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;118:635−640)**

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 640 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

Table 1
Clinical characteristics

Value	All (N=905)	Early revascularization (N=222)	No early revascularization (N=683)	P-value
Age (years ± SD)	61.4±11.9	60.0±9.6	61.9±12.6	0.41
Men	688 (76%)	177 (80%)	511 (75%)	0.14
Smoker	300 (33%)	81 (36%)	219 (32%)	0.22
Hypertension	260 (29%)	61 (27%)	199 (29%)	0.64
Hypercholesterolemia	283 (31%)	100 (45%)	183 (27%)	<0.001
Heart failure	198 (22%)	76 (34%)	122 (18%)	<0.001
Diabetes mellitus	117 (13%)	28 (13%)	89 (13%)	0.87
Previous revascularization	73 (8%)	5 (2%)	68 (9%)	<0.001
Previous MI	519 (57%)	166 (75%)	353 (52%)	<0.001
Medications				
ACE-inhibitors	303 (33%)	95 (43%)	208 (30%)	<0.001
ß-blockers	381 (42%)	121 (55%)	260 (82%)	<0.001
Calcium-channel blockers	294 (32%)	98 (44%)	196 (29%)	<0.001
Diuretics	170 (19%)	51 (23%)	119 (17%)	0.07
Nitrates	397 (44%)	148 (67%)	249 (36%)	<0.001
Echocardiographic results				
Rest WMSI	1.68±0.60	1.76±0.55	1.65±0.61	0.01
Peak WMSI	1.79±0.55	1.94±0.52	1.74±0.54	<0.001
Peak WMSI >1.7	445 (49%)	138 (31%)	307 (69%)	<0.001

MI = myocardial infarction; WMSI = wall motion score index.
Values are expressed as means ± SD or numbers (%).

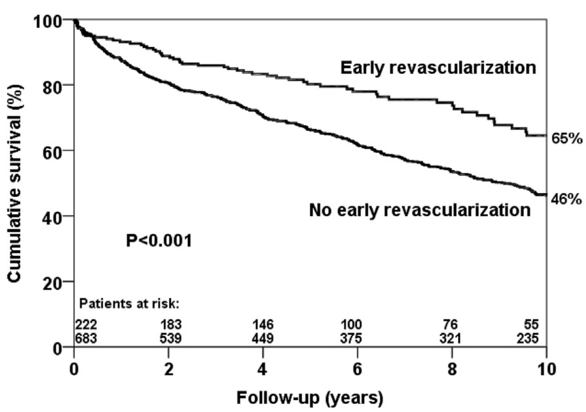

Figure 1. Kaplan-Meier curves for all-cause mortality according to strata of early coronary revascularization.

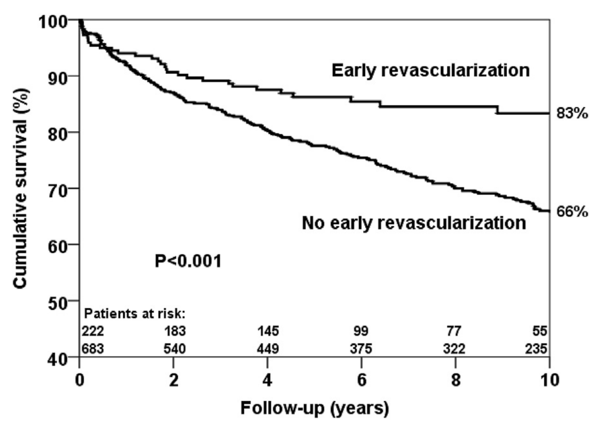

Figure 2. Kaplan-Meier curves for cardiac mortality according to strata of early coronary revascularization.

1.79 ± 0.50, respectively. Both rest WMSI and peak WMSI were significantly higher in patients who underwent early revascularization (Table 1). This probably has contributed to the reason for intervention.

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 patients with myocardial ischemia on DSE who underwent early revascularization had a lower risk for all-cause mortality (event-free survival: 80% vs 65% at 5 years, 65% vs 46% at 10 years; overall p <0.001, Figure 1) and cardiac mortality (event-free survival: 86% vs 77% at 5 years, 83% vs 66% at 10 years; overall p <0.001, Figure 2). Figures 3 and 4 demonstrates the event-free survival for all-cause mortality and cardiac mortality, respectively, according to strata of revascularization and peak WMSI. In the 445 patients with markedly abnormal DSE results, early revascularization was associated with better long-term outcomes compared with those without early revascularization (all-cause mortality [Figure 3] and cardiac mortality [Figure 4] both p <0.001). Also, in the 460 patients with mild-to-moderately abnormal DSE results, early revascularization was associated with better long-term outcomes compared with those without early revascularization (all-cause mortality, p <0.008, Figure 3; cardiac mortality, p <0.001, Figure 4).

Univariable associations of long-term outcome are presented in Tables 2 and 3. Univariable predictors of all-cause mortality were age, male gender, hypertension, hypercholesterolemia, history of heart failure, previous revascularization, and rest and peak WMSI (Table 2). Univariable predictors of cardiac mortality were age, male gender, hypercholesterolemia, history of heart failure, previous revascularization, previous MI, and rest and peak WMSI (Table 3). The univariable analysis demonstrated

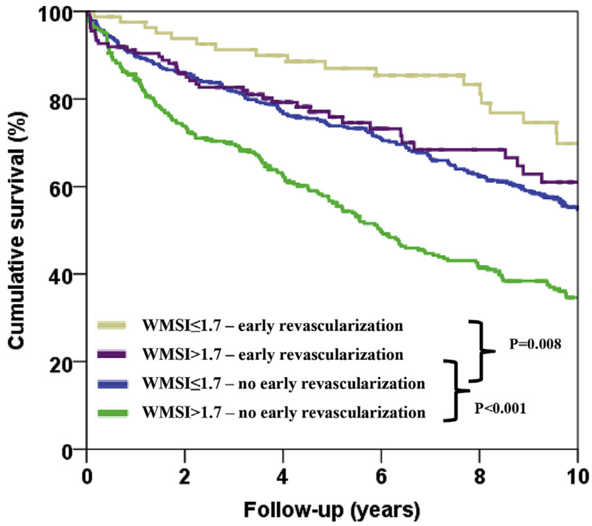

Figure 3. Kaplan-Meier curves for all-cause mortality according to strata of WMSI and early coronary revascularization.

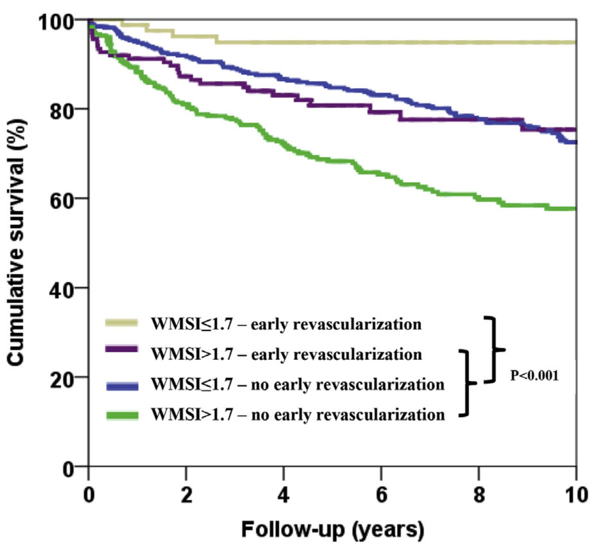

Figure 4. Kaplan-Meier curves for cardiac mortality according to strata of WMSI and early coronary revascularization.

that early revascularization was inversely related to both end points of interest.

Multivariable predictors of clinical data, DSE results, and early revascularization are listed in Tables 2 and 3. Age, hypertension, hypercholesterolemia, smoking, history of heart failure, and previous revascularization were associated with both all-cause mortality (Table 2) and cardiac mortality (Table 3). A multivariable Cox regression model revealed that 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).

Table 2
Univariable and multivariable predictors of all-cause mortality

Variable	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Age*	1.05	1.04-1.06	1.05	1.04-1.06
Men	1.31	1.06-1.63	1.24	0.98-1.56
Hypertension	1.33	1.10-1.61	1.46	1.18-1.79
Diabetes mellitus	0.92	0.76-1.29	1.06	0.80-1.40
Hypercholesterolemia	0.67	0.54-0.84	0.69	0.55-0.88
Smoking	1.19	0.99-1.43	1.48	1.21-1.82
Heart failure	1.46	1.18-1.81	1.30	1.02-1.66
Previous revascularization	0.44	0.25-0.77	0.42	0.23-0.76
Previous MI	1.10	0.92-1.32	0.94	0.77-1.16
Rest WMSI	1.51	1.29-1.75	1.31	0.90-1.89
Peak WMSI	1.53	1.29-1.80	1.34	0.90-2.01
Early revascularization	0.64	0.50-0.83	0.60	0.46-0.79

MI = myocardial infarction; WMSI = wall motion score index.
* Per unit increment.

Table 3
Univariable and multivariable predictors of cardiac mortality

Variable	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Age*	1.06	1.05-1.07	1.06	1.04-1.07
Men	1.46	1.06-1.99	1.29	0.93-1.79
Hypertension	1.13	0.86-1.49	1.33	1.00-1.77
Diabetes mellitus	0.95	0.65-1.38	1.04	0.71-1.52
Hypercholesterolemia	0.62	0.45-0.84	0.65	0.47-0.90
Smoking	1.29	1.00-1.67	1.55	1.18-2.03
Heart failure	1.80	1.35-2.38	1.50	1.10-2.04
Previous revascularization	0.32	0.13-0.78	0.26	0.10-0.64
Previous MI	1.46	1.12-1.90	1.27	0.96-1.68
Rest WMSI	1.67	1.36-2.04	1.13	0.69-1.88
Peak WMSI	1.74	1.39-2.18	1.65	0.96-2.84
Early revascularization	0.54	0.38-0.78	0.49	0.34-0.72

MI = myocardial infarction; WMSI = wall motion score index.
* Per unit increment.

Discussion

In this study, the impact of early coronary revascularization ($\leq$90 days) on long-term outcomes was assessed in 905 patients with myocardial ischemia. During a median follow-up duration of 10 (range 8 to 15 years), 474 patients died, of which 241 deaths were due to cardiac causes. Kaplan-Meier survival curves showed that early revascularization (PCI or CABG) after an ischemic DSE had a beneficial effect on all-cause and cardiac mortality. This benefit was apparent during the entire follow-up period, with survival curves diverging up to 10 years. Both in patients with a mild-to-moderately abnormal DSE (peak WMSI $\leq$ 1.7) and in patients with a markedly abnormal DSE (peak WMSI > 1.7), early revascularization was associated with better long-term outcomes. When adjusting for clinical characteristics and DSE results, as the multivariable analysis demonstrates, early revascularization had a beneficial effect on all-cause mortality (40% reduction) and cardiac mortality (51% reduction) during long-term follow-up.

In the present study, patients with markedly abnormal DSE (peak WMSI > 1.7) had benefit from early revascularization. This is in line with previous data,[13] indicating that a certain amount of ischemia has to be present for revascularization to be beneficial.[14] Also, contrary to previous studies,[15] patients with a mild-to-moderately abnormal DSE (peak WMSI $\leq$ 1.7) who underwent early revascularization had lower mortality compared with those without early revascularization.

To date, CAD is the leading cause of mortality worldwide. Patients with ischemic heart disease may be treated with either medical therapy alone or combined with revascularization (PCI or CABG). In patients with CAD, it has been shown that left ventricle dysfunction may be reversible after coronary revascularization.[16,17] Two randomized trials were undertaken to study the potential benefit of coronary revascularization compared with medical therapy in patients with stable CAD. The COURAGE trial[2] included 2,287 patients who had objective evidence of myocardial ischemia and significant coronary artery disease and studied PCI as the revascularization procedure. Both patients in the PCI group and those in the medical therapy group had a preserved left ventricular ejection fraction (mean left ventricular ejection fraction [LVEF] 60.8% vs 60.9%, respectively). During a median follow-up of 4.6 years, the investigators concluded that there was no benefit of PCI on death and MI. More recently, during the long-term follow-up of up to 15 years in these patients, the investigators did not find a benefit of survival of PCI in 1,211 patients with stable ischemic heart disease, objective evidence of ischemia, and significant coronary artery disease.[5] Additionally, in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial, 2,368 diabetic patients with evidence of ischemia, or symptoms of angina in the presence of angiographic-defined CAD, were studied with either PCI or CABG.[18] Both revascularization techniques showed no benefit on survival. From a clinical perspective, both mentioned trials have important implications; patients with the characteristics of the included patients of these trials need intensive medical therapy and lifestyle intervention. In the present study, the impact of early coronary revascularization of patients with myocardial ischemia on DSE was evaluated. The present study differs from these previous trials, demonstrating that survival was significantly different between patients with revascularization and those without during long-term follow-up. Jeremias et al[19] performed a meta-analysis and demonstrated that both PCI and CABG were associated with improved survival in patients with nonacute CAD. The findings of the present study (describing also patients with nonacute CAD) are in line with this meta-analysis. There are several explanations why early revascularization in the present patient cohort had a beneficial effect on long-term outcomes. In the present study, we describe a high-risk group of patients who were unable to perform an exercise test. Previous mentioned trials enrolled low-risk patients in contrast to the present study. Also, 57% of the 905 patients (vs 38%) had previous myocardial infarction and 22% of the 905 patients (vs 4.7%) had known heart failure compared with the COURAGE trial; this also may have caused beneficial effect of early coronary revascularization in this patient cohort.

Despite major developments of PCI, advanced techniques of CABG, and improvements in medication, the optimal therapy in patients with CAD remains controversial. The guidelines of the European Society of Cardiology indicate revascularization in case of a large area of ischemia (defined as >10% of the left ventricle).[3] The American guidelines recommend CABG in preference to PCI to improve survival in patients with multivessel CAD.[20] In both guidelines, special considerations are made for diabetic patients; revascularization should be considered for diabetic patients whose symptoms compromise their quality of life. Also, in diabetic patients with stable CAD and an acceptable surgical risk, CABG is recommended over PCI. The present study included 117 patients (13%) with diabetes mellitus. Clearly, multiple factors influence the decision to perform coronary revascularization, including symptoms, presence of myocardial ischemia, coronary anatomy, and comorbid conditions. Moreover, daily clinical practice requires the need of balancing between invasive CABG and less invasive PCI. The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial (including >8,000 patients with at least moderate ischemia on an ischemia test) aims to demonstrate whether patients will benefit from a treatment of cardiac catheterization, revascularization, and medical therapy or a treatment of medical therapy alone with cardiac catheterization specially for those who fail medical therapy.[21]

Patients with stable CAD and myocardial ischemia who undergo no or delayed revascularization are at increased risk of adverse events. This may have several reasons. First, chronic myocardial ischemia may result in hibernating or scarred myocardium and an impairment of LV function.[17] Second, patients with myocardial ischemia are at increased risk of developing ventricular arrhythmias, especially those with a severely impaired LV function.[22] Third, natural progression of CAD may result in adverse events, including myocardial infarction.

Patients in the present study were unable to perform exercise testing because of comorbid conditions. DSE may be a valuable alternative method for the evaluation of myocardial ischemia in these patients. DSE has been established as a relatively safe stress technique.[23] Noncardiac side effects (nausea, headache, chills, urgency, and anxiety) are usually well tolerated, without the need for test termination. The most common cardiovascular side effects are angina, hypotension, and cardiac arrhythmias.[23] Life-threatening complications are rare, and in patients at increased risk for these complications (those with impaired LV function and/or a previous infarction), close monitoring is required also during the recovery phase, and any possible cardiovascular or neurologic symptoms should be addressed immediately. The risk-benefit ratio of DSE should always be evaluated carefully.

This study has some limitations. First, the decision to revascularize was made on clinical grounds. The decision to perform early coronary revascularization may have been influenced by multiple factors like age, life expectancy, and comorbid conditions. These factors may also have influenced long-term outcomes. Second, at the time of data collection, contrast-enhanced stress echocardiography was not routinely performed. The use of an ultrasound contrast agent could further increase the accuracy and simultaneous evaluation of myocardial function and perfusion.[24] Medications that reduce mortality in patients with CAD include β blockers, angiotensin-converting enzyme inhibitors, and statins. At the time of data collection, however, these medications were underused, probably because the beneficial effect of these medications was not yet fully understood.[25] Finally, at the time of data collection, LVEF was not routinely performed in our center. Information about LVEF could have improved the present analysis.

Disclosures

The authors have no conflicts of interest to disclose.

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