Acute coronary syndromes in high risk groups: patients with diabetes, the elderly, and women

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Abstract

Among patients with acute coronary syndromes (ACS), patients with diabetes, elderly patients and women represent groups at high risk for adverse outcomes. Higher risk patients sustain a high proportion of the mortality and morbidity that accompanies ACS, yet also potentially derive greater absolute benefit from effective management strategies and interventions. This review focuses on information regarding the increased risk, as well as select aspects of management of ACS, for patients with diabetes, the elderly, and women. Special attention is given to aspects of prognosis or management that may differ from general patients with ACS.

Key words: myocardial infarction, diabetes mellitus, aging, women.

Introduction

Advances in diagnostic and therapeutic management over the last two decades have greatly improved outcomes for patients with acute coronary syndrome (ACS), a term which encompasses ST-elevation myocardial infarction (STEMI), and unstable angina or MI not accompanied by ST-elevations, grouped together as non-ST-elevation (NSTE) ACS. Despite these improvements, the risk of recurrent adverse events including death, recurrent myocardial infarction (MI), and cardiac rehospitalization after an ACS remains high for many patients. While risk varies across a wide spectrum for patients with ACS, high risk subgroups, including patients with diabetes mellitus (DM), the elderly, and women, shoulder a disproportionate share of these events. Higher risk patients also generally derive greater absolute benefit from effective management strategies and interventions. To achieve optimal outcomes for ACS, care of patients with diabetes, elderly patients, and women, demands special attention to particular aspects of their pathophysiology and careful individualized consideration of the potential risks and benefits of available diagnostic and therapeutic interventions. Nevertheless, despite their higher risk of worse outcome, in clinical practice it has repeatedly been observed that patients in these subgroups are generally less likely to receive many guideline recommended, evidence-based treatments than lower risk patients [1-3].

The general goals of management of patients with suspected ACS include (1) an immediate relief of ischemia or ongoing infarction and (2) prevention of serious adverse outcomes such as death or recurrent MI.

The current ACC/AHA practice guidelines for STEMI [4] and NSTE ACS [5] recommend that this is best accomplished with an approach that generally includes prompt reperfusion therapy when indicated, anti-ischemic therapy, antithrombin and antiplatelet therapy, ongoing risk stratification, and a risk-based decision regarding an invasive or conservative management strategy. Although the presence of DM, older age, or female sex each represent conditions associated individually with higher risk, it is important to recognize that risk stratification of patients with ACS should not be limited to one or even just a select few variables, but should consider a comprehensive assessment of multiple factors, a process that can be facilitated using risk prediction tools, such as the TIMI, GRACE, and PURSUIT Risk Scores [6-8]. This review will focus on outcomes and management of these select high risk groups of patients with ACS: patients with diabetes, the elderly, and women. Special attention will be given to aspects of their prognosis or management where care of these patients may differ from general patients with ACS.

Patients with diabetes mellitus

Increased risk of adverse outcome

Overall, mortality from coronary heart disease has declined substantially over the last 40 years [9]. When examined more closely, while mortality due to ischemic heart disease declined dramatically among men and women without DM from 1971 to 1993, men with DM experienced only about a third of the decrease of men without DM and women with DM had over a 10% increase in ischemic heart disease-related mortality over the same period [9]. These statistics gain even greater significance when considering the increasing prevalence of DM. From 1990 to 2001 in the United States, the prevalence of DM increased 61% [10], and is projected to further double by 2025 [11]. Currently, 20-30% of patients hospitalized with ACS have DM, and up to 50% have hyperglycemia at presentation or during the early course [12]. When systematically tested in one notable study, among MI patients with no prior history of DM, the prevalence of undiagnosed DM or impaired glucose tolerance exceeded 65% [13]. Patients with DM and hyperglycemic patients without DM have higher rates of short and long term mortality and morbidity after ACS. Even after controlling for other co-morbidities, DM remains an independent predictor of adverse outcome after ACS, and elevated plasma glucose and glycated hemoglobin predict worse prognosis among patients with and without DM [12]. Among patients with either STEMI or NSTE ACS, DM is associated with higher rates of reinfarction, heart failure and cardiogenic shock [14, 15], and a 1.4 to 2.3-fold higher rate of death during follow-up ranging from 30 days to 7.5 years [3, 16-18] (Figure 1). The high mortality risk of the ACS patient with DM and no previous history of cardiovascular disease is as high or higher than that of non-diabetic patients with a history of MI or established cardiovascular disease [3, 19].

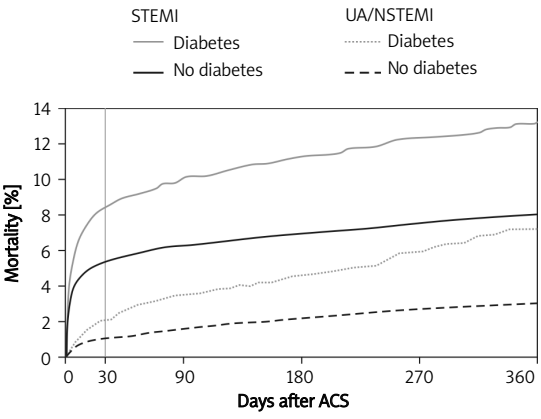

Figure 1. Incidence of mortality through 1 year after ACS according to diabetic status among 62,036 patients in 11 TIMI study group randomized clinical trials that evaluated ACS therapies. By 1 year after ACS, the cumulative mortality in patients with DM vs. without DM was higher in NSTE ACS (UA/NSTEMI) (7.2 vs. 3.1%, $p < 0.001$) and STEMI (13.2 vs. 8.1%, $p < 0.001$), and accrued at a higher rate in patients with DM than in patients without DM. Reproduced from Donahoe SM, Stewart GC, McCabe CH, *et al*. Diabetes and mortality following acute coronary syndromes. JAMA 2007; 298: 765-75 [17]

The precise mechanism of the increased risk in ACS patients with DM is unknown, but multiple factors have been identified that may theoretically confer a higher likelihood of adverse events. Patients with DM hospitalized for ACS have a higher rate of co-morbidities; on average they are older, more often female, and more likely to have a history of hypertension and heart failure on presentation than patients without DM. Yet even after adjusting for co-morbidities, DM remains associated with an increased risk of mortality and morbidity, suggesting the specific consequences of DM and hyperglycemia on hematologic factors, the vasculature and/or the myocardium may significantly affect outcome. In angiographic and pathologic studies, compared with patients without DM, ACS patients with DM have more diffuse and extensive atherosclerosis and a higher prevalence of severe multivessel coronary artery disease [17, 20, 21]. Patients with DM not only have more atherosclerotic plaque, they also appear to have a higher incidence of vulnerable or fissured plaques that could predispose them to a higher rate of atherothrombotic events [22]. Diabetes mellitus has further been linked to functional coronary

abnormalities with abnormal coronary endothelium-dependent vasomotion and reduced coronary flow reserve. Even after successful epicardial artery reperfusion by primary PCI, STEMI patients with DM have a higher incidence of poor myocardial perfusion assessed by angiographic myocardial blush grade [23]. Patients with DM have a greater reduction in left ventricular ejection fraction after STEMI, which may be related to abnormalities of myocardial metabolism, impaired ischemic pre-conditioning, impaired microvascular function and/or impaired collateral formation [24-27]. Diabetes mellitus is also associated with significant changes in hemostatic variables that suggest a prothrombotic state. Of particular relevance to therapy, patients with DM show enhanced in vitro platelet aggregability, increased platelet thromboxane synthesis, increased levels of fibrinopeptide A reflecting increased thrombin activity, and reduced plasma fibrinolytic activity [28-30].

Select aspects of management

Any patient presenting with ACS – with or without DM – has a potentially high risk of early death or severe disability; management should be based on an accelerated, comprehensive approach to diagnosis and treatment using evidence-based interventions. Diagnostic and therapeutic interventions do not necessarily differ among patients solely based on presence or absence of DM, but should be tailored to the patient in the context of multifactorial risk stratification. Nevertheless, given their higher risk of adverse outcomes and added vulnerability to metabolic derangements, to optimally care for ACS patients with DM requires attention not only to the relief of myocardial ischemia and prevention of adverse thrombotic events, but also demands special attention to glycemic management.

Observational studies have shown that ACS patients with DM present to the hospital later after the onset of symptoms and with a higher frequency of atypical symptoms [31], making the diagnosis of STEMI or NSTE ACS more challenging. As a result, at initial evaluation the index of suspicion for ACS should be raised among patients with DM presenting with vague or atypical complaints. When ACS is suspected, an electrocardiogram should be obtained as rapidly as possible and immediate management decisions based on the presence or absence of ST segment elevations.

Reperfusion therapy for ST-elevation myocardial infarction

For patients with STEMI, evaluation for reperfusion therapy should be accomplished as quickly as possible. Both fibrinolysis and primary PCI have proven efficacy for diabetic patients with STEMI. At least in part due to their higher risk, prompt reperfusion therapy for patients with DM is associated with greater absolute mortality reduction than patients without DM. In a meta-analysis of large scale placebo controlled randomized trials of fibrinolysis, among STEMI patients with DM, assignment to receive fibrinolytic therapy was associated with more than double the number of lives saved per 1000 treated patients compared with non-diabetic patients (37 vs. 15 per 1000) [32]. Furthermore, primary PCI may have enhanced benefit in STEMI patients with DM. In a pooled analysis of randomized trials of primary PCI vs. fibrinolytic therapy in patients with STEMI with a focus on the effect of time delay to treatment on outcome, patients with DM were more common among late presenters (especially > 6 h) [33]. Among the group of patients with DM presenting at ≥ 2 h, the 30-day mortality was 50% lower with primary PCI compared with fibrinolytic therapy, and the number needed to treat to avoid one death was only 17.

Invasive versus conservative management

For general patients with NSTE ACS, the current ACC/AHA practice guidelines [5] recommend that early management should include clinical risk stratification and a risk-based decision regarding an invasive or conservative management strategy. According to the guidelines, decisions regarding whether to proceed with an invasive strategy with cardiac catheterization and coronary angiography vs. conservative management with in hospital monitoring and non-invasive stress testing should be similar in patients with and without DM.

Anti-thrombin therapy

Suspected ACS patients without contra-indications, including those with DM, should receive prompt treatment with antiplatelet and anti-thrombin therapy. Available antithrombins with proven efficacy for NSTE ACS include unfractionated heparin, enoxaparin, fondaparinux, and bivalirudin. Currently no randomized clinical trial data has been reported to suggest that a particular antithrombin agent has inferior or superior efficacy for treating NSTE ACS patients with DM, although a recent subgroup analysis of the 3,852 patients with DM in the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial suggested that monotherapy with bivalirudin appeared to provide similar protection from ischemic events at 30 days with less bleeding than heparin plus a glycoprotein IIb/IIIa inhibitor [34]. In the setting of STEMI, a pre-specified subgroup analysis of the EXTRACT-TIMI 25 trial, where 20,479 patients with STEMI treated with fibrinolysis were randomly assigned to receive

a strategy of enoxaparin (for up to 8 days) or unfractionated heparin (for 48 h), examined the effect of enoxaparin vs. unfractionated heparin for STEMI patients with DM. Among the 3060 patients with DM, who were also observed to be at > 50% higher risk for death, MI or stroke than nondiabetic patients, assignment to the enoxaparin strategy resulted in reduced 30-day mortality (9.5 vs. 11.8%, relative risk [RR] 0.81, 95% CI 0.66-0.99), reduced death or MI (13.6 vs. 17.1%, RR 0.80; 95% CI 0.67-0.94), and a trend toward higher major bleeding (2.6 vs. 1.6%, RR 1.63, 95% CI 0.99-2.69). The net clinical benefit that includes combined death/MI and major bleeding favored enoxaparin (14.8 vs. 18.0%, RR 0.83, 95% CI 0.70-0.97). Of note, although the quantitative difference in outcomes appeared greater for patients with DM, formal testing of heterogeneity of the effect of antithrombins by DM status was nonsignificant. These results nevertheless suggest that compared with unfractionated heparin, enoxaparin can significantly improve outcomes for STEMI patients with DM who are being treated with fibrinolysis [35].

Anti-platelet therapy

Antiplatelet therapy is important for all patients with ACS, and may have particular added importance for ACS patients with DM. Multiple studies have demonstrated increased baseline platelet aggregability for patients with DM [29, 30, 36, 37]. The current ACC/AHA practice guidelines for management of patients with for STEMI [4] and NSTE ACS [5] suggest that higher risk patients, including patients with DM, may benefit from more intensive combination antiplatelet therapy compared with nondiabetic patients. Early treatment with aspirin is recommended for all patients without a history of aspirin intolerance, and clopidogrel for any patient unable to take aspirin. Relevant to this is the clinical trial evidence regarding the effect of glycoprotein (GP) IIb/IIIa inhibitors on outcomes for ACS patients with DM. In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial [38], the addition of the small molecular weight GP IIb/IIIa inhibitor tirofiban vs. placebo to standard antithrombotic therapy with heparin and aspirin in patients with DM resulted in a 70% relative reduction in death and MI at 30 days (p = 0.002) that was significantly greater (test for interaction p = 0.007) than the effect observed in non-diabetic patients [39]. In addition, pooled data from three placebo-controlled trials of abciximab in the setting of PCI showed that among the 1,462 patients with DM, abciximab significantly reduced the one-year mortality from 4.5 to 2.5%, the level observed in placebo-treated non-diabetic patients [40]. Of note, a subsequent meta-analysis of the diabetic populations enrolled in 6 large-scale GP IIb/IIIa inhibitor ACS trials demonstrated that platelet GP IIb/IIIa inhibition was associated with a significant 26% reduction in mortality at 30 days among the 6,458 patients with DM and no reduction in mortality among the 23,072 non-diabetic patients (test for interaction p = 0.036) [41] (Figure 2). Although these studies were predominantly conducted before the use of routine dual oral antiplatelet therapy with aspirin and a thienopyridine, they suggest that the potent antiplatelet effects of pharmacologic IIb/IIIa inhibition have strong benefit that may reduce mortality among ACS patients with DM. The concept that more potent antiplatelet drug effects may improve outcome for ACS patients with DM has now also been reinforced by results from the recent TRITON-TIMI 38 [42] study that compared clopidogrel to a new, more potent thienopyridine, prasugrel. In the study, 13,608 patients with moderate- to high-risk NSTE ACS scheduled to

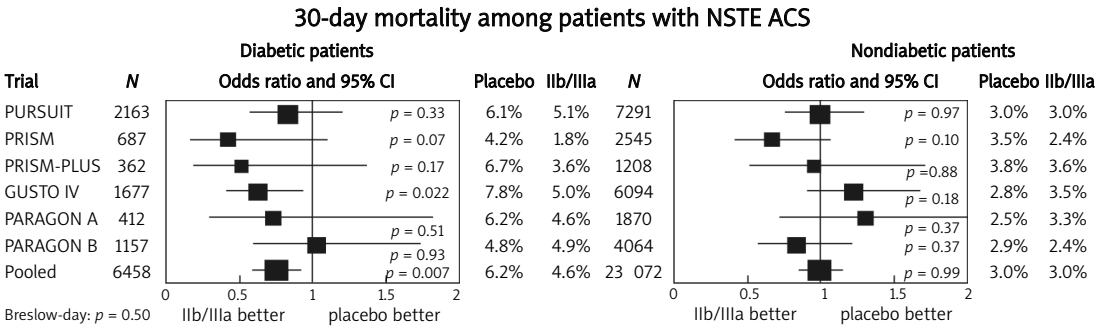

Figure 2. Odds Ratio (OR) with 95% CIs and corresponding p values for treatment effect on 30-day mortality among NSTE ACS patients with and without DM enrolled in randomized trials of glycoprotein IIb/IIIa inhibitors. Values to left of 1.0 indicate a survival benefit of platelet GP IIb/IIIa inhibition. Modified from Roffi M, Chew DP, Mukherjee D, *et al*. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. Circulation 2001; 104: 2767-71 [41]

undergo PCI were randomly assigned to receive clopidogrel or prasugrel and followed for a median 14.5 months. The overall trial showed a 19% relative reduction in the primary efficacy end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke, and a 32% increase in TIMI major bleeding by prasugrel compared with clopidogrel. In the trial 3146 (23.1%) patients had a preexisting history of DM. In a prespecified subgroup analysis [43], assignment to prasugrel resulted in a 14% reduction in the primary end point among subjects without DM [9.2 vs. 10.6%; hazard ratio (HR), 0.86; $p = 0.02$] and 30% reduction among subjects with DM (12.2 vs. 17.0%; HR 0.70; $p = 0.001$, p for interaction = 0.09). The rate of TIMI major bleeding for clopidogrel and prasugrel was similar among subjects with DM (2.6 vs. 2.5%; HR 1.06; $p = 0.81$, p for interaction = 0.29), and the net clinical benefit regarding the combined adverse ischemic and bleeding endpoints with prasugrel was greater for subjects with DM (14.6 vs. 19.2%; HR, 0.74; $p = 0.001$) than for subjects without DM (11.5 vs. 12.3%; HR, 0.92; $p = 0.16$, p for interaction = 0.05) [43]. These results suggest that the more intensive antiplatelet effects of prasugrel (compared with the already beneficial clopidogrel) – resulting in a greater reduction in ischemic events without an increase in major bleeding – may have particular benefit for NSTE ACS patients with DM.

Anti-ischemic therapy

Along with antithrombin and antiplatelet therapy, patients with ACS benefit from agents with anti-ischemic efficacy. β-Adrenergic blocker therapy has been shown to reduce adverse ischemic outcomes, both when started early in the course of treatment of ACS and long term. Nevertheless, clinicians may be hesitant to prescribe β-blockers to patients with DM because of concerns regarding worsened glucose control and masking of symptoms of hypoglycemia, resulting in under-utilization of this potentially strongly beneficial therapy. Gottlieb *et al*. examined the effect of treatment with β-blockers among 201,752 patients after MI included in the Cooperative Cardiovascular Project, comparing mortality among patients treated vs. untreated with β-blockers during two years of follow-up after MI [44]. They observed, as expected, that patients with DM had worse outcome after MI than patients without DM, but also that treatment with β-blockers was associated with a highly favorable 36% reduction in mortality.

Treatment of hyperglycemia

Elevated blood glucose is common among patients with ACS and predicts a higher risk of mortality for both diabetic and nondiabetic patients [12]. Clinical trial data support the concept that intensive treatment to reduce hyperglycemia acutely and long-term may favorably affect outcomes [12, 45]. In the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, 620 patients with DM hospitalized with AMI were randomized to intensive IV followed by subcutaneous insulin vs. routine anti-diabetic treatments. Blood glucose and HbA_{1c} measurements improved more in patients on intensive insulin treatment than in the control group. At an average of 3.4 years, mortality was 25% lower in patients in the intensive insulin vs. control group (33 vs. 44%, $p = 0.011$) [45]. To address whether the benefit was due to the early intensive insulin-glucose infusion or to the chronic insulin therapy, a second DIGAMI trial was conducted where 1253 patients with DM and suspected AMI were randomly assigned to one of three groups, intensive acute insulin-glucose infusion and long-term insulin, intensive acute insulin-glucose and long-term standard glucose control, and routine management. At a median of 2.1 years, HbA_{1c} did not differ significantly among groups, and mortality was not lowered among the intensive insulin groups or among the chronic insulin vs. standard care groups [46]. Unfortunately, however, there were difficulties with patient recruitment in DIGAMI 2 that limit our ability to draw confident conclusions. Expressing confidence in the data linking intensive glycemic control with favorable outcomes, the ACC/AHA practice guidelines [5] recommend (class I) that for NSTE ACS patients with DM, efforts should be directed to aggressively manage glycemic control, with goals of therapy that should include a pre-prandial glucose of less than 110 mg/dl and a maximum daily glucose of less than 180 mg/dl. It is further recommended (class IIa) that it is reasonable to administer aggressive insulin therapy to achieve glucose levels of less than 150 mg/dl during the first 3 hospital (intensive care unit) days and between 80 and 110 mg/dl thereafter whenever possible. The goal of therapy recommended after hospital discharge is an HbA_{1c} of less than 7%.

Underutilization of effective therapies

Despite the higher risk and therefore potentially greater absolute benefit from efficacious treatments of ACS patients with DM, disparities have been observed between treatment of patients with and without DM in several important large scale registries examining care in practice of patients hospitalized with ACS such that patients with DM are often undertreated. In the international OASIS registry [3], patients with DM were less likely to be treated with β-blockers and more likely to be treated with calcium channel blockers, agents that have been associated with an increase in adverse

outcome in some populations. In the CRUSADE registry reflecting practice patterns across over 400 hospitals in the United States from over 46,000 ACS patients, insulin-treated patients with DM had a higher risk of mortality, but were less likely than nondiabetic patients to be treated with aspirin, heparin, GP IIb/IIIa inhibitors and β-blockers, and less likely to undergo cardiac catheterization, especially within 48 h [47]. In the GRACE registry, patients with DM were less likely to receive aspirin, β-blockers and thrombolytic agents, and more likely to be treated with calcium channel blockers [14]. In data from The National Registry of Myocardial Infarction 2 (NRMI 2) database that reviewed the treatment of over 84,000 STEMI patients considered eligible for reperfusion, in multivariable analysis DM was an independent predictor of increased in-hospital mortality, but patients with DM were one-third less likely to be treated with reperfusion therapy [48]. In summary, in practice, despite their higher risk of adverse outcomes, ACS patients with DM are generally less likely to be treated with certain well-proven, evidence-based beneficial therapies.

The elderly

Increased risk of adverse outcome

Increasing age is one of the most powerful predictors of worsened outcome for patients with ACS, and elderly patients with ACS are therefore on average at high baseline risk for death and adverse ischemic events. Compared with younger patients, elderly patients with ACS less commonly present with typical chest pain and more commonly present with atypical symptoms, such as dyspnea, diaphoresis, nausea and syncope, making establishing the diagnosis and initiating management more challenging [49]. In addition, the elderly are at higher risk than younger patients for complications with diagnostic and therapeutic interventions, thus posing significantly greater challenges for clinical management. Since the elderly represent one of the fastest growing segments of the population, clinicians are likely to find themselves facing these challenges more frequently in the near future.

Given that the relationship between chronologic age and physiologic age among older individuals is not readily predictable and variable across a very wide spectrum, there is no objective standard definition of "elderly." Any definition will therefore be arbitrary, and the generalizability of group statistics based on age to a single individual may be suspect. Nevertheless, observations regarding risk prediction and the comparative effects of therapeutic interventions for patients with ACS based on age groupings can serve an important role by helping to inform clinicians regarding management decisions. In many earlier studies, "elderly" referred to patients who were 65 years and older, but among most contemporary studies the term more commonly refers to patients who are 75 years and older [50, 51]. The elderly comprise a substantial proportion of patients hospitalized with ACS. In the National Registry for Myocardial Infarction (NRMI) and GRACE registries, patients older than 75 years comprised about 28% of patients hospitalized with STEMI [50]. In the CRUSADE registry, 35% of patients hospitalized with NSTE ACS were older than 75 years and 11% older than 85 years [52]. These older patients shoulder a disproportionate share of the adverse outcomes that occur in patients with ACS. Among patients with NSTE ACS included in the TACTICS-TIMI 18 trial of management strategy, the 43% of patients who were ≥ 65 years of age accounted for > 70% of all deaths by 6 months in the trial [53].

In patients with STEMI the increase in adverse events including mortality with increasing age is exponential [54], such that the rate of in-hospital death (observed in the GISSI-2 study) increased from 2.8% for patients ≤ 60 years old to 19% for patients older than 70 years and 31.9% for patients more than 80 years old. Similar adverse trends have been observed among patients with NSTE ACS. For NSTE ACS patients managed conservatively in the TACTICS-TIMI 18 trial, the rate of death or non-fatal MI at 6 months increased from 4.8% for patients aged 55 years or younger to 21.6% for patients older than 75 years [53]. In addition the rate of complications with invasive procedures also increased substantially with age; among those patients managed invasively in TACTICS-TIMI 18, the rate of major bleeding increased from 3.6% for patients aged 55 years or younger to 16.6% for patients older than 75 years. These observations suggest that, compared with younger patients, the elderly are at particularly high risk for death and other important adverse outcomes when presenting with ACS.

Select aspects of management

Although the variable representation of the elderly in clinical trials [55] may limit confidence in estimating the quantitative effects of many treatments, elderly patients with ACS appear to sustain important benefit from pharmacologic interventions with antiplatelet, antithrombotic, and anti-ischemic therapies. Given their higher baseline risk for adverse outcomes, elderly patients generally have the potential to derive greater absolute benefit than younger patients with therapeutic interventions, both in the setting of STEMI and NSTE ACS. This implies that clinicians caring for elderly patients with ACS may need to consider the entire range of available evidence-based diagnostic and

therapeutic interventions, including early invasive management and potent antiplatelet therapies, to optimally reduce that risk, despite natural hesitation to prescribe aggressive care based on concern for complications. Management decisions for elderly patients should be individualized in the context of each patient's comorbidities, life expectancy, functional and cognitive status, and with consideration for the patient's personal preferences, while not arbitrarily withholding potentially beneficial interventions based solely on chronologic age.

Reperfusion therapy for ST-elevation myocardial infarction

Fibrinolysis represents an intervention where there is strong evidence of mortality benefit for general patients with STEMI, but application in the elderly has been controversial, and patient age has been found to play a significant role in clinician underutilization of reperfusion therapy. Among patients with ST elevation or bundle branch block treated with fibrinolytic therapy within 12 h on onset of symptoms examined in a meta-analysis of large scale placebo controlled, randomized trials, the absolute number of lives saved was greater for patients older than 75 years of age compared with younger patients (34 vs. 28 per 1000 treated patients, respectively) [56]. Despite these encouraging observations in clinical trial patients, conflicting data exist about the safety and efficacy of fibrinolytic therapy for elderly patients in practice. Analyzing retrospective data on 2673 patients age 75 to 86 years with AMI from the Cooperative Cardiovascular Project (CCP) registry, Thiemann *et al*. [57] observed that the 1607 patients who were treated with fibrinolytic agents had lower survival than untreated patients. Among the treated patients in that study, however, many had traditional contraindications to fibrinolysis. An independent study of 2659 elderly patients (≥ 65 years old) admitted to Minnesota community hospitals with AMI between 1992 and 1996 found that 735 (27.6%) were treated with fibrinolytic therapy [58]. Of those who received fibrinolytic therapy, 38% had contraindications to treatment, which was strongly associated with an increased risk of mortality compared with patients who did not receive fibrinolytic therapy. Of 719 patients who were deemed eligible for reperfusion therapy, 63% received fibrinolysis and there was a 4% increase in the risk of death for every 1-year increase in age for all fibrinolytic recipients compared with nonrecipients, such that fibrinolysis was associated with a mortality reduction among eligible patients younger than 80 years but patients age 80-90 years experienced an increased risk of mortality compared with untreated patients (OR 1.4). Two additional registry analyses with assessment of outcomes at 1 year did not confirm net excess hazard to fibrinolytic therapy for elderly patients with STEMI. In a separate examination of the CCP registry by Berger *et al*. [59] that included 14,341 patients age 65 or older who received fibrinolytic therapy, at one year treatment was associated with a survival benefit (OR 0.84; 95% CI: 0.79 to 0.89). Likewise, for the 3897 patients who received fibrinolytic therapy from among 6891 unselected patients 75 years and older with STEMI in the Swedish RIKS-HIA registry, fibrinolytic therapy was associated with a 13% adjusted relative reduction in the composite of mortality and cerebral bleeding complications after 1 year (95% confidence interval, 0.80-0.94; $p = 0.001$) [60]. Nevertheless, in an analysis of 84,663 patients enrolled in the National Registry of Myocardial Infarction 2 who were considered eligible for reperfusion therapy, age > 75 years was a strong independent predictor that a patient would not receive any reperfusion therapy (OR = 0.40) [48]. These results point to an age-related underutilization of fibrinolytic therapy, and suggest that when necessary, reperfusion by cautious use of fibrinolytic agents can benefit carefully selected elderly patients with STEMI. It should be recognized, however, that the risk of hazard with fibrinolysis does appear to increase with age.

Reperfusion of elderly patients with STEMI by primary PCI has also been investigated and compared with fibrinolytic therapy. In a pooled analysis of 22 randomized trials of treatment of patients ($n = 6763$) with STEMI by primary PCI vs. fibrinolytic therapy, primary PCI resulted in greater mortality reduction than fibrinolysis. Although the relative mortality advantage of primary PCI over fibrinolysis appeared similar among age groups, the absolute mortality advantage of primary PCI increased from 1% for patients < 65 years old to 5.1% for patients age 75-84 years and 6.9% for patients age ≥ 85 years [33, 50]. Because of their higher risk of stroke with fibrinolytic therapy and the dramatically (> 90%) lower risk of hemorrhagic stroke with primary PCI [61], the elderly may also gain a greater safety advantage with primary PCI than younger patients [50].

Pharmacologic therapies for non ST-elevation acute coronary syndrome

For elderly patients with NSTE ACS, the ACC/AHA 2007 Guidelines [5] recommend (class I) that older patients with NSTE ACS should be evaluated for therapeutic interventions in a similar manner as younger patients, including consideration of use of aspirin, a β-blocker, low molecular weight heparin or unfractionated heparin, clopidogrel, and a glycoprotein IIb/IIIa inhibitor. The guidelines also provide class I recommendations for the factor X antagonist

fondaparinux and the direct thrombin inhibitor bivalirudin, with potential preferences for particular agents based on selection of an invasive or conservative management strategy for the patient in question.

Nevertheless, diminishment in renal and hepatic function that commonly accompanies aging may affect pharmacokinetics of many drugs used to treat ACS, requiring careful attention to the choice of agent and dosing considerations. In fact, an important observational study of patients with NSTE ACS included in the CRUSADE registry [62] suggested that, in practice, patients aged 75 years or older were more likely than younger patients to be prescribed excessive doses of low molecular weight heparin (16.5 vs. 12.5%), unfractionated heparin (38.4 vs. 28.7%), and glycoprotein IIb/IIIa inhibitors (64.5 vs. 8.5%), and excess doses were associated with a significantly increased hazard of major bleeding.

Invasive versus conservative management

Choice of management strategy may also significantly impact outcome for elderly patients with NSTE ACS. An invasive strategy implies early (often within 48 h of hospitalization) cardiac catheterization with determination of management, especially the need for revascularization, based on the results of coronary angiography, while a conservative strategy implies close observation and pre-discharge evaluation by stress testing. Several trials, including FRISC II, RITA-3, and TACTICS-TIMI 18 have indicated that a routine early invasive management can benefit general patients with NSTE ACS [63-66], while two other studies, VANQWISH and ICTUS, have suggested that a routine early invasive strategy is not superior and might even have hazard for older patients [67, 68]. Since older ACS patients face increased risks of complications with invasive procedures and revascularization relative to younger patients, the effect of early invasive management on the elderly has particularly been questioned. A prospective analysis of the effect of age on outcomes in the TACTICS-TIMI 18 trial, where all patients were treated with aspirin, heparin, and the glycoprotein IIb/IIIa inhibitor tirofiban, was specifically designed to address the question of whether the elderly derive benefit or harm from early invasive management [53]. The results of this analysis showed that, at 6 months, older patients (age ≥ 65) achieved greater absolute (4.8 vs. 1.0%) and relative (39 vs. 6%) reductions in the incidence of death or MI by an early invasive strategy than younger patients. Among elderly patients age > 75 the early invasive strategy conferred an absolute 10.8% and relative 56% reduction in death or non-fatal MI at 6 months (10.8 vs. 21.6%, $p = 0.016$) compared with conservative management, which included > 70% relative reduction in non-fatal MI (Figure 3). With respect to hazard, the risk of in-hospital major bleeding was significantly increased (6.5 vs. 16.6%, $p = 0.009$) by the early invasive approach. In terms of judging practical clinical benefit for older vs. younger ACS patients for the reduction of ischemic events, the number needed to treat with early invasive management to prevent 1 death or MI at 6 months was 250 among those < 65, compared with 21 among those ≥ 65, and just 9 for those ≥ 75 years of age. These observations suggest that application of a routine early invasive strategy is strongly beneficial for reducing death or nonfatal MI among elderly patients, an effect that is greater among older compared with younger patients, and that both the absolute and relative benefits increase with increasing age. These benefits are obtained, however, at the added expense of an increase in major bleeding among patients older than 75 years [53].

Lipid lowering therapy

Regarding secondary prevention, although the elderly may be more sensitive to drug effects and toxicity, aspirin, β-blockers, angiotensin converting enzyme inhibitors have all been found to have equivalent or greater benefit in older vs. younger patients and are indicated for elderly patients without contraindications or intolerance after AMI. In addition, use of intensive statin therapy to achieve a target low density lipoprotein cholesterol (LDL-C) of < 70 mg/dl (1.8 mmol/l) in patients after ACS has been shown to reduce adverse outcomes at late follow-up [69]. However, analysis of registry data [70, 71] suggests that elderly patients are less likely than younger patients to receive lipid-lowering therapy at hospital discharge following ACS, perhaps suggesting that clinicians are uncertain whether the benefits of statins extend to the older age group. Data relevant to this issue has been obtained from an investigation of the effect of intensive vs. moderate lipid lowering by statin among 634 elderly patients (age 70 or older) included in the PROVE IT-TIMI 22 trial [72], where achievement of an LDL-C of < 70 mg/dl in older patients was associated with an 8% absolute and a 40% relative lower risk of events vs. corresponding benefits of 2.3 and 26% in 3150 younger patients. Compared with patients not at goal, achievement of this target goal (NCEP "optional" LDL-C goal) among elderly patients would prevent 80 events at 2 years for every 1000 patients, compared with 23 events prevented in younger patients. These observations of greater absolute benefit of intensive lipid lowering among elderly compared with younger patients suggest that routine use of statin therapy after ACS targeted

to achieve the NCEP LDL-C optional goal of LDL-C < 70 mg/dl would be an effective intervention for secondary prevention among the elderly.

Underutilization of effective therapies

Despite evidence of benefit of early invasive management and of antiplatelet and antithrombin therapy for elderly patients with ACS, there is evidence that these interventions are inconsistently applied among elderly patients. In an analysis of 56,963 patients with NSTE ACS in the CRUSADE registry, Alexander *et al*. [73] observed that the use of acute antiplatelet and antithrombin therapy within the first 24 h declined with age, and, despite their higher risk characteristics, elderly patients were less likely to undergo invasive management or revascularization. Elderly patients were furthermore less likely to be discharged on clopidogrel or lipid lowering therapy. In-hospital mortality increased with age, but importantly, elderly patients who received more recommended therapies had lower adjusted mortality than those who did not.

Women

Increased risk of adverse outcome

Among patients with ACS, women represent another important higher risk subgroup characterized by distinct features of presentation, management and outcome that deserve special attention. Women hospitalized with ACS have more adverse baseline characteristics than men: women are generally older and more likely to have co-morbidities, including a history of hypertension, DM, and CHF, and more often they present without chest pain and/or with atypical symptoms [74]. These factors can contribute to greater challenges in diagnosis and treatment among women than men with ACS, which may translate into the potentially higher risk of adverse outcome. Nevertheless, by coronary angiography women have less extensive CAD and a higher proportion of nonobstructive CAD than men, which has been interpreted to suggest that ACS in women may have different pathophysiology than ACS in men [75, 76].

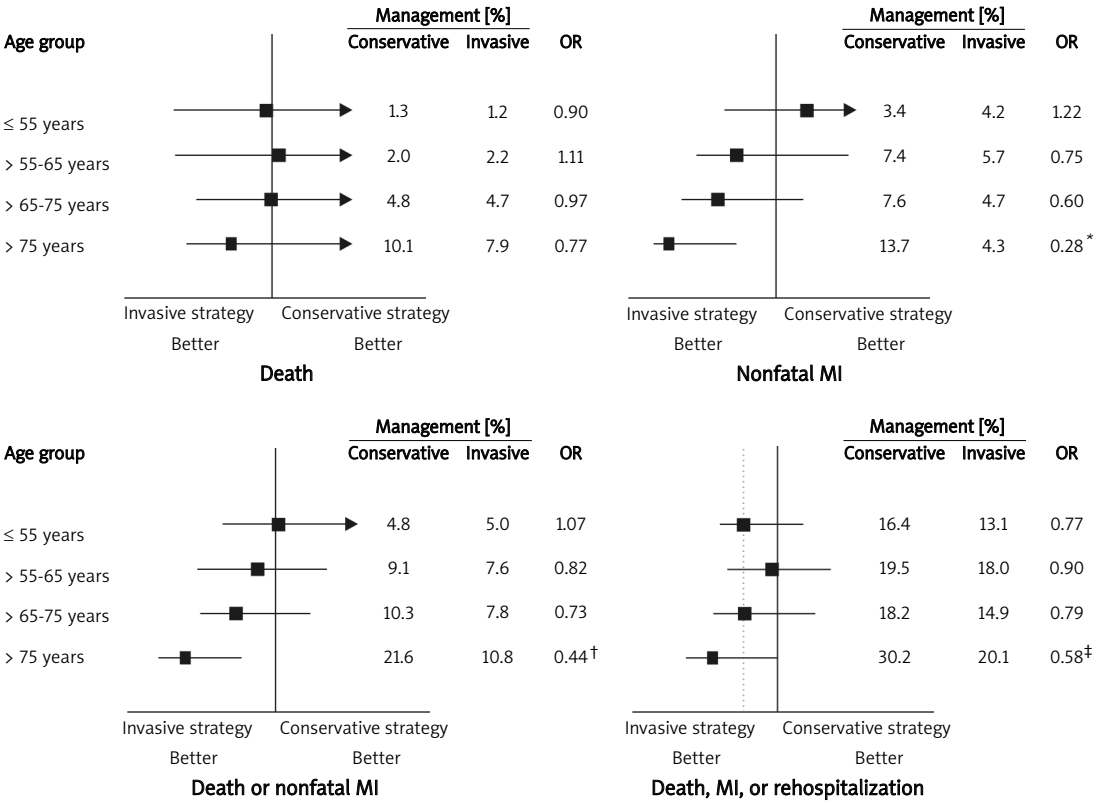

Figure 3. Odds ratios (ORs) with 95% CIs for death; nonfatal MI; death or nonfatal MI; and death, MI, or rehospitalization for ACS at 6 months in patients with NSTE ACS, stratified by age group, enrolled in the TACTICS–TIMI 18 trial. Reproduced from Bach RG, Cannon CP, Weintraub WS, *et al*. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. Ann Intern Med 2004; 141: 186-95 [53]
**p = 0.010, †p = 0.016, ‡p = 0.05*

While women with ACS represent a group with generally higher risk than men for mortality and adverse outcome, the relationship between gender and outcome is not simple. Two recent landmark studies suggest that there appears to be heterogeneity for the relative outcome differences between men and women according to age and diagnostic classification. In an analysis of 3662 women that were compared with 8480 men with ACS enrolled in the GUSTO-2 trial, Hochman *et al*. [77] observed that women had a higher mortality in univariate analysis, but after adjustment for age and baseline characteristics, outcomes overall appeared similar for men and women. When examined more closely, women with STEMI had a nonsignificant trend toward worse adjusted outcomes than men, women and men with NSTE MI had similar outcomes, and women with unstable angina experienced better outcomes than men. In another analysis of over 150,000 women hospitalized with AMI included in the NRMI-2 registry, Vaccarino *et al*. [78] observed that there was a significantly higher adjusted mortality among younger women with MI. For patients under age 50, women had more than double the in-hospital mortality compared to men; this gender-related difference diminished with age and after age 74 no significant difference in mortality was observed between men and women.

Select aspects of management

Pharmacologic therapies

In general, management of women with ACS should include consideration of the same pharmacologic interventions as men. Women and men appear to have similar benefit from aspirin in secondary prevention after ACS [79, 80]. Use of dual antiplatelet therapy with aspirin and clopidogrel also seems to provide similar protection to women and men with NSTE ACS [81]. Despite this, women with ACS generally receive less intensive pharmacologic interventions than men, and are treated less often with effective antiplatelet and antithrombin agents [2].

The effect of glycoprotein IIb/IIIa inhibitors in women with ACS has been less consistent across trials. In the PURSUIT trial of eptifibatide for patients with NSTE ACS [82], women did not appear to have the same magnitude of reduction of adverse ischemic events as men, while in the PRISM-PLUS trial of tirofiban in the a similar patient population, tirofiban appeared to have similar efficacy in men and women [38]. A meta-analysis of 6 large-scale, randomized, controlled clinical trials of intravenous glycoprotein IIb/IIIa inhibitors including 31,402 patients suggested that there was a significant treatment-by-gender interaction, such that there was a benefit observed in a reduction in death or MI at 30 days with treatment among men (OR 0 81, 95% CI 0.75-0.89) but not among women (OR 1 15, 95% CI 1.01–1.30; p for interaction < 0.0001). Women with positive troponin, however, appeared to have benefit similar to that observed among men [83].

Despite the potential for reducing death and MI for higher risk women with ACS, use in practice of glycoprotein IIb/IIIa inhibitors in women carries a substantially greater risk of developing major bleeding than use in men (OR, 2.78 vs. 1.98) [84], a hazard that may be partly explained by a higher frequency of excess dosing of these agents in women [62]. These observations suggest that glycoprotein IIb/IIIa inhibitors reduce adverse ischemic outcomes in both high risk men and women, especially those who are troponin-positive, but that women patients should be carefully selected and careful attention paid to appropriate dosing of these agents.

Invasive versus conservative management

In practice, the selection of management strategy is an important yet often challenging early care decision faced by a clinician for a patient with ACS. Regarding selection of management strategy specifically for women with ACS, the results of randomized clinical trials have been inconsistent, at least for NSTE ACS. In the FRISC II and RITA 3 trials, both of which concluded that a routine invasive strategy was overall beneficial for management of higher risk patients with NSTE ACS, women did not experience the same benefit as men or even had worsened outcomes with the invasive approach [65, 85]. In FRISC II, at 12 months the composite endpoint of death or MI was reduced among the 1708 men by assignment to invasive management (9.6% vs. 15.8%, $p < 0.001$), while among the 749 women included in the study there was no statistical difference between the invasive and conservative strategies, with more events in the invasively managed group (12.4 vs. 10.5%, p = NS). The interaction between gender and management strategy was highly significant ($p = 0.008$) [85]. Similarly, in the RITA 3 trial, at 1 year among the 1128 men there was a lower incidence of death or MI in the invasive group vs. the conservative group (7.0 vs. 10.1%, adjusted OR 0.63, 95% CI 0.41-0.98) while among the 682 women the incidence of death or MI was higher in the invasive group (8.6 vs. 5.1%, adjusted OR 1.79, 95% CI 0.95-3.35) and there was a significant interaction between gender and management strategy (p for interaction = 0.007) [65, 86].

In contrast to the worse outcomes for women related to invasive management of NSTE ACS observed in FRISC II and RITA 3, the TACTICS TIMI 18 trial found more similar outcomes for men and women based on management strategy [63]. In

TACTICS-TIMI 18, all patients were treated with the glycoprotein IIb/IIIa inhibitor tirofiban. Among the 757 women in the trial, the reduction in composite endpoint of death or MI at 6 months by the invasive strategy (adjusted OR 0.45, 95% CI, 0.24-0.88) was similar to the benefit observed in the 1463 men (adjusted OR 0.68, 95% CI, 0.43-0.1.05; $p = 0.60$ for interaction) [87]. Of note, in an exploratory analysis within the TACTICS-TIMI 18 population, elevated biomarkers, and perhaps TIMI risk score, appeared to help predict benefit from invasive management among women. Women with elevated troponin T levels and women with intermediate (3 to 4) or high (5 to 7) TIMI risk scores appeared to benefit from invasive management with reductions in the primary composite endpoint of death, MI and rehospitalization for ACS that were similar to men (Figure 4). However, among women with negative troponin T, or those with low TIMI risk score (0 to 2), there was a higher incidence of death, MI and rehospitalization for ACS associated with invasive management (OR 1.46, 95% CI 0.78-2.72; and 1.59, 95% CI, 0.69-3.67, respectively). It must be recognized that the number of events in these subgroups was small and the 95% CI were wide; the test for interaction between management strategy, gender, and elevated troponin T level on outcome yielded $p = 0.02$ while that for TIMI risk score did not achieve significance ($p = 0.09$).

It is notable, furthermore, that in a subsequent meta-analysis [88] combining data from 8 randomized clinical trials comparing an invasive vs. conservative treatment strategy in patients with NSTE ACS that included 3075 women and 7075 men found that the invasive strategy resulted in comparable reduction in the composite of death, MI or recurrent ACS in men and high-risk women. However, there was a suggestion that low risk women defined by absence of elevated biomarkers do not benefit and may be harmed by an invasive strategy. Among women who were biomarker-positive, an invasive strategy was associated with a 33% lower odds of death, MI, or ACS (OR, 0.67; 95% CI, 0.50-0.88) and a nonsignificant 23% lower odds of death or MI (OR, 0.77; 95% CI, 0.47-1.25). In the subgroup of women who were biomarker negative, the invasive strategy was associated with a nonsignificant 35% higher risk of death or MI (OR 1.35, 95% CI, 0.78-2.35; p for interaction = 0.08).

These results suggest that women with ACS at higher risk, defined by elevated biomarkers or possibly risk score, appear to benefit from an early invasive strategy, while low risk women, a group potentially with a low prevalence of obstructive coronary artery disease at angiography, do not benefit and may even have excess risk from a invasive management. The updated ACC/AHA practice guidelines for NSTE ACS [5] specifically recommend (class I) that (1) for women with ACS and high risk features, strategy should be determined similarly to men, while (2) women with ACS and low risk features should be managed conservatively.

Underutilization of effective therapies

Given there greater heterogeneity in extent of obstructive CAD and greater hazard of complications such as bleeding with certain interventions, selection of management strategy and

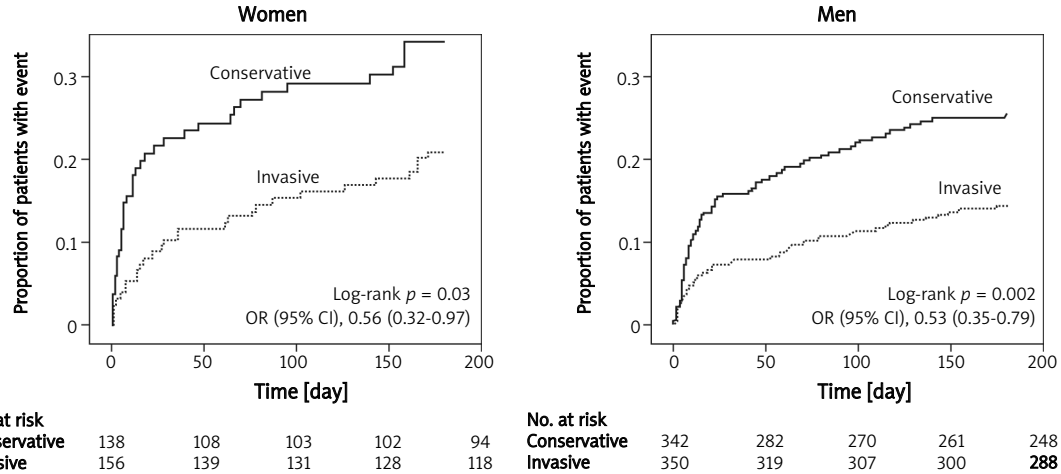

Figure 4. Death, MI, and rehospitalization for ACS at 180 days for women and men with NSTE ACS and elevated troponin T levels enrolled in the TACTICS-TIMI 18 trial, according to early invasive vs. conservative management strategy; OR indicates odds ratio; CI, confidence interval. Reproduced from Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. JAMA 2002; 288: 3124-9 [87]

treatment may be more challenging for women. Nevertheless, like patients with DM and the elderly, women with ACS and indications for treatment may not receive those effective diagnostic and therapeutic interventions as frequently as men. An analysis of 224,377 patients hospitalized with suspected acute MI included in the Cooperative Cardiovascular Project data base, of whom 49% were women, suggested several important disparities between men and women [89]. Among patients considered ideal candidates for treatment in that study, women were less likely to receive aspirin or a fibrinolytic agent. Women were also significantly less likely than men to undergo cardiac catheterization, a difference that was even more pronounced among older age patients. Gender-related differences in referral for cardiac catheterization and revascularization have been observed in other cohorts of patients with ACS [90-92], although a separate analysis that included an examination of the appropriateness of cardiac catheterization concluded that a difference between men and women was seen only among the subgroup of patients with equivocal indications, and that there was no variation by gender in procedure use among patients who had strong indications for cardiac catheterization [93].

Conclusions

Among patients with ACS, patients with diabetes, elderly patients and women represent groups at particularly high risk for adverse outcomes. Evidence from clinical trials and registry experience reviewed above suggest that care of these patients demands special attention to particular aspects of their distinctive patho-physiology and clinical features to reduce the risk of complications and to optimize outcomes. More consistent application of invasive management when indicated and conservative management when appropriate, more consistent use of potent pharmacologic agents in the context of patient risk, and more consistent attention to additional factors such as hyperglycemia among patients with DM, would contribute to more optimal management. Given their higher risk, improved adherence to guideline recommended, evidence-based management among patients in these special groups promises to substantially reduce the high rate of morbidity and mortality associated with ACS.

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