Pathway for Pharmacological Treatment of Chronic Stable Angina

This guidance refers to the management of patients with stable angina. All patients with unstable symptoms should be admitted directly to hospital. All patients with a history of a previous CABG or angioplasty should be considered for referral to a cardiologist if their symptoms deteriorate.

Immediate short term relief

1. **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 shelf life of GTN spray is three years once open. Once a bottle of sublingual nitroglycerin tablets are open its effective shelf life is variable (3-6 months).
   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 GTN prior to the initiation of the activity. However, once symptoms require several GTN per day to control, then instituting a more regular schedule of anti-anginal therapy is warranted.

Outcome modifying drugs

2. **Aspirin**
   Dose - 75mg to 150mg once daily. If a true allergy or contra-indication to aspirin exists, which would include a history of angioedema, urticaria or wheezing (only if induced by aspirin) then the patient should not be challenged with aspirin and clopidogrel 75 mg/day should be initiated.

3. **HMG Co A reductase inhibitors (Statins)**
   During the last decade, the development of the statins, has contributed greatly to cholesterol lowering therapy and cardiovascular risk reduction. These agents are well tolerated and efficacious. Benefits include reductions in the risks for myocardial infarction, and coronary, cardiovascular and all-cause mortality, stroke and the need for coronary revascularisation. Results of the recently completed Heart Protection Trial have clearly confirmed the results of the earlier trials and support the use of statin therapy in secondary prevention such as patients with angina. It is recommended that simvastatin (20mg/ 40mg) be used first line where appropriate

4. **ACE inhibitors**
   ACE inhibitors are considered beneficial in a broad range of patients including those with angina without evidence of LV systolic dysfunction or heart failure who are at high risk for cardiovascular events.
Symptom improving therapy

First line therapy

5. **Beta-Blockers**
   The dose of the beta-blocker should be initiated at a low dose (e.g. atenolol 25 mg od) and titrated upward until symptoms are controlled or a side effect such as symptomatic bradycardia prevents further increase in the dose. Care should be taken not to acutely discontinue beta-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. Monotherapy with a beta-blocker should be first line therapy for several reasons. Beta-blockers have been shown to be more effective in reducing episodes of silent ischemia, reducing the early AM peak of ischemic activity and are effective in improving mortality after Q wave MI. CCB and beta-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.

**Absolute Contraindications**
- AV Block/ Sinus Node Dysfunction (severe bradycardia). Alternative anti-anginals such as one of the dihydropyridine calcium channel blockers or a long acting nitrate should be considered.
- Decompensated CHF
- COPD/Asthma

**Relative Contraindications**
- LVEF < 30%. Careful titration of beta-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.
- Peripheral Vascular Disease
- Diabetes. If there is a risk for significant hypoglycemia, one should consider the use of other antianginal agents
- Fatigue/CNS Depression

6. **Calcium Channel Blockers**
   Diltiazem or verapamil are non-dihydropyridine CCBs of choice.

   In a patient who is unable to tolerate diltiazem or verapamil, or when a beta-blocker is used in combination with a CCB, a dihydropyridine (long acting nifedipine, amlodipine or felodipine) should be considered. 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.

**Contraindications**
- 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.
• 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.
• Using Dihydropyridines. Use of short-acting nifedipine is 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. A 5-10% increase in HR is expected when these drugs are used as monotherapy.

7. **Long acting nitrates**
The term long acting nitrates is used in contrast to short acting nitrates such as sublingual GTN. They include intermediate acting nitrates such as Isosorbide Mononitrate which is used twice daily. It is important that twice daily dosing of these nitrate preparations be eccentric (7-8hrs apart) to allow for a nitrate free period and avoid the development of tolerance. Patients using transdermal nitrate patches should apply them daily and remove them for a 12-hour period preferably during sleeping hours to prevent tolerance.

8. **Potassium Channel Opener - Nicorandil**
Nicorandil is not usually given as first line therapy for patients with angina but may be used in patients who fail to tolerate other treatments. Its efficacy has been studied in patients who are on other antianginal therapy. The IONA study looked at 5126 patients with angina who were randomly assigned 20 mg nicorandil twice daily or identical placebo in addition to standard antianginal therapy. The study showed a significant improvement in outcome due to a reduction in major coronary events by antianginal therapy with nicorandil in patients with stable angina.

9. **If inhibitor - Ivabradine**
Ivabradine inhibits a specific sinus node pacemaker current, thereby lowering the heart rate. It is used in symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contraindication or intolerance for beta-blockers. Its effects are similar to atenolol in comparative trials.

**Combination Therapy**

Monotherapy may be optimal for one patient. For others, combination therapy with lower doses of two agents may be preferable due to inability to tolerate one agent at a higher dosage. Combination therapy is also useful in patients who have 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.

**Failure of Monotherapy with a β-blocker**
If a patient continues to have angina despite maximal therapy with a β-blocker, a long acting dihydropyridine such as amlodipine or felodipine should be added to the β-blocker. Caution has to be exercised in the use of diltiazem with a β-blocker as there is potential hazard of heart rate slowing and prolonging AV conduction. If a patient is unable to tolerate combination therapy with both a CCB and a β-blocker then one of these agents can be combined with a long acting nitrate.

**Failure of Monotherapy with a Calcium Channel Blocker**
If monotherapy fails with a CCB and a β-blocker is contraindicated then combination therapy with a nitrate or nicorandil should be attempted to control symptoms.
**Triple Therapy**

This option should only be utilized in those patients who are awaiting cardiac consultation and have symptoms despite therapy with 2 agents. Situations in which patients may remain on triple therapy include the following:

1. Concomitant medical problems prohibit further cardiac working up and treatment (e.g. PTCA or CABG)
2. Cardiac working up 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.

**Further Information**

Further information on the pharmacological management of angina may be obtained from the following sources:


Management of Stable Angina – A national clinical guideline. Scottish Intercollegiate Guidelines Network. www.sign.ac.uk