POST-MI

Troubleshooting Practical Issues

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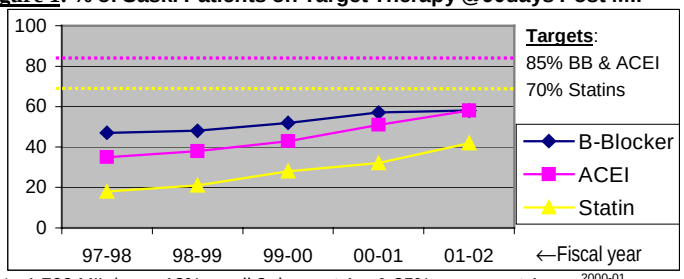
Key Message:

- Four types of medication (ACE-Inhibitors, beta-blockers, statins & ASA) have been shown to reduce cardiovascular risk in post-MI patients. [1] These benefits are in addition to risk factor management (eg. diet [2,3,4], lifestyle, exercise) and occur regardless of the presence of hypertension, dyslipidemia, or LV dysfunction. Clinical judgment is essential to assess risk/benefit for individual patients.

How are we doing in Saskatchewan?

- An analysis of Saskatchewan dispensing rates by the HQC suggests that important drugs are underutilized (See Figure 1).

Figure 1: % of Sask. Patients on Target Therapy @90days Post-MI. [HQC]



* ~1,700 MI's/year; 18% on all 3 drugs at 1yr & 35% on none at 1year [2000-01]; project 45 lives saved/year if benchmark [14] usage rates maintained long-term [15]

PRACTICAL ISSUES – ACE Inhibitors (ACEI)

Which patients will benefit?

- All post MI patients without contraindications [1] (indefinitely)
- Shown to reduce risk of CV events in post-MI patients who are high risk [5,6,7] (elderly, LV dysfunction); some benefit also in lower risk [8,9] patients (e.g. young, no LV dysfunction)
- Beneficial when initiated soon after acute MI [1] (~first 24hrs) AHA'04

Initiation & dosing in patients with renal dysfunction [10]

- Ensure SCr is stable before initiating ACEI therapy
- Start with low doses, slowly titrating towards targets with close monitoring. A moderate rise in SCr (that stabilizes within 1 week) may occur after each dose increase. (Of note: ACEI beneficial if existing renal impairment but may consider nephrology consult; trials exclude patients with high SCr (e.g. >200umol/l TRACE).
- Check SCr, BUN, and lytes at baseline and 7-14 days after each dose increase. **If SCr rise (above baseline) is**: [10]
  - **<30%** - continue titration / no concern
  - **30-50%** – decrease ACEI dose by 50% and recheck SCr in 7-10 days. If SCr rise still >30%, stop the ACEI
  - **>50%** – stop ACEI
  - When SCr rise is >30% consider investigating for renal artery stenosis and rule out other reversible causes.
  - Common reversible causes include: heart failure, **aggressive diuresis, volume depletion**, NSAIDs/coxibs & dehydration.
- Potassium levels above 5.6mmol/L during ACEI therapy should prompt reassessment of ACEI.

Initiation in patients with hyperkalemia

- Potassium should be ≤ 5.0mmol/L before initiating
- Identify reversible causes of the baseline hyperkalemia: Concurrent NSAIDs/coxibs or potassium sparing diuretics eg. spironolactone [11], dietary indiscretion -dietician counseling may be helpful.

Role of angiotensin receptor blockers (ARBs)

- Acceptable alternative when ACEIs not tolerated [1]
- Studied only in post-MI patients with LV dysfunction; valsartan at very high dosage showed equivalency to ACEI VALIANT [12]; losartan at lower dose was less effective than an ACEI OPTIMAL [13]
- Combination of an ACEI + ARB no more effective but more adverse effects than either ACEI or ARB alone VALIANT

PRACTICAL ISSUES – Beta-blockers (BB)

Which patients will benefit?

- Shown to reduce all-cause mortality in all post-MI patients regardless of LV function, especially those at high risk (when initiated within 4 weeks ~ideally first 24hrs of MI and continued for up to 4 years) [1,16]
- Beta-blockers may be especially underutilized in the elderly.[1]

Contraindications – myths and preconceptions

- Many conditions that previously contraindicated the use of beta-blockers are not "absolute". With cautious initiation and close monitoring, benefits may outweigh the risks in the following[17]:
  - COPD, diabetes, peripheral artery disease, & compensated HF; mild asthma (cardioselective BBs in those well controlled with inhaled steroids)[18]

PRACTICAL ISSUES – Statins

Which patients will benefit?

- ALL post-MI patients appear to benefit from statin therapy regardless of lipid levels (HPS ~40% patients post-MI history) [19, 1 AHA'04]

Should "high dose" statins be used in acute MI?

- Aggressive dose (atorvastatin 80mg OD) was better than moderate dose (pravastatin 40mg OD) when initiated <10 days after acute MI and continued for 2 years. [20 PROVE IT] {LDL achieved was 1.6mmol/L. Caution: risk of adverse effects (liver, muscle) with aggressive statin doses [20, 21,22 MIRACL]. Potentially conflicting A-Z trial data [21]}

Monitoring

- Guidelines recommend baseline transaminase and CK levels before starting any patient on a statin [AHA 23, ATP III 24]
- Frequent laboratory monitoring may be necessary in patients at high risk for adverse effects (ie. drug interactions, elderly, renal / hepatic dysfunction, high dose statins, niacin or fibrate combinations)

PRACTICAL ISSUES – ASA

- Recommend **81mg** enteric coated daily (75mg-162mg) [1 AHA'04, 25 ATC'02]
- Consider *H. pylori* eradication and cytoprotection for patients at high-risk of a GI bleed, even for ≤100mg ASA [26]
- Minimize [1,27] regular use of ibuprofen *MOTRIN, ADVIL* with ASA since antiplatelet effects may be blocked (conflicting data [28])
- High-dose NSAIDs/COXIBs may be associated with adverse heart outcomes [heart failure, MI] (eg. rofecoxib *VIOXX* [29, 30; APPROVe])

For specific drug & dosage considerations, see Page 2 - Table 1.

Table 1: Post-MI –Drug & Dosage Considerations

Prepared by D. Jorgenson, B. Jensen, L. Regier - www.RxFiles.ca - **Oct 2004**

	POST-MI TARGET DOSES (CONTROLLED TRIALS)		$/30d	BENEFITS	RISKS	COMMENTS
ACEI	Ramipril ALTACE	10mg HS HOPE; 5mg BID AIRE 31	41	◆ all-cause mortality: 17-29% RRR when started 2-16 days after event & continued for 4-5 yrs in pts with LV dysfx AIRE, TRACE, SAVE; {TRACE: NNT=13 over 4yrs 42.3 vs 34.7%,n=1749} ◆prevents ventricular remodeling;↓proteinuria ◆16% RRR in all cause mortality when started in high risk pts with remote history of MI and continued for 5 years HOPE; NNT HOPE = 56	◆Adverse effects include cough <10%, hypotension/dizzy ~2%, hyperkalemia ~2-11%, renal insufficiency (in pts with renal artery stenosis) & angioedema 0.4%, Blacks 0.7% 36; taste changes, rash; Rare: pancreatitis & blood dyscrasias.	◆AHA STEMI Guidelines 2004 suggest to use ACE inhibitors in **all pts indefinitely**. Most benefit if anterior infarction, pulmonary congestion or EF<0.4, tachycardia, in the absence of hypotension (SBP <100mm Hg or < 30mm Hg below baseline) ◆Contraindicated in pts with bilateral renal artery stenosis (or unilateral stenosis if only 1 kidney), history of angioedema to ACEI, & pregnancy ◆Combo ACEI+ARB: option with persistent HF CHARM (more adverse effects & no greater efficacy VALIANT)
	Trandolapril MAVIK	4mg OD TRACE 6	41			
	Lisinopril ZESTRIL/PRINIVIL	10mg OD GISSI-3 32	30			
	(high dose)	~35mg OD ATLAS 33 (HF)	65			
	Perindopril COVERSYL	8mg OD EUROPA 9	45			
	Enalapril VASOTEC	20mg OD CONSENSUS-II 34	48			
	Captopril CAPOTEN	50mg TID SAVE 7, BID in ISIS4 35	52			
	Generally start low-dose & titrate up to target dose if tolerated. eg. ramipril 2.5mg OD x1wk, 5mg od x3wk then 10mg od HOPE >50% POST MI					
ARB	Valsartan DIOVAN	160mg BID VALIANT 12	82	◆ all-cause mortality: valsartan, captopril 50mg TID, or combo equally effective VALIANT, n=14703, ~2yr ◆ ↓ proteinuria 39 even in pts with SCr<265 40, 41	Angioedema (17 of 26 pts safely put on ARB after ACEI) 42; More: ↓BP & ↑SCr 4.9 VS 3% VALIANT Less: cough 1.7 VS 5% VALIANT, rash & taste changes than ACEI. VALIANT	◆**Alternative if ACEI not tolerated & HF/LVEF<0.4** 1 (ARB: less cough & somewhat less angioedma) ◆captopril 50mg TID reduced CV-death in post-MI pts more than losartan 50mg OD OPTIMAAL
	Candesartan ATACAND	32mg OD CHARM (HF trial) 37,38	87			
	Generally start low-dose & titrate up to target dose if tolerated. eg. candesartan 4-8mg od, doubling ~q2wk →32mg od (>50% Ischemic Heart Disease in the CHARM Heart Failure trial)					
β- BLOCKER	Metoprolol♥ LOPRESSOR	100mg BID HJALMARSON 43	16	◆ all-cause mortality: 23% RRR when started in any pt within 5-28 days of MI & continued for up to 4yr;Meta-analysis: NNT=42 over 2yr (best long-term evidence with propranolol, metoprolol & timolol) FREEMANTLE n=24,974 16 ◆↓ sudden death, reinfarction & arrhythmias ◆Less benefit: ISA agents (pindolol; acebutolol?) 1,51 ◆Cardioselective agents (♥) preferred for mild asthma & diabetes	Adverse effects 52 include hypotension, dizziness, bradycardia, fatigue <10%, insomnia, vivid dreams, & sexual dysfunction ~4%; PAD, cold extremities; mask hypoglycemia .	◆AHA STEMI Guidelines 2004 suggest to use beta-blockers in **all pts indefinitely** {benefit less in low-risk pts eg. ~normal left ventricular fx, successful reperfusion, absence of significant ventricular arrhythmias} ◆Contraindicated in pts with severe/poorly controlled asthma, 2nd or 3rd degree heart block, HR<50, SBP <90, & decompensated heart failure 53 ◆some believe carvedilol better than metoprolol for HF but equivalent doses may not have been used COMET 54 ◆CNS adverse effects (depression, impotence, fatigue) overestimated; common in placebo groups & may not be solely related to beta-blockers 52
		≤200mg SR OD MERIT-HF 44,45	24			
	Atenolol♥ TENORMIN	100mg OD ISIS-1 46	20			
	Carvedilol COREG ☎	25mg BID CAPRICORN 47	58			
	Propranolol INDERAL	60-80mg TID BHAT 48	14			
	Timolol BLOCADREN	10mg BID NMCG 49	25			
	Acebutolol♥& ISA MONITAN	200mg BID APSI 50	22			
	Start low-dose & titrate up to target dose if tolerated, eg. **metoprolol 12.5mg BID**; **double dose ↑ q2wk**. (atenolol 25mg OD; carvedilol 3.125mg BID). **Tolerability**: Gradual dose titration & pt education regarding initial side effects improves tolerability. (e.g. 64% of MERIT-HF reached metoprolol 200mg/d) 45 **If withdrawing** beta-blocker therapy, do so gradually if possible over a few weeks to minimize risk of precipitating angina/MI.					
STATINS	Simvastatin ZOCOR	20-40mg OD 4S 55, HPS 19	46	◆ all-cause mortality: 22-29% RRR in post MI pts with ↑ cholesterol (LDL 3.9-4.9mmol/L) 4S, LIPID; 4S NNT=30 11.5 vs 8.2%, n=4444 simvastain 20-40mg/d, 5.4yr ◆ ↓ in major CV events NNT=18 & stroke NNT=62 (over 5 years) HPS 19 in pts at high CV risk ◆most trials enrolled pts >3months post-MI HPS, LIPID, CARE ◆No major statin trial enrolled pts age >82yrs 61	◆Adverse effects include GI upset, muscle aches, elevated LFTs <2%, myopathy <1%, rhabdomyolysis <0.2%, impotence; Rare: lupus-like symptoms, periph neuropathy.	◆AHA STEMI Guidelines 2004 suggest to use statins **in all patients** (even when baseline LDL < 2.5 mmol/L) ◆ATP-3 LDL target option: 1.8 mmol/L if very high risk 24 ◆If TG >5.6mmol/L, consider niacin or fibrate ◆Options for low HDL: lifestyle (exercise, ↓wt, smoking), fibrate (gemfibrozil 600mg BID VA-HIT $42) 62 or niacin ◆Contraindicated in pts with active liver disease, high alcohol consumption & pregnancy
	Atorvastatin LIPITOR	10mg OD ASCOT (not post-MI) 56	67			
	(high-dose in ACS)	80mg OD PROVE IT 20,22	87			
	Pravastatin PRAVACHOL	40mg OD LIPID 57, CARE 58	44			
	(Rosuvastatin CREST OR -no outcome trials yet; 59,60 10mg OD Higher levels in Asians; rhabdomyolysis cases at doses ≥10mg/d)		56			
	May start at target dose unless high risk for side effects (ie. elderly, renal/hepatic dysfx, niacin or fibrate combos, drug interactions, high dose or hx of intolerance)					
ANTI-PLATELET	**ASA**	**80-162mg** OD	5	◆all-cause mortality:10% RRR,NNT=91 over 2yr ATC ◆25% RRR in vascular events in previous MI patients treated with antiplatelet agents for 27 months ATC 25	◆Adverse effects: GI upset, hypersensitivity, GI bleed; major bleed. ◆Maj bleed/ hemorrhagic stroke ~ 0.5% / 5 years (NNH=200) ATC, USPSTF 68 {high risk pts, i.e. CAPRIE ASA 325mg/d 1.9 yrs; Bleeding: GI=2.7%; All severe =1.6%} 66	◆AHA STEMI Guidelines 2004 suggest using ASA **indefinitely** 75 to 162 mg/d if not contraindicated. ◆Contraindicated in pts with recent/active bleeding, major GI intolerance or history of ASA allergy ◆For pts with a true allergy to ASA consider clopidogrel 75mg OD or warfarin (INR target **2.5-3.5**) as useful alternatives 1 ◆ Combo: ASA+PLAVIX: ↑ efficacy but ↑ bleeding {CURE NNT=48, NNH 99,over 9 months; MATCH 69 post stroke NNH=77}
	Generally start at ~ 81mg enteric coated OD; {ASA ≤100mg as effective/less bleeding than 325mg, especially with Plavix CURE} 63					
	{see also RxFiles Antiplatelet & Antithrombotic Chart 64}					
	Clopidogrel PLAVIX ☎	75mg OD CURE 65, CAPRIE 66	96	◆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 →then D/C Plavix after ~1 yr. 1		
	Warfarin COUMADIN	1-10mg OD WARIS II 67	15			

OTHER: **Spironolactone** ALDACTONE 12.5-25mg OD $8 for severe HF Class III-IV RALES 70 ;DI:↑ K^+ level with ACEI, ∴monitor K^+ avoid if K+≥5mmol/L & renal fx. {Eplerenone in USA: for select post-MI pts with LV dysfx EPHESUS 71}

$=retail cost ☎=Exceptional Drug Status ♂=male ♀=female **A1C**=glycosylated hemoglobin **ACEI**=angiotensin converting enzyme inhibitor **ARB**=angiotensin receptor blocker **ATC**=Antithrombotic Trialists' Collaboration **ARR**=absolute risk reduction **BMI**=body mass index **BP**=blood pressure **CK**=creatine kinase **CV**=cardiovascular **DI**=drug interaction **EF**=Ejection Fraction **Fx**=function **FPG**=fasting plasma glucose **GI**=stomach **HF**=heart failure **HQC**=Health Quality Council **HR**=heart rate **Hx**=history **K^+**=potassium **LV**=left ventricular **MI**=myocardial infarction **NNT(H)**=number needed to treat (harm) **PAD**=peripheral arterial disease **PPBG**=postprandial blood glucose **Pts**=patients **RRR**=relative risk reduction **SCr**=Serum creatinine **TG**=triglycerides **wk**=week **wt**=weight

RISK Factors: 72,75 **Cholesterol:↑LDL** (ApoB/ApoA1 ratio used in INTERHEART), **Smoking**, **Diabetes**, **↑BP** esp. systolic, **Abdominal obesity**: **waist/hip ratio** (♂ ≥0.95; ♀ ≥0.9), BMI >25, Waist size 73 (♂ >102cm,40inch; ♀ >88cm,35inch), **stress & depression; lack** of **vegetables**, **fruits, exercise** (30-45mins 3-5x/week or more) **& alcohol** (0-2drinks/d ♂=14/week ♀=9/week); Low HDL ≤1, Family history of premature heart disease (Age: ♂ <55, ♀ <65) 73, Microalbuminuria 73, renal dysfx 74 & Age (♂ >55, ♀ >65).

Targets: **BP** Canadian 2004 (75): General <**140/90**; Diabetes < **130/80** if no proteinuria; <**125/75** if proteinuria >1g/d. **LIPID** Canadian 2003 (76) Post MI/High Risk→ LDL<**2.5**; Total Cholesterol/HDL Ratio<**4**

GLUCOSE: Canadian 2003 (77) Target for most: **A1C ≤7%**; **FPG 4-7** mmol/L; **PPBG** 2hr post **5-10** mmol/L **if** can be done **safely** without hypoglycemia.

Not recommended Post-MI: vitamin C, vitamin E & HRT 1

Lifestyle changes for DIET, EXERCISE & stop SMOKING!

References: RxFiles Post-MI

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