Critical Pathway for the Pharmacological Treatment of Chronic Stable Angina

*For a more complete review of each area, please refer to the recently published ACC/AHA /ACP-ASIM Chronic Stable Angina Guidelines.1

1. Aspirin

Since the majority of clinical trials for angina and post myocardial infarction have studied the effectiveness of aspirin at a dose of 325 mg, this is the preferable dosage to begin with in the treatment of patients with chronic stable angina. It should be understood that much higher doses of aspirin can have a hypercoaguable effect on platelets. Doses lower than 325 mg per day theoretically should be effective as the anti-platelet effects persist down to doses as low as 81 mg per day, however these lower doses have not been studied in detail with respect to treatment of angina. If there is gastrointestinal intolerance of the higher aspirin dosage of 325 mg per day, the dosage should be lowered to 81 mg per day and the enteric-coated form should be used prior to discontinuation of aspirin.

Aspirin Allergy

If a true allergy to aspirin exists, which would include a history of angioedema, urticaria or wheezing then the patient should not be challenged with aspirin and clopidogrel should be initiated. A consult to allergy should be considered to evaluate the patient for possible desensitization to aspirin.

2. Sublingual Preparations/Spray

For the treatment of acute anginal symptoms both the sublingual formulation and the oral spray have been utilized with good success. The advantage of the spray is that the cost (per unit dose) is only marginally higher than the sublingual preparation, but its shelf life is three years once open. Once a bottle of sublingual nitroglycerin tablets are open its effective shelf life is variable (3-6 months) and care must be taken to question the patient during each visit as to the effectiveness and age of his current supply. Recommend replacing supply every 3 months. The spray preparation may be more bioavailable, especially in the elderly, compared with the pill.

3. Prophylaxis of Anginal Symptoms

For some patients who have a very predictable pattern of angina (particularly those in whom a particular exertional activity prompts the anginal symptoms) then it may be appropriate to use prophylactic sublingual TNG prior to the initiation of the activity. Isosorbide dinitrate is also available in a sublingual preparation and is effective for up to one hour when used in the prevention of anginal symptoms. However, once symptoms require several TNG per day to control, then instituting a more regular schedule of anti-anginal therapy is warranted.

4. Beta-Blockers

The beta-Blockers listed in the pathway are the only agents FDA approved for the treatment of angina. These agents should be avoided in the following patients:
Absolute Contraindications

A. AV Block/ Sinus Node Dysfunction (severe bradycardia)
B. Decompensated CHF
C. Variant Threshold Angina

Relative Contraindications

D. LVEF < 30% (use with caution, careful titration)
E. Peripheral Vascular Disease or COPD/Asthma
F. Diabetes
G. Fatigue/CNS Depression

Absolute Contraindications

A. AV Block/Sinus Node Dysfunction

In the setting of AV block or sinus node dysfunction one could consider the use of a b-blockers with intrinsic sympathetic activity (ISA) [i.e. pindolol] however these agents are not currently approved for the treatment of angina. Alternative anti-anginals such as one of the dihydropyridine calcium channel blockers or a long acting nitrate should be considered. Placement of a permanent pacemaker can also be considered to allow use of b-blocker therapy.

B. Decompensated CHF

In patients with evidence of symptomatic and acute symptoms of congestive heart failure b-blocker therapy is contraindicated.

C. Variant Threshold Angina

When alterations in coronary vasomotor tone (i.e. coronary spasm) are believed to be responsible for a patient’s anginal symptoms (i.e. chest pain with no set exertional pattern, particularly common in smokers and possible evidence of ST segment elevation on ambulatory monitoring during symptoms) then b-blockers are contraindicated and monotherapy should be initiated with a CCB or long-acting nitrate.

Relative Contraindications

D. Depressed Left Ventricular Function

Although b-blockers have proved efficacious in patients with depressed ejection fractions, initiation of this therapy in a patient with severely depressed left ventricular function or with overt evidence of congestive heart failure can be detrimental and is still considered experimental at this time. Careful titration of b-blockade in a patient with severely depressed left ventricular function and angina is best attempted in an inpatient setting or a very closely monitored outpatient setting if the patient is reliable. Alternative antianginal agents should be considered including long acting nitrates and the dihydropyridine calcium channel blockers.
E. Peripheral Vascular Disease or COPD/Asthma

In patients with significant peripheral vascular disease or COPD/Asthma non-selective b -Blockers including propranolol and nadolol should be avoided. Low doses of beta-1 selective agents including atenolol and metoprolol may be tolerated without difficulty.

F. Diabetes

Unless a patient is prone to episodes of severe hypoglycemia, most β-Blockers can be safely used in this population. If there is a risk for significant hypoglycemia, one should consider the use of other antianginal agents and possibly the use of a β -Blocker with ISA.

G. Fatigue/Depression/Sexual Dysfunction

In a patient with complaints of easy fatigability, depression or sexual dysfunction on β-Blocker therapy, one could consider decreasing the current dose or changing to an agent with lower lipid solubility. The agents with the lowest lipid solubility are atenolol and nadolol.

5. Miscellaneous Issues Regarding Management of Patient on β-Blocker Therapy

A. Cardioselective vs Nonselective β-blockers

Although non cardioselective β-blockers (i.e. inderal) have proven to be more effective in the prevention of sudden death after myocardial infarction, there is no evidence that these agents are superior over the cardioselective agents (i.e. atenolol, metoprolol) in the treatment of chronic stable angina. Overall, the cardioselective agents are better tolerated by patients as they are typically not associated with common side effects of the nonselective agents such as central nervous system slowing, depression, fatigue, sexual dysfunction, bronchospasm (in patients with underlying COPD/asthma) and peripheral vasoconstriction in patients with significant peripheral vascular disease. From an economic vantage the non-cardioselective β-blockers are favorable, however if significant side effects decrease the compliance rate among patients, this advantage is diminished. The final choice of specific β-blocker should be individualized for each patient and take into consideration comorbid conditions which would favor the use of a cardioselective agent or another type of antianginal agent altogether. If a nonselective agent is initially used and poorly tolerated, the patient should be changed to one of the cardioselective agents prior to discontinuation of this therapy altogether.

B. Dose Goal

The dose of the β-Blocker should be initiated at a low dose (i.e. atenolol 25 mg po qd or bid) and titrated upward until symptoms are controlled or a side effect such as symptomatic bradycardia prevents further increase in the dose. It is important to realize that many patients can tolerate heart rates in the 40’s and sometimes this low heart rate may be required to control symptoms. Asymptomatic bradycardia is not an indication to decrease or stop treatment. It is important to realize that the once daily dosage of a long acting β-blocker may better serve the patient if it is given in the evening so that the patient has maximal effect during the early morning hours (4AM-8AM) when most myocardial infarctions and unstable angina episodes occur. Alternatively, the longer acting β-blockers can be dosed twice daily with a smaller dose given in the evening (i.e. atenolol 50mg po q AM and 25 mg po q PM).

C. WARNING!
Care should be taken not to acutely discontinue b-blocker therapy in a patient as this may precipitate acute withdrawal with a sudden rebound in blood pressure and anginal symptoms. A slow taper of the medication over several days is preferable when possible.

D. Minority Groups

It should be recognized that in certain minority groups (i.e. Afro-American patients), especially those with hypertension and angina that b-blockers are not the optimal monotherapy medication to begin with; this group of patients typically responds better to calcium channel blockers for control of their blood pressure.

E. Effects on Lipids

b-blockers do tend to cause a small decline in HDL levels and increase triglyceride levels. The effects on the lipid profile, however are outweighed by their overall beneficial effects on the treatment of stable angina and the prevention of myocardial infarction.

F. Other Benefits of b-blockade

Groups of patients who may receive additional benefit from b-blockers are those with hypertension, supraventricular tachyarrhythmias, and history of a Q wave myocardial infarction.2

6. Calcium Channel Blockers

Verapamil is the first non-dihydropyridine CCB of choice due to economic considerations if used as monotherapy. In a patient who is unable to tolerate verapamil (or when a b-blocker is used in combination with a CCB), a dihydropyridine (long acting nifedipine, amlodipine or felodipine) should be considered. Please see the text below for further considerations.

It should be noted that currently felodipine is not FDA approved for the treatment of chronic stable angina.

In the event that a patient enters University Health System already taking a calcium channel blocker such as long acting verapamil or diltiazem for the treatment of chronic stable angina and his/her symptoms are well controlled, then the physician may choose to continue this agent rather than initiate the pathway recommendations. This decision should remain with the patient and physician, however if treatment with this agent fails then the patient should be placed on alternative monotherapy such as a b-blocker or combination therapy with a b-blocker or long-acting nitrate.

A. Depressed Left Ventricular Function and AV Block

The non-dihydropyridine CCB (i.e. diltiazem and verapamil) should be avoided in patients with active CHF, significantly depressed left ventricular function and AV block. These patients are usually able to tolerate one of the dihydropyridine agents. It should be noted that among the dihydropyridines, nifedipine exerts the most negative inotropic effect, thus for patients with significantly depressed left ventricular function and/or active CHF, a newer generation dihydropyridine (i.e. amlodipine or felodipine) is preferred over nifedipine.1

B. After Myocardial Infarction

If at all possible, CCBs should be avoided after Q wave myocardial infarction. There is evidence
that diltiazem improves morbidity (preventing reinfarction and severe angina) after NQWMI in patients.\textsuperscript{3} The relative benefit of β-blockers vs. CCB post NQWMI is uncertain, however studies are in progress.

C. Using Dihydropyridines

These agents (particularly nifedipine) should be used in combination with a β-blocker when possible to prevent the expected reflex tachycardia. A 5-10% increase in HR is expected when these drugs are used as monotherapy.

D. Long Acting vs. Short Acting

Due to preliminary evidence that short acting preparations of these agents may increase the risk of myocardial infarction, whenever possible one should use the longer acting preparations in the treatment of chronic stable angina.\textsuperscript{4}

7. Nitrates

A. Preparations

Long acting preparations are available orally as qd and bid dosing. It is important that bid dosing of the long-acting dinitrate or mononitrate preparations be eccentric (7-8hrs apart) to allow for a nitrate free period and avoid the development of tolerance. For those patients and physicians who prefer the TNG patch it should be applied daily and removed for a 12-hour period preferably during sleeping hours to prevent tolerance. As of now there is not a distinct advantage of one preparation over another. Short acting preparations are available as tid and qid dosing and may be useful in the initial titration of dose, however due to the risk of developing tolerance it would not be optimal to continue these preparations on a long-term basis.\textsuperscript{5} For a more complete review of this topic please consult the review of Parker et al.\textsuperscript{6}

8. Monotherapy vs. Combination Therapy

While monotherapy with a β-blocker may be optimal for one patient, combination therapy with lower doses of each agent may be preferable for another due to inability to tolerate one agent at a higher dosage or poor control of anginal symptoms despite optimal doses of a single agent. Each patient’s individual situation should be taken into consideration when deciding upon a treatment plan.

Monotherapy with a β-blocker should be first line therapy for several reasons. β-blockers have been shown to be more effective in reducing episodes of silent ischemia\textsuperscript{7}, reducing the early AM peak of ischemic activity\textsuperscript{8} and are effective in improving mortality after Q wave MI.\textsuperscript{2} CCB and β-blockers appear equivalent in the improvement of anginal symptoms and exercise tolerance and in those patients without a history of prior MI there appears to be no difference in mortality, cardiovascular events or quality of life between these 2 classes of drugs.\textsuperscript{9,11} The cost is much less for most preparations of β-blockers.

A. Failure of Monotherapy with a β-blocker

If a patient continues to have angina despite maximal therapy with a β-blocker, a CCB should either be substituted for or added to the β-blocker. While a large multicenter study\textsuperscript{10} showed no benefit of combination therapy (with respect to symptom relief or other ischemic parameters),
other studies show more effectiveness when a CCB is added to a b-blocker.8, 12, 13 If there is evidence or suspicion of vasospastic angina (i.e. ST elevation on ambulatory Holter monitoring during CP episode), b-blocker therapy is contraindicated and should be discontinued and a calcium channel blocker initiated. Use of short-acting nifedipine would be contraindicated in a patient with angina due to the reflex tachycardia and preliminary evidence that these agents are associated with an increased risk of myocardial infarction.

B. Failure of Monotherapy with a Calcium Channel Blocker

If a patient has not been previously treated with a b-blocker then the CCB should be discontinued and monotherapy with a b-blocker should be initiated. If monotherapy fails with a CCB and a b-blocker is contraindicated then combination therapy with a CCB and long acting nitrate should be attempted to control symptoms.

C. Failure of Monotherapy with both a Calcium Channel Blocker and b-Blocker -->

Combination Therapy

In the event that a patient fails monotherapy with both a calcium channel blocker and b-blocker then initiation of combination therapy with a calcium channel blocker and b-blocker is indicated. [Since there are potential hazards (HR slowing and prolonging AV conduction) of using verapamil or diltiazem with a b-blocker, combination therapy of a b-blocker with a CCB should be with a long acting dihydropyridine.] Often, if a patient has had maximal therapy with a b-blocker then the addition of a calcium channel blocker such as verapamil may not be possible due to the potential of further decreasing the heart rate, worsening AV block or depressing systolic function. In these situations, initiation of a long-acting dihydropyridine CCB such as long-acting nifedipine, amlodipine or felodipine would be indicated to further improve coronary blood flow without the above mentioned effects. If a patient is unable to tolerate combination therapy with both a CCB and a b-blocker then one of these agents can be combined with a long acting nitrate.

D. Monotherapy with a Long Acting Nitrate

This should never be primary therapy for the control of symptoms from chronic stable angina, as it has been shown to be less effective than monotherapy with b-blockers or CCBs. However, if a patient is intolerant of therapy with CCBs or b-blockers, then primary treatment with long acting nitrates is indicated and subsequent referral to a cardiologist for further assessment (i.e. pacemaker placement so that CCB and β-blockers can be used or a PTCA, CABG to control symptoms.

9. Triple Therapy

This option should only be utilized in those patients who are awaiting cardiac consultation and have symptoms despite therapy with 2 agents. If the addition of the third agent does not improve symptoms within the first 3 days of treatment then it should be discontinued. Situations in which patients may remain on triple therapy include the following:

1. Concomitant medical problems prohibit further cardiac w/u and treatment (i.e. cath, PTCA or CABG)
2. Cardiac w/u discloses that medical therapy is the best option for this patient or patient chooses medical therapy over surgical or catheter intervention.

3. Patient who is unable to tolerate maximal doses of antianginal agents, but has well-controlled symptoms on triple therapy.