Revascularization Therapy in Stable Coronary Artery Disease

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Introduction: In patients with stable coronary artery disease, there are controversial studies that compare the optimal medical therapy with revascularization therapy in reducing the risk of cardiovascular events.
Material and method: The study included 221 patients with stable coronary artery disease who underwent coronarography and had objective evidence of significant coronary disease. Of these, 73 underwent percutaneous coronary intervention, 71 underwent coronary artery bypass grafting, both subgroups with optimal medical therapy, and 77 received optimal medical therapy alone. Primary outcomes were cardiac death and non fatal myocardial infarction, during a follow-up period of 4.5 years. Secondary outcomes were persistent disabling angina (quality of life) and the need for repeat revascularization.
Results: There were 15 primary events in the medical-therapy group, 5 events in the surgical group and 5 events in the percutaneous coronary intervention group. In subgroups analysis, among patients with non-high risk criteria (one or two-vessel disease, without significant ventricular dysfunction), the primary outcome was 2.5% in the medical group and 1.78% in the PCI group, while the persistent disabling angina occurred in 22.5% in the medical group versus 12.50% in the interventional group versus 18.75% in the coronary artery bypass grafting group ($p = 0.42$). Among high-risk criteria patients there was a tendency for increased repeat target vessel revascularization in the interventional group vs surgical group (17.64% vs 5.45%). The primary outcome was similar in both groups (11.76% vs 9.09%).
Conclusion: For patients with stable angina that is not significantly interfering with the quality of life and without high-risk characteristics, medical therapy rather than immediate revascularization seems to be the right option. Patients with high-risk criteria benefit from a more complete revascularization by coronary artery bypass grafting, but most often the patient will prefer the interventional aproach.

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 percutaneous coronary intervention (PCI) to coronary artery bypass grafting (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 asses the value of these three different therapeutic approaches in patients with stable coronary artery disease.

Material and method

Patients

This study includes 221 patients with Canadian Cardiovascular Society (CCS) class II–IV stable angina and/or evidence of myocardial ischemia on the resting electrocardiogram (ECG) or during stress test. All patients underwent coronary arteriography at the Department of Interventional Cardiology of the Institute of Cardiovascular Disease and Transplantation, Târgu Mureş between January 1, 2006 and December 31, 2007. 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.

Table I. Baseline clinical and angiographic characteristics

Characteristic	Medical group (n=77)	PCI group (n=73)	CABG group (n=71)	p Value
Demographic				
Age (years)	62.17±9.18	59.51±8.78	60.83±7.66	
Sex – no. (%)				0.74
Male	61 (79.22)	54 (73.97)	54 (76.06)	
Female	16 (20.78)	19 (26.03)	17 (23.94)	
Clinical				
History – no. (%)				
Diabetes	15 (19.48)	17 (23.87)	16 (22.53)	0.83
MI	51 (66.23)	36 (49.31)	36 (50.70)	0.067
H	50 (64.93)	44 (60.27)	35 (49.29)	0.14
PAD	8 (10.39)	3 (4.11)	9 (12.67)	0.17
Echocardiographic				
FEVS <40%	13 (16.88)	8 (10.96)	9 (12.67)	0.55
Angiographic				
Vessels with disease				
1	26 (33.76)	35 (47.95)	2 (2.82)	
2	18 (23.37)	23 (31.50)	18 (25.35)	
3	26 (33.76)	7 (9.59)	31 (43.66)	
Left Main	5 (6.49)	2 (2.74)	18 (25.35)	
Proximal LAD	2 (2.63)	6 (8.22)	2 (2.81)	

†Plus-minus values are means±standard deviations. MI = myocardial infarction. H = hypertension. PAD = peripheral arterial disease. LAD = left anterior descending artery.

Patients were then divided in three groups, according to the therapeutic approach: CABG, PCI and medical therapy alone. High-risk patients were defined as those with left main coronary artery disease (at least 50% stenosis), three vessel disease, proximal left anterior descending artery disease and reduced ventricular ejection fraction below 40%. Follow-up period was about 4.5 years.

Treatment

All patients received optimal antiischemic therapy, including beta-blockers, calcium channel blockers, and nitrates, alone or in combination, along with angiotensin converting enzyme (ACE) inhibitors, as well as antiplatelet therapy with either aspirin or clopidogrel. Patients also received lipid-lowering therapy, including administration of a statin, and glycemic control in diabetics. Exercise was recommended to achieve further improvements in the lipid profile.

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 about a half 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 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), as well as the need for repeat revascularization. In our follow-up we concentrated on two subgroups: the non-high risk patients and the high risk patients.

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.

Table II. Risk distribution in groups

Risk	Medical events no (%)	PCI events no. (%)	CABG events no (%)	p Value
High-risk patients	37 (48.05)	17 (23.29)	55 (77.46)	p<0.0001
Non-high risk patients	40 (51.95)	56 (76.71)	16 (22.54)	

Table III. Percutaneous coronary intervention (PCI) - type of stent

	BMS	DES	P Value
	37 (50.68%)	36 (49.32%)	
Repeat revascularization	8 (21.62%)	4 (11.11)	0.34
Death and non-fatal myocardial infarction	3 (8.10%)	2 (5.5%)	–

BMS = bare metal stent; DES = drug eluting stent

Results

Baseline Characteristics and Angiographic Data

Our study included a total of 221 patients. Of these, 77 patients received medical therapy alone, 73 underwent PCI and 71 underwent CABG. Clinical and angiographical characteristics of the patients are summarized in Table I.

The average age was about 60 years, and most patients were men (75%). High-risk patients have prevailed in the surgical group, while the most non-high risk patients were in the interventional group (Table II).

There were 20 patients with left main disease in these two groups, of which 2 underwent PCI with DES and actually are free of symptoms. The other 18 underwent CABG and 15 have survived with excellent quality of life. Diabetes and prior myocardial infarction was equally represented in both groups. Drug-eluting stents were used in about 50% of cases when PCI was performed (Table III).

Table IV. Primary and secondary outcomes

Outcome	Medical events no (%)	PCI events no. (%)	CABG events no (%)	p Value
Primary outcomes				
Cardiac death	9 (11.68)	3 (4.11)	5 (7.04)	0.21
Non-fatal myocardial infarction	6 (7.79)	2 (2.74)	-	-
Cardiac death & non-fatal myocardial infarction	15 (19.48)	5 (6.85)	5 (7.04)	0.02
Secondary outcomes				
Disabling angina	25 (32.47)	10 (13.69)	10 (14.08)	0.005
In stent restenosis	–	12 (16.44)	–	–
Repeat revascularization	–	16 (21.92)	6 (8.45)	0.0247

Primary Outcome

The primary outcome (a composite of cardiac death and nonfatal myocardial infarction) occurred in 5 patients in the PCI group, 5 patients in the CABG group, and 15 patients in the medical group (p=0.02) (Table IV). The estimated 4-year survival curves in the high-risk patients for the 3 groups are depicted in Figure 1 (p=0.23).

Secondary Outcomes

At a median follow-up of 4.5 years, about 86% of patients who underwent revascularization (CABG or PCI) were free of disabling angina, while about a third (32.47%) of patients in the medical group presented CCS class III-IV angina (p=0.005) (Table IV). Among patients who required repeat coronarography, in stent restenosis ocurred in 8% of patients with BMS, and just 4% with DES. Repeat revascularization was required in both groups, but the difference is statistically significant in favor of CABG (8.45% vs 21.92%, p=0.02) (Table IV).

Subgroup Analyses

Among patients with non-high risk criteria (one or two-vessel disease, without significant ventricular dysfunction – FEVS >40%), the primary outcome was 2.5% in the medical group and 1.78% in the PCI group. There were no primary events in the CABG group. Persistent disabling angina occurred in 22.5% in the medical group versus 12.50% in the PCI group and 18.75% in the CABG group (p=0.42) (Table V). There was no statistically difference for repeat revascularization between the two methods of revascularization.

Table V. Primary and secondary outcomes in non-high risk patients

Characteristic	Medical (40)	PCI (56)	CABG (16)	p Value
1 or 2 vessels with disease, FE > 40%	events no. (%)	events no. (%)	events no. (%)	
Primary outcomes				
Cardiac death	1 (2.5)	1 (1.78)	0	
Non-fatal myocardial infarction	0	0	0	
Cardiac death & non-fatal myocardial infarction	1 (2.5)	1 (1.78)	0	–
Secondary outcomes				
Persistent disabling angina	9 (22.5)	7 (12.50)	3 (18.75)	0.42
Repeat revascularization	–	13 (23.21)	3 (18.75)	–

Among high-risk criteria patients there was a statistically significant difference between the three groups (p=0.002). Relief of severe angina and repeat revascularization were also in favor in CABG (Table VI).

Table VI. Primary and secondary outcomes in high risk patients

Characteristic	Medical (37)	PCI (17)	CABG (55)	p Value
1 or 2 vessels with disease, FE > 40%	events no. (%)	events no. (%)	events no. (%)	
Primary outcomes				
Cardiac death	8 (21.62)	2 (11.76)	5 (9.09)	
Non-fatal myocardial infarction	6 (16.22)	0	0	
Cardiac death and non-fatal myocardial infarction	14 (37.84)	2 (11.76)	5 (9.09)	0.002
Cardiac death – LM			3 (16.66)	
Secondary outcomes				
Persistent disabling angina	16 (43.24)	4 (23.53)	7 (12.72)	0.04
Repeat revascularization	–	3 (17.64)	3 (5.45)	–

Discussions

Effects on survival

Among non-high risk patients, CABG offered no significant overall mortality benefits compared to medical therapy alone in trials from the 1970s [9–12]. Also, most studies reported no mortality benefit with PCI [13,14]. The COURAGE trial, at a median follow-up of 4.6 years, found no significant difference between the medical and PCI treatment for the primary end point of death from any cause and non-fatal MI (19.0% in the PCI group and

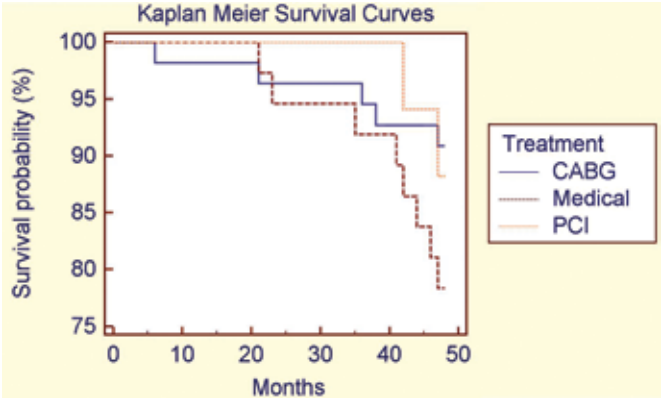

Fig. 1. Kaplan-Meier survival curves

18.5% in the medical-therapy group (p=0.62) [7]. At 4.5 years, we found a difference between the two groups – primary outcome 2.5% versus 1.78, in favor of PCI, but our data are limited in this case.

The high-risk patients in the medical group either did not have a coronary anatomy suitable for bypass grafting, or refused surgery. So, patients with extensive vessel disease or ventricular dysfunction (FEVS <40%) treated only medically had a poor prognosis (primary outcome – 37.84%) (Table VI).

Patients with untreated left main and left main equivalent disease have worse outcomes with medical therapy alone because of the large amount of myocardium at risk. Coronary artery bypass graft surgery (CABG) was 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). However, the survival advantage of CABG versus medical therapy declines over time [9]. The CASS registry demonstrated similar results [10,11]. In our study patients with left main disease rather underwent CABG, with a primary outcome of 16.66% (Table VI). This finding is comparable with that obtained in other study (15.8%) [12]. In the PCI group we had just 17 high-risk patients in order to make comparisons between groups (11.76% primary events for PCI group). There were just 2 patients with left main disease who underwent PCI with DES and they survived symptoms-free. 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 was comparable in both groups [15,16,17]. In adittion, the MAIN-COMPARE study, o five year follow up registry, brings support for PCI aproach of left main lesion [18].

The survival curve for the three groups 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 (13.69 vs. 14.08% vs. 32.47%, p=0.05) (Table IV). 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 and five years [19]. By 10 years, this difference had disappeared. Quality of life was addressed in a separate report from COURAGE trial [20]. There was no significant difference at 36 months. This trial excluded patients with high risk. In our study, in non-high risk subgroup, the difference between these two groups at 4.5 years is no statistically significant (p=0.27).

Repeat revascularization

In the MASS-II trial [21], 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, the need for repeat revascularization was significantly higher for patients in the PCI group (21.92% vs 8.45%, p = 0.02) (Table IV).

The need for repeat target vessel revascularization was reduced with DES over BMS (11.11% vs 21.62%, p=0.34) (Table III). Other studies have reached statistical significance [22].

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, medical therapy rather than immediate revascularization seems to be the right option. Patients with high-risk criteria benefit from a more complete revascularization by coronary artery bypass grafting, but the most often the patient will prefer the interventional aproach.

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