

Medical Versus Revascularization Therapy in the Management of Stable Angina Pectoris

Pretorian A.¹, Borda Angela², Suciu C.³, Pretorian Ana-Maria⁴

¹ Municipal Hospital Gheorgheni, Cardiology Department

² Department of Pathology, Faculty of Medicine, UMPH Târgu Mureş

³ Department of Interventional Cardiology, Institute of Cardiovascular Disease and Transplantation, Târgu Mureş

⁴ Municipal Hospital Gheorgheni, Cardiology Department

Background: In patients with stable coronary artery disease, there are very few studies that compare the value of optimal medical therapy with revascularization therapy in reducing the risk of cardiovascular events.

Aim: To compare three therapeutic options for stable angina pectoris: percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and medication alone.

Methods: We studied 98 randomized patients with stable angina pectoris who underwent coronarography and had objective evidence of significant coronary disease. We assigned 36 patients to undergo PCI, 28 patients to undergo CABG, both subgroups with optimal medical therapy, and 34 patients with optimal medical therapy alone. Primary outcomes were cardiac death and non fatal myocardial infarction, during a follow-up period of 3 years.

Results: There were 3 primary events in the medical-therapy group, 1 event in the CABG group and 1 event in the PCI group. The 3-year cumulative primary-event rates were 2.8% in the PCI group, 3.6% in the CABG group and 11.8% in the medical-therapy group ($P = 0.16$).

Conclusion: In patients with disabling stable angina pectoris without high-risk criteria, the revascularization has the advantage of improving the long-term quality of life. In some patients with high-risk criteria, the percutaneous coronary intervention using drug-eluting stents can be a viable alternative to surgical revascularization.

Keywords: stable coronary artery disease percutaneous coronary intervention coronary artery bypass grafting

Introduction

Untreated coronary heart disease (CHD) generally results in progressive angina, myocardial infarction (MI), left ventricular dysfunction, and ultimately death [1]. The treatment of stable angina has two major purposes. The first is to prevent MI and death (improvement in survival). The second is to alleviate symptoms of angina and occurrence of ischemia, which should improve the quality of life. Treatment guidelines advocate an initial approach with intensive medical therapy, a reduction of risk factors, and lifestyle intervention (known as optimal medical therapy) [2,3].

Recommendations for the treatment of stable angina were largely based upon older clinical trials comparing interventional to medical therapy and PCI to CABG. There are, however, a number of important limitations concerning the applicability of the results of these initial trials to current clinical practice: a) intensive risk factor modification for patients with established CHD recommended by ATP III and the 2006 ACC/AHA guidelines [4,5,6] was not widespread in the previous studies; b) in patients in later trials who received a bare metal stent (BMS), current antithrombotic regimens (eg, clopidogrel) were not employed; in the most recent trial, COURAGE, drug-eluting stents (DES) that markedly reduce the rate of restenosis and therefore repeat revascularization were used in only 15 percent of patients [7]; c) most CABG trials were conducted at a time when saphenous vein graft use was prevalent rather than internal mammary (thoracic) arteries that are associated with improvements in long-term

graft patency and patient survival [8]. In our study, all patients received optimal medical therapy and most could benefit from drug-eluting stents and internal mammary artery grafting.

Given the above, we sought to assess the value of these three different therapeutic approaches in patients with stable coronary artery disease.

Material and method

Patients

Study includes 98 patients with Canadian Cardiovascular Society (CCS) class II–IV stable angina or evidence of myocardial ischemia on the resting electrocardiogram (ECG) or during stress test who underwent coronary arteriography at the Department of Interventional Cardiology of the Institute of Cardiovascular Disease and Transplantation, Târgu Mureş between January 1 and December 31, 2007. All patients gave informed consent before intervention. Demographic and clinical data, as well as coronarography results, were entered in our database at the time of the procedures.

Entry criteria included stenosis of at least 70% in at least one epicardial coronary artery and objective evidence of myocardial ischemia (classic angina or substantial changes in ST-segment depression or T-wave inversion on the resting ECG or inducible ischemia with exercise stress). Exclusion criteria included an ejection fraction of less than 30% and severe comorbidities that affect survival. Follow-up period was 3 years.

Table I. Baseline Clinical and Angiographic Characteristics †

Characteristic	Medical Group (N=34)	PCI Group (N=36)	CABG Group (N=28)	P Value
Demographic				
Age – years	64.06±9.88	60.03±9.11	61.35±6.23	
Sex – no. (%)				0.27
Male	28 (82.4)	26 (72.2)	18 (64.3)	
Female	6 (17.6)	10 (27.8)	10 (35.7)	
Clinical				
History – no. (%)				
Diabetes	3 (8.8)	8 (22.2)	7 (25)	0.19
MI	22 (64.7)	18 (50)	8 (28.6)	0.017
Echocardiographic				
FEVS <40%	5 (14.7)	1 (2.8)	2 (7.1)	0.18
Angiographic				
Vessels with disease				
1	11 (32.4)	13 (36.1)	0	
2	7 (20.6)	14 (38.9)	6 (21.4)	
3	11 (32.4)	3 (8.3)	13 (46.4)	
Left Main	3 (8.8)	1 (2.8)	7 (25)	
Proximal LAD	4 (11.8)	4 (11.1)	2 (7.1)	

† Plus-minus values are means ±standard deviations. LAD = left anterior descending artery

Treatment

All patients received antiplatelet therapy with aspirin at a dose of 75 to 150 mg per day. Medical anti-ischemic therapy included beta-blockers, calcium channel blockers, and nitrates, alone or in combination, along with angiotensin converting enzyme (ACE) inhibitors, statin therapy and glycemic control in diabetics.

Percutaneous revascularization was performed in patients with CCS class II–IV angina and/or evidence of myocardial ischemia and at least 70% stenosis in at least one proximal epicardial coronary artery with suitable anatomy for intervention. PCI with DES was the procedure of choice in the majority of patients. Patients undergoing PCI have received aspirin and clopidogrel, the last for an average of 12 months.

CABG has been preferred in patients with left main coronary disease and diffuse three-vessel coronary disease, particularly in patients with diabetes.

Follow-up and end points

Follow-up was obtained by review of hospital databasis, as well as by telephone interviews. Primary end points were

Table III. Primary and Secondary Outcomes

Outcome	Events – no (%)			P value
	Medical Group	PCI Group	CABG Group	
Primary Outcomes				
Cardiac Death	4 (11.8%)	1 (2.8%)	1 (3.6%)	0.16
Cardiac Death	3 (8.8%)	1 (2.8%)	1 (3.6%)	0.33
Nonfatal myocardial infarction	1 (2.94)	–	–	
Secondary Outcomes				
Disabling angina	12 (35.3%)	7 (19.4%)	5 (17.85%)	0.19
In stent restenosis		3 (8.3%)		
Graft occlusion			5 (17.9%)	

BMS = bare metal stent; DES = drug eluting stent

Table II. Percutaneous coronary intervention (PCI) – type of stent

PCI	
BMS	DES
17 (47.2%)	19 (52.8%)

BMS = bare metal stent; DES = drug eluting stent

cardiac death and non fatal myocardial infarction. Cardiac death was defined as death due to acute myocardial infarction, congestive heart failure, life-threatening arrhythmias, or cardiac arrest; unexpected, otherwise-unexplained sudden death also was considered cardiac death. Myocardial infarction was defined as the appearance of new symptoms of myocardial ischemia or ischemic ECG changes accompanied by increases in markers of myocardial necrosis. Secondary end points were quality of life and persistent disabling angina (CCS class III–IV angina).

Statistical analysis

Categorical variables were compared by use of the chi-square test and continuous variables were compared by use of the ANOVA test. Estimates of the cumulative event rate were calculated by the Kaplan-Meier method. A level of significance of less than 0.05 was used for all subgroup analyses and interactions.

Results

Baseline Characteristics and Angiographic Data

Our study included a total of 98 patients. Of these, 34 patients received medical therapy alone, 36 underwent PCI and 28 underwent CABG. Clinical and angiographical characteristics of the patients are summarized in Table I.

In all groups the average age was about 60 years, and most patients were men (75%). A total of 48 patients (49%) had a prior myocardial infarction (mostly in the medical and PCI group), while just 8 patients (8%) had an ejection fraction below 40%. Among patients who underwent revascularization, most high-risk patients were in the CABG group, with 7.1% patients with ejection fraction < 40%, 25% with left main disease and 46.4% with three-vessel disease. Diabetes was equally represented in both groups (22.2 versus 25%). Drug-eluting stents were used in 52.8% of cases (Table II).

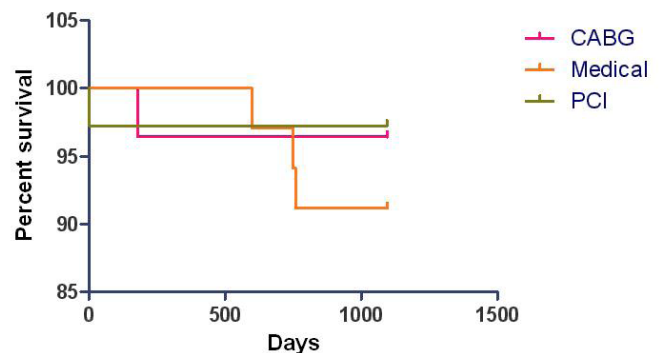


Fig. 1. Estimated 3-year cumulative primary event rates

Table IV. Primary outcomes stratified by clinical and angiographical characteristics

Characteristic	Medical	PCI	CABG
	Events – no (%)	Events – no (%)	Events – no (%)
FEVS			
>40%	3 (8.8)	1 (2.7%)	–
<40%	1 (25)	–	–
Vessels with disease, FE > 40%			
1 or 2	1 (5.55)	1 (3.7%)	–
3	3 (25%)	–	–
LM	–	–	1 (14.28)

Primary Outcome The primary outcome (a composite of cardiac death and nonfatal myocardial infarction) occurred in 1 patient in the PCI group, 2 patients in the CABG group, and 4 patients in the medical group (Table III). The estimated 3-year cumulative primary event rates were 2.8% in the PCI group, 3.6% in the CABG group and 11.8% in the medical-therapy group (Figure 1).

Secondary Outcomes At a median follow-up of 3 years, one fifth (19.4%), a quarter (25%), and a third (35.3%) of patients in the PCI group, CABG group, and medical group, respectively, presented CCS class III–IV angina angina (p = 0.31). Among patients with disabling angina who required repeat coronarography, in stent restenosis occurred in 12% of patients with BMS, and just 5% with DES, while graft occlusions occurred in 18% after CABG.

Subgroup Analyses Among patients with one or two-vessel disease, without significant ventricular dysfunction (FEVS > 40%), the primary outcome was 5.55% in the medical group and 3.7% in the PCI group (p = 0.74). Among high-risk criteria patients there was a major percentage of primary events (14% in the left main subgroup of the CABG group) (Table IV).

Discussions

Effects on survival

CABG offered no significant overall mortality benefits compared to medical therapy alone in trials from the 1970s [9–12]. However, survival was improved in selected patients with severe CAD. These included patients with left main coronary artery stenosis or left main equivalent disease, three vessel disease, particularly with a reduced ventricular ejection fraction (LVEF < 40 percent), and more than a 75 percent stenosis in the left anterior descending (LAD) artery proximal to the first major septal artery (Table V).

In our study, these high-risk patients in the medical group either did not have a coronary anatomy suitable for bypass grafting, or refused surgery. So, patients with three vessel disease or ventricular dysfunction (FEVS < 40%) treated only medically had a poor prognosis (primary outcome – 25%) (Table IV).

Patients with untreated left main and left main equivalent disease have worse outcomes with medical therapy

Table V. Summary of randomized trials of CABG versus medical therapy for stable angina: subgroup results at 5 years [12]

Subgroup	Mortality rate, percent		Odds ratio (95<W> CI)
	Surgical	Medical	
Number of diseased vessels			
1	5.4	9.9	0.18 (0.22-1.33)
2	9.7	11.7	0.84(0.54-1.32)
3	10.7	17.6	0.58 (0.42-0.80)
Left main artery	15.8	36.5	0.32 (0.15-0.70)
LAD disease	9.2	14.6	0.58 (0.34-1.01)
LV function			
Normal	8.5	13.3	0.61 (0.46-0.81)
Abnormal	16.5	25.2	0.59 (0.39-0.91)

LAD: left anterior descending coronary artery; LV: left ventricular. Data from Yusuf, S, Zucker, D, Peduzzi, P, et al, Lancet 1994; 344:563.

alone because of the large amount of myocardium at risk. Coronary artery bypass graft surgery (CABG) is the preferred approach for revascularization of a left main lesion, particularly if unprotected (absence of patent bypass graft in the left anterior descending or circumflex artery). In our study patients with left main disease rather underwent CABG, with a primary outcome of 14.28%. This finding is comparable with that obtained in other study [12] (Table V). There were too few patients in our PCI and medical groups in order to make comparisons between groups. However, the survival advantage of CABG versus medical therapy declines over time [9]. The CASS registry demonstrated similar results [10,11].

This is a preliminary report of our study, and could not be processed all the data. Subsequently we will analyze the primary outcomes of patients with left main disease treated surgically versus drug eluting stent implantation. The evidence from randomized trials supporting either CABG or PCI in patients with left main disease is limited. In the recent studies, the rate of survival and MACE were comparable in both groups [13,14, 15].

The COURAGE trial randomly assigned patients with stable coronary heart disease to either aggressive medical therapy alone or aggressive medical therapy plus PCI with bare metal stenting [7]. At a median follow-up of 4.6 years there was no significant difference between the two treatment strategies for the primary end point of death from any cause and non-fatal MI (19.0% in the PCI group and 18.5% in the medical-therapy group (P=0.62). At three years, we found a small difference between the two groups in patients with one or two vessel disease and preserved ventricular function – primary outcome 5.55 versus 3.7, in favor of PCI (p = 0.74). In the Courage trial, drug-eluting stents were used in only 15 percent, while in our study more than fifty percent of the patients could benefit from drug-eluting stents. On the other hand, patients with three vessel disease and preserved ventricular function had a poor prognostic, but our data were limited in this case.

The survival curve for the three groupes is represented in Figure 1.

Relief of angina.

Rates of angina were consistently lower in the PCI and CABG groups than in the medical-therapy group during follow-up (19.4 vs 17.85% vs 35.3%, $p = 0.19$). Most patients have an improvement in or complete relief of angina immediately after CABG. The Coronary Artery Surgery Study (CASS) performed in the late 1970s and early 1980s showed that more patients remained symptom-free after CABG compared to medical therapy at one year (66 versus 30 %) and five years (63 versus 38%) [16]. By 10 years, this difference had disappeared (47 versus 42%). Quality of life in general, and less angina in particular, was addressed in a separate report from COURAGE trial [17]. At three months, significantly more patients who received PCI were free of angina (53 versus 42%); however, there was no significant difference at 36 months (59 versus 56%). In our study, the difference was maintained at three years.

In the MASS-II trial [18], after one-year follow-up, 8.3% of medical treated patients and 13.3% of PCI patients underwent to additional interventions, compared with only 0.5% of CABG patients. In our study, just 1 patient (2.7%) in the PCI group required surgical revascularization.

Conclusions

All patients with coronary heart disease, including those stable angina, should be treated with aggressive risk factor reduction. For patients with stable angina that is not significantly interfering with the quality of life and without high-risk characteristics (ie, three vessel disease, left main or proximal LAD disease, FEVS < 40%) we suggest medical therapy rather than immediate revascularization.

Patients with high-risk criteria, regardless of anginal severity, require coronary angiography followed by revascularization. The procedure of choice depends on coronary anatomy and patient preference, but in many situations we encourage the interventional approach using drug-eluting stents. However, this is a preliminary report, and data processing for the first three years of study are in progress.

References

1. Moliterno, DJ, Elliott, JM. - Randomized trials of myocardial revascularization. *Curr Probl Cardiol* 1995; 20:125.

2. Fraker, TD Jr, Fihn, SD, Gibbons, RJ, et al. - 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *J Am Coll Cardiol* 2007; 50:2264.
3. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. - ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention -- summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;113:156-175.
4. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *Circulation* 2002; 106:3143.
5. Smith, SC Jr, Allen, J, Blair, SN, et al. - AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. *J Am Coll Cardiol* 2006; 47:2130.
6. Grundy, SM, Cleeman, JI, Merz, CN, et al. - Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110:227.
7. Boden, WE, O'Rourke, RA, Teo, KK, et al. - Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; 356:1503.
8. Loop, FD, Lytle, BW, Cosgrove, DM, et al. - Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med* 1986; 314:1
9. Kaiser, GC. - CABG: Lessons learned from the randomized trials. *Ann Thorac Surg* 1986; 42:3.
10. Murphy, ML, Hultgren, HN, Detre, K, et al. - Treatment of chronic stable angina: A preliminary report of survival data of the randomized Veterans Administration cooperative study. *N Engl J Med* 1977; 297:621.
11. Myocardial infarction and mortality in the coronary artery surgery study (CASS) randomized trial. *N Engl J Med* 1984; 310:750.
12. Yusuf, S, Zucker, D, Peduzzi, P, et al. - Effect of coronary artery bypass graft surgery on survival: Overview of 10-year results from randomized trials by the Coronary Artery Bypass Surgery Trialists Collaboration. *Lancet* 1994; 344:563.
13. Meliga, E, Garcia-Garcia, HM, Valgimigli, M, et al. - Longest available clinical outcomes after drug-eluting stent implantation for unprotected left main coronary artery disease: the DELFT (Drug Eluting stent for LeFT main) Registry. *J Am Coll Cardiol* 2008; 51:2212.
14. Serruys, PW, Morice, MC, Kappetein, AP, et al. - Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; 360:961.
15. Buszman, PE, Kiesz, SR, Bochenek, A, et al. - Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol* 2008; 51:538.
16. Rogers, WJ, Coggin, CJ, Gersh, BJ, et al. - Ten-year follow-up of quality of life in patients randomized to receive medical therapy or coronary artery bypass graft surgery: The Coronary Artery Surgical Study (CASS). *Circulation* 1990; 82:1647.
17. Weintraub, W, Spertus, J, Kolm, P, et al. - Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 2008; 358:677.
18. Hueb, W, Soares, PR, Gersh, BJ, et al. - The Medicine, Angioplasty, or Surgery Study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. *J Am Coll Cardiol* 2004; 43:1743.