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Trials and Tribulations Associated With Angina and Traditional Therapeutic Approaches

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Summary

Ischemic heart disease is the foremost cause of death in the United States and the developed countries. Stable angina is the initial manifestation of ischemic heart disease in one half of the patients and becomes a recurrent symptom in survivors of myocardial infarction (MI) and other forms of acute coronary syndromes (ACS). There are multiple therapeutic modalities currently available for treatment of anginal symptoms in patients with stable CAD. These include anti-anginal drugs and myocardial revascularization procedures such as coronary artery bypass graft surgery (CABGS), percutaneous transluminal coronary angioplasty (PTCA) and percutaneous coronary intervention (PCI). Anti-anginal drug therapy is based on treatment with nitrates, beta blockers, and calcium channel blockers. A newly approved antianginal drug, ranolazine, is undergoing phase III evaluation. Not infrequently, combination therapy is often necessary for adequate symptom control in some patients with stable angina. Howerever, there has not been a systematic evaluation of individual or combination antianginal grug therapy on hard clinical end points in patients with stable angina. Most revascularization trials that have evaluated treatment with CABGS, PTCA, or PCI in patients with chronic CAD and stable angina have not shown significant improvement in survival or decreased incidence of non-fatal MI compared to medical treatment. In the CABGS trials, various post-hoc analyses have identified several smaller subgroups at high-risk in whom CABGS might improve clinical outcomes. However, there are conflicting findings in different reports and these findings are futher compromised due to the heterogeneous groups of patients in these trials. Moreover, no prospective randomized controlled trial (RCT) has confirmed an advantage of CABGS, compared to medical treatment, in reduction of hard clinical outcomes in any of the high-risk subgroups. Based on the available data, it appears reasonable to conclude that for most patients (except perhaps in those with presence of left main disease >50% stenosis) there is no apparent survival benefit of CABGS compared to medical therapy in stable CAD patients with angina. Although these trial have reported better symptom control associated with the revascularization intervention in most patients, this has not been adequately compared using modern medical therapies. Available data from recent studies also suggest treatment with an angiotensin converting enzyme inhibitor (ACEI), a statin and a regular exercise regimen in patients with stable CAD and angina pectoris.

Key words: ACE, ACIP, ACME, ACTION, AVERT, beta-blockers, CASS, ECSS, MASS, MERLIN, nitrates, perindopril, PTCA, RCT, RITA-2, SAGE, SCRIP, TIME, VACSS

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Introduction

Despite the decline in cardiovascular mortality, ischemic heart disease remains the leading cause of death in the United States and the developed countries.[1,2] Stable angina is the initial manifestation of ischemic heart disease in one-half of the patients. However, many patients who survive myocardial infarction (MI) and other forms of acute coronary syndromes also manifest

anginal symptoms after the acute event.[3] It can be estimated that there are 30 cases of stable angina for every patient with infarction who is hospitalized.[1] Although this estimate does not include patients who do not seek medical attention for their chest pain or whose chest pain has a noncardiac cause. Stable angina is important not only because of its high prevalence, but also because of its associated morbidity and mortality.

In many patients, anginal symptoms could be disabling and frightening and present a challenge for the clinician on a frequent basis. Effective treatment for symptom control in patients with chronic stable angina is an essential therapeutic goal to improve quality of life and clinical outcomes.

The pathophysiologic basis of chronic stable angina has been discussed elsewhere in this monograph. In brief, angina occurs whenever there is regional myocardial ischemia due to an imbalance between myocardial perfusion and myocardial oxygen requirements. In most patients myocardial ischemia occurs owing to a flow limiting coronary stenotic lesion secondary to atherosclerotic process. However, it is important to recognize that although the high grade stenotic lesions are responsible for the impaired coronary blood flow it is the less stenotic (<50%) vulnerable plaques that are responsible for acute coronary events. Therefore, the treatment of patients with chronic stable angina should not only consist of symptom relief by correcting the imbalance between myocardial oxygen demand and supply but should also be directed toward stabilization of the vulnerable plaque to reduce the risk of future coronary events.

Symptom control is an important therapeutic target in patients with chronic stable angina. Although there are multiple medical and revascularization modalities available for treatment of anginal symptoms, recent data suggest that current therapies are not universally effective in controlling symptoms. For example, some recent studies have shown that despite optimal percutaneous revascularization many patients continue to have anginal symptoms and as many as two thirds of the patients might require one or more antianginal agents.[1,3] It is also known that persistence of symptoms in patients with stable angina is associated with depression and poor quality of life.[4] Additionally, the currently available antianginal drugs are contraindicated or not well tolerated by some patients. In this review we will examine and compare the effectiveness of the current therapeutic modalities for treatment of patients with angina and stable coronary-artery disease (CAD).

Current Therapeutic Approaches for Symptom Control

There are multiple therapeutic modalities currently available for treatment of anginal symptoms in patients with stable CAD. These include antianginal drugs and myocardial revascularization procedures. Until recently the antianginal drug therapy primarily consisted of nitrates, beta-blockers, and calcium channel blockers (CCBs). Although antianginal drug therapy is effective in most patients it is not infrequent that many patients are subjected to percutaneous or surgical revascularization.

Antianginal Drug Therapy

Several antianginal agents primarily nitrates, beta-blockers, and CCBs (Table 1) have been used in the management of symptoms in patients with chronic CAD and stable angina pectoris.[1,2,5–7] Although these drugs have been found to be effective antianginal agents, there is lack of data on the effect of such therapies on clinical outcomes including MI and death in patients with chronic CAD and stable angina.[1,5,6] Despite the popularity of nitrates and beta-blockers in patient with angina, these drugs have not been evaluated in prospective randomized clinical trials regarding their impact on hard clinical endpoints such as MI and cardiac death.

Nitrates

Nitrates exert their beneficial effects primarily by venodilatation resulting in venous pooling of blood, which reduces cardiac work and chamber size. Nitrates are also systemic as well as coronary arterial vasodilators; however, to what extent these effects account for their antianginal efficacy is not well established (except in patients with coronary artery spasm). It is well established that sublingual nitroglycerine is the most effective therapy for relief of anginal symptoms and all patients with anginal symptoms should be given sublingual nitroglycerine. The long-acting nitrates are often prescribed as prophylactic antianginal drugs and are particularly effective in patients who are nitrate responders. However, because of the problem of nitrate tolerance during long-term therapy it is essential to use eccentric dosing scheme that provides a minimum of 10–12 h nitrate free interval.[1,5,6] Although effective in symptom control, nitrate therapy has not been evaluated regarding impact on cardiovascular outcomes.

Beta-blockers

Beta-blockers have been found to be effective antianginal therapy by increasing exercise tolerance and decreasing the frequency and severity of anginal episodes.[1,2,5,6,8] Beta-blockers exert their effects through a reduction in myocardial oxygen demand, which includes a decrease in ventricular inotropy, decreased heart rate and a decrease in the maximal velocity of myocardial fiber shortening. Therapy with beta-blockers has been associated with

TABLE 1 Pathophysiologic effects of antianginal drugs

Class	Heart rate	Arterial pressure	Venous return	Myocardial contractility	Coronary flow
Beta-blockers	↓	↓	↔	↓	↔
DHP CCB	↑ *	↓	↔	↓	↑
NonDHP CCB	↓	↓	↔	↓	↑
Long-acting nitrates	↑ / ↔	↓	↓	↔	↑
Late Na+ current inhibitors	↔	↔	↔	↔ †	↔

* Except amlodipine.
† Ranolazine: no direct effect but may prevent ischemia-related decline.

a reduced risk of death (sudden and nonsudden) and reduced risk of MI in patients who survived an acute MI. However, it is not known whether similar benefit would occur in those without MI.

Although no prospective, randomized, controlled trial (RCT) has evaluated the effect of therapy with beta-blocker(s) on clinical outcomes in patients with chronic CAD and stable angina, there is limited data available regarding the impact of beta-blocker therapy on clinical outcomes in asymptomatic or minimally symptomatic patients with CAD. The atenolol silent ischemia study (ASIST)[9] evaluated the effects of atenolol on clinical outcomes and ischemia during daily life in patients with documented CAD who were asymptomatic or minimally symptomatic (CCS class I or II). Compared to placebo, treatment with atenolol was associated with a significantly lower risk (11.1 vs. 25.3%, respectively) of the primary combined end-point that included death, resuscitation from ventricular tachycardia/ fibrillation (VT/VF), nonfatal MI, hospitalization for unstable angina, aggravation of angina requiring known antianginal therapy, or need for myocardial revascularization during the follow-up period of 12 months. There were no differences between the treatment groups on the incidence of individual hard end-points such as death and nonfatal MI most likely because of a lack of power to identify significant differences.

Calcium Channel Blockers

CCBs are potent coronary and systemic arterial vasodilators and these agents reduce blood pressure as well as cardiac contractility. CCBs have been shown to increase coronary blood flow and are highly effective antianginal agents in patients with coronary artery spasm. CCBs have become popular in treatment of patients with angina primarily because of the relatively lower incidence of side effects. However, like other antianginal drugs their impact on cardiovascular outcomes has not been systematically evaluated in RCT. There is limited information available from the ACTION study, a coronary disease trial investigating outcomes with nifedipine gastrointestinal therapeutic system (GITS),[10] which evaluated the effects of the long-acting CCB nifedipine (nifedipine GITS) on the combined end-point defined as death, acute MI, refractory angina, congestive heart failure, nonfatal stroke, or need for peripheral arterial revascularization in patients with stable symptomatic CAD. Compared to placebo, therapy with nifedipine GITS was associated with similar rates of the combined primary end-point as well as the individual end-points of death, MI, and stroke. Therapy with nifedipine GITS was associated with a small, but statistically significant, reduction in the "softer" end-points of need for coronary angiography and need for coronary artery bypass graft surgery (CABGS).

Newer Antianginal Drugs

The recently approved new antianginal drug, ranolazine, with novel mechanism of action (see article by Chaitman) is being evaluated in the (MERLIN)-TIMI 36 trial, which is a phase III, randomized, double-blind, parallel-group, placebo-controlled, multinational clinical trial to evaluate the efficacy and safety of ranolazine, during long-term treatment of patients with NSTE-ACS receiving standard therapy ($n = 6500$). Ranolazine has been shown to reduce ischemia in patients with chronic stable angina by inhibiting the late sodium current, thereby reducing cellular sodium and calcium overload. The primary end-point is the time of first occurrence of any element of the composite of cardiovascular death, MI, or recurrent ischemia. Recruitment began in October 2004.

Combination Therapy

Combination therapy is often necessary for adequate symptom control in some patients with stable angina. It is important to realize that the best combination therapy is the one that provides maximum symptoms relief with relatively few adverse effects. In general, combination therapy should use a beta-blocker with nitrate or CCB based on patient's underlying co-morbid conditions. Such combination may allow the clinician to use lower doses of each agent to achieve symptom control with minimal side effects. There has not been a systematic evaluation of combination therapy on hard clinical end-points in patients with stable angina.

Myocardial Revascularization

Several modalities of myocardial revascularization have been evaluated and compared to medical treatment in patients with chronic stable angina. These revascularization modalities include CABGS and percutaneous coronary angioplasty (PTCA) with or without stent deployment percutaneous coronary intervention (PCI). In general, both myocardial revascularization techniques are effective in relieving the anginal symptoms. However, despite myocardial revascularization some patients might continue to experience symptoms. It is also important to note that revascularization procedures are often performed in asymptomatic patients with the hope of reducing coronary events and cardiac death in patients with stable CAD.

Comparison of Myocardial Revascularization with Medical Therapy

During the past three decades several studies have compared the impact of medical therapy vs. myocardial revascularization in patients with CAD and stable angina. In general the results of these studies have shown that myocardial revascularization is usually more effective in symptom control compared to the available antianginal drug therapy. However, it is important to note that since these trials were conducted the medical therapy of patients with stable angina has improved considerably with the routine use of beta-blockers, antiplatelet agents, angiotensin converting enzymes inhibitors (ACEIs), and lipid-lowering therapy with statins. A number of trials using these drugs have shown that medical therapy may be as effective as revascularization in controlling symptoms and, when aggressive risk factor modification is implemented, it is more effective in reducing the risk of future coronary events in patients with CAD and stable angina. In the following section we will briefly review the results of the major clinical trials that have compared the outcome of medical therapy with myocardial revascularization in patients with stable CAD and angina pectoris.

During the 1970s three major randomized CABGS studies were conducted in patients with angina and stable CAD. These studies were the Veterans Administration Cooperative Study of Surgery (VACSS) for coronary arterial occlusive disease, [11–17] the European coronary surgery study (ECSS),[18–23] and the National heart, lung, and blood institute coronary artery surgery study (CASS).[24–27] The CASS trial also included a group of post-MI asymptomatic patients.

In these trials, all randomized patients continued to receive medical measures as needed for control of symptoms. In the VACSS, ECSS, and CASS studies, structured antianginal regimens were not provided, dosages were not controlled, and medical treatment was provided according to individual clinical practice patterns, thereby making the comparisons less meaningful. The VACSS and CASS trials included short- and long-acting nitrates as well as propranolol as antianginal agents. In the ECSS antianginal therapy was left to the clinical judgment. Also, in all three trials, reduction in risk factors was suggested but not enforced.

Various post hoc high-risk groups were identified in each of the trials. The VACSS[12,13] included patients with left main coronary (LMC) artery involvement; LMC + (abnormal left ventricular function (LVF) or normal LVF); no-LMC, 2v + abnormal LVF; 3v + abnormal LVF; 1v, 2v, 3v, impaired LVF, nonimpaired LVF; high angiographic risk (3v + impaired LVF); and low angiographic risk ([1-2v + impaired LVF] or [1v-3v + normal LVF]). The ECSS[18] included patients with LMC; 2v; 3v; normal LVF; abnormal LVF; 2v + p-LAD (<or >= 0.50 stenosis); 3v + p-LAD (<or >= 0.50 stenosis); p-LAD. The CASS[24,25] post hoc high-risk subgroups included patients with 1, 2, or 3v; (LVEF <0.50); (LVEF >= 0.50); LVEF (< or >= 0.50) + (1, 2, or 3v); ST ↓ (< 1 >= 1, >2 mm); ETT stages (= <1, 2, > = 3); ETT (angina or no-angina) + (impaired LVF); CHF; CCSC angina; LMC; LAD (proximal, mid, distal).

Using an intention to treat (ITT) analysis approach the VACSS, ECSS, and CASS trials revealed similar mortality rates between the main CABGS and medical therapy arms.[14,19,26,27] The ECSS is the only trial that showed on long-term follow-up a small, but statistically significant, improvement in mortality rate with CABGS.[19] The rates of fatal and nonfatal MI) in these trials were similar between the patients who underwent CABGS, compared to patient who did not undergo CABGS.[17,23,25] The VACSS is the only trial that reported a small, but statistically significant, increase in the incidence of nonfatal MI among patients who underwent CABGS.[17]

Several post hoc subgroups analyses were conducted in each of these trials. The first report by the VACSS was on the relatively small (n = 113) subgroup of patients with involvement of the left main coronary (LMC) disease.[12] Although compared to medical therapy, CABGS was associated with a significant lower mortality risk (29.3% vs. 7.1%, respectively) by 36 months of follow-up the mortality difference between the two groups was not statistically significant. This is likely related, in part, to the progressive shrinking size of the subgroup due to mortality during follow-up. In a subsequent report,[15] patients were further subgrouped into those with a LMC showing a 50–75% stenosis (n = 47) and those with a LMC stenosis >75% (n = 44). The subgroup with a LMC showing a 50–75% stenosis revealed no difference in mortality between the CABGS and no-CABGS arms. However, the subanalysis of patients with a LMC showing >75% stenosis revealed an impressive, and statistically significant, reduction (17% vs. 52%,

respectively) in mortality among CABGS patients compared to patients who continued medical therapy. On the basis of the findings from these subanalyses[12,15] a recommendation to offer CABGS was issued for patients receiving medical therapy. Subsequently it became standard practice to perform CABGS for patients with LMC showing >50% stenosis. As such, no further attempts have been made to confirm the results of VACSS in patients with involvement of the LMC in any subsequent prospective randomized trials. Interestingly, in the ECSS trial, the post hoc analysis of the LMC subgroup revealed no difference in mortality between the CABGS and no-CABGS arms.[19]

In an ensuing report, the VACSS evaluated another subgroup without LMC involvement. This was the angiographic-high risk subgroup (3-vessel CAD + impaired LV function).[17] In this angiographic-high risk subgroup, compared to the medical therapy arm, CABGS improved survival up to 132 months of follow-up after which this difference disappeared.

The ECSS evaluated the subgroups with 2-vessel and 3-vessel CAD.[18,20–22] In the subgroup with 2-vessel CAD there was no difference in mortality between the CABGS and medical therapy groups.[18,20–22] However, in the subgroup with 3-vessel CAD there was a statistically significant difference in survival favoring the CABGS group.[19] Further analysis of the 2-vessel CAD subgroup was carried out into those with involvement (>=50% stenosis) of the proximal-LAD (p-LAD) and those without involvement (<50% stenosis) of the p-LAD.[21] This analysis revealed that in patients with 2-vessel CAD + p-LAD involvement CABGS, compared to medical therapy, was associated with a relatively small, but statistically significant, improved survival. When the subanalysis was carried out with the p-LAD showing a >=75% stenosis therapy with CABGS, compared to medical therapy, was associated with an even smaller, but still statistically significant, improved survival.[23] Following these sub-analyses, the subgroup with p-LAD involvement (> = 50% stenosis) and presence of 2-vessel or 3-vessel CAD was evaluated.[19] This analysis revealed that CABGS, compared to medical therapy, was associated with a significantly lower mortality rate. On the basis of this subanalysis,[19] patients with p-LAD involvement were identified as a high-risk subgroup that appeared to derive benefit from therapy with CABGS.

In contrast, in the CASS trial, analysis of the subgroup with LAD involvement (>=70% stenosis in its proximal, mid, or distal sections) revealed no difference in mortality rates between patients with CABGS and those with medical therapy.[27] However, further analysis of the CASS data in group-B patients (mild-moderate angina + LVEF >=35% but <50%) revealed improved mortality rates with CABGS compared to medical therapy.[26,27] Additionally, in the CASS study CABGS, compared to medical therapy, was associated with improved survival in the subgroup with LVEF <50% as well as in the subgroup with LVEF <50% + 3-vessel involvement. In these two subgroups the improved survival with CABGS became statistically significant at the follow-up mark of 84 months.[26,27] However, during the next analysis (at 120 months) in the subgroup with LVEF <50% + 3-vessel involvement the survival benefit of CABGS was found not significant anymore. Except for these findings there was no difference in mortality between the treatment arms in patients subgrouped by 1v, 2v, or 3v involvement.[26,28] On the basis of these findings patients with LVEF <50% +3-vessel involvement were identified as a high-risk subgroup that appeared to benefit from therapy with CABGS. Of the many subgroups previously identified as being at high-risk, only the subgroup with involvement of the proximal-LAD was subsequently evaluated in a prospective manner in the medicine, angioplasty or surgery study-1 (MASS-1).[29,30]

Additional studies were conducted in the 1990s, which evaluated the role of CABGS, PTCA, or medical treatment in patients with stable CAD. These include the asymptomatic cardiac ischemia pilot (ACIP)[31,32] and the MASS trials.[29,30,33]

The ACIP study[31,32] evaluated the effects of medical or revascularization (PTCA or CABGS) treatment strategies in patients with stable angiographic CAD (> = 50% stenosis) with or without angina, myocardial ischemia on ambulatory electrocardiography (AECG), and evidence of ischemia on an exercise treadmill test or pharmaceutical stress perfusion study. In this complex, partly blinded study, the three treatment strategies were angina-guided medical therapy; angina-guided plus AECG ischemia-guided medical therapy; and myocardial revascularization of major coronary arteries. Use of > = 1 unblinded antianginal medication(s) for control of symptoms was necessary on 77, 70 and 39% of the treatment arms, respectively. The primary end-point was complete suppression of ischemia on 48 h ambulatory ECG. Secondary clinical outcomes at 12 months included death, MI, cardiac arrest, unstable angina, sustained ventricular tachycardia and congestive heart failure. Compared to the medical therapy arms, myocardial revascularization was associated with a significantly greater proportion of patients free of ischemia on AECG. However, compared to the medical therapy arms, revascularization therapy was associated with a similar risk of MI or stroke. Compared to angina-guided medical therapy only, revascularization was associated with a significantly lower mortality rate (4.4% vs. 0.0%, respectively). Although, mortality rates were similar between the two medical treatment arms and between the revascularization and angina-guided plus AECG-guided medical therapy (1.6%).[31,32]

The MASS trial compared the effect of these therapies in patients with proximal-LAD (MASS-1)[29,30] and in patients with multi-vessel CAD (MASS-2).[33] In the

MASS trials, all patients were placed on an optimal medical regimen that included: nitrates, aspirin, beta-blockers, CCBs, ACEI, or a combination of these drugs. In addition, a statin along with a low-fat diet was provided on an individual basis.[29,30,33]

In the prospective MASS-1 trial[29,30] in patients with p-LAD involvement ($> = 0.80$ stenosis) compared to PTCA and medical therapy, CABGS was associated with a modest benefit on the combined outcome that consisted of cardiac death, MI, or angina requiring revascularization (the benefit was predominantly related to a less frequent need for subsequent revascularization).[29,30] It is important to note that compared to CABGS, medical therapy was associated with a similar reduction in the risk of hard events (mortality or MI). Treatment with PTCA appeared to be an inferior option compared to the other treatment strategies.

In the MASS-2 trial[33] of patients with stable multivessel CAD there was no difference in mortality between medical therapy, medical therapy + PTCA, and medical therapy + CABGS. The group treated with medical therapy + CABGS had the best outcome for the primary end-point that consisted of cardiac death, Q-wave MI, or anginal symptoms requiring revascularization. The group with medical therapy + PTCA appeared to have the worse outcome due to increased risk of MI and higher mortality.

In summary, most trials that have evaluated treatment with CABGS in patients with chronic CAD and stable angina have not shown significant improvement in survival or decreased incidence of nonfatal MI. Post hoc analyses of various smaller subgroups have shown some superiority of CABGS. However, there are conflicting findings in different studies and these results are further compromised owing to the heterogeneous groups of patients in these trials. Therefore, it appears reasonable to conclude that for most patients (except perhaps in those with presence of left main disease >50% stenosis) there is no apparent survival benefit of CABGS compared to medical therapy in stable CAD patients with angina. Although these trials have reported that CABGS is associated with better symptom control in most patients this has not been adequately compared using modern medical therapies.

Medical Therapy vs. Percutaneous Revascularization or Strategies Comparing Invasive vs. Optimum Medical Therapy

Only a few trials have carefully examined the strategy of initial angiography/revascularization vs. medical therapy in patients with stable CAD and angina pectoris.[34–40]

The Angioplasty compared to medicine study (ACME),[35] in patients with stable angina, a positive exercise stress test (defined as ST segment depression of $> = 3$ mm) and angiographic 70–99% stenosis of a major epicardial coronary artery evaluated the effect of PTCA or medical treatment on exercise parameters. Compared to medical treatment, therapy with PTCA was associated with a greater proportion of patients free of angina (46% vs. 64%, respectively, $p < 0.01$) and increased total exercise time ($p < 0.0001$). Mortality and MI rates were similar between the groups. However, this study was not powered to detect meaningful differences on these clinical outcomes between the treatment groups. Furthermore, compared to medical therapy, more patients in the PTCA arm underwent repeat PTCA and CABGS.

The trial of invasive vs. medical therapy in elderly patients (TIME)[36,37] with chronic symptomatic CAD was a prospective, randomized, multi-center study in patients aged ⩾75 years with angina class II or more (Canadian Cardiac Society classification [CCS]) despite treatment with ⩾2 antianginal drugs. This study compared the invasive strategy of left-heart catheterization followed by either PCI or CABGS, with a strategy of optimized medical therapy aimed at increasing in the number of antianginal drugs and their doses to reduce anginal pain as much as possible. Additionally, antiplatelet agents and lipid-lowering drugs were advised. Compared to optimum medical therapy, the invasive strategy was associated with a lower risk of admission for acute coronary syndromes (ACS) requiring revascularization. However, compared to optimum medical therapy, the invasive strategy was associated with a similar risk of death or incidence of MI.

The second randomized intervention treatment of angina (RITA-2) trial[38,39] was designed to compare the effects of initial strategies of coronary angioplasty and conservative (medical) care over a follow-up ⩾ 5 years. Compared to medical treatment for symptom relief, treatment with PTCA was associated with similar risk of the primary combined end-point (death or definite MI) or secondary end-point (death). The pattern of unstable angina was similar in both groups. Although both groups remained symptomatic, an early intervention with PTCA was associated with greater, albeit temporary, symptomatic improvement in angina.

A meta-analysis from 11 randomized studies[40] on 2,950 patients with chronic CAD evaluated the effect of PCI, compared to conservative medical treatment, on the risk of death, MI and subsequent revascularization. The large majority of these patients had at least some anginal symptoms, although four studies described 9–20 percent of patients without symptoms. The findings from this meta-analysis revealed that, compared to conservative medical treatment, PCI therapy resulted in similar rates of death, nonfatal MI, combined end-point of death and nonfatal MI, and rates of subsequent revascularization by CABGS or PCI in patients with nonacute CAD and anginal symptoms.

Other Drugs in Patients with Stable Angina

Angiotensin Converting Enzyme Inhibitors (ACEI)

Because of the well demonstrated vasculoprotective effects of ACEI two recent studies evaluated their effects in patients with stable CAD or diabetes and at least one other cardiovascular factor.[41,42] The Heart Outcomes Prevention Evaluation (HOPE) trial[41] evaluated the effect of ramipril 10 mg daily, in a high-risk population characterized by patients with history of CAD, stroke, peripheral vascular disease, or diabetes and at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria). These patients had no prior history of heart failure and had no evidence of depressed LV systolic function. Compared to placebo, treatment with the ACEI was associated with a significantly lower absolute risk (17.8% vs. 14%, respectively) of experiencing the composite end-point (MI, stroke or CV-death) as well as a significantly lower risk of each individual end-point.[41] Secondary end-points were death from any cause, admission to hospital for congestive heart failure or unstable angina, complications related to diabetes, and cardiovascular revascularization.[41] Compared to placebo, the ramipril arm underwent significantly fewer cardiovascular revascularizations (18.3% vs. 16%, $p = 0.002$) and experienced fewer complications related to diabetes (7.6% vs. 6.4%, $p = 0.03$). The incidence of other secondary end-points was similar between the groups.

The European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA) study[42] evaluated the effect of another ACEI, perindopril, on clinical outcomes in patients with stable CAD and angina. In this study, compared to placebo, the therapy with perindopril resulted in a relatively small but significantly lower risk (9.9% vs. 8%, respectively) of the composite end-point (NFMI, CV-death, or resuscitated arrest). Of the individual end-points only the risk of NFMI was significantly lower during therapy with perindopril.

A meta-analysis of six studies[43] including the HOPE and the EUROPA evaluated the effect of ACEI therapy in patients with CAD and preserved LV systolic function. The findings from this meta-analysis revealed that, compared to placebo, therapy with an ACEI was associated with a modest, statistically significant favorable effect resulting in reduced rates of CV-death, all cause mortality, and nonfatal MI.

On the basis of the findings of these two trials and the findings of the recent meta-analysis, an ACEI should be considered in stable patients who are considered to be at high-risk of cardiovascular events and in patients with stable CAD and angina pectoris.

Lipid-Lowering Therapy

A number of studies during the last two decades have shown that lipid-lowering therapy with statins not only reduces the risk of major acute coronary events (MACE) but it also reduces the need for revascularization as well as decreases the signs and symptoms of myocardial ischemia in patients with angina pectoris.[44–48]

The atorvastatin vs. revascularization treatment (AVERT)[46] trial was a randomized study that evaluated the impact of lipid-lowering therapy on outcomes in patients, with stable CAD and angina, who received atorvastatin and compared them to patients who underwent percutaneous myocardial revascularization, with or without stent implantation. Treatment with atorvastatin 80 mg daily was associated with a lower risk of the primary composite end-point defined as at least one of the following: death from cardiac causes, resuscitation after cardiac arrest, nonfatal MI, cerebrovascular accident, CABGS, angioplasty, and worsening angina with objective evidence resulting in hospitalization. There was no difference between the treatment groups in rates of cardiac death, nonfatal MI, or need for CABGS. It is important to note that as expected treatment with PTCA was associated with significantly greater improvement in the severity of anginal symptoms as assessed by CCS. The quality of the AVERT study was not as robust compared to the previous trials because it was conducted in an unmasked manner and it was unclear if randomization was concealed.

The study assessing goals in the elderly (SAGE) evaluated the effect of intensive vs. moderate lipid-lowering therapy on the duration and frequency of myocardial ischemia in older patients with CHD as measured by 48-h AECG monitoring.[48] The preliminary results of SAGE showed comparable and significant reduction in the total duration of myocardial ischemia with both intensive as well as moderate lipid-lowering therapies. These results from SAGE complement the earlier findings from several other studies that had shown beneficial effects of lipid-lowering therapy with statins on myocardial ischemia in patients with CAD.[44–47] Although the precise mechanism of statins' anti-ischemic effects is not well defined, it is postulated to be related to improvement in endothelial function as well as the well demonstrated anti-inflammatory effects of these agents.

The results of these studies suggest that treatment with a statin in patients with chronic stable angina not only reduces the risk of future coronary events, but such therapy also has the potential of reducing myocardial ischemia and the associated symptoms. Therefore, it is recommended that all patients with chronic, stable angina should be treated with a statin to a goal of LDL-C of <70 mg/dl.

Role of Exercise Training and Risk Factor Modification in Patients with Angina

A small, randomized but uncontrolled study in patients with chronic angina (CCS class 1–3) and documented myocardial ischemia during stress ECG and or scintigraphy imaging study in patients with stable CAD[49] compared the effect of PTCA with exercise training on clinical symptoms and the combined clinical outcome described as cardiac death, stroke, CABGS, PTCA, MI or worsening angina resulting in hospitalization during a 12-month follow-up. Exercise training was defined as exertion on a bicycle ergometer for 20 min per day at 70% of maximal heart rate achieved during symptom-limited exercise. In addition, patients were asked to participate in one 60-min group training session of aerobic exercise per week. During the follow-up at 12 months, compared to PCI, exercise training was associated with a significantly lower risk (30% vs. 11.7%, respectively) of the combined primary end-point (defined as cardiac death, stroke, CABGS, angioplasty, acute MI, or worsening angina with objective evidence resulting in hospitalization). The increased risk in the PCI arm was owing to a higher rate of the more subjective need for PTCA associated with hospitalization due to worsening angina.

Multiple Risk Factor Intervention

The Stanford Coronary Risk Intervention Project (SCRIP) study[50] evaluated the effects of an intensive multifactor risk reduction, which included lifestyle changes and therapy with lipid-lowering medications for 4 years, compared to usual care, on the rate of narrowing of the minimal diameter of coronary artery segments affected with angiographic plaques. Clinical outcomes included cardiac death or sudden death, nonfatal MI, CABGS and primary PTCA. The findings from this study revealed that, compared to the usual care arm, therapy with risk reduction was associated with a significantly lesser rate of narrowing of a diseased coronary segment and a significant, but moderate, reduction in the rate of the combined end-point (44% vs. 25%, respectively) that included cardiac death, hospitalization for nonfatal MI, PTCA (primary procedures only), and CABGS. However, there was no difference between the groups on the individual clinical end-points.

Conclusions

There are many therapeutic options available for the treatment of anginal symptoms in patients with stable CAD—namely nitrates, beta-blockers and CCBs. Combination therapy is often necessary for symptomatic relief but there has not been an evaluation of combination therapy on hard clinical end-points in such patients. Clinical outcome data is generally lacking with traditional therapies. Trials have shown that medical therapy is as effective as revascularization in controlling symptoms and, along with aggressive risk factor modification, is more effective in reducing the risk of future coronary events. There is a need for more definitive outcomes studies, which examine the role of existing therapies and newer agents that are currently available for the treatment of patients with stable angina.

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