

Review of Medical Treatment of Stable Ischemic Heart Disease

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Abstract

Medical treatment is the initial treatment strategy and is the cornerstone of management in patients with stable ischemic heart disease (IHD). Many patients are not suitable for percutaneous or surgical revascularization because of unfavourable anatomy, or the presence of co-morbidities. In addition, many patients have recurrence of angina following revascularization due to restenosis or incomplete revascularization. Furthermore, randomized clinical trials comparing optimal medical treatment to revascularization have not clearly shown that myocardial revascularization is superior to optimal medical treatment. Traditional drugs for angina treatment include β -blockers, calcium channel blockers and nitrates. Newer drugs are available with different mechanisms of action and with equal efficacy that do not cause significant hemodynamic deterioration. The availability of these newer drugs expands the therapeutic potential of medical treatment to even a wider population with stable IHD. Revascularization in patients with stable ischemic heart disease has never been shown to reduce hard endpoints (death or myocardial infarction) in randomized clinical trials.

Keywords

Medical Treatment; Stable; Ischemic Heart Disease; Novel Anti-Ischemic Therapy; Anti-Anginal Agents; Coronary Artery Disease

1. Introduction

Stable angina is the most common manifestation of ischemic heart disease. Based on the Rose Angina Questionnaire, it is estimated to affect about 6% of people across 31 countries, and is predicted to increase further in the future due to aging societies [1]. The prevalence increases with age and approximately 50% of patients an-

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gina is the initial manifestation of IHD. The condition affects about 9 million Americans and about 2 million people in UK. The economic impact of caring for patients with IHD is vast, estimated at 171 billion dollars in USA for both direct and indirect costs in 2010. While considered relatively benign in terms of prognosis, it carries a higher risk of cardiovascular events than that in the general population, with an average annual mortality of 1.2% - 2.4% per annum. It substantially reduces the quality of life with one in three patients with chronic stable angina having an angina attack once a week [2] [3].

Despite the advances in revascularization procedures, many patients are not candidates for revascularization by percutaneous intervention (PCI) or coronary bypass graft surgery (CABG) for multiple reasons, such as diffuse coronary anatomy, severe impairment of LV function, comorbidities such as renal impairment or advanced age. A substantial number of patients undergoing revascularization procedures do not achieve complete revascularization and experience the symptom of angina. Additionally, many patients experience recurrence of angina following revascularization with either PCI or CABG, due to restenosis or graft failure particularly saphenous vein grafts [4] [5]. Therefore, in many situations, medical treatment is the cornerstone of management of stable angina. The goals of medical treatment are listed in **Table 1**.

Evidence-based sets of pharmacologic interventions are indicated to reduce the risk of future events. The presumed mechanism by which these interventions are effective is by stabilizing the coronary plaque to prevent rupture and thrombosis. Stable angina management has not been rigorously evaluated in large randomized controlled trials, as other cardiac conditions. However, certain medications improve survival in patients with stable ischemic heart disease. These include antiplatelet agents; lipid lowering agents; in particular statins, B-blockers in post-MI patients with angina, angiotensin converting enzyme inhibitors (ACE inhibitors) in patients with LV dysfunction. Newer agents and some of the traditional agents like nitrates and calcium channel blockers (CCBs) have not been proven to have survival benefit.

Pharmacologic treatment of stable angina has, until recently, been limited to the traditional agents that decrease the myocardial oxygen demands and/or increase myocardial blood supply (**Table 2**). In recent years, new anti-anginal medications have become available that use different mechanisms of action. These agents with a metabolic action can be used in combination with the hemodynamically active traditional medications, because they do not alter the blood pressure or the heart rate.

2. Life Style Modification

Initial approach to all patients should be focused on eliminating unhealthy behaviours such as smoking and effectively promoting lifestyle changes that reduce cardiovascular risk such as increasing weight loss physical activity, and adopting a healthy diet **Table 3**. Quitting smoking is associated with 36% reduction in mortality after myocardial infarction (MI). Recently, a large study conducted with Mediterranean diet reduced the incidence of major CV events in patients at high risk of CV events but without prior CV disease [2] [3].

Table 1. The objectives of treating patients with stable IHD are.

- 1) To modify CV risk factors
- 2) To improve prognosis by preventing CV death and complications of stable IHD, including nonfatal AMI and CHF
- 3) To restore quality of life and minimize or abolish symptoms and improve exercise tolerance

Table 2. Traditional agents for treatment of angina and IHD.

- 1) Beta-blockers
- 2) Calcium channel blockers
- 3) Nitrates
- 4) Antiplatelets
- 5) Angiotensin Enzyme Converting Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARBs)
- 6) Lipid lowering agents

Table 3. Lifestyle modifications for patients with CAD.

- Tobacco cessation
- Weight reduction
- Physical activity
- Low fat diet < 10%
- Low sodium diet

3. Lipid Therapy (Statins)

There is substantial evidence that statins can benefit patients with coronary artery disease (CAD) [6]-[9]. These trials **Table 4** have convincingly shown that statins treatment improves survival, prevent MI, stroke and reduces the need for revascularization procedures. Serious adverse events such as rhabdomyolysis are rare (less than 0.1%). Several trials examined have examined the role of intensive statin treatment in patients with CAD. In PROVE-IT-TIMI22 trial, Atorvastatin 80 mg was compared to Pravastatin 40 mg [10]. The combined endpoint was reduced by 16%. In the treatment to new target trial (TNT), which enrolled about 10,000 patients with CAD who had cholesterol level of 130 mg per dL (3.37 mmol/L) or greater and were treated with atorvastatin to a goal of less than 70 mg/dL (1.8 mmol/l) or less than 100 mg. Lipitor 80 mg reduced the risk of major CV events by 22% compared with Lipitor 10 mg in stable CAD patients [11].

Statins exert their effects is by plaque stabilization and making them less vulnerable to rupture, anti-inflammatory action and by improving endothelial function. The NCEP Adult Treatment Panel III recommends using statins to achieve LDL < 100 mg per dl (2.59 mmol/L) in patients with CAD, and for those at high risk, a goal of less than 70 mg per dL (1.8 mmol/L) [12]. Statin treatment is a class I level of evidence A in ACC and European guidelines [2] [3].

4. Antiplatelet Therapy

Aspirin inhibits cyclo-oxygenase reducing prostaglandin and thromoxane-A₂ production and preventing platelet aggregation. It significantly reduces the risk of thrombotic events in patients with CAD [13] [14]. Treatment with aspirin 75 - 162 mg daily should be continued indefinitely in the absence of contraindication. This is a class I (level of evidence A) in the ACC and European guidelines [2] [3]. Clopidogrel inhibits ADP receptors, thereby inhibiting platelet aggregation. Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with stable angina. This is a class I (level of evidence B) in ACC guidelines. In the CHARISMA trial [15], patients at high risk for ischemic events were randomized to clopidogrel plus aspirin versus aspirin, no benefit of the combination in reducing cardiovascular events was found. Thus, clopidogrel should not be added to aspirin therapy in patients with stable CAD to prevent future MI. Treatment with both aspirin 75 - 162 mg and clopidogrel 75 mg daily might be reasonable in certain high risk patients with stable IHD. This is a class IIb (level of evidence) indication by ACC guidelines [2].

5. Beta-Blockers

Although there are no large long term studies assessing the effect of b-blockers on mortality, beta-blockers are the mainstay of angina therapy and they have anti-ischemic and anti-arrhythmic properties. They reduce workload of heart by decreasing heart rate, negative inotropic effect, and by reducing blood pressure. They also increase coronary perfusion by prolongation of diastole. They have survival advantage particularly in patients with angina and LV dysfunction (EF < 40%), and in patients with prior MI. In patients with LV dysfunction only carvedilol, bisoprolol, or metoprolol succinate should be used.

Beta-blockers have been proven to provide benefit in reducing long-term mortality and morbidity after MI. In post-MI patients, B-blockers are associated with 30% reduction in risk of CV death and MI [16] [17]. B-blockers are have a class 1 level of evidence B indication in patients with stable IHD, and class 1 level of evidence A in patients with LV dysfunction or patients with prior MI. Tolerability is a limiting factor in use of beta-blockers at least at optimal doses. Side effects of beta-blockers include hypotension, fatigue, depression, bradycardia, bronchospasm and sexual dysfunction.

Table 4. Key statin trials in secondary prevention in IHD.

| Trial | Follow Up | Baseline LDL mg/dl (mmol/l) | End Points | Relative Risk Reduction |
|-------------------------------|-----------|-----------------------------|--|-------------------------|
| 4S Simvastatin 20 - 40 mg [6] | 5.4 yrs | 188(4.9) | -All cause mortality -NFMI, CHD death | 30% 34% |
| CARE Pravastatin 40 mg [7] | 5 yrs | 139(3.6) | NFMI or CHD death | 24% |
| LIPID Pravastatin 40 mg [8] | 6.1 yrs | 150(3.9) | NFMI or CHD death | 24% |
| HPS Simvastatin 40 mg [9] | 5 yrs | 131(3.4) | -All cause mortality -Fatal or nonfatal vascular events | 13% 24% |

NFMI = nonfatal MI, CHD = coronary heart disease.

6. Nitrates

They produce vasodilatation of coronary arteries and reduce preload and small anti-aggregant effect. Nitrates are available in many forms (spray, patches, and sustained release tablets). They are used only for symptom relief; there are no data on mortality or myocardial infarction in patients with stable angina. There is a risk of tolerance with continuous use; in addition they should not be used concomitantly with phosphodiesterase inhibitors. There are no randomised trials using nitrates in angina. However, they are included in the guidelines as first line agents for symptomatic relief of angina because of their efficacy [2] [3]. Their principal side effects are headache and hypotension.

7. Calcium Channel Blockers (CCBs)

Inhibit movement of calcium ions through slow channels in the cardiac and smooth muscle cell membrane producing negative inotropic effect on cardiac muscle and vasodilatation. Their major mechanism of action is through vasodilatation of coronary vessels thus increasing blood supply, while some CCBs (non-dihydropyridine) also reduce myocardial oxygen demands by lowering heart rate. Like other antianginal medications, their effect on mortality in patients with stable coronary disease has not been evaluated in randomized clinical trials. The ACTION trial (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) is the first ever placebo controlled clinical outcome trial in stable angina. Nifedipine GITS was compared to placebo in 7665 patients, with a mean follow-up of 4.9 years. The primary endpoint was a combined endpoint of death, acute MI, refractory angina, new onset heart failure, stroke and peripheral revascularization. There was no significant difference in the combined endpoint. There was a significant difference in a secondary endpoint of need for coronary angiography and need for coronary bypass surgery [18]. Unlike b-blockers, there is no evidence of survival advantage in patients with LV dysfunction, or post MI patients. CCBs may be used for symptom relief in the treatment of angina in patients with contraindication or are intolerant to beta-blockers. The European guidelines recommend CCBs as first line treatment of stable angina with similar class of recommendation as b-blockers (class 1 level of evidence A) for symptom relief, while the ACC guidelines recommend b-blockers as first line of treatment (class 1, level of evidence B), for patients in whom b-blockers are contraindicated or intolerant to b-blockers, and as second line treatment (class IIa level of evidence B) as alternative to b-blockers [2] [3]. Side effects of CCBs include flushing, hypotension, constipation. The dihydropyridine group (amlodipine and nifedipine) may produce reflex tachycardia and ankle edema which may limit their use, while diltiazem and verapamil should not be used in patients with LV dysfunction.

8. ACE Inhibitors and Angiotensin Receptor Blockers (ARBs)

There is evidence supporting ACE inhibitors use in stable coronary artery disease and in patients with IHD and LV dysfunction. ACE inhibitors decrease morbidity and mortality in coronary artery disease, even in the absence of LV dysfunction. The EUROPA trial (European trial on reduction of cardiac events among patients with stable coronary artery disease) was conducted in patients with stable coronary artery disease without LV dysfunction, and who were on background antianginal therapy including b-blockers, aspirin, and statins. Perindopril treatment was associated with 20% relative risk reduction in cardiovascular death, MI, or cardiac arrest, compared to placebo [19]. The HOPE trial (the heart outcomes prevention evaluation study) showed 22% relative risk reduction in primary endpoint (composite of MI, stroke, and cardiovascular death) with ramapril in a high risk population [20]. The main side effects of ACE inhibitors are cough, renal dysfunction, angioedema and skin rash. ARBs can be used when there are side effects from ACE inhibitors like cough. ACE inhibitors should be prescribed in all patients with stable angina and hypertension, diabetes, LV dysfunction or chronic kidney disease unless contraindicated, (Class I level of evidence A in both the ACC and the European guidelines [2] [3]).

9. Novel Anti-Ischemic Agents

Due to limitations in currently available agents, newer agents have been evaluated (Tables 5 and 6). These agents include.

9.1. Nicorandil

Is an nitrate derivative of nicotinamide. It acts by activating adenosine triphosphate-sensitive potassium channels,

Table 5. Limitations of currently available anti-ischemic drugs.

- 1) Bradycardia (beta-blockers and CCBs)
- 2) Hypotension (beta-blockers, CCBs, nitrates)
- 3) Fatigue and depression (beta-blockers)
- 4) Decreased contractility (CCBs)
- 5) Erectile dysfunction (beta-blockers)

Table 6. Novel anti-ischemic therapy.

- 1) Ranolazine: reduces late Na influx and Ca influx into myocardial cells during ischemia, reduces diastolic myocardial tension and increases blood flow to ischemic zones
- 2) Trimetazidine: modulates myocardial metabolism, inhibits use of FFAs as energy source and shifting the myocardial metabolism to glucose utilization which requires less oxygen than FFAs
- 3) Nicorandil: activates (opens) ATP sensitive K channels and promotes K ions outflow from cells resulting in hyperpolarization of membrane with reduction in vascular tone (preconditioning)
- 4) Ivabradine: selective I_f channel blocker in sinus node. Slows the rate of diastolic depolarization and heart rate
- 5) Allopurinol: inhibits xanthine oxidase (XO)

which causes hyperpolarization, which inhibits calcium influx into muscle cells and promotes relaxation (indirect calcium channel blocking effect). It also reduces both preload and afterload. Unlike nitrates there appears to be absence of hemodynamic tolerance to nicorandil. It can be used for the prevention and long term prevention of stable angina, and may be added after b-blocker and CCBs. The Impact of Nicorandil in Angina (IONA) trial assessed the cardioprotective effects of nicorandil in patients with angina. Patients were randomized to nicorandil 20 mg twice daily or placebo in addition to standard antianginal therapy. Nicorandil improved the primary outcome (CHD death, nonfatal MI, hospitalization for chest pain). There was significant 17% relative risk reduction in the nicorandil group [21]. It is EMA but not FDA approved and therefore currently is unavailable for use in USA. The main side effects are flushing, headache and rarely buccal and anal ulcerations.

9.2. Fasudil

Rho kinase triggers vasoconstriction through accumulation of phosphorylated myosin. Fasudil is a rho kinase inhibitor. Fasudil is approved in Japan for prevention of cerebral vasospasm following subarachnoid hemorrhage. Vicori *et al.* reported a trial of fasudil as adjunctive antianginal treatment in 84 patients with class II-III angina. Fasudil improved exercise duration and the exercise time to ≥ 1 mm ST depression compared to placebo group [22]. Side effects are uncommon and include headache, skin and vascular disorders.

9.3. Trimetazidine

Trimetazidine acts as anti-ischemic agent by metabolic modulation. Angina patients accumulate free fatty acids (FFAs), which the cardiac muscle oxidise for their energy requirements. FFAs oxidation demands more ATP to breakdown FFAs than glucose oxidation. This demands more oxygen to be supplied to the ischemic myocardium. This is prevented by trimetazidine which shifts metabolism from FFAs (β -oxidation) to glucose (glycolysis). It also has modulatory effects on intracellular calcium.

In the TACT study, 177 patients with CCS I-II angina despite treatment with b-blockers, and long acting nitrates were randomized to trimetazidine or placebo. When trimetazidine added to a b-blocker and nitrate treatment, it improved myocardial ischemia with reduction in the number of symptomatic episodes of angina [23]. It can be added to standard antianginal therapy in patients who are refractory or intolerant to other drugs and not suitable for revascularization. Trimetazidine has no effect on blood pressure or myocardial contractility. The main side effects are gastric discomfort, nausea, headache and movement disorders. It is contraindicated in Parkinson's disease, tremors, restless leg syndrome and other movement disorders and in the presence of severe renal impairment. Trimetazidine is currently approved as a second line agent by EMA, but not yet approved by FDA for use in USA.

9.4. Ivabradine (Procoralan)

Heart rate reduction is one of the main goals in the treatment of angina, because heart rate is one of the major determinants of myocardial oxygen consumption. It also increases myocardial perfusion by allowing more blood

flow during diastole. However, existing medications do not exclusively reduce heart rate and their use is often associated with unwanted side effects. Ivabradine is the first pure heart rate lowering drug. It acts by selective inhibition of the cardiac pacemaker *if* current that controls the spontaneous diastolic depolarization in the sinus node. The *if* current is an inward Na^+/K^+ current that controls pacemaker cell activation in sinus node. Ivabradine blocks this current in pacemaker cells in sinus node thereby reducing the slope of this current resulting in slowing of heart rate. It has no effect on myocardial contractility or the blood pressure. Unlike beta-blockers, the most commonly used agents in the treatment of angina it does not produce bronchoconstriction or sexual dysfunction.

The INITIATIVE trial (International Trial on the Treatment of Angina with Ivabradine versus Atenolol) is a multicenter randomized double-blind 4 months trial in patients with CCS class I-III angina, designed to investigate the efficacy of ivabradine 7.5 mg bid relative to high dose atenolol 100 mg daily. The study demonstrated that ivabradine was as effective as atenolol in the treatment of stable angina with similar increases in total exercise duration and time until 1 mm ST depression on treadmill testing [24]. In another double-blind study ivabradine 7.5 mg bid was compared to amlodipine 10 mg daily, in 1195 patients with stable angina. Ivabradine was as effective as amlodipine with similar increases in the total exercise duration time, time to angina onset and time to 1-mm ST segment ST segment depression on exercise testing [25]. The associate trial evaluated the anti-anginal and anti-ischemic efficacy of ivabradine in patients with chronic stable angina receiving b-blocker therapy, in a double-blind randomized fashion. 889 patients with stable angina were randomized to receive placebo or ivabradine 5 mg bid for two months, and 7.5 mg bid for another 2 months. The total exercise time was increased significantly for both doses of ivabradine compared to placebo [26].

In the BEAUTIFUL trial (morbidity-mortality evaluation of the *If* inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), 10917 patients with coronary artery disease and LV dysfunction ($\text{EF} < 40\%$) were enrolled in a randomised double-blind placebo controlled multicenter trial. All patients received appropriate medical therapy for IHD, including b-blockers in 87% of patients. Patients were followed up for a median of 19 months. In the overall population, ivabradine had no effect on the primary composite endpoint of cardiovascular death, or admission to hospital for MI, or new onset or worsening heart failure. However in a pre-specified subgroup with a heart rate $> 70/\text{min}$, Ivabradine reduced the composite endpoint of cardiovascular death hospitalization with heart failure and MI [27]. In a subgroup analysis of the BEAUTIFUL trial, 1507 patients with limiting angina, ivabradine reduced the risk of CV death, hospitalization for MI, and heart failure by 24% and hospitalization for MI by 42%. The benefit of ivabradine was even more striking in angina patients with high resting heart rate (>70 beats/min), where ivabradine significantly reduces the primary endpoint of CV death, hospitalization for MI, and heart failure by 31%, the risk of hospitalization for MI by 73%, and the need for coronary revascularization by 59% [28]. Ivabradine was approved by the European Medicines Agency (EMA) for therapy of stable angina in patients intolerant or inadequately controlled by b-blocker and whose heart rate exceeded 60/min. It not yet approved by FDA in USA for use in stable angina.

The main side effects of ivabradine are bradycardia and dose related visual symptoms, thought to be due to ivabradine acting on the retinal *I_h* channel which is similar to the *I_f* channel. The visual effects are transient and reversible, the majority being phosphene-like events (luminous phenomenon).

9.5. Allopurinol

Allopurinol inhibits xanthine oxidase (XO), a potent mediator of oxidative stress and consequently reduces tissue oxidative stress (Table 7). Experimental work suggested that allopurinol decreases myocardial oxygen consumption and has been shown to reduce endothelial dysfunction.

Allopurinol in high doses has been shown to prolong the time to chest pain and to ST segment depression during exercise in patients with chronic stable angina. In the Dundee university study involving 65 angina patients, those who received allopurinol were able to walk for 25% longer before they complained of chest pain [29]. Another randomized double-blind placebo controlled trial has shown that allopurinol improves endothelial

Table 7. Advantages of allopurinol.

- 1) Inhibits Xanthine oxidase (XO)
- 2) Improves vascular and myocardial oxidative stress, decreases endothelial dysfunction and reduces myocardial oxygen demands
- 3) Safe, cost effective and well tolerated
- 4) Useful in developing countries where access to expensive drugs or invasive procedures is limited

function [30]. Allopurinol has been used to treat gout for decades, so we know it's safe and it's relatively cheap. Allopurinol is another option for patients who do not respond well to existing drugs. Concerns have been raised to the high dose used to treat stable angina. Allopurinol can cause hypersensitivity and severe cutaneous adverse reactions including rarely Stevens-Johnson syndrome and toxic epidermal necrolysis. These rare reactions can occur with higher doses or in the presence of renal impairment.

9.6. Ranolazine

Traditional pharmacologic therapies reduce determinants of MVO₂ (heart rate, myocardial contractility, wall stress). Combination of these therapies may provide incremental antianginal efficacy but may also produce side effects. Ranolazine is a new antianginal with a novel mechanism of action that does not affect heart rate, contractility, or blood pressure (Table 8). It may also lower fasting glucose and HbA1C.

Ischemia is associated with increased Na⁺ influx into cardiac cells which in turn leads to increased intracellular calcium through Na⁺/Ca²⁺ exchange. Intracellular Ca²⁺ overload causes mechanical dysfunction with increased diastolic stiffness with impairment of relaxation and reduces coronary perfusion by causing vascular compression. It also leads to electrical instability. Ranolazine is a selective inhibitor of late sodium current (late I_{Na}) with anti-ischemic and metabolic properties. By inhibiting the late inward sodium entry, it decreases the calcium overload thus improving relaxation and myocardial perfusion in diastole. It also shifts ATP production from fatty acid to more oxygen efficient carbohydrate oxidation during ischemia. Doses of 500 - 2000 mg daily reduced angina and increased exercise capacity without changes in heart rate or blood pressure. The EMA approved ranolazine as add on therapy in patients who are not controlled or intolerant of first line agents such beta-blockers. It is safe and effective when used alone or in combination with other antianginal medications. When used as monotherapy for angina ranolazine, improves exercise performance in the absence of significant hemodynamic effects. It has also been shown to increase exercise capacity when added to background therapy. Ranolazine was approved by FDA in US in 2006 for management of stable chronic angina.

Most patients have relative intolerances to maximum doses of traditional antianginal agents (b-blockers, CCBs and nitrates). B-blockers and CCBs have depressive hemodynamic effects on CV system. Antianginal drugs without these limitations are needed. Benefits have been shown in the monotherapy assessment of ranolazine instable angina (MARISA) trial. Compared to placebo, ranolazine significantly improved total exercise duration, the time to angina onset, and the time to 1mm ST segment depression on stress test compared to placebo [31]. In the combination assessment of ranolazine instable angina (CARISA) trial, ranolazine was added to standard antianginal therapy with amlodipine, diltiazem or b-blocker in patients who are still symptomatic while taking those medications. Ranolazine significantly decreased angina frequency, nitroglycerin consumption, exercise duration and time to 1 mm ST depression on stress test compared to placebo [32].

In ERICA trial (Efficacy of Ranolazine in Chronic Angina), ranolazine provided additional well-treated antianginal efficacy in patients who remain symptomatic despite maximal CCB therapy [33]. In TERISA trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina), ranolazine was more effective than placebo in reducing angina frequency and sublingual nitroglycerin use in patients with type 2 diabetes, and chronic angina who remain symptomatic despite treatment with one or two antianginal agents [34]. In the large MERLIN-TIMI (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes) randomized placebo controlled trial, involving more than 3500 patients with angina, ranolazine was added to b-blocker treatment. Ranolazine was very effective in reducing recurrent ischemia and worsening angina [35].

In all these trials ranolazine was well tolerated without any clinically significant effects on blood pressure or heart rate. It can be safely used in patients with hemodynamic compromise. Ranolazine is given a class IIa recommendation (level of evidence B) in ACC guidelines for symptoms relief in patients in whom b-blockers are contraindicated or leads to unacceptable side effects. It can also be used in combination with b-blockers for symptoms relief (class IIa, level of evidence A).

Table 8. Ranolazine.

- 1) Metabolic modulation reduces late Na⁺ current 2
- 2) Decreases angina frequency, reduces nitrate consumption, and increases exercise tolerance
- 3) Hemodynamically neutral
- 4) Useful in patients who remain symptomatic despite maximal antianginal therapy

Side effects are few and include dizziness, headache, constipation, and nausea. It causes slight QT prolongation and should be used with caution in patients with QT prolongation or patients who are taking drugs that cause QT prolongation.

10. Role of Revascularization

More than one million percutaneous interventions (PCI) are performed yearly in USA, the majority of which are performed electively in patients with stable IHD. PCI has been shown to reduce the mortality and nonfatal MI in the setting of acute coronary syndromes. However, in stable IHD, PCI has never been shown to reduce death or MI compared to optimal medical treatment (OMT). Several randomized trials comparing PCI and OMT to OMT alone in stable IHD have failed to show improvement in hard outcomes (death or MI) in the interventional group. The COURAGE trial (the clinical outcomes utilizing revascularization and aggressive drug evaluation), is a multicenter randomized 2287 patients with stable IHD, and angiographically documented CAD to PCI or to OMT, with a mean follow up of 4.6 years. Baseline characteristics were well balanced between the two groups. Medical therapy in both groups consisted of evidence based treatment with beta-blockers, aspirin, statins, ACE inhibitors and nitrates. The primary endpoint was death or nonfatal MI. The primary endpoint was similar between the two groups on follow up (19.0% vs. 18.5% respectively, $P = 0.62$). In addition, freedom from angina was higher in the PCI group than OMT alone at 1 and 3 years; by 5 years the rates were similar between the two groups. The conclusion of this study that PCI can be deferred and in the majority of stable IHD patients can be treated effectively with medical therapy and aggressive risk factor reduction [36].

The BARI-2D trial randomized 2368 patients with type II diabetes to prompt revascularization (with PCI or CABG) or to OMT. The mean follow up was 5.3 years. The primary endpoint was death from any cause, with a secondary composite endpoint that included death, MI and stroke. No statistically significant difference was found in the 5 years survival between the prompt revascularization group and the intensive medical therapy group (88.3% vs. 87.8; $P = 0.97$). There were no significant differences in the secondary endpoints (77.2% vs. 75.9; $P = 0.70$) [37].

In the STITCH trial (Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction), 1212 patients with IHD and heart failure were randomized to CABG plus OMT or OMT alone. There was no significant difference in the primary outcome from death from any cause (36% and 41% respectively) [38].

In a recently published a rigorous comprehensive systematic meta-analysis of 12 randomized controlled trials comparing revascularization with PCI to optimal medical therapy (OMT) in 7182 patients, Pursnani *et al.*, concluded that PCI did not reduce the risk of mortality, cardiovascular death, nonfatal MI, or revascularization. PCI however, provided a greater angina relief compare with OMT (secondary endpoint) [39]. The FAME-2 trial (Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease) concluded that FFR guided PCI plus medical therapy in patients with stable coronary artery disease was superior to medical therapy alone. The primary endpoint was a composite of death, MI, or urgent revascularization. The difference however, was driven by a lower rate of urgent revascularization in the PCI group. The study therefore did not show a difference in survival or MI [40].

Therefore, no study yet has shown a difference in hard endpoints namely death or MI with revascularization in patients with stable coronary disease. Further studies are needed to clarify the role of revascularization versus optimal medical therapy in stable coronary artery disease patients. The ISHEMIA trial (International Strategy of Comparative Health Effectiveness with Medical and Invasive Approaches) is currently recruiting patients to determine whether an initial invasive strategy of catheterization and revascularization (by PCI or CABG) plus OMT is superior to OMT alone. The study will randomize 8000 patients with moderate or severe ischemia by non-invasive testing with a planned follow up for 4 years. The primary endpoint is death or MI. A major secondary endpoint is freedom from angina and quality of life [41].

11. Conclusion

Medical treatment is the cornerstone of management of chronic ischemic heart disease. Traditional agents particularly beta-blockers are very effective in the treatment of angina and some groups improve survival in certain patients. However, many patients remain uncontrolled due to side effects or refractory symptoms. In those patients, newer antianginal medications can be added, without deleterious hemodynamic compromise as these agents have different mechanisms of action from the traditional agents. PCI has not been shown to be superior to

optimal medical therapy in stable IHD.

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List of Abbreviations

IHD: Ischemic heart disease
 PCI: Percutaneous intervention
 CABG: Coronary bypass graft surgery
 MI: Myocardial infarction
 CAD: Coronary artery disease
 CCBs: Calcium channel blockers
 ARBs: Angiotensin receptor blockers
 FFAs: Free fatty acids
 CCS: Canadian cardiovascular society
 OMT: Optimal medical therapy
 CHD: Coronary heart disease
 NFMI: Nonfatal myocardial infarction