Impact of Early Coronary Revascularization on Long-Term Outcomes in Patients With Myocardial Ischemia on Dobutamine Stress Echocardiography

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The role of early coronary revascularization in the management of stable coronary artery disease remains controversial. The aim of this study was to evaluate the impact of early coronary revascularization on long-term outcomes (>10 years) after an ischemic dobutamine stress echocardiography (DSE) in patients with known or suspected coronary artery disease. Patients without stress-induced ischemia on DSE and those who underwent late coronary revascularization (>90 days after DSE) were excluded. The final study cohort consisted of 905 patients. A DSE with a peak wall motion score index of 1.1 to 1.7 was considered mild to moderately abnormal (n = 460), and >1.7 was markedly abnormal (n = 445). End points were all-cause and cardiac mortality. The impact of early coronary revascularization on outcomes was assessed using Kaplan-Meier survival analysis and Cox's proportional hazard regression models. Early coronary revascularization was performed in 222 patients (percutaneous coronary intervention in 113 [51%] and coronary artery bypass grafting in 109 patients [49%]). During a median follow-up time of 10 years (range 8 to 15), 474 deaths (52%) occurred, of which were 241 (51%) due to cardiac causes. Kaplan-Meier survival curves showed that both in patients with a markedly abnormal DSE and a mild-to-moderately abnormal DSE, early revascularization was associated with better long-term outcomes. Multivariable analyses revealed that early revascularization had a beneficial effect on all-cause mortality (hazard ratio 0.60, 95% confidence interval 0.46 to 0.79) and cardiac mortality (hazard ratio 0.49, 95% confidence interval 0.34 to 0.72). In conclusion, early coronary revascularization has a beneficial impact on long-term outcomes in patients with myocardial ischemia on DSE. Early coronary revascularization was associated with better outcomes not only in patients with a markedly abnormal DSE but also in those with a mild to moderately abnormal DSE. **(Am J Cardiol 2016;■:■−■)**

Coronary artery disease (CAD) remains the leading cause of mortality worldwide.[1] Medical therapy and revascularization (either percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) are both valuable treatment options of patients with stable CAD.[2,3] Major advances in medical therapy and invasive coronary procedures have contributed to improved outcomes. In patients with acute coronary syndrome, it has been shown that coronary revascularization substantially reduces mortality.[4] However, the role of early coronary revascularization in the management of stable CAD remains controversial. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evalution (COURAGE) trial, among patients with stable ischemic heart disease, demonstrated no difference in long-term mortality rates with medical therapy and PCI compared with medical therapy alone.[5] Information on the impact of coronary revascularization on long-term outcome in patients with myocardial ischemia at dobutamine stress echocardiography (DSE) is scarce. The follow-up period in previous studies was on average 3 years.[6,7] Accordingly, the objectives of the present study were twofold: (1) to evaluate the impact of early coronary revascularization on long-term (>10 years) mortality after an ischemic DSE and (2) to evaluate whether the amount of ischemia determines the prognostic benefit of revascularization.

Methods

The study population consisted of 3,922 consecutive patients with known or suspected CAD who underwent DSE from January 1990 to January 2003. Only patients with stress-induced ischemia on DSE were included (n = 1,191). Early coronary revascularization was defined as PCI or CABG ≤90 days after DSE. Patients who underwent late revascularization (defined as >90 days after DSE) were excluded (n = 286). The reason for this exclusion was based on the primary goal of the present study, that is, to evaluate the impact of early revascularization (≤90 days after DSE).

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See page 6 for disclosure information.

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The decision to revascularization was made on clinical grounds. The final study cohort consisted of 905 patients. The test was requested for diagnostic reasons in 517 patients (57%), for preoperative cardiac risk assessment in 211 (23%), or for evaluation of viable myocardium in 177 (20%) with left ventricular dysfunction. Clinical data were collected at the time of DSE. Hypercholesterolemia was defined as total cholesterol >200 mg/dl or use of lipid-lowering medications. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. Diabetes was defined in the presence of fasting blood glucose ≥140 mg/dl or requirement for insulin or oral hypoglycemic agents. Heart failure was defined according to the New York Heart Association classification.[8] This study was not subject to the Dutch Medical Research Involving Human Subjects Act. Therefore, approval from the local research ethics committee to conduct this prospective follow-up study was not required at the time of enrollment. The study was conducted according to the Declaration of Helsinki.[9] All patients consented participation in this study.

After baseline echocardiography, dobutamine was infused at a starting dose of 5 μg/kg/min for 3 minutes, followed by 10 μg/kg/min for 3 minutes (low-dose stage). The dobutamine dose was increased by 10 μg/kg/min every 3 minutes, up to a maximum dose of 40 μg/kg/min. Atropine (up to 1 mg) was administered intravenously at the end of the last stage if the target heart rate was not achieved. End points of the test were an achievement of the target heart rate (85% of the maximal heart rate predicted for age), the maximal dose of dobutamine and atropine, >2 mV downsloping ST-segment depression measured 80 ms from the J point compared with baseline, hypertension (blood pressure >240/120 mm Hg), a decrease in systolic blood pressure of >40 mm Hg, and significant arrhythmias. Typical angina during dobutamine stress testing was defined as substernal chest discomfort provoked by dobutamine stress and relieved by withdrawing dobutamine.

Echocardiographic images (2 dimensional, using standard views) were acquired at rest and continuously during the test and recovery. The interpretation of images was performed by 2 independent blinded observers. In case of disagreement, a third observer also interpreted the images. In our laboratory, the inter- and intraobserver agreement for DSE assessments are 92% and 94%, respectively.[10] Regional wall motion and systolic wall thickening were scored using a standard 16-segment left ventricular model. Each segment was scored using a 5-point scale as follows: 1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, and 5 = dyskinesis. Ischemia was defined as new or worsened wall motion abnormalities during stress, which is indicated by an increase of ≥1 grade in ≥1 segment of the wall motion score. A biphasic response in an akinetic or severely hypokinetic segment was considered as an ischemic response. When akinetic segments at rest became dyskinetic during stress, this was not considered as ischemia.[11] DSE results were defined as abnormal if there was ischemia during stress or fixed wall motion abnormalities. The wall motion score index (WMSI) was calculated by dividing the sum of segment scores by 16. The WMSI was obtained at rest and at peak stress. A DSE with a peak WMSI of 1.1 to 1.7 was considered mild to moderately abnormal and >1.7 was markedly abnormal.[12]

Outcome data were obtained by a questionnaire, evaluation of hospital records, contacting the patient's general practitioner, and/or review of civil registries. The online municipal civil registry was used to determine the patient's present survival status. The date of response was used to calculate follow-up time. The end points considered were all-cause and cardiac mortality. Causes of death were obtained from the Central Bureau of Statistics Netherlands. A death caused by acute MI, significant arrhythmias, refractory heart failure, or sudden death without other explanation was defined as cardiac mortality.

Continuous data were presented as mean ± SD and were compared using the Student *t* test. Categorical data were presented as percentages and were compared using the chi-square test. Correlation between continuous variables was estimated with Pearson's correlation coefficient. Survival curves were generated using the Kaplan-Meier method to assess the probability of (event free) survival and were compared using the log-rank test. The impact of early coronary revascularization on survival was investigated using univariable and multivariable Cox's proportional hazard regression models. The multivariable model was performed using known prognostic factors, including clinical characteristics and DSE results. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval; $p < 0.05$ was considered statistically significant. All analyses were performed with IBM SPSS statistical software, version 22, Armonk, New York.

Results

The clinical characteristics of the 905 patients with myocardial ischemia on DSE are presented in Table 1. The mean age was 61 years, and the majority of the patients were men (76%). During the dobutamine stress test, heart rate increased from a mean of 70 ± 13 beats/min to 128 ± 19 beats/min ($p < 0.001$), whereas overall systolic blood pressure did not significantly change (132 ± 25 mm Hg at rest and 132 ± 29 mm Hg at stress). During dobutamine stress testing, 295 patients (33%) experienced typical angina, and ST-segment changes occurred in 293 patients (32%).

All patients had myocardial ischemia on DSE. A total of 445 patients (49%) had a peak WMSI >1.7. Patients with a peak WMSI >1.7 had more cardiac mortality compared with those with a peak WMSI ≤1.7 (30% vs 23%, respectively, $p = 0.013$). Early coronary revascularization was performed in 222 patients (25%); a total of 113 patients underwent PCI (51%) and 109 patients underwent CABG (49%); a total of 3 patients (1%) underwent both PCI and CABG. The mean interval between DSE and early revascularization was 37 ± 6 days. The remaining 683 patients with myocardial ischemia were treated medically. Patient groups were comparable according to age, male gender, smoking, hypertension, diabetes mellitus and the use of diuretics, digoxin, and platelet inhibitors. Patients who underwent early revascularization more frequently had a history of cardiac disease (previous MI and heart failure) and less frequently had a previous revascularization. Mean rest WMSI and mean peak WMSI were 1.68 ± 0.60 and