od ASA 75-150mg od Antithrombotic Trialists' Collaboration BMJ 2002	**80mg od** $5 **81mg EC od** $5 (75mg od HOT, SALT **325mg od** CAPRIE $2 **325mg every other day** PHS $1
Dipyridamole (with ASA) – antiplatelet and vasodilatory effects via inhibition of cAMP and blockade of adenosine uptake				
Dipyridamole + ASA **AGGRENOX** ☎ ✆ C/D 200mg extended release + ASA 25mg capsule	**Secondary Prevention:** dipyridamole combined with ASA (Aggrenox) (**NNT= 37** over 2yrs to prevent 1 stroke or death in pts with a hx of stroke or TIA **vs** ASA$_{25mg\ bid}$ alone ESPS2) ☎ **EDS** criteria: pts with recurrent stroke or TIA while on ASA	**More SE vs ASA alone:** **Headache ~ 30%** GI upset ~ 15% Dizziness ~ 10% Any GI bleed 1.2% ESPS2	**Good choice** CHEST"04 maybe drug of choice for embolic stroke or TIA (but **poor tolerability**) More effective than aspirin$_{25mg\ bid}$ alone ESPS2 **CI**: Bleeding disorders, allergy & possibly asthma **M**: CBC if indicated	**200/25mg bid** ☎ ✆ ESPS2 **$66**
Thienopyridines– irreversibly prevents ADP induced platelet aggregation				
Clopidogrel **PLAVIX** ☎▼ B 75mg tablet	**Secondary Prevention:** **CAPRIE:** PLAVIX (**NNT= 200** / yr to prevent 1 vascular death, MI, or stroke **vs** ASA $_{325mg/d}$; although **most benefit** in pts with **peripheral arterial disease** (& more benefit in diabetics); **no better than ASA in patients with previous MI or stroke**) (**Substudy:** For pts with Prior Stroke or MI History the NNT was **71** / yr) [40] **CURE:** PLAVIX {**NNT= 48** for 9months to prevent 1 cardiovascular death, MI, or stroke when combined **with ASA vs** ASA $_{75\text{-}325mg/d}$ alone in pts with **ACS** (but ↑ major **bleeding** 3.7 vs 2.7%, **NNH=99; less bleeding** with **≤100mg ASA** without loss of efficacy [25])} **CLASSICS:** no difference between PLAVIX or TICLID in 1st 28days **post-stenting** **MATCH**: [48] with TIA hx21% or ischemic stroke79%→PLAVIX +/-ASA 75mg od {ischemic events 15.7 combo vs 16.7% NS; major **bleeding** 2.6 combo vs 1.3%;n=7599 ~18mon}	GI upset ~10% (⇨**diarrhea**) Headache, dizziness >5% **Rash** 6%→severe 0.26% Caprie **Any GI bleed** 2.0% Caprie **Severe GI bleed** 0.5% Caprie Blood dyscrasias rarely <1% -aplastic anemia, neutropenia 0.1%, **thrombotic thrombocytopenic purpura (TTP) 20 cases** -often in 1st 2 weeks of starting & can relapse; (? occurs in >20 per 3 million patients NEJM 2000)	**PLAVIX**: Good choice CHEST'04 for embolic stroke/TIA Stop therapy 5 days prior to scheduled CABG **Loading dose if:** ◆**post-stenting** 300mg x1→75mg od x 4-52wks (Stenting→If on ASA+warfarin INR 2-3 for anticoagulation then D/C Plavix after:≥1month-bare metal; ≥3month-sirolimus; ≥6month-paclitaxel. If only on ASA+Plavix→D/C after ~1yr) [45] ◆Acute Coronary Syndrome (ACS) 300mg x1 dose **CI**: Bleeding disorders & allergy **M**: CBC q-week x 4 weeks **if** indicated → catch TTP	**75mg od** CAPRIE,CLASSICS,CURE ☎▼ **$96** No loading dose for 2°prevention {If using **ASA + Plavix**, ASA dose should usually be ≤100mg to minimize risk of bleeding} [25]
Ticlopidine ☎▼ B **TICLID**/Generics 250mg tablet	Reductions in stroke incidence for PLAVIX(CAPRIE 3.5→3.3% & CURE 1.4→1.2%) were NOT statistically significant {Expert Reviewer comment} **AAASPS**: **black pts** n=1809; ≤2yr; recurrent MI, stroke or vascular death 14.7% (Ticlid $_{250mg\ bid}$) vs 12.3% (**ASA** $_{325mg\ po\ bid}$). P=0.12 ☎ **EDS** criteria: Plavix & Ticlid: Pts with **recurrent** vascular episodes TIA/stroke or MI ◆ while on ASA ◆ intolerant to ASA (ie GI hemorrhage) ◆ allergic to ASA (ie nasal polyps, asthma) Plavix: Acute coronary syndrome & post coronary stenting for 1yr	GI upset ~10%, ↑ LFT ~1% **Diarrhea** 20%→severe 6% TASS **Rash** 12%→severe 3% TASS **Neutropenia 2.4%** WBC< 1.2 Blood dyscrasias <1% -aplastic anemia, **TTP** (**>1/ 5000** -peak incidence at **3-4weeks, seldom relapses**)	**Clopidogrel PLAVIX preferred** vs TICLID: ◆similar efficacy but ↓ **toxicity** (less rash, GI upset, blood dyscrasias) ◆better tolerated, more convenient, ↓ laboratory monitoring & ADR costs ◆no comparative trial of clopidogrel vs ticlopidine in 2° prevention **TICLID** not recommended CHEST'04 esp. because of side effects **M**: CBC q2wk x 3months→catch neutropenia/TTP;LFT	**250mg bid** CATS,TASS,AAAPSP ☎▼ **$47** No loading dose for 2°prevention

✱ Most likely scenarios where combo therapy indicated; other situations possible. See references on page 13.

Evidence for: Lifestyle changes for DIET, EXERCISE, moderate alcohol use & stop SMOKING!
Consider Thiazides (HCT 12.5-25mg od $4) Multiple Trials, ACEIs: (ramipril 10mg od $41) HOPE; (perindopril 4mg od $34 + indapamide 2.5mg od $12) PROGRESS-perindopril alone did NOT ↓ stroke
Statins: Pravastatin 40mg od $44; Simvastatin 20-40mg od $46. ?Vitamin Trials: ($B_{12}$ 400ug, B_6 25mg, Folate 2.5mg :no benefit VISP JAMA Feb 2004 41) (awaiting VITATOPS 42)

Name/ TRADE (strength & forms)	INDICATIONS	ADVERSE EFFECTS	COMMENTS / CONTRAINDICATIONS (CI) / MONITOR (M)	$/30 Days
Warfarin	**– inhibition of Vitamin K dependent clotting factors (II, VII, IX, X)**	**Common**: nausea, diarrhea, abdominal cramping, fever **Bleeding** ≤10%, major bleed 1.3% if INR 2-3 but ↑ to 7% in **high risk** pts [Chest 01.] Vitamin K IV/SC/PO [27-33] ↓'s INR if required. (give PO if only mild/moderate ↑INR without major bleeding) **Rare**: skin necrosis, purple toe syndrome, alopecia, urticaria, dermatitis & hematoma, ≤ 1% renal tubular necrosis, jaundice & vasculitis **INR 3-4.5** had ↑↑ **major bleeding** in pts with TIA/minor stroke[SPIRIT]. Highest risk includes: >65yr, on multiple drugs & first 6 months of starting treatment.	◆Dosing per therapeutic INR Range (usually 2.0-3.0) ◆Hold ~4days before surgery (heparin/LMWH maybe needed) ◆Loading dose often not required: reduces risk of elevated INR & hypercoaguable state during initial treatment ◆**Initially** give 4-5mg OD (10mg x1 an option for low risk outpts[16]) starting (**Reduce dose** in pts at high risk of bleeding, elderly (age > 70), pts with impaired nutrition/liver dx, or other hemorrhagic risk factors) **Monitoring M: CBC & INR as indicated** **First INR measurement** not until day 2 or 3; then daily INR until therapeutic for at least **2 consecutive days**, followed by INR 2-3 times weekly x 1-2 weeks. Further monitoring as per stability of INR. Can gradually reduce frequency of INR testing to once every 4 weeks if stable. Coagulation factors half-life vary from 6-72h and the half-life of warfarin is 2.5 days-thus **changes** made in the warfarin dose are **not completely reflected** in the INR **until day 3 or 4.** **Drug Interactions** **Increased Warfarin Response**: **Major** Clinical Significance: Allopurinol, Amiodarone, Anabolic steroids, Azole antifungals (e.g. fluconazole), Cimetidine, Ciprofloxacin, Erythromycin, Fibrates, Metronidazole, NSAIDs and Salicylates (warfarin & ASA may be combined under close medical supervision), Paroxetine, Phenylbutazone, Quinidine, Quinine, Statins[some], Sulfonamides, Thyroid hormones, ticlopidine,Vitamin E (doses > 800 IU). ◆**herbal preps** can ↑ warfarin response & bleeding (see Herbal [RxFiles Chart]) **Decreased Warfarin Response**: **Major** Clinical Significance: Antithyroid drugs (e.g.PTU), barbiturates (e.g. phenobarbital) , carbamazepine, phenytoin, rifampin & Vit. K rich supplements/foods **CI**: Pregnancy, Active bleeding, Hemorrhagic disorders & tendencies, Previous warfarin-induced skin necrosis, Recent/contemplated surgery & anesthesia of: CNS, eye, traumatic surgery resulting in large open spaces. **Caution**: Noncompliant or unreliable patients & Fall history. **Hemorrhagic Risks** **Pt factors**: Age >80, Hx of GI bleeding, Hx of cerebral vascular dx, Serious co-morbid condition (e.g. kidney/liver dx), **Interacting** meds, **INR above** therapeutic range & **length** of therapy.	13-18 for ≤5mg od

Primary and Secondary Prevention of thrombus:

Indication	Duration	INR
Venous		
◆post-op prophylaxis total hip or total knee replacement….	≥10d (longer if higher-risk)	**2.0 to 3.0**
◆treatment of VTE or PE		
calf vein thrombosis (symptomatic, isolated)……..	≥3mon	
proximal thrombosis (known, reversible risk factor)…	≥3mon	
1st episode idiopathic VTE…….	≥ 6-12mon	
recurrent idiopathic VTE or continued risk factor (ie cancer [consider LMWH first 3-6 months],clotting factor problems).	indefinite	
{After ≥3mon, warfarin (INR **1.5-2** vs placebo) is effective to prevent recurrent VTE[17], but warfarin (**INR 2-3** vs 1.5-1.9;NNT=100) was more effective without increased bleeding.[21]}		
Arterial		
◆atrial fibrillation ↑ (chronic, high risk, select intermediate risk pts)	indefinite	**2.0 to 3.0**
◆atrial fibrillation (elective cardioversion [≥48hr or unknown duration])	3wk prior + 4wk after	
Intracardiac		
◆native valve disease with embolism history or atrial fib...	indefinite	
◆bioprosthetic/tissue valve♥…….	3mon	
◆mechanical valve♥ in aortic position (St. Jude, Carbomedics, Medtronic-Hall) ……	indefinite	
◆mechanical valves♥ in aortic position + atrial fibrillation	indefinite	**2.5-3.5**
◆mechanical valves♥ in mitral position ..……..	indefinite	
Other		
◆antiphospholipid syndrome with prev thrombosis(INR >3)[Chest01]	indefinite	**2-3**[22]
◆post-MI esp. if high risk pts (WARIS-II [n=3,630 over 4yrs]) [20] warfarin [INR 2.8-4.2] or warfarin [INR 2-2.5] + ASA [75mg od] or ASA [160mg od] Warfarin +/- ASA most effective but ↑non-fatal major bleed[NNH= 250/yr]	indefinite (ACC/AHA 2004)	**2-3**[45] with ASA

Apo, Gen, Taro-WARFARIN/ COUMADIN
1mg ς *pink*
2mg ς *lavender*
2.5mg ς *green*
3mg ς *tan*
4mg ς *blue*
5mg ς *peach*
6mg ς✗▼ *teal*
7.5mg ς✗▼ *yellow*
10mg ς *white*

(color coded tabs)

Generics are interchangeable in SK

Cost based on generic & markup. **ACE** angiotensin converting enzyme **BP** blood pressure **Dx** disease **EC** enteric coated **Fx** function **GI** stomach **Hx** history **LFT** liver function tests **MI** myocardial infarction **NNH** number needed to harm **NNT** number needed to treat to benefit one **OTC** over the counter **PE** pulmonary embolism **Pts** patients **SE** side effects **TIA** transient ischaemic attack **VTE** venous thromboembolism **WBC** white blood cell ☎ EDS in Sask. ✗ Non formulary in Sk. ✆ prior approval for NIHB ⊗ not covered by NIHB ▼ covered by NIHB

↑ Atrial Fibrillation Risk → **High** prior stroke/TIA, systemic embolus, hypertension, poor Left Ventricular fx, >75yr old, diabetes, rheumatic mitral valve dx, prosthetic valve. **Intermediate** 65-75yr, no other risk factors. Treat: warfarin or ASA 325mg/d **Low** <65yr & no other risk factors, use **ASA 325mg** OD. {Warfarin **vs** ASA: 2x more effective in Primary; 3x in Secondary [37]}

ς=scored tablet **www.RxFiles.ca**

♥ Onset of anticoagulant effect ranges from 2-7days; if rapid anticoagulation required (eg VTE, post valve insertion) then heparin or LMWH and warfarin should be initiated the same time with overlap of at least 4 days. Heparin or LMWH is continued for ≥5days and then stopped when INR therapeutic for 2 consecutive days. Certain situations (eg chronic stable atrial fib) are not urgent & warfarin can be initiated without heparin or LMWH.

Risk Factors for VTE: Surgery, Trauma (major or lower extremity), Immobility (paresis), Malignancy, Cancer therapy (hormonal, chemotherapy or radiotherapy), Previous VTE, Older age, Pregnancy & postpartum period, Birth control pills, Hormone replacement therapy, Raloxifene, acute medical illness, heart or respiratory failure, Inflammatory bowel dx, Nephrotic syndrome, Myeloproliferative dx, Paroxysmal nocturnal hemoglobinuria, Obesity, Smoking, Varicose veins, Central venous catheterization & Inherited or acquired thrombophilia.

Stroke Risk Factors Modifiable: atrial fibrillation, **hypertension**, diabetes, high cholesterol, left ventricular hypertrophy, high fat & salt diet, obesity, **smoking** & high alcohol intake. Non modifiable: older age, hx of TIA, race & ♂'s.

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