Outcomes of patients with left main coronary artery disease undergoing medical or surgical treatment: a propensity-matched analysis

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Objective **To evaluate the outcomes of patients with significant (≥ 50%) left main coronary artery disease (LMCAD) undergoing medical treatment (MT) or coronary artery bypass grafting surgery (CABG).**

Methods **A total of 181 patients with significant LMCAD were followed for 4 ± 2 years. MT was done when patients refused CABG or because of either thin native vessels or high clinical risk. Events were defined as all-cause death, myocardial infarction, percutaneous coronary intervention, or subsequent CABG. Logistic regression analysis was used to identify independent predictors of death. A propensity score was created to compare outcomes of patients from the two treatment groups.**

Results **CABG was performed in 78.5% of the patients. Overall, there were no significant differences in the incidences of death or other events between treatment groups. In patients with normal left ventricular (LV) function (ejection fraction, ≥ 45%), there were no significant differences in event rates with MT or CABG (death, 7.7 vs. 12.1%; myocardial infarction, 0 vs. 1.9%; percutaneous coronary intervention, 3.8 vs. 5.6%). For patients with LV dysfunction, death was more frequent with MT than with CABG (53.8 vs. 22.9%, $P < 0.001$), whereas the incidence of other events was not statistically different. Age and LV dysfunction, but not treatment type, were independent predictors of death. When comparing propensity-matched patients from both treatment groups, there was also no difference in survival.**

Conclusion **Patients with 50% or more LMCAD and LV dysfunction had increased survival with CABG. However, outcomes of patients with 50% or more LMCAD and normal LV function were not significantly different with either MT or CABG.** *Coron Artery Dis* **22:585–589 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Left main coronary artery disease (LMCAD) has traditionally been a straightforward indication for coronary artery bypass grafting surgery (CABG), independent of the presence of symptoms, and it is currently considered as a class I indication for CABG, as stated in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for stable angina, the ACC/AHA guidelines for CABG, the guidelines of the European Society of Cardiology, and the European Association for Cardiothoracic Surgery, supported by appropriateness criteria of the ACC Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, AHA, and the American Society of Nuclear Cardiology [1–4]. Nonetheless, the scientific evidence behind those guidelines result from old, nonrandomized trials with small numbers of patients with LMCAD and suboptimal pharmacologic interventions according to current standards (e.g. statins were not available and β-blockers and aspirin were not used as largely as today) [5,6]. In addition, a number of trials have been recently published comparing the benefits of optimal medical treatment (MT) with revascularization, either surgical or percutaneous, in the setting of multivessel coronary artery disease (CAD), and have concluded that optimized medical therapy is at least comparable with revascularization in terms of event-free survival [7,8]. Finally, although guidelines provide a general assessment of when revascularization may or may not be likely to improve health outcomes or survival, they are not substitutes for sound clinical judgement, as many patients seen in clinical practice my not be represented in trials.

There is inherent difficulty in the design of a randomized study of patients with significant LMCAD, once the surgical indication is straightforward according to current standards of care. Therefore, we decided to undertake a retrospective analysis of patients with LMCAD from a tertiary care, specialized hospital, who underwent CABG or not (for specific medical reasons or due to patients'

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refusal), assuming that patients treated medically received the best MT possible, compatible with current recommendations (optimized doses of β-blockers and statins, as well as antiplatelet therapy), compared with conventional on-pump CABG. We hypothesized that this real-world setting might be useful to understand the true benefits of CABG for this subset of patients and may serve as hypothesis generating for further randomized trials.

Methods

This was a retrospective study of patients with 50% or more LMCAD treated at the National Institute of Cardiology in Rio de Janeiro, Brazil. All results of diagnostic coronary angiographic studies performed between January 2001 and December 2005 were screened and patients aged 18 years or more with 50% or more LMCAD ($\geq$ 50% luminal narrowing, by visual assessment, measured in the worst-view angiographic projection) were considered eligible, regardless of the presence of other coronary artery lesions. Exclusion criteria were a history of CABG, significant valve disease or prior valve surgery, cardiomyopathies of any other etiology than ischemic or any significant medical condition that could affect prognosis. Patients were also excluded if they had combined surgical procedures (e.g. ventricular reconstruction or valve surgery and CABG) as the initial treatment. A search for the type of treatment each patient underwent after the index catheterization was performed in patients' medical records.

Therapeutic strategy

At our institution, according to current guidelines, all patients with LMCAD are considered for CABG. However, the patient's preference is also taken into account and integrated with an estimation of surgical risk, and therefore, different therapeutic options, such as MT or percutaneous coronary intervention (PCI), may be indicated in individual cases. Therefore, in this study, CABG might not have been used due to physician's decision (either because of native vessels considered unsuitable for CABG or operative risk considered excessive) or when patients refused CABG.

All patients included in the study were treated at the hospital's outpatient clinic. MT was performed according to current standards of care [1] [with β-blockers or calcium channel blockers with negative chronotropic effects, in patients with asthma/chronic obstructive pulmonary disease, both aiming at a resting heart rate of 60 bpm; antiplatelet agents, either alone or in combination (aspirin and clopidogrel); statins, with standard goals of low-density lipoprotein-cholesterol and high-density lipoprotein-cholesterol; and nitrates for the control of anginal symptoms]. PCI used bare-metal stents, as drug-eluting stents are not available at our institution. CABG was performed on-pump, with at least one arterial conduit, and was completely anatomically driven (for coronary lesions $\geq$ 50%) whenever possible. The left internal thoracic artery was anastomosed to the left anterior descending coronary artery in all patients included in the study.

Left ventricular dysfunction was defined as left ventricular (LV) ejection fraction of less than 45% (measured by two-dimensional echocardiogram). Chronic renal failure was considered present if a patient had glomerular filtration rate of less than15 ml/min or underwent chronic dialysis of any type.

Follow-up

Data with regard to vital status, current symptoms, and the occurrence of events were obtained from the hospital's records, if a patient had any outpatient visit to the hospital-out admission in the previous 30 days, or if not, by phone with a standard questionnaire. In the latter case, if any event was reported, confirmation was obtained by review of the appropriate diagnostic tests (echocardiogram, cardiac enzymes, imaging tests) or procedure reports (in the case of PCI or CABG), copies of medical records or death certificate.

The primary endpoint was the occurrence of all-cause death during follow-up. The incidence of other cardiovascular events [nonfatal acute myocardial infarction (AMI), cerebrovascular accident (CVA), PCI, or subsequent CABG] was also registered. Categorical variables were compared using the χ^2-test and continuous variables by Student's *t*-test. Independent predictors of the primary endpoint were identified with multivariable logistic regression analysis. As the study was nonrandomized, a propensity score was created with variables frequently used by the clinician when deciding the best treatment for each patient (age, sex, body mass index, serum creatinine, presence of diabetes mellitus, presence and severity of angina, concomitant carotid artery disease, and LV ejection fraction) to balance patient characteristics and to generate propensity-matched Kaplan–Meier survival curves for the two treatment groups. The propensity score was developed using the MatchIt software, version 2.4–16 [9]. All analyses were performed using R statistical package, version 2.12.1 [10]. A *P* value of less than 0.05 was considered statistically significant.

Results

One hundred and eighty-one patients were included in this study. Of those, 22% underwent MT and 78% had CABG; none had PCI as a first choice of treatment. Baseline unadjusted characteristics of patients undergoing MT or CABG are shown in Table 1. The mean age, the proportion of women, and the prevalence of LV dysfunction were not significantly different between groups. Statistically significant differences were found in the subgroup of patients with Canadian Cardiovascular Society IV angina, all of whom underwent CABG, and in the presence of chronic renal failure, which was more frequent in patients under MT. Of note, LV dysfunction

Table 1 Baseline characteristics

	Medical treatment ($n=39$)	CABG ($n=142$)
Age (years)	65.6 ± 10.7	62.3 ± 9.8
Men	26 (66.7)	100 (70.4)
Diabetes mellitus	16 (41.0)	48 (33.8)
Hypertension	32 (82.1)	117 (83.0)
Hypercholesterolemia	19 (48.7)	94 (66.2)
Smoking	10 (26.3)	55 (38.7)
Clinical presentation		
Asymptomatic	1 (2.6)	3 (2.1)
Stable angina CCS I-III	20 (51.3)	71 (50.0)
Stable angina CCS IV	0	5 (3.6)*
Unstable angina	9 (23.1)	43 (30.7)
Acute MI	7 (17.9)	16 (11.4)
CHF	2 (5.1)	2 (1.4)
Triple-vessel CAD	17 (44.7)	64 (45.4)
Ejection fraction	52.6 ± 17.9	57.2 ± 14.6
Left ventricular dysfunction	13 (33.3)	35 (24.6)
Chronic renal failure	10 (25.6)	11 (7.7)*
Peripheral artery disease	5 (12.8)	12 (8.5)
Carotid artery disease	2 (5.1)	15 (10.6)
Prior MI	16 (41.0)	63 (44.7)

Values are expressed as *n* (%) or mean ± SD.
CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; MI, myocardial infarction; SD, standard deviation.
*$P<0.05$

was frequently found in both groups (33.3 vs. 24.6%, respectively), yet none of the patients received implantable defibrillators, which otherwise might have influenced their prognosis.

With regard to instituted therapies, 100% of the patients undergoing MT took a combination of a β-blocker, a nitrate, aspirin, and a statin. Those who underwent CABG received a mean of 2.8 grafts; 97.5% received two or more grafts, and 65% received three or more grafts. Postoperatively, 93.8% took a β-blocker, 62.5% took nitrates, 100% used aspirin, and 87.5% used statins (P = not significant for all comparisons of frequencies of drug used by patients undergoing MT or who had CABG).

Patients were followed for 4 ± 2 years. During follow-up, over 50% of patients in both groups were asymptomatic, in contrast to pretreatment status, when slightly more than 2% reported no symptom. In addition, there was a large decrease in the prevalence of stable angina with both types of treatment. There were no significant differences in the incidences of either death or other cardiac events between treatment groups (Table 2). Interestingly, although no significant difference in the occurrence of AMI and CVA was found between patients who underwent MT or CABG, these events were only found among the latter.

When stratified according to LV function (Table 3), patients with normal LV function did not have any significant differences in event rates when undergoing MT or CABG (death, 7.7 vs. 12%; myocardial infarction, 0 vs. 2%; PCI, 3.8 vs. 5.6%). For those with LV dysfunction, death was more frequent in patients undergoing MT than in those who had CABG (53.8 vs. 22.9%, $P < 0.001$), whereas the incidence of other events was not significantly different. No subsequent CABG occurred in either group.

Table 2 Clinical status and cardiac events during follow-up in patients undergoing medical treatment or coronary artery bypass grafting

	Medical treatment ($n=39$)	CABG ($n=142$)
Asymptomatic	22 (56.4)	86 (60.6)
Stable angina CCS I-III	3 (7.7)	7 (4.9)
Stable angina CCS IV	0	0
Unstable angina	1 (2.6)	8 (5.6)
PCI	1 (2.6)	6 (4.2)
AMI	0	3 (2.1)
Death	9 (23.1)	21 (14.8)
CVA	0	1 (0.7)

Values are expressed as *n* (%).
AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; MT, medical treatment; PCI, percutaneous coronary intervention.

Table 3 Cardiac events during follow-up according to the presence of left ventricular dysfunction and treatment type

	Without left ventricular dysfunction ($n=133$)		With left ventricular dysfunction ($n=48$)	
	Medical treatment ($n=26$)	CABG ($n=107$)	Medical treatment ($n=13$)	CABG ($n=35$)
No event	20 (76.9)	74 (69.2)	5 (38.5)	19 (54.3)
Unstable angina	1 (3.8)	6 (5.6)	0	2 (5.7)
AMI	0	2 (1.9)	0	1 (2.9)
PCI	1 (3.8)	6 (5.6)	0	0
Death	2 (7.7)	13 (12.1)	7 (53.8)	8 (22.9)*
CVA	0	0	0	1 (2.9)

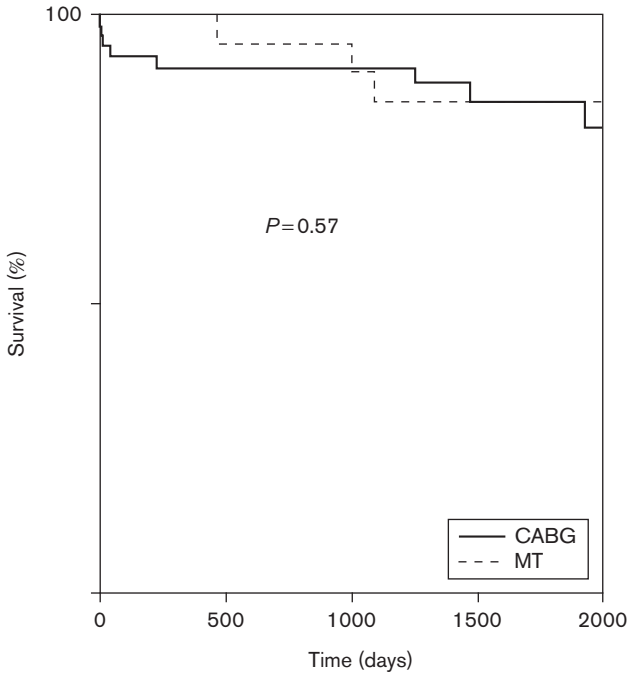
Values are expressed as *n* (%).
AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; PCI, percutaneous coronary intervention.
*$P<0.05$.

In multivariable analysis, age ($\chi^2 = 5.6$) and LV dysfunction ($\chi^2 = 9.2$) but not treatment type, were the independent predictors of death. Propensity-matched patients from both treatment groups had no significant difference in survival free of cardiac death, as demonstrated in the adjusted Kaplan–Meier curves (Fig. 1).

Discussion

LMCAD has been considered a determinant of elevated cardiac mortality. The first series of medically treated patients has shown survival rates of 73 and 65% in 12 and 24 months of follow-up, respectively, compared with 89 and 86% in patients who had CABG [11]. Over the subsequent years, patients with LMCAD continued to have survival benefit with CABG [12]. In a long-term observational study of patients with LMCAD, CABG determined a reduction of symptoms and an increased survival (mean, 13 years vs. 6.6 years with MT) [13]. Currently, CABG for LMCAD is rated with the maximal appropriateness level [4].

Fig. 1



Kaplan–Meier curves of propensity-matched patients undergoing medical treatment (MT) or coronary artery bypass grafting surgery (CABG).

However, the long-term prognosis of certain subgroups of patients with LMCA is highly variable. In the Coronary Artery Surgery Study (CASS), when LM stenosis was less than 70%, with normal LV function, the outcome was favorable no matter what type of treatment was chosen [13]. Detre *et al.* [14], in a subgroup analysis of the veterans trial, showed no significant benefit of CABG for less than 70% LMCAD with normal LV function. Furthermore, observational studies have demonstrated consistently low adverse event rates of stable patients with LMCAD while waiting for cardiac surgery [15–17]. Therefore, this study sought to compare the outcomes of patients with LMCAD undergoing MT or CABG to evaluate the effect of current, optimized MT on the survival of these patients, possibly serving as another step in the direction of future prospective, randomized trials.

Our population consisted of 181 consecutive patients who had a diagnosis of LMCAD in coronary angiography performed for various reasons (chronic ischemic heart disease, postacute coronary syndromes, etc.). These patients were treated medically alone or in combination with cardiac revascularization, the former as a result of patients' unwillingness to be operated or because of medical considerations regarding adequacy (either anatomic or clinical) for a surgical strategy. In both groups (MT or CABG), patients were predominantly men in the seventh decade of life and had a high prevalence of hypertension, diabetes, and hypercholesterolemia. In addition, in both groups stable angina was the most common initial presentation, except for patients with Canadian Cardiovascular Society IV stable angina, who were more frequently found in the surgical group, reflecting the need for an invasive therapeutic strategy in the face of persistent symptoms with optimized medical therapy.

Triple-vessel CAD was similarly frequent in patients undergoing MT or CABG (44.7 vs. 45.4%, $P > 0.05$) and LV dysfunction (33.3 vs. 24.6%, $P > 0.05$). In contrast, chronic renal failure was significantly more common in patients assigned to MT, possibly because that condition was considered to excessively increase surgical risk. The equivalent anatomic and functional severity of CAD in both treatment groups and the seemingly higher clinical risk of patients under MT, in the face of comparable outcomes of patients undergoing MT or CABG, underscore the merits of MT in the management of LMCAD. Nonetheless, in view of the observed mortality rates (4.1% overall, 5.8% for medically treated patients), which place the studied population in a low-risk or moderate-risk category, our results may not be generalizable to all patients with 50% or more LMCAD.

In this study, morbidity and mortality were not significantly different among patients with LMCA undergoing MT or CABG. Both treatment strategies determined a large decrease in symptoms, and there were no significant differences in the incidences of death or other cardiac events between treatment groups. Those results are in accord with Légaré *et al.* [16], who reported very low (< 1%) short-term mortality and low (< 10%) clinical worsening of patients with LMCAD while waiting for CABG. Interestingly, in our study, destabilization of CAD leading to the occurrence of AMI was not found in patients undergoing MT. AMI was found only among patients who underwent CABG and CVA, both considered surgical complications. We must note that 100% of the patients in the MT group took a combination of aspirin, β-blocker, nitrate, and a statin; however, we do not have data on cholesterol, heart rate or blood pressure levels during follow-up, and therefore, may only assume that these patients underwent optimal medical therapy. Although patients who underwent CABG had lower rates of postoperative use of nitrates, as expected after successful myocardial revascularization, and to a lesser extent also lower rates of use of statins and β-blockers, differences in drug use in comparison with medically treated patients were not statistically different.

Overall, with any type of treatment (medical or surgical), patients with LV dysfunction had more events than those with normal LV function. Patients with normal LV function did not have any significant differences in event rates when undergoing MT or CABG. Among patients with LV dysfunction, the incidence of death was increased with MT when compared with CABG (53.8 vs. 22.9%, $P < 0.001$), but other event rates were not significantly

different. This reinforces the importance of LV function for prognosis, as already demonstrated [13,18,19]. In the randomized CASS [18], LV function was the most powerful determinant of prognosis, however, patients with LMCAD were excluded from the trial. In the CASS registry [19], which included patients with LMCAD, even though the anatomic extent of coronary disease was directly related to survival, LV ejection fraction was a more important predictor of survival than the number of diseased vessels.

Our results are in line with the issue raised by Gyenes and Ghali [20], who have raised interesting considerations about the contemporary management of LMCAD. Although they focus on asymptomatic LMCAD, the authors made a thoughtful review of the management of LMCAD in general, and listed six issues to be thought of when choosing a therapeutic strategy for LMCAD (ranging from the old evidence supporting CABG for LMCAD to the possible adverse consequences of premature CABG). On the basis of our data, we share the idea of the 'need to revisit the care paradigm for patients with asymptomatic LMCAD'.

Study limitations

Lesion severity may be a determinant factor in prognosis of LMCAD patients. Available evidence indicted that intermediate stenoses (50–70%) may be less implicated with adverse prognosis less than 70% lesions [14]. In this study, because of the limited number of patients, we did not have further stratifications according to lesion severity over 50%. Nonetheless, it is possible that, over and above stenosis severity, functional noninvasive evaluations or fractional flow reserve may better identify patients who benefit from CABG [21].

This was a small, retrospective study, which may be hypothesis generating but whose results are in line with prior assumptions with regard to the prognosis of LMCAD and its interaction with LV function. As in previous reports, we emphasize the need for new trials, ideally randomized, in which medical therapy will include the latest pharmacologic advances for the treatment of atherosclerotic CAD, but also new technology for operative support.

Conclusion

For patients with LMCAD, older age and LV dysfunction but not treatment type (MT or CABG), are independent predictors of cardiac death. Patients with LMCAD and normal LV function seem to have favorable prognosis, independently of the treatment modality used. In contrast, for patients with LV dysfunction, MT leads to reduced survival when compared with CABG.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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