Utilization of Early Invasive Management Strategies for High-Risk Patients With Non–ST-Segment Elevation Acute Coronary Syndromes

Results From the CRUSADE Quality Improvement Initiative

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Context The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of non–ST-segment elevation acute coronary syndromes (NSTE ACS) recommend early invasive management for high-risk patients, given the benefits with this approach demonstrated in randomized clinical trials.

Objectives To determine the use and predictors of early invasive management strategies (cardiac catheterization <48 hours following presentation) in high-risk patients with NSTE ACS and to examine the association of early invasive management with mortality.

Design, Setting, and Patients The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) Quality Improvement Initiative evaluated care patterns and outcomes for 17926 high-risk NSTE ACS patients (positive cardiac markers and/or ischemic electrocardiographic changes) based on ACC/AHA guidelines recommendations at 248 US hospitals with catheterization and revascularization facilities between March 2000 and September 2002.

Main Outcome Measures Use of early invasive management within 48 hours of presentation, predictors of early invasive management, and in-hospital mortality.

Results Of the 17926 patients analyzed, 8037 (44.8%) underwent early cardiac catheterization less than 48 hours following presentation. Predictors of early invasive management included cardiology care, younger age, lack of prior or current congestive heart failure, lack of renal insufficiency, ischemic electrocardiographic changes, positive cardiac markers, white race, and male sex. Patients treated with early invasive management were more likely to be treated with medications and interventions recommended by the ACC/AHA guidelines and had a lower risk of in-hospital mortality after adjusting for differences in clinical characteristics and after comparing propensity-matched pairs (2.5% vs 3.7%, $P<.001$).

Conclusions An early invasive management strategy is not utilized in the majority of high-risk patients with NSTE ACS. This strategy appears to be reserved for patients without significant comorbidities and those cared for by cardiologists and is associated with a lower risk of in-hospital mortality.

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In the past decade, several advances have occurred in the management of non–ST-segment elevation acute coronary syndromes (NSTE ACS). Pharmacotherapies, such as intravenous platelet glycoprotein (Gp) IIb/IIIa inhibitors, low-molecular-weight heparin, and clopidogrel, have demonstrated incremental benefits for patients with NSTE ACS.[1-4] Complemen-

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tary to advances in antithrombotic and antiplatelet therapies, catheterization-based strategies for revascularization have also improved.[5] Randomized clinical trial data collectively support the use of an early invasive approach with prompt cardiac catheterization compared with an initial conservative approach that reserves cardiac catheterization for patients who develop recurrent ischemia despite medical therapy.[6,7] The Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-Thrombolysis in Myocardial Infarction (TIMI)-18 trial found that catheterization within the first 48 hours after presentation was superior to an initial strategy of medical management, particularly in high-risk patients with elevated troponin levels or ST-segment depression.[6] Similarly, The Fast Revascularization during Instability in Coronary artery disease (FRISC II) trial demonstrated a significant reduction in long-term mortality with early invasive management for NSTE ACS.[8]

Professional practice guidelines have rapidly incorporated advances in the treatment of NSTE ACS.[9,10] However, there is a time lag between clinical trial advances, revision of guidelines, dissemination of recommendations to practicing physicians, and integration into clinical practice.[11] Therefore, we sought to characterize the contemporary utilization of early invasive management strategies and determine the relationship between early invasive management and mortality in a group of high-risk NSTE patients included in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA [American College of Cardiology/American Heart Association] Guidelines) Quality Improvement Initiative.

METHODS

Patients, Inclusion Criteria, and Data Collection

Patients included in the ongoing CRUSADE Quality Improvement Initiative have ischemic symptoms at rest within 24 hours prior to presentation and high-risk features including ST-segment depression, transient ST-segment elevation, or positive cardiac markers (elevated troponin I or T and/or creatine kinase-MB > upper limit of normal for participating institutions).[12]

Data were collected only during the hospitalization in an anonymous fashion without informed consent after the institutional review board of each institution approved participation in this quality improvement initiative. Data collected included baseline clinical characteristics, use of acute medications (within 24 hours of hospital arrival), use and timing of invasive cardiac procedures, laboratory results, in-hospital clinical outcomes, and discharge therapies and interventions. Decisions regarding the use of invasive procedures were made by the treating physicians. Contraindications to specific therapies given Class IA or IB recommendations by the ACC/AHA guidelines were recorded.[9,13] Data collectors at each participating site classified patients according to race and/or ethnicity based on chart abstraction using standard definitions that were provided. These data were collected as part of baseline demographic information to see if there were differences in care based on race/ethnicity.

Analysis Cohort

To account for the expected delays in timing of diagnostic cardiac catheterization, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) for patients presenting to institutions without full revascularization capabilities, patients presenting to hospitals without angioplasty or surgical facilities were excluded from the analysis. Furthermore, we excluded patients who were transferred in from other institutions or transferred out from the initial presenting institution since complete presenting characteristics, acute treatments, clinical outcomes, and use and timing of invasive procedures were not available for these patients. Thus, the final analysis cohort comprised patients who presented directly to hospitals with catheterization laboratories and angioplasty or cardiac surgical capabilities.

Statistical Analysis

Baseline characteristics and hospital features were compared among patients who did or did not receive early invasive management (cardiac catheterization within 48 hours of hospital presentation per the ACC/AHA guidelines recommendations). Medians with 25th and 75th percentiles were reported for continuous variables and frequencies for categorical variables. χ^2 Tests were used for categorical variables, and Wilcoxon rank-sum tests were used to compare continuous variables.

To determine the factors that predict the likelihood of early invasive management, a multiple logistic regression model was developed using the stepwise approach. The predictive ability of this model was summarized using a C-index.

Since CRUSADE is an observational study, patients were not randomized by treatment. In comparing patients who underwent early catheterization to those who did not undergo early catheterization with respect to in-hospital outcomes (eg, postadmission infarction, cardiogenic shock, congestive heart failure [CHF], red blood cell transfusion, death, and the composite outcome of postadmission infarction or death), we adjusted for baseline patient clinical risk factors including age, sex, body mass index, race, family history of coronary artery disease, hypertension, diabetes, smoking status, hypercholesterolemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ST-segment depression, transient ST-segment elevation, positive cardiac markers, signs of CHF, heart rate, systolic blood pressure, and insurance status as well as for provider and hospital characteristics (physician specialty, total number of hospital beds, region of the country, PCI or CABG capabilities, and type of hospital [academic or nonacademic]) and hours of presentation. For these analyses, generalized estimating equation (GEE) models were used to adjust for correlations among clustered re-

sponses (eg, within-hospital correlations) since patients within a single hospital are more likely to be similar.[14] Furthermore, since patients who died within 48 hours would not have the chance to receive early catheterization, we performed sensitivity analyses to investigate the relationship between early catheterization and in-hospital mortality after excluding early deaths within 24 to 48 hours. We also performed subgroup analyses to explore further the association between early catheterization and in-hospital mortality across different subgroups.

Table 1. Clinical and Hospital Characteristics*

Characteristic	No Early Invasive Care (n = 9889)	Early Invasive Care (n = 8037)	*P* Value
Demographics			
Age, median (IQR), y	73 (60-81)	63 (53-73)	<.001
Female sex	4511 (45.6)	2842 (35.4)	<.001
BMI, median (IQR)	27.3 (24-30.3)	28.1 (25.2-32)	<.001
White race	7446 (75.3)	6521 (81.1)	<.001
Insurance status			
HMO/private	3834 (38.8)	4181 (52.0)	<.001
Medicaid/Medicare	5437 (55.0)	3120 (38.8)	<.001
Self/none	618 (6.3)	736 (9.2)	<.001
Risk factors			
Family history of CAD	3096 (31.3)	3376 (42.0)	<.001
Hypertension	7120 (72.0)	5283 (65.7)	<.001
Diabetes mellitus	3641 (36.8)	2229 (27.7)	<.001
Current/recent smoker	2157 (21.8)	2591 (32.2)	<.001
Hypercholesterolemia	4259 (43.1)	4026 (50.1)	<.001
Medical history			
Prior myocardial infarction	3429 (34.7)	2178 (27.1)	<.001
Prior PCI	2046 (20.7)	2095 (26.1)	<.001
Prior CABG	2289 (23.2)	1518 (18.9)	<.001
Prior CHF	2780 (28.1)	684 (8.5)	<.001
Prior stroke	1419 (14.3)	518 (6.4)	<.001
Renal insufficiency†	1945 (19.7)	530 (6.6)	<.001
Presenting characteristics			
Heart rate, median (IQR), beats/min	86 (72-102)	80 (68-94)	<.001
SBP, median (IQR), mm Hg	145 (125-166)	148 (130-168)	<.001
ST depression	4098 (41.4)	3490 (43.4)	.008
Transient ST elevation	780 (7.9)	1041 (13.0)	<.001
Positive cardiac markers	8391 (84.9)	6855 (85.3)	.41
CHF at presentation	2983 (30.2)	977 (12.2)	<.001
Hospital characteristics			
CABG facility	9251 (93.5)	7755 (96.5)	<.001
Hospital beds, median (IQR), No.	428 (291-554)	419 (288-545)	<.001
COTH hospital	3579 (36.2)	2390 (29.7)	<.001
Region			
Northeast	2092 (21.2)	1236 (15.4)	<.001
South	3347 (33.8)	2882 (35.8)	
West	983 (9.9)	808 (10.1)	
Midwest	3467 (35.1)	3111 (38.7)	
Cardiology care‡	4468 (45.2)	5577 (69.4)	<.001
Off-hours presentation§	5819 (58.8)	4319 (53.7)	<.001

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; COTH, Council of Teaching Hospitals; HMO, health maintenance organization; IQR, interquartile range; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
*Data are presented as number and percentage unless otherwise indicated. Clinical characteristics and medical history were obtained from chart abstraction.
†Defined as creatinine level greater than 2.0 mg/dL (176.8 μmol/L), calculated creatinine clearance less than 30 mL/min (0.5 mL/s), or need for chronic renal dialysis.
‡Admitted to a primary cardiology service.
§Presentation from 5 PM to 7 AM on weekdays and anytime on weekends.

The Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) 30-day mortality risk model for NSTE ACS was modified for this analysis to predict the risk of in-hospital mortality in the original PURSUIT population from presenting clinical characteristics.[15] The original PURSUIT population was divided into equal tertiles based on the adjusted risk of in-hospital mortality. The tertiles of patients were then categorized as low-risk, moderate-risk, and high-risk. The modified PURSUIT model was then applied to the CRUSADE population, which was divided into risk groups based on the predicted in-hospital mortality rate calculated for each patient from presenting clinical characteristics. The association between early catheterization and unadjusted in-hospital mortality was examined within each risk group to characterize further the impact of early catheterization among patients with similar baseline risk features.

As an additional way of accounting for nonrandom treatment assignment, we adjusted for factors favoring selection of one treatment over another using propensity scores.[16] Using multivariable GEE, a propensity score model was created to estimate the likelihood of early catheterization. Greedy matching techniques were used to match each patient with another patient of similar propensity score of receiving early catheterization.[17] The Pearson χ^2 test was used to compare mortality rates for these matched pairs between patients who did and did not undergo early catheterization.

A *P* value of <.05 was established as the level of statistical significance for all tests. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC).

RESULTS

Patients

The population for this analysis consisted of 30 295 patients with high-

risk NSTE ACS who were treated at 248 US hospitals between March 1, 2000, and September 30, 2002. After we excluded 8816 patients who were either transferred in from other hospitals or transferred out from the presenting institution, a total of 21 479 patients were left. Among these patients, 185 did not have information on hospital surgical capabilities, 1140 were admitted to hospitals without catheterization capabilities, and 2228 were admitted to hospitals without PCI or CABG capabilities. After excluding these patients, 17 926 were included in the final analysis population who presented to 248 US hospitals with diagnostic cardiac catheterization facilities and capabilities for PCI or CABG or both.

Use of Invasive Procedures

Among the 17 926 patients included in this analysis, 11 153 (62.2%) underwent cardiac catheterization at some point during their hospitalization, 8037 (44.8%) underwent early invasive management (cardiac catheterization within 48 hours of presentation), and 3116 (17.4%) underwent cardiac catheterization more than 48 hours following presentation. Of the 8037 patients who underwent early invasive management, 75% were revascularized: 4733 (58.9%) underwent PCI and 1296 (16.1%) underwent CABG. There was a large variation in the use of early invasive management at the 248 hospitals included in this analysis as the median use of early catheterization was 47.8%, but the interquartile range was 33.3% to 57.6%. Temporal analyses demonstrated a slight upward trend in the use of early invasive management from the third quarter of 2001 until the third quarter of 2002 (46.8%, 41.2%, 43.4%, 44.4%, and 48.6%, respectively).

Clinical Characteristics and Predictors of Early Invasive Management

Patients who underwent early catheterization were younger, more often male and white, more likely to be admitted to a cardiology service, and less likely to have CHF or renal insufficiency (TABLE 1). The strongest independent predictors of early invasive management included cardiology care, younger age, lack of renal insufficiency, lack of prior CHF, slower presenting heart rate, and lack of signs of CHF on presentation (TABLE 2). The C-index for the predictive model was 0.761.

Care Patterns

Patients who underwent early invasive management were more likely to receive ACC/AHA guidelines–recommended acute and discharge medications and interventions compared with patients who did not undergo early invasive management (TABLE 3, TABLE 4).

Clinical Outcomes

The unadjusted incidence of in-hospital mortality was 2.0% for patients who underwent early invasive management within 48 hours compared with 6.2% for patients who did not undergo early invasive management. The unadjusted frequencies of other adverse outcomes were lower in patients who underwent early invasive management (TABLE 5). The adjusted risks of

Table 2. Predictors of Early Invasive Management*

Variable	χ^2	Odds Ratio (95% CI)	*P* Value
Cardiology care	513.5	2.21 (2.06-2.37)	<.001
Age (per 10 y)†	218.0	0.80 (0.77-0.82)	<.001
Prior CHF	176.8	0.49 (0.44-0.55)	<.001
Renal insufficiency‡	132.6	0.51 (0.46-0.58)	<.001
Presenting heart rate (per 10/min)†	102.3	0.92 (0.91-0.93)	<.001
CHF at presentation	77.9	0.66 (0.60-0.72)	<.001
Transient ST elevation	71.0	1.61 (1.43-1.81)	<.001
ST depression		1.26 (1.16-1.36)	
Positive cardiac markers	60.6	1.51 (1.36-1.67)	<.001
White race	48.5	1.36 (1.25-1.48)	<.001
Prior PCI	48.3	1.35 (1.24-1.47)	<.001
CABG capabilities	46.5	1.68 (1.43-1.98)	<.001
Hospital angioplasty capabilities		1.41 (1.12-1.76)	
Off-hours presentation§	44.6	0.80 (0.75-0.85)	<.001
Prior stroke	42.7	0.68 (0.60-0.72)	<.001
Presenting SBP (per 10 mm Hg)†	37.6	1.03 (1.02-1.04)	<.001
Northeast (vs South) region	34.3	0.82 (0.74-0.91)	<.001
Midwest (vs South) region		1.10 (1.02-1.19)	
West (vs South) region		1.07 (0.95-1.21)	
Prior MI	33.8	0.79 (0.73-0.85)	<.001
Hypercholesterolemia	28.1	1.21 (1.13-1.29)	<.001
COTH hospital	25.7	0.80 (0.74-0.87)	<.001
Female sex	17.9	0.86 (0.80-0.92)	<.001
Prior CABG	17.5	0.83 (0.76-0.91)	<.001
Family history of CAD	15.3	1.15 (1.07-1.24)	<.001
BMI (per 5 units)	14.1	1.05 (1.03-1.08)	<.001
Hospital beds (per 100)†	13.7	0.96 (0.95-0.98)	<.001
Medicare/Medicaid vs HMO/private insurance	10.6	0.89 (0.82-0.96)	<.001
Self/none vs HMO/private insurance		0.92 (0.81-1.05)	
Current/recent smoking	4.2	1.09 (1.00-1.18)	.04
Diabetes mellitus	4.1	0.93 (0.86-1.00)	.04

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COTH, Council of Teaching Hospitals; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
*Model C-index=0.761.
†Continuous variables.
‡Defined as creatinine level greater than 2.0 mg/dL (176.8 µmol/L), calculated creatinine clearance less than 30 mL/min (0.5 mL/s), or need for chronic renal dialysis.
§Presentation to hospital between 5 PM to 7 AM during weekdays or anytime during weekends.

death and death or MI were lower in patients who underwent early invasive management, whereas the adjusted risks of cardiogenic shock and red blood cell transfusion were higher. Median length of stay was also lower in patients undergoing early invasive management (3 days: 25th, 75th percentiles: 2, 6 days) compared with patients not treated with this approach (5 days: 25th, 75th percentiles: 3, 8 days) ($P<.001$).

Sensitivity analyses (eg, excluding deaths within 24 or 48 hours) demonstrate similar findings with respect to the association between an early invasive strategy and lower mortality as seen in the overall analysis (FIGURE 1). Analyses of patient subgroups revealed similar reductions in mortality with early invasive management except for the subgroups of patients aged 75 years or older and those who were troponin-negative (Figure 1).

Patients were also stratified into low, medium, and high clinical risk based on the modified PURSUIT risk score. In all 3 risk categories, patients undergoing early invasive management had a significantly lower risk of unadjusted in-hospital mortality, although the highest-risk patients appeared to derive the greatest absolute benefit from early invasive management (FIGURE 2).

Propensity matching of patients by early invasive management status produced groups (5486 patients in each group) that were similarly matched for clinical, demographic, and hospital characteristics (all P values $>.05$ except smoking) (TABLE 6). In this propensity-matched pairs sample, the frequency of in-hospital mortality was lower in patients who underwent early invasive management (2.5% vs 3.7%, $P<.001$).

Table 3. Acute Care (<24 Hours) Patterns by Early Invasive Management*

	No Early Invasive Care, % (n = 9889)	Early Invasive Care, % (n = 8037)
Aspirin	87.7	93.8
Clopidogrel	26.1	51.3
β-Blocker	71.9	77.7
Any heparin	73.7	88.8
Unfractionated heparin	42.4	63.3
LMW heparin	36.0	32.7
Gp IIb/IIIa inhibitor	14.2	50.9

Abbreviations: Gp, glycoprotein; LMW, low-molecular-weight.
*Among patients without listed contraindications. All P values <.001.

Table 4. Discharge Care Patterns by Early Invasive Management*

	No Early Invasive Care, % (n = 9889)	Early Invasive Care, % (n = 8037)
Aspirin	85.2	92.6
Clopidogrel	38.9	63.4
β-Blocker	78.8	82.3
Statin†	70.2	76.0
ACE inhibitor‡	58.4	59.5
Diet modification counseling	64.3	73.2
Smoking cessation counseling	50.1	64.8
Cardiac rehabilitation referral	27.8	47.5

Abbreviation: ACE, angiotensin-converting enzyme.
*Among survivors without listed contraindications. All P values <.001, except for ACE inhibitor (P=.22)
†For patients with history of hypercholesterolemia or measured low-density lipoprotein cholesterol level greater than 100 mg/dL (2.59 mmol/L).
‡For patients with ejection fraction less than 40%, congestive heart failure, diabetes mellitus, or hypertension.

Table 5. In-Hospital Outcomes by Early Invasive Management

	No Early Invasive Care, % (n = 9889)	Early Invasive Care, % (n = 8037)	Adjusted Odds Ratio (95% CI)*
Mortality	6.2	2.0	0.63 (0.52-0.77)
Postadmission MI	3.7	3.1	0.95 (0.79-1.14)
Death or MI	8.9	4.7	0.79 (0.69-0.90)
Cardiogenic shock	2.3	2.6	1.88 (1.47-2.40)
CHF	13.6	6.5	0.89 (0.78-1.01)
Stroke	1.0	0.8	1.07 (0.73-1.57)
Any RBC transfusion	15.3	13.7	1.25 (1.12-1.38)

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; RBC, red blood cell.
*Adjusted risk of outcome for early invasive management vs no early invasive management as detailed in the "Methods" section.

COMMENT

We have demonstrated that utilization of an early invasive management strategy was associated with a significantly lower risk of in-hospital mortality in high-risk patients with NSTE ACS presenting to US hospitals with both catheterization and revascularization capabilities, although less than half of patients were managed with this approach. Patients undergoing early invasive management were younger and more commonly cared for by cardiologists, whereas older patients with comorbidities were less likely to undergo early invasive management. The relationship between early invasive management and improved guidelines adherence for acute and discharge medication use indicates that appropriate overall guidelines-based care is more commonly delivered to patients treated with an early invasive strategy.

The updated ACC/AHA guidelines recommend an early invasive strategy for NSTE ACS patients presenting with high-risk features including ischemic electrocardiographic changes, elevated troponin levels, new CHF symptoms, left ventricular dysfunction, prior PCI within 6 months, prior CABG, and hemodynamic instability.[9] Whereas ischemic electrocardiographic changes, positive cardiac markers, and prior PCI were significant predictors of early invasive management in this analysis, patients with prior CABG, prior or current CHF, and faster presenting heart rate were significantly less likely to undergo early invasive management. These findings may be explained by the strong association of cardiology care with early invasive management, as cardiologists have been shown to provide appropriate evidence-based care more commonly than general practitioners, but also suggest that features that may be perceived to increase the risks associated with invasive procedures (renal insufficiency, advanced age, CHF) also strongly influence decisions regarding use of invasive cardiac procedures.[18,19] Factors influencing physician decision making are difficult to

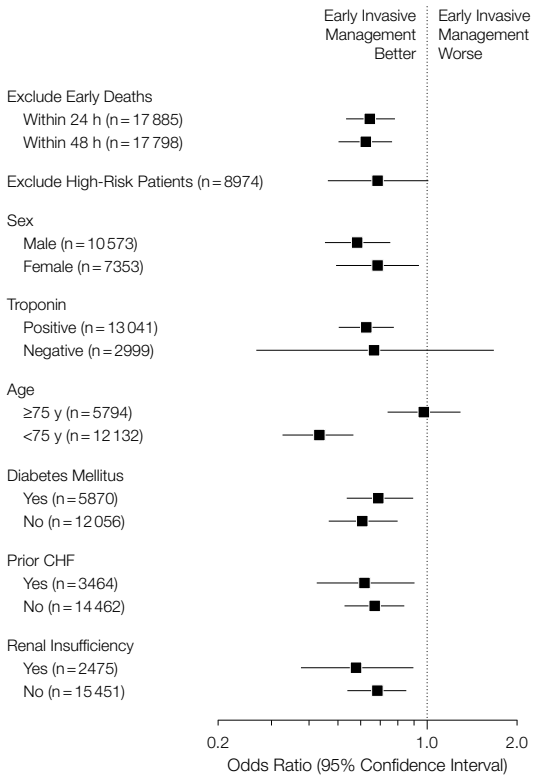
ascertain, but it appears that younger, healthier patients selectively undergo early invasive management in the United States, while older patients with more comorbidities are treated conservatively, even though these patients have a higher risk of mortality and may derive greater absolute benefit from aggressive management.

Disparities in the utilization of invasive cardiac procedures demonstrated in this analysis appear to be related to longstanding treatment biases. A previous registry of NSTE ACS patients from the last decade showed that elderly patients, women, and minorities were significantly less likely to be referred for cardiac catheterization during the initial hospitalization.[20] Other studies have also demonstrated similar referral biases and underutilization of cardiac catheterization in the elderly, women, and minorities.[21,22] Even though recent studies have shown significant reductions in adverse clinical outcomes with early invasive management and revascularization in patients with NSTE ACS who are at highest risk for adverse outcomes, the elderly, and those with renal insufficiency, we have shown high-risk features, advanced age, and renal insufficiency are negative predictors of early invasive management.[23-27] Thus, preexisting treatment biases present significant obstacles that must be overcome to improve the outcomes of undertreated subgroups of patients with NSTE ACS who are unlikely to be managed aggressively in current practice.

Notwithstanding biases in the use of invasive procedures, the greater use of acute evidence-based medical therapies in patients receiving early invasive management suggests that overall guidelines adherence tends to mirror trends in procedural utilization. Antiplatelet therapies, including clopidogrel and intravenous Gp IIb/IIIa inhibitors, have been shown to reduce the composite of death or MI in patients with NSTE ACS, and these therapies were used much more commonly in patients undergoing early invasive management.[1,4,28,29] Furthermore, patients undergoing early invasive management also more commonly received other acute and discharge therapies designated as Class IA or IB recommendations by the ACC/AHA guidelines.[9,13] While the differential impact of multiple medical therapies and revascularization on clinical outcomes in an observational analysis is difficult to elucidate and highly confounded by the periprocedural use of medications (heparin, clopidogrel, Gp IIb/IIIa inhibitors) in patients undergoing PCI, these results suggest that evidence-based medical therapies are underutilized in higher-risk patients in the same fashion as early invasive management strategies.

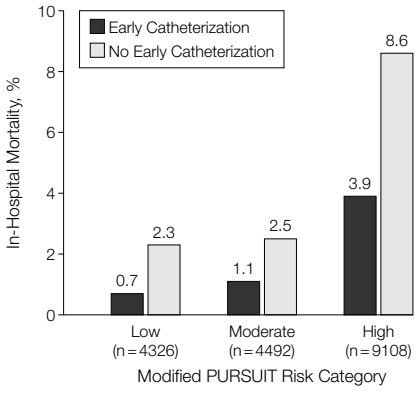
Several contemporary randomized clinical trials have shown clinical benefits with a strategy of early invasive management and revascularization, but early invasive management was asso-

Figure 1. Sensitivity and Subgroup Analyses for Adjusted In-Hospital Mortality by Utilization of an Early Invasive Management Strategy (N = 17 926)



High-risk is defined as age older than 80 years, chronic renal insufficiency, prior congestive heart failure (CHF), prior stroke, signs of CHF at presentation, or presenting systolic blood pressure less than 90 mm Hg. There are missing data for troponin positive and negative as some patients qualified for entry based on creatine kinase-MB or electrocardiographic criteria and did not have a troponin measurement.

Figure 2. Unadjusted In-Hospital Mortality Rates by Early Catheterization Among Risk Categories Determined From Presenting Clinical Characteristics



P values for comparisons within each risk group were <.001. PURSUIT indicates the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy trial.

ciated with a significant survival benefit only in the FRISC II trial.[6,8] Older trials such as Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) did not find a benefit with an early invasive strategy, but technological advances such as intracoronary stents and better adjuvant pharmacotherapies may explain the difference between VANQWISH and trials such as TACTICS-TIMI 18 or FRISC II and perhaps the current finding from CRUSADE.[23,24,30] Whereas the mortality benefit with early invasive management in FRISC II was not apparent until after 3 months,[8] the survival advantage demonstrated in CRUSADE occurred during the initial hospitalization, but the higher rate of in-hospital mortality in CRUSADE compared with clinical trials may have led to a greater degree of absolute benefit. However, the relationship of lower mortality with early invasive management in CRUSADE may have been somewhat overestimated given the significant selection biases demonstrated in the use of early invasive management. Finally, there is also a greater separation of strategies in this analysis from CRUSADE compared with randomized trials (in which patients assigned to a conservative approach would still undergo catheterization and revascularization for recurrent or inducible ischemia).

Table 6. Baseline Characteristics Comparisons on Propensity-Matched Pairs by No Early Catheterization vs Early Catheterization*

Characteristic	No Early Invasive Care (N = 5486)	Early Invasive Care (N = 5486)	*P* Value
Demographics			
Age, median (IQR), y	66 (55-77)	66 (56-76)	.27
Female sex	2189 (39.90)	2173 (39.61)	.76
BMI, median (IQR)	28 (25-32)	28 (25-32)	.59
White race	4249 (77.45)	4290 (78.20)	.35
Insurance status			
HMO/private	2488 (45.35)	2578 (46.99)	.08
Medicaid/Medicare	2530 (46.12)	2479 (45.19)	.33
Self/none	468 (8.53)	429 (7.82)	.17
Risk factors			
Family history of CAD	2052 (37.40)	2074 (37.81)	.66
Hypertension	3816 (69.56)	3758 (68.50)	.23
Diabetes mellitus	1742 (31.75)	1721 (31.37)	.67
Current/recent smoker	1502 (27.38)	1609 (29.33)	.02
Hypercholesterolemia	2676 (48.78)	2634 (48.01)	.42
Medical history			
Prior myocardial infarction	1653 (30.13)	1633 (29.77)	.68
Prior PCI	1377 (25.10)	1344 (24.50)	.47
Prior CABG	1171 (21.35)	1156 (21.07)	.73
Prior CHF	630 (11.48)	667 (12.16)	.27
Prior stroke	464 (8.46)	467 (8.51)	.92
Renal insufficiency†	478 (8.71)	499 (9.10)	.48
Presenting characteristics			
Heart rate, median (IQR), beats/min	82 (70-97)	82 (70-96)	.58
SBP, median (IQR), mm Hg	147 (129-168)	147 (128-167)	.49
ST depression	2233 (40.70)	2175 (39.65)	.26
Transient ST elevation	554 (10.10)	593 (10.81)	.22
Positive cardiac markers	4648 (84.72)	4661 (84.96)	.73
CHF at presentation	890 (16.22)	895 (16.31)	.89
Hospital characteristics			
CABG facility	5246 (95.63)	5247 (95.64)	.96
Hospital beds, median (IQR), No.	426 (291-552)	428 (291-552)	.08
COTH hospital	1846 (33.65)	1799 (32.79)	.34
Region			.82
Northeast	965 (17.59)	985 (17.95)	
South	1952 (35.58)	1933 (35.24)	
West	542 (9.88)	559 (10.19)	
Midwest	2027 (36.95)	2009 (36.62)	
Cardiology care‡	3346 (60.99)	3351 (61.08)	.92
Off-hours presentation§	3051 (55.61)	3094 (56.40)	.41

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; COTH, Council of Teaching Hospitals; HMO, health maintenance organization; IQR, interquartile range; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
*Data are presented as number and percentage unless otherwise indicated.
†Defined as creatinine level greater than 2.0 mg/dL (176.8 µmol/L), calculated creatinine clearance less than 30 mL/min (0.5 mL/s), or need for chronic renal dialysis.
‡Admitted to a primary cardiology service.
§Presentation from 5 PM to 7 AM on weekdays and anytime on weekends.

This early CRUSADE experience clearly documents a gap between the evidence-based ACC/AHA guidelines recommendations and actual clinical practice. Indeed, lack of compliance with guidelines appears to be prevalent across a variety of medical conditions.[31] In the case of application of an early invasive strategy, perhaps part of the reluctance of physicians to apply the guidelines is due to concerns that the guidelines may not be valid in certain subsets of high-risk patients encountered in daily clinical practice[32] but not enrolled or underrepresented in clinical trials, such as women or elderly patients or those with heart or renal failure. However, observational analyses such as this one may provide some degree of reassurance of the applicability of randomized trial data to patients treated in routine practice.[25] Another possible reason for the disconnect between guidelines recommendations and actual practice may have to do with inadequacies in the way that care for ACS is delivered and it may be best approached as health care systems' deficiencies rather than as an individual practitioner's shortcoming.[33] For example, regionalization of care for NSTE ACS at "heart attack" centers, in a man-

ner analogous to trauma centers, has been proposed as a means to improve care, which would certainly lead to an appropriate increase in use of an early invasive strategy, especially if community hospitals were specifically directed to transfer rapidly high-risk NSTE ACS patients for early catheterization, but significant political obstacles must be overcome before this type of system could be implemented.[34]

As a dynamic quality improvement initiative, CRUSADE will attempt to modify practice via continuous feedback to participating institutions regarding benchmarked adherence to the ACC/AHA guidelines, implementation of quality improvement interventions such as standardized admission orders, and other educational efforts. Within this context, the slight upward trends in the use of early invasive management during the study period are encouraging. The CRUSADE initiative will complement other ongoing efforts to improve cardiovascular care through adherence to established guidelines, such as the AHA's Get with the Guidelines program and the ACC's Guidelines Applied in Practice Initiative.[35,36]

Limitations

There are certain limitations in this retrospective, observational analysis. First, the revisions to the ACC/AHA guidelines that gave a Class IA recommendation for early invasive management were first released in March 2002 and were not published until October 2002 (spanning the end of the study period), so this study may not have been long enough to evaluate the full effect of the updated guidelines on practice patterns.[9] However, the original 2000 ACC/AHA guidelines for NSTE ACS gave a Class IB recommendation for early invasive management, so presumably this approach should have been considered in the same fashion as other generally accepted Class IB acute care recommendations from the 2000 guidelines, such as β-blockers and heparin.[13] Second, these data may represent a "best-case" scenario, as sites participate in CRUSADE on a voluntary basis and may have had an interest in quality improvement and therefore may have been more likely to adhere to practice guidelines than other US hospitals. Third, cardiology care was the strongest predictor of early invasive management, but this variable only described the primary admitting service and did not account for the impact of cardiology consultation on treatment decisions. Fourth, the decision to perform cardiac catheterization was not randomized but was at the discretion of the treating physician. Unmeasured confounding variables may have accounted for some of the differences in mortality, although propensity matching and sensitivity analyses were performed to attempt to address this limitation. Fifth, there may have been appropriate contraindications to cardiac catheterization that were not collected, unlike the situation with medications where contraindications were documented and were used to determine medication usage rates in "ideal" patients. Sixth, the impact of revascularization procedures following catheterization on clinical outcomes was not assessed in this analysis, so the impact of an early invasive management strategy was not fully characterized. Seventh, because long-term outcomes are not followed in CRUSADE, the long-term outcomes of early invasive management were not determined. Finally, we analyzed treatment only at hospitals with revascularization capabilities, but the underutilization of early invasive management may be even greater for patients who initially present to community hospitals without catheterization or revascularization facilities and exclusion of these patients from the analysis represents a selection bias.

Conclusions

An early invasive management strategy is associated with lower in-hospital mortality in NSTE ACS patients treated in routine clinical practice. This strategy, already validated in randomized clinical trials, is utilized in a minority of high-risk NSTE ACS patients and appears to be preferentially reserved for younger patients without comorbidities who were cared for by cardiologists. Therefore, quality improvement efforts should focus on educational interventions that target noncardiologists involved in the care of NSTE ACS patients and on improving the appropriate use of invasive cardiac procedures and other guidelines recommendations for all high-risk patients.

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Acquisition of data: Bhatt, Roe, Peterson, Cannon, Cohen, Kleiman, Peacock, Pollack, Gibler.
Analysis and interpretation of data: Bhatt, Roe, Peterson, Li, Chen, Harrington, Greenbaum, Berger, Cannon, Cohen, Gibson, Saucedo, Hochman, Boden, Brindis, Peacock, Smith, Pollack, Gibler, Ohman.
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Study supervision: Roe, Peterson, Gibson, Ohman.
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