Acute Coronary Care in the Elderly, Part II: ST-Segment–Elevation Myocardial Infarction: A Scientific Statement for Healthcare Professionals From the American Heart Association Council on Clinical Cardiology: In Collaboration With the Society of Geriatric Cardiology

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AHA Scientific Statement

Acute Coronary Care in the Elderly, Part II
ST-Segment–Elevation Myocardial Infarction
A Scientific Statement for Healthcare Professionals From the American Heart Association Council on Clinical Cardiology

In Collaboration With the Society of Geriatric Cardiology

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Background—Age is an important determinant of outcomes for patients with acute coronary syndromes. However, community practice reveals a disproportionately lower use of cardiovascular medications and invasive treatment even among elderly patients who would stand to benefit. Limited trial data are available to guide care of older adults, which results in uncertainty about benefits and risks, particularly with newer medications or invasive treatments and in the setting of advanced age and complex health status.

Methods and Results—Part II of this American Heart Association scientific statement summarizes evidence on presentation and treatment of ST-segment–elevation myocardial infarction in relation to age (<65, 65 to 74, 75 to 84, and ≥85 years). The purpose of this statement is to identify areas in which the evidence is sufficient to guide practice in the elderly and to highlight areas that warrant further study. Treatment-related benefits should rise in an elderly population, yet data to confirm these benefits are limited, and the heterogeneity of older populations increases treatment-associated risks. Elderly patients with ST-segment–elevation myocardial infarction more often have relative and absolute contraindications to reperfusion, so eligibility for reperfusion declines with age, and yet elderly patients are less likely to receive reperfusion even if eligible. Data support a benefit from reperfusion in elderly subgroups up to age 85 years. The selection of reperfusion strategy is determined more by availability, time from presentation, shock, and comorbidity than by age. Additional data are needed on selection and dosing of adjunctive therapies and on complications in the elderly. A "one-size-fits-all" approach to care in the oldest old is not feasible, and ethical issues will remain even in the presence of adequate evidence. Nevertheless, if the contributors to treatment benefits and risks are understood, guideline-recommended care may be applied in a patient-centered manner in the oldest subset of patients.

Conclusions—Few trials have adequately described treatment effects in older patients with ST-segment–elevation myocardial infarction. In the future, absolute and relative risks for efficacy and safety in age subgroups should be reported, and trials should make efforts to enroll the elderly in proportion to their prevalence among the treated population. Outcomes of particular relevance to the older adult, such as quality of life, physical function, and independence, should also be evaluated, and geriatric conditions unique to this age group, such as frailty and cognitive impairment, should be considered for their influence on care and outcomes. With these efforts, treatment risks can be minimized, and benefits can be placed within the health context of the elderly patient. (***Circulation***. 2007;115:2570-2589.)

Key Words: AHA Scientific Statements ■ acute coronary syndromes ■ elderly

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This American Heart Association (AHA) scientific statement is the second of a 2-part review of current knowledge and practice in the care of the elderly with acute coronary syndromes (ACS). Part I reviews presentation and treatment of non–ST-segment–elevation ACS and includes the methods section applicable to both.[1] Part II focuses on the presentation and treatment of ST-segment–elevation myocardial infarction (STEMI) in the elderly. The importance of this effort is emphasized by the fact that clinical trials often have inadequate sample sizes within the elderly subgroup to reach certainty about treatment benefits and risks. Moreover, the heterogeneity among community-treated elderly patients is greater than among elderly patients enrolled in clinical trials. Therefore, it is important to consider the role of comorbidities and concomitant medications. Anticipated outcomes in elderly subgroups must still be viewed with overall trial findings to provide perspective. In the setting of age-related alterations in physiology and greater comorbid disease, treatment risks may attenuate expected benefits. In addition, assessments of benefit in the elderly should include consideration of the patients' goals from care.

Therefore, this scientific statement will (1) review evidence in elderly subgroups from trials that form the basis for guidelines-recommended treatments for STEMI and consider their use in practice, (2) identify areas in which evidence is sufficient or requires further clarification, and (3) suggest a framework to improve future care for elderly patients with STEMI.

Methods

This statement considers the risks and benefits in the elderly subgroup for treaments recommended in the American College of Cardiology (ACC)/AHA STEMI guidelines. By drawing from large community databases, including the Global Registry of Acute Coronary Events (GRACE) and the National Registry of Myocardial Infarction (NRMI), and the combined Virtual Coordinating Center for Global Collaborative Cardiovascular Research (VIGOUR)–coordinated STEMI trial dataset, baseline and presentation characteristics of the elderly in trials and community practices are compared (Table 1). Comparisons of STEMI treatment and outcomes in registries are added for perspective. Evidence for adjunctive treatments such as lipid-lowering agents, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and nitrates in elderly post–myocardial infarction (MI) patients are discussed. In addition, ethical issues and patient preferences that pose unique challenges to rapid decision making in older adults are also discussed.

STEMI in the Elderly

Comparing Trial and Community Elderly

Patients ≥75 years of age constitute 14% of the VIGOUR trials population but 28% of the GRACE and NRMI registry populations (Figure 1). Numerous differences are observed in baseline and presenting characteristics of STEMI patients in NRMI and those enrolled in the VIGOUR trials (Table 2). The ability to generalize expected outcomes observed from trials to the community setting is limited by differences between studied and treated populations.[2,3] In addition to more elderly, a rightward shift in average age is occurring, with greater percentages aged 75 to 84 years (20.7% versus 12.2%) and ≥85 years of age (8.2% versus 1.5%). Community patients are more likely to have hypertension, prior stroke, acute heart failure, higher systolic blood pressure, and higher heart rate than are trial patients in every age group. In addition, left bundle-branch block is more common with age in both populations, and it accounts for more than a third of ECGs among patients ≥85 years of age in the community. When a STEMI death prediction model developed in the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO)-I population is applied across age groups in community and trial populations, the risk appears similar[4] (Table 2). However, this model considers chronological age and acute presentation variables (eg, heart rate, blood pressure, Killip class, anterior infarct) but does not and cannot by definition (because all were eligible for fibrinolytic therapy) consider patient eligibility or other age-related factors that may alter treatment risk and benefit.

When the inclusion and exclusion criteria for the GUSTO-I trial were rigorously applied to a contemporary cohort of STEMI patients in NRMI, only 15.4% of the NRMI elderly (>65 years of age) would have been eligible for trial enrollment.[5] This emphasizes the heavy selection for trial participation that occurs from among the heterogeneous STEMI patients in the community. In addition, the mortality rate in the selected community patients was similar to that observed in GUSTO-I, suggesting that baseline and presen-

TABLE 1. STEMI Data Sources

Population	Enrollment (Years)	N	Age ≥75 y	Randomized Treatment and Population Descriptors
VIGOUR (pooled)		101 982	13.7%	International AMI trials
GUSTO-I—[28]	1990–1993	40 946	12.3%	Streptokinase and subcutaneous heparin versus streptokinase and intravenous heparin versus tPA and intravenous heparin versus tPA and streptokinase and intravenous heparin
GUSTO-IIb[29]	1994–1996	4131	15.0%	tPA versus PTCA
				Unfractionated heparin versus hirudin
GUSTO-III[129]	1995–1997	15 059	16.0%	Reteplase versus tPA
ASSENT-2[31]	1997–1998	16 995	14.7%	Tenecteplase versus tPA
ASSENT-3[32]	2000–2001	6115	14.3%	Tenecteplase and unfractionated heparin versus tenecteplase and LMWH versus tenecteplase and low-dose unfractionated heparin and abciximab
ASSENT-3 PLUS[35]	2000–2002	1637	19.6%	Prehospital setting, tenecteplase and LMWH versus tenecteplase and unfractionated heparin
HERO-2[130]	1998–2001	17 088	12.7%	Bivalirudin and streptokinase versus unfractionated heparin and streptokinase
NRMI 2-4[131]		775 680	28.9%	National AMI Registry
GRACE[132]		14 574	24.7%	International AMI Registry

AMI indicates acute myocardial infarction; GUSTO, Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries; tPA, tissue plasminogen activator; PTCA, percutaneous transluminal coronary angioplasty; ASSENT, Assessment of the Safety of a New Thrombolytic; LMWH, low-molecular-weight heparin; and HERO, Hirulog and Early Reperfusion or Occlusion.

Seven clinical trials were included in the VIGOUR pooled dataset for STEMI.

tation differences that select for trial exclusion may also explain the observed variation in outcomes between populations.

Acute Presentation

Although the absolute number of patients with STEMI increases with age, STEMI accounts for a smaller proportion of all ACS admissions in older subgroups (<30% ≥75 years of age).[6] The frequent occurrence of left bundle-branch block in the elderly is an important confounder in the ability to electrocardiographically classify these forms of ACS. Among STEMI patients in the NRMI registry, ST-segment elevation was present on the ECG of 96.3% of patients <65 years but

only 69.9% of those ≥85 years of age (Figure 2). Conversely, left bundle-branch block occurred in 5% of those <65 years but 33.8% of those ≥85 years of age (Table 2). In addition, the elderly often have atypical symptoms. In NRMI, chest pain at presentation occurred in 89.9% of STEMI patients <65 years versus 56.8% of those ≥85 years of age (Figure 2). Acute heart failure as evidenced by Killip class ≥2 at presentation occurred in 11.7% of STEMI patients <65 years versus nearly half (44.6%) of those ≥85 years of age (Figure 2). The common occurrence of heart failure and atypical symptoms in older patients may divert diagnostic suspicion away from an acute ischemic event. Accordingly, a diagnosis of "other" (as opposed to unstable angina, rule-out MI, or MI)
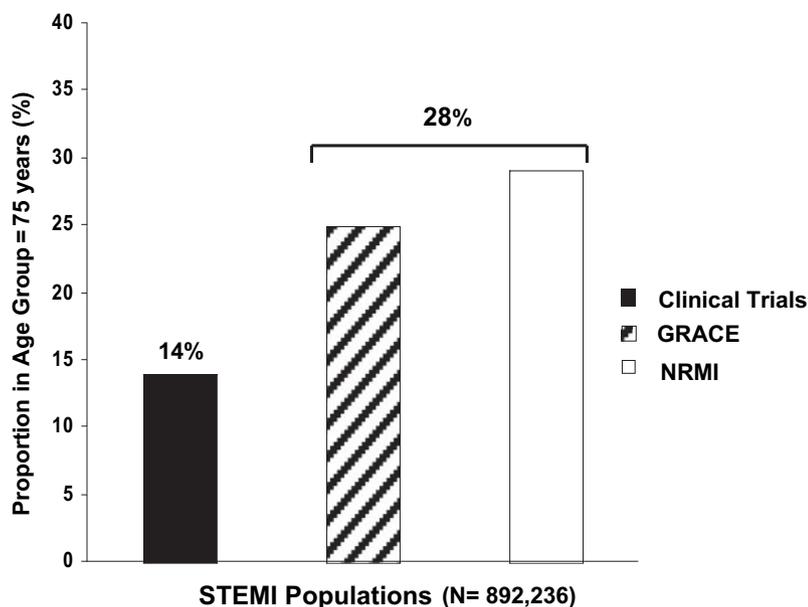
Figure 1. Representation of elderly (≥75 years of age) trial versus community populations.

TABLE 2.   Baseline Characteristics of STEMI Patients in Trial (VIGOUR) and Registry (NRMI) Populations by Age Group

Population	Age Group			
	<65 y	65–74 y	75–84 y	≥85 y
Age group, %*				
Trials	59.0	27.4	12.2	1.5
Registry	46.4	24.6	20.7	8.2
Age, y				
Trials	53.5 (7.5)	69.6 (2.8)	78.7 (2.7)	85.5 (0.4)
Registry	53.2 (7.9)	70.0 (2.9)	79.5 (2.8)	89.0 (3.3)
Female, %				
Trials	16.7	33.4	46.4	57.7
Registry	23.6	38.6	51.3	65.7
Hypertension, %				
Trials	35.5	47.7	49.5	49.3
Registry	43.1	55.0	59.3	59.2
Diabetes, %				
Trials	13.0	18.7	18.3	14.4
Registry	20.7	29.8	28.9	21.2
Weight, kg				
Trials	81.2 (14.1)	76.2 (12.8)	71.9 (12.1)	67.6 (11.2)
Registry	82.1 (17.5)	76.8 (15.1)	71.6 (14.5)	64.9 (14.6)
Prior cerebrovascular accident, %				
Trials	1.0	2.9	4.1	6.0
Registry	3.2	8.1	12.5	14.3
Killip class II–IV				
Trials	10.7	19.0	24.3	33.3
Registry	11.7	23.4	33.3	44.6
Left bundle-branch block, %				
Trials	0.5	1.5	2.1	3.0
Registry	4.8	14.7	24.0	33.8
MI location,† % other				
Trials	3.7	4.1	4.6	5.2
Registry	11.5	19.5	27.3	36.4
Heart rate, bpm				
Trials	75.4 (15.8)	74.9 (16.5)	75.9 (16.8)	78.1 (16.6)
Registry	81.0 (21.5)	83.2 (24.2)	86.3 (25.1)	89.6 (25.0)
Systolic blood pressure, mm Hg				
Trials	131.3 (21.2)	132.6 (22.2)	132.8 (23.7)	132.9 (28.4)
Registry	139.6 (30.5)	140.0 (33.1)	140.3 (33.7)	137.6 (33.8)
High-risk tertile, % of age group				
Trials	9.3	55.8	91.7	99.8
Registry	12.1	57.7	91.1	99.5

*Age group as percentage of overall population. Other variables are shown as percentages within age group. Continuous variables are mean and SD.

†Localization of MI to anterior, inferior, other.

was more often recorded at admission in older adults (5% of those <65 versus 24% of those ≥85 years of age).

Prehospital delays are also common in older adults and prevent prompt treatment. Atypical symptoms may slow the patient's own recognition of an acute cardiac event, and these atypical symptoms are further confounded by socioeconomic and cognitive factors. First cardiac events are also more likely to be associated with presentation delays.[7–9] Demographic factors, including older age, female sex, and nonwhite race, were predictive of delayed arrival (>6 hours after symptom onset) in the Cooperative Cardiovascular Project and the Worcester Heart Attack Study.[8,10] The mean time from
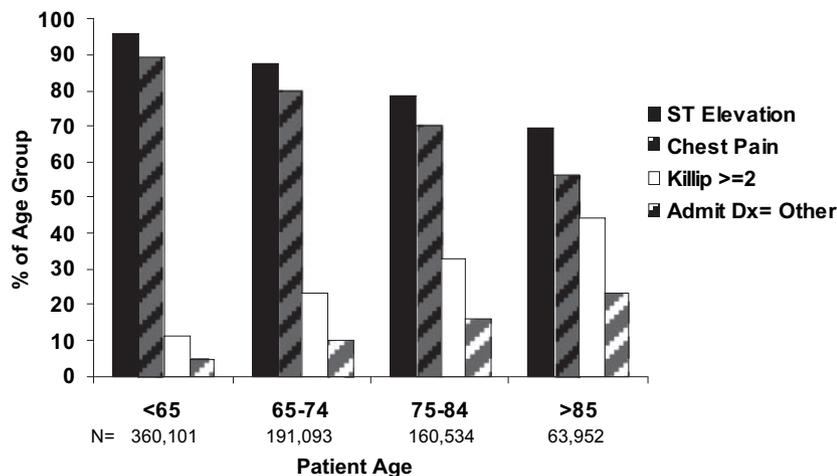
Figure 2. Presentation of STEMI and age (NRMI 2–4).

symptom onset to presentation in community elderly (≥75 years of age) was notably longer than among the elderly in fibrinolytic trials (4.7 versus 2.1 hours, respectively).[8,11] However, even in trial populations, older age is associated with delayed presentation as well as the increased risk of adverse in-hospital events that accompanies it.[11,12]

Reperfusion Eligibility

Although three quarters of younger NRMI patients received reperfusion (72% of those <65 years of age), this proportion declines with age (Figure 3). Prompt presentation and diagnosis are necessary for the delivery of reperfusion therapy to eligible STEMI patients. The guidelines recommend that STEMI patients without contraindications be treated if they present within 12 hours. However, in the GRACE registry, 30% of STEMI patients presenting within 12 hours of symptoms did not receive reperfusion therapy (either percutaneous coronary intervention [PCI] or fibrinolytic therapy).[13] Factors associated with failure to receive reperfusion therapy were similar to those associated with presentation delay. These include older age (≥75 years; odds ratio [OR], 2.63; 95% CI, 2.04 to 3.38), female sex, absence of chest pain, and congestive heart failure.[13]
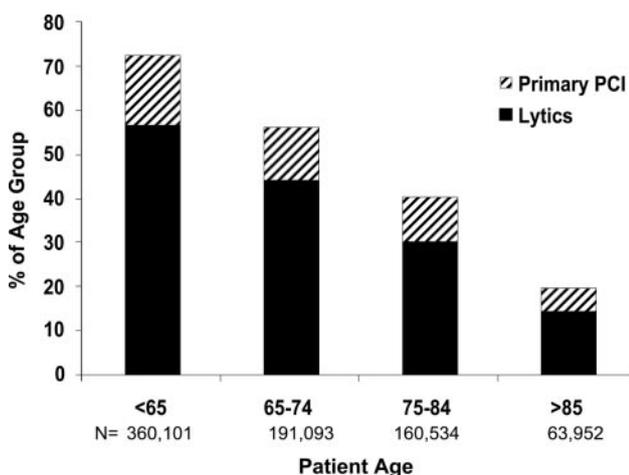

Figure 3. Reperfusion therapy for STEMI (NRMI 2–4).

Many elderly STEMI patients also do not meet ideal criteria for reperfusion therapy for either PCI or fibrinolysis. Common reasons for excluding elderly from reperfusion are their delayed presentation (>6 hours from symptom onset) and ECG changes that are abnormal at baseline or of unclear duration.[14] In addition, many elderly present without ongoing chest pain, and up to 9% have absolute contraindications to fibrinolytic therapy.[5] Relative contraindications like poorly controlled hypertension, prior stroke, dementia, and chronic anticoagulation (eg, warfarin) are even more common than absolute contraindications in the elderly.[15] Nevertheless, these factors still do not account for all of the decreased use of fibrinolytic therapy in the oldest age groups.[16] An analysis from Canada found the most common reasons for not prescribing fibrinolytic therapy in eligible patients were absence of ECG criteria (50%), late arrival (19.4%), and "other" (19.1%), followed by nondiagnostic ECG (10.6%), age (5.6%), and contraindications (6.9%).[17] The "other" category may well include those with baseline cognitive or functional impairment. An analysis of elderly STEMI patients (≥89 years of age) also found that 22% of "contraindications" to fibrinolytic therapy were attributed to patient preferences.[18] Therefore, uncertain symptoms or ECGs at presentation, coexisting comorbid geriatric conditions, and patient preferences may contribute to observed treatment patterns in the elderly.

Outcomes

Morbidity and mortality rates with STEMI increase with age.[11,19] In the GUSTO-I trial, the 30-day mortality rate increased 10-fold, from 3.0% among patients <65 years to 30.3% among those ≥85 years of age.[11] Total stroke and nonfatal disabling stroke increase more gradually with age and occur less commonly than death. For example, in GUSTO-I, the overall stroke rate was <3% among patients ≥85 years of age (Figure 4). Similarly, in a community population of elderly (≥75 years of age) treated with fibrinolytic therapy, death occurred in 25% to 32%, whereas stroke occurred in 2% to 5%.[20] Although strokes are often fatal, death from other causes is still the most common adverse outcome in the elderly with STEMI.
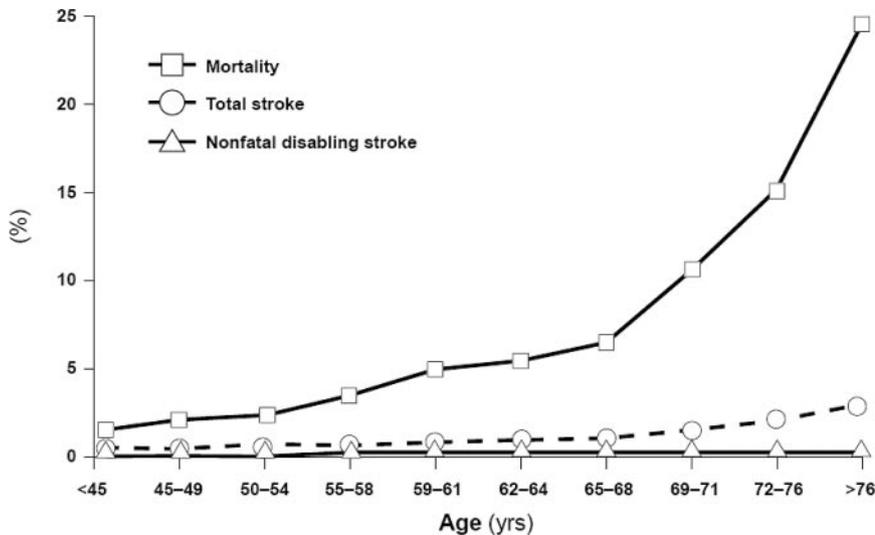
Figure 4. Death and stroke after fibrinolysis in GUSTO-I, categorized by age.

The high rate of death in the elderly corresponds to the frequent occurrence of electric and mechanical catastrophes.[21] These age-related mechanical catastrophes may be explained by changes in cardiac physiology or decreased vascular compliance, ventricular hypertrophy and remodeling, and diminished response to β-adrenergic stimulation in the elderly.[22–24] Heart failure and pulmonary edema, complications along this spectrum of adverse occurrences, occur in more than half of patients ≥ 75 years and 65% of patients ≥ 85 years of age.[6] Shock (hypotension with hypoperfusion) occurs in $>10\%$ of patients ≥ 75 years of age and is known to be due to ventricular or papillary muscle rupture or to advanced ventricular dysfunction.[21,25,26] Myocardial edema, contraction band necrosis, and intramyocardial hemorrhage are commonly noted at autopsy in elderly hearts after fibrinolysis.[27] In 706 elderly STEMI patients (≥ 75 years of age), free wall rupture occurred in 17.1% treated with fibrinolytic therapy versus 4.9% who received PCI and 7.9% who received no reperfusion.[20] Fibrinolytic therapy may have unique adverse myocardial effects in those of advanced age. The ability of STEMI treatments to improve outcomes in the very elderly, given their known physiological differences, is a question for future research.

Overview Summary

- The proportion of patients eligible for reperfusion decreases with advancing age, with elderly STEMI patients more often having relative and absolute contraindications.
  - Elderly STEMI patients are still less likely to receive reperfusion (PCI or fibrinolytic therapy) even if eligible.
- Many elderly present with atypical symptoms, abnormal baseline ECGs, or comorbidities that contribute to clinical uncertainty.
- The elderly have a higher likelihood of death after STEMI, much of which is attributed to electric and mechanical complications, and more than half the elderly (≥ 75 years of age) experience heart failure from either diastolic or systolic dysfunction.

Reperfusion

General agreement exists that eligible STEMI patients who receive reperfusion therapy (fibrinolytic therapy or PCI) have a lower risk of death than those who receive no reperfusion. The guidelines recommend considering time to presentation, time to PCI, and risk of STEMI, along with contraindications to treatment, when selecting reperfusion strategy; all of these factors are altered by age.[15] Numerous clinical trials have compared fibrinolytic regimens with each other[28–35] or have compared fibrinolytic regimens with direct PCI.[29,36–41] However, many of these trials excluded those ≥ 75 years of age on the basis of either age or other factors. Lack of consensus on reperfusion for acute MI in the elderly includes lack of clinical trial data, as well as comorbidity and delayed presentation.[42] In addition, availability of reperfusion determines its selection, with fewer than half of elderly with STEMI ($\approx 40\%$ of those ≥ 75 years of age) currently presenting to hospitals with PCI capability.[43] The one best reperfusion strategy for elderly STEMI patients will likely remain undefined, but patient and treatment factors do determine its success.

Fibrinolytic Therapy

Subgroup comparisons from trials have shown that fibrinolytic therapy, as compared with placebo, reduces mortality rates in the elderly. The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group demonstrated a greater absolute reduction in death in elderly subjects (≥ 75 years of age) treated with fibrinolytic therapy than in younger patients.[44] The original FTT population included patients with all types of ECG changes (including ST-segment depression, in which fibrinolytic therapy is not now indicated) and presentation within 24 hours and demonstrated a nonsignificant relative reduction in mortality rate of 4% (absolute 10 lives saved per 1000 patients treated). However, a second analysis that limited the original population to those meeting contemporary eligibility criteria for fibrinolytic therapy (presentation within 12 hours and ST-segment elevation or bundle-branch block) demonstrated a significant relative reduction in mortality rate of 15% ($P=0.03$) in patients ≥ 75 years of age[45] (Figure 5). Although the relative reduction was less in the elderly than in younger patients (<55 years of age), the absolute benefit in terms of lives saved was 3-fold higher (34 lives per 1000 treated versus 11 lives per 1000 treated) and

extended to age 85 years. Fibrinolytic therapy has also been shown to be as effective in the elderly as in younger patients for achieving Thrombolysis in Myocardial Infarction (TIMI)-3 flow.[46]
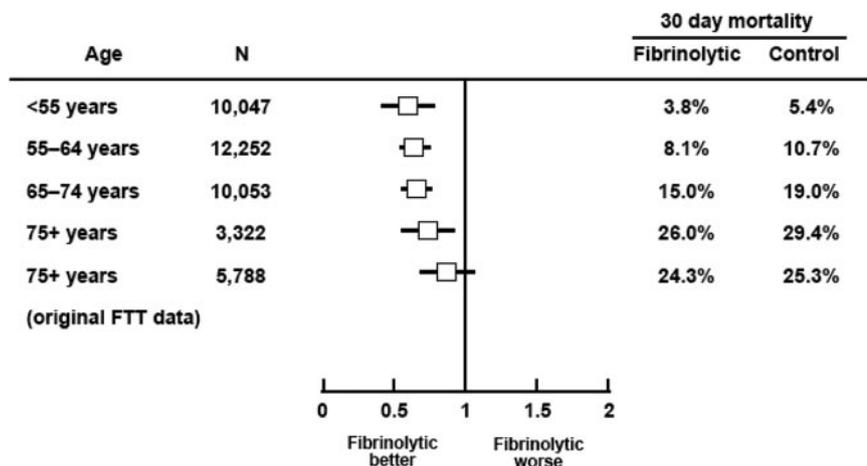
Registries have also compared use of fibrinolytic therapy with no reperfusion in the elderly.[21,47–51] Among reperfusion-eligible elderly (≥65 years of age) in one community population, the 30-day mortality rate was 13.5% among fibrinolytic-treated patients, 13.0% among those undergoing PCI, and 20.6% among those not given any reperfusion therapy.[50] This likely reflects nonrandomized treatment selection biases, as well as therapeutic benefit. In registries with long-term follow-up, the mortality rate was significantly lower among elderly patients receiving fibrinolytic therapy than among those not receiving reperfusion therapy (OR range, 0.58 to 0.88).[50,51] Although observational, these data support the trial evidence for benefit from fibrinolytic therapy in the elderly subgroup.

Intracranial hemorrhage (ICH) and nonhemorrhagic stroke are devastating complications of fibrinolysis that increase with age. However, these complications are rare in trial populations (1.5% overall and 2.9% of those >85 years of age).[11] In fact, nonfatal stroke is not increased dramatically with age, and most elderly with ICH die[52] (Figure 4). However, age and comorbidity are risk factors for ICH and stroke. In addition, in trial populations, ICH is associated with low body weight (<70 kg), elevated diastolic blood pressure (≥95 mm Hg), and recent head trauma, and nonhemorrhagic stroke is associated with atrial fibrillation, diabetes, and prior cerebrovascular disease.[53] In community populations, age, weight, blood pressure, and prior stroke, black race, female gender, and excessive anticoagulation with international normalized ratio ≥4 were also independent predictors of ICH with fibrinolytic therapy.[54] These factors increase with age and are common in community populations (Table 2). ICH has also been shown to increase with fibrin-specific agents (tissue plasminogen activator [tPA]) in community and trials populations.[28,54–57] In GUSTO-I, net clinical benefit (death and nonfatal disabling stroke) was greater with tPA than with streptokinase in patients up to age 84 years, but streptokinase was better past age 85 years.[11] In the Assessment of the Safety of a New Thrombolytic (ASSENT-2) trial, tenecteplase was also associated with lower rates of ICH (1.1% versus 3.0%) compared with tPA in the elderly (≥75 years of age).[58] Others have demonstrated that lower doses of unfractionated heparin can reduce the rate of ICH associated with fibrinolytic therapy in the elderly.[31,59]

The ideal adjunctive antithrombin therapy with fibrinolysis is of relevance to the elderly. In the Assessment of the Safety and Efficacy of a New Thrombolytic 3 (ASSENT-3 PLUS) trial, higher rates of ICH were seen with enoxaparin as opposed to unfractionated heparin when administered with tenecteplase in the elderly (≥75 years of age) (enoxaparin 6.7% versus unfractionated heparin 1.2%; $P=0.01$).[35] The Enoxaparin Versus Unfractionated Heparin With Fibrinolysis for ST-Elevation Myocardial Infarction (ExTRACT-TIMI-25) trial modified the dosing scheme for enoxaparin in the elderly (≥75 years of age) and those with severe kidney disease (creatinine clearance <30 mL/min) for its comparison with unfractionated heparin when given with fibrinolysis.[60] The composite end point for clinical benefit was better with enoxaparin in the overall population and trended to benefit in those ≥75 years of age. Although the relative risk reduction was larger in younger patients, the absolute risk reductions were similar in young and old. Moreover, major bleeding was still higher with enoxaparin overall (1.4% for unfractionated heparin versus 2.1% for enoxaparin; $P<0.001$), but the difference in the older cohort was nonsignificant (2.9% for unfractionated heparin versus 3.3% for enoxaparin; $P=0.52$), suggesting that dose reductions were successful in limiting enoxaparin-associated bleeding. A post hoc analysis from a clinical trial that randomized STEMI patients to clopidogrel or aspirin found that bleeding was not significantly different for low-molecular-weight heparin or unfractionated heparin when used in conjunction with fibrinolytic regimens.[61]

The ideal adjunctive antiplatelet therapy with fibrinolysis is also of interest in this population. The addition of clopidogrel to aspirin in STEMI patients was studied in 2 trials, one of which did not enroll any patients >75 years of age.[61] The other found that clopidogrel without a loading dose in addition to aspirin was beneficial over placebo for reducing the rates of death, MI, or stroke in the overall population, but this was not significant in any subgroup, including those

Age	N	30 day mortality		
			Fibrinolytic	Control
<55 years	10,047		3.8%	5.4%
55–64 years	12,252		8.1%	10.7%
65–74 years	10,053		15.0%	19.0%
75+ years	3,322		26.0%	29.4%
75+ years (original FTT data)	5,788		24.3%	25.3%

Figure 5. Fibrinolytic therapy and age (excluding patients presenting beyond 12 hours, with normal ECGs, with only T-wave inversion or ST depression).

determined by age.[62] There were increases in bleeding with dual antiplatelet regimens but no differing trend in risk as a function of older age.

Newer agents are also entering the therapeutic arena. The Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) trial studied fondaparinux, a novel factor Xa inhibitor, along with standard care in STEMI patients. This newer agent was beneficial in reducing the rate of 30-day death or MI in patients receiving fibrinolytic therapy or no reperfusion; however, its use in those undergoing PCI was less beneficial.[63] Among the older group of patients (≥62 years of age), fondaparinux demonstrated greater absolute risk reduction for the primary end point (2.7% versus 0.5%) along with a lower rate of bleeding. Although the debate over ideal adjunctive therapy continues, newer agents or strategies of care may enter into consideration in terms of their safety and efficacy in the elderly.

Reduced- or Alternative-Dose Regimens
Reduced-dose fibrinolytic therapy with adjunctive antithrombin therapy was investigated in hopes of minimizing treatment risks. In the GUSTO-V trial, however, the addition of glycoprotein IIb/IIIa antagonists to reduced-dose fibrinolytic therapy had no benefit on mortality rate. Elderly subjects (≥75 years of age) who received full-dose reteplase had a 30-day mortality rate similar to those who received half-dose reteplase plus full-dose abciximab (18.3% versus 17.9%; $P=0.83$); however, ICH doubled in the half-dose–reteplase–plus–abciximab group (1.1% versus 2.1%; $P=0.07$).[33] In fact, although abciximab plus half-dose reteplase was associated with a lower risk of ICH than was full-dose reteplase in patients <70 years of age, this risk was higher in patients ≥70 years of age.[64] In the ASSENT-3 trial, the 30-day mortality rate was highest among the group randomized to half-dose tenecteplase plus abciximab (22.3% versus 15.9% for tenecteplase plus unfractionated heparin and 15.6% for tenecteplase plus enoxaparin). In addition, major bleeding was highest in the half-dose–tenecteplase–plus–abciximab group (4.4% versus 2.2% with tenecteplase plus unfractionated heparin and 3.0% with tenecteplase plus enoxaparin).[32] At this time, the balance of safety and efficacy with combination glycoprotein IIb/IIIa antagonists and reduced-dose fibrinolytic therapy has not been shown to be favorable, particularly in patients ≥75 years of age.

Fibrinolytic Therapy Summary
- A mortality benefit of fibrinolytic therapy, as compared with no reperfusion, has been demonstrated for those without contraindications in trials and registries alike up to the age of 85 years.
  - This includes treatment-related deaths resulting from ICH, stroke, shock, and myocardial rupture.
  - Nonfatal stroke remains rare even among the oldest old (<3% among those ≥85 years of age).
  - The interaction between age and reduced dosing of adjunctive heparin minimizes risks of bleeding without compromising efficacy.
  - Although unfractionated heparin appears preferable in some studies, low-molecular-weight heparin, when delivered in an adjusted dose, has been shown to result in superior outcomes.
  - The interaction between age and combination therapy for major bleeding and the higher risk of myocardial rupture and intramyocardial hemorrhage suggest that risks of reperfusion in the oldest old (≥85 years of age) may differ from those 75 to 84 years of age and need to be studied further.

PCI Versus Fibrinolytic Therapy
Few trials comparing primary PCI with fibrinolytic therapy enrolled adequate numbers of older patients. Existing subset analyses from trials that randomized patients to primary PCI or fibrinolytic therapy suggest that PCI is a preferred strategy in older patients. The Primary Angioplasty in Myocardial Infarction (PAMI-I) study, published in 1993, randomized patients to immediate PCI or fibrinolytic therapy (tPA). Of the 395 patients enrolled, 38% were ≥65 years and 20.5% were ≥70 years of age.[36] Compared with patients who received fibrinolytic therapy, patients who underwent PCI had a trend toward fewer in-hospital deaths (2.6% versus 6.5%; $P=0.06$) and less death or recurrent MI (5.1% versus 12.0%; $P=0.02$).[36] In the elderly subgroup (≥65 years of age), PCI was also associated with a lower composite of death or MI than was fibrinolytic therapy (8.6% versus 20.0%; $P=0.048$).[65] Elderly patients were more likely to have stroke (3.3% versus 0.8%; $P=0.07$) or ICH (2.7% versus 0.0%; $P=0.01$) than were younger patients, but none of these rare events occurred in the PCI group. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes-IIb (GUSTO-IIb) trial also showed a strong trend toward a lower 30-day mortality rate with PCI as compared with fibrinolytic therapy in the elderly (≥70 years of age; n=300). This was in contrast to no superiority between approaches in younger patients (<70 years of age; n=837).[29] The Danish Multicenter Randomized Study on Fibrinolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) study compared PCI transfer within 2 hours from symptom onset versus on-site tPA in 1572 patients with STEMI.[39] Again, PCI was associated with a significant reduction in 30-day death, MI, or stroke as compared with tPA overall and in the elderly (>63 years of age: OR for PCI versus tPA, 0.53 [0.36 to 0.90]). At 3 years, higher TIMI risk at admission was an important predictor of better outcomes with PCI over tPA ($P<0.0008$). Patients with higher TIMI risk scores (≥5) were also those who were elderly (≥75 years of age; 55% versus 8%), who had shock (systolic blood pressure <100 mm Hg; 21% versus 3%), who had higher Killip class 3 to 4 (26% versus 3%), and who delayed presentation (>4 hours; 52% versus 27%). This provides consistent evidence of greater benefit with PCI as a function of risk, with age being one of those risk factors.[66]

Three small trials have been performed to specifically address the question of fibrinolytic therapy or PCI in elderly STEMI patients. The first trial randomized patients >75 years of age (n=87) to PCI versus fibrinolytic therapy (streptokinase). Patients treated with PCI had lower rates of death, MI, or stroke at 30 days (9% versus 29%; $P=0.01$).[67] Another trial randomized patients ≥70 years of age (n=130) to PCI (with stenting) versus fibrinolytic therapy (tPA). At 6 months, there was no difference in mortality rate, but there were significantly fewer subsequent revascularization proce-
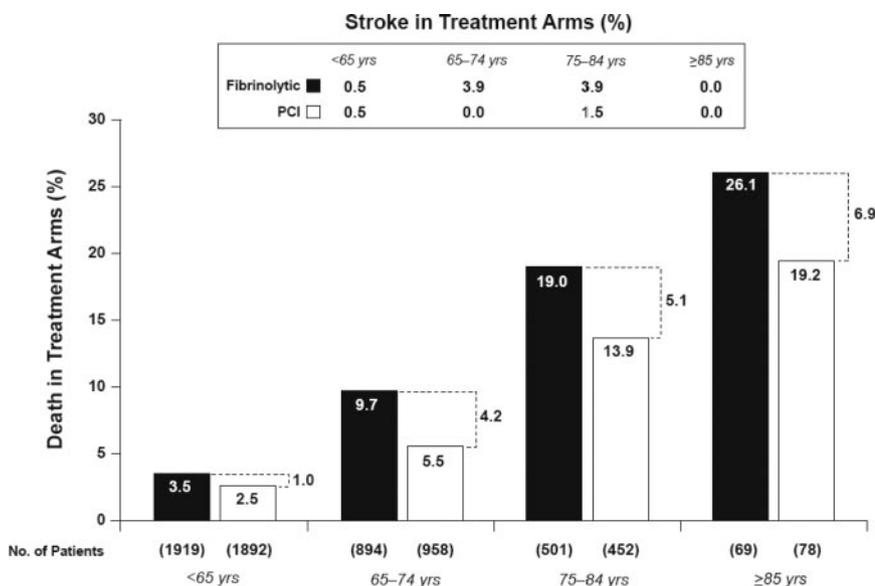
Figure 6. PCAT-2.

dures in the PCI group (9% versus 61%; *P*=0.001) and a lower composite of death, MI, or revascularization (29% versus 93%; *P*=0.001).[40] The Senior PAMI trial randomized patients ≥70 years of age (n=481) presenting <12 hours from symptom onset to PCI versus fibrinolytic therapy. In this study, there was a nonsignificant 36% reduction in death or nonfatal stroke (11.3% PCI versus 13% thrombolytic therapy; *P*=0.57) and a 55% significant reduction in death, stroke, or reinfarction (11.6% PCI versus 18% thrombolytic therapy; *P*=0.05) favoring PCI. No difference between reperfusion strategies was seen in the small subgroup ≥80 years of age (n=131).[68] This important trial also confirmed the role of reduced-dose heparin and rescue angioplasty in the better-than-expected outcomes with fibrinolytic therapy in the elderly.

Pooled trials analyses can provide statistical confirmation of the mortality advantage with PCI in individual trials. Among 2606 patients in 10 trials from 1985 through 1995, PCI was favored for reducing the 30-day mortality rate (PCI 4.4% versus fibrinolytic therapy 6.5%; *P*=0.02) and stroke (0.7% versus 2.0%; *P*=0.007).[69] A review of 23 trials of PCI versus fibrinolytic therapy with longer follow-up (6 to 18 months) also found PCI to be superior for the reduction of death, reinfarction, stroke, and ICH.[41] The Primary Coronary Angioplasty Trialists' (PCAT) investigators pooled 11 randomized trials of PCI versus fibrinolytic therapy conducted from 1989 through 1996 (n=2635).[70] In this analysis, PCI was favored for reducing the 30-day mortality rate (13.3% versus 23.6%; *P*<0.05) among the elderly (≥70 years of age; n=640). Although relative risk reductions were similar across age, the number needed to treat to save 1 life with PCI over fibrinolytic therapy was 8 among the elderly (≥70 years of age) versus 23 among younger patients (<60 years of age).[70] The absolute mortality benefits of PCI were greater in high-risk patients, and the risk for hemorrhagic stroke was lower with PCI (relative risk=0.34; *P*=0.009).

The PCAT-2 investigators expanded the analysis to include 22 randomized trials of PCI versus fibrinolytic therapy. There was a benefit with PCI, particularly if the patient arrived 2 hours after symptom onset of if the patient was ≥65 years of age.[71] A subgroup analysis found that the absolute mortality advantage of PCI increased with age from 1% at 65 years to 6.9% at ≥85 years of age (Figure 6).

Therefore, PCI is an effective strategy in preventing reinfarction and future revascularization. In the elderly, PCI is appealing because it can be applied in the absence of clear ST-segment elevation or chest pain and is effective despite hemodynamic status.[15] PCI also has its own risks, including exposure to contrast dye, cholesterol embolization, adjunctive antithrombotic agents, and risk of bleeding from arterial injury.[41]

The timing and availability of PCI often involve transfers. The Primary Angiography in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis-2 (PRAGUE-2) trial found no difference in death/MI with PCI or fibrinolytic therapy (streptokinase) if subjects were treated within 3 hours from symptom onset (7.4% versus 7.3%).[72] The Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial shortened this interval to 2 hours and found that fibrinolytic therapy had a mortality advantage in this window (2.2% versus 5.7%; *P*=0.058).[73] However, the Beyond 12 hours' Reperfusion AlternatiVe Evaluation (BRAVE-2) trial demonstrated that delayed PCI in STEMI patients who present >12 hours from symptom onset still reduced infarct size.[74] This is important because the elderly often present late, and average delays to treatment are longer in practice settings than in clinical trials. However, in acutely ischemic subjects fibrinolytic therapy provides benefit from early reperfusion, but the risk–benefit ratio shifts in relation to time to treatment and patient risk. Elderly subjects at high risk who present with shock or are >3 hours from symptom onset should be transferred for PCI when possible. Transfer to a PCI-capable hospital for PCI should also be considered for the elderly with contraindications to fibrinolytic therapy, particularly if the door to balloon time will be <90 minutes.

The mortality rate for STEMI patients with shock is high regardless of reperfusion.[75,76] The small number of elderly

TABLE 3. Mortality in 3 Large Trials of Intravenous β-Blockade

	n	Mortality, %			Change, %	P
		Active	Control	Difference		
Atenolol						
ISIS-1[84]	16 027					
<65 y	10 805	2.5	2.6	−0.1	−4.0	NS
≥65 y	5222	6.8	8.8	−2.0	−22.7	0.001
Metoprolol						
Goteborg[85]	1395					
<65 y	917	4.5	5.7	−1.2	−21.1	NS
65–74 y	478	8.1	14.8	−6.6	−45.0	0.03
MIAMI[83]	5778					
<60 y	2965	1.9	1.8	+0.1	+3.1	NS
61–74 y	2813	6.8	8.2	−1.5	−17.8	NS
Pooled totals	23 200					
Younger	14 687	2.5	2.6	−0.1	−5.0	NS
Older	8513	6.9	8.9	−2.1	−23.2	0.0005

MIAMI indicates Metoprolol in Acute Myocardial Infarction.

patients enrolled in the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? (SHOCK) trial (n=56 ≥75 years of age) did not benefit from revascularization. This prompted ACC/AHA guidelines to recommend early revascularization only for those <75 years of age. However, elderly patients in the SHOCK registry (n=277 ≥75 years of age) who underwent early revascularization (n=44) had a >50% lower mortality rate than those who did not (n=233) (relative risk, 0.46; 95% CI, 0.28 to 0.75; P=0.002).[77] This benefit to early revascularization in registry patients represents selection from among a critically ill elderly group of those most likely to benefit.[78] Therefore, although elderly with shock randomized to early revascularization in a clinical trial do not benefit, elderly with shock selected on the basis of clinical judgment do benefit from revascularization.

Observational studies have suggested that fibrinolytic therapy may be harmful in the elderly.[47,50,79] In the GRACE registry, patients ≥70 years of age (n=2975) who underwent PCI versus fibrinolytic therapy had less reinfarction and death.[80] Among 20 683 patients (≥65 years of age) in the Cooperative Cardiovascular Project database, PCI was also associated with modest short- and long-term mortality benefits versus fibrinolytic therapy.[81] The 1-year mortality benefit strongly favored PCI (14.4% versus 17.6%; P=0.001) among eligible patients. The incremental benefits between therapies are small, and the decision to use PCI, fibrinolytics, or neither in patients ≥75 years of age should always be considered carefully.

PCI Versus Fibrinolytic Therapy Summary
- Risk–benefit ratio favors PCI over fibrinolytic therapy in the elderly in small randomized trials, meta-analyses, and observational studies, but more data are needed in patients ≥80 years of age.
  ○ The major benefit from PCI is a reduction in reinfarction and need for target-vessel revascularization. Mortality reductions trend in the same direction but are less robust.

  ○ Adjusting the dose of adjunctive antithrombin agents with fibrinolytic therapy improves its outcome profile.
- Availability and time to reperfusion are key determinants of myocardial salvage and clinical benefits regardless of strategy.
  ○ PCI can be applied without ST-segment elevation or ongoing chest pain and is preferable in the setting of shock or high TIMI risk scores.
  ○ PCI and fibrinolytic therapy have similar outcomes when delivered within 3 hours from symptom onset; PCI seems preferable past 6 hours and still affects myocardial salvage after 12 hours from symptom onset.

Adjunctive Therapy

β-Blockers
β-Blockers, administered intravenously for ongoing chest pain and followed by oral administration in the absence of contraindications, are recommended in the guidelines as adjunctive treatments for patients with MI without regard to age or MI type.[14] β-Blockers have been shown to reduce progression to MI in patients with unstable angina and to reduce the mortality rate in all MI patients, including the elderly.[82–85] Three large randomized trials evaluated the effects of early administration of intravenous β-blockers on mortality rate among patients with STEMI (Table 3).[83–85] Although conducted before widespread implementation of reperfusion therapies, in all cases the absolute benefit was greater in older patients, and in 2 of the studies the beneficial effect was statistically significant only among the elderly.[84,85] Pooled data indicate that early intravenous β-blockade was associated with a nonsignificant 5% reduction in mortality rate among younger patients but a significant 23% reduction in mortality rate (P=0.0005) in older patients. Of note, both metoprolol studies excluded patients ≥75 years of age, and outcomes among patients ≥75 years of age in the Interna-

tional Study of Infarct Survival (ISIS)-1 have not been reported.

In contrast, a prespecified analysis from GUSTO-I confirmed that patients who received intravenous and oral atenolol did better than those who did not, specifically with regard to reduced myocardial rupture and death. However, those who received intravenous atenolol had a higher likelihood of early death, heart failure, shock, recurrent ischemia, and pacemaker use than those who received oral atenolol.[86] Patients who died in the first 24 hours were excluded, and therefore the authors concluded that atenolol was beneficial. Similarly, the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) randomized 45 852 patients with acute MI (93% of whom had ST elevation or left bundle-branch block) to intravenous metoprolol or placebo and found that metoprolol did not reduce all-cause deaths or the composite of death, reinfarction, or cardiac arrest.[87] Despite a lower risk of reinfarction and ventricular arrhythmias, those treated with intravenous and oral metoprolol had a 30% greater risk of developing cardiogenic shock (5.0% versus 3.9%; OR, 1.30; 95% CI, 1.19 to 1.41). Among the 11 934 patients ≥70 years of age, the total mortality rate was higher with metoprolol than with placebo (13.6 versus 13.3%; $P=NS$), but there was a 6.7% increase in death or cardiogenic shock combined. With a higher rate of heart failure and hemodynamic instability in elderly STEMI patients in general, they are certainly at risk for these adverse effects of β-blockers. Therefore, intravenous β-blockers should be given with caution in the elderly with acute MI, particularly in the setting of hemodynamic compromise or Killip class >1 at presentation.

Although concern exists about intravenous β-blockers, low doses of oral agents with careful uptitration are supported by evidence. Numerous large, multicenter randomized trials have confirmed the benefit of oral β-blocker therapy in lowering mortality rate and recurrent coronary ischemic events with similar or greater efficacy in older compared with younger patients after acute MI.[85,88–92] Although none of these studies included patients ≥75 years of age, several smaller trials as well as observational studies provide strong evidence that long-term β-blocker therapy improves outcomes after MI in patients up to 90 years of age.[82,93–95] In an observational analysis of 58 165 Medicare beneficiaries ≥65 years of age, β-blocker use was associated with a lower in-hospital mortality rate after adjustment for demographic, clinical, and treatment variables.[96] By age subgroup, β-blocker treatment was associated with a relative risk reduction in in-hospital mortality rate among patients 65 to 74 years (16%), 75 to 84 years (21%), and ≥85 years (13%) of age. In another study, β-blocker treatment was associated with a relative risk reduction 2-year mortality rate among patients 65 to 74 years (50%), 75 to 84 years (44%), and ≥85 years (28%) of age.[95]

Renin–Angiotensin Blockade

Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico (GISSI)-3 and ISIS-4 studied treatment with oral lisinopril or captopril within 24 hours of MI and demonstrated small but significant reductions in mortality rate

during follow-up of 42 and 35 days, respectively.[97,98] Among patients ≥70 years of age in ISIS-4, captopril demonstrated no effect on mortality rate.[98] Among patients ≥70 years of age in GISSI-3, lisinopril demonstrated no effect on mortality rate but lowered the combination of death, heart failure, or severe left ventricular dysfunction at 6 months (30.6% versus 33.8%; $P=0.01$).[99] The Survival of Myocardial Infarction Long-term Evaluation (SMILE) trial studied zofenopril in patients with anterior MI who were not candidates for thrombolytic therapy. There was a 34% reduction in the incidence of death or severe heart failure at 6 weeks as compared with those randomized to placebo.[100] In patients ≥65 years of age, the absolute benefit of zofenopril was 3-fold greater than in younger patients (absolute risk reduction, 5.2% versus 1.6%, respectively), although this was not statistically significant.

Long-term treatment with ACE inhibitors after acute MI has been shown to reduce the mortality rate in patients with a left ventricular ejection fraction ≤40% or clinical heart failure.[101,102] In the Salvage and Ventricular Enlargement (SAVE) trial, captopril therapy initiated 3 to 16 days after MI was associated with a 23% reduction in mortality rate at 42 months of follow-up among patients ≥65 years (27.9% versus 36.1%; $P=0.017$) versus a nonsignificant 9% mortality rate reduction in patients <65 years of age.[101] In the Acute Infarction Ramipril Efficacy (AIRE) trial, ramipril therapy initiated 2 to 10 days after MI in patients with clinical heart failure was associated with a 36% reduction in mortality rate among patients ≥65 years versus a nonsignificant 2% mortality rate reduction among patients <65 years of age.[102] Neither of these trials enrolled a significant number of patients ≥75 years of age. However, a retrospective analysis of data on 14 129 patients who were ≥65 years of age hospitalized with acute MI found that an ACE inhibitor at the time of hospital discharge was associated with a significant reduction in 1-year mortality rate among patients 65 to 80 years of age, as well as in those ≥80 years of age.[103]

The use of angiotensin receptor blockers versus placebo has been studied in several trials of acute MI. In the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), patients ≥50 years of age with acute MI accompanied by heart failure, anterior Q waves on ECG, or left ventricular systolic dysfunction (ejection fraction <35% or end-diastolic dimension >65 mm) were randomly assigned to captopril or losartan within 10 days after the index event. The mean age was 67.4 years, 26.8% of patients were ≥75 years of age, and ≈30% of patients had a non–Q-wave MI. During a mean follow-up period of 2.7 years, the mortality rate was nonsignificantly higher in the losartan group than in the captopril group (18.2% versus 16.4%; relative risk, 1.13; $P=0.069$), and the results were consistent across age groups.[104] In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), patients with acute MI and clinical heart failure or reduced left ventricular ejection fraction were randomized to valsartan, captopril, or both.[105] During a 2-year follow-up period, mortality rates were similar in all 3 arms (19.9% with valsartan, 19.5% with captopril, 19.3% with the combination; $P=NS$), but side effects and withdrawals were more frequent in patients

receiving combination therapy. Age subgroup data from VALIANT demonstrated that outcomes did not differ between the 3 study treatments (captopril, valsartan, or both) in any age group (<65, 65 to 74, 75 to 84, and ≥85 years), although adverse events were more common in the elderly.[106] On the basis of these findings, ACE inhibitors or angiotensin receptor blockers are helpful adjunctive treatments for heart failure or left ventricular systolic dysfunction after MI in the elderly.

Aldosterone blockade has also been demonstrated to be beneficial in patients with left ventricular dysfunction after myocardial infarction. In the Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study (EPHESUS), the addition of eplerenone, a selective aldosterone blocker, to standard care reduced the mortality rate in the overall population (relative risk, 0.83; 95% CI, 0.72 to 0.94); however, this was not true for the subgroup ≥65 years of age.[107] Similarly, the subgroup ≥75 years of age (n=1326) had a relative risk of 1.0 (P=NS) with eplerenone treatment as compared with placebo.[108] Because of the risk of hyperkalemia when creatinine clearance is <50 mL/min, a common occurrence in the elderly, risks of eplerenone seem to outweigh the benefits in this subgroup.

Nitrates
In the GISSI-3 and ISIS-4 trials, early administration of nitrates did not improve outcomes in a broad range of patients with acute MI.[98,99] However, among patients ≥70 years of age in GISSI-3, transdermal nitroglycerin administered within 24 hours of symptom onset significantly reduced the combined end point of death, heart failure, or severe left ventricular dysfunction at 6-month follow-up by 12% (30.9% versus 33.5%; P=0.04).[99] These subgroup findings support the use of nitrates, especially with persistent or recurrent ischemia, pulmonary congestion, or hypertension, in the elderly.[15] Nitrates are contraindicated in patients with hypotension or hemodynamically significant right ventricular infarction.

Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors (Statins)
Lipid-lowering therapy in patients with ACS to achieve a target low-density lipoprotein level of <100 mg/dL is recommended by the guidelines without regard to age.[15] The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial randomized non–ST-segment elevation ACS patients to atorvastatin 80 mg or placebo in the acute setting (24 to 96 hours after admission).[109] At 16-week follow-up, patients in the atorvastatin arm experienced a 16% reduction in the combined end point of death, nonfatal MI, rehospitalization for ischemia, or resuscitated cardiac arrest (P=0.048). The mean age of patients was 65 years, but no age interaction with treatment was noted. Lipid trials have compared intensive versus standard lipid-lowering strategies after ACS. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, patients with a spectrum of acute coronary syndromes (36% STEMI) were randomized to pravastatin 40 mg or atorvastatin 80 mg. During 2-year follow-up, there was a 16% reduction in the primary end

point (death, MI, stroke, late revascularization, or readmission for unstable angina) in patients randomized to high-dose atorvastatin (P=0.005).[110] Subgroup analysis revealed that the benefit of atorvastatin was most pronounced in patients with non–ST-segment–elevation ACS or unstable angina (versus STEMI). Lowering low-density lipoprotein to targets <70 mg/dL after MI also prevented more death/MI/unstable angina over the subsequent 2 years of follow-up in patients ≥70 years of age (78 events) than in younger patients (20 events).[111] The Z phase of the A-to-Z trial also included patients with a spectrum of acute coronary syndromes (STEMI and non–ST-segment–elevation ACS) randomized to early intensive or delayed conservative treatment with simvastatin and found nonsignificant trends toward improved outcomes in the intensive arm overall and among those ≥65 years of age (mean trial age, 61 years).[112] However, none of these trials present subgroup data for subjects ≥75 years of age.

Secondary prevention trials, such as Cholesterol and Recurrent Events (CARE), Scandinavian Simvastatin Survival Study (4S), and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), support a benefit of lipid lowering after MI.[113–115] Although these trials excluded patients ≥75 years of age (4S upper age limit, 69 years), they demonstrate a benefit of statins among younger elderly.[116,117] The Heart Protection Study (HPS) compared simvastatin with placebo in patients (52% ≥65 years of age; upper age limit, 80 years).[118] In this study, the 5806 high-risk patients ≥70 years of age had the same absolute risk reduction with simvastatin as in those <65 years of age (5.1% versus 5.2%). The Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial compared pravastatin with placebo in 5804 high-risk elderly (≥70 years of age) and demonstrated a 15% relative and 2.1% absolute risk reduction in death or MI at 3.2 years.[119,120] The pleiotropic effects of statins are of theoretical benefit in the elderly given their effects on endothelial function and the inflammatory milieu.[111] Although none of these studies have robust sample sizes, the amassed data support a benefit of statins in the elderly; however, cost and side effects must be considered, particularly when higher doses are used.

Adjunctive Therapy Summary
- Greater short- and long-term benefits of adjunctive therapy are found in elderly subgroups in which data are available.
  - β-Blockers have greater benefits in the elderly for the prevention of subsequent MI and death than in younger groups. Given the potential hypotensive and bradycardic effects of intravenous β-blockers, their use in STEMI with hemodynamic compromise is not advised.
  - ACE inhibitors and angiotensin receptor blockers are beneficial in the elderly, particularly in the setting of heart failure or reduced left ventricular function.
  - Statins have greater benefits in the elderly for the prevention of subsequent MI and death than in younger subgroups.
  - Nitrates may be useful adjunctive treatments in the elderly, in particular because of their effects on preload, afterload, and reducing recurrent ischemia.

Medical Ethics and Acute Care of the Elderly

Many ethical considerations in the acute care of the elderly patient emanate from the scientific uncertainty that persists around standard treatments, as well as the multiplicity of preferences among older patients. Providing high-quality care in the elderly includes adhering to the basic principles of medical ethics, which include the following: (1) autonomy (respect for patient preferences); (2) beneficence (acting commensurate with the patient's best interests); (3) nonmalfeasance (doing no harm); and (4) justice (fairness in distribution of resources).[121] These principles describe the ideal healthcare relationship between patient and physician with regard to the assessment of evidence and care. Applying these principles to the elderly with ACS brings out the limitations in our healthcare system, our evidence base, and societal views on aging. The expanding geriatric population and complex healthcare environment will magnify these issues in the setting of healthcare spending at unprecedented levels in the coming years.[122–124]

The principle of autonomy emphasizes a patient's right to self-determination in choosing treatments most likely to result in a preferred health outcome. Elderly patients are often vulnerable and ill-equipped to advocate for themselves in healthcare settings. Informed consent should ensure autonomy when risks are substantial, yet the process is challenging in the elderly with ACS. The urgency of the situation limits leisurely exchanges of medical information and discussion of preferences. Communication may be further limited by a patient's hearing or visual deficits, less formal education, or impaired cognition. Objective evidence is very limited to clarify risk and benefit in this subgroup. In addition, often patients have not determined their preferences before arrival in the emergency department, and even if they have preferences, they do not discuss them with providers.[125] The elderly are also more likely to abdicate medical decision making to physicians or family members. Moreover, some elderly patients may feel dependent on family; thus, they may not be in a position to make truly autonomous decisions. This dynamic is of particular concern because family members often make decisions divergent from those the patients themselves would have chosen if given time and opportunity.[126] Healthcare providers must be alert to these barriers and encourage collaborative decisions in the elderly. Most importantly, older adults should discuss their preferred health outcomes with loved ones well in advance of a health crisis.

The principle of beneficence enjoins providers to act in the best interests of their elderly patients with MI and better approximates realities of practice. However, determining what constitutes best interest and best outcome in the elderly involves ill-defined tradeoffs between quality and quantity of life, which are at times directly opposed. Quality-of-life outcomes after ACS in the elderly are not well described, and the role of patient-specific factors in modulating such outcomes is poorly understood. When the elderly experience adverse outcomes, their care quickly becomes the responsibility of others outside of the healthcare setting. Therefore, family and other support networks are important stakeholders in treatment.

The principle of nonmalfeasance encourages physicians to do no harm. Treatments that afford no benefit only expose the elderly patient to inherent risks. The inherent risks are more obvious to the healthcare provider than the less well-characterized quality-of-life outcomes. Trying to resolve these issues in an emergency setting can be overwhelming, and therefore providers default to less aggressive treatment to avoid these risks. Although for some this may be a good choice, for many others it is not. Therefore, the identification of patients likely to benefit for whom treatment is not futile is important. Interventions that prolong dying without improving pain or suffering should be avoided, and understanding medical futility and its implications will prevent unnecessary harm to elderly patients.

Finally, the principle of justice encourages physicians to allocate medical resources in an equitable manner, providing a similar level of care for all. "Ageism" occurs when elderly patients are dismissed as unsuitable candidates for care because of a devaluation of their quantity and quality of life. The frail or less educated elderly may be particularly vulnerable to ageism. The elderly should not be excluded from receiving appropriate medical and surgical interventions solely on the basis of age.[127] Whenever feasible, physicians should also apply their knowledge to help fulfill the societal goal of controlling healthcare costs. Healthcare expenditures are highest near the end of life, when financial resources are often limited. As healthcare costs escalate, it is imperative that outcomes be balanced against costs to ensure the cost-effectiveness of health care in all patients. A national dialogue on allocation of limited resources is needed to ensure continued value from healthcare spending as the population ages.[128]

Medical Ethics and Care of the Elderly Summary

- Ethical uncertainty in the acute care of the elderly arises from the limited evidence base and multiplicity of patient preferences.
  - Risk–benefit ratios are needed to inform treatment selection.
  - Interventions with questionable benefit or significant risk of harm should be avoided.
  - More data on quality-of-life outcomes are needed.
- Elderly individuals should engage in conversations with loved ones about health preferences well in advance of a healthcare crisis.
  - Patients' healthcare wishes are paramount in ensuring autonomous and beneficent care.
  - Discussing risk–benefit ratio and preferences in the acute care setting is challenging, so care should be guided by the principle of beneficence as a default.

Summary

Patient heterogeneity, atypical presentations, and limited trial representation are common themes in management of STEMI and non–ST-segment–elevation ACS in the elderly. Up to age 85 years, a benefit is associated with reperfusion. The selection between fibrinolytics or PCI is determined by shock, time from presentation, and comorbidity, which often tip the balance toward PCI in the elderly. The safety and efficacy of reperfusion, specifically fibrinolytic therapy, in

the very elderly (≥85 years of age) remain significant questions for future investigation. In addition, the high rate of shock, myocardial rupture, and death in the oldest old make understanding pathophysiology related to ischemia in the aging heart important.

More information from registries and increased enrollment of elderly in clinical trials will answer some questions on risk and benefit. Age subgroup results should be presented in terms of absolute and relative risk differences, and data on quality-of-life outcomes are needed to enable the elderly to make informed decisions about their care. With this additional information, providers and society will be better prepared to manage the burgeoning elderly population presenting with ACS in a manner that is both patient centered and cost-effective.[129–132]

- Many questions remain about risk and benefit of interventions in the elderly (≥75 years of age) and particularly in the oldest age subgroup (≥85 years of age).
  - Better evidence is needed on selection and dosing of adjunctive therapies.
  - Better evidence is needed on management of complications in the elderly.
  - Quality-of-life outcomes are needed to inform patient-centered decisions.
- Multicenter trials comparing fibrinolytic therapy with primary PCI in the very elderly would be desirable but are unlikely.
- Enrollment will be challenging, and randomization cannot account for the importance of clinical judgment in achieving best outcomes in the complex elderly.
  - Community registries are important to reflect on risks and benefits of acute care in the oldest patients from real-world practice.
- System-based practices to reduce prehospital and emergency department delays in identification and treatment of acute MI in the elderly are needed.

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Harlan M. Krumholz	Yale University	None	Colorado Foundation for Medical Care†; American College of Cardiology† (research contracts)	None	None	UnitedHealthCare*; VHA, Inc†; Massachusetts Medical Society†; CV Therapeutics†; Colorado Foundation for Medical Care†; Amgen†; Alere†; Centegen†	Lanier Law Firm* (expert witness)
Mary D. Naylor	University of Pennsylvania	None	None	None	None	None	None
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E. Magnus Ohman	University of North Carolina	Bristol-Myers Squibb†; Sanofi-Aventis†; Schering-Plough†; Millennium Pharmaceuticals†; Eli Lilly†; Berlex†	None	None	Inovise*; Savacor*; Medtronic*	Inovise†; Savacor†; Liposcience Response*; Biomedical*; The Medicines Company*; Datascope*; Abiomed*	None
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W. Douglas Weaver	Henry Ford Hospital	None	None	None	None	None	None
Harvey D. White	Green Lane Hospital	Merck Sharpe & Dohme†; Pfizer†; Wyeth†; Roche†; Medicines Company†; Sanofi-Aventis†; Alexion†; Eli Lilly†; Neuren Pharmaceuticals†; National Institutes of Health†; Fournier Laboratories†; Schering-Plough†; Johnson & Johnson†; Procter & Gamble†; GlaxoSmithKline†; Boehringer Ingelheim†; Novartis†; AstraZeneca†; Bayer†; Janssen-Cilag†	None	Sanofi-Aventis*; Medicines Company*	None	Medicure*; Medicines Company*; Neuren Pharmaceuticals*; GlaxoSmithKline*	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12 month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Elliott M. Antman	Brigham and Women's Hospital	Sanofi-Aventis†	None	Sanofi-Aventis*	None	None	Sanofi-Aventis*	None
Daniel Forman	Brigham and Women's Hospital	None	None	None	None	None	None	None
Gary Gerstenblith	Johns Hopkins Hospital	None	None	None	None	None	None	None
Eric D. Peterson	Duke University	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire that all reviewers are required to complete and submit. A relationship is considered to be "Significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "Modest" if it is less than "Significant" under the preceding definition.

*Modest.
†Significant.

References

1. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, Van de Werf F, White HD, Weaver WD, Naylor MD, Gore JM, Krumholz HM, Ohman EM. Acute coronary care in the elderly, part I: non–ST-segment–elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology. *Circulation*. 2007;115: 2549–2569.
2. Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C. Threats to applicability of randomised trials: exclusions and selective participation. *J Health Serv Res Policy*. 1999;4:112–121.
3. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA*. 2001;286:708–713.
4. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM; GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41,021 patients. *Circulation*. 1995;91:1659–1668.
5. Krumholz HM, Gross CP, Peterson ED, Barron HV, Radford MJ, Parsons LS, Every NR. Is there evidence of implicit exclusion criteria for elderly subjects in randomized trials? Evidence from the GUSTO-1 Study. *Am Heart J*. 2003;146:839–847.
6. Mehta RH, Rathore SS, Radford MJ, Wang Y, Wang Y, Krumholz HM. Acute myocardial infarction in the elderly: differences by age. *J Am Coll Cardiol*. 2001;38:736–741.
7. Yarzebski J, Goldberg RJ, Gore JM, Alpert JS. Temporal trends and factors associated with extent of delay to hospital arrival in patients with acute myocardial infarction: the Worcester Heart Attack Study. *Am Heart J*. 1994;128:255–263.
8. Goldberg RJ, Yarzebski J, Lessard D, Gore JM. Decade-long trends and factors associated with time to hospital presentation in patients with acute myocardial infarction: the Worcester Heart Attack Study. *Arch Intern Med*. 2000;160:3217–3223.
9. Gurwitz JH, McLaughlin TJ, Willison DJ, Guadagnoli E, Hauptman PJ, Gao X, Soumerai SB. Delayed hospital presentation in patients who have had acute myocardial infarction. *Ann Intern Med*. 1997;126: 593–599.
10. Sheifer SE, Rathore SS, Bersh BJ, Weinfurt KP, Oetgen WJ, Breall JA, Schulman KA. Time to presentation with acute myocardial infarction in the elderly: associations with race, sex, and socioeconomic characteristics. *Circulation*. 2000;102:1651–1656.
11. White HD, Barbash GI, Califf RM, Simes RJ, Granger CB, Weaver WD, Kleiman NS, Aylward PE, Gore JM, Vahanian A, Lee KL, Ross AM, Topol EJ. Age and outcome with contemporary thrombolytic therapy: results from the GUSTO-I trial: Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries Trial. *Circulation*. 1996;94: 1826–1833.

12. Newby LK, Rutsch WR, Califf RM, Simoons ML, Aylward PE, Armstrong PW, Woodlief LH, Lee KL, Topol EJ, Van de Werf F; GUSTO-1 Investigators. Time from symptom onset to treatment and outcomes after thrombolytic therapy. *J Am Coll Cardiol*. 1996;27:1646–1655.
13. Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, Lopez-Sendon J; GRACE Investigators. Practice variation and missed opportunities for reperfusion in ST-segment–elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet*. 2002;359:373–377.
14. Krumholz HM, Friesinger GC, Cook EF, Lee TH, Rouan GW, Goldman L. Relationship of age with eligibility for thrombolytic therapy and mortality among patients with suspected acute myocardial infarction. *J Am Geriatr Soc*. 1994;42:127–131.
15. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: executive summary: a report of the ACC/AHA Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *J Am Coll Cardiol*. 2004;44:671–719.
16. French WJ. Trends in acute myocardial infarction management: use of the National Registry of Myocardial Infarction in quality improvement. *Am J Cardiol*. 2000;85:5B–9B.
17. Boucher JM, Racine J, Thanh TH, Rahme E, Brophy J, LeLorier J, Theroux P; Quebec Acute Coronary Care Working Group. Age-related differences in in-hospital mortality and the use of thrombolytic therapy for acute myocardial infarction. *CMAJ*. 2001;164:1285–1290.
18. Martinez-Selles M, Datino T, Bueno H. Influence of reperfusion therapy on prognosis in patients aged ≥89 years with acute myocardial infarction. *Am J Cardiol*. 2005;95:1232–1234.
19. Maggioni AP, Maseri A, Fresco C, Franzosi MG, Mauri F, Santoro E, Tognoni G; The Investigators of the Gruppo Italiano per lo Studio della Sopravvivenza nell Infarto Miocardico (GISSI-2). Age-related increase in mortality among patients with first myocardial infarction treated with thrombolysis. *N Engl J Med*. 1993;329:1442–1448.
20. Bueno H, Martinez-Selles M, Perez-David E, Lopez-Palop R. Effect of thrombolytic therapy on the risk of cardiac rupture and mortality in older patients with first acute myocardial infarction. *Eur Heart J*. 2005;26: 1705–1711.
21. Ornato JP, Peberdy MA, Tadler SC, Strobos NC. Factors associated with the occurrence of cardiac arrest during hospitalization for acute myocardial infarction in the Second National Registry of Myocardial Infarction in the US. *Resuscitation*. 2001;48:117–123.
22. Goldberg RJ, Gore JM, Gurwitz JH, Alpert JS, Brady P, Strohsnitter W, Chen ZY, Dalen JE. The impact of age on the incidence and prognosis of initial acute myocardial infarction: the Worcester Heart Attack Study. *Am Heart J*. 1989;117:543–549.

23. Burns TR, Klima M, Teasdale TA, Kasper K. Morphometry of the aging heart. *Mod Pathol*. 1990;3:336–342.

24. Nixon JV, Hallmark H, Page K, Raven PR, Mitchell JH. Ventricular performance in human hearts aged 61 to 73 years. *Am J Cardiol*. 1985;56:932–937.

25. Thompson CR, Buller CE, Sleeper LA, Antonelli TA, Webb JG, Jaber WA, Abel JG, Hochman JS. Cardiogenic shock due to acute severe mitral regurgitation complicating acute myocardial infarction: a report from the SHOCK Trial Registry: SHould we use emergently revascularize Occluded Coronaries in cardiogenic shocK? *J Am Coll Cardiol*. 2000;36(suppl A):1104–1109.

26. Menon V, Webb JG, Hillis LD, Sleeper LA, Abboud R, Dzavik V, Slater JN, Forman R, Monrad ES, Talley JD, Hochman JS. Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK Trial Registry: SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK? *J Am Coll Cardiol*. 2000;36(suppl A):1110–1116.

27. Waller BF, Rothbaum DA, Pinkerton CA, Cowley MJ, Linnemeier TJ, Orr C, Irons M, Helmuth RA, Wills ER, Aust C. Status of the myocardium and infarct-related coronary artery in 19 necropsy patients with acute recanalization using pharmacologic (streptokinase, r-tissue plasminogen activator), mechanical (percutaneous transluminal coronary angioplasty) or combined types of reperfusion therapy. *J Am Coll Cardiol*. 1987;9:785–801.

28. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673–682.

29. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med*. 1997;336:1621–1628.

30. Cannon CP, Gibson CM, McCabe CH, Adgey AA, Schweiger MJ, Sequeira RF, Grollier G, Giugliano RP, Frey M, Mueller HS, Steingart RM, Weaver WD, Van de Werf F, Braunwald E; Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. *Circulation*. 1998;98:2805–2814.

31. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators; Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, Betriu A, Binbrek AS, Califf R, Diaz R, Fanebust R, Fox K, Granger C, Heikkila J, Husted S, Jansky P, Langer A, Lupi E, Maseri A, Meyer J, Mlczoch J, Mocceti D, Myburgh D, Oto A, Paolasso E, Pehrsson K, Seabra-Gomes R, Soares-Piegas L, Sugrue D, Tendera M, Topol E, Toutouzas P, Vahanian A, Verheugt F, Wallentin L, White H. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomized trial. *Lancet*. 1999;354:716–722.

32. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomized trial in acute myocardial infarction. *Lancet*. 2001;358:605–613.

33. Topol EJ; GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet*. 2001;357:1905–1914.

34. White H; Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet*. 2001;358:1855–1863.

35. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Makijarvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS Randomized Trial in Acute Myocardial Infarction. *Circulation*. 2003;108:135–142.

36. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC, et al; the Primary Angioplasty in Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med*. 1993;328:673–679.

37. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med*. 1993;328:680–684.

38. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van't Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med*. 1999;341:1413–1419.

39. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS; DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med*. 2003;349:733–742.

40. Goldenberg I, Matetzky S, Halkin A, Roth A, Di Segni E, Freimark D, Elian D, Agranat O, Har Zahav Y, Guetta V, Hod H. Primary angioplasty with routine stenting compared with thrombolytic therapy in elderly patients with acute myocardial infarction. *Am Heart J*. 2003;145:862–867.

41. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361:13–20.

42. Mehta RH, Granger CB, Alexander KP, Bossone E, White HD, Sketch MH Jr. Reperfusion strategies for acute myocardial infarction in the elderly: benefits and risks. *J Am Coll Cardiol*. 2005;45:471–478.

43. Thiemann DR, Coresh J, Oetgen WH, Powe NR. The association between hospital and survival after acute myocardial infarction in elderly patients. *N Engl J Med*. 1999;340:1640–1648.

44. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet*. 1994;343:311–322.

45. White HD. Thrombolytic therapy in the elderly. *Lancet*. 2000;356:2028–2030.

46. Lesnefsky EJ, Lundergan CF, Hodgson JM, Nair R, Reiner JS, Greenhouse SW, Califf RM, Ross AM. Increased left ventricular dysfunction in elderly patients despite successful thrombolysis: the GUSTO-1 angiographic experience. *J Am Coll Cardiol*. 1996;28:331–337.

47. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation*. 2000;101:2239–2246.

48. Angeja BG, Rundle AC, Gurwitz JH, Gore JM, Barron HV. Death or nonfatal stroke in patients with acute myocardial infarction treated with tissue plasminogen activator: participants in the National Registry of Myocardial Infarction 2. *Am J Cardiol*. 2001;87:627–630.

49. Soumerai SB, McLaughlan TJ, Ross-Degnan D, Christiansen CL, Gurwitz JH. Effectiveness of thrombolytic therapy for acute myocardial infarction in the elderly: cause for concern in the old-old. *Arch Intern Med*. 2002;162:561–568.

50. Berger AK, Radford MJ, Wang Y, Krumholz HM. Thrombolytic therapy in older patients. *J Am Coll Cardiol*. 2000;36:366–374.

51. Stenestrand U, Wallentin L; Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). Fibrinolytic therapy in patients 75 years and older with ST-segment-elevation myocardial infarction: one-year follow-up for large prospective cohort. *Arch Intern Med*. 2003;163:965–971.

52. Gore JM, Granger CB, Simoons ML, Sloan MA, Weaver WD, White HD, Barbash GI, Van de Werf F, Aylward PE, Topol EJ, et al. Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial: Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation*. 1995;92:2811–2828.

53. Kandzari DE, Granger CB, Simoons ML, White HD, Simes J, Mahaffey KW, Gore J, Weaver WD, Longstreth WT Jr, Stebbins A, Lee KL, Califf RM, Topol EJ; Global Utilization of Streptokinase and tPA for Occluded Arteries-I Investigators. Risk factors for intracranial hemorrhage and nonhemorrhagic stroke after fibrinolytic therapy (from the GUSTO-I Trial). *Am J Cardiol*. 2004;93:458–461.

54. Brass LM, Lichtman JH, Wang Y, Gurwitz JH, Radford MJ, Krumholz HM. Intracranial hemorrhage associated with thrombolytic therapy for elderly patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. *Stroke*. 2000;31:1802–1811.

55. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Mio-cardioco. GISSI-2: a factorial randomized trial of alteplase versus strep-tokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet*. 1990;336:65–71.

56. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet*. 1992;339:753–770.

57. Simoons ML, Maggioni AP, Knatterud G, Leimberger JD, de Jaegere P, van Domburg R, Boersma E, Franzosi MG, Califf R, Schroder R, et al. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet*. 1993;342:1523–1528.

58. Van de Werf F, Barron HV, Armstrong PW, Granger CB, Berioli S, Barbash G, Pehrsson K, Verheugt FW, Meyer J, Betriu A, Califf RM, Li X, Fox NL; ASSENT-2 Investigators: Assessment of the Safety and Efficacy of a New Thrombolytic. Incidence and predictors of bleeding events after fibrinolytic therapy with fibrin-specific agents: a com-parison of TNK-tPA and rt-PA. *Eur Heart J*. 2001;22:2253–2261.

59. Curtis JP, Alexander JH, Huang Y, Wallentin L, Verheugt FW, Arm-strong PW, Krumholz HM, Van de Werf F, Danays T, Cheeks M, Granger CB; ASSENT-2 and ASSENT-3 Investigators. Efficacy and safety of two unfractionated heparin dosing strategies with tenecteplase in acute myocardial infarction (results from Assessment of the Safety and Efficacy of a New Thrombolytic Regimens 2 and 3). *Am J Cardiol*. 2004;94:279–283.

60. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, Budaj A, Lopez-Sendon JL, Guneri S, Jiang F, White HD, Fox KA, Braunwald E; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myo-cardial infarction. *N Engl J Med*. 2006;354:1477-1488.

61. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E; CLARITY-TIMI 28 Investigators. Addition of clopi-dogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005;352:1179–1183.

62. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366:1607–1621.

63. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA; OASIS-6 Trial Group. Effects of fondaparinux on mortality and rein-farction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 Randomized Trial. *JAMA*. 2006;295: 1519–1530.

64. Savonitto S, Armstrong PW, Lincoff AM, Jia G, Sila CA, Booth J, Terrosu P, Cavallini C, White HD, Ardissino D, Califf RM, Topol EJ. Risk of intracranial haemorrhage with combined fibrinolytic and glyco-protein IIb/IIIa inhibitor therapy in acute myocardial infarction: dichotomous response as a function of age in the GUSTO V trial. *Eur Heart J*. 2003;24:1807–1814.

65. Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O'Keefe J, Hartzler GO, Overlie P, Donohue B, Chelliah N, et al. Predictors of in-hospital and 6-month outcome after acute myocardial infarction in the reperfusion era: the Primary Angioplasty in Myocardial Infarction (PAMI) trial. *J Am Coll Cardiol*. 1995;25:370–377.

66. Thune JJ, Hoefsten DE, Lindholm MG, Mortensen LS, Andersen HR, Nielsen TT, Kober L, Kelbaek H; Danish Multicenter Randomized Study on Fibrinolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI)-2 Investigators. Simple risk stratification at admission to identify patients with reduced mortality from primary angioplasty. *Circulation*. 2005;112:2017–2021.

67. de Boer MJ, Ottervanger JP, van't Hof AW, Hoorntje JC, Suryapranata H, Zijlstra F; Zwolle Myocardial Infarction Study Group. Reperfusion therapy in elderly patients with acute myocardial infarction: a ran-domized comparison of primary angioplasty and thrombolytic therapy. *J Am Coll Cardiol*. 2002;39:1723–1728.

68. Grines C. Senior PAMI: a prospective randomized trial of primary angioplasty and thrombolytic therapy in elderly patients with acute myocardial infarction. Presented at Transcatheter Cardiovascular Ther-apeutics; Washington, D; October 16–21, 2005.

69. Weaver WD, Simes RJ, Betriu A, Grines CL, Zijlstra F, Garcia E, Grinfeld L, Gibbons RJ, Ribeiro EE, DeWood MA, Ribichini F. Com-parison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA*. 1997;278:2093–2098.

70. Grines C, Patel A, Zijlstra F, Weaver WD, Granger C, Simes RJ; PCAT Collaborators; percutaneous transluminal coronary angioplasty. Primary coronary angioplasty compared with intravenous thrombolytic therapy for acute myocardial infarction: six-month follow up and analysis of individual patient data from randomized trials. *Am Heart J*. 2003;145: 47–57.

71. Boersma E; The Primary Coronary Angioplasty vs. Thrombolysis Group. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J*. 2006;27:779–788.

72. Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, Branny M, St'asek J, Formanek P; 'PRAGUE' Study Group Inves-tigators. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction: final results of the ran-domized national multicentre trial—PRAGUE-2. *Eur Heart J*. 2003;24: 94–104.

73. Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien PY, Cristofini P, Leizorovicz A, Touboul P; Comparison of Angioplasty and Pre-hospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) Inves-tigators. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation*. 2003;108:2851–2856.

74. Schomig A, Mehilli J, Antoniucci D, Ndrepepa G, Markwardt C, Di Pede F, Nekolla SG, Schlotterbeck K, Schuhlen H, Pache J, Seyfarth M, Martinoff S, Benzer W, Schmitt C, Dirschinger J, Schwaiger M, Kastrati A; Beyond 12 Hours Reperfusion AlternatiVe Evaluation (BRAVE-2) Trial Investigators. Mechanical reperfusion in patients with acute myo-cardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. *JAMA*. 2005;293:2865–2872.

75. Hochman JS, Buller CE, Sleeper LA, Boland J, Dzavik V, Sanborn TA, Godfrey E, White HD, Lim J, LeJemtel T. Cardiogenic shock compli-cating acute myocardial infarction—etiologies, management and outcome: a report from the SHOCK Trial Registry: SHould we emer-gently revascularize Occluded Coronaries for cardiogenic shocK? *J Am Coll Cardiol*. 2000;36(suppl A):1063–1070.

76. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH; SHOCK Investigators. Early revascularization in acute myocardial infarction complicated by cardiogenic shock: should we emergently revascularize occluded coronaries for cardiogenic shock? *N Engl J Med*. 1999;26:625–634.

77. Dzavik V, Sleeper LA, Cocke TP, Moscucci M, Saucedo J, Hosat S, Jiang X, Slater J, LeJemtel T, Hochman JS; SHOCK Investigators. Early revascularization is associated with improved survival in elderly patients with acute myocardial infarction complicated by cardiogenic shock: a report from the SHOCK Trial Registry. *Eur Heart J*. 2003;24:828–837.

78. Dauerman HL, Ryan TJ Jr, Piper WD, Kellett MA, Shubrooks SJ, Robb JF, Hearne MJ, Watkins MW, Hettleman BD, Silver MT, Niles NW, Malenka DJ. Outcomes of percutaneous coronary intervention among elderly patients in cardiogenic shock: a multicenter decade-long expe-rience. *J Invasive Cardiol*. 2003;15:380–384.

79. Tiefenbrunn AJ, Chandra NC, French WJ, Gore JM, Rogers WJ. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). *J Am Coll Cardiol*. 1998;31:1240–1245.

80. Mehta RH, Sadiq I, Goldberg RJ, Gore JM, Avezum A, Spencer F, Kline-Rogers E, Allegrone J, Pieper K, Fox KA, Eagle KA; GRACE Investigators. Effectiveness of primary percutaneous coronary inter-vention compared with that of thrombolytic therapy in elderly patients with acute myocardial infarction. *Am Heart J*. 2004;147:253–259.

81. Berger AK, Schulman KA, Gersh BJ, Pirzada S, Breall JA, Johnson AE, Every NR. Primary coronary angioplasty vs thrombolysis for the man-agement of acute myocardial infarction in elderly patients. *JAMA*. 1999; 282:341–348.

82. Krumholz HM, Radford MJ, Wang Y, Chen J, Heiat A, Marciniak TA. National use and effectiveness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. *JAMA*. 1998;280:623–629.

83. The MIAMI Trial Research Group. Metoprolol in Acute Myocardial Infarction (MIAMI): a randomised placebo-controlled international trial. *Eur Heart J*. 1985;6:199–226.

84. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet*. 1986;11:57–66.

85. Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Malek I, Nyberg G, Ryden L, Swedberg K, Vedin A, Waagstein F, Waldenstrom A, Waldenstrom J, Wedel H, Wilhelmsen L, Wilhelmsson C. Effect on mortality of metoprolol in acute myocardial infarction: a double-blind randomised trial. *Lancet*. 1981;11:823–827.

86. Pfisterer M, Cox JL, Granger CB, Brener SJ, Naylor CD, Califf RM, van de Werf F, Stebbins AL, Lee KL, Topol EJ, Armstrong PW. Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: the GUSTO-I experience: Global Utilization of Streptokinase and TPA (Alteplase) for Occluded Coronary Arteries. *J Am Coll Cardiol*. 1998;32:634–640.

87. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, Xie JX, Liu LS; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366:1622–1632.

88. A randomized trial of propranolol in patients with acute myocardial infarction, I: mortality results. *JAMA*. 1982;247:1707–1714.

89. A randomized trial of propranolol in patients with acute myocardial infarction, II: morbidity results. *JAMA*. 1983;250:2814–2819.

90. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med*. 1981;304:801–807.

91. Gundersen T, Abrahmsen AM, Kjekshus J, Ronnevik PK. Timolol-related reduction in mortality and reinfarction in patients ages 65–75 years surviving acute myocardial infarction: prepared for the Norwegian Multicentre Study Group. *Circulation*. 1982;66:1179–1184.

92. Pedersen TR. Six-year follow-up of the Norwegian Multicenter Study on timolol after myocardial infarction. *N Engl J Med*. 1985;313:1055–1058.

93. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction ≥40% treated with diuretics plus angiotensin-converting-enzyme inhibitors. *Am J Cardiol*. 1997;80: 207–209.

94. Park KC, Forman DE, Wei JY. Utility of beta-blockade treatment for older postinfarction patients. *J Am Geriatr Soc*. 1995;43:751–755.

95. Soumerai SB, McLaughlin TJ, Spiegelman D, Hertzmark E, Thibault G, Goldman L. Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. *JAMA*. 1997;277:115–121.

96. Krumholz HM, Radford MJ, Wang Y, Chen J, Marciniak TA. Early beta-blocker therapy for acute myocardial infarction in elderly patients. *Ann Intern Med*. 1999;131:648–654.

97. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardioco. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet*. 1994;343: 1115–1122.

98. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet*. 1995;345: 669–685.

99. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardioco. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after myocardial infarction: the GISSI-3 Trial. *J Am Coll Cardiol*. 1996;27: 337–344.

100. Ambrosioni E, Borghi C, Magnani B; Long-Term Evaluation (SMILE) Study Investigators. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med*. 1995;332:80–85.

101. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al; the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med*. 1992; 327:669–677.

102. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet*. 1993;342:821–828.

103. Krumholz HM, Chen YT, Wang Y, Radford MJ. Aspirin and angiotensin-converting enzyme inhibitors among elderly survivors of hospitalization for an acute myocardial infarction. *Arch Intern Med*. 2001;161: 538–544.

104. Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial: Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet*. 2002;360:752–760.

105. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349: 1893–1906.

106. White HD, Aylward PE, Huang Y, Dalby AJ, Weaver WD, Barvik S, Marin-Neto JA, Murin J, Nordlander RO, van Gilst WH, Zannad F, McMurray JJ, Califf RM, Pfeffer MA; VALIANT Investigators. Mortality and morbidity remain high despite captopril and/or valsartan therapy in elderly patients with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction: results from the Valsartan in Acute Myocardial Infarction Trial (VALIANT). *Circulation*. 2005;112:3391–3399.

107. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003; 348:1309–1321.

108. Inspra (eplerenone) [package insert]. New York, NY: Pfizer Inc; 2003.

109. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T; Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL Study: a randomized controlled trial. *JAMA*. 2001;285:1711–1718.

110. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350: 1495–1504.

111. Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:1425–1433.

112. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E; A to Z Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292:1307–1316.

113. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344: 1383–1389.

114. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E; Cholesterol and Recurrent Events Trial investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001–1009.

115. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.

116. Miettinen TA, Pyorala K, Olsson AG, Musliner TA, Cook TJ, Faergeman O, Berg K, Pedersen T, Kjekshus J. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation*. 1997;96:4211–4218.

117. Hunt D, Young P, Simes J, Musliner TA, Cook TJ, Faergeman O, Berg K, Pedersen T, Kjekshus J. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are

equal to or exceed those seen in younger patients: results from the LIPID Trial. *Ann Intern Med*. 2001;134:931–940.

118. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.

119. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; PROSPER Study Group: PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet*. 2002;360:1623–1630.

120. Ray KK, Bach RG, Cannon CP, Cairns R, Kirtane AJ, Wiviott SD, McCabe CH, Braunwald E, Gibson CM; PROVE IT-TIMI 22 Investigators. Benefits of achieving the NCEP optional LDL-C goal among elderly patients with ACS. *Eur Heart J*. 2006;27:2310–2316.

121. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, DC: Dept of Health, Education, and Welfare; 1979. Publication (OS)-78-0013 and (OS)-78-0014.

122. CDC. Public health and aging: trends in aging: United States and worldwide. *MMWR*. 2003;52:101–106.

123. Braunwald E. Shattuck lecture: cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med*. 1997;337:1360–1369.

124. Institute of Medicine. Corrigan L, Donaldson M, eds. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 2000.

125. Hamel MB, Lynn J, Teno JM, Covinsky KE, Wu AW, Galanos A, Desbiens NA, Phillips RS. Age-related differences in care preferences, treatment decisions, and clinical outcomes of seriously ill hospitalized adults: lessons from SUPPORT. *J Am Geriatr Soc*. 2000;48(suppl):S176–S182.

126. Layde PM, Beam CA, Broste SK, Connors AF Jr, Desbiens N, Lynn J, Phillips RS, Reding D, Teno J, Vidaillet H, et al. Surrogates' predictions of seriously ill patients' resuscitation preferences. *Arch Fam Med*. 1995; 4:518–523.

127. Parmley WW, Passamani ER, Lo B. 29th Bethesda Conference: ethics in cardiovascular medicine (1977): introduction. *J Am Coll Cardiol*. 1998; 31:917–925.

128. Callahan D. Controlling the costs of health care for the elderly: fair means and foul. *N Engl J Med*. 1996;335:744–746.

129. A comparison of reteplase with alteplase for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. *N Engl J Med*. 1997;337:1118–1123.

130. Topol EJ; GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet*. 2001;357:1905–1914.

131. National Registry of Myocardial Infarction Web site. Available at: http://www.nrmi.org. Accessed June 10, 2005.

132. GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J* 2001; 141:190–199.