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Clinical Risk Stratification Correlates With the Angiographic Extent of Coronary Artery Disease in Unstable Angina

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OBJECTIVES We sought to determine whether clinical risk stratification correlates with the angiographic extent of coronary artery disease (CAD) in patient with unstable angina.

BACKGROUND The Agency for Health Care Policy and Research (AHCPR) guidelines stratify patients with unstable angina according to short-term risk of myocardial infarction or death. Whether these guidelines are useful in predicting the extent of CAD is unknown.

METHODS All residents of Olmsted County, Minnesota, undergoing emergency department evaluation from January 1, 1985 through December 31, 1992 for unstable angina without a history of prior coronary artery bypass grafting, and who underwent early angiography (within seven days of presentation) were classified into low, intermediate and high risk subgroups based on AHCPR criteria.

RESULTS Seven hundred ninety-five patients underwent early angiography: 159 high risk, 572 intermediate risk and 64 low risk patients. Logistic regression analysis demonstrated that low risk patients had a greater likelihood of normal or mild CAD relative to intermediate risk (odds ratio [OR], 4.67; 95% confidence interval [CI], 2.70–8.06; $p < 0.001$) and high risk (OR, 11.1; 95% CI, 5.71–22.2; $p < 0.001$). Significant 1-, 2-, 3-vessel coronary disease or left main coronary disease was more likely in high relative to low risk (OR, 8.09; 95% CI, 4.22–15.5; $p < 0.001$), intermediate relative to low risk (OR, 4.11; 95% CI, 2.34–7.22; $p < 0.001$), and high relative to intermediate risk (OR, 1.97; 95% CI, 1.31–2.96; $p = 0.0012$).

CONCLUSIONS Among patients with unstable angina undergoing early coronary angiography, risk stratification according to the AHCPR guidelines correlates with the angiographic extent of CAD. (J Am Coll Cardiol 2001;37:2053–8) © 2001 by the American College of Cardiology

The evaluation and management of patients with unstable angina is an important clinical issue; in the U.S. alone, there are approximately 850,000 hospital admissions for unstable angina annually. Determining the prognosis of patients with unstable angina is hampered by a wide variation in the definition of unstable angina, duration of follow up and treatment differences.

In 1994, the Agency for Health Care Policy and Research (AHCPR) published a definitive guideline for the diagnosis and management of unstable angina (1). In a stepwise approach, the guideline stratifies patients with unstable angina into low, intermediate and high risk subgroups, according to the likelihood of coronary artery disease (CAD) and the short-term risk of myocardial infarction (MI) or death. The AHCPR guidelines have been validated in a population-based registry with regard to short-term prognosis (2). However, whether these guidelines are useful in predicting the presence and degree of CAD as assessed by coronary angiography is unknown. If it could be shown that risk stratification based on clinical (AHCPR) criteria correlates with angiographic coronary disease in addition to prognosis, this could provide a useful method for determining which patients with unstable angina may be suitable for early coronary intervention.

Therefore, we reviewed our population-based database to determine whether the presence and degree of CAD correlate with short-term cardiovascular risk according to AHCPR guidelines in patients presenting with unstable angina undergoing coronary angiography early in their evaluation.

METHODS

Patient population. The study retrospectively identified all residents of Olmsted County, Minnesota presenting to one of the county's three emergency departments with acute chest pain during the period January 1, 1985 through December 31, 1992. The complete medical records of this population were reviewed by an experienced nurse abstracter who identified the subset of patients from this group who had symptoms consistent with an unstable coronary syndrome. This was defined according to the Diamond classification as follows: new onset or a worsening pattern of

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Abbreviations and Acronyms

AHCPR = Agency for Health Care Policy and Research
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CI = confidence interval
ECG = electrocardiogram
FRISC = Fragmin and fast Revascularization during InStability of Coronary artery disease
MI = myocardial infarction
OR = odds ratio

ischemic chest pain (anterior or left lateral) occurring at rest or with minimal exertion and alleviated by sublingual nitroglycerin and/or rest (3).

Patients were excluded if they had ST-segment elevation indicative of acute MI on their baseline electrocardiogram (ECG), new left bundle branch block or a definitive nonischemic etiology for their chest pain at the time of presentation.

Data collection. For all eligible patients, the medical record was abstracted, including the history and detailed physical examination findings at the qualifying episode, as well as past medical history. This was carried out utilizing the resources of the Rochester Epidemiology Project, which allows capture of the health care experience of all residents of Olmsted County, Minnesota (4). Patients undergoing early angiography (≤7 days of their index emergency department visit) were identified. Using the AHCPR criteria for the short-term risk of MI and/or death, patients were retrospectively classified based on their initial emergency department presentation information into low, intermediate and high risk subgroups (see Definitions section).

DEFINITIONS

Low risk according to AHCPR criteria was defined as at least one of the following: increased angina frequency, severity or duration; angina provoked at a lower threshold; new onset angina within two weeks to two months; with normal or unchanged ECG (with no high risk or intermediate risk features present). *Intermediate risk* was defined as at least one of the following: rest angina that had resolved; rest angina of >20 min duration relieved with sublingual nitroglycerin; angina with dynamic T-wave changes; nocturnal angina; new-onset Canadian Cardiovascular Society class III or IV angina in the past two weeks; Q-waves or ST-depression <1 mm in multiple leads; or age >65 years (and no high risk features present). *High risk* was defined as at least one of the following: prolonged ongoing rest pain; pulmonary edema; angina with new or worsening mitral regurgitation murmur; rest angina with dynamic ST-changes ≥1 mm; angina with S_3 or rales; or angina with hypotension.

A history of CAD was determined based on symptoms and/or prior abnormal results of functional test, a history of MI or a history of prior coronary angiography demonstrating at least moderate coronary disease. A history of *vascular disease* included a history of CAD (as above), cerebrovascular disease including transient ischemic attack or stroke, or symptomatic or asymptomatic peripheral vascular disease. *Myocardial infarction* was considered to have occurred when at least two of the following three criteria were met: 1) chest pain >30 min; 2) persistent electrocardiographic changes suggestive of ischemia; or 3) greater than or equal to twofold elevations in serum creatine kinase levels with elevation of the MB isoform.

The degree of CAD as determined by angiography was classified as follows: 1) normal coronary angiogram; 2) mild CAD (<50% stenosis in one or more epicardial vessels); 3) moderate CAD ≥50% stenosis but <70% stenosis in one or more epicardial vessels); 4) significant single-vessel CAD (≥70% stenosis in one major epicardial vessel); 5) significant two-vessel CAD (≥70% stenosis in two major epicardial vessels); 6) significant three-vessel CAD (≥70% stenosis in all three major epicardial vessels); or 7) significant left main CAD (≥50% stenosis of the left main coronary artery) (5).

Statistical analysis. Logistic regression analysis was used to assess the correlation between the AHCPR risk profile and the presence and degree of CAD. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Additionally, sensitivity, specificity, positive and negative predictive values to correlate the degree of CAD with AHCPR risk grouping were performed. Spearman's rank correlation was used to test the correlation between a calculated myocardial jeopardy score (6) and the AHCPR risk categories.

RESULTS

Of the 6,801 residents of Olmsted County presenting to emergency departments for acute chest pain during the study period, 2,282 (33.4%) met eligibility criteria for unstable angina. Of these, 435 patients (19.1%) were classified as high risk, 1,562 patients (68.4%) were classified as intermediate risk and 285 patients (12.5%) were classified as low risk based on AHCPR guidelines. Of these 2,282 patients, 795 patients who underwent early angiography and without prior coronary artery bypass grafting (CABG) comprise the study cohort. Of patients referred for early angiography, 159 patients (20%) were classified as high risk, 572 patients (72%) were classified as intermediate risk and 64 patients (8%) were identified as low risk (Table 1). High risk patients were more likely to be older, with a prior history of CAD and MI, congestive heart failure and coronary revascularization. The incidence of hypercholesterolemia, diabetes and hypertension increased with higher AHCPR risk. High risk unstable angina patients were also more likely to have their conditions evolve into a non-ST-elevation MI during the first 24 h of hospitalization. The rates of coronary revascularization during the index hospi-

Table 1. Early Angiography: Patients and Demographics

	Low Risk (n = 64)	Intermediate Risk (n = 572)	High Risk (n = 159)	p Value
Age of patient (yr)	51.0 ± 9.4	61.1 ± 12.8	64.0 ± 13.6	< 0.00001
Male	40 (62.5)	387 (67.7)	105 (66.0)	0.68
History of MI	0 (0.0)	92 (16.1)	35 (22.0)	0.0003
History of CHF	0 (0.0)	33 (5.8)	31 (19.5)	< 0.00001
History of PTCA	0 (0.0)	34 (5.9)	10 (6.3)	0.13
History of CAD	0 (0.0)	144 (25.2)	61 (38.4)	< 0.00001
History of vascular disease	1 (1.6)	204 (35.7)	72 (45.3)	< 0.00001
Never smoked	28 (43.8)	220 (38.5)	58 (36.5)	0.60
Current smoker (past 3 yr)	15 (23.4)	138 (24.1)	41 (25.8)	0.90
Cholesterol ≥240	34 (53.1)	392 (68.5)	105 (66.0)	0.045
Diabetes	3 (4.7)	84 (14.7)	33 (20.8)	0.009
Hypertension	13 (20.3)	262 (45.8)	77 (48.4)	0.0003
MI at index presentation	11 (17.5)	169 (29.6)	98 (61.6)	< 0.00001
Mean time from ED admission date to angiogram (days)	1.5 ± 1.4	1.9 ± 1.6	1.9 ± 2.0	0.610
Jeopardy score	2.7 ± 5.1	6.8 ± 7.6	9.1 ± 8.2	< 0.00001
Percutaneous revascularization during index hospitalization	6 (9.4)	170 (29.7)	58 (36.5)	0.0003
CABG during index hospitalization	5 (7.8)	95 (16.6)	32 (20.1)	0.08
Percutaneous revascularization or CABG during index hospitalization	11 (17.2)	265 (46.3)	90 (56.6)	< 0.00001

The numbers in parentheses are percentages of the total in each group.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; ED = emergency department; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

talization also increased in frequency with higher AHCPR risk profile.

A normal coronary angiogram or mild CAD was most frequent in the low risk subgroup (Table 2). Although significant single-vessel disease was noted among 18.8% of low risk patients undergoing angiography, the frequency of multivessel disease, particularly three-vessel disease or left main CAD, was low. Conversely, among patients at intermediate or high risk, the incidence of multivessel disease was high, with three-vessel or left main CAD occurring in 14.2% of intermediate risk patients and 21.4% of high risk patients undergoing angiography. Moreover, significant 1-, 2-, 3-vessel, or left main CAD was present in 63.5% of intermediate risk patients and 77.4% of high risk patients undergoing angiography.

When excluding patients with normal coronary arteries or mild CAD, the AHCPR risk grouping no longer correlated with the extent of significant CAD (Table 3).

Logistic regression. Logistic regression analysis demonstrated that low risk patients had a greater likelihood of having angiographically normal coronary arteries or mild CAD relative to intermediate risk (OR, 4.67; 95% CI, 2.70−8.06; $p < 0.001$) and high risk (OR, 11.2; 95% CI, 5.71–22.2; $p < 0.001$). The presence of three-vessel coronary artery disease or left main CAD was associated with increasing AHCPR risk group (high risk relative to intermediate risk group OR, 1.65; 95% CI, 1.06–2.58; $p = 0.028$; intermediate risk relative to low risk group OR, 5.11; 95% CI, 1.23–21.3; $p = 0.025$; and high risk relative to low risk OR, 8.43; 95% CI, 1.96 to 36.2; $p = 0.004$). The presence of significant 1-, 2-, 3-vessel coronary disease or left-main CAD also correlated to increasing AHCPR risk grouping (high relative to intermediate risk group OR, 1.97; 95% CI, 1.31–2.96; $p = 0.0012$; intermediate relative to low risk group OR, 4.11; 95% CI, 2.34 to 7.22; $p < 0.001$; and high relative to low risk group OR, 8.09; 95% CI, 4.22–15.5; $p < 0.001$).

Table 2. Angiographic Results by Agency for Health Care Policy and Research Risk Group

	Low Risk (n = 64)	Intermediate Risk (n = 572)	High Risk (n = 159)	p Value
Normal angiogram	23 (35.9)	67 (11.7)	12 (7.5)	<0.00001
Mild CAD	19 (29.7)	99 (17.3)	11 (6.9)	0.0001
Moderate CAD	3 (4.7)	42 (7.3)	13 (8.2)	0.66
Significant 1-vessel CAD	12 (18.8)	177 (30.9)	51 (32.1)	0.11
Significant 2-vessel CAD	5 (7.8)	105 (18.4)	38 (23.9)	0.020
Significant 3-vessel CAD	1 (1.6)	44 (7.7)	21 (13.2)	0.011
Significant left main CAD	1 (1.6)	37 (6.5)	13 (8.2)	0.19
1-, 2-, 3-vessel or left main CAD	19 (29.7)	363 (63.5)	123 (77.4)	<0.00001
3-vessel or left main CAD	2 (3.1)	81 (14.2)	34 (21.4)	0.0018

The numbers in parentheses are percentages of the total in each group.
CAD = coronary artery disease.

Table 3. Angiographic Results by Agency for Health Care Policy and Research Risk Group Excluding Normal Angiograms and Mild CAD Patients

Variable	Low Risk (n = 22)	Intermediate Risk (n = 406)	High Risk (n = 136)	p Value
Moderate CAD	3 (13.6)	42 (10.3)	13 (9.6)	0.84
Significant 1-vessel CAD	12 (54.5)	177 (43.6)	51 (37.5)	0.24
Significant 2-vessel CAD	5 (22.7)	105 (22.9)	38 (27.9)	0.83
Significant 3-vessel CAD	1 (4.4)	44 (10.8)	21 (15.4)	0.20
Significant left main CAD	1 (4.5)	37 (9.1)	13 (9.6)	0.75
1-, 2-, 3-vessel or left main CAD	19 (86.4)	363 (89.4)	123 (90.4)	0.83
3-vessel or left main CAD	2 (9.1)	81 (20.0)	34 (25.0)	0.18

Numbers in parentheses are percentage of the total.
CAD = coronary artery disease.

The sensitivity and specificity of high risk classification correlating with significant 1-, 2-, 3-vessel or left main CAD was 24% and 88%, respectively, with positive and negative predictive values of 77% and 40%, respectively. Combining high and intermediate risk subgroups increased the sensitivity to 96%, but decreased the specificity to 16%, whereas positive and negative predictive values were 66% and 70%, respectively. It should be noted that predictive values are dependent on disease prevalence in the index population, and it is possible that the prevalence for CAD is higher in patients who were selected to undergo angiography than in those who were not and, therefore, these results should be interpreted accordingly.

Among the patients undergoing angiography, the mean myocardial jeopardy score correlated with the AHCPR risk categories. Low risk patients had a mean score of 2.7 ± 5.1, intermediate risk patients had a score of 6.8 ± 7.6 and high risk patients had a score of 9.1 ± 8.2 ($r = 0.19$, $p < 0.001$).

DISCUSSION

The current study demonstrates that among patients presenting with unstable angina who are referred for coronary angiography, clinical risk stratification according to AHCPR guidelines correlates with the angiographic extent of CAD. Specifically, normal coronary arteries or mild CAD were more likely to be seen in low risk patients, whereas significant CAD (1-, 2-, 3-vessel, or left main CAD) was more likely to be observed in intermediate and high risk patients. This clinical risk stratification also correlates with the previously reported method of assessing the burden of CAD (myocardial jeopardy score) (6).

Risk stratification in unstable angina. Accurate determination of the short-term prognosis of the individual patient presenting with unstable angina is hampered by the wide variability in the definition of unstable angina and treatment modalities employed in earlier studies. However, the importance of risk stratification of patients with unstable angina has increasingly been recognized. The AHCPR guidelines were published in 1994, outlining steps for the diagnosis, risk stratification and management of patients presenting with unstable angina (1). The validity of these guidelines with respect to predicting short-term prognosis of patients presenting with unstable angina has been demonstrated (2). Interestingly, it has also been shown that the AHCPR risk profile correlates with long-term prognosis as well, such that event-free survival is lower with increasing AHCPR risk group (7). Therefore, prompt identification of patients at increased risk may guide appropriate treatment, possibly impacting both short- and long-term outcome.

Early invasive strategy for unstable angina. Significant controversy exists with respect to the use of an early invasive strategy in the assessment of patients presenting with unstable angina. Although early coronary angiography is frequently utilized in the U.S., significant regional as well as intercountry variations exist in practice, primarily dictated by physician preferences, patient expectations, as well as the availability of catheterization facilities (8–12). Numerous previous studies have demonstrated either no benefit (12,13) or even a detrimental effect (14) on the rates of death or MI in patients with non-ST-elevation acute coronary syndromes undergoing an early invasive strategy. Potential explanations for the lack of any observed benefit include high rates of crossover from the noninvasive to the invasive arms, with convergent rates of angiography and subsequent coronary revascularization between the two treatment groups over time. As such, the relative benefit of one strategy versus another may not be apparent during short- or intermediate-term follow up. In addition, these studies were not designed to test the concept of risk stratification and, therefore, are unable to answer the question as to whether certain subsets of patients are more or less likely to benefit from an early invasive strategy. We have recently demonstrated that an early invasive strategy (coronary angiography performed within seven days of index presentation) was associated with a significant survival benefit during the course of long-term follow up in the intermediate and high risk patients, but not low risk patients, according to AHCPR guidelines (15). These findings are in accord with the recently published Fragmin and Fast Revascularization during Instability of Coronary artery (FRISC) II trial, which demonstrated that early coronary angiography preceded by pretreatment with low molecular weight heparin, was associated with a significant reduction in death or MI with up to 1 year of available follow up (16). Taken in total, the available data suggest that there are subsets of patients who are likely to benefit from an early invasive strategy;

similarly, there are patients who are unlikely to benefit from an early invasive strategy. The concept of risk stratification, therefore, is crucially important to identifying these respective subgroups.

Effect of coronary revascularization on survival. It has been clearly demonstrated that surgical coronary revascularization is associated with improved long-term survival in certain subsets of patients, that is, those with severe 3-vessel coronary disease or left main CAD (17–19). Although the current study does not include a large proportion of patients with such "high risk" anatomy, 3-vessel disease or LMCA disease accounted for a significant minority of patients in the intermediate and high risk categories (19% and 26.2%, respectively). In large part, the data regarding the survival benefit in these subgroups apply to those patients with chronic ischemic heart disease, although the Veterans Administration study of unstable angina demonstrated an early survival advantage (which disappeared by 10 years of follow-up) with surgical revascularization as compared to medical therapy in patients with unstable coronary syndromes and reduced left ventricular ejection fraction (20). However, we have shown that coronary revascularization, either percutaneous or surgical, during the index hospital admission for unstable angina, is associated with significant long-term survival benefit (15). Additionally, the FRISC II trial demonstrates improved survival free of MI in patients with unstable angina undergoing early angiography with a high rate of coronary revascularization (16). Therefore, there appears to be an increasing body of evidence to suggest that early revascularization in patients with acute non-ST-elevation coronary syndromes may also be associated with improved event-free survival. As such, early identification of patients with unstable angina and significant CAD may be important, since these patients appear to be most likely to benefit from an early invasive strategy leading to coronary revascularization. The AHCPR risk classification scheme appears to be useful in this regard, insofar as 65% of intermediate risk patients have significant (1-, 2-, 3-vessel, or left main) disease whereas 77% of high risk patients demonstrated angiographic evidence of significant coronary disease. When excluding patients with normal coronary angiograms or mild CAD, the AHCPR risk grouping no longer correlated with the extent of CAD on angiography. This is certainly in keeping with the fact that increasing AHCPR risk profile is associated with a much lower likelihood of insignificant CAD; indeed, most patients who were low risk had normal coronary angiograms or mild CAD, whereas only 14.5% of high risk patients had insignificant CAD.

The fact that significant coronary disease was noted in 19 low risk patients (29.7% of low risk patients undergoing angiography and 6.6% of all low risk patients) warrants further examination. Of these patients, 11 patients went on to have their conditions evolve into MI based on elevated serial serum creatine phosphokinase levels, as well as serial ECGs. Thus, although it has been previously stated that low risk patients have relatively low event rate and therefore can be dismissed safely from the emergency department based on clinical criteria, these data would suggest that an observation period in a facility such as an emergency department-based chest pain unit with subsequent determination of cardiac enzyme levels 6 to 8 h after initial presentation may be reasonable in these patients. This may potentially reduce the rate of missed MI in the emergency department setting, which would have been 3.9% in this study (11 of 285 low risk patients) if they had been dismissed directly from the emergency department setting. A routine invasive strategy in low risk patients at present does not appear to be justified; additionally, such a strategy is not cost favorable (21). However, the addition of cardiac markers to the clinical risk stratification scheme may guide the appropriate utilization of an early invasive strategy in low risk patients as well.

STUDY LIMITATIONS

This study is limited by the biases innate to a retrospective registry review. The retrospective application of the AHCPR guidelines to data present in the medical record may or may not be as accurate as prospective use of these guidelines. Referral for coronary angiography was at the discretion of the attending cardiologist, and we have previously demonstrated differences in baseline characteristics between those patients referred for coronary angiography versus those who were not. We excluded patients with prior CABG, since the myocardial jeopardy score has not been validated in this population of patients. These results apply to the population of patients with unstable angina referred for angiography from this dataset, but may not necessarily apply to the entire population of patients with unstable angina presenting for emergency room department evaluation.

CONCLUSIONS

The current study demonstrates that among patients with unstable angina who are referred for early coronary angiography, risk stratification according to the AHCPR guidelines correlates with the angiographic extent of CAD, such that intermediate and high risk patients have a high likelihood of angiographically significant coronary disease.

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