Special Article

DETERMINANTS OF THE USE OF CORONARY ANGIOGRAPHY AND REVASCULARIZATION AFTER THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Background Clinical trials and practice guidelines have identified clinical criteria for the use of coronary angiography and revascularization procedures after thrombolysis for acute myocardial infarction. The effect of these criteria on clinical practice has not been extensively evaluated.

Methods We used classification-and-regression-tree (CART) and logistic-regression models to study the patients in the first Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial, to identify the variables that best predicted the use of angiography and revascularization procedures after thrombolysis.

Results Among the 21,772 U.S. patients in the trial, 71 percent underwent coronary angiography before discharge from the hospital. Of these, 58 percent underwent revascularization (73 percent receiving angioplasty). The CART model for the use of angiography showed that age was the variable most predictive of angiography; only 53 percent of patients at least 73 years of age underwent angiography, as compared with 76 percent of those under 73. Among the older patients, age was again the most predictive factor; among the younger patients, the availability of angioplasty was a more important predictor (67 percent of patients in hospitals without angioplasty facilities underwent angiography, as compared with 83 percent in hospitals with such facilities). The next most important variable was recurrent ischemia, which was more predictive at hospitals without angioplasty facilities than at those with them. Both statistical models identified coronary anatomy as the most important predictor of the use and type of revascularization.

Conclusions More patients treated with thrombolysis underwent angiography and revascularization before discharge than might be expected. Younger age and the availability of the procedures appeared to be the major determinants of the use of coronary angiography, whereas coronary anatomy largely determined the use and type of revascularization. This process appeared to select low-risk patients for intervention rather than those at higher risk, who would be the most likely to benefit. (N Engl J Med 1996; 335:1198-205.)

PHYSICIANS routinely make difficult decisions about which patients with acute myocardial infarction should undergo angiography, which to refer for revascularization, and which type of revascularization procedure to use.[1] Although clinical trials have evaluated the effect of different strategies on outcome, the behavior and practice of physicians have rarely been studied in large trials.[2-7] In most practice guidelines, clinical risk factors are used to identify candidates appropriate for certain treatments.[8-10] Whether in clinical practice these characteristics identify patients suitable for the treatments remains unknown. The first prospective Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial (GUSTO-1) provided a large cohort of patients with acute myocardial infarction.[11] Because coronary angiography and revascularization were performed at the discretion of the treating physicians, this study offers an excellent opportunity to examine the use of these procedures in current clinical practice.

METHODS

Study Population

We studied the 21,772 U.S. patients enrolled in the GUSTO-1 study,[11] excluding 2371 patients in the angiographic substudy.[12] Patients with acute myocardial infarction who presented within six hours of the onset of pain and ST-segment elevation were eligible. The criteria for exclusion from the study were related to bleeding and risks of allergy to the study treatment.

The study patients were randomly assigned to one of four thrombolytic strategies. Because the use of cardiac procedures did not differ significantly according to treatment assignment, the four groups were combined for this analysis.[13,14] Information on the patients' clinical characteristics, the use of angiography, and the use of revascularization procedures was collected on data forms, and information on the characteristics of the hospitals was obtained by matching the GUSTO-1 and American Hospital Association data bases.[15,16]

From Montreal General Hospital, Montreal (L.P.); the Cleveland Clinic Foundation, Cleveland (D.P.M., J.S.R., E.J.T.); Duke University, Durham, N.C. (R.M.C.); and the University of Washington, Seattle (W.D.W.). Address reprint requests to Dr. Topol at the Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195.

Statistical Analysis

Demographic and clinical information was expressed as percentages in the case of categorical variables and as medians in the case of continuous variables.

Logistic-Regression Models

We used multiple logistic-regression analysis with specified predictor variables to predict three binary outcomes: the in-hospital use of angiography, of revascularization procedures, and of bypass surgery as compared with angioplasty. We calculated odds ratios and 95 percent confidence intervals in the case of continuous variables by using the difference between the 25th and 75th percentiles as the exponent of the regression coefficient.

Classification-and-Regression-Tree Models

We used the classification-and-regression-tree (CART) technique to construct models with the same binary outcomes as the logistic-regression models. The independent predictors of angiography and revascularization in the logistic-regression models were compared qualitatively with those in the CART models.

CART modeling identifies variables that delineate subgroups of patients with distinct patterns of postinfarction use of cardiac procedures.[17,18] First, the overall probability of the outcome is estimated. Then, the overall population is divided into subgroups based on the categorical variables (or, in the case of continuous variables, the categories chosen on the basis of the CART algorithm) that best reflect the probability of the outcome. This process continues with each subgroup until the added level of complexity cannot be justified by efforts at validation. Because the subgroups become smaller with each division, the model becomes less stable after three or four divisions.

Both the logistic-regression model and the CART model are described more completely in material deposited with the National Auxiliary Publications Service.*

Independent Variables

In-hospital complications that occurred only before angiography or revascularization were included in the model. The categorical variables included the Killip class (1, 2, 3, or 4) and the location of the infarct (inferior, anterior, or other). Continuous variables were represented by spline functions in the regression models, if appropriate.

In the models predictive of the use of revascularization and the type of procedure used, we included angiographic information in addition to the variables used to predict the use of angiography. A variable representing the extent of coronary disease[8,9] was added to the CART models, but not to the regression models, to avoid collinearity with the degree of stenosis. Single-vessel (or left main) disease was considered to be present when there was at least 70 percent stenosis of an artery; for double-vessel or triple-vessel disease to be considered present, at least 50 percent stenosis of one or two additional arteries was required.

To account for missing information about non–infarct-related arteries, we first constructed models under the assumption that the missing values for all stenoses equaled zero, because clinically significant stenoses were most likely to have been included and clinically insignificant stenoses were most likely to have been omitted. Because the models yielded similar results whether they were constructed under this assumption, whether patients for whom there was missing information were excluded from the analysis, whether variables (for other missing data) were imputed in the logistic regression, or whether we assigned variables to different categories in the CART models, we have reported models that are based on complete data.

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RESULTS

Overall, 15,471 U.S. patients (71 percent of the study population) underwent angiography in the hospital (Table 1). Among these patients, 8973 (58 percent) underwent revascularization — of this group, 2467 (27 percent) underwent bypass surgery and 6506 (73 percent) underwent angioplasty.

Logistic-regression modeling identified several independent predictors of the use of angiography among 18,837 patients (Fig. 1). The major predictors of the use of angiography (those with odds ratios of at least 1.5) were reinfarction, recurrent ischemia, acute mitral regurgitation, the availability of angiography, and the availability of bypass surgery. Cardiogenic shock, stroke, and older age predicted a decreased use of angiography (odds ratio, <0.65). Other predictors of the use of a procedure that were included in the regression models but that did not reach this level of statistical significance were congestive heart failure, the presence of a ventricular septal defect, diabetes, smoking, hypertension, hypercholesterolemia, family history of myocardial infarction, sex, Killip class, infarct location, peak creatine kinase level, left ventricular ejection fraction, time from the infarction to thrombolysis, prior infarction, prior angina, prior angioplasty, type of hospital ownership, teaching status of the hospital, hospital location, and hospital size. The relation between the use of angiography and age was nonlinear, with an increasingly inverse relation in older patients (Fig. 2).

The CART model indicated that age was the primary determinant of the use of angiography (Fig. 3). Patients 73 years of age or older (the age cutoff chosen by the CART algorithm) had only a 53 percent chance of undergoing angiography, whereas those under 73 had a 76 percent chance. Among the patients at least 73 years old, the next division was also according to age: patients 79 years old or older had only a 38 percent chance of undergoing angiography, whereas those under the age of 79 had a 60 percent chance. Among the 1003 patients who were at least 79 years old, the only additional factor that was important was again age — that is, whether they were younger than 87 years (in which case they had a 40 percent chance of undergoing angiography, as compared with a 14 percent chance if they were 87 or older). Among patients between the ages of 73 and 79 years, however, the next most important determinant was the presence or absence in the hospital of facilities for bypass surgery (chance of undergoing angiography, 67 percent vs. 53 percent, respectively).

Among patients under the age of 73, the primary predictor of the use of angiography was the presence in the hospital of facilities for angioplasty, followed by

TABLE 1. BASE-LINE CHARACTERISTICS, ANGIOGRAPHIC CHARACTERISTICS, AND OUTCOMES OF THE STUDY PATIENTS.

VARIABLE	ANGIOGRAPHY*		REVASCULARIZATION†		ANGIOPLASTY	BYPASS SURGERY
	YES	NO	YES	NO		
No. of patients	15,471	6236	8973	6387	6506	2467
Median age (yr)	60	66	60	59	59	63
Female sex (% of patients)	25	33	25	25	26	23
Cardiac history (% of patients)						
Myocardial infarction	17	19	16	17	14	23
Angina	36	34	38	33	37	43
Bypass surgery	6	6	5	7	4	6
Angioplasty	6	4	7	5	7	6
Infarction characteristics						
Killip class 1 (% of patients)	89	83	89	89	90	86
Median peak creatine kinase (IU/liter)	1,537	1558	1488	1635	1497	1458
Anterior infarction (% of patients)	36	35	35	38	33	39
Complications before angiography (% of patients)						
Ischemia	27	12	33	18	33	32
Shock	6	10	7	5	6	7
Congestive heart failure	17	21	17	16	15	13
Acute MR, VSD, or tamponade‡	4	4	4	4	3	5
Any arrhythmia	22	28	25	18	21	35
Clinical outcome (% of patients)						
In-hospital death	3	17	3	3	3	4
Death within 30 days	3	17	3	3	3	4
Reinfarction	5	2	6	2	6	6
Emergency angiography (%)	18	—	23	10	26	17
Median left ventricular ejection fraction (%)	50	—	50	50	52	50
No. of diseased coronary vessels (% of patients)§						
0	12	—	2	25	2	2
1	35	—	39	29	51	8
2	30	—	32	26	32	32
3	22	—	24	18	14	50
4	2	—	3	2	1	9

*A total of 21,707 patients were studied because data on whether angiography was performed were missing for 65 patients.

†A total of 15,360 patients were studied because data on which type of revascularization procedure was performed were missing for 111 patients.

‡MR denotes mitral regurgitation, and VSD ventricular septal defect.

§Because of rounding, values do not total 100 percent in each column.

the presence of recurrent ischemia. Recurrent ischemia was more predictive of the use of angiography at sites without facilities for angioplasty (84 percent of patients with recurrent ischemia underwent angiography vs. 63 percent of patients without recurrent ischemia) than at sites with such facilities (91 percent vs. 81 percent). Among patients with recurrent ischemia, younger age was the variable next most predictive of angiography.

The 5668 patients without recurrent ischemia who were treated at sites without facilities for angioplasty had a 63 percent chance of undergoing angiography. In contrast, the 7146 patients without recurrent ischemia who were treated at sites with angioplasty facilities had an 81 percent chance of undergoing angiography.

Major predictors of revascularization in the logistic-regression model (those with an odds ratio of at least 1.5) were reinfarction, on-site facilities for bypass surgery, emergency angiography, and the degree of stenosis, especially of the left anterior descending artery (Fig. 1). Severe stenoses of the left anterior descending and right coronary arteries carried the highest odds of revascularization. Patients with total occlusions were less likely to undergo revascularization, but the threshold for revascularization was lower in the case of stenoses of the left main coronary artery. Among the predictors with

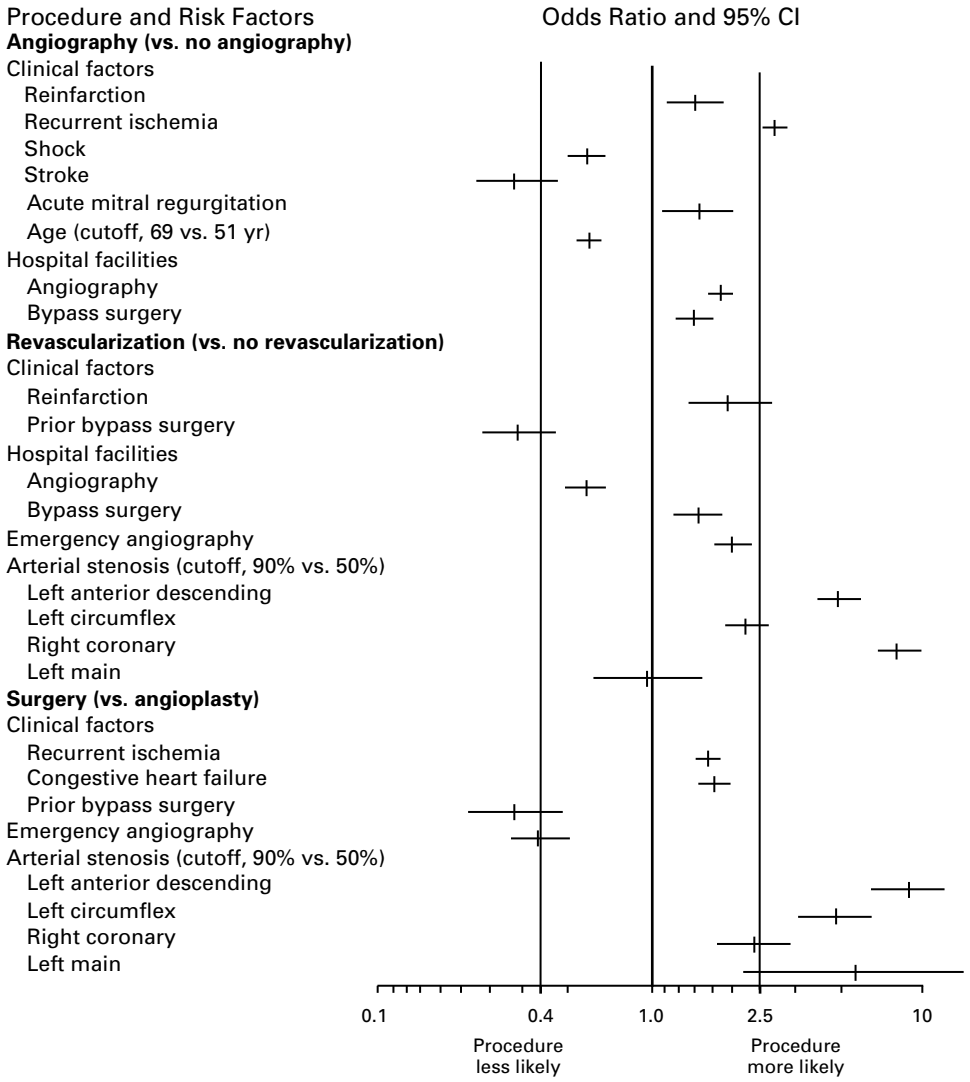

Figure 1. Odds Ratios and 95 Percent Confidence Intervals (CI) for Factors Influencing the Use of Cardiac Procedures before Hospital Discharge in Patients with Acute Myocardial Infarction.

odds ratios below 0.65 were prior bypass surgery and on-site facilities for angiography.

In the CART model, the distribution and severity of stenoses, particularly those of the infarct-related artery, were the principal determinants of revascularization. Only 13 percent of patients with less than 75 percent stenosis of the infarct-related artery underwent revascularization, as compared with 67 percent of patients with stenoses of at least 75 percent. The latter group was subdivided further according to the degree of occlusion. In those without total occlusion (1218 patients), a greater degree of stenosis ($\geq$90 percent vs. $<$90 percent) increased the probability of revascularization (75 percent vs. 57 percent), but total occlusion carried a lower probability of revascularization than did partial occlusion (48 percent vs. 71 percent). In patients with total occlusions, revascularization followed emergency angiography more often than it followed elective angiography (75 percent vs. 39 percent).

In the logistic-regression model, the major independent predictors of bypass surgery as compared with angioplasty (the variables with odds ratios of at least 1.5) were recurrent ischemia, congestive heart failure, and a greater degree of stenosis of the right, left circumflex, left anterior, and left main coronary arteries (Fig. 1). The distribution of stenoses predictive of revascularization generally predicted bypass surgery as compared with angioplasty. Predictors that had odds ratios below 0.65 were prior bypass surgery and emergency angiography.

The classifications in the CART model that dis-

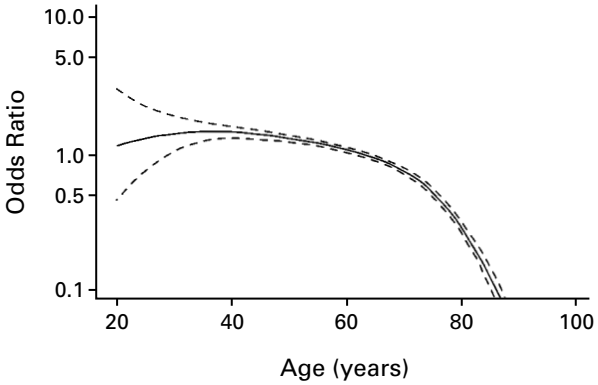

Figure 2. Spline Function of the Relation between Age and the Use of Angiography.

The odds ratio represents the odds of undergoing angiography for a person of a specified age, as compared with the group median. The associations are not linear, and a variable for age that takes into account this lack of linearity was included in the regression analysis. The dashed lines indicate the 95 percent confidence interval.

criminated between patients who underwent bypass surgery and those who underwent angioplasty mainly reflected the extent of coronary artery disease. Among patients with three-vessel or left main disease, the likelihood of undergoing bypass surgery as compared with angioplasty was 64 percent, whereas it was 16 percent among those with no more than two diseased vessels. Patients with single-vessel disease had only a 5 percent chance of undergoing bypass surgery, but the rate increased to 59 percent in those who had stenoses of at least 46 percent in the left main coronary artery. Prior bypass surgery was the only other risk factor described in the model; patients with previous bypass surgery were less likely than other patients to undergo surgery.

DISCUSSION

The majority of this large group of U.S. patients treated with thrombolysis for acute myocardial infarction underwent angiography and revasculariza-

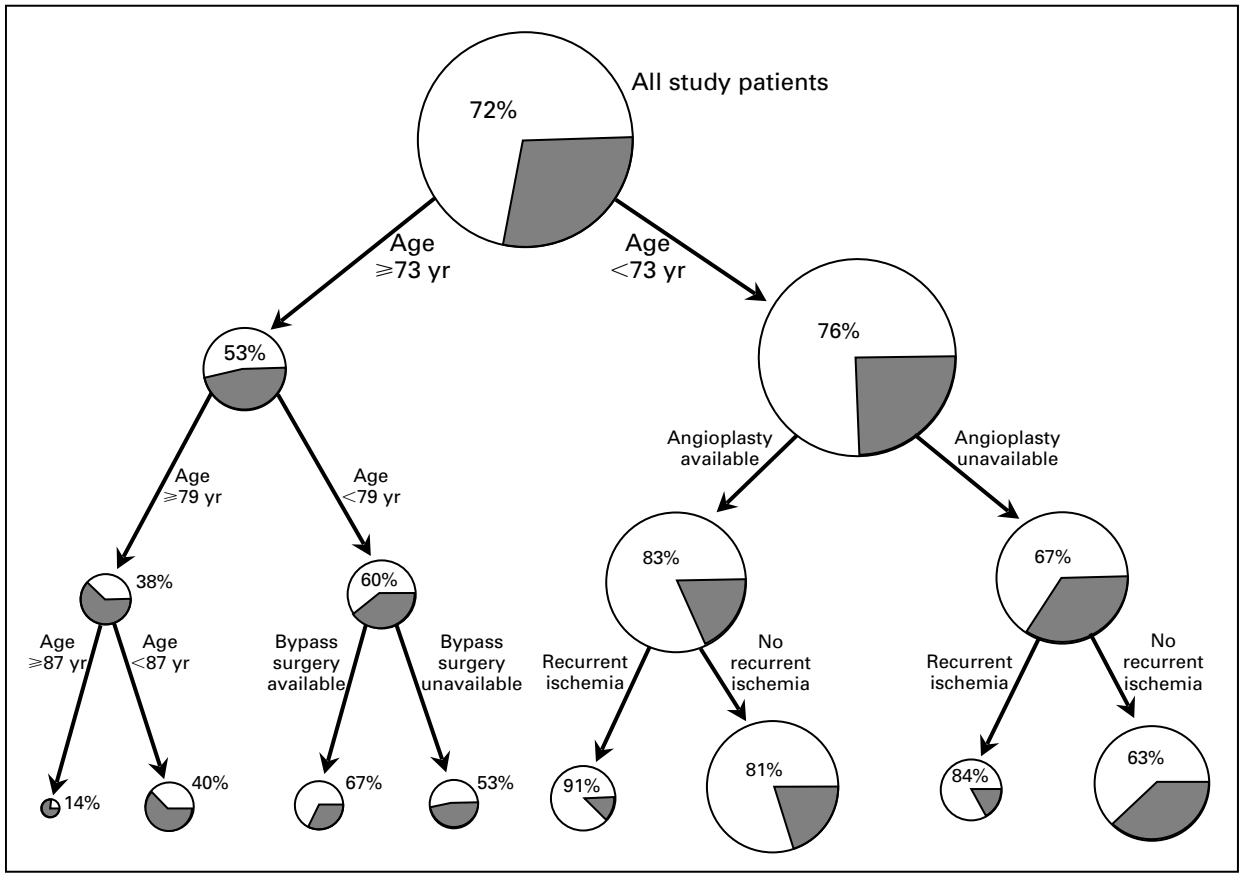

Figure 3. CART Model Showing the Variables Used to Discriminate between Subgroups According to the Likelihood of the Patients' Undergoing Angiography after Thrombolysis for Acute Myocardial Infarction.

The white area of each pie chart represents the percentage of patients in that subgroup in whom angiography was used, and the overall area of the pie chart indicates the size of the subgroup relative to the total population.

tion before discharge, although in multiple clinical trials no advantage has been shown for an aggressive use of angiography (one that includes revascularization) as compared with a conservative approach.[2-7] Furthermore, younger age and the availability of the procedure in the same hospital were major predictors of the use of angiography, whereas recurrent ischemia, cardiogenic shock, and other high-risk characteristics — all of which are major indications for angiography in the published guidelines — were less important. Once angiography was performed, however, the coronary anatomy chiefly determined the use of revascularization and the choice of the procedure. This process appeared to decrease the chance that patients at high risk, the group most likely to benefit from intervention, would undergo such procedures.

The large proportion of patients undergoing cardiac procedures and the variables that predicted the use and type of the procedures are not completely consistent with the criteria identified in published guidelines and clinical trials. These sources suggest that uncomplicated infarction has an excellent prognosis regardless of whether efforts at revascularization are made, whereas patients with complications have the most to gain from the procedure. In our study, patients under the age of 80 who had cardiogenic shock or congestive heart failure had a likelihood of undergoing angiography similar to that of patients without these complications. This effect is tempered by a high mortality rate in this high-risk group. Even among survivors, however, the rate of angiography was still higher among patients without the complications. Moreover, patients with left ventricular dysfunction and triple-vessel disease or left main disease had a rate of revascularization identical to that of patients with left ventricular ejection fractions above 50 percent, single- or double-vessel disease, and stenoses of less than 50 percent in the left anterior descending artery.

Thus, in clinical practice, the use of angiography appears to be influenced not only by known indicators of the need for revascularization, but also by a low-risk profile. Spertus and coworkers came to a similar conclusion in an analysis of 4823 infarct survivors.[19] In their study, except for recurrent ischemia, clinical variables predictive of higher mortality were associated with a lower likelihood of angiography and angioplasty.

We found that age was the primary predictor of the use of cardiac procedures in clinical practice. The relation between age and the use of angiography was nonlinear, with a particularly steep negative slope after the age of 73, although even among patients less than 73 years old, younger patients were more likely to undergo angiography than older ones (Fig. 2).

Age has been an independent predictor of 30-day mortality in almost all studies of acute[20,21] and chronic[22,23] ischemic heart disease. In GUSTO-1, the patients in the highest quartile of the age distribution (those at least 70 years old) were 3.9 times more likely to die within 30 days than the patients in the lowest quartile (those 52 years old or less).[24] Furthermore, age has been shown to be directly related to the presence of multivessel disease. Among the U.S. patients under the age of 50 in the GUSTO-1 study who underwent angiography, the incidence of left main disease or three-vessel disease was 15 percent, as compared with 34 percent among patients between the ages of 70 and 80 years.

Recent overviews of randomized trials of bypass surgery and angioplasty show that higher-risk patients gain more from revascularization than lower-risk patients.[25,26] Large observational studies have found more benefit of revascularization in older patients and in those with cardiogenic shock.[27,28] Since all patients in GUSTO-1 were eligible for thrombolysis, extensive coexisting conditions are not likely to explain the lower use of angiography in the older patients.

The second determinant of the use of angiography in our study was whether the admitting institution could perform angioplasty. Other studies have also found the presence of on-site facilities for angioplasty to be an independent predictor of the use of that procedure.[16,29,30] In this study, after adjustment for the severity of illness, rural and teaching hospitals were less likely to perform angiography, whereas larger hospitals and those owned by investors were more likely to do so. These numerous complex factors highlight the need for health systems that promote treatment on the basis of the patient's needs rather than the characteristics of the admitting hospital.

Most guidelines for postinfarction management stress the importance of recurrent ischemia as a criterion for the use of angiography. The emergence of recurrent ischemia as a critical factor in this study is reassuring; however, 84 percent of patients under the age of 73 who had recurrent ischemia underwent angiography if the angioplasty facilities were not available in the hospital, as compared with 91 percent of such patients if the facilities were available on the site. Recurrent ischemia was only a minor factor in patients over the age of 73. The results of the recent Danish Acute Myocardial Infarction Study, a multicenter, randomized trial of invasive as compared with conservative treatment of patients with inducible ischemia, suggest a better outcome among patients treated aggressively.[31] These findings reinforce the importance of an aggressive approach in patients with recurrent ischemia.

Patients with left ventricular dysfunction derive more benefit from revascularization than do those with normal function.[27-30,32] In a systematic overview,[25] patients with left ventricular dysfunction

gained 12 months of life as compared with almost 3 months for patients with normal ventricular function. In our adjusted analysis, however, patients with heart failure, higher peak levels of creatine kinase, and prior infarctions were less likely to undergo angiography, whereas those with anterior infarctions were more likely to undergo angiography.

Several groups have recommended that patients with cardiogenic shock undergo angiography,[33-35] yet the presence of cardiogenic shock was associated with a substantial reduction in the use of angiography. Although this finding may be explained in part by the occurrence of early deaths before angiography could be performed, the results are problematic; if the clinical guidelines are to be followed, better systems are needed to ensure that these patients can have more rapid access to angiography facilities.

The severity and distribution of coronary-artery stenoses were the primary determinants of the use of revascularization and the choice of procedure. The choice of angioplasty as compared with bypass surgery followed the pattern of "angioplasty for one-vessel disease" and "bypass surgery for triple-vessel or left main disease," as is consistent with current guidelines.[10] However, more patients underwent revascularization than would be expected from the guidelines. Many patients with one- or two-vessel disease (without involvement of the left anterior descending artery) underwent revascularization without having recurrent ischemia, even though evidence is lacking that these procedures affect the outcome in such patients.

These findings point to a divergence between an ideal decision-making strategy and the reality of clinical practice. First, practitioners appear to see younger age as a key factor, either because they misunderstand the manner in which a likely benefit should be assessed or because they simply identify with younger patients. Second, in many cases the convenience of having facilities available seems to outweigh the needs of the patient. Finally, practitioners appear to be selecting the patients likely to have good procedural outcomes rather than those who would derive the most benefit from a procedure. In an ideal world, clinicians would develop an overall estimate of the likely outcome given one treatment as compared with another, and would preferentially allocate resources to patients with more potential for benefit. If this had occurred in the cases we studied, angiography would have been performed much more often in older patients who had evidence of left ventricular dysfunction, and the majority of revascularization procedures would have been done in patients with left main or three-vessel disease, for whom there is substantial evidence of enhanced survival.

The two analytic methods we used provide an interesting contrast in perspectives. The CART model provides a streamlined way to identify the major factors associated with an outcome, whereas logistic regression allows the joint effects of multiple characteristics to be evaluated simultaneously. In the delivery of health care and the allocation of resources, identifying large groups in which procedures are used in distinct patterns is a useful aid to decision making; for this purpose, the CART model provides a simple pattern that is easily grasped but that may not include uncommon characteristics (such as cardiogenic shock and severe mitral regurgitation) that are critical to individual patients. The logistic-regression model provides a more complex picture that may be more difficult for policy makers and clinicians to understand, because of the simultaneous interplay of multiple factors. We believe that including both approaches provides a complementary overview of clinical practice patterns.

Many study subjects were excluded from the modeling of the use and choice of revascularization procedures because information on their coronary anatomy was missing. Since a blank is often left on the data-entry form when there is no stenosis, we repeated our analysis using values of zero to represent the missing data; very similar results were obtained in the logistic-regression and CART models in which patients with missing values were excluded. Furthermore, the clinical profiles and outcomes of the patients with missing values were similar to those of the patients without missing values. Results of provocative testing for ischemia were not recorded in this trial. Despite the importance of such testing in the stratification of risks, preliminary findings from the GUSTO-IIa study indicate that less than 30 percent of patients are tested.[36] Finally, we lacked information on coexisting conditions (other than infarct-related complications and cardiac risk factors), which could have affected the decision to perform angiography or revascularization.

In conclusion, the use of cardiac procedures after thrombolysis for acute myocardial infarction is more prevalent in U.S. clinical practice than would be expected from the current guidelines. Instead of the presence of high-risk clinical characteristics, which is associated with a greater benefit from revascularization, younger age appears to be the primary predictor of the use of coronary angiography. Aside from age, the availability of facilities for cardiac procedures predominantly determines the use of angiography, although once angiography is performed, the coronary anatomy largely determines the use of revascularization and the choice of the procedure.

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