Drug-Eluting Stent Supported Percutaneous Coronary Intervention for Unprotected Left Main Disease

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ABSTRACT

BACKGROUND
No data exist about the efficacy and safety of drug-eluting stenting of unprotected left main disease in unselected patients. This study sought to determine the clinical and angiographic outcomes of unselected patients receiving drug-eluting stents for unprotected left main disease.

METHODS
Consecutive patients with unprotected left main disease were considered eligible for drug-eluting stent supported percutaneous coronary intervention (PCI). The surgical risk score (risk of death within 1 month) of each patient was calculated according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) model.

RESULTS
One-hundred-one patients with unprotected left main disease underwent PCI. The mean EuroSCORE was 19 ± 23. Successfully left main stenting was performed in 98 patients (primary success rate 97%). The overall 1-month mortality rate was 9.9%. The 1-month mortality rate was 50% in patients with acute myocardial infarction (AMI) on presentation, and 4.5% in patients without AMI on presentation. The 1-month mortality rate of patients with a risk score <13 was 3%, while it was 21% in patients with a risk score ≥13. At 6 months, the mortality rate of the entire cohort of patients increased to 12.8%, and the one of the non-AMI patients to 7.8%. Survival rate was 86% ± 4 (mean follow-up 295 ± 175 days). Target vessel revascularization was performed in 14 patients (16%). The 6-month in-segment restenosis rate was 16%.

CONCLUSIONS
Drug-eluting stent supported PCI may provide early and mid-term outcomes comparable or superior to those expected from coronary artery surgery.

Currently, surgical revascularization is considered the first option therapy for patients with left main disease, since surgical revascularization as compared to medical treatment improves patient survival also in asymptomatic or mildly symptomatic patients [1,2], and the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines do not support percutaneous revascularization as an alternative therapeutic strategy to bypass coronary artery surgery [3,4]. The results of several series of percutaneous coronary intervention (PCI) for left main disease in the pre-drug-eluting stent era, have arised concerns on the safety and mid-term efficacy of PCI due to the relatively high incidence of restenosis and the clinical relevance of recurrent ischemia due to left main restenosis [5-10]. Conversely, preliminary results of drug-eluting stents for left main disease in selected patients have provided encouraging results [11-13].
However, both surgical and PCI studies, included patients selected according to the operator’s assessment of the feasibility and the procedural risk, and no data exist about the efficacy and safety of drug-eluting stenting of unprotected left main disease in unselected patients.

This study sought to determine the clinical and angiographic outcomes and the predictors of clinical outcome of unselected patients receiving drug eluting stent for unprotected left main disease.

**METHODS**

**Patients**

From July 2003 to December 2004, all consecutive patients with unprotected left main disease were considered eligible for PCI without any exclusion criteria based on age, or clinical status on presentation, or coronary angiographic anatomy. Unprotected left main disease was defined as > 50% left main stenosis in the absence of patent coronary grafts to the major branches of left coronary artery. The only exclusion criterion from PCI was the inability to obtain informed consent to PCI as the first option therapy. Patients with acute myocardial infarction (AMI) were included as well as patients with cardiogenic shock. ST-segment elevation myocardial infarction was defined as chest pain persisting more than 30 minutes associated with ST-segment elevation of at least 0.1 mV in 2 or more contiguous electrocardiographic leads. Cardiogenic shock due to predominant ventricular failure was defined as systolic blood pressure < 90 mm Hg (without inotropic or intraaortic balloon support) that was thought to be secondary to ventricular dysfunction and associated with signs of end-organ hypoperfusion such as cold or diaphoretic extremities, or altered mental status, or anuria. The surgical risk score (risk of death within 1 month) of each patient was calculated according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) model [14].

Written informed consent was obtained from every patient, or relative, or legal guidant.

**Treatment protocol**

All patients received aspirin (325 mg, orally) and a loading dose of 600 mg of clopidogrel before coronary angiography, or after PCI in emergent cases. The treatment protocol included also the administration of abciximab (ReoPro, Centocor, Malvern, Pa.). Patients received abciximab immediately before the procedure as a bolus of 0.25 mg per kilogram of body weight followed by a 12-hour infusion at a rate of 0.125 µg per kilogram per minute. Heparin was given as an initial bolus of 70 U per kilogram, and additional boluses were administered during the procedure to achieve an activated clotting time of 200 to 300 seconds. Heparin was continued for 12 hours. Patients were routinely treated with aspirin (325 mg/day indefinitely), and clopidogrel (75 mg daily for at least 6 months).

PCI techniques included conventional stenting (predilation before stenting), or directional or rotational atherectomy before stenting, or direct stenting at discretion of operator. Stenting techniques for bifurcation or trifurcation lesions included stenting of left main and a major branch of the left coronary artery and provisional stenting of the other branch, the "V"stenting technique, the "T" stenting technique, the "culotte"stenting technique, and the "crush"stenting technique at discretion of the operator, and according to the characteristics of the lesion and of the left coronary artery anatomy. The 2 types of available drug-eluting stents (Cypher, Cordis, Johnson and & Johnson Company, and Taxus, Boston Scientific Corporation) were used at discretion of the operator. The nominal diameter of the available stents ranged 2.5 mm to 3.5 mm. In patients with a reference left main diameter > 3.5 mm the final stented vessel diameter was the result of dilation with a balloon with a nominal diameter > 3.5 mm, or with 2 balloons inflated simultaneously with an expected composite diameter > 3.5 mm. A kissing balloon inflation had to be the final step of the procedure in all cases of bifurcation or trifurcation lesions.

Creatine kinase (CK) measurements were systematically performed on admission and every 3 hours for the subsequent 24 hours, and then every 12 hours for 2 days. The peak value of CK-MB and the time-to-peak CK-MB were estimated for each patient. Non-Q-wave myocardial infarction was defined as a CK-MB
value > 3 fold the baseline value.

Coronary angiography was required for all eligible patients 6 months after the procedure. Unscheduled angiography was allowed on the basis of clinical indication. Quantitative coronary angiography included the reference infarct artery diameter, minimum lumen diameter, and the reference and minimum lumen diameters before the procedure, immediately after the procedure, and at the 6-month follow-up. These quantitative angiographic parameters were assessed using a semiautomated edge-contour-detection computer analysis system (ANCOR II, Siemens, Solna, Sweden). Angiographic in-segment restenosis was defined as > 50% luminal narrowing at the segment site including the stent and 5 mm proximal and distal the stent edges of the target vessel on the scheduled or unscheduled follow-up angiography.

Follow-up
The following clinical events were considered: death from any cause, myocardial infarction, and target vessel revascularization (TVR). Patients with more than one event were assigned the highest ranked event according to the previous list. Myocardial infarction was defined as chest pain with ST segment or T wave changes and elevation of cardiac enzymes. TVR was defined as repeat PCI or coronary surgery performed due to in-segment restenosis or reoclusion of the target vessel with or without objective evidence of ischemia or viable myocardium.

Statistical analysis
Discrete data are summarized as frequencies, while continuous as mean + SD. A 2-tailed student's test was used to test differences among continuous variables. Chi-square test was used for comparison of categorical variables. Survival curve was generated using the Kaplan-Meier method. The contribution of clinical, angiographic and procedural variables to the clinical outcome was evaluated with multivariate Cox proportional hazards model. Variables with an univariate value  0.10 were entered into the multivariate models. The odds ratio and their 95% confidence intervals were calculated. A P value < 0.05 was considered significant. Statistical tests were performed using SPSS 7.0 (SPSS Inc., Chicago, Illinois).

RESULTS
From July 2003 to December 2004, 106 consecutive patients with unprotected left main disease were admitted to our center. Out of the 106 patients, 1 patient with AMI and cardiogenic shock died during the diagnostic angiography and before any PCI attempt, and 4 with stable angina did not give informed consent for PCI and underwent elective coronary surgery. Thus, the resulting study population includes 101 patients. Table 1 summarizes the baseline clinical characteristics of the 101 patients. The mean age was 70 + 10 years, and one third of patients were over 75. The incidence of other unfavourable baseline clinical characteristics such as diabetes mellitus, hypercholesterolemia, hypertension, history of myocardial infarction, increased creatinine serum level was very high. The clinical presentation of left main disease was unstable angina or AMI in the majority of patients, and only one fifth of patients had stable angina on admission. The mean value of the surgical risk score of the entire population assessed according to the EuroSCORE model was 19 + 23, and more than one third of patients had a score ≥ 13.
Table 2 summarizes the angiographic and procedural characteristics. The target lesion was located at the distal portion of the left main and involved one or both ostia of the major branches of the left coronary artery in the large majority of cases (87%). In 2 patients previously treated with coronary bare stents, the target lesion was diffuse in-stent-restenosis. In 62% of patients, atherosclerotic disease involved the 3 major coronary arteries, and 21% of patients had a chronically occluded right coronary artery.
Successfully left main stenting was performed in 98 patients (primary success rate 97%). Overall, 140 drug eluting stents were implanted. Primary PCI failure due to the inability to cross the target lesion by the coronary wire occurred in 1 patient with AMI and cardiogenic shock, while 1 patient, with acute myocardial infarction and cardiogenic shock, did not receive stents because of refractory severe arterial hypotension despite intraaortic balloon support and successfully recanalization and balloon dilation with restoration of a TIMI grade 2 flow of the target vessel. Both patients died of refractory cardiogenic shock. One patient with unstable angina, distal left main disease and chronic occlusion of the right coronary artery died of refractory cardiac arrest during kissing balloon predilation. Atherectomy before stenting was performed in the minority of cases. According to the location of the target lesion most patients had stenting of the left main and of at least a major branch. The large majority of patients (80%) had stenting of lesions other than left main lesion, and 21 patients had right coronary artery PCI.

Table 3 summarizes the clinical and angiographic outcomes. At 1 month, there were 10 deaths. Among patients with AMI there were 6 deaths, all due to refractory cardiogenic shock (1 patient with primary PCI failure, 1 patient with successful PCI who did not receive stents, and 4 with successful coronary stenting). Four other deaths occurred in patients without AMI on presentation: 1 death occurred during PCI, 1 death was due to subacute left main stent thrombosis on day 4, 1 death occurred suddenly in a patient who after hospital discharge discontinued antiplatelet treatment, and 1 death was due to septic respiratory failure in a patient with severe chronic pulmonary disease. Thus, the overall 1-month mortality rate was 9.9%. The 1-month mortality rate was 50% in patients with AMI on presentation, and 4.5% in patients without AMI on presentation. The 1-month mortality rate of patients with a risk score <13 was 3%, while it was 21% in patients with a risk score ≥13. At 1 month, there were 1 periprocedural non-Q-wave myocardial infarction, and no TVR. At 6 months, 3 other deaths occurred: 1 patient died of refractory congestive failure, 1 of cancer, and 1 of bleeding complication after coronary artery surgery. Thus, the 6-month mortality rate of the entire cohort of patients increased to 12.8%, and the one of the subgroup of patients without AMI to 7.8%. Figure 1 shows the survival curve of the study population. The survival rate was 86% ± 4 (mean follow-up 295 ± 175). TVR was performed in 14 patients. All but one TVR were performed.
percutaneously.

The 6-month angiographic follow-up rate was 96%. The angiographic in-segment restenosis rate was 16%. Restenosis was focal (< 10 mm in length) in 9 patients, and multifocal or diffuse in the remaining 5 patients.

By multivariate analysis the independent predictors of death at 6 months were diabetes mellitus (OR 4.55, 95% CI 1.40-14.74, P = 0.011), left ventricular ejection fraction (OR 0.93, 95%CI 0.89-0.98, P = 0.010), and Euroscore value (OR 1.03, 95%CI 1.0-1.06, P = 0.024).

**DISCUSSION**

The results of this study show that in an unselected population of patients with unprotected left main disease, PCI including the routine use of drug-eluting stents provides a good early and mid-term outcome. Consistent with the results of previous studies based on selected patients [12, 13], this study shows that the location of the unprotected left main target lesion is distal and involves the ostia of the major branches.
of the left coronary artery in the large majority of cases. Thus, PCI for unprotected left main disease is frequently a complex bifurcation or trifurcation lesion procedure. In order to have an enrolled population representative of the "real world" of patients with unprotected left main disease we considered eligible for PCI all patients without any restriction based on age, the risk of clinical status on presentation, and the characteristics of coronary anatomy. The resulting study population was very old and had a high surgical risk. In patients with AMI the early mortality rate was high and similar to the one reported in previous studies [15, 16]. Conversely, in patients without AMI on presentation, the 1-month mortality rate is 4.5%, and this value compares favourably with the predicted surgical risk of 1-month death. The 6-month clinical and angiographic outcomes confirm the good performance of drug eluting stents when considering that the majority of the PCI involved the bifurcation or trifurcation of the left main. Moreover, in most cases, the restenosis was focal or multifocal, and this morphological pattern makes repeat percutaneous treatment easy and associated with a low risk of recurrence [12, 17].

There are few data on drug-eluting stenting of unprotected left main disease. The first large series of drug-eluting stenting for unprotected left main disease was published by Park et al. and included 102 patients [11]. In this study the restenosis rate was 7%, and the event-free survival rate at 1 year 98.0 + 1.4%. This was a highly selected population and most patients had a preserved left ventricular function and underwent elective procedures. Stankovic et al. published the results of a series of 85 patients with unprotected left main disease treated with drug-eluting stents [12]. The 6-month mortality rate and the TVR rate were 3.5% and 18.8%, respectively. In this study, all procedures were elective and criteria for PCI were a suitable coronary anatomy for stenting associated with patient's preference, or comorbidities and high surgical risk. In a series of 95 patients with protected or unprotected left main disease treated at the Rotterdam Cardiology Hospital, the mortality rate was 14%, while TVR rate was 6% (median follow-up = 503 days) [13]. In the Rotterdam study, elective patients were evaluated by both interventional cardiologist and cardiac surgeon, and the decision for PCI or surgery was reached by consensus and patient's preference. Other 2 studies based on smaller series of patients report at mid-term follow-up a mortality rate of 0 and 1.6%, and a TVR rate of 2% and 8.2%, respectively [18, 19]. The impact of different criteria for the patient selection process may explain the variability of the results reported in these studies, and at the same time makes the comparison of the results with those of our study difficult. Other confounding variables in published PCI series are the undetermined percentage of patients deemed inoperable and who account for the majority of post-PCI deaths, and the relatively subjective and variable criteria used for the definition of a poor surgical candidate.

Some figures of our study should be highlighted to put the results into a proper perspective. This is the largest series of consecutive patients with unprotected left main disease who were treated percutaneously without any clinical and angiographic exclusion criterion. As a result, our patients were by far older as compared to the other studies, with a difference in age mean > 7 years. The majority of patients had an acute coronary syndrome on presentation, and as a consequence the majority of the procedures were performed on an urgent or emergent basis. Other associated unfavourable characteristics resulted in a very high surgical risk, and one third of patients had an Euroscore ≥ 13. The results of this study show that PCI is highly feasible also in very high risk unprotected left main disease patients, and indirectly suggest that drug-eluting stent supported PCI may provide early and mid-term outcomes comparable or superior to those expected from coronary artery surgery.

Study limitations. This is a prospective non-randomized study and ongoing trials will compare PCI with surgery for unprotected left main disease. It can be anticipated that in these randomized studies the patient selection process for randomization will require consensus of the cardiologist and surgeon resulting in the exclusion of patients who after the subjective evaluation of the operators are not candidates for surgical or percutaneous revascularization. This study, despite the non-randomized design, provide a real world perspective of drug-eluting stent supported PCI for unprotected left main disease, and confirm that the use of drug-eluting stents may decrease the incidence of recurrence and improve mid- and long-term outcome of this high-risk coronary patient subset.


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