

The Effect of Routine, Early Invasive Management on Outcome for Elderly Patients with Non–ST-Segment Elevation Acute Coronary Syndromes

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Background: Although increasing age is an important risk factor for adverse outcome among patients with acute coronary syndromes, elderly patients are more often managed conservatively.

Objective: To examine outcome according to age and management strategy for patients with unstable angina and non–ST-segment elevation myocardial infarction (MI).

Design: Randomized, controlled trial conducted from December 1997 to June 2000.

Setting: 169 community and tertiary care hospitals in 9 countries.

Patients: 2220 patients hospitalized with unstable angina and non–ST-segment elevation MI who were randomly assigned to an early invasive or conservative management strategy.

Interventions: Medical therapy and coronary angiography at 4 to 48 hours versus medical therapy and predischARGE exercise testing.

Measurements: Rates of 30-day and 6-month mortality, nonfatal MI, rehospitalization, stroke, and hemorrhagic complications.

Results: Among patients 65 years of age and older, the early invasive strategy compared with the conservative strategy yielded

an absolute reduction of 4.8 percentage points (8.8% vs. 13.6%; $P = 0.018$) and a relative reduction of 39% in death or MI at 6 months. Outcomes of the 2 strategies were similar, however, among patients younger than 65 years of age (6.1% vs. 6.5%; $P > 0.2$). Among patients older than 75 years of age, the early invasive strategy conferred an absolute reduction of 10.8 percentage points (10.8% vs. 21.6%; $P = 0.016$) and a relative reduction of 56% in death or MI at 6 months. The additional cost per death or MI prevented with the early invasive strategy was lower for elderly patients, but major bleeding rates were higher with this strategy in patients older than 75 years of age (16.6% vs. 6.5%; $P = 0.009$).

Limitations: Because this study involved patients in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction (TACTICS–TIMI) 18 trial, its generalizability to elderly patients with excluded comorbid conditions is unknown.

Conclusion: Despite an increased risk for major bleeding in patients older than 75 years of age, a routine early invasive strategy can significantly improve ischemic outcomes in elderly patients with unstable angina and non–ST-segment elevation MI.

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Unstable angina and non–ST-segment elevation myocardial infarction (MI) result in more than 1.4 million hospital admissions in the United States each year (1). Most of these admissions involve patients older than 65 years of age, and increased age has been identified as an important risk factor for death or recurrent MI. Physicians caring for these patients are faced with immediate decisions about substantially different management strategies that may significantly affect short- and long-term outcome.

The early invasive strategy entails routine cardiac catheterization and revascularization when deemed appropriate. The conservative strategy calls for in-hospital observation and predischARGE stress testing; cardiac catheterization is reserved for spontaneous or inducible high-risk ischemia. Results of the recent Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction (TACTICS–TIMI) 18 trial (2), the Fast Revascularisation during InStability in Coronary artery disease (FRISC) II trial (3, 4), the Randomized Intervention Trial of unstable Angina 3 (RITA 3) (5), and other studies (6, 7) suggest that routine early invasive management yields superior outcomes in a broad population of patients with unstable an-

gina and non–ST-segment elevation MI. However, because elderly persons are at greater risk for complications with catheterization and revascularization procedures, the benefit of such a strategy in this subgroup remains uncertain.

Elderly persons have traditionally been underrepresented in clinical trials of acute coronary syndromes (8). Previous studies examining outcomes in elderly patients with non–ST-segment elevation acute coronary syndromes who were randomly assigned to an invasive or conservative strategy have shown conflicting results. Among patients 65 years of age and older, the TIMI IIIB trial (9) demonstrated reduced occurrence of death or nonfatal MI at 1 year in those randomly assigned to a routine invasive strategy. However, for patients 60 years of age and older who had non–Q-wave MI, early invasive management in the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial (10) resulted in increased rates of death and MI at 6 months. In current clinical practice, older patients with acute coronary syndromes are less likely to undergo invasive procedures than are younger patients (11–15). In addition, the cost-effectiveness of an invasive management strategy in elderly persons has not been well defined. Therefore, to help resolve current un-

certainties regarding appropriate management of elderly patients with non-ST-segment elevation acute coronary syndromes, we analyzed clinical outcome by age in patients who were randomly assigned to an early invasive or conservative management strategy in the TACTICS-TIMI 18 trial.

METHODS

Study Sample

The study group included the 2220 patients participating in the TACTICS-TIMI 18 trial. The design and methods (16, 17) and primary results (2) have been reported elsewhere. In brief, eligible patients were older than 18 years of age, presented to 169 participating hospitals in 9 countries between 18 December 1997 and 22 December 1999, and had had an episode of angina in the preceding 24 hours. The episode of angina had to be characterized by an accelerating pattern and prolonged (>20 minutes) or recurrent episodes at rest or with minimal effort. In addition, patients had to be candidates for coronary revascularization and had to have at least 1 of the following: ST-segment depression of 0.05 mV or greater, transient (<20 minutes) ST-segment elevation (≥ 0.1 mV), or T-wave (≥ 0.3 mV) inversion in 2 or more leads not known to be old; elevated levels of cardiac markers; or documented history of coronary disease. Patients were excluded if they had persistent ST-segment elevation; secondary angina; percutaneous coronary revascularization or coronary bypass surgery within the previous 6 months; a history of gastrointestinal bleeding, platelet disorder, or thrombocytopenia; any history of hemorrhagic cerebrovascular disease or a history of nonhemorrhagic cerebrovascular disease or transient ischemic attack within 1 year; left bundle-branch block or paced rhythm; severe congestive heart failure or cardiogenic shock; clinically important systemic disease; serum creatinine concentration greater than 220 $\mu\text{mol/L}$ (>2.5 mg/dL); treatment with a glycoprotein IIb/IIIa antagonist within the past 96 hours; or ongoing long-term treatment with ticlopidine, clopidogrel, or warfarin.

The institutional review board at each center approved the study protocol. Written informed consent was required from all patients before participation.

Interventions

The protocol directed that participants receive aspirin, 325 mg/d (unless contraindicated); intravenous unfractionated heparin at an initial bolus of 5000 U, followed by an infusion at a rate of 1000 U/h for 48 hours titrated to an activated partial thromboplastin time of approximately 60 to 85 seconds; and tirofiban (Aggrastat, formerly owned by Merck & Co., West Point, Pennsylvania; currently owned by Guilford Pharmaceuticals Inc., Baltimore, Maryland), administered intravenously in a loading dose of 0.4 $\mu\text{g/kg}$ of body weight per minute for 30 minutes and followed by a maintenance infusion of 0.1 $\mu\text{g/kg}$ per minute for 48 hours or until revascularization (and for ≥ 12 hours after

Context

Older patients with coronary disease are often managed conservatively.

Contribution

This multicenter trial involved 2220 patients with unstable angina and non-ST-segment elevation myocardial infarction (MI). Subgroup analyses by age showed the following absolute reductions in 6-month death and MI for patients randomly assigned to early invasive therapy involving angiography versus medical therapy: 0.4 percentage point in patients younger than age 65 years, 4.8 percentage points in patients age 65 years or older, and 10.8 percentage points in patients older than age 75 years. Patients older than age 75 years had an absolute increase of 10.1 percentage points in major bleeding with early invasive therapy.

Implications

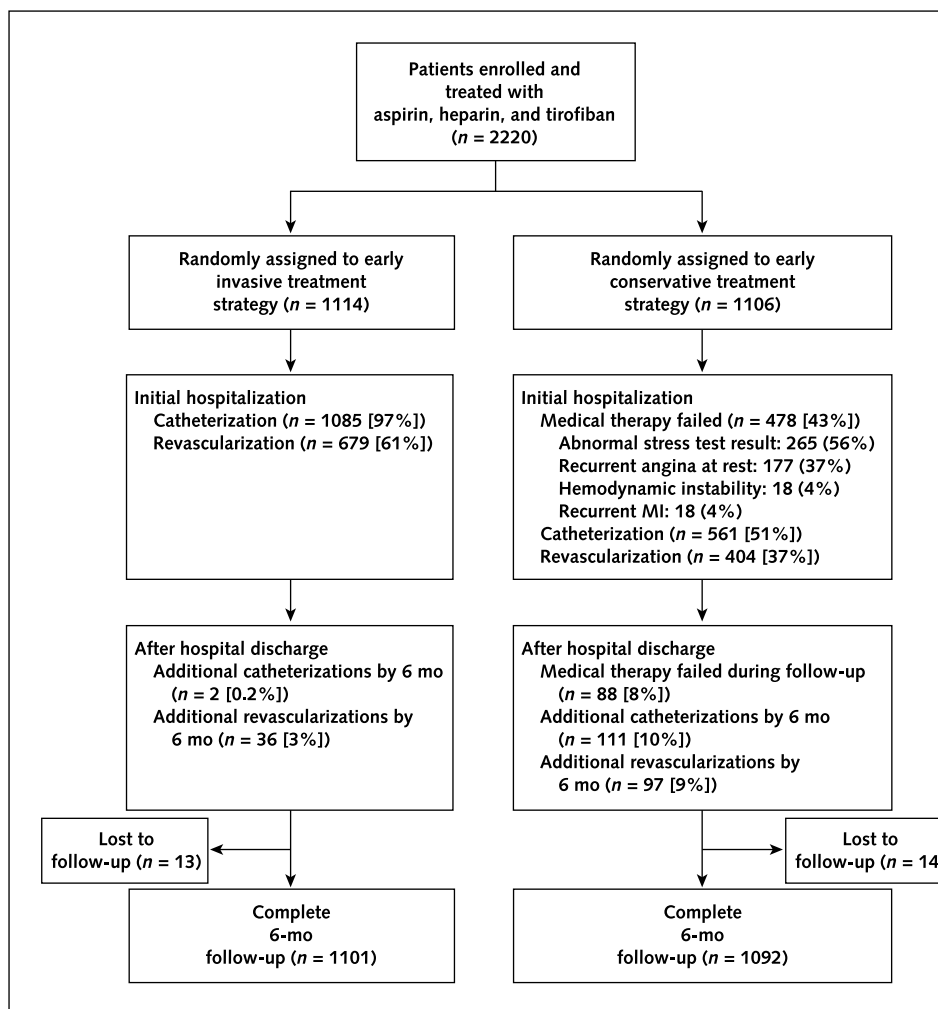
Older patients with unstable angina and non-ST-segment elevation MI have fewer ischemic but more bleeding events with early invasive therapy than do younger patients.

—The Editors

percutaneous coronary revascularization procedures). The treating physician decided whether to use other medications, such as β -blockers or angiotensin-converting enzyme inhibitors.

Through a centralized system, patients were randomly assigned, stratified by center, to the early invasive or conservative treatment strategy (Figure 1). Patients assigned to the early invasive treatment strategy were to undergo coronary angiography 4 to 48 hours after randomization and have revascularization when appropriate. Patients assigned to the early conservative strategy were treated medically and, if stable, underwent an exercise tolerance test before discharge. Coronary angiography was reserved for patients who had certain high-risk characteristics consistent with failure of medical therapy or stress-induced ischemia (16). Creatine kinase and the MB isoform of creatine kinase were measured on site every 8 hours for 24 hours after randomization, as well as for episodes of recurrent angina suggestive of MI and after all revascularization procedures. The TIMI risk score for patients with unstable angina and MI without ST-segment elevation was determined at baseline; this is a simple prognostication scheme providing a numerical score by summing 7 variables (age ≥ 65 years, ≥ 3 risk factors for coronary artery disease, previous coronary stenosis of $\geq 50\%$, ST-segment deviation on electrocardiogram at presentation, ≥ 2 anginal events in the previous 24 hours, use of aspirin in the previous 7 days, and elevated serum levels of cardiac markers) that predict death and ischemic events (18). The TIMI risk score groupings

Figure 1. Flow diagram of the study.



of 0 to 2, 3 to 4, and 5 to 7 have been previously shown to predict low, intermediate, and high risk for death and ischemic events (16).

Outcomes and Follow-up

Each patient was monitored for clinical end points before hospital discharge and had a follow-up telephone interview at day 30 and at 6 months. The last follow-up was completed in June 2000. Medical records were examined to verify all end points. Twenty-seven patients (1.2%) were lost to follow-up at 6 months and were censored at time of last documented contact. End points were defined by using standard TIMI definitions (19). The primary end point of the overall TACTICS-TIMI 18 trial was the combined incidence of death, nonfatal MI, and rehospitalization for an acute coronary syndrome at 6 months. We chose the composite of death and nonfatal MI as the primary outcome measure to provide an objectively determined and widely used end point for similar outcome trials of acute coronary syndromes. Patients were monitored on site for complications of management, and bleeding was

monitored for at least 24 hours after the study medication was withdrawn. Major bleeding was defined as a decrease in blood hemoglobin level of at least 50 g/L (≥ 5 g/dL), bleeding requiring transfusion of 2 or more units of blood, bleeding requiring corrective surgery, intracranial or retroperitoneal hemorrhage or cardiac tamponade, or any combination of these events. An independent committee whose members were unaware of patients' treatment assignments adjudicated all primary end points.

Statistical Analysis

The comparison of end points in patients stratified by age (<65 years vs. ≥ 65 years) was a prespecified analysis of the protocol. An additional post hoc analysis stratified patients into 4 age groups: 55 years of age or younger, older than 55 to 65 years of age, older than 65 to 75 years of age, and older than 75 years of age. Pearson chi-square analysis was used to compare categorical end points. Logistic regression analysis was used to evaluate the treatment effect on the clinical end points and to assess the interaction between age and treatment. Because age is one of the vari-

Table 1. Baseline Characteristics of Patients by Age Group*

Characteristic	Patients <65 Years of Age (n = 1258)	Patients ≥65 Years of Age (n = 962)	P Value
Mean age ± SD, y	53.4 ± 7.2	72.9 ± 5.6	<0.001
Women, %	29.2	40.5	<0.001
White ethnicity, %	73.0	83.6	<0.001
Previous MI, %	39.6	38.3	>0.2
Previous aspirin use, %	65.0	68.5	0.085
ST-segment changes, %	34.7	43.2	<0.001
ST-segment or T-wave changes, %	56.1	63.2	<0.001
MI without ST-segment elevation, %	36.4	38.3	>0.2
Troponin T level > 0.01 μg/L, %	50.2	59.3	<0.001
Diabetes, %	25.9	29.8	0.041
Arrhythmias, %	26.4	33.8	<0.001
History of angina, %	12.1	14.0	0.175
History of CHF, %	4.7	10.6	<0.001
History of hypertension, %	62.1	71.3	<0.001
Current smoker, %	39.8	11.6	<0.001
History of hypercholesterolemia, %	62.2	58.6	0.091
β-Blockers at admission, %	22.7	25.1	>0.2
Nitrates at admission, %	23.7	27.0	0.072
ACE inhibitors at admission, %	9.1	8.8	>0.2
TIMI risk score, %			<0.001
0–2	37.0	9.4	
3–4	56.8	63.7	
5–7	6.2	26.9	

* ACE = angiotensin-converting enzyme; CHF = congestive heart failure; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

ables of the TIMI risk score, the interaction between age and TIMI risk score with treatment was analyzed by logistic regression with the age variable removed from the score. In-trial costs for all U.S. patients who were not veterans were estimated from hospital bills and other patient-reported resource use; cost-effectiveness was evaluated in terms of additional cost per death or MI prevented (20).

Role of the Funding Source

The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Among the 2220 patients enrolled in TACTICS–TIMI 18, 962 (43%) were 65 years of age or older. All but 27 patients (1.2%) completed 6 months of follow-up. Table 1 shows the baseline characteristics of patients younger than 65 years of age and those 65 years of age or older. Compared with younger patients, patients 65 years

of age or older were more often women and more often white. Certain characteristics traditionally associated with higher risk among patients with acute coronary syndromes, including diabetes mellitus and congestive heart failure, ST-segment changes on electrocardiography, and elevated levels of serum troponin T, were more common among patients 65 years of age or older. The proportion of patients enrolled with a diagnosis of non–ST-segment elevation MI did not differ between the 2 groups. Cigarette smoking was less common among elderly persons. The distribution of TIMI risk score among patients 65 years of age or older differed significantly from that among younger patients. Intermediate to high TIMI risk scores (scores ≥3) characterized 90.6% of the elderly patients, whereas only 63.0% of patients younger than 65 years of age had similar scores ($P < 0.001$).

Table 2 shows the use of cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass graft surgery during the index hospitalization in pa-

Table 2. Cardiac Procedures Performed, according to Age and Treatment Group

Procedure	Patients ≤55 Years of Age, %	Patients >55–65 Years of Age, %	Patients >65–75 Years of Age, %	Patients >75 Years of Age, %	P Value
Cardiac catheterization					
Invasive strategy	97.9	98.4	96.9	95.0	0.15
Conservative strategy	48.0	51.2	54.6	48.9	>0.2
Percutaneous coronary intervention					
Invasive strategy	43.0	37.5	42.4	42.5	>0.2
Conservative strategy	24.5	21.9	25.8	20.9	>0.2
Coronary artery bypass graft surgery					
Invasive strategy	13.7	23.7	22.4	19.4	0.006
Conservative strategy	9.0	16.5	14.8	11.5	0.020

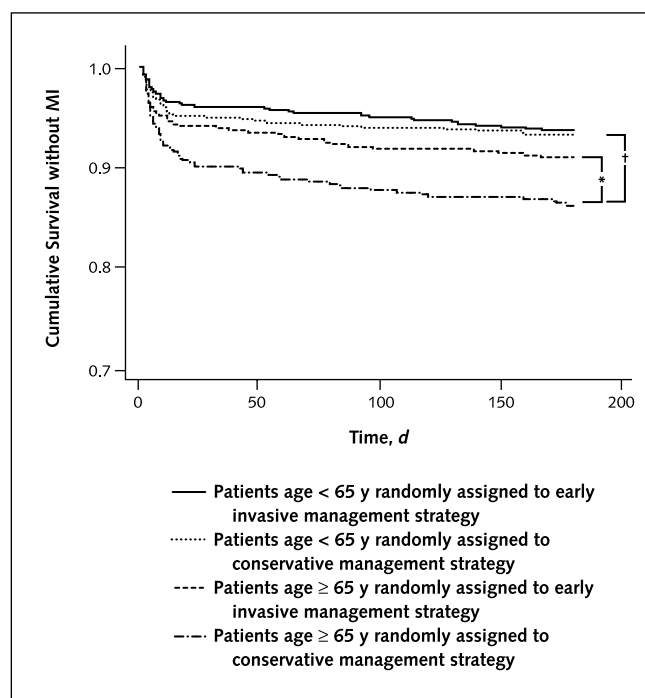
Table 3. Clinical Outcomes Associated with the Early Invasive Strategy Compared with the Conservative Strategy in Younger and Older Patients*

Outcome	Patients <65 Years of Age			Patients ≥65 Years of Age		
	Invasive Strategy (n = 623), %	Conservative Strategy (n = 635), %	Odds Ratio (95% CI)	Invasive Strategy (n = 491), %	Conservative Strategy (n = 471), %	Odds Ratio (95% CI)
30 d						
Death	1.1	0.6	1.79 (0.52–6.15)	3.7	3.0	1.24 (0.61–2.53)
MI	2.9	4.3	0.67 (0.37–1.23)	3.3	7.9	0.40 (0.22–0.72)
Death or MI	3.9	4.9	0.78 (0.45–1.35)	5.7	9.8	0.56 (0.34–0.91)
Rehospitalization for ACS	3.9	5.2	0.73 (0.43–1.25)	2.9	5.9	0.46 (0.24–0.89)
Death, MI, or rehospitalization for ACS	6.7	8.5	0.78 (0.51–1.18)	8.2	13.2	0.59 (0.38–0.89)
6 mo						
Death	1.8	1.7	1.02 (0.44–2.37)	5.3	5.9	0.88 (0.51–1.53)
MI	4.7	4.9	0.95 (0.57–1.60)	4.9	9.6	0.49 (0.29–0.81)
Death or MI	6.1	6.5	0.94 (0.60–1.48)	8.8	13.6	0.61 (0.41–0.92)
Rehospitalization for ACS	11.7	14.2	0.80 (0.58–1.12)	10.2	13.2	0.75 (0.50–1.11)
Death, MI, or rehospitalization for ACS	14.9	17.8	0.81 (0.60–1.09)	17.1	21.7	0.75 (0.54–1.03)

* ACS = acute coronary syndrome; MI = myocardial infarction.

tients stratified by age. In this analysis, cardiac catheterization was performed at equivalent rates across all age groups in at least 95% of patients randomly assigned to early invasive management and in 48% to 55% of conservatively managed patients. This demonstrates general ad-

Figure 2. Kaplan–Meier curves for 6-month death or nonfatal myocardial infarction (MI) according to age and treatment strategy among patients with unstable angina and non–ST-segment elevation MI.

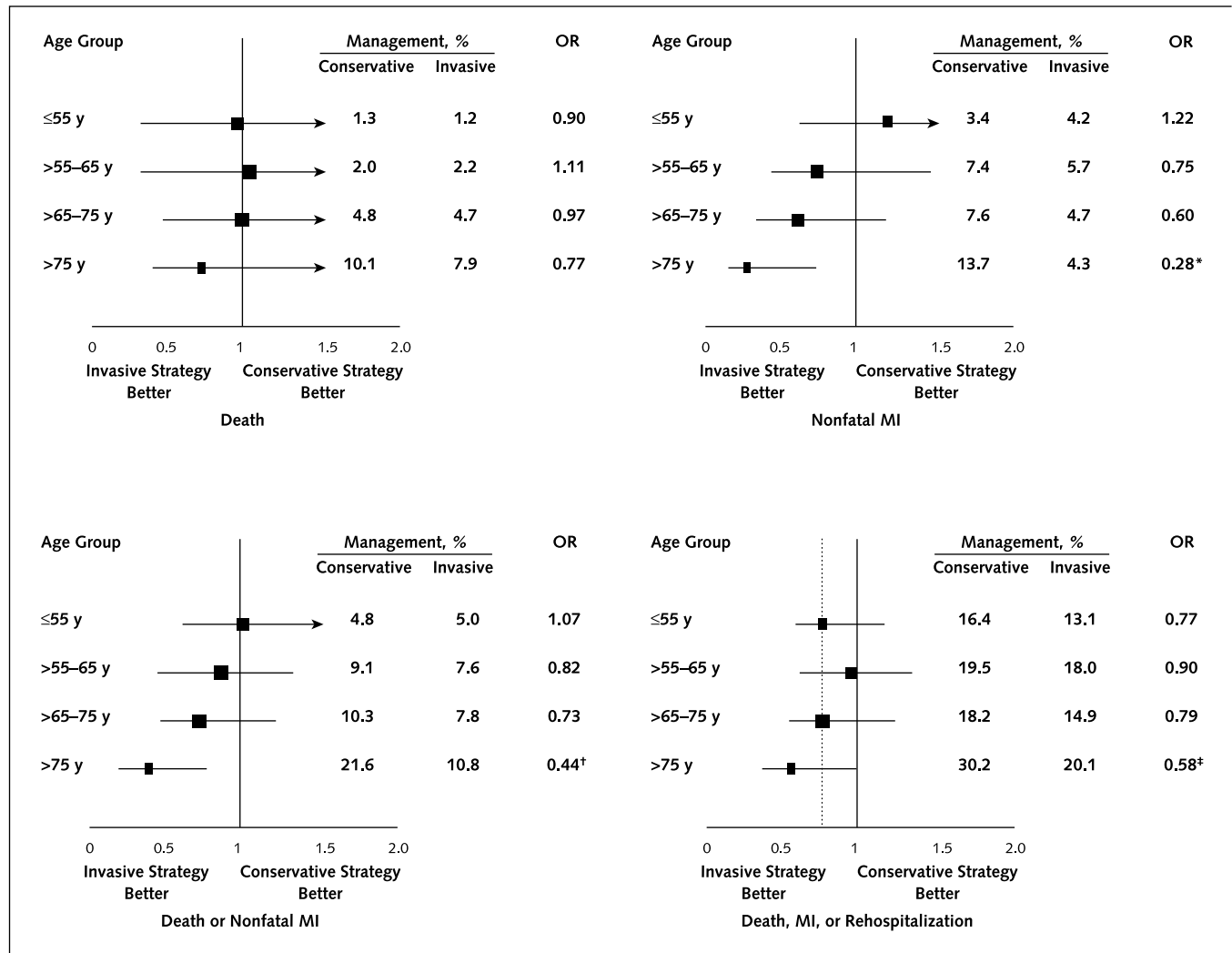


* $P = 0.02$ for early invasive management vs. conservative management among patients ≥ 65 years of age. † $P < 0.001$ for conservative management and $P = 0.09$ for invasive management among patients < 65 years of age vs. those ≥ 65 years of age; $P > 0.2$ for early invasive management vs. conservative management among patients < 65 years of age.

herence to the study design across age groups ($P > 0.10$ for all comparisons). The rate of percutaneous revascularization or coronary artery bypass graft surgery did not differ significantly in patients younger than 65 years of age compared with patients 65 years of age or older (data not shown). When patients were divided into subgroups by age (≤ 55 years, > 55 to 65 years, > 65 to 75 years, and > 75 years) (Table 2), the rate of percutaneous coronary intervention did not differ significantly but the rate of revascularization by coronary artery bypass graft surgery did. Patients 55 years of age or younger had the lowest rate of surgery in both the early invasive and conservative management groups.

Table 3 and Figure 2 compare clinical outcomes (stratified by age < 65 years and age ≥ 65 years) at 30 days and 6 months for patients randomly assigned to the early invasive or conservative strategy. Of note, patients 65 years of age or older had a markedly higher risk for death (54 of 962 [5.6%] vs. 22 of 1258 [1.7%]) and MI (69 of 962 [7.2%] vs. 60 of 1258 [4.8%]) at 6 months than did younger patients. Although patients 65 years of age or older made up 43% of the study group, they accounted for 71% of all deaths and 53% of all MIs at 6 months. When treatment strategies were compared across age groups, mortality rates did not differ significantly at 30 days or 6 months. However, among patients 65 years of age or older, randomization to an early invasive rather than a conservative strategy resulted in an absolute reduction of 4.1 percentage points (5.7% vs. 9.8%; $P = 0.019$) and a relative reduction of 44% in the composite incidence of death or nonfatal MI at 30 days, as well as an absolute reduction of 4.8 percentage points (8.8% vs. 13.6%; $P = 0.018$) and a relative reduction of 39% at 6 months. Among patients younger than 65 years of age, the early invasive strategy compared with the conservative strategy conferred a non-significant absolute reduction of 1.0 percentage point and a

Figure 3. Odds ratios (ORs) for death; nonfatal myocardial infarction (MI); death or nonfatal MI; and death, MI, or rehospitalization for acute coronary syndromes at 6 months in patients with unstable angina and non-ST-segment elevation MI.



Data are stratified by age group: ≤ 55 years ($n = 716$), $>55-65$ years ($n = 614$), $>65-75$ years ($n = 612$), and >75 years ($n = 278$). The dotted line indicates the point estimate for the primary end point among all patients in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction (TACTICS-TIMI) 18 trial. * $P = 0.010$. † $P = 0.016$. ‡ $P = 0.05$.

22% relative reduction in incidence of death or nonfatal MI at 30 days; findings were similar at 6 months (6.1% vs. 6.5%; $P > 0.2$).

Figure 3 presents clinical outcomes for patients stratified by age (≤ 55 years, >55 to 65 years, >65 to 75 years, and >75 years). Among patients randomly assigned to conservative management, the absolute risk for death or nonfatal MI increased more than 4-fold with age when those ≤ 55 years of age or younger were compared with those older than 75 years of age (4.8% vs. 21.6%, respectively). The early invasive strategy showed an increasing efficacy advantage in terms of absolute and relative risk reductions for death or nonfatal MI with increasing age. Among elderly patients older than 75 years of age, the early invasive strategy compared with conservative management conferred an absolute reduction of 10.8 percentage points

(10.8% vs. 21.6%; $P = 0.016$) and a relative reduction of 56% for death or nonfatal MI at 6 months; there was a relative reduction of more than 70% for nonfatal MI by 6 months. A test for interaction between age and treatment strategy for death or nonfatal MI yielded a P value greater than 0.2 at 30 days and a P value of 0.065 at 6 months. By multiple logistic regression modeling, among patients stratified by age (≤ 55 years to >75 years), the interaction between age and treatment strategy yielded P values of 0.012 for 6-month nonfatal MI, 0.044 for death or MI, and 0.045 for stroke after we controlled for TIMI risk score. Tests for interaction between age and treatment for all other end points at 30 days or 6 months yielded P values greater than 0.2.

With respect to the absolute risk reduction for death or nonfatal MI at 6 months, for every 1000 patients

Table 4. Rates of Stroke and Bleeding Complications Associated with the Early Invasive Strategy Compared with the Conservative Strategy, according to Age Group

Variable	Patients ≤55 Years of Age			Patients >55–65 Years of Age			Patients >65–75 Years of Age			Patients >75 Years of Age		
	Invasive Strategy (n = 337), %	Conservative Strategy (n = 379), %	P Value	Invasive Strategy (n = 317), %	Conservative Strategy (n = 297), %	P Value	Invasive Strategy (n = 321), %	Conservative Strategy (n = 291), %	P Value	Invasive Strategy (n = 139), %	Conservative Strategy (n = 139), %	P Value
Major bleeding*	3.6	1.6	0.100	4.7	6.4	>0.2	9.0	6.5	>0.2	16.6	6.5	0.009
Minor bleeding*	14.0	8.7	0.026	12.9	9.1	0.129	15.6	12.4	>0.2	29.5	19.4	0.051
Transfusion*	3.6	1.3	0.082	3.2	5.1	>0.2	9.7	7.6	>0.2	20.9	7.9	0.002
Stroke†	0.9	0	0.104	0.3	0.3	>0.2	0.3	1.0	>0.2	0.7	1.4	>0.2

* During index hospitalization.

† By 30 days.

treated, the invasive strategy would prevent 4 deaths or MIs among patients who were younger than 65 years of age versus 48 deaths or MIs among patients 65 years of age and older. In patients with unstable angina and non-ST-segment elevation MI who were younger than 65 years of age and 65 years of age or older, respectively, the numbers needed to treat for benefit to prevent 1 death or nonfatal MI at 6 months were 250 and 21, respectively. Among patients older than 75 years of age, 108 deaths or nonfatal MIs would be prevented for every 1000 patients treated, and treatment of only 9 patients with an early invasive strategy would prevent 1 death or nonfatal MI at 6 months.

For persons who were not veterans, the average increased 6-month cost of early invasive therapy versus conservative management was similar among younger and older patients (\$586 for patients <65 years of age, \$582 for patients ≥65 years of age, and \$907 for patients >75 years of age). At 6 months, the incremental cost per death or MI averted with the early invasive strategy was \$39 067 for patients younger than 65 years of age, \$10 393 for patients 65 years of age or older, and \$9967 for patients older than 75 years of age.

Table 4 shows the incidence of bleeding events and stroke according to age and treatment strategy. By 30 days, regardless of patient age, the early invasive management strategy had not increased the incidence of periprocedural death or MI (defined as occurring within 48 hours) or stroke. The frequency of bleeding complications increased with increasing age among both conservatively and invasively managed patients. Among patients older than 75 years of age, the early invasive strategy significantly increased the rate of in-hospital major bleeding (16.6% vs. 6.5%; $P = 0.009$) and blood transfusion (20.9% vs. 7.9%; $P = 0.002$) compared with conservative management.

DISCUSSION

Although TACTICS-TIMI 18 and 4 other randomized trials (2–7) have demonstrated benefit with early invasive management of patients hospitalized with unstable angina and non-ST-segment elevation MI, clinicians have

been hesitant to subject elderly patients to aggressive care (11–15). In our current analysis of the effect of age on outcomes in the TACTICS-TIMI 18 trial, we came to 6 main conclusions. First, compared with younger patients, elderly patients with unstable angina and non-ST-segment elevation MI have a markedly increased rate of adverse ischemic outcomes. Second, a routine early invasive strategy reduces death or nonfatal MI among elderly patients. Third, this strategy has greater absolute benefit for reduction of death or nonfatal MI in older patients than in younger patients, and both the absolute and relative benefits increase with increasing age. Fourth, the early invasive strategy may be more cost-effective in the elderly, largely because it more effectively prevents death or MI in this group. Fifth, a routine early invasive strategy does not increase the incidence of stroke even among the elderly. Sixth, the early invasive strategy significantly increased major bleeding among patients older than 75 years of age.

Previous analyses of the effect of age on outcome in randomized studies of management strategies for patients with non-ST-segment elevation acute coronary syndromes have yielded conflicting results. While the TIMI IIIB trial found that the early invasive strategy conferred no advantage for rates of death or nonfatal MI at 1 year in the total study sample, the reduction in these outcomes among patients 65 years of age or older was statistically significant compared with conservative management (relative reduction, 36% [12.5% vs. 19.5%]; $P = 0.03$) (9). The VANQWISH trial, which randomly assigned patients with non-Q-wave MI to early invasive management or conservative management, showed no advantage with the early invasive strategy. Subgroup analysis suggested that a routine invasive strategy had potentially significant hazard for patients 60 years of age or older, an effect putatively attributed to a high incidence of adverse events associated with coronary artery bypass graft surgery (10). The TIMI IIIB and VANQWISH trials were conducted in the early 1990s, before glycoprotein IIb/IIIa antagonists were available and before widespread application of coronary stenting. Our results may reflect the additional efficacy of a routine early invasive strategy in high-risk patient sub-

groups supported by upstream glycoprotein IIb/IIIa antagonism with intravenous tirofiban, as well as routine availability of stents during percutaneous coronary intervention.

As might have been expected, our analysis of participants' baseline characteristics according to age showed that those 65 years of age or older had more high-risk features, including a higher prevalence of diabetes mellitus and congestive heart failure, a higher frequency of ST-segment changes on the qualifying electrocardiogram, and a significantly higher incidence of elevated levels of serum troponin T. As a result, when baseline risk factors were compiled and expressed according to the TIMI risk score, elderly persons showed a significant shift toward higher risk. Among elderly persons, 90.6% had intermediate to high TIMI risk scores (scores ≥ 3), compared with only 63.0% of patients younger than 65 years of age ($P < 0.001$). These observations suggest that the early invasive strategy may have yielded greater benefit in elderly patients in our study because of its increased effectiveness in patients with higher baseline risk. Nevertheless, and of note, the interaction between age and treatment strategy for 6-month death or nonfatal MI yielded a P value of 0.044 even when we controlled for TIMI risk score in the model; this is consistent with a significantly greater benefit among elderly participants.

In studies of physician management of unstable angina and non-ST-segment elevation MI, investigators have almost universally observed that use of invasive cardiac procedures declines as patients get older. Despite a higher prevalence of baseline characteristics associated with an increased risk for adverse ischemic events and more severe and extensive coronary artery disease, elderly patients with unstable angina and non-Q-wave MI enrolled in the prospective TIMI III registry were less likely to undergo coronary angiography and revascularization procedures (8). These patients in turn had worse in-hospital mortality rates and increased incidence of recurrent ischemia. In an observational study of patients with unstable angina who were admitted to a tertiary care hospital, Giugliano and colleagues (12) reported that older patients with acute coronary syndromes were less likely than younger patients to undergo invasive procedures. Hasdai and colleagues (13) performed a prospective trial in which patients with acute coronary syndromes but without persistent ST-segment elevation were randomly assigned to treatment with the glycoprotein IIb/IIIa antagonist eptifibatid or to placebo. Management strategy was left to the discretion of the treating physician. Despite having more extensive coronary artery disease and a significantly higher risk for death and adverse ischemic outcomes, older patients in Hasdai and colleagues' study underwent coronary angiography and percutaneous coronary revascularization less often than younger patients (13). Similarly, recent results from a large prospective multicenter registry (14) suggest that in current practice, older patients hospitalized with unstable angina

and non-ST-segment elevation MI are significantly less likely than younger patients to receive early invasive management.

The results of our analysis of outcome according to age stand in direct contrast with current physician practice. For 6-month death or nonfatal MI, we found that an early invasive strategy yields substantially greater absolute benefit in older patients than in younger patients. The practical therapeutic implications of these results suggest that the numbers of deaths and MIs prevented at 6 months with early invasive management in patients 65 years of age or older and in patients older than 75 years of age are more than 10-fold and more than 20-fold higher, respectively, than in younger patients. Fewer elderly patients need to be treated to prevent 1 death or nonfatal MI at 6 months. In addition, estimates of cost per death or MI prevented for the early invasive strategy versus the conservative strategy were more favorable in the subgroups of older patients, largely because the early invasive strategy was more effective at preventing death or MI in the elderly.

Clinicians' reluctance to use an invasive strategy of risk stratification and treatment for elderly patients with unstable angina or acute MI has been potentially justified by higher risk for complications. In an analysis of management strategies from a large prospective registry of patients with suspected unstable angina and non-ST-segment elevation MI, Yusuf and colleagues (15) observed a higher risk for stroke associated with an invasive management strategy. In our study, we observed no such increase among elderly persons. Of note, we observed a significant increase in the rates of major bleeding and blood transfusions during the index hospitalization among the oldest patients, that is, those older than 75 years of age, who were managed with a routine early invasive strategy; these patients made up 12.5% of the study sample. In younger patients, invasive management did not significantly increase the risks for major bleeding and blood transfusion, despite universal use of aspirin, unfractionated heparin, and an intravenous glycoprotein IIb/IIIa antagonist. While the precise cause of this increase in major bleeding is unclear, Hasdai and colleagues (13) also observed a significant increase in moderate or severe bleeding in association with eptifibatid use in elderly persons, despite a lower rate of invasive procedures in the older age groups.

These observations suggest that clinicians should anticipate a higher risk for bleeding in elderly patients who receive a glycoprotein IIb/IIIa antagonist and undergo invasive procedures. However, this risk should be balanced against the benefits of such procedures in older patients, including a greater than 70% relative risk reduction in the incidence of MI and a number needed to treat of only 9 to prevent 1 death or MI at 6 months in patients older than 75 years of age with unstable angina and non-ST-segment elevation MI. With heightened awareness of the increased bleeding risk, as well as ongoing developments in arterial closure devices, newer antithrombin medications with

reduced bleeding risks, and better anticoagulant and antiplatelet monitoring tools, we speculate that hemorrhagic complications can be reduced while preserving the benefit associated with routine early invasive management in even very elderly patients.

Our study has limitations. The TACTICS–TIMI 18 protocol excluded patients with severe comorbid conditions or other serious systemic illness. Therefore, the elderly patients included in our study may be healthier than the general population of elderly patients with unstable angina and non–ST-segment elevation MI. The extrapolation of these results to practice should be carefully tempered by recognition of this limitation. Because we focused on a subgroup of the larger TACTICS–TIMI 18 trial, our analyses may also be underpowered for certain end point comparisons. However, the TACTICS–TIMI 18 trial included a relatively large number of patients 65 years of age or older ($n = 962$) who were studied prospectively and randomly assigned to an early invasive or conservative management strategy. Our observations of significant benefit for the routine invasive strategy in the elderly subgroup are consistent with the benefit observed for the primary end point in the overall population of TACTICS–TIMI 18. In addition, while the age stratification of younger than 65 years of age or at least 65 years of age was a prespecified analysis of the TACTICS–TIMI 18 protocol, the additional age stratifications described were derived from a retrospective post hoc analysis. Nevertheless, relatively few previous data from randomized clinical trials have thus far been available on the relationship between management strategy and outcome in patients older than 75 years of age with non–ST-segment elevation acute coronary syndromes.

In conclusion, routine early invasive management is a cost-effective way to improve ischemic outcomes in elderly patients who are hospitalized with unstable angina and non–ST-segment elevation MI and are treated with a glycoprotein IIb/IIIa antagonist. Reduction of long-term adverse events, such as death or nonfatal MI, with early invasive management is greater in older patients than in younger patients. The absolute benefit appears to increase with increasing age, at the expense of an increase in major bleeding among patients older than 75 years of age. Given the markedly increased frequency of adverse ischemic outcomes in the elderly, our results support an evidence-based approach favoring routine early invasive management in elderly patients with unstable angina and non–ST-segment elevation MI.

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