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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: In Collaboration With the Society of Geriatric Cardiology

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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

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 (ACS); however, community practice reveals a disproportionately lower use of cardiovascular medications and invasive treatment even among elderly patients with ACS who would stand to benefit. Reasons include limited trial data to guide the care of older adults and uncertainty about benefits and risks, particularly with newer medications or invasive treatments and in the setting of advanced age or complex health status.

Methods and Results—This 2-part American Heart Association scientific statement summarizes evidence on patient heterogeneity, clinical presentation, and treatment of non–ST-elevation ACS in relation to age (<65, 65 to 74, 75 to 84, and ≥85 years). In addition, we review methodological issues that influence the acquisition and application of evidence to the elderly patients treated in community practice. A writing group combining international cardiovascular and geriatric perspectives convened to summarize available data from trials (5 combined Virtual Coordinating Center for Global Collaborative Cardiovascular Research [VIGOUR] trials) and 3 registries (Global Registry of Acute Coronary Events, National Registry of Myocardial Infarction, and the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines national quality improvement initiative [CRUSADE]) to provide a conceptual framework for future work in the care of the elderly with acute cardiac disease. Treatment for non–ST-segment–elevation ACS (Part I) and ST-segment–elevation myocardial infarction (Part II) are reviewed. In addition, ethical considerations pertaining to acute care and secondary prevention are considered (Part II). The primary goal is to identify the areas in which sufficient evidence is available to guide practice, as well as to determine areas that warrant further study. Although treatment-related benefits should rise in an elderly population with high disease risk, data to assess these benefits are limited, outcomes of importance vary, and heterogeneity among the elderly increases treatment-related risks. Although a uniform approach to care in the oldest of the old is unlikely, understanding the major contributors to benefits and risks from treatment will advance the ability to apply guideline-based care in this subset of patients.

Conclusions—Although a few recent trials have described treatment effects in older patients, others continue to exclude patients on the basis of age. Going forward, prospective trials should enroll elderly subjects proportionate to their prevalence among the treated population to define risk and benefit. Findings from age subgroup analyses should be reported in a consistent manner across trials, including absolute and relative risks for efficacy and safety. Outcomes of particular relevance to the elderly, such as quality of life, physical function, and independence, should also be

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considered. Creatinine clearance should be calculated for every elderly patient to enable appropriate dosing. In addition, physicians need an understanding of conditions unique to older patients (eg, frailty, cognitive impairment) that influence treatment goals and outcomes. With these efforts, treatment risks can be minimized, and benefits can be placed in the health context of the elderly patient with ACS. (***Circulation*. 2007;115:2549-2569.**)

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

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Ischemic heart disease is the leading cause of death among patients in the United States, Europe, and the world.[1] In 2004, acute coronary syndromes (ACS) accounted for 35% of all deaths among persons ≥65 years of age in the United States.[2] Moreover, among people who died of ischemic heart disease, 83% were >65 years of age.[3] Cardiovascular morbidity and mortality rates rise rapidly past 75 years of age, a group that accounts for only 6% of the US population but 60% of myocardial infarction (MI)–related deaths.[4] The World Health Organization predicts that coronary heart disease (CHD) deaths will increase by 120% for women and 137% for men over the next 2 decades.[5] In large part, this is due to the expansion of the older population. According to the National Center for Health Statistics, the average life expectancy in the United States reached an all-time high in 2002 of 77.3 years and continues to rise.[6] With lengthening of life expectancy, it is projected that from the years 2000 to 2030, the proportion of people ≥65 years of age will increase from 12.4% to 19.6% in the United States.[7] During this same time interval, the absolute number of the oldest old (≥85 years of age) in the United States will double, from 9.3 to 19.5 million.

Age is a powerful predictor of adverse events after ACS.[8–10] After accounting for other factors, the odds for in-hospital death increase by 70% for each 10-year increase in age (odds ratio [OR] 1.70, 95% confidence interval, 1.52 to 1.82).[8] The average age at which individuals experience a first heart attack is 65.8 years for men and 70.4 years for women.[11] When placed in the context of life expectancy, these first events by no means occur at the end of life. According to US life expectancy statistics, at 65 years of age, a man can expect 16 remaining years of life, and at 70 years of age, a woman can expect to live up to 17.5 more years.[2] Furthermore, actuarial tables suggest that 1 in 4 men who are currently 65 years of age will live past age 92, and 1 in 4 women currently 65 years of age will live past age 94 (source: Society of Actuaries Annuity 2000 Mortality Tables, Society of Actuaries, Schaumburg, Ill). These population estimates, although likely altered by a cardiac event, provide perspective on the potential years recoverable in this population.

Over the past decade, the management of patients with ACS has evolved rapidly with the development of new therapeutics and strategies of care. These medical advancements have led to improved survival and gains in life expectancy, yet these have primarily been realized in younger persons (<65 years of age) and in men.[3,12] The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) recently updated their treatment guidelines for non–ST-segment–elevation (NSTE) ACS to reflect these advances.[13,14] These guidelines emphasize intensive and early medical and interventional therapy, particularly for those at high risk for short-term events. The elderly are a subgroup known to be at high risk, but community practice patterns continue to demonstrate less use of cardiac medications and invasive care even among elderly individuals likely to benefit.[15] Limited randomized clinical trial data to guide acute care in elderly patients, coupled with lingering uncertainty about benefit and risk with advanced age, likely explain this practice.[16] For gains in quality life-years after ACS to continue, survival from acute heart disease will need to also extend to the very elderly population.[12,17] Understanding how treatments are effective in realizing patient-centered outcomes in this subgroup is important.

Therefore, the purpose of this 2-part scientific statement is to provide a comprehensive summary of the best available evidence for treatment of the elderly with ACS, both for NSTE ACS (Part I) and for ST-segment–elevation myocardial infarction (STEMI; Part II). In addition, a review of the heterogeneity of this population in relation to trial enrollment and clinical care emphasizes the methodological issues faced

TABLE 1. ACC/AHA Guidelines for Management of NSTE MI: Class I Recommendations in Elderly Patients

1.	Decisions on management should reflect considerations of general health, comorbidities, cognitive status, and life expectancy. (Level of Evidence: C)
2.	Attention should be paid to altered pharmacokinetics and sensitivity to hypotensive drugs. (Level of Evidence: B)
3.	Intensive medical and interventional management of ACS may be undertaken but with close observation for adverse effects of these therapies. (Level of Evidence: B)

Levels of evidence are based on the guidelines from which these recommendations are taken.

in advancing the evidence in this important subset of patients. None of the trials reviewed had adequate sample sizes to enable the elderly subgroup to be examined in isolation because the subgroups were small, with wide confidence intervals around treatment effects. Therefore, overall trial results are reviewed, in addition to those of the elderly subgroups when available. In addition, differences between younger and older patients with ACS and between trial and community elderly populations are considered. The purpose of this statement is to (1) review current knowledge of ACS in elderly subgroups from evidence supporting recommended treatments, (2) identify areas in which evidence is sufficient to guide practice or requires further clarification, and most importantly, (3) consider this evidence in terms of the heterogeneity of the elderly and the methodological barriers and opportunities this poses for improving their future care.

Methods

Format and Definitions

The term "elderly" has been used to describe a variety of age subgroups in the literature. The 2002 ACC/AHA practice guidelines for management of patients with unstable angina and non-STEMI categorize elderly patients (defined as individuals ≥75 years of age) as a special at-risk group.[14] However, the guidelines do not distinguish evidence on the basis of age but recommend that consideration be given to general health, cognitive status, and life expectancy in older patients (Table 1). To compare older patients with younger ones, age cut points must be used, and these often are selected on the basis of the average age of a population. For the present statement, we selected 4 subgroups of progressively older individuals (<65, 65 to 74, 75 to 84, and ≥85 years of age) for prospectively evaluated data and clarified age subgroups defined by the literature cited. However, there is such heterogeneity in older-age subgroups defined by chronological age cut points that this must be considered in the interpretation of the evidence and the care of this cohort. Therefore, comparisons between older-age subgroups in trials and community practice and between older and younger patients with ACS is necessary to interpret the age subgroup data. Accordingly, large datasets representing contemporary community practice and recent clinical trials have been acquired for the purpose of writing the present statement. The comparison of like-aged subgroups from practice and trials, as well as a review of the key differences in disease presentation and health context of the elderly, is necessary to provide key perspectives for understanding the available evidence in this population.

The term "NSTE ACS" describes populations presenting with acute chest pain lasting >20 minutes and either positive cardiac markers or dynamic ST-segment changes on the initial ECG without persistent ST-segment elevation. The ACC/AHA and ESC guidelines form the basis for the evidence reviewed and are cited where applicable in providing specific evidence-based recommendations.[13,14] We evaluated randomized trial publications that formed the basis of guideline-recommended treatments for inclusion of elderly, average age of trial participants, and age subgroup findings. Trials and meta-analyses were selected for review if they described the population with NSTE ACS and were cited in the guidelines or provided key information for treatment. Because the benefit of each therapy is determined by absolute risk with or without treatment, we have reported the absolute risk reduction in the elderly subgroup when possible. Furthermore, when multiple aspects of risk vary within a subgroup (which is particularly true for the elderly), tests for heterogeneity of response may be necessary to understand age comparisons. With these caveats in mind, benefits and risks for specific therapies in elderly patients with ACS are considered.[18,19] Adjunctive therapies for secondary prevention, such as lipid-lowering agents, β-blockers, and angiotensin-converting enzyme inhibitors, as well as ethical considerations pertaining to ACS in general, are considered in Part II of this statement.

Clinical Trial and Community Practice Datasets

Three large community registries contributed data describing community elderly with ACS. These include the National Registry of Myocardial Infarction (NRMI), the Global Registry of Acute Coronary Events (GRACE), and the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) National Quality Improvement Initiative. For comparison, the Virtual Coordinating Center for Global Collaborative Cardiovascular Research (VIGOUR) clinical trials group contributed data pooled from 5 NSTE ACS trials. Data were reported as percentages and as means and standard deviations for each of 4 age subgroups. Contemporary use of medical and interventional treatments and in-hospital, 30-day, and 1-year outcomes are reported. Although the registries and the CRUSADE initiative have unique methods for identifying patients, the databases show remarkable concordance and capture similar populations (Table 2).[20–27]

The National Registry of Myocardial Infarction (NRMI) is a large US observational registry in which >1600 participating hospitals record demographic, procedural, therapeutic, and outcomes data on patients with a discharge diagnosis of acute myocardial infarction (AMI). Confirmation of an AMI is based on an *International Classification of Diseases, 9th Revision* (ICD-9) discharge diagnosis code of 410.X1 (required in NRMI 3, 4, and 5) or patient history and presentation suggestive of AMI accompanied by positive cardiac markers, ECG evidence, or nuclear medicine testing. Estab-

TABLE 2. Data Sources

NSTE ACS Populations	Enrollment (Years)	No. of Subjects	Age ≥75 y, %	Regions	Randomized Treatment
VIGOUR (pooled)	1994–2000	34 266	18.1	International	NSTE ACS trials
GUSTO IIb[20]	1994–1996	8011	19.5	9 Countries	Hirudin vs heparin
Paragon A[21]	1995–1995	2282	19.1	20 Countries	GP IIb/IIIa (lamifiban) vs UFH
Paragon B[22]	1997–1999	5225	17.8	26 Countries	GP IIb/IIIa (lamifiban) vs placebo
PURSUIT[23]	1995–1997	10 948	14.6	28 Countries	GP IIb/IIIa (eptifibatide) vs placebo
GUSTO IV-ACS[24]	1998–2000	7800	22.7	24 Countries	GP IIb/IIIa (abciximab) vs placebo
NRMI 2–4[25]	1994–2003	1 076 796	38.3	United States	NSTE MI registry
GRACE[26]	1999–2004	11 968	31.6	International: 14 countries	NSTE ACS registry
CRUSADE[27]	2001–2003	56 963	39.9	United States	NSTE ACS QI initiative

QI indicates quality improvement. Five clinical trials were included in the VIGOUR pooled data set for NSTE ACS.

lished in 1990, NRMI collects data on both NSTE ACS (58% of total enrollment) and STEMI patients. The baseline characteristics, treatments, and outcomes of >1 million NSTE ACS patients enrolled in NRMI 2 to 4 between 1994 and 2003 were considered for the present scientific statement.

The Global Registry of Acute Coronary Events (GRACE) is a large, multinational, prospective registry in which 109 hospitals in 14 countries collect baseline characteristics and clinical management, therapeutic, and outcomes data on patients admitted with a presumptive diagnosis of ACS with follow-up to 1 year. Established in 1999, GRACE enrolls both NSTE ACS (45% of total enrollment) and STEMI patients, with the only exclusion being another major diagnosis concurrent with the coronary syndrome. GRACE has collected data on >55 000 ACS patients. The baseline characteristics, treatments, and outcomes of 12 000 international NSTE ACS patients enrolled in GRACE between 1999 and 2004 were considered for the present scientific statement.

The CRUSADE Quality Improvement Initiative was a national quality improvement initiative promoting collaboration between emergency medicine physicians and cardiologists and included 400 participating US hospitals. Established in 2001, CRUSADE enrolled >200 000 patients with NSTE ACS. CRUSADE enrolled a high-risk NSTE ACS population and collected information on presenting symptoms, use of ACC/AHA guidelines–recommended treatments and their timing, and in-hospital outcomes. Data from >55 000 CRUSADE patients enrolled from 2001 to 2004 were considered for this scientific statement.

The VIGOUR group represents an international collaboration of coordinating centers for cardiovascular clinical trials and was the source for the pooled trials data. Since working on the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) study,[28] VIGOUR has collaborated on multiple clinical trials on the treatment and prevention of cardiovascular disease.[29] The baseline characteristics and outcomes of >34 000 NSTE ACS patients enrolled in 5 VIGOUR trials between 1994 and 2000 were considered for the present report. Data from the 5 trials were combined at the individual patient level into a pooled dataset. In addition to the randomized treatments in each trial, aspirin was protocol recommended for all patients; other treatments were given at the discretion of the physician.

NSTE ACS in the Elderly

Clinical trial evidence is limited with regard to the efficacy and hazards of pharmacological and invasive management of NSTE ACS in the elderly. In 1989, the US Food and Drug Administration published "Guidelines for the Study of Drugs Likely to be Used in the Elderly," which stated that the population studied should reflect the population treated, yet no incentive exists to encourage this level of evidence in the elderly in the drug approval process.[30] More than half of all trials for coronary disease in the past decade failed to enroll any patient ≥75 years of age, with this subgroup accounting for just 9% of all patients enrolled in trials.[16] Although explicit age exclusions in clinical trials have become less common since 1990, age-based exclusions continue.[31] From the datasets provided in support of this document, we have found the median age of patients in NSTE ACS clinical trials to be 65 years (quartile range 56 to 72 years), whereas the median age of patients in NSTE ACS community populations is 68 years (quartile range 56 to 79 years). Similarly, a recent analysis from the CRUSADE Quality Improvement Initiative found that among a community population with NSTE ACS, patients who were enrolled in a clinical trial (2.5% of the overall CRUSADE population) were younger (median 65 versus 68 years), more often male (67.9% versus 59.3%), had less renal insufficiency (8.5% versus 13.5%), and had less heart failure (13.2% versus 19%) than those not enrolled in trials.[32] In addition to comorbidity, older populations are heterogeneous in ways not captured by standard assessments. Age-related cardiovascular changes include decreased arterial compliance, increased cardiac afterload, and left ventricular diastolic dysfunction.[33] Physical and cognitive functioning, comorbid diseases, and drug metabolism are also known to vary in older adults and may alter the course of ACS and response to therapies.[34] In addition, an acute stress may alter these factors, making the treatment–effect relationship a dynamic one. Thus, evidence-based recommendations from trials do not account for the age-based differences in physiology and disease that may alter these relationships.

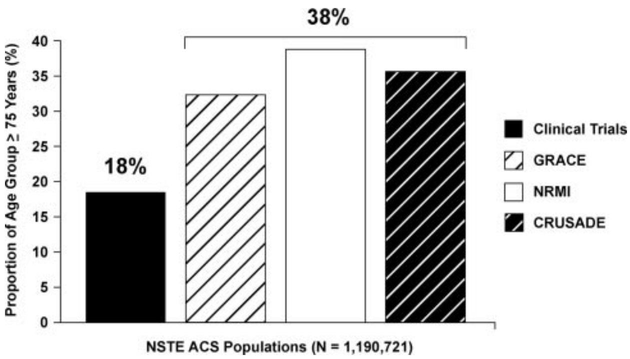

Figure 1. Representation of the subgroup ≥75 years of age as a proportion of the total trial and community populations described in the present statement. Community populations include GRACE, NRMI, and CRUSADE. Trial populations include VIGOUR.

Comparing Trial and Community Elderly

The elderly, particularly the oldest old, are more prevalent among community populations. First, patients ≥75 years of age in the 5 combined VIGOUR trials of NSTE ACS constituted 18% of the population but were twice as prevalent in GRACE (32%), NRMI (37%), and CRUSADE (38%; Figure 1). Patients ≥85 years of age constitute just 2% of trial populations, but this increases 5-fold in community populations (11%; Table 3). Thus, the age gap between trials and community populations begins at age 75 years and widens with age. The proportion of women also increases with advancing age in trials and community populations. The NRMI 2 to 4 registries confirmed a substantial increase in the absolute number of women presenting with ACS over time, which corresponds with a rise in patient age, a trend that should continue with demographic shifts.[35] Interestingly, women constitute more of those ≥85 years of age in community populations (62% versus 57%), which suggests a sex differential in the oldest old as well (Table 3).

The elderly included in trials are also systematically different from the elderly in the community.[32] Trial populations demonstrate lower rates of traditional cardiovascular risk factors, less comorbidity, and better hemodynamics and renal function in each age subgroup than do community populations (Table 3). The oldest old have fewer risk factors than do younger elderly cardiac populations. The prevalence of cardiovascular risk factors, such as hyperlipidemia and diabetes mellitus, increases to age 75 years, then decreases. Smoking demonstrates a linear decrease after 65 years, dropping 10-fold between 65 to 74 years (46%) of age. Conversely, hypertension continually increases with age (Figure 2A; Table 3).

Comorbidity is more prevalent among community populations than like-aged trial populations. Congestive heart failure (CHF), prior stroke, and renal insufficiency rise continuously with age (Figure 2B). CHF is present in 26% and 36% of the 2 oldest subgroups in the community compared with 16% and 22% in comparable age subgroups in trials (Table 3). Another important difference is the 2-fold higher rate of prior stroke in community elderly (≥85 years of age) compared with those enrolled in trials (CRUSADE 18% versus trials 8%). Differ-

TABLE 3. Selected Baseline Characteristics of Trial (VIGOUR) and Community (CRUSADE) Populations by Age Subgroup

	Age Group			
Population	<65 y	65–74 y	75–84 y	≥85 y
Age group				
Trials	49	33	16	2
Community	42	23	24	11
Female				
Trials	28	38	48	57
Community	31	39	48	62
Hypertension				
Trials	47	58	59	57
Community	62	73	75	73
Hyperlipidemia				
Trials	44	41	32	21
Community	49	53	45	28
Diabetes mellitus				
Trials	17	25	25	20
Community	30	39	36	25
Current smoker				
Trials	41	16	7	3
Community	46	22	10	4
Body mass index, kg/m^2				
Trials	28±5	27±4	26±4	25±4
Community	30±8	29±6	27±6	25±5
CHF				
Trials	6	10	16	22
Community	10	19	26	36
Prior stroke				
Trials	3	6	9	8
Community	6	11	17	18
Prior MI				
Trials	27	35	37	41
Community	27	33	35	35
ST depression				
Trials	44	56	61	64
Community	38	42	42	40
Heart rate, bpm				
Trials	74±14	75±15	76±15	78±16
Community	84±21	85±24	87±24	90±24
Systolic blood pressure, mm Hg				
Trials	134±21	138±22	139±23	138±24
Community	146±30	146±32	145±32	142±33
High-risk tertile, % of age group*				
Trials	9	48	76	93
Community	15	55	83	94

All data shown are mean±SD for continuous variables and percentages for dichotomous variables.

*Risk of 30-day death/MI based on PURSUIT trial population. Five variables include age, ST-segment depression, systolic blood pressure, positive cardiac markers, and admission heart rate.[29]

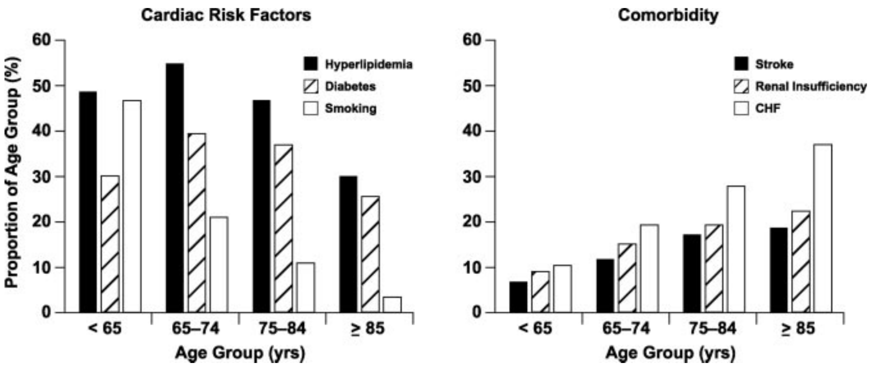

Figure 2. Proportion of age subgroups with cardiac risk factors and comorbidity from the CRUSADE Quality Improvement Initiative. Smoking indicates current smokers.

ences are also noted in presenting vital signs and renal function. Presentation heart rate and blood pressure, independent predictors of death, are higher across every age group in community populations compared with trial populations.[8,9]

Kidney dysfunction, especially if unrecognized, may add to the risk of adverse outcomes and increase the risk of bleeding in older populations.[36] Renal dysfunction, as evidenced by a creatinine concentration of ≥2 mg/dL, was present in 9% of the CRUSADE community population but in only 0.6% in the combined VIGOUR trial population. This is partly because 2 of the 5 VIGOUR trials had exclusion criteria for patients with serum creatinine ≥2 mg/dL. To illustrate how differences in age and creatinine affect estimates of renal function, we estimated creatinine clearance, using the Cockcroft-Gault equation (Figure 3).[37,38] On average, trial populations 75 to 84 years of age have moderate kidney dysfunction (creatinine clearance ≤60 mL/min), yet community populations demonstrate this level of kidney dysfunction 10 years earlier. Moreover, patients ≥85 years of age in trials still demonstrate moderate-range kidney dysfunction (39.4 mL/min), whereas in the community, this age group has severe dysfunction (27.5 mL/min; Figure 3). Many

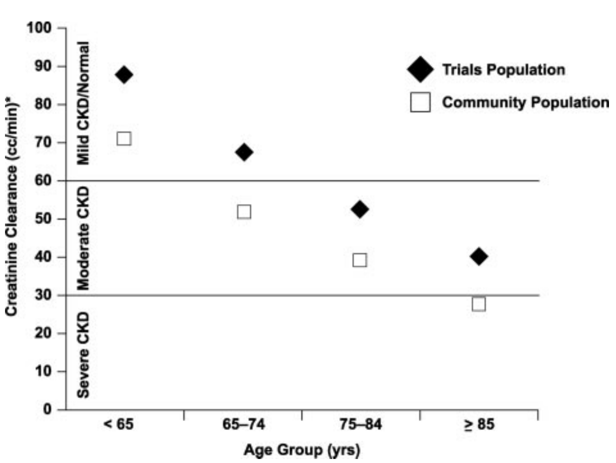

Figure 3. Estimated creatinine clearance according to age subgroups in trial (VIGOUR) and community (CRUSADE) populations. Creatinine clearance (CrCl) expressed as median values in cc/min calculated by formula of Cockroft and Gault.[41] Lines drawn at 30 and 60 cc/min distinguish stages that reflect the severity of chronic kidney disease (CKD) according to recommendations from the National Kidney Foundation[43]: normal to mild CKD (CrCl ≥60 cc/min), moderate CKD (CrCl 30 to 59 cc/min), and severe CKD (<30 cc/min).

cardiovascular drugs are cleared by renal mechanisms, which underscores the importance of these differences in organ function and metabolism among treated populations.[39]

As cardiac risk increases in older populations, the absolute benefit of treatment should increase as well, provided treatment risks do not exceed benefits.[40] However, the differences between elderly patients in trials and community populations may be sufficient to alter assumptions about the balance of risk and benefit derived from trials when therapies are applied broadly.[41]

Acute Presentation

The initial cardiac evaluation begins with a determination that symptoms indicate the presence of an ACS. Atypical symptoms (defined as absence of chest pain) occur more often among elderly patients with NSTE ACS. In GRACE, the average age of patients presenting with atypical symptoms was 72.9 years, whereas the average age of patients presenting with typical symptoms was 65.8 years. In NRMI, only 40% of those ≥85 years of age had chest pain on presentation compared with 77% of those <65 years of age (Figure 4). Although chest pain remains a common presentation of ACS regardless of age, elderly patients were more likely to present with dyspnea (49%), diaphoresis (26%), nausea and vomiting (24%), and syncope (19%) as a primary complaint; hence, MI may go unrecognized.[42] Underscoring the presenting symptom of dyspnea, the likelihood of signs of CHF (pulmonary rales, jugular venous distention) also increases with age (Figure 4). Not surprisingly, just over half of the very elderly in the NRMI were admitted with an initial diagnosis of MI, rule-out MI, or unstable angina (56% of those ≥85 years of age), yet all of these patients were determined at discharge to have had an MI (Figure 4).

In the Framingham cohort, silent or unrecognized infarctions were also more common in the elderly, which suggests that patients themselves fail to attribute atypical symptoms to a cardiac cause. Whereas silent or unrecognized infarctions accounted for 25% of all MIs, they accounted for up to 60% of MIs in patients >85 years of age.[42,43] ACS is more likely to develop in elderly patients who have another acute illness or worsening of a comorbid condition (eg, pneumonia, chronic obstructive pulmonary disease, a fall). These "secondary" coronary events occur in the setting of increased myocardial oxygen demand or hemodynamic stress in patients with underlying atherosclerotic disease. Thus, nonspecific symptoms and comorbid diseases may confuse the initial

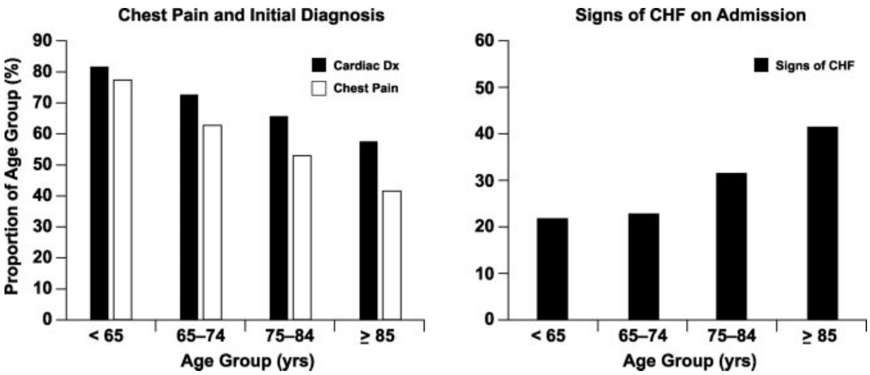

Figure 4. Admission signs, symptoms, and initial diagnosis according to age groups from NRMI (Chest Pain, Cardiac Dx) and CRUSADE (Signs of CHF). In NRMI, initial diagnosis is collected as one of the following: MI, rule-out MI, unstable angina, or other. Cardiac diagnosis (Dx) represents patients who were diagnosed with one of the first 3 cardiac options as opposed to "other." In the CRUSADE Initiative, CHF on presentation is defined as signs of CHF (jugular venous distention, rales, S_3, or pulmonary edema on initial chest radiograph) documented by a physician in the initial history and physical examination.

presentation and contribute to treatment delays. Atypical presentations have been shown to portend a worse prognosis (a 3-fold higher risk of in-hospital death [13% versus 4%, $P<0.001$]), in part because of delays in diagnosis and treatment and less use of evidence-based medications.[42,43] Because of the high prevalence of atypical features and associated worse outcomes in the elderly, a high index of suspicion for ACS is advisable.

Risk Stratification

Initial management includes an assessment of short-term risk of death or MI as estimated from the patient's age, findings on initial physical examination (heart rate, systolic blood pressure), ECG (ST-segment depression), and laboratory evaluation (cardiac markers).[14] The ACC/AHA and ESC guidelines recommend that a 12-lead ECG be obtained immediately (within 10 minutes) in patients with chest discomfort or other symptoms consistent with ACS.[13,14] Only one third of all patients in CRUSADE received an initial ECG within this 10-minute window after arrival in the emergency department. In fact, the average time between presentation and first ECG was 40 minutes; it was 7 minutes longer in the group ≥85 than in those <65 years of age. Women ≥85 years of age had an average 45-minute delay from presentation to first ECG. Elderly patients are more likely to have nondiagnostic ECGs. The proportion of NSTE ACS patients in NRMI presenting with nondiagnostic ECGs increased from 23% to 43% for those <65 versus those ≥85 years of age. The lack of chest pain on presentation likely contributes to these delays (Figure 4). Delays in ACS recognition contribute to lower use of early antithrombotic therapy for ACS in elderly patients.[44] In addition, among those undergoing cardiac catheterization in CRUSADE, mean time from arrival to catheterization was 34.4 hours in patients <65 years and 59 hours for patients ≥85 years of age.

According to the ACC/AHA guidelines, all patients ≥70 years of age are at intermediate risk and patients ≥75 years of age are at high risk for short-term death or nonfatal MI. Risk of 30-day death or MI among clinical trial and registry populations was compared by applying a model developed from the Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial population.[10] When this model for 30-day death or MI is applied in both community and trial populations, ≈80% of the elderly (≥75 years of age) are deemed to be at high risk (83% in community and 78% in trials). When chronological age is removed from the model, the elderly (≥75 years of age) remain at relatively higher risk than the younger population (<75 years of age). Greater relative risk from ST-segment depression, systolic blood pressure, elevated markers, and heart rate explain this higher risk in older populations. Comorbid factors such as CHF, renal insufficiency, cancer, and lung disease also identify elderly at-risk individuals.[45]

Health Context

The initial management of elderly patients with NSTE ACS on the basis of their disease-related risk is best understood when placed in a broader health context.[41] The ACC/AHA guidelines for NSTE ACS state that "decisions on management should reflect considerations of general health, comorbidities, cognitive status, and life expectancy" of the elderly patient as a Class I recommendation (Table 1).[14] Although age itself is a nonmodifiable risk factor, certain age-associated conditions (eg, anemia, kidney disease, frailty, disability, cognitive dysfunction) may be understood as distinct from age. Diminished organ reserves and altered functional and cognitive status influence disease presentation, treatment, and recovery. The term "frailty" has been used to describe a state of declining reserves in strength and function that occurs in elderly populations. Frailty, distinct from cardiovascular disease, disability, or comorbidity, overlaps with these conditions in numerous ways. Using one definition, 6.9% of community-dwelling elders >65 years, 9.5% between 75 and 79 years, 16.3% between 80 and 84 years, and 25% ≥85 years of age were found to be frail.[46] In addition to having more comorbid conditions (eg, diabetes mellitus, hypertension), frail individuals demonstrate inflammatory dysregulation, with baseline elevation in inflammatory markers (C-reactive protein and interleukin-6), all of which may contribute to ACS risk and outcomes.[47] Domains for mobility (activities of daily living), physiological reserves (frailty), nutritional status (albumin, weight loss), and function (strength and activity level) are all important markers of elderly at risk.[48] In addition, those who take a broad view of elder health include social, cognitive, and psychological issues in the construct.[49] In the Heart Protection Study, 34% of community-dwelling elderly people >70 years of age had mild cognitive impairment.[50] Altered cognition, hearing, and vision may delay presentation and impair communication. Older individuals are also less likely to be connected to sources of information or support, have fewer college degrees, and are more likely to live alone.[51] All of these factors

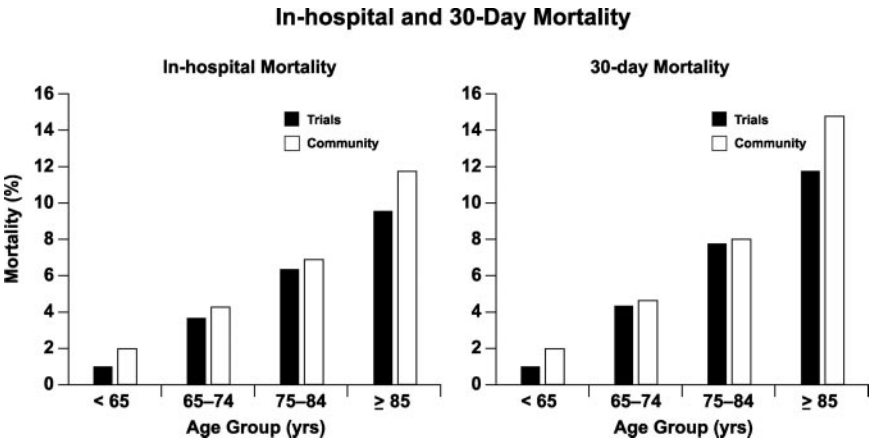

Figure 5. In-hospital and 30-day death rates according to age groups in trial (VIGOUR) and community (GRACE) populations.

are unlikely to be represented in a risk assessment but require extra time and attention in the clinical setting. A better understanding of age-related health issues separate from disease-related risk is needed.

Outcomes

In current practice, patients ≤65 years of age with NSTE ACS have a 1 in 100 chance of dying during their hospitalization, but this risk is 1 in 10 for patients ≥85 years of age (Figure 5). The progressive death rate with advancing age is higher in community populations by several percentage points (Figure 5). Among hospital survivors, the higher risk in the elderly continues from 30 days to 1 year (1-year death rate from GRACE: 75 to 84 years of age, 15%; ≥85 years of age, 25%). In addition, coexisting conditions such as chronic obstructive pulmonary disease, renal failure, and cerebral disease may also lead to higher morbidity and mortality rates over time. Nonetheless, the chance of dying at 1 year after NSTE ACS for patients ≥75 years of age is 1 in 5, and for those ≥85 years of age, it is more than 1 in 4, which underscores the continuing risk after the hospital phase of care.

Complications with NSTE ACS also increase with age. Recurrent MI, bleeding, and CHF commonly occur in community and trial elderly populations alike. In CRUSADE, recurrent MI is higher in those ≥75 years than in those <75 years of age (4% versus 2.8%), as is CHF (15% versus 6.3%, respectively). Patients ≥75 years of age enrolled in trials have higher rates of recurrent MI (9.5%) but lower rates of CHF (8.6%) than community elderly, perhaps because the former are influenced by trial event adjudication and the latter by healthy enrollment bias. Bleeding rates are difficult to compare because of varying definitions; however, rates of transfusion increase with age in both trial and community populations among noninvasively and invasively managed patients (Figure 6). Transfusion in community populations is likely influenced by both patient factors (eg, risk of bleeding, preexisting anemia) and process-of-care factors (eg, drug dosing, invasive procedures). Most notably, the risk of transfusion after percutaneous coronary intervention (PCI) in the oldest patients is higher than expected from other trend comparisons (Figure 6). One in 5 patients ≥85 years of age who undergoes PCI in the community receives a blood transfusion.

- The term "elderly" is used to describe a range of age subgroups. Although it is necessary to define age groups for treatment and outcome comparisons (<65, 65 to 74, 75 to 84, and ≥85 years of age), biological age can vary widely in relation to chronological age.
- Elderly NSTE ACS patients in the community are at greater disease-related risk than are elderly in trials and have more comorbidity.

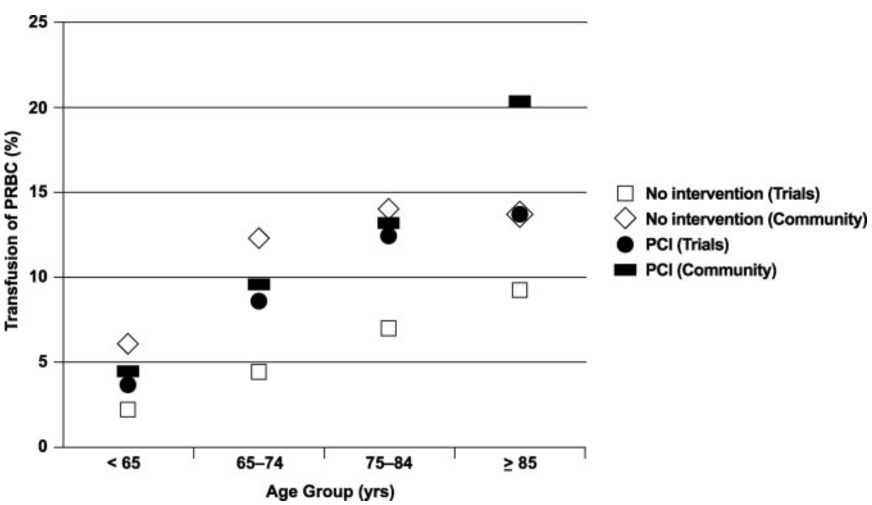

Figure 6. Blood transfusions according to age groups and percutaneous intervention in trial (VIGOUR) and community (CRUSADE) populations. PRBC indicates packed red blood cells. Patients designated as "no intervention" had no PCI. Patients undergoing coronary artery bypass grafting were not included.

TABLE 4. Recommended Dosing for Therapies in NSTE ACS

1.	Aspirin: (no adjustment) 81–325 mg daily
2.	Clopidogrel: (no adjustment) 75 mg daily
3.	UFH: weight-based bolus of 60 U/kg and infusion of 12 $U \cdot kg^{-1} \cdot h^{-1}$. Suggested maximum dose of 4000-U bolus and 900-U/h infusion, or 5000-U bolus and 1000-U/h infusion if patient weight >100 kg.
4.	LMWH: weight-based dose of 1 mg/kg every 12 hours, with adjustment in infusion for renal function (if CrCl <30 mL/min) to 1 mg/kg subcutaneously every 24 hours
5.	GP IIb/IIIa inhibitors—eptifibatide: weight-based bolus of 180 μg/kg and infusion of 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with adjustment in infusion for renal function (if CrCl <50 mL/min) to 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$
6.	GP IIb/IIIa inhibitors—tirofiban: weight-based bolus of 12 μg/kg and infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with adjustment in infusion for renal function (if CrCl <30 mL/min) to bolus of 6 μg/kg and infusion to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$

CrCl indicates creatinine clearance.

- The current approach to enrolling elderly in trials limits the applicability of available evidence.
- A better understanding of age-related risk distinct from disease-related risk is needed; specifically, physiological impairment (frailty), comorbidity (cancer, CHF, renal failure), psychological impairment (depression, isolation), disability (limited activities of daily living), and cognitive impairment all impact long-term outcomes after an acute cardiac event.
- Atypical presentations, absence of chest pain, and nondiagnostic ECGs are common in elderly with NSTE ACS, so a high index of suspicion is warranted.
- Recognition that ACS may also occur in the setting of other acute illnesses is important.
- In addition to higher short-term and long-term death rates, older NSTE ACS populations experience more CHF and bleeding complications.
- Given the common occurrence of renal dysfunction and factors that alter drug metabolism, attention to therapeutic dosing is crucial. Creatinine clearance should be calculated for all elderly patients (≥75 years of age) at the time of care.

Pharmacological Management

Elderly patients are known to have altered pharmacodynamic responses and vulnerability to drugs with hypotensive actions (eg, nitrates, calcium antagonists) and cerebral effects (eg, β-blockers). Impaired renal and hepatic function, in addition to other coexisting conditions, may alter pharmacokinetics. Drugs that are cleared by the kidney require dose adjustment based on package labeling more often in the elderly (Figure 3; Table 4). Use of multiple medications increases the possibility of drug–drug interactions. Moreover, age-associated decreases in total and lean body mass make weight an additional consideration for drug dosing.

Antiplatelet Therapy

Oral Antiplatelet Agents (Aspirin, Clopidogrel)

The ACC/AHA and European guidelines recommend the use of aspirin when an ACS is suspected and daily thereafter in a dose of 81 to 325 mg in the absence of contraindications and without modification based on age.[13,14] The benefit of aspirin is well established for the prevention of nonfatal MI, affording a 22% risk reduction.[52] Compared with younger patients, the subgroup ≥65 years of age had a greater absolute reduction (4.5% versus 3.3%) and a similar relative reduction (19.4% versus 23.1%) in vascular end points with aspirin use.[52] In a Medicare population, patients ≥65 years of age also demonstrated a 22% lower death rate with aspirin treatment after MI.[53] Thus, the relative benefit of aspirin does not appear to be affected by age, and its absolute benefit is greatest in populations at highest risk, such as the elderly.[53]

The guidelines recommend clopidogrel in addition to aspirin or as an alternative in aspirin-intolerant patients (Class I recommendation).[13,14,53] Clopidogrel should be continued for up to 9 months; however, initiation of clopidogrel is determined by its relative benefit in preventing cardiovascular events versus its bleeding risk, particularly among those requiring bypass surgery.[54] In the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial, clopidogrel when used in addition to aspirin was associated with an additional 20% relative reduction in the composite of cardiovascular death, nonfatal MI, or stroke at 1 year in the overall trial population.[55] Compared with younger patients, the subgroup ≥65 years of age had a similar absolute reduction (2.0% versus 2.2%) and a smaller relative reduction (13.1% versus 28.9%) with the addition of clopidogrel, although in both groups, clopidogrel was significantly more effective than placebo.[55] In the PCI CURE trial, clopidogrel was associated with a 31% risk reduction in cardiovascular death/MI at 1 year in the overall trial population.[56] Compared with younger patients, the subgroup ≥65 years of age had both a smaller absolute (3.5% versus 3.9%) and relative (20.7% versus 39.8%) reduction, and the trend to better outcomes with clopidogrel was not statistically significant. Whereas no gradient favoring a larger benefit with clopidogrel in older patients was seen in either study, the subgroups undergoing PCI with higher Thrombolysis In Myocardial Infarction (TIMI) risk scores or prior revascularization were more likely to benefit.[56,57] Recent evidence has confirmed that the efficacy of aspirin is not enhanced by doses in excess of 75 to 150 mg/d and that higher doses increase risk for gastrointestinal toxicity and bleeding.[52,58] Although no age subgroups for safety were reported, this dosing reduction may be of particular relevance to the elderly.

In-hospital use of antiplatelet therapy decreases with advancing patient age.[15,35,44,59] Between <65 and ≥85 years of age, in-hospital aspirin use decreased from 95% to 87% in GRACE, and acute use of aspirin (first 24 hours) decreased similarly from 93% to 89% in CRUSADE.[44] In-hospital use of clopidogrel is more notably affected by patient age, decreasing from 52% to 30% in GRACE and from 45% to 30% in CRUSADE between <65 and ≥85 years of age. This trend is only partly explained by the lower use of PCI in the elderly.

- Absolute and relative benefits of aspirin therapy are greater in high-risk patients, including the elderly.

- Absolute benefits of clopidogrel are similar, but relative benefits are less in the elderly; however, subgroups undergoing PCI, with higher TIMI risk scores or prior revascularization are more likely to benefit.
- When using dual-antiplatelet therapy, aspirin doses in excess of 100 mg per day are associated with increased bleeding without greater efficacy, but elderly subgroup data are not available.

Intravenous Glycoprotein IIb/IIIa Inhibitors

The glycoprotein (GP) IIb/IIIa inhibitors prevent recurrent MI in high-risk NSTE ACS, especially in the setting of positive markers or if patients are undergoing an early invasive approach. The ACC/AHA and ESC guidelines recommend their use in addition to aspirin and heparin in patients in whom catheterization and PCI are planned without modification based on age (Class I recommendation).[13,14] The addition of a small-molecule GP IIb/IIIa inhibitor (tirofiban or eptifibatide) is also recommended for patients with high-risk features in whom an invasive strategy is not planned (Class IIa).[14] Given their concurrent use with oral antiplatelet and antithrombin therapy, the bleeding risk with GP IIb/IIIa inhibitors must be considered in elderly patients.[60] Tirofiban and eptifibatide, the agents approved for use in NSTE ACS, are cleared renally, and dosing adjustments based on creatinine clearance are recommended (Table 4).[61,62]

The PURSUIT trial, which had a large older population (30.7% were ≥70 years of age), examined the role of GP IIb/IIIa inhibitors in patients with advanced age.[22] In the overall trial population, treatment with eptifibatide resulted in a 1.5% absolute and 9.6% relative reduction in death or MI at 30 days, with a 2.9% absolute and 22.6% relative increase in moderate or severe bleeding.[23] Compared with a significant benefit in younger patients (<65 years of age), the subgroup ≥65 years of age demonstrated only a slight trend in favor of eptifibatide for death or nonfatal MI. An age-subgroup report from PURSUIT explored safety and efficacy end points in more detail; there was an increase in bleeding with eptifibatide compared with placebo in all patients, and most notably in those ≥70 years of age.[63] In this analysis, patients who were 60 to 69 years of age had a 0.8% absolute and 5.3% relative risk reduction in death or MI, whereas the subgroup that was 70 to 79 years of age had a 1.8% absolute and 9.0% relative reduction in death or MI with eptifibatide. However, the point estimate for eptifibatide in reducing death or MI shifted to favor placebo in the >500 patients ≥80 years of age. In patients ≥80 years of age, eptifibatide was associated with a 5.6% absolute and 23.6% relative increase in death or MI at 30 days, along with a 7.2% absolute and 71.3% relative increase in moderate or severe bleeding.[63] An age–treatment interaction term was not significant for efficacy or safety end points; however, this shift in relative risk and benefit in older subgroups raises concerns.

GP IIb/IIIa inhibitors have been shown to be beneficial in the setting of PCI, whether performed electively or in the setting of ACS. The ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) trial had 19% of its patients enrolled in the setting of an NSTE ACS, all of whom were patients randomly assigned to eptifibatide or placebo at the time of stent implantation. This trial excluded patients on the basis of renal function. Compared with younger patients in this population, the subgroup ≥65 years of age demonstrated a greater absolute (7.2% versus 1.3%) and relative (52.6% versus 16%) benefit of eptifibatide in reducing the combined end point of death, MI, or revascularization.[64] This suggests patient selection is important in the balance of risk and benefit. In addition, dose adjustment (or lack thereof) in the setting of renal insufficiency in the elderly is another contributor to the outcomes observed with GP IIb/IIIa inhibitors and other agents cleared by the kidney.[39]

The tirofiban trials, Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) and the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS), excluded patients with a creatinine level >2.5 mg/dL.[65,66] Interestingly, in these trials, no augmented or diminished treatment effects were evident with advancing age, although patients ≥80 years of age were not reported separately. In the PRISM trial, the subgroup ≥65 years of age had a significant benefit with tirofiban over heparin.[65] In PRISM-PLUS, the subgroup ≥65 years of age had a greater absolute (5.7% versus 4.0%) and similar relative (24% versus 32%) reduction in 7-day death, MI, or refractory ischemia with the addition of tirofiban compared with younger patients.[66] In a meta-analysis by Boersma and colleagues,[67] GP IIb/IIIa inhibitor treatment was associated with lower 30-day death or MI; however, there was a declining trend in the benefit of GP IIb/IIIa treatment with advancing age and a nonsignificant treatment effect in patients >60 years of age (P=0.10 for age–treatment interaction). In this meta-analysis, there was a significant interaction between GP IIb/IIIa treatment and sex, with adverse effects seen in women; however, when the sex analysis was restricted to include only those with positive troponins, men and women benefited similarly from GP IIb/IIIa inhibitors. These studies all reveal the importance of patient selection in determining the benefit of therapy.

The use of GP IIb/IIIa inhibitors in GRACE and CRUSADE decreased with advancing age.[15] This decreased use was due in part to the lower use of invasive care but persisted after procedure use was taken into consideration.[44] The use of GP IIb/IIIa inhibitors decreased from 45% to 13% in CRUSADE and from 34% to 12% in GRACE for subjects <65 versus ≥85 years of age. Nevertheless, the elderly who are given GP IIb/IIIa inhibitors are much more likely to receive them in excess of recommended doses (65% excess among those ≥75 years of age).[39] In addition, an association also exists between the number of antithrombin and antiplatelet agents used and the risk of major bleeding in those ≥75 years of age (from 2 to 3 agents, 9% to 13% transfusion rate), but this is not seen in younger subgroups 65 to 74 years of age.[68]

- Relative cardiovascular benefits of the GP IIb/IIIa inhibitors vary in the older age subgroups, with worse outcomes observed in some but similar benefits in others.
- Greater benefits have been observed in older subgroups when given at the time of intervention and when those with renal dysfunction are excluded. Clarification of the benefit

of GP IIb/IIIa inhibitors with and without revascularization in elderly patients is of high priority.

- More bleeding is seen in elderly populations treated with GP IIb/IIIa inhibitors, and the number of patients with bleeding increases with the number of antithrombotic agents used.
- The majority of elderly who receive GP IIb/IIIa inhibitors in the community are given excess doses, which emphasizes the importance of estimating creatinine clearance and weight.

Antithrombin Therapy

The ACC/AHA and ESC guidelines recommend use of antithrombin therapy as an adjunct to aspirin in patients with NSTE ACS without modification based on age (Class Ia recommendation)[13,14]; however, the efficacy and balance of benefit and risk from the use of these agents may be altered by age-related changes in thrombosis and fibrinolysis.[69] Unfractionated heparin (UFH) dosing is performed by weight-based algorithms; however, alterations in body composition and protein levels may result in overestimates of the required dose in elderly patients.[70] Observational studies have linked advanced age to higher heparin levels in the blood and activated partial thromboplastin time and greater risk of heparin-associated bleeding.[71] The anticoagulant activity (anti-Xa levels) of low-molecular-weight heparins (LMWHs), which are cleared renally, has also been shown to be higher in the elderly.[72,73] Although this may result in a greater therapeutic effect with LMWH in the elderly, this has not been confirmed in multivariable analyses.[74] The trials of antithrombotic therapy can be divided into those that compare UFH with placebo and those that compare one form of heparin with another. Few of these antithrombotic therapy trials report efficacy outcomes, and none report bleeding in the older age subgroups.

UFH or LMWH Versus Placebo

Five randomized trials (1353 patients) compared UFH with control and 2 trials (1639 patients) compared LMWHs (dalteparin, nadroparin) with placebo in NSTE ACS.[75–81] In these trials, UFH was associated with a 34% reduction in death or MI, and LMWH was associated with a 61% reduction in death or MI.[82] The mean age in these trials was 63 years, and no age subgroup data were reported. The Fragmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) trial was the only trial to report age subgroup data, but it enrolled no patients ≥75 years of age.[83] In FRISC II, patients were treated with UFH or dalteparin for 5 days and then were randomized to long-term treatment with dalteparin or placebo. There was a nonsignificant reduction in death or MI with dalteparin at 3 months. The absolute (1.9% versus 0.8%) and relative (18.4% versus 16%) reduction in events with dalteparin was greater in patients ≥65 years (event rates 8.4% versus 10.3%) than in those <65 years of age (event rates 4.2% versus 5.0%).[83] Although antithrombin therapy with UFH or LMWHs in the early phase of an ACS was beneficial compared with placebo in these trials, its relative effectiveness in elderly compared with younger patients could not be determined from these data. A large observational study of heparin use in elderly Medicare patients did not demonstrate a benefit in reducing the rate of 30-day death.[84]

UFH Versus LMWH

Nine randomized antithrombin trials in NSTE ACS (27 034 patients) directly compared LMWHs (dalteparin, enoxaparin, or nadroparin) with UFH.[76,80,85–91] Taken together, LMWHs were associated with a nonsignificant 1.1% absolute and 11% relative reduction in death or MI at 30 days compared with UFH (8.9% versus 10.0% events; OR 0.92; 95% confidence interval 0.85 to 1.0).[82] No efficacy or safety age subgroup data were reported for either agent.[92] In the FRagmin In unstable Coronary artery disease (FRIC) trial, dalteparin increased the composite of death, MI, or recurrent angina in patients ≥70 years of age relative to UFH (event rates 17.1% versus 15.2%), whereas the opposite was observed in patients <70 years of age (event rates 10.5% versus 11.2%).[85] In the FRAXiparine in Ischemic Syndrome (FRAXIS) trial, no difference in efficacy between UFH and nadroparin was found by age.[87] Bleeding complications for age groups were not reported. The enoxaparin trials (21 946 patients) showed more homogeneous results.[76,88,90,93] Enoxaparin was associated with a 0.9% absolute and 8% relative risk reduction in cardiovascular events compared with UFH (10.1% versus 11.0%; OR 0.91; 95% confidence interval 0.83 to 0.99), with an increase in major bleeding.[92] In the A to Z trial, patients <65 and ≥65 years of age had similar but nonsignificant absolute (1.0% versus 1.2%) and relative (13.5% versus 10.0%) risk reductions in cardiovascular events with enoxaparin compared with UFH.[88] In the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) trial, patients ≥65 years of age had greater relative benefit with enoxaparin than did younger patients by ORs, but more specific age subgroup results were not given.[94,95] A recent meta-analysis of 6 trials of enoxaparin versus UFH found enoxaparin superior in reducing death or MI at 30 days (enoxaparin OR 0.91 [95% confidence interval 0.83 to 0.99]) when given early in ACS, but no age subgroup results were given.[96]

In current practice, use of antithrombin therapy decreases with age. In the international GRACE registry, LMWH was used more often than UFH across all age subgroups, but in US populations, this is the case only in the oldest subgroup. In GRACE, LMWH use decreased from 61% for individuals <65 to 52% for those ≥85 years of age, and UFH use decreased from 53% to 42%, respectively. In CRUSADE, LMWH use increased from 36% for individuals <65 to 39% for those ≥85 years of age, whereas UFH use decreased from 56% to 37%, respectively.

Direct Thrombin Inhibitors and Factor Xa Inhibitors

Direct thrombin inhibitors have some theoretical biological and pharmacokinetic advantages over the heparins, which make them attractive for use in the elderly, but they are not currently recommended for use in NSTE ACS.[14] Direct thrombin inhibitors are not dependent on plasma protein for binding or renal function for clearance and are active on both circulating and clot-bound thrombin. Six published randomized trials have compared the efficacy and safety of direct thrombin inhibitors to standard therapy in patients with NSTE ACS. Direct thrombin inhibitors investigated to date include efegatran, inogatran, fondaparinux, and hirudin; treatment duration varied from 48 to 72 hours.[97–103] The only published phase III study comparing a direct thrombin inhibitor with heparin in an NSTE ACS population was the Global Use of Strategies To Open occluded arteries in acute coronary syndromes (GUSTO-IIb) trial (hirudin).[103] Treatment with a direct thrombin inhibitor was associated with a statistically significant 1.1% reduction in the incidence of death or MI at 30 to 35 days (8.6% versus 7.7% event rate; OR 0.89, 95% confidence interval 0.81 to 0.98) compared with UFH.[82] In these studies, death rate was not significantly reduced, but major bleeding was more common with a direct thrombin inhibitor than with UFH.

However, 2 other studies have examined bivalirudin in broad populations undergoing PCI, some of whom also had ACS. These include the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial and, more recently, the Randomized Trial to Evaluate the Relative PROTECTion against post-PCI microvascular dysfunction and post-PCI ischemia among antiplatelet and antithrombotic agents (PROTECT TIMI 30).[104–107] In these populations, lower rates of bleeding with comparable suppression of ischemia were noted with bivalirudin, particularly in patients with renal impairment.[106] In addition, whereas the overall trial results of the REPLACE-2 trial favored bivalirudin, a statistically significant reduction in 1-year death was demonstrated only in the subgroup ≥75 years of age.[107]

The OASIS 5 study (Fifth Organization to Assess Strategies in acute Ischemic Syndromes) compared the indirect, reversible factor Xa inhibitor fondaparinux with enoxaparin in the treatment of ACS and found comparable efficacy, with superior safety and less bleeding at 9 days with fondaparinux.[100] The elderly subgroup (≥65 years of age) demonstrated a nonsignificant benefit favoring fondaparinux, whereas the younger subgroup demonstrated a nonsignificant benefit favoring enoxaparin for the combination end point of death, MI, or refractory ischemia. Both subgroups did significantly better with regard to safety (major bleeding) with fondaparinux; however, the elderly subgroup (≥65 years of age) demonstrated a greater (50.9%) relative risk reduction in bleeding with fondaparinux (2.7% versus 5.5% with enoxaparin) compared with younger patients who had a 33.3% relative risk reduction (1.4% versus 2.1% with enoxaparin). The authors attributed differences in efficacy outcomes to differences in bleeding; however, concern remains about the risk of catheter thrombosis in those treated with selective factor Xa inhibitors. Therefore, the counterbalance between bleeding risk and thrombotic events must be carefully weighed in the elderly, but newer agents show promise for optimizing these outcomes.

- There is a notable lack of age subgroup data on efficacy and safety of antithrombin therapy from randomized trials.
- Age-related changes in thrombosis may make certain agents more appealing in the elderly, but further work is needed to describe the safety and efficacy of antithrombin therapy in the context of care.

Early Invasive Strategy Versus Ischemia-Guided Strategy

An early invasive strategy refers to routine cardiac catheterization within 48 hours of ACS presentation, whereas a conservative or ischemia-guided strategy refers to an initial plan for medical therapy, with catheterization only for recurrent symptoms or stress-induced ischemia. The ACC/AHA and ESC practice guidelines recommend an early invasive strategy in patients with NSTE ACS who have high-risk indicators, including recurrent angina, ischemia with low level of activity despite anti-ischemic therapy, elevated cardiac markers, ST-segment depression, CHF or depressed ejection fraction (<0.40), prior coronary artery bypass grafting, or prior PCI within 6 months.[13,14] Although therapy should be tailored to the level of risk, studies have established superiority of an early invasive strategy in a broad population of patients, including the elderly, with unstable angina and NSTE MI.[108–112]

Early Trials Before GP IIb/IIIa Inhibitors and Stents

Trials comparing conservative and invasive strategies for NSTE ACS differ in the proportional use of stents and GP IIb/IIIa inhibitors, population risk (positive creatine kinase-MB, ECG changes), and MI definitions. The TIMI IIIB trial and the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital study (VANQWISH) were conducted before stenting and GP IIb/IIIa inhibitors and before clopidogrel was a common adjunctive treatment with PCI.[113–115] The TIMI IIIB trial employed a 2×2 design with early invasive versus conservative strategy and tissue plasminogen activator versus placebo for patients with unstable angina and non–Q-wave MI.[113] In the overall population, the 2 strategies were equivalent with regard to the rate of death, MI, or inducible ischemia on a 6-week stress test (16.2% versus 18.1%, P=not significant). The invasive strategy did result in more rapid relief of angina, fewer rehospitalizations, and a shorter length of stay. The average age of the TIMI IIIb population was 59 years, and only 3% were ≥75 years of age. The subgroup ≥65 years of age demonstrated a 6.9% absolute and 46% relative reduction in death or MI with the early invasive strategy (7.9% versus 14.8%, $P<0.005$); however, younger patients who were assigned to invasive care had an absolute and relative increase in death and MI at 42 days with a significant age–treatment interaction ($P=0.005$).[114] This benefit with invasive care in the older subgroup was sustained to 1 year.[114] The VANQWISH trial tested the efficacy of invasive and conservative management strategies in patients with non–Q-wave MI and positive creatine kinase-MB.[115] The mean age of the population was 61 years, and only 8% were ≥75 years of age. There were treatment arm crossovers, and some of the highest-risk patients were eliminated from the study. Overall, no significant difference was seen between groups with respect to death or MI at a follow-up of 23 months; however, rates of death at hospital discharge ($P=0.004$) and at 1 month ($P=0.012$) were higher in the

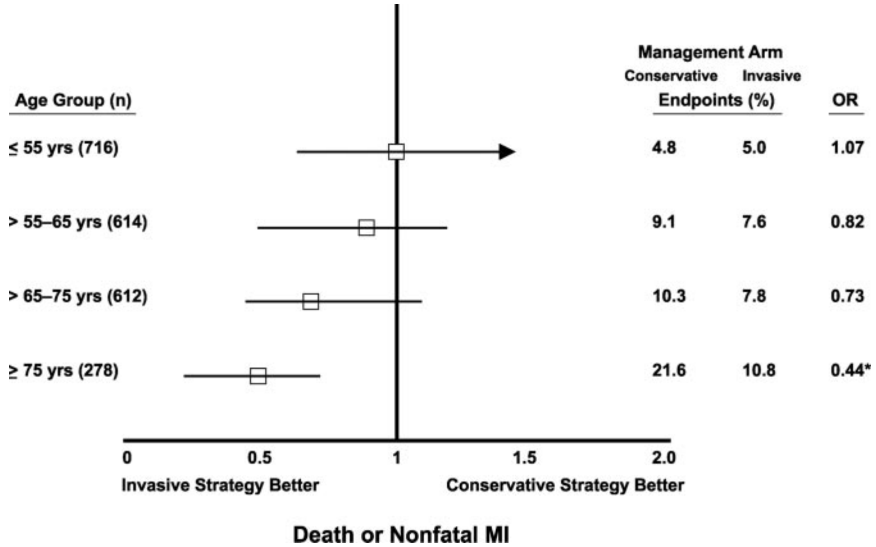

Figure 7. Benefit of invasive care in older patients in reducing the risk of death or MI combined from the TACTICS-TIMI 18 trial.[117]

invasively managed group. In this study, the subgroup >60 years of age was 1 of 4 subgroups that fared significantly better with conservative care[115]; however, the subgroup at high risk by TIMI score fared better with an invasive strategy.[116]

Recent Trials

More recent trials—FRISC-II,[81] Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction (TACTICS-TIMI 18),[108] and Randomized Intervention Trial of unstable Angina (RITA-3)[117]—were conducted in the setting of higher use of stents (65%, 83%, and 88%, respectively) and adjunctive GP IIb/IIIa inhibitors (10%, 95%, and 25%, respectively). FRISC-II was the first randomized comparison of an invasive and conservative strategy to show a significant event rate reduction in favor of an invasive strategy in the overall population. The protocol incorporated a 4-day stabilization period before intervention; thus, it was a "delayed invasive" strategy. The 6-month rate of death or MI was lower with the invasive arm versus the conservative arm (8.3% versus 10.3%, $P=0.03$), and at 1 year the death rate was significantly reduced (2.2% versus 3.9%, $P=0.016$).[118] This study did not enroll any patients ≥75 years of age, although the subgroup ≥65 years of age had a greater absolute (5.3% versus 0%) and relative (33.5% versus 0%) reduction in death or MI at 6 months compared with the younger subgroup. This benefit was sustained over a 2-year follow-up.[119] The positive influence of an invasive strategy in FRISC-II may be explained by the high rate of revascularization (78% in the invasive arm) and concurrent medical therapy, which optimized the benefit of revascularization. Also, the invasive strategy was beneficial only in patients who were troponin positive or who had ST-segment changes.[119]

The RITA-3 trial compared an invasive strategy with optimum medical care with angiography in recurrent ischemia.[117] In RITA-3, a common definition of MI was used irrespective of treatment strategy, whereas in the FRISC II and TACTICS-TIMI 18 trials, the threshold for diagnosis of MI differed between those undergoing revascularization and those treated conservatively. In RITA-3, patients managed with the invasive strategy had a lower rate of death, MI, or angina at 4 months than those treated with a conservative strategy (9.6% versus 14.5%, $P<0.001$). RITA-3 did not report age subgroup results. The 5-year follow-up from RITA-3 demonstrated that the benefit of invasive treatment over conservative care continued to widen after year 1, demonstrating the greatest benefits in those in high-risk quartiles, with age being the strongest predictor of risk.[120] Thus, RITA-3 confirmed that early outcomes with the invasive strategy were superior to an ischemia-provoked approach to revascularization in moderate-risk patients with unstable angina or NSTE MI.

The most contemporary study, TACTICS-TIMI 18, assigned patients to early invasive or conservative strategy.[108] Patients also received treatment with aspirin, heparin, and tirofiban. At 6 months, the primary composite end point of death, MI, or rehospitalization was lower in the invasive arm than in the conservative arm (15.9% versus 19.4%, $P=0.026$). An age subgroup analysis from this trial described the benefits and risks in the elderly.[112] In this analysis, a substantial treatment effect in favor of an invasive strategy for the reduction of death or MI was observed with advancing age (Figure 7). Compared with younger patients, the early invasive strategy yielded a greater absolute (4.1% versus 1%) and relative (42% versus 20.4%) risk reduction in death or MI at 30 days in the subgroup ≥65 years of age. Similarly, among patients ≥75 years of age, the absolute (10.8%) and relative (56%) reduction in death or MI with the early invasive strategy was even greater (event rates: 10.8% versus 21.6%, $P=0.02$). A significant age–treatment interaction was present in favor of better outcome with invasive care in those ≥75 years of age ($P=0.044$). This benefit coexisted with a 3-fold higher risk of major bleeding with the early invasive strategy in patients ≥75 years of age (16.6% versus 6.5%; $P=0.009$). From a clinical perspective, the number needed to treat with invasive care to prevent 1 death or MI was 250 among those <65, 21 among those ≥65, and just 9 for those ≥75 years of age. Consistent with the findings from FRISC II and TIMI IIIB, younger patients ($<$65 years of age) had good outcomes regardless of the treatment strategy.

Thus, compared with younger patients, the elderly gain greater absolute and relative benefits from an early invasive strategy, but at a cost of increased bleeding. A collaborative meta-analysis of these trials along with 2 smaller trials, Value of first day angiography/angioplasty In evolving NOn–ST segment elevation myocardial infarction (VINO)[110] and Medicine versus Angiography in Thrombolytic Exclusion (MATE),[121] confirmed that the majority of the benefit from the invasive strategy originated from data in trials published after 1999 (FRISC II, TACTICS, VINO, and RITA) and for patients with positive troponins or cardiac biomarkers. In addition, the significant benefit was seen in reduction of the combined end point of death or MI, with a trend to reduction in death.[122] A recent trial comparing selective invasive versus routine invasive care (Invasive versus Conservative Treatment in Unstable Coronary Syndromes [ICTUS]) in patients with positive troponins and NSTE ACS demonstrated no overall differences with regard to the combined end point (death, MI, or rehospitalization for angina) at 1 year but a trend to less angina and more nonfatal MI among invasively managed patients. The average age was 62 years, but in the elderly subgroup ($\geq$65 years of age), there was a nonsignificant trend that favored early invasive care.[123] A recent observational analysis in a community population failed to show an early benefit from an invasive strategy on in-hospital survival in the elderly subgroup ($\geq$75 years of age), which highlights the need for continued caution in the uniform application of trial results in the elderly.[124] Selection of elderly patients for an early invasive strategy is complex, given the need to consider risk from disease and risk from intervention, but given the benefits observed in recent trials, age should not preclude but rather intensify its consideration.

Timing of Intervention

Consideration has been given to the timing of the invasive approach after hospital arrival. In FRISC-II, patients received 4 days of pretreatment with dalteparin before intervention, and other trials have suggested a reduction in coronary thrombus burden in patients who are given GP IIb/IIIa inhibitors before intervention. The hypothesis that antithrombotic pretreatment is beneficial was rigorously studied in the Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-COOL) trial.[125] Patients were randomly assigned to antithrombotic treatment for either 3 to 5 days or 6 hours before invasive care. In both groups, the antithrombotic regimen consisted of intravenous UFH, aspirin, clopidogrel, and the GP IIb/IIIa inhibitor tirofiban. The primary outcome of death or MI at 30 days was higher in those with delayed versus early intervention (11.6% versus 5.9%, $P=0.04$), which emphasizes the importance of prompt invasive care. The incidence of major bleeding was similar in both groups (3.0% in the early invasive group versus 3.9% in the conservative treatment group). Compared with other management strategy trials, the ISAR-COOL population was the oldest and had the highest proportion of ST-segment abnormalities and the highest prevalence of diabetes mellitus.[10,67,126,127] No subgroups were reported, but half the patients were $>$70 years of age, which makes the overall trial age comparable to older community populations.

Despite their higher risk, elderly patients are more often managed without early invasive care, even if there are no apparent contraindications. An analysis from the CRUSADE population showed that for each 10 years of advancing age, there is a 20% declining likelihood of invasive care.[124] Current estimates from community populations for invasive care in patients $<$65 versus $\geq$85 years of age are as follows: CRUSADE, 57% versus 21%; NRMI, 65% versus 13%; and GRACE, 69% versus 18%. Even among the combined VIGOUR trial population, diagnostic catheterization during hospitalization decreased by age group from $<$65 to $\geq$85 years (57% versus 21%).

- The elderly demonstrate greater absolute and relative benefits in reducing death/MI with early invasive care, and long-term follow-up suggests the superiority of revascularization for survival and symptom improvement.
- These benefits coexist with an increase in major bleeding, which occurred in 17% of patients $\geq$75 years of age treated with an invasive strategy.
- Atypical symptoms in elderly patients must be considered when a strategy of symptom-guided management is chosen.
- Patient preferences are important in determining management and may instruct the decision for invasive strategy and for revascularization separately.
- There is a notable lack of subgroup data for patients $>$80 years of age in these trials, and most studies excluded elderly with significant comorbid conditions. Additional studies are needed to clarify the role of invasive treatment, particularly in the oldest and frailest patients.

Summary

The elderly with ACS have a high risk of death and adverse events. Accordingly, they often have greater absolute treatment benefits than do younger patients. Despite the large and expanding elderly population presenting for ACS care, existing evidence is limited and insufficient to guide management in this subgroup to the same degree of certainty as in younger populations. Subgroup results, when available, suggest greater benefits with some therapies but reversal of benefits with others. Patient selection and dosing emerge as important and likely explanations for these age–treatment interactions. Frailty, functional status, and social aspects of care in the elderly are rarely included in clinical investigation. Most trials also lack information on side effects, including bleeding rates associated with antithrombotic therapies and renal failure after cardiac catheterization in the elderly. Such limitations prevent a full assessment of the risk-to-benefit ratio for elderly patients. These observations underscore the need for prospective clinical trials with adequate representation of the elderly when age–treatment interactions are detected.

The suggested approach to further investigation is as follows: First, reporting of safety and efficacy results by age subgroup will help clarify the balance of risk and benefit in the elderly. In certain instances, prospective trials performed exclusively in the elderly may be warranted. In addition, understanding geriatric syndromes (such as frailty and cognitive impairment) as they overlap with ACS will help place therapeutic risks and benefits within the global health context of the elderly at highest risk. Community registries will continue to complement our knowledge base and provide this aspect of information about the elderly.

- Trial populations should represent treated community populations to the best extent possible. To increase enrollment of elderly, age-based exclusions and other exclusions that disproportionately reduce enrollment of the elderly should be eliminated where possible.
- Standard reporting of age groups across trials and registries is needed to facilitate comparisons and pooling of data. We recommend the following age subgroups: <65, 65 to 74, 75 to 84, and ≥85 years. Alternatively, we recommend the age groups <75 and ≥75 years if insufficient numbers of the elderly group are present for the oldest subgroup.
- Results should be reported for age subgroups such that absolute and relative risk reductions can be determined and tested for age interaction.
- Elderly-specific trials may be needed in certain therapeutic areas to increase certainty about treatment effects and to further our understanding of age-related variability.

Age influences process of care, so efforts should be focused on reducing gaps in the use of acute therapies and invasive care in the elderly likely to benefit from them, as well as improving the safety of care delivery.

- Registries should monitor use of treatment in the elderly and should surveil for potential harm in elderly subgroups, particularly when trials have insufficient data to evaluate safety.
- Creatinine clearance should be calculated for all patients ≥75 years of age who present with ACS.

Modifiers of risks and benefits in the elderly are multiple. Frail or cognitively impaired elderly should be identified in registry and trial populations. This would further our understanding of the overlap between geriatric syndromes and the presentation and outcomes after ACS.

- Clinical trials should include cognitive and physical function assessments in the oldest old, particularly when therapies are anticipated to either benefit or negatively affect these outcomes.
- Registries should include cognitive and physical function assessments in the elderly to determine their associations with health status and cardiovascular treatments over time.

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†Significant.

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*Modest.

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