ABSTRACT

Current treatment of coronary artery disease and tails both non invasive and invasive modalities. In the former one could include pharmaceutical therapy as well as exercise rehabilitation. As regards pharmaceutical therapy β-blockers, statins, antiplatelet drugs and probably AC inhibitors are considered essential for life prolongation. Night rates offer adequate symptomatic help. The same can be stated for calcium channel blockers. Some novel drugs may offer additional benefit such as ivabradin which selectively slows heart rate and drugs affecting metabolism in favor of glucooxidation such as trometazidine and ranolazine. Chronic exercise in rehabilitation both dynamic and resistance decreases the anginal frequency and at least in the former may improve survival after a myocardial infarction. Invasive therapy can be divided into two parts: the non-revascularization therapy includes external enhanced counterpulsation and spinal cord distimulation neither of which has found a definite place in everyday treatment. Laser myocardial revascularization is practically extinct. A pragmatic approach to the selection of medical therapy or revascularization is tried: revascularization can be omitted in the absence of left main disease, multivessel disease with proximal left anterior descending critical stenosis or in the absence of stress-induced myocardial ischemia or intractable angina. It should not be forgotten that both conservative and invasive treatment offer a high degree of symptom palliation and in many cases improvement in prognosis. The adequate knowledge and utilization of both modalities is essential.
The Medical treatment of coronary artery disease (CAD) comprises two aspects:
1. Pharmaceutical treatment
2. Other means, the most important of which is exercise rehabilitation and the adoption of a healthy lifestyle, especially smoking cessation.

Medical treatment has acquired great importance in the last years because in many well studied and implemented studies and trials it has been found equally effective to surgical and interventional treatment.

The outlook of any therapeutic modality should aspire to:
- Improvement of prognosis, i.e. the avoidance of death.
- The amelioration of the quality of life and the prevention of morbidity and disability.

In this review I will try to deal with both of these aspects. Also, some non-revascularization but invasive therapies will be discussed.

I. Pharmaceutical Therapy (PT)
PT can said to have started with the use of:

1. Nitrates, which were introduced in 1867.

In appreciation of their historic credentials they will be described first.

Their main mode of action is to exert a strong vasodilatory action, mainly on the venous side and less weakly on the arterial side, by upgrading the production of NO oxide by the endothelium.

By decreasing venous return they lower both blood pressure and intraventricular filling volume. Thus they reduce the rate – pressure product, through the Laplace equation oxygen consumption, and accordingly anginal threshold. However, the arterial dilating action may also prove of importance, if they could diminish the stenosis produced by the plaque, increasing coronary flow reverse. In fact, we have shown that even when they reduce blood pressure, the do not affect the coronary flow reserve.

An important aspect of this action is the relief of coronary arterial spasm. Another potential action of nitrates is by producing late preconditioning, as Leesar et al have shown.

Whatever their action, short acting nitrates offer robust and prompt relief of angina pectoris. However, the main concern regarding the use of long – acting nitrates is development of tolerance. A large number of substances has been proposed to counteract this effect. However, the main modality remains intermittent dosage, with adequate drug-free intervals, although with this technique entails the danger of rebound symptoms.

Nitrates have not been found to improve prognosis or reduce mortality. However, their judicious use may well improve the quality of life of the anginal patient. My favorite regimen is mononitrate in the morning and a nitroglycerin patch in the afternoon, which is taken off at night. A sublingual tablet or puff should be added at bedtime in pts with angina decubitus and early in the morning for many people who only develop angina when they first undergo activity at this time.

Their most common adverse effect is orthostatic hypotension. Thus, they should be started with as low a dose as possible and pts, especially the elderly, should be adequately warned. Nitrates have also indirectly created another problem, their
potentially dangerous interaction with drugs used against erectile dysfunction. Practically, any of these drugs should not be used on the same day with nitrates. For this reason, shorter acting agents are preferable.

2. β-blockers.
These agents also have been used for a long time, with propranolol as the original prototype. Their main action is also exerted through lowering of the pressure – rate product. The contribution of the decrease of contractility is difficult to judge. Another very important facet is their antiarrhythmic action, both against ventricular and supraventricular arrhythmias. They have been thus shown to decrease mortality by up to 23% in long term post – infarction trials. Their excellent performance in reducing mortality in chronic heart failure has also been well described over the last years. However, as Fox et al point out no proof exists that they lower mortality by long – term use in angina. Also, their mortality – lowering action in the acute myocardial infarction setting is less clearly delineated: The main reasons are that they may inordinately lower blood pressure and heart rate if given indiscriminately intravenously early at the infarct onset. However, their measured use in pts with tachycardia and hypertension is very efficacious.

The main side effects of β-blockers are thus bradycardia and hypotension, as shown in Table 1. In this table only the agents still used in practice are mentioned. Some β-blockers are less bradycardic than others especially if they possess an intrinsic sympathomimetic action (ISA). My preferred agent in this aspect is celiprolol, while pindolol is being used much less frequently. Bronchospasm is another main drawback. Usually, except in the more severe cases, this can be circumvented by using cardioselective agents, of which acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, metoprolol are representative. Probable the most cardioselective and preferable in this aspect is nebivolol, which however needs very careful titration because it is bradycardic. Its endothelium favorable effects are of greater importance in hypertension.

A bradycardic effect can be particularly important in atrial fibrillation in which atenolol, metoprolol and nebivolol are my preferences, while carvedilol has – in my experience - proven difficult to titrate. It is – of course - the preferred agent if heart failure co-exists. The rebound increase of heart rate and blood pressure are of great importance and should be avoided especially in those agents a shorter plasma half life.

With judicious use of β-blockers one can hope to achieve relief from angina in about 75% of patients. In the remaining, one can add the aforementioned nitrates, or another drug family:

3. Calcium channel blockers (CCBs)
The cardiovascular effects of these drugs differ quite significantly as regards heart rate and blood pressure. The most bradycardic drugs are verapamil and especially diltiazem, the non –dihydropyridines, while the most vasodilatatory are nifedipine-the
hydropyridine prototype and amlodipine. Other drugs used in angina are nisoldipine, while most of the other antagonists are employed in hypertension (Table 2).

The antianginal action of these drugs can be ascribed to their bradycardic and/or blood pressure lowering effects, as well as to an effect on myocardial contractility which becomes more evident in agents with lesser vasodilatatory action, which indirectly increases contractility by sympathetic activation.

However, they also have an important relaxation effect on the coronary arteries 12. They are excellent agents in the treatment of vasospastic angina.

Where would one prefer CCBs to the \( \beta \)-blockers?

The main indication is bronchospasm with the use of even the most cardioselective \( \beta \)-blockers. The main representatives are verapamil and diltiazem. Actually, the APSIS study 13 showed that metoprolol and verapamil were equally effective on fatal and non-fatal cardiovascular end – points. Post thrombolysis, diltiazem has proved safe in INTERCEPT in patients without heart failure, in whom it should be avoided 14.

Where would one add a CCB, in pts under \( \beta \)-blockers? Many previous studies by now forgotten, extolled the benefit of adding verapamil to \( \beta \)-blockers. The safety margin is so low it is not worth the physician’s anxiety. Also 300mg tablets of diltiazem are prone to cause bradycardia. I would never use any of these two agents together with amiodarone. Sooner or later severe bradycardia may emerge.

The main indication would be incomplete relief of angina, where a strongly vasodilatatory drug could be helpful.

In ACTION 15 long – acting nifedipine proved safe. I also use nisoldipine for this purpose in pts with persistent angina despite full \( \beta \)-blocker and nitrate use.

The main side-effects of CCB are constipation and pedal edema. The latter is more marked with some agents such as amlodipine, but is a common feature of all.

Flushing can be a problem with the hydropyridines.

Some data suggest that CCBs may have an atherosclerotic action, especially when added to lipid lowering agents 16; however the real clinical impact of this quality remains to be proven.

Here two more drugs should be mentioned, which share qualities with the above mentioned drugs:

**Ivabradine.** This drug has a specific heart – rate lowering action through a selective blocking action on the sinoatrial node pacemaker current I(f). This drug showed excellent results in a randomized, double – blind, placebo – controlled trial in 360 pts with chronic stable angina over 3 months as regards exercise tolerance and time to development of ischemia 17. The long – term influence of this drug on mortality and morbidity has not been studied. However, in some studies the reduction of some \( \beta \)-blockers on cardiovascular mortality has been found to correlate to their heart – rate lowering effect 18, 19.

I have been using Ivabradine in some cases in whom \( \beta \)-blockers or CA could not be used because of side – effects, mainly bronchospasm or hypotension. Its profile is appealing. Future data are awaited on its value in the treatment of heart failure.

**Nicorandil.** This drug has a dual action. It is a potassium channel (\( \text{K}_{\text{ATP}} \)) opener and it also has a nitrate – like effect. Both qualities make it a coronary vasodilator 20. Additionally, thought its former action it has a preconditioning – like, cardioprotective effect 21. Within these very attractive actions it is surprising that this drug has not been
used in a greater scale. In the IONA trial it was evaluated as additional treatment in 5126 pts with chronic stable angina who were otherwise receiving full antianginal therapy, for a follow-up of 1.6 years. The administration of the drug was associated with a reduction of 17% coronary death, nonfatal myocardial infarction or unplanned hospitalization for angina pectoris. The drug has also been advocated for use during primary PCI in acute myocardial infarction.

4. ACE inhibitors
These drugs have been mainly used for the treatment of hypertension and heart failure, where they are considered as treatment of first choice. They are potent vasodilators and also have cardioprotective effects: valsartan, an angiotensin receptor blocker (ARB) has been shown to re-instate preconditioning in the failing heart. Their anti-ischemic effects are not completely convincing. Their effectiveness in the treatment of ischemic heart disease has been assessed in 3 trials. In HOPE, ramipril was associated with a 22% reduction in cardiovascular events in high risk patients (diabetes, hypertension, peripheral vascular disease). This trial was followed by EUROPA, in which perindopril was given to patients with stable CAD, who were on full-treatment therapy. This drug, as compared to placebo, was associated with a 20% - significant – reduction in cardiac or sudden death or myocardial infarction. These favorable data were not corroborated by the findings of PEACE, in which trandolapril showed no benefit. There are many postulations for the discrepancies among these trials, which are beyond the scope of this review. One should not forget that after an acute coronary event these drugs are considered essential for the improvement of prognosis. Their role can be considered essential in patients with stable angina pectoris who also have cardiac dysfunction and/or hypertension. Here the results of the CAMELOT trial should be mentioned, in which amlodipine was compared to enalapril in normotensive pts with CAD. Both agents reduced events. Agents with ARB action are considered analogous to ACE inhibitors in hypertension and heart failure. However, their role in angina pectoris has not been adequately assessed.

5. Lipid – lowering agents
These drugs, especially the statins have proven to be extremely valuable. They have been shown in many consecutive trials to reduce mortality and the occurrence of MI by about 25-30%; a similar reduction in the need for coronary revascularization has also been reported. A recent report suggests that the lower the LDL levels achieved, the greater is the event reduction achieved. Thus, in pts with chronic stable angina an LDL level of 70mg is recommended. However, the discussion of some recent trials is interesting. In stable CAD, the ALLIANCE trial, in which 2442 pts were randomized to 80mg atorvastatin or usual care. At 4 years, a 14% RR, mainly driven by a large reduction of non-fatal MI was seen.
In the TNT trial \(^{38}\), in which 10001(!) pts were randomized to either 10 or 80mg atorvastatin. At 5 years a 22% RR in primary end-points was seen. However, the results of the IDEAL study \(^{39}\) in which 80mg atorvastatin was compared to 20mg simvastatin were less conclusive, although when more end-points were added, a statistical benefit towards the same direction was seen. Hauslay et al suggest that with intensive LDL lowering, the major additional effect is mostly seen as regards non-fatal MI \(^{40}\).

Is well proven that intensive lipid-lowering treatment is very effective after an acute coronary event, as shown in the MIRACL \(^{41}\) and PROVE-IT trials \(^{42}\). Initially, some trials had tried to ascertain the regression of the stenotic coronary lesion. In FATS \(^{43}\), a modest regression but a significant non-progression was seen \(^{43}\). In the more recent trials, REVERSAL \(^{44}\) and ASTEROID \(^{45}\), the non-progression and stenosis reduction/regression was analogous to the degree of LDL reduction, which is nowadays much greater that in earlier trials through the use more potent statins and the addition of ezetimibe. The latter study also suggests an important action of HDL increase. However, the main effect of statins seems to be their effect on plaque stabilization, since unstable coronary lesions are considered responsible for a considerable proportion of ischemic coronary events \(^{40}\).

A very important question is whether statins possess pleiotropic activities apart from their lipid-lowering action \(^{46}\). This is widely considered as an additional beneficial effect. However, recent studies have showed some doubt on this possibility, suggesting that LDL lowering exerts the main influence as regards anti-inflammatory and antithrombotic action \(^{47}\).

6. Antithrombotic drugs

They have been the mainstay of anti-ischemic therapy over many years.

**a. Aspirin** is the oldest drug used and remains the one most widely employed, with a clear – cut 33% reduction of vascular events in the meta-analysis of the Antithrombotic Trialists \(^{48}\). It also emerges from the SAPAT trial \(^{49}\) that pts with unstable angina derive a greater benefit (43%) than those with stable angina (34%). The recommended dosage range from 75 to 325mg; higher dosages are followed by more gastrointestinal side effect, especially bleeding; without evidence of added benefit \(^{49}\).

Aspirin resistance has emerged as a problem in recent years. It is postulated to occur in about 25% \(^{50}\). In these patients, the suitable alternative is considered to be **Clopidogrel**. This is a thienopyridine, which blocks the adenosine diphosphate-mediated platelet activation. It has practically replaced ticlopidine which has been shown to cause leukopenia and platelet reduction. The latter effect has also very rarely seen to occur with clopidogrel (C).

It is not clear whether C added to aspirin exerts additional benefits in CAD. In the CAPRIE study, it did not \(^{51}\). Results of the CHARISMA trial suggest that this may be case: A lower occurrence of vascular events with combined use of the two agents in pts with already existing manifestations of CAD, prior MI, ischemic stroke, or symptomatic peripheral arterial disease \(^{52}\).
More trials and the assessments of newer agents such as parsugrel are awaited. The use of oral and IV agents in acute coronary syndromes is beyond the scope of this review.

OTHER AGENTS
Inhibitors of free fatty acid (FFA) oxidation.
The heart normally consumes FFA in preference to glucose. However, FFA consumption is less oxygen-efficient and may be toxic. Drugs that shift energy production from FFA to glucose oxidation have been used as anti-anginal agents.

Trimetazidine. This drug has been widely studied. In an early trial – TEMS – we showed that this drug is equally effective to propranolol in stable angina pectoris, as regards clinical effect, ischemic episodes at Holter monitoring and ischemia at exercise testing. In a more recent trial, TRIMPOL II in 426 pts with stable angina, trimetazidine added to metoprolol gave better results than placebo at 12 weeks with approximately the same criteria.

A Cochrane database analysis (23 studies, 137 pts) also indicates favorable effects using the same criteria. We have shown that trimetazidine given to the isolated rat heart before ischemia/reperfusion diminishes post ischemic dysfunction and necrosis, while it only affects stunning when given at reperfusion.

The drug has also been found to ameliorate cardiac dysfunction in chronic ischemic cardiomyopathy in some small but well-designed studies.

Ranolazine. This drug with the same qualities has also been tested in some prospective studies, showing significant relief of chronic angina as compared to placebo, both in diabetic and non-diabetic pts. However, it should be remembered that ranolazine exerts a prolongation of the QT interval which is dose dependent but has not shown any pro-arrhythmic effect. These two drugs could be considered for use in pts with chronic stable angina either as additive therapy to β-blockers or CCBs, or in the face of contra-indications, such as bradycardia or hypotension.

Perhexiline. This is a very old drug, used about 20 years ago. It was discontinued because of hepatic toxicity and peripheral neuropathy. Lower doses have been permitted its re-emergences and applications mainly in Australia.

In conclusion, my treatment program in a patient with stable chronic angina not considered a candidate for revascularization would include the following:
My staple therapy would be β-blockers, given with a resting HR ~ 60min as a goal. If β-blockers cannot be tolerated because of bronchospasm, I would use diltiazem with the same HR goal. If low blood pressure is a problem, ivabradine could be a valid consideration.

I would consider adding nitrates or a vasodilatory CCB in resistant angina despite optimal β-blocker treatment. The judicious use of nitrates is a part of the art of medicine. The timely use of SL therapy or a patch can change a patient’s symptoms. Trimetazidine or ranolazine could be add-ons.

Of course, aspirin, or incase of contraindications or resistance clopidogrel are essential.

Statins to the goal of LDL<70mg with ezetimibe if needed should be given to all pts.

If despite maximal treatment as delineated above, symptoms persists the following non-invasive therapeutic modalities can be considered:
**Exercise Rehabilitation**

This modality has two aspects:

Post – myocardial infarction. The best known review has shown that systematic rehabilitation in this group of patients decreases mortality 64, 65. Exercise exerts many beneficial influences especially improving endothelial function and coronary perfusion 66-68. A significant aspect is that it reverses the increased risk of a myocardial infarction after an unplanned bout of exercise 69, 70.

Apart from these aspects, Hambrecht et al have shown that regular exercises relieves chronic stable angina to a degree equal to that of interventional techniques 71.

Unfortunately, regular exercise is not often employed in the treatment of chronic angina, as shown in the Euroheart II survey, according to which in Europe, only 43% of these pts were advised to undergo cardiac rehabilitation after an ischemic event 72.

Another beneficial aspect of regular exercise is that it may induce ischemic preconditioning (IP). In fact in a very recent study, Hausenloy et al showed that remote preconditioning as induced by 3 five minute inflations of the upper arm diminished perioperative necrosis at CABG 73.

Most of the rehabilitation exercise programs feature endurance training. However, resistance exercise has been recently given more attention.

Earlier doubts about its safety have been assuaged. Indeed, isometric exercise has not generally been found to produce ischemic or arrhythmic manifestations 74. In type 2 diabetes groups both types of exercise improved glycemic control 75.

In the American College of Sports Medicine / American Heart Association update the following key recommendations for healthy adults are given: 76

- Moderate – Intensity aerobic exercise for at least 30 minutes, 5 days a week, or vigorous activity of at least 20 minutes, 3 days a week.
- Activities to maintain or increase muscle strength for at least 2 nonconsecutive days per week.

**Smoking Cessation**

Most of the data on its benefit are derived from post – myocardial infarction studies, all of which show a significant risk reduction 77.

There is no doubt, however, that smoking cessation should not only be advised by also implemented by all available techniques 78. Moderate alcohol consumption is not only enjoyable, but decreases mortality 79. The correct dosage seems to be two glasses per day 80.

If despite all the above mentioned measures anginal symptoms persist, the following “invasive” but non-revascularizing measures have been tried:

**Spinal cord stimulation**, in the T1 to T3 level. It reduces cardiac sympathetic activity 81. It has been shown to reduce symptoms 82, and actually in the ESBY trial 83 it relieved angina equally to CABG, which was associated with better objective reduction of ischemic indices but with higher six – month mortality in high surgical risk pts.

**Enhanced external balloon counterpulsation**

In one trial and two multicenter registries a 72% improvement in angina and a 52% cessation of nitroglycerin treatment 84-86.
However, the employment of this technique has not been widely agreed upon. Transmyocardial laser revascularization. This technique has been practically abandoned.

Before concluding this review, one should be practical: In whom should only “non-revascularization” treatment been advised?

The patient without target vessels.
This patient is very rare indeed. I have estimated that in the Onassiss Cardiac Surgery Center, with approximately 1800 CABG operations and 1200 PCIs per year, less than 6 pts are considered ineligible/year.

The patient who does not need revascularization.
The benefits of invasive treatment are amply covered elsewhere. However, I will try to summarize my views:
Medical treatment should be reversed for patients:
1. Without critical stenoses in major vessels (left main or proximal LAD)
2. Without cardiac dysfunction
3. Without extensive ischemia even at moderately workloads by any of the stress techniques
4. Who are adequately relieved by this modality.
During non-invasive treatment symptoms should be frequently and carefully assessed. Cardiac function and the occurrence of ischemia should be monitored at approximately yearly intervals. If at any time the condition of the patient changes, his coronary arterial state and the possibility of revascularization should be considered. Of course, further modification of his medical treatment should always be considered. An increase of β-blockers, judicious use of nitrates or the addition of a vasodilative CCB or a metabolic modulator can produce a very significant improvement.
One should not forget the very good prognosis of pts with stable angina in the COURAGE trial by both medical and invasive treatment modalities with a death incidence of around 6% at 4.5 years. Moreover, as Daly et al have shown, increase in guideline adherence can bring a significant (32%) decrease in new MI and mortality within a year.

This review deals mainly with chronic stable angina. The same would hold time for the post ACS patient. However, after an acute Q-wave myocardial infarction, cardiac dysfunction would necessitate consideration of an implantable defibrillator insertion and cardiac resynchronization. Skinner and Minhas give a very nice comment on last the NICE guidelines on secondary prevention after a myocardial infarction.

QUESTIONS
1. In which groups of patients do β-blockers increase survival?
2. Please delineate different actions of different families of calcium channel blocking agents.
3. What is the main angina relieving mechanism of nitrates?
4. Which are the main antiplatelet drugs used today?
5. What is proposed level of LDL cholesterol in chronic stable angina by many authors? What is the underlying rationale proposed?
REFERENCES


Table 1. Characteristics of β-blockers

<table>
<thead>
<tr>
<th>B-blockers</th>
<th>ISA</th>
<th>Cardioselectivity</th>
<th>Plasma half-life (h)</th>
<th>Dose range/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>-</td>
<td>-</td>
<td>3-5</td>
<td>40-320</td>
</tr>
<tr>
<td>Atenolol</td>
<td>-</td>
<td>+</td>
<td>6-9</td>
<td>25-200</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>+</td>
<td>+</td>
<td>3-4</td>
<td>200-800</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>-</td>
<td>+</td>
<td>14-22</td>
<td>10-40</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>-</td>
<td>+</td>
<td>13-14</td>
<td>2.5-20</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>-</td>
<td>-(a, β1, β2, blocking action)</td>
<td>6-7</td>
<td>3.125-50</td>
</tr>
<tr>
<td>Metoprolol*</td>
<td>-</td>
<td>+</td>
<td>3-7*</td>
<td>50-300</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>+</td>
<td>+</td>
<td>4-5</td>
<td>100-400</td>
</tr>
<tr>
<td>Nebivolol+</td>
<td>-</td>
<td>++</td>
<td>21</td>
<td>1.25-10</td>
</tr>
<tr>
<td>Pindolol</td>
<td>++</td>
<td>-</td>
<td>3,4</td>
<td>2.5-20</td>
</tr>
</tbody>
</table>

ISA : intrinsic sympathomimetic activity
* : sustained release preparations available
+ : endothelium dependent vasodilatation

Table 2. Characteristics of calcium blockers

<table>
<thead>
<tr>
<th>Class-agent Dihydropyridines</th>
<th>Action</th>
<th>Daily dose mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>- ↑</td>
<td>20-180</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>-</td>
<td>5-20</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>-</td>
<td>5-30</td>
</tr>
<tr>
<td>Felodipine</td>
<td>-</td>
<td>5-20</td>
</tr>
</tbody>
</table>

Non-dihydropyridines

| Verapamil                    | - ↓    | 80-320        |
| Diltiazem                    | ↓      | 90-300        |

No half-life values are given, because most of these drugs are also given as slow-release preparations