

Generic/ TRADE (Strength & forms)	INDICATIONS	ADVERSE EFFECTS	COMMENTS/ CONTRAINDICATIONS (CI) / MONITOR (M)	DOSE \$ [Canada Flag] /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				
<p>Aspirin/ASA [C/D] OTC ENTROPHEN/Generics</p> <p>150^x & 650^x mg supp OTC 80^x, 325^x mg regular tab OTC 81^x, 162^x, 325^x, 500^x, 650^x, 975^x mg EC tab OTC</p> <p>(Note: only 325 & 650mg EC tabs covered on Sask. formulary)</p> <p>325^x, 650^x mg EC caplet OTC</p>	<p>Primary MI Prevention ⁷ only if: (consider ASA if 10yr CAD risk ≥10% AHA 2002⁷)</p> <ul style="list-style-type: none"> ♦ diabetes >40yr old ADA 2004³⁹ ♦ >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}) <p>Secondary Prevention to ↓ MI, stroke 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-analysis²: 16%→12.9% NNT=33)</p> <p>ASA Combination Treatment Options: but combo ASA&clopidogrel ↑bleeding^{MATCH}</p> <ol style="list-style-type: none"> 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 	<p>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</p>	<p>♦ 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 (Chest⁰⁴→ maybe drug of choice) ♦ AGGRENOX (not recommended) ♦ PLAVIX or (TICLID) (not recommended) ♦ ASA + PLAVIX but combo ↑bleeding^{MATCH} NNH=77 1.5yr ♦ ↑dose of ASA (?≤325mg/d if on ~80mg/d)</p> <p>♦ in select pts mortality benefit shown by using other therapies (eg. thiazides, ACEIs & statins).</p> <p>CI: Bleeding disorders, allergy & possibly asthma M: CBC if indicated</p>	<p>80mg od \$5 81mg EC od \$5 (75mg od) HOT, SALT 325mg od CAPRIE \$2 325mg every other day PHS \$1</p>
Dipyridamole (with ASA) – antiplatelet and vasodilatory effects via inhibition of cAMP and blockade of adenosine uptake				
<p>Dipyridamole + ASA AGGRENOX ☹ ☹ [C/D] 200mg extended release + ASA 25mg capsule</p>	<p>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</p>	<p>More SE vs ASA alone: Headache ~ 30% GI upset ~ 15% Dizziness ~ 10% Any GI bleed 1.2%^{ESPS2}</p>	<p>Good choice^{CHEST⁰⁴} 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</p>	<p>200/25mg bid ☹ ☹^{ESPS2} \$66</p>
Thienopyridines– irreversibly prevents ADP induced platelet aggregation				
<p>Clopidogrel PLAVIX ☹ ▽ [B] 75mg tablet</p>	<p>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_{75-325mg/d} alone in pts with ACS (but ↑ major bleeding^{3,7} vs 2.7%, NNH=99; less bleeding with ≤100mg ASA without loss of efficacy²⁵)} CLASSICS: no difference between PLAVIX or TICLID in 1st 28days post-stenting MATCH: ⁴⁸ with TIA hx^{21%} or ischemic stroke^{79%}→PLAVIX +/-ASA_{75mg od} (ischemic events 15.7 combo vs 16.7% NS; major bleeding^{2,6} combo vs 1.3% n=7599 -18mon)</p>	<p>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})</p>	<p>PLAVIX: Good choice^{CHEST⁰⁴} 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</p> <p>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</p>	<p>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</p>
<p>Ticlopidine ☹ ▽ [B] TICLID/Generics 250mg tablet</p>	<p>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</p>	<p>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)</p>	<p>TICLID not recommended^{CHEST⁰⁴} esp. because of side effects M: CBC q2wk x 3months →catch neutropenia/TTP;LFT</p>	<p>250mg bid CATS, TASS, AAASPS ☹ ▽ \$47 No loading dose for 2° prevention</p>

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), **ACEIs**: (ramipril 10mg od \$4), **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: (B₁₂ 400ug, B₆ 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)	♦Dosing per therapeutic INR Range (usually 2.0-3.0) ♦Hold ~4days before surgery (heparin/LMWH maybe needed) ♦Loading dose <u>often not</u> required: reduces risk of elevated INR & hypercoagulable 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 <u>every 4 weeks if stable</u> . 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
Warfarin [X] Apo, Gen, Taro- WARFARIN/ COUMADIN 1mg ^s pink 2mg ^s lavender 2.5mg ^s green 3mg ^s tan 4mg ^s blue 5mg ^s peach 6mg ^s teal 7.5mg ^s yellow 10mg ^s white (color coded tabs) Generics are interchangeable in SK	Primary and Secondary Prevention of thrombus: Indication Duration INR Venous ♦post-op prophylaxis total hip or total knee replacement.... ≥10d longer if higher-risk ♦treatment of VTE or PE calf vein thrombosis (symptomatic, isolated)..... ≥3mon 2.0 proximal thrombosis (known, reversible risk factor)... ≥3mon to 3.0 1st episode idiopathic VTE..... ≥ 6-12mon 3.0 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 ♦atrial fibrillation (elective cardioversion ≥48hr or unknown duration) 3wk prior + 4wk after 2.0 to 3.0 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} ♦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 ^{NNT= 250yr}	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 ^{SPRIT} . Highest risk includes: >65yr, on multiple drugs & first 6 months of starting treatment.		

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. ☹=scored tablet **www.RxFiles.ca**
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 Secondary³⁷}

♥ 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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