Current perspectives

Therapeutic approach in patients with stable angina

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Key words:
Angina; Coronary artery disease; Revascularization.

Which therapeutic strategy among medical, interventional and surgical options should be preferred in patients with chronic stable ischemic heart disease is an important public health problem. The available scientific evidence does not help much to facilitate the choice among the three available strategies of medical treatment, percutaneous coronary intervention and coronary artery bypass grafting. In this area practice-based medicine overwhelms evidence-based medicine. However, existing findings are discussed. The present experience in diabetic patients is highlighted; in such patients surgery is generally recommended but the results obtained by percutaneous coronary intervention with the currently available tools are improving markedly.

Pharmacological therapy is also improving, particularly in the prevention of the progression of atherothrombosis and consequently of cardiovascular events. Actually two categories of drugs should be recognized: those prescribed to prevent death and myocardial infarction and those with antianginal and anti-ischemic effects aimed at alleviating symptoms and reducing ischemia. The first group of drugs includes antiplatelet-antithrombotic agents, lipid-lowering agents and angiotensin-converting enzyme inhibitors; the second group includes beta-blockers, calcium antagonists and nitrates. A good integration of the two classes of drugs, combined with an appropriate use of coronary revascularization procedures, should yield the maximum possible benefit in the individual patient.

(Ital Heart J 2005; 6 (1): 1-8)

Received September 14, 2004; revision received December 21, 2004; accepted December 22, 2004.

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Introduction

The definition of the best therapeutic strategy for outcome improvement in patients with chronic stable ischemic heart disease is an important public health problem because of the huge number of patients involved and the great economic implications. In western countries more than 30 000 per million patients develop stable angina every year and the disease prevalence increases with age in both sexes[1].

Surgical and interventional revascularization

Coronary artery bypass grafting (CABG) has been used for more than 30 years and the historical comparisons between bypass surgery and medical management are well known. A meta-analysis of these trials published in 1994 confirmed the survival benefit achieved by surgery at 10 postoperative years for patients with three-vessel disease, two-vessel disease or even one-vessel disease that included a stenosis of the proximal left anterior descending coronary artery[2]. The survival benefit applied to patients with both normal and abnormal left ventricular function. These results have been later confirmed by observational studies[3,4]. Obviously, today both surgery and medical management have changed and percutaneous coronary interventions (PCIs) are now playing an increasing role in the treatment of patients with chronic ischemic heart disease. More recent studies addressed the comparison between PCI and medical management or PCI and surgery. No large trials testing surgery vs medical management have been published to date.

A meta-analysis of six randomized controlled trials, including the Medicine, Angioplasty or Surgery Study (MASS), Randomized Intervention Treatment of Angina (RITA-2) and Atorvastatin Versus Revascularization Treatment (AVERT) trials performed in the last decade with a total of 1904 relatively low-risk patients, was published in 2003[5]. In patients treated with angioplasty compared with patients treated medically there was a 30% risk reduction

for angina, although a non-significant trend toward increased rates of revascularization and death was observed. The conclusion of the authors was rather conservative; they suggested that revascularization procedures have to be reserved to patients whose symptoms of angina were not well controlled by medical treatment. This was not the conclusion of the Asymptomatic Cardiac Ischemia Pilot (ACIP) study which included patients with coronary artery disease (CAD) who were either free of angina or had symptoms that were well controlled with medical therapy, but at least one episode of asymptomatic ischemia documented during 48-hour ambulatory ECG monitoring[6]. The three arms of the study were medical management guided by angina, medical management based on ambulatory ECG monitoring, and revascularization (either CABG or PCI). At 2 years of follow-up, patients randomized to revascularization had a significantly lower death rate than those in the medical management group. However, patients with ischemia on ambulatory ECG monitoring frequently had multivessel disease, severe proximal stenosis and complex plaques, thus suggesting that they constituted a rather different population from those included in the just reported meta-analysis.

Comparison between CABG and PCI is a very hot issue. A meta-analysis of thirteen randomized controlled trials comparing CABG with angioplasty has been published recently[7]. Stents were used routinely in only four trials. About 30% of patients had unstable angina. No significant differences for death and myocardial infarction (MI) were noted between the two therapeutic approaches. There was a higher risk for angina and additional revascularization following angioplasty, but this risk decreased by 50% with the use of stents. No significant difference for single-vessel proximal CAD was evident.

Several randomized trials of PCI vs surgery have been carried out in recent years, with a technical approach closer to that routinely used in our cardiology units today. In the Stent or Surgery (SoS)[8], ERACI II[9] and Arterial Revascularization Therapies Study (ARTS) trials[10] the percentage of patients with unstable angina ranged from 20% (SoS) to 90% (ERACI II). The follow-up duration was also different. The results are not consistent in terms of hard endpoints: the mortality was higher in the CABG group of the ERACI II study and in the PCI groups of the other two trials, but all trials did not have enough power to measure differences in low-incidence hard endpoints such as mortality and MI. In a recent study, which refers to a single-center US experience, the outcome of patients treated with multivessel coronary stenting has been compared with that of patients matched for clinical characteristics who underwent surgical revascularization[11]. At 2.8 years of follow-up, the mortality and MI rate were similar while, as expected, the repeat revascularization rate was higher in stented patients. The global costs of PCI procedures were markedly lower than those of surgery.

A further trial, the Medicine, Angioplasty or Surgery study (MASS-II)[12], was carried out comparing three strategies of optimal medical treatment, PCI plus medical treatment and CABG in 611 patients with multivessel CAD, stable angina, and a preserved ventricular function. At 1-year of follow-up 88% of the patients in the CABG group, 79% in the PCI group and 46% in the medical treatment group were free of angina. However, the mortality rates were 4% for CABG, 3.5% for PCI, and 1.5% for medical treatment; the Q wave MI rates were 2% for CABG, 8% for PCI, and 5% for medical treatment. It is conceivable that if MI would have been defined according to more sensitive criteria than the conventional Q waves, the periprocedural rates of MI would have been much higher in the revascularization groups. Compared with other therapeutic strategies CABG was superior in improving the event-free survival. Similar results were obtained in the long-lasting (7 years) follow-up of the RITA-2 trial[13]. Moreover recently, the AVERT trial showed that in low-risk patients with stable CAD, aggressive lipid-lowering therapy is at least as effective as angioplasty plus usual care in reducing the incidence of major cardiac events[14], and in a randomized controlled trial Hambrecht et al.[15] showed that physical training is not less effective than PCI in controlling symptoms in CAD patients.

Stenting has improved the outcome of PCI procedures in terms of the endpoint angina relief. The more than 45 randomized controlled trials reported to date suggest that PCI with stenting is superior to medical therapy and probably similar to surgery, whereas there is no definite evidence that it is better than CABG or medical therapy in terms of the reduction in the incidence of hard events. The pooled risk ratios for some hard endpoints from six randomized trials comparing PCI with medical treatment are reported in figure 1[16]. The crude late mortality has not improved in the last years. The 1-year mortality after a first PCI was 3.6% in the mid '80s and rose to 5.6% in the late '90s. This is probably related to the differences in the populations undergoing PCI: in fact, after adjusting for baseline differences, the mortality rates were similar. The benefits and risks of PCI in stable angina may be summarized as follows[17]:

- procedural success in > 95% of cases;
- in-hospital mortality rate < 0.2% in single-vessel and < 0.5% in multivessel procedures;
- need for emergency bypass surgery < 1% (0.3% European Registry 1999);
- rate of Q wave MI ~ 1%;
- rate of "biochemical" periprocedural MI ~15%;
- well established safety of PCI in multivessel revascularization;
- need for repeat procedures reduced by 50%;
- low mortality at 1-2 years.

Although more data on drug-eluting stents are expected, surgery still remains the preferred choice for complex anatomical subsets.

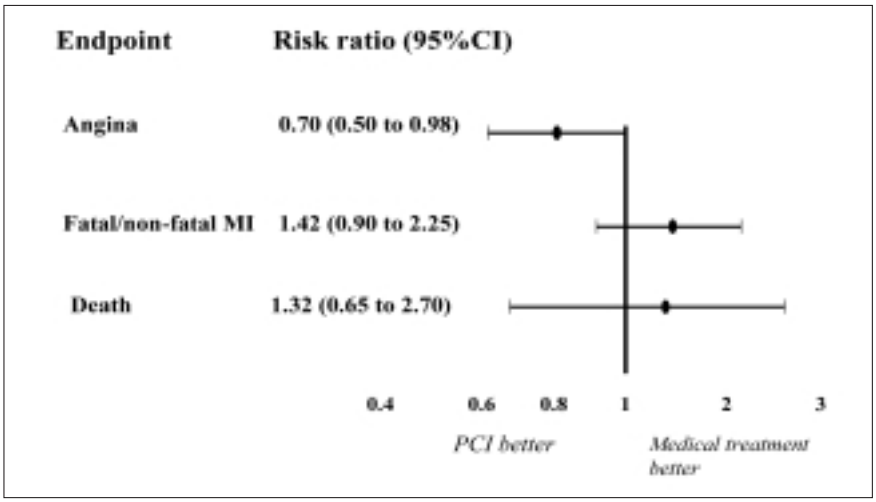

Figure 1. *Pooled risk ratios for angina, myocardial infarction (MI) and death from six randomized trials comparing percutaneous coronary intervention (PCI) with medical treatment. CI = confidence interval. From Bucher et al.[16], modified.*

Special attention should be reserved to patients with old venous grafts, as saphenous vein graft lesions are prone to rapid progression and thrombotic occlusion. A low threshold for angiographic evaluation is recommended for patients who develop chronic stable angina more than 5 years after surgery[18].

A still open issue relates to patients with previous bypass surgery who develop angina refractory to medical treatment. Randomized studies of invasive therapy for chronic angina have all excluded patients with previous bypass surgery. The few existing data indicate that: 1) patients with ischemia produced by vein graft stenosis are at higher risk with medical treatment alone than patients with native vessel disease; 2) the risks of coronary reoperation are increased relative to the risks of primary coronary bypass procedure; 3) the risks of percutaneous treatment of vein graft stenosis are also increased, and the long-term outcome is not as good as that reported for the treatment of native vessel lesions[17].

Stenting of saphenous graft lesions has been proved to determine lower restenosis rates and better outcomes (in terms of freedom from death, MI and repeat revascularization) in comparison with bare balloon angioplasty in three randomized clinical trials (US Palmaz-Schatz Stent Study[19], Coronary Angioplasty Versus Excisional Atherectomy Trial II[20] and Saphenous Vein *De Novo* Trial[21]). The Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial enrolled patients with refractory angina, at high risk for an adverse outcome[22]. One of the determinants of high risk was a previous coronary surgical intervention.

From 1995 to 2000, 142 male patients were randomized to PCI or reoperation, 719 entered a physician-directed registry and 119 a patient-choice registry and, according to the physician's opinion or their choice, underwent PCI or CAGB. After 3 years 25% of the patients were dead. The survival was similar among patients treated with reoperation or PCI, entered either in the randomized trial or the physician-directed registry. In the patient-choice registry, the 36-month survival was significantly better in the PCI group. Recently, data from the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry regarding the effect of prior revascularization on the outcome following PCI have been reported (Table I)[23]. The in-hospital mortality was lower and the procedural success higher among patients with prior PCI only. Patients with prior CABG had higher rates for the combined endpoint of death and MI at 1 year compared to patients with no prior procedures. However, in a multivariate regression analysis, neither prior PCI nor prior CABG was an independent predictor of death or MI at 1 year. Patients with prior procedures had a higher prevalence of angina at 1 year. The highest rate of hard events in patients with prior CABG is probably related to the unfavorable baseline characteristics of the study population. Several reports published in the '80s and '90s showed that balloon angioplasty in saphenous vein grafts was usually safe but the restenosis rate was high[17]. Further studies showed that stenting decreases the restenosis rate, which however remains higher than for *de novo* lesions. No differences in the rates of death or MI at 1 year have been reported[24]. The experience of the Dy-

Table I. Events after percutaneous coronary intervention (PCI) in patients with prior revascularization: 1-year cumulative event rate (NHLBI Dynamic Registry[23]).

	No prior procedure	Prior PCI	Prior CABG	p
No. patients	2357	883	661	
Death-MI	9.6%	8.8%	13.1%	< 0.05
CABG-PCI	16%	24%	24%	< 0.01
Angina	20%	25%	30%	

CABG = coronary artery bypass grafting; MI = myocardial infarction.

namic Registry confirms both the safety of repeat PCI, and a slightly higher probability of recurrent angina and of further interventions[23].

Diabetes: coronary artery bypass grafting or percutaneous coronary intervention?

Chronic angina patients with diabetes constitute a special subset. Such patients are known to be at higher risk than non-diabetics. A recent review reported that in a large population of about 145 000 patients undergoing CABG, 28% suffered from diabetes. The 30-day mortality was 3.7% in diabetics vs 2.7% in non-diabetics with an adjusted odds ratio of 1.23. The mortality was higher in patients with insulin-dependent diabetes[25].

A critical, open issue is whether patients with diabetes should be revascularized by PCI or surgery. In the Bypass Angioplasty Revascularization Investigation (BARI) trial, the 5-year survival among diabetic patients on hypoglycemic treatment was 80.6% in the CABG group vs 65.5% in the PCI group[26]. The BARI Investigators also observed more vascular lesion progression and development of new atherosclerotic plaques at 5 years among diabetic patients undergoing PCI as compared with CABG patients. The survival benefit obtained in CABG patients was mainly provided by the use of internal mammary artery grafts.

A clinical alert was prompted by the NHLBI after the publication of the BARI results that discouraged the PCI approach in diabetic patients. However, the alert was eventually unsuccessful as no change in the PCI rates was observed in the following 4 years[27].

A meta-analysis of five randomized controlled trials (including BARI) comparing balloon angioplasty with surgery in diabetic patients with multivessel disease showed a mortality rate of 30% in patients allocated to PCI vs 19% in those allocated to surgery during a follow-up of 1-8 years[28].

In contrast, seven registries evaluating the same outcome in an apparently very similar population showed long-term mortalities (5-12 years) of 27.8% in patients treated by PCI and of 26.3% in patients treated by surgery, thus showing a mortality rate quite similar for the two groups and different from the results obtained in diabetic subgroups of randomized controlled trials[28]. The reason for the discrepancy between the subgroup analyses of clinical and observational data is unclear, even though it is well known that CABG patients in registries are usually much more compromised than those undergoing PCI.

The use of stents improved the outcome in diabetic patients as well as in non-diabetics undergoing a PCI. More than 10 000 patients were clinically followed in observational studies and about 5000 had an angiographic follow-up[28]. The 6-month restenosis rate decreased by about 30% and the incidence of total occlusion as well as the 1-year mortality and MI rates decreased by 50%.

In three trials comparing stenting versus surgical treatment (follow-up ranging from 1 to 2 years) in diabetics with multivessel disease and either stable or unstable angina, the results were somewhat discordant and inconclusive, probably because of the differences in the populations and the small size of the subsets of diabetic patients[8-10].

Indeed in the NHLBI Dynamic Registry, diabetic patients undergoing PCI appeared older and more likely to have advanced CAD, heart failure, hypertension, and several comorbidities in comparison with patients without clinically evident diabetes[29]. The crude in-hospital mortality was 2.3% in diabetics and 1.3% in non-diabetics. In multivariate analysis, the adjusted risk did not turn out to be significantly different in the two populations, even though at 1 year patients with diabetes had a significantly higher adjusted risk of mortality and need for repeat revascularization.

In summary, on the basis of the findings reported in the literature some conclusions may be drawn: CABG has been shown to provide a better outcome than PCI. However, 1) most of the findings were obtained by subanalyses; 2) most of the techniques and pharmacological support employed in the investigations are outmoded; 3) several potentially important issues, such as the adequacy of glycemic control, the management of other risk factors, adjunctive therapy, and the status of the distal vascular bed were not addressed.

A potential solution to some problems is represented by drug-eluting stents. In the SIRIUS trial, 27% of the enrolled patients were diabetics. Overall, the in-segment restenosis rate was much higher in diabetics than in non-diabetic patients in both groups receiving coated and uncoated stents; however, the benefit of drug-eluting stents in preventing restenosis was quite evident even in diabetic patients[30].

Ongoing trials will probably answer the important question on how to treat diabetic patients with CAD.

Drug therapy

The role of pharmacological treatment in the general care of patients with stable ischemic heart disease is clearly stated in the American guidelines: "*A minority of patients with stable angina have a demonstrated survival advantage with revascularization. For most patients, for whom no demonstrated survival advantage is associated with revascularization, medical therapy should be attempted before angioplasty or surgery is considered*"[17]. The pharmacological treatment of stable angina has two major purposes. The first is to prevent MI and death and thereby increase life expectancy. The second is to reduce the symptoms of angina and the occurrence of ischemia which should improve the quality of life. Accordingly, there are two categories of

treatment: those prescribed to prevent death and MI and those with antianginal and anti-ischemic effects aimed at alleviating symptoms and reducing ischemia[18]. Obviously, the two categories partially overlap. The first group of drugs includes antiplatelet-antithrombotic agents, lipid-lowering agents, and angiotensin-converting enzyme (ACE)-inhibitors.

In contrast to the traditional habit of privileging anti-ischemic drugs for the long-term treatment of patients with chronic ischemic heart disease, whether symptomatic (i.e. stable angina) or asymptomatic but inducible, the current American guidelines[17] give priority to drugs in the first group. The different classes of drugs in the first group (antiatherosclerotic and antithrombotic agents) cannot be examined individually here, but the importance of defining the rationale behind their use may be supported by considering ACE-inhibitors. After having been successfully tested in heart failure, systemic hypertension and acute and subacute MI, ACE-inhibitors were assessed in patients considered to be at risk of cardiovascular events in both the Heart Outcomes Prevention Evaluation (HOPE)[31] and EUROPA[32] trials. The effectiveness and safety of ramipril and perindopril, respectively, have been clearly demonstrated even in patients who were not hypertensive. EUROPA is particularly relevant in this context because it specifically enrolled patients with chronic ischemic heart disease, since the criterion for inclusion in the study was the presence of CAD associated with any level of risk. The main results of the EUROPA study are reported in table II[32].

Given that ACE-inhibitors effectively prevent the clinical progression of coronary atherosclerosis, many investigators have tried to assess whether these drugs are also effective in reducing the ischemic burden of patients with CAD and inducible myocardial ischemia.

Table II. Main results of the EUROPA trial[32].

	Perindopril (n=6110)	Placebo (n=6108)
CV mortality, MI, cardiac arrest	488 (8.0%)	603 (9.9%)
Total mortality, MI, UA, cardiac arrest	904 (14.8%)	043 (17.1%)
CV mortality, MI	484 (7.9%)	596 (9.8%)
CV mortality, MI, UA	753 (12.3%)	885 (14.5%)
Total mortality	375 (6.1%)	420 (6.9%)
CV mortality	215 (3.5%)	249 (84.1%)
MI, fatal and non-fatal	320 (5.2%)	418 (6.8%)
UA	342 (5.6%)	367 (6.0%)
Cardiac arrest	6 (0.1%)	11 (0.2%)
Stroke	98 (1.6%)	102 (1.7%)
Revascularization	577 (9.4%)	601 (9.8%)
HF requiring hospital admission	63 (1.0%)	103 (1.7%)

CV = cardiovascular; HF = heart failure; MI = myocardial infarction; UA = unstable angina.

About twenty out of some small published studies suggest that ACE-inhibitors are indeed effective in this context. However, two recent randomized studies demonstrated the opposite. The Quinapril Antischemia and Symptoms of Angina Reduction (QUASAR) trial was aimed at determining whether an ACE-inhibitor prevents transient ischemia (effort and spontaneous) in patients with CAD and stable angina[33]. Three hundred and thirty-six patients without hypertension, left ventricular dysfunction or previous MI were randomly assigned to quinapril or placebo. After 8 weeks the two groups did not differ at all in terms of the indexes assessing myocardial ischemia such as the ischemic threshold during exercise, the ischemic burden as evaluated at ambulatory recordings and the scores of the Seattle Angina Questionnaire. These results match those from another trial – Quinapril on Vascular ACE and Determinants of Ischemia (QUO VADIS) study – including 149 patients with ischemic heart disease randomized to quinapril or placebo 4 weeks before elective bypass surgery and then followed for 1 year[34]. Again, no differences in the indicators of ischemia between the two groups were observed. Major adverse cardiac events have been also considered as predefined endpoints for this small trial and it is interesting to note that fewer adverse cardiovascular events were recorded in the quinapril group compared with the placebo-group (4 vs 15%, $p = 0.02$).

The complex scenario of the action of ACE-inhibitors in ischemic heart disease therefore suggests that there is a clear distinction between antianginal and antiatherosclerotic-antithrombotic drugs, the former being effective in reducing the ischemic burden but having little or no effect on the progression of CAD, the latter having little or no effect on the ischemic burden but significantly modulating the progression of CAD. An optimal integration of the two classes of drugs, combined with appropriate use of coronary revascularization procedures, should yield the maximum possible benefit in the individual patient.

The agents belonging to the second category, expected to be the most effective for relieving ischemia and angina, are beta-blockers, calcium antagonists, and nitrates. Clinical pharmacological research dealing with chronic ischemic heart disease is scanty. Not surprisingly, a huge amount of resources is usually spent for research in the area of prevention and interventional cardiology but much less in the more difficult and less rewarding field of anti-ischemic drugs. Importantly, almost all studies compare different drugs; thus, we do not know the efficacy of each drug *per se*.

Beta-blockers represent a large, relatively heterogeneous family of drugs with antagonist properties toward the β_1-β_2 receptors and, for some of them even the α-adrenergic receptors. The current guidelines do not privilege any specific drug, stating that in clinical practice all beta-blockers appear to be equally effective in angina pectoris (Table III)[17]. Indeed, only a few, small

Table III. Beta-blockers vs calcium antagonists in stable angina[17].

Trial	No. patients	Beta-blocker	Calcium antagonist	Follow-up	Outcome	OR (95% CI)
APSIS	809	Metoprolol	Verapamil	3 years	Death-MI	1.0 (0.6-1.6)
TIBET	458	Atenolol	Nifedipine	2 years	Death-MI	1.22 (0.6-2.4)
IMAGE	127	Metoprolol	Nifedipine	6 weeks	Death-MI	0.5 (0.0-5.8)
Others	592	Atenolol				
		Metoprolol	Nifedipine			
		Bisoprolol	Diltiazem	4 weeks	Death-MI	
Total	1986		58 vs 62 events		Death-MI	1.06 (0.7-1.5)

CI = confidence interval; MI = myocardial infarction; OR = odds ratio.

and short-lasting randomized trials have been carried out in non-MI, non-hypertensive patients usually vs other anti-ischemic drugs with a total of 1986 patients enrolled. The occurrence of cardiovascular death or MI in the short-term follow-up was the same in the different treatment groups of patients. A detailed analysis of the studies comparing beta-blockers vs calcium antagonists for angina relief is reported in the American College of Cardiology/American Heart Association guidelines[17]. The drugs appear equivalent in relieving angina. The results are also similar for the time to 1 mm ST-segment depression during exercise. In non-comparative studies a 1 min increase in the exercise time has been reported for an effective drug. The side effects of beta-blockers are known. A 15% reduction in the total maximum work achievable by patients has been described. True impotence is rare, but erectile dysfunction has been reported in 25% of cases[35].

Among calcium antagonists, short-acting dihydropyridines have the potential of enhancing the risk of adverse cardiac events and should be avoided. Long-term calcium antagonists are effective in relieving symptoms. In combination with beta-blockers, calcium antagonists may yield a slightly greater antianginal effect.

Finally, nitrates are used in patients with stable angina owing to their vasodilator action which results in a decrease in myocardial oxygen requirements and improves myocardial perfusion. In a meta-analysis published in *JAMA* in 1999, twelve studies of nitrates vs beta-blockers and 4 of nitrates vs calcium antagonists were reported[36]. No significant differences in outcome were seen even though a non-significant trend toward a greater frequency of anginal episodes in patients taking nitrates was observed. A *post-hoc* analysis of the data prospectively acquired in an observational study (Multicenter Study of Myocardial Ischemia or MSMI)[37] and in a randomized trial (Multicenter Diltiazem Post-Infarction Trial or MDPIT)[38] which included patients who had recovered from an acute coronary event has been conducted. Long-term nitrates appeared to be associated with a significantly increased mortality risk, raising concern about the potential adverse effects of long-acting nitrate therapy in chronic coronary disease. The same concern has been expressed and discussed in a recent editorial[39]. Despite the limitations of the *post-hoc* analysis and the need of a randomized trial to address the hypothesis generated by that investigation, it should be concluded that the available evidence on the prognosis of post-MI patients does not entirely apply to stable angina patients for whom nitrates are still indicated for the relief of symptoms.

In conclusion, two meta-analyses on the pharmacological approach to stable angina have been recently published. One reported the results of trials comparing beta-blockers, calcium antagonists and nitrates in patients taking only one class of drugs[36], the other reported the results of trials comparing the same drugs in association[40]. The conclusions of the latter are reported in table IV[40].

Hormone replacement therapy in postmenopausal women deserves some commenting because a few years ago epidemiological evidences supported a beneficial effect in women with manifest CAD. Subsequent randomized controlled trials, in the areas of both secondary and primary prevention, showed no benefits, and possibly harms by the same treatment. Accordingly there is no evidence for adding or continuing estrogens in postmenopausal women with a clinically evident CAD unless they are prescribed for other well-established indications and no better alternative therapies are available[41].

Table IV. A meta-analysis on monotherapy vs combination drug regimens in chronic stable angina[40].

Calcium antagonists vs calcium antagonists + beta-blockers:
10 studies, 399 patients monotherapy, 388 patients combined treatments
- Time to 1 mm ST ↓: 8% higher (33 s, $p < 0.001$) with combined therapy
- Exercise duration: 5% longer (23 s, $p = 0.002$)

Beta-blockers vs beta-blockers + calcium antagonists:
22 studies, 630 patients monotherapy, 615 patients combined treatments
- Time to 1 mm ST ↓: 9% higher (41 s, $p < 0.001$) with combined therapy
- Exercise duration: 4% (17 s, p = NS)

Conclusion

The goal of therapy in patients with stable CAD is to reduce the incidence of recurrent ischemia and to prevent MI and cardiovascular death. Standard treatment in these patients includes antiplatelets, lipid-lowering agents and ACE-inhibitors which proved effective in reducing the occurrence of ischemic events, as well as beta-blockers, calcium antagonists and nitrates which are currently used only to control symptoms caused by myocardial ischemia. The current first-line treatment recommended by the American guidelines includes drugs of the first group since they proved effective in preventing the progression of atherosclerosis and in improving survival whereas beta-blockers and calcium antagonists are considered equally effective in reducing ischemia and angina.

For more than 30 years revascularization by CABG has been considered the best treatment for symptomatic patients with multivessel disease or even with one-vessel disease and a proximal stenosis of the left anterior descending coronary artery. However, results of recent clinical trials failed to demonstrate a significant survival benefit in patients who underwent surgical revascularization compared to those treated with pharmacological treatment, thus suggesting that CABG should be considered only in patients with angina unresponsive to conventional drug therapy. Moreover, PCI procedures have been significantly improved by the use of conventional and drug-eluting stents, and they are now considered equally effective to the surgical approach in reducing ischemic symptoms although as yet there is no evidence that PCI is better than medical treatment in reducing cardiovascular death. Clinical trials have also demonstrated that CABG may be superior to PCI in diabetic patients. However, limitations in statistical analysis and several other important issues (glycemic control, adjunctive therapy, outmoded PCI techniques) shed some doubts on the results of these studies. Another still open issue relates to patients who have undergone surgical revascularization and develop new-onset angina which is refractory to pharmacological treatment. Recent studies demonstrate the safety of PCI of saphenous vein grafts thus suggesting that it may be an alternative approach to surgery in these patients, although the rate of restenosis is significantly higher than that for native coronary lesions.

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