DERLEMELER
REVİEWS

Coronary Angiography as a Prognostic Tool

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Coronary angiography was introduced into clinical practice more than 40 years ago revolutionizing the clinical understanding of the coronary artery disease and setting the stage for all the modern treatments such as coronary bypass surgery (CABG), percutaneous coronary angioplasty (PTCA), and thrombolysis. Coronary angiography has well-known pitfalls and limitations in the detection of coronary atherosclerosis. It is not very unusual to see in the routine clinical practice that the coronary angiography is less well appreciated as a prognostic tool. One reason for this may be the traditional teaching of the coronary angiography that favors the technical aspects of the catheterization and the radiographic interpretation skills. In this paper, the prognostic significance of coronary angiographic findings is reviewed and the clinical issues encountered in daily practice are highlighted. *(Ana Kar Der, 2001; 1: 189-196)*

Introduction

Coronary angiography was introduced into clinical practice more than 40 years ago revolutionizing the clinical understanding of the coronary artery disease and setting the stage for all the modern treatments such as coronary bypass surgery (CABG), percutaneous coronary angioplasty (PTCA), and thrombolysis. It is one of the most commonly performed diagnostic procedures worldwide.

Coronary angiography has well-known pitfalls and limitations in the detection of coronary atherosclerosis (1). However, the clinically relevant question is often the severity of luminal obstruction rather than the mere presence of atherosclerosis in the artery wall. This question can be reliably answered by coronary angiography (2). Coronary angiography also provides prognostic information valuable in risk assessment and treatment decisions. However, it is not very unusual to see in the routine clinical practice that the coronary angiography is less well appreciated as a prognostic tool. One reason for this may be the traditional teaching of the coronary angiography that favors the technical aspects of the catheterization and the radiographic interpretation skills.

In this paper, the prognostic significance of coronary angiographic findings will be reviewed. This is by no means intended to be an exhaustive review of the available literature. It is rather intended to highlight the clinical issues encountered in daily practice. Coronary angiographic findings are also very powerful predictors of coronary angioplasty outcomes, but this issue is not included in this article.

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Limitations of Coronary Angiography in the Diagnosis of Coronary Artery Disease

Coronary angiogram is a 2-dimensional silhouette of the 3-dimensional coronary artery lumen. This causes some of the well-known pitfalls of the coronary angiography including foreshortening, overlapping, eccentricity, and ambiguity of the lumen borders (such as plaque disruption and dissections after angioplasty).

Significant coronary atherosclerosis may be present despite the absence of a significant narrowing on the angiogram. Severity of the coronary disease may be underestimated when diffuse atherosclerosis results in uniform narrowing of the lumen (3). The relation between the expected diameter of a given vessel and its distal bed size may help in the detection of diffuse disease (4). Another mechanism by which a significant atherosclerotic plaque may be missed on the angiogram is the Glagov phenomenon (5). According to Glagov et al. (5), the segment of the artery with atherosclerotic plaque grows outwards (remodeling), without encroaching the lumen, until the atherosclerotic plaque area is about 40% of the vessel area.

Another limitation of coronary angiography is the intra- and inter-observer variability. Intra-observer variability may be especially important for the lesions causing mild to moderate luminal narrowing (6). Quantitative coronary angiography or semiquantitative methods such as caliper assisted measurements have been proposed to improve the reproducibility of measurements (7). The absolute value of minimum lumen diameter has been proposed to avoid problems caused by the unreliability of defining of a "normal" reference segment. Nevertheless, quantitative angiography also subject to limitations described above (8). Moreover, application of QCA to routine clinical setting is difficult despite its value in teaching and research. Another technique to decrease the variability is the panel reading of coronary angiograms. This technique has been used in various studies on the regression and progression of coronary disease (9).

Coronary Angiography and the Natural History of Coronary Artery Disease

With the widespread application of revascularization techniques the natural history of angiographically documented coronary artery disease is significantly altered. Data from large registries and the medical treatment arms of the randomized studies firmly established the correlation between the angiographic extent of coronary disease and the future risk of death or need for revascularization procedures. In one of the earliest studies, Proudfit et al. (10) reported the natural history of CAD in 10-year follow-up of 601 non-surgical patients. Excluded were the 249 patients who underwent bypass surgery during this time period. The patients with at least 50% stenosis of one major artery had a mortality rate of 2.4% per year for the first 4 years and 5.2% per year during the subsequent 6 years. Survival decreased with the increasing number of vessels diseased and with >=50% left main narrowing. This was true even when the second vessel had only 30-50% narrowing. Among the patients with single vessel disease, left anterior descending artery (LAD) involvement was associated with the worst prognosis. In the group of two vessel disease patients, the worst 5 and 10 year prognosis (37.8% and 25.0%) was noted in patients with total right coronary artery (RCA) occlusion associated with subtotal LAD occlusion. Contrast left ventriculography, which is an integral component of coronary angiography, also provided very important prognostic information in that the aneurysm or diffuse hypokinesis predicted a very poor 10-year survival (18.2 and 11.1%, respectively). The effect of left ventricular dysfunction was seen in all strata of vessel disease categories (one, two or three vessel).

Mock et al. (11) reported the medical treatment outcomes in 20,088 patients in Coronary Artery Surgery Study Registry between 1975 and 1979. A significant stenosis was described as 70% or more luminal narrowing. The survival and need for surgery at 4 years were significantly determined by the number of diseased vessels and the left ventricular dysfunction. The presence of 50% or more severe left main disease independently worsened the prognosis especially in the three-vessel disease group. Patients with less than 70% stenosis (which included patients with or without angiographic narrowing) had the best prognosis (97% at 4 years) (see below).

Coronary Angiography and the Prediction of Benefit From Revascularization

The effects of revascularization on the survival depend on the extent of coronary artery disease as documented by coronary angiography. Randomized studies comparing medical and surgical treatment of coronary disease defined that survival benefit from surgery is predicted by the baseline coronary angiographic findings (12). These studies also emphasized the importance of clinical presentation and exercise tolerance as significant predictors of the prognosis (Figure 1). More recently, Mark et al. (13) in Duke Cardi-

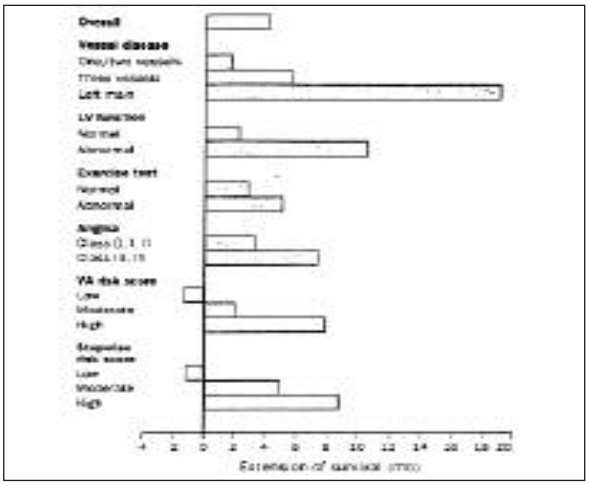


Figure 1: The survival advantage with coronary bypass surgery over medical treatment is determined by the extent of coronary artery disease and left ventricular function. (Reproduced from reference 12 with permission).

ovascular Disease Databank compared medical, surgical and interventional outcomes according to the coronary angiographic disease severity. There was a survival advantage for CABG over medical therapy for three-vessel and two-vessel disease severe (associated with 95% proximal left anterior descending stenosis). For less severe disease treatment choices were between medicine and PTCA. The survival benefit with PTCA over medical treatment was modest.

Importance of the Quantitation of the Extent of Coronary Disease

The relatively simple, traditional one-, two- and three-vessel disease classification does not necessarily take into consideration the size of jeopardized myocardial territory. The prognostic power of coronary angiography can be improved further by assessing the degree of narrowing together with a quantitative measure of the jeopardized myocardium. Various scoring systems have been described, but the coronary artery jeopardy score described by Califf et al. (14) may be especially useful in the clinical setting (Figure 2). By using a modification of this scoring system, we (15) were able to identify patients with left ventricular dysfunction who had good versus poor long-term survival after coronary angioplasty (Figure 3).

Patients With No Or Minimal Obstructions on the Coronary Angiogram

It is important to make the distinction between an angiogram with all smooth lumen borders and the angiogram with mild obstructions or plaques. Kemp et al. (16) reported the 7-year survival data in 4,051 patients from CASS registry. Angiograms were entirely normal in 3,136 and showed less than 50% stenosis in one or more segments in 915 patients. The survival at 7 years was significantly better in patients with no angiographic abnormalities (96 vs. 92%). Papanicolau et al. (17) reported 5 and 10 year follow-up results in 1,491 patients with angiographically "normal" (less than 25% narrowing) and 486 with insignificantly narrowed (25-50%) coronary arteries. The 10-year survival was very good (>98%) and similar between these two groups, however, patients with insignificant (25%-50%) disease had a higher incidence of myocardial infarctions (MI free survival, 98% vs. 90 %). When the numbers of arteries with 50% and 25% lesions were incorporated to an index, this index predicted the subsequent events better than the number of arteries involved. Again in

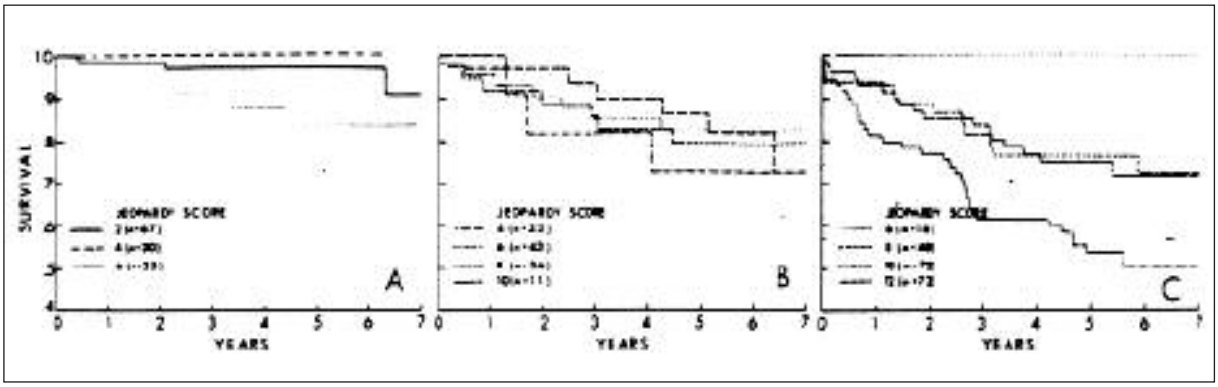


Figure 2: The survival curves illustrate that the coronary jeopardy score allows further risk stratification in patients with one-vessel (A), two-vessel (B), and three-vessel disease (C). (Reproduced from reference 14 with permission of American College of Cardiology).

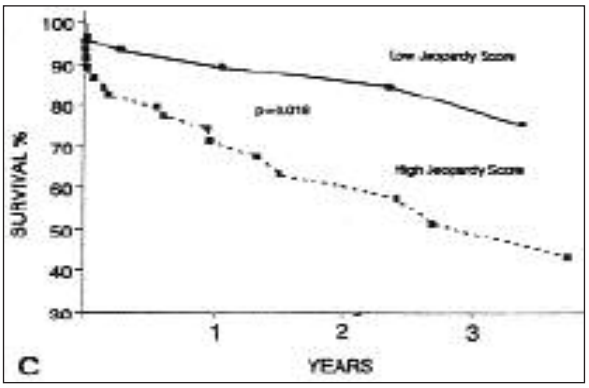


Figure 3: In a group of patients with poor left ventricular function before coronary angioplasty, a high (>0.30) modified coronary jeopardy score identified the subgroup with worse long-term survival. (Reproduced from reference 15 with permission).

this study the annual rate of events increased after 5 years. Another interesting finding is that 70% or more of these patients continued to be functionally limited despite the reassuring initial coronary angiographic findings.

Can Myocardial İnfarction Be Predicted From Coronary Angiography?

Myocardial infarction caused by sudden and unpredictable changes in atherosclerotic plaque determines survival in patients with coronary artery disease. It is clear that identification of patients who are at high risk for myocardial infarction can have a significant impact on the mortality and morbidity of coronary artery disease. Accordingly several authors investigated this problem.

Moise et al. (18) analyzed 313 patients who underwent two angiograms more than 3 months apart without intervening revascularization procedures. Time interval between angiograms, unstable presentation and age were multivariate independent predictors of progression of coronary disease. The progression was seen more often in lesions with greater than 75% narrowing. A score based on the number of 50-75% lesions on the first angiogram was also an independent predictor. These authors also analyzed the new total occlusions, which occurred in 98 (31%) of the patients. Total occlusion was associated with development of myocardial infarction and decreased ejection fraction. In this group the severity of the initial lesions (greater than 80% luminal narrowing) was a significant predictor. Extent of coronary disease, smoking and male gender were other factors. Taeymans et al. (19) analyzed 38 lesions that progressed to cause an acute myocardial infarction (AMI) over the course of 3 years and compared the results to 64 segments that remained stable. At baseline, the lesions progressed to AMI were more severely narrowed, more often located at a bifurcation and had steeper inflow and outflow angles by quantitative angiography. Ellis et al. (20) compared angiograms in 132 patients who had LAD disease (>=30% luminal narrowing) and developed anterior myocardial infarction during a 3-year follow up and in 141 patients with no infarction. Risk of infarction was low (1.9%-2.3%) when the lesion severity was less than 50% by any of the six angiographic measurement methods utilized. The risk increased to 15% (confidence interval, 7.1% to 30.9%) for lesions with 90-98% narrowing by quantitative angiography at baseline. The number of >=50% narrowings in the LAD territory also increased the risk in a linear fashion (0: 1.9%, 1: 5.9%, >=2: 10.7%). Interestingly the risk of myocardial infarction was lower in the group with >=98% (subtotal) occlusions suggesting that some of these may actually be chronic total occlusions with recanalization and/or collaterals. Lichtlen et al. (21) analyzed 230 patients with two angiograms over a period of 3 years. In this study quantitative coronary angiography was used. A 20% or more worsening was noted as often as regression in lesions measured as 1-10% luminal narrowing. However, progression was twice and three times more frequent than regression in lesions with 10-20% stenosis and lesions with >20% stenosis, respectively. A worsening or progression was seen in only 15% of the lesions over 3 years. Cigarette smoking was associated with development of new lesions, while high cholesterol was associated with progression of existing lesions. Coronary artery occlusion was seen 2.6% of the lesions. As many low grade asymptomatic lesions led to myocardial infarctions as did high grade, symptomatic ones. In another analysis from the same investigators (22) the progression of coronary artery disease was found to be dependent on the diameter of the lumen (more in vessels with >2 mm diameter), and proximal and mid, as opposed to distal, location of the lesion. Little et al. (23) analyzed 58 patients who had an angiogram done before and after myocardial infarction. Most severe lesion on the initial angiogram was responsible for only 38% of the myocardial infarctions. In 60% of the patients, the culprit lesion was less than 50% on the first angiogram. Similarly, Giroud et al. (24) analyzed serial angiograms in 92 patients with AMI and reported that 78% of the segments were not severely stenosed on the initial angiogram. Ambrose et al. (25) compared serial angiograms between 23 patients with AMI and 15 with new total occlusion without AMI. In AMI group only 22% of the lesions that progressed to AMI was >70% as compared to 61% of lesions in total occlusion group. Dacanay et al. (26) compared the angiographic progression of coronary narrowings in patients with Q-wave and non-Q-wave infarctions who underwent an angiogram before the acute event. Most patients with Q-wave myocardial infarction had moderate lesions that were ulcerated or eccentric as compared to either minimal or severe and nonulcerated lesions in non-Q-wave infarction group. In 20 patients with an angiog-

ram done 1 week before a myocardial infarction, Ojio et al. (27) noted a lesion severity of >50% in 95% of the patients, and about 70% of the plaques were of eccentric, Ambrose II type. On the other hand in 20 control patients with an angiogram 1 year before AMI the lesion was <50% in 95% of the patients, and Ambrose type II was noted in only 10%.

In summary, it can be stated that the more severe the initial stenosis, and more extensive the coronary involvement, the higher the risk of progression to total occlusion and myocardial infarction. However, most of the myocardial infarctions result from initially insignificant narrowings because there is a higher incidence of these lesions.

Prognostic Significance of Coronary Angiographic Findings After AMI or Acute Coronary Syndromes

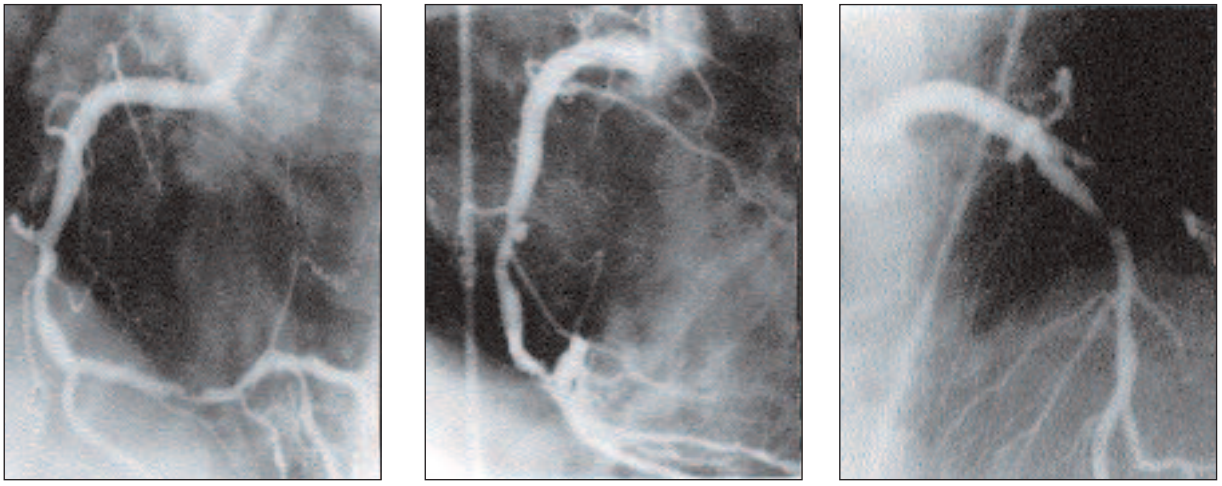
Recurrent ischemic events resulting in myocardial necrosis, death or repeat hospital admissions are frequent after an acute coronary event. Patients with unstable angina experience more frequent events than those with stable angina. Chen et al. (28) compared 95 patients with unstable angina to 200 patients with stable angina. All patients had a baseline angiogram and placed on a waiting list for angioplasty. Average 8+4 months later coronary angiograms were repeated. More than 20% progression occurred in 15% of unstable and 7 % of stable lesions. Complex lesions showed significantly more progression. Even the complex plaques not associated with acute coronary syndromes are more prone to progression, and regression is seen less often (29). Significant stenosis progression with increased likelihood of acute coronary events was associated more frequently with complex plaques (22% vs. 4%) in 94 patients awaiting coronary angioplasty (30). However complex lesions were associated with slightly higher degree of luminal narrowing at baseline.

Goldstein et al. (31) analyzed angiograms in 253 patients with acute myocardial infarction. Multiple complex plaques were documented in 100 (39.5%) of these patients. Patients with multiple complex lesions underwent surgery more often (27.2 % vs. 5.2%). During the year after MI, recurrent acute coronary syndrome, angioplasty and coronary bypass surgery were significantly more frequent in this group. The incidence of multiple complex plaques may be higher than it is seen on the angiogram. Asakura et al. (32) by performing angioscopy, found as many yellow (that is, potentially vulnerable) plaques in non-infarct vessels as in infarct vessels (3.4+1.8 vs. 3.7+1.6 plaques per artery). Angiograms in Figure 4 illustrate multiple complex plaques in a patient who presented with acute inferior myocardial infarction.

In GUSTO study, mortality at 30 days and 1 year was correlated to open infarct artery (33). Identification of the angiographic factors that may predict later occlusion is important in this group of patients. In-hospital reocclusion in "TIMI-4" study was predicted by TIMI-2 flow, ulcerated lesion, and the presence of collaterals (34). White et al. (35) analyzed the incidence of infarct artery occlusion at 4 weeks and 1 year after acute myocardial infarction. At 1 year, 25% of the 154 patients had reocclusion of the infarct artery. At 4 weeks, the incidence of reocclusion was a function of the residual stenosis in the initial angiogram (9.2 % risk in <50% stenosis, 11.6% in 50-69% stenosis, 30.4% in 70-89% stenosis, and 70% in >=90% stenosis). In APRICOT study (36) baseline angiogram at 48 hr and control angiogram at 3 months revealed that lesions with >90% stenosis occluded in 42% of the patients, as compared to 23% incidence of occlusion in those with <90% narrowing. Interestingly, reocclusion rate was higher in smooth lesions (34%) as compared with complex lesions (23%). Davies et al. (37), on the other hand, found that irregular coronary lesion morphology as assessed by plaque ulceration index was significantly higher in patients who experienced early instability, while the severity of stenosis, eccentricity, location, filling defect and collaterals were not predictive. In smaller series, lesion severity greater than 58% (38), or greater than 75% (39), and minimum lesion diameter <0.6 mm (40) or minimum lesion area <0.4 mm2 (41) were predictive of reocclusion after thrombolysis. Infarct artery residual narrowing <60% (42) or < 75% (43) was associated with better survival and left ventricular function. A minimum lumen diameter >1.5 mm was also predictive of better left ventricular function.

Coronary Angiography For The Assessment of Coronary Artery Flow: Prognostic İmplications in Patients With AMI

In recent years the importance of myocardial microcirculation in the setting of thrombolytic or angioplasty treatment of AMI has been increasingly appreciated. In-hospital mortality after thrombolytic treatment of AMI is



A B C

Figure 4: Angiograms illustrate multiple complex plaques (Mid RCA, distal RCA and mid LAD) in a patient with acute inferior myocardial infarction. Right coronary artery in LAO cranial (A) and RAO (B) positions, and the left anterior descending artery in AP cranial position (C).

closely correlated to TIMI-3 (normal) flow in the infarct artery (44). TIMI frame count has been proposed as a more reliable and reproducible measurement of the velocity of blood flow on the coronary angiogram. In 1248 patients the mortality rates in the hospital and at 30-42 days were corrrelated to a higher TIMI frame count (slower flow). Patients with TIMI-3 flow and corrected TIMI frame count <=20 had an overall 7.9% risk of adverse complications as compared to 15.5% risk in those with TIMI-3 flow but >20 frame counts (45). Some authors, on the other hand, questioned the dependency of frame count to heart rate and other variables (46). Coronary angiographic TIMI myocardial perfusion grade has been proposed by Gibson et al. (47) as a semiquantitative measure of actual myocardial perfusion at the microcirculation level. These authors reported that in a study of 762 patients, the absence of normal myocardial perfusion grade was associated with 4-5 times higher mortality in the group with angiographic TIMI-3 flow in the epicardial vessel (Figure 5).

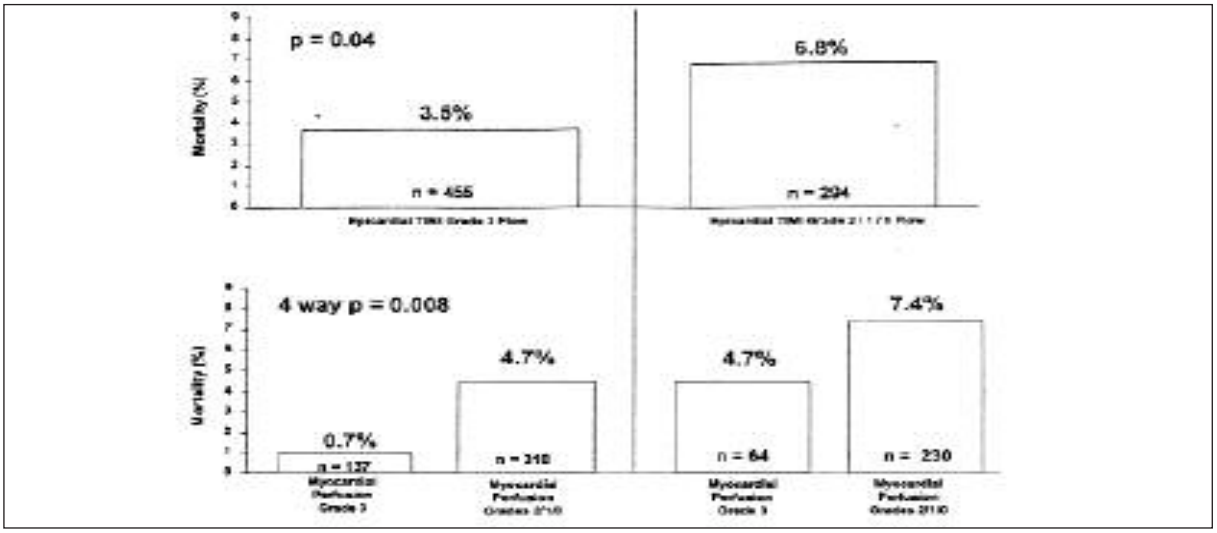


Figure 5: Top portion of the graph illustrates significantly better 30-day mortality rates in the group with TIMI-3 (normal) epicardial blood flow after thrombolysis. It is important to note that in this group of patients (bottom) those with normal myocardial perfusion (perfusion grade 3) have a significantly better mortality rate (0.7%) as compared to those with less than normal myocardial perfusion grades (4.7%). (Reproduced from reference 47 with permission).

Prognostic İnformation From Saphenous Vein Graft Angiography

Saphenous vein grafts develop progressive obstructive atherosclerosis 5 to 7 years after surgery. Occlusion of vein grafts are the main cause of recurrent ischemic events in these patients (48). However, there are limited data on the prognostic significance of graft angiographic findings. Ellis et al. (49) analyzed 1095 segments in 103 patients who underwent a PTCA procedure and were restudied in a protocol-mandated fashion. Although most recurrent ischemic events occurred as a result of the treated SVG sites, progression of SVG disease was noted more often than progression of native lesions. Events occurring > 12 months after initial treatment resulted most frequently from ischemia from progression of narrowing at untreated SVG sites (46%). Ischemic events from initially untreated SVG sites were correlated with initial percent stenosis (initial, 41% to 50%; 45% events, 31% to 40%; 18% events, < or = 30%; 2% events, p <0.001) and reference SVG diameter (p = 0.003). Campos et al. (50) identified 62 patients with 131 normal or mildly diseased (<35% stenosis) vein grafts average 6 years after surgery and restudied these grafts 5 years later (total of 11 years after initial surgery). 53% of the grafts remained normal or mildly diseased but 29% developed severe disease or totally occluded. In another study (51) 339 patients were followed for 5 years after undergoing a 3-month angiography following initial CABG. The risk of AMI or angina was not predicted by any of the coronary angiographic features except a low postoperative ejection fraction. On the other hand, lipid levels were predictive of these events.

Conclusion

Routine coronary angiography provides a wealth of information on the short- and long-term prognosis of coronary artery disease. This information should be enhanced by the clinical and functional test data to improve clinical risk assessment and treatment decisions.

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