Outcomes in High-risk Patients with Stable Coronary Artery Disease: Four-year Follow-up

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Introduction: In the past decades there were many studies that compared different therapeutic approaches in stable coronary artery disease. Since then major pharmacological and technical advances occurred on the management of stable angina. It is only in recent years that these advances were widely used. Given the above, the objective of our study was to evaluate the clinical outcome of high-risk patients with stable angina pectoris who received modern treatment — medical therapy, percutaneous revascularization or surgical revascularization.
Material and method: Study included 115 patients with stable coronary disease and high-risk criteria for major adverse cardiac events (MACEs) – left main or proximal left anterior descending artery stenosis > 50%, 2 or 3-vessel disease with impaired left ventricular function. Of these, 39 underwent percutaneous coronary intervention (PCI), 44 underwent coronary artery bypass grafting (CABG), both subgroups with optimal medical treatment (MT), and 32 received optimal MT alone. Primary outcomes were cardiac death and non-fatal myocardial infarction, and secondary outcomes were persistent disabling angina (quality of life) and the need for repeated revascularization. The follow-up period was 4 years.
Results: The primary outcome was 25.00% in the MT group, 5.12% in the PCI group and 4.54% in the CABG group (p=0.006). There was no statistically significant difference in primary events between PCI and CABG group (p=1.00), but the primary events were significantly higher in the MT group vs CABG group (p=0.014) and versus PCI group (p=0.03). Angina persists in 50.00% of patients in MT group versus 20.51% in the PCI group (p=0.01) and 9.09% in the CABG group (p=0.0001). There is no difference between the last two groups (p=0.21). In addition we found a tendency for increased repeated target vessel revascularization in the interventional group (15.38%) versus surgical group (2.27%) (p= 0.04). Drug eluting stents were used in 56.41% of cases.
Conclusions: All patients with stable coronary disease should receive modern medical treatment and aggressive risk factor reduction. Early coronarography represents an important step in risk stratification of these patients. Patients with extensive coronary disease, especially associated with impaired left ventricular function, or left main disease, benefit from CABG. Patients with less severe coronary disease may experience relief of symptoms after PCI, but repeated revascularization is often required.

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

Introduction

The prevalence of angina (according to Rose angina questionnaire) increases from <1% in women, respectively 2–5% in men aged 45–54, to 10–15% in women, respectively 10–20% in men aged 65–74 [1,2,3]. Untreated coronary heart disease results in progressive angina, myocardial infarction (MI), left ventricular dysfunction, and death. Therefore, the treatment of stable angina has two major purposes: to prevent MI and death (improvement in survival); to alleviate the symptoms of angina (improvement in quality of life). Before treatment, every patient with angina requires risk stratification using clinical evaluation, stress testing, and echocardiography. Then patients with high-risk at non-invasive tests require coronary arteriography. According to current guidelines [4], certain categories of patients require myocardial revascularization to improve prognosis: those with left main (LM) stenosis >50%, proximal left anterior descending artery (pLAD) stenosis >50%, 2 or 3-vessel disease with impaired left ventricular (LV) function, proven large area of ischemia (>10% left ventricul), or single remaining pattent vessel >50% stenosis.

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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 these results to current clinical practice: no widespread use of modern medical treatment (MT) and intensive risk factor modification; no long term use of dual antiplatelet therapy after stenting; saphenous vein graft use was prevalent to internal mammary in surgical revascularizations. In our study, all patients received modern MT 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 and high-risk for cardiovascular events.

Material and method

Patients

This study included 115 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 un-

derwent coronary arteriography at the Department of Interventional Cardiology of the Institute of Cardiovascular Disease and Transplantation, Tîrgu Mureş between January 1, 2006 and March 31, 2008. Demographic, clinical and echocardiographical data, as well as coronarography results, were entered in our database at the time of the procedures and at subsequent admissions.

The inclusion criteria were: LM stenosis >50%, pLAD stenosis >50%, 2 or 3-vessel disease with left ventricular ejection fraction (LVEF) ≤45% and objective evidence of myocardial ischemia (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 LVEF <30% and severe comorbidities that affect survival.

Patients were divided into three groups, according to the therapeutic approach: surgical (CABG), interventional (PCI) and medical therapy (MT) alone. Of these, 39 underwent PCI, 44 underwent CABG, both subgroups with modern MT, and 32 received MT alone.

Treatment

All patients received optimal antiischemic therapy, including beta-blockers, calcium channel blockers, and nitrates, alone or in combination, along with angiotensin converting enzyme inhibitors (ACEI), 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. Target level of low-density lipoprotein (LDL) was 100mg/dl and was achieved in about one third of cases in each group. Physical exercise was recommended to achieve further improvements in the serum lipid profile. Percutaneous coronary revascularization was followed by dual antiplatelet therapy for a minimum of nine month. 41% of patients use them both indefinitely and the rest use aspirin alone indefinitely. 56.4% of patients received drug eluting stents. CABG has been the preferred approach in patients with left main coronary disease and diffuse three-vessel coronary disease, particularly in patients with diabetes. The internal mammary artery was used to bypass the LM and LAD.

Follow-up and end points

Follow-up period was 4 years. Data were obtained by review of hospital databasis, subsequent admissions, ambulatory evaluations, 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 was also 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 the quality of life and persistent disabling angina (CCS class III–IV angina), as well as the need for repeated revascularization.

Statistical analysis

Categorical variables were compared by use of the chi-square test and continuous variables were compared by use of the ANOVA test. A level of significance of less than 0.05 was used for all subgroup analyses and interactions.

Results

Baseline characteristics and angiographic data

Clinical, echocardiographic and angiographical characteristics of the patients are summarized in Table I.

The average age was about 60 years, and most patients were men (>80%). The widespread of comorbidities (diabetes, periferal artery disease, and stroke) was similar in the three groups, with a lower incidence of hypertension in the CABG group. Most patients with left ventricular dysfunction belong to medical group (50%), while just about a third of patients treated invasivelly had impaired left ventricular function. Patients treated with MT alone either had a coronary anatomy unsuitable for revascularization, or refused surgery. Of these, 19% had 3-vessel disease, 19% had LM disease, and 37% had pLAD disease. In PCI group, most of patients had pLAD disease (77%), and just 5% had 3-vessel disease respectively LM disease. In CABG group, 48% had LM disease and 40% had pLAD disease (Table I).

Table I. Baseline Clinical and Angiographic Characteristics†

Characteristic	Medical Group (N=32)	PCI Group (N=39)	CABG Group (N=44)	P Value
Demographic				
Age – years	64.09±10.59	59.77±8.47	60.05±8.09	
Sex – no. (%)				0.09
Male	27 (84.37)	32 (82.05)	37 (84.09)	
Female	5 (15.62)	7 (17.95)	7 (15.91)	
Clinical				
History – no. (%)				
Diabetes	3 (9.37)	8 (20.51)	9 (20.45)	0.37
MI	22 (68.75)	21 (53.85)	23 (52.27)	0.31
H	22 (68.75)	24 (61.54)	16 (36.36)	0.01
PAD	3 (9.37)	2 (5.13)	8 (18.18)	0.10
Stroke	2 (6.25)	1 (2.56)	2 (4.54)	0.75
Echocardiographic				
FEVS <45%	17 (53.12)	12 (30.77)	12 (27.27)	0.04
Angiographic				
Vessels with disease				
2*	8 (25.00)	5 (12.82)	0	
3*	6 (18.75)	2 (5.13)	5 (11.36)	
LM	6 (18.75)	2 (5.13)	21 (47.72)	
pLAD – 1 vessel	3 (9.37)	18 (46.15)	3 (6.81)	
pLAD – 2 vessels	2 (6.25)	8 (20.51)	8 (18.18)	
pLAD – 3 vessels	7 (21.87)	4 (10.26)	7 (15.91)	

†Plus-minus values are means ±standard deviations. MI = myocardial infarction. H = hypertension. PAD = peripheral arterial disease. LM = left main disease. pLAD = proximal left anterior descending artery. * No LM, no pLAD disease.

Table II. Primary and secondary outcomes (4 years follow-up)

Outcome	Events – no. (%)			P Value
	Medical Group (N=32)	PCI Group (N=39)	CABG Group (N=44)	
Primary outcomes				
Cardiac death	5 (15.63)	1 (2.56)	2 (4.54)	0.07
Nonfatal MI	3 (9.38)	1 (2.56)	0	–
Cardiac death & nonfatal MI	8 (25.00)	2 (5.12)	2 (4.54)	0.0065
Secondary outcomes				
Disabling angina	16 (50.00)	8 (20.51)	4 (9.09)	0.0002
Repeat revascularization	-	6 (15.38)	1 (2.27)	0.04

MI = myocardial infarction

Table III. Left main disease – Primary and Secondary Outcomes (4 years follow-up)

Outcome	Events – no. (%)			P Value
	Medical Group (N=32)	PCI Group (N=39)	CABG Group (N=44)	
Primary outcomes				
Cardiac death	1 (16.66)	0	2 (9.52)	–
Nonfatal MI	0	0	0	–
Cardiac death & nonfatal MI	1 (16.66)	0	2 (9.52)	0.54
Secondary outcomes				
Disabling angina	1 (16.66)	1 (50)	0	–
Repeat revascularization	-	1 (50)	0	–

MI = myocardial infarction

Primary Outcome

There was not a statistically significant difference between the three groups regarding cardiac death (p=0.07), however we found a trend of increased mortality in the medical group (15.63% MT, 2.56% PCI, 4.54 CABG). The primary outcome (a composite of cardiac death and nonfatal myocardial infarction) occurred in 25% of patients in the medical group, 5.12% of patients in the PCI group, and 4.54% in the CABG group (p=0.006) (Table II). There was no difference between the two methods of revascularization (p=1.00), while primary event rate was significantly increased in the medical group (25%, p=0.006).

Secondary outcomes

Repeated revascularization was required in both groups, but the difference is statistically significant in favor of CABG (2.27% vs 15.38%, p = 0.04) (Table II). In the PCI group 50% of patients who required revascularization received drug eluting stents.

At a median follow-up of 4 years, about 9% of patients in the CABG group, 20% in the PCI group and 50% in the medical group had disabling angina. There was no statistically significant difference between the PCI and CABG group (p=0.21). Conservatively treated patients had high rates of disabling angina versus PCI (p=0.01) and versus CABG (p=0.0001) (Table II).

Left main disease. Of the 6 patients with LM disease in the medical group, there was one death, while the remaining 5 survived free of myocardial infarction and with only mild symptoms. The 2 patients with LM in the PCI group survived both, but one developed disabling angina and required surgical revascularization. Most patients with LM disease (21) were in the CABG group. Of these, after 4 years of follow-up, 19 survived free of myocardial infarction and disabling symptoms, and 2 died (Table III).

Table IV. Summary of recommendations on myocardial revascularization

Subset of CAD by anatomy	Favours CABG	Favours PCI
Left main > 50%	I A	II a B – isolated or 1VD, ostium/ shaft
Any proximal LAD > 50%	I A	II a B – 1VD or 2VD
2VD or 3VD with impaired LV function	I B	II a B – simple lesions, full functional revascularization achievable with PCI

CAD = coronary artery disease; VD = vessel disease; LV = left ventricle

Discussions

Current European [4] and American [5] guidelines stress that there is a category of patients who benefit in terms of prognosis (cardiac death, nonfatal myocardial infarction) from myocardial revascularization. The highest recommendation goes to surgical revascularization, but sometimes PCI is an option too. We summarized these recommendations in Table IV. In our study we selected these very patients to assess their outcome depending on chosen therapy.

Among the most important contemporary studies that address this topic are SYNTAX, MASS II, and BARI 2D. Earlier studies did not benefit from modern treatment strategies, therefore are not mentioned here.

SYNTAX trial [6] enrolled 1800 patients with 3-vessel disease and/or LM disease, randomly assigned for surgical revascularization or drug eluting stenting (DES). Patients amenable for only one treatment approach formed PCI and CABG registries. Last reports (september 2010) are from a 3-years follow-up. CABG offered no significant overall mortality benefits compared to the PCI group in the randomized arm (6.7% vs 8.6%, p=0.13). Also, the incidence of death/nonfatal MI and stroke was similar in the two groups (14.1 vs 12.0, p=0.21). The need for repeated revascularization was significantly higher for patients in the PCI group (19.7% vs 10.7%, p<0.001) (Table V).

MASS II [7] was a single-center study (Brazil) where 611 patients were randomly assigned to CABG, PCI or medical treatment alone. This study included a ten years

Table V. SYNTAX Trial — major adverse cardiac events (3 years follow-up)

	PCI (DES)	CABG	P value
Overall mortality	6.7	8.6	0.13
Death/Nonfatal MI/Stroke	14.1	12.0	0.21
Repeat revascularization	19.7	10.7	<0.001

Values are percentages. DES = drug eluting stent. MI = myocardial infarction.

Table VI. MASS II Study - major adverse cardiac events (10 years follow-up)

	Medical	PCI	CABG	P value
Overall mortality	31.0	24.1	25.1	0.089
Cardiac death	20.7	14.3	10.8	0.019
Nonfatal MI	20.7	13.3	10.3	0.010
Repeat revascularization	39.4	41.9	7.4	0.001
Stroke	6.9	5.4	8.4	0.550

Values are percentages. MI = myocardial infarction.

follow-up (till august 2010) of patients with multivessel disease and preserved ventricular function (>40%). Findings are shown in Table VI. The 10-year cardiac death rates were 20.7% with medical therapy alone, 14.3% with PCI, and 10.8% with CABG (p=0.019). There was no statistically significant difference between PCI vs CABG (p=0.37) and PCI vs MT (p=0.09), but there was a higher mortality in the medical versus surgical group (p=0.009). Strangely, overall mortality (MT 31%, PCI 24.1%, and CABG 25.1%, p=0.089) did not differ significantly between the three groups, so there were more non cardiac death in the PCI/CABG subsets (procedure related?). In terms of nonfatal MI, CABG and PCI were significantly superior to MT (10.3% vs 20.7%, p=0.006, and 13.3% vs 20.7%, p=0.04). Additional revascularization procedures were frequent in the PCI group (41.9% PCI vs 7.4% CABG, p<0.0001). Unfortunately only a fraction of patients received treatment with statins and a target level of LDL was not pursued.

BARI 2D trial [8] randomly assigned 2368 patients with type 2 diabetes and stable coronary disease. First group, including patients with extensive coronary disease, underwent CABG with intensive MT or intensive MT alone, and second group underwent PCI with MT vs MT alone (two-by-two factorial design). Patients were excluded if they had LM disease and few patients had impaired LV function (LVEF<50%). The 5-years results are summarized in Table V. All patients received intensive medical therapy in accordance with clinical guidelines, and most patients had met treatment goals for levels of LDL cholesterol. There were no differencies in mortality between MT and PCI (11.9% vs 12.8%, p=0.48) or between MT and CABG (16.9% vs 14.0%, p=0.33). Patients in CABG group benefited from a lower rate of nonfatal myocardial infarction compared to MT group (14.6% vs 7.4%, p=0.0017). There was no such difference between MT and PCI groups (10.2% vs 11.3%, p=0.52). Stroke rate was similar in all groups.

In our study, patients with left main disease and those with pLAD and 3-vessel disease were treated mainly with CABG, and only a small percentage with PCI. PCI was the approach chosen for patients with pLAD and 1 or 2-vessel disease. Therefore, mortality and myocardial infarction rates were very similar (p~1.00). The medical group included the most severely ill patients – 53% with impaired ventricular function, 19% with LM disease, ~40% with

Table VII. MASS II Study - major adverse cardiac events (10 years follow-up)

	Medical (807)	PCI (798)	P value	Medical (385)	CABG (378)	P value
Mortality	11.9	12.8	0.48	16.9	14.0	0.33
Nonfatal MI	10.2	11.3	0.52	14.6	7.4	0.0017
Stroke	2.9	2.9	1.00	2.6	1.9	0.62

Values are percentages. MI = myocardial infarction.

3-vessel disease – which justify the higher rates of major adverse events, comparable to those in BARI 2D trial (second group).

These findings suggest that high-risk patients with severe coronary disease, especially if they associate impaired left ventricular function, benefit in terms of prognostic (less nonfatal MI) from surgical approach. There is a controversial debate if PCI can stand out in this regard, particularly against an optimal medical treatment. In addition percutaneous revascularization is encumbered with the need for repeated revascularization or higher rates of disabling angina compared with CABG. Drug eluting stents have not been shown to reduce rates of death or major cardiovascular events comparative to bare metal stents [9]. However, in simple coronary lesions, PCI can aleviatte symptoms with the convenience of reduced perioperative stress.

Further studies are needed to clarify these issues.

Conclusions

In summary, current data suggest that patients with stable coronary disease should be treated with modern medical treatment and aggressive risk factor reduction. Early routine cardiac catheterization is controversial, but represents an important step in risk stratification of these patients. However, patients with extensive coronary disease, especially associated with impaired left ventricular function, benefit from CABG. Patients with less severe coronary disease may experience relief of symptoms after PCI, but repeated revascularization is often required.

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.

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