Journal of the American College of Cardiology
Vol. 43, No. 3, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2003.08.044

Published by Elsevier Inc.

Coronary Artery Disease

Importance of Increasing Age on the Presentation and Outcome of Acute Coronary Syndromes in Elderly Patients

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OBJECTIVES The study examined differences in presentation and outcome between elderly (≥70 years) and very elderly (≥80 years) patients hospitalized for acute coronary syndromes (ACS).

BACKGROUND The elderly constitute an increasingly important sector of patients with ACS but have been underrepresented in many therapeutic trials.

METHODS We compiled a registry of 449 consecutive patients, 251 elderly (70 to 79 years) (septuagenarians, group 1) and 198 very elderly (≥80 years) (group 2), to examine outcomes in relation to baseline characteristics and treatment. We recorded survival over a period of 24 ± 4 months and rehospitalization and symptomatic status at 16 ± 4 months.

RESULTS At index hospitalization, the older cohort (group 2) more often had acute myocardial infarction (35% vs. 9.7%, $p < 0.0001$), heart failure (33.3% vs. 19.4%, $p < 0.001$), and renal dysfunction (21.6% vs. 12.3%, $p = 0.01$). They were less likely to undergo coronary angiography (29.3% vs. 43.8%, $p = 0.002$), but those selected for angiography more often underwent revascularization so that revascularization rates were similar (22.7% group 2 vs. 24.3% group 1, p = NS). Two-year survival rate was poorer in group 2 (67.4 ± 3.5% vs. 83.5 ± 2.5% in group 1, $p < 0.0001$). Repeat rehospitalization was similar (53.0% vs. 48.2%, respectively, $p = 0.31$), but improvement in well-being of survivors was greater (60.0% vs. 46.3%, $p = 0.01$).

CONCLUSIONS The study demonstrated important differences between elderly (70 to 79 years) and very elderly (≥80 years) patients hospitalized with ACS. The older cohort was sicker on admission and had poorer outcome, but a subgroup selected for angiography and possible intervention had two-year outcomes similar to the younger cohort. (J Am Coll Cardiol 2004;43:346–52)

The elderly constitute an increasing proportion of patients presenting with acute coronary syndromes (ACS). While age itself is a prominent marker of high risk for adverse events (1,2), the elderly have usually been underrepresented in clinical trials of ACS. In studies involving interventional strategies in the elderly (3), participants were carefully selected to comply with rigid entry criteria and, therefore, poorly represent the average patient who often has significant comorbid conditions. In a recently published global registry of patients with ACS (4), over half the patients were over the age of 65 years, emphasizing the growing importance of examining outcomes in the elderly age group.

Concepts regarding the definition of elderly are changing, and it is no longer sufficient to group all patients above a certain age cutoff together. Particularly in older patients, an age difference of 5 to 10 years may be associated with major differences in biological function. Differences in patient mix in a "real world" older population may, therefore, have important bearing on the outcomes of clinical trials as well as the results of routine patient care (4–6). The present study examined outcomes in an unselected cohort of elderly patients hospitalized for ACS. We investigated differences in outcome between septuagenarians and patients who were older by a decade or more and examined the additional determinants of clinical outcome.

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Manuscript received June 25, 2003; revised manuscript received August 6, 2003, accepted August 18, 2003.

METHODS

Patient population. All patients ≥70 years of age hospitalized with an admission diagnosis of ACS in the cardiology or any of three internal medicine departments in a single medical center were entered into the Lady Davis Carmel Medical Center geriatric cardiovascular registry. The registry included 449 consecutive patients: 251 patients age 70 to 79 years (group 1) and 198 patients ≥80 years (group 2). Group 2 patients were enrolled during one calendar year (January 1 through December 31, 2000), while those in group 1 were enrolled during the same time period, but because this group was considerably larger, six representative calendar months spaced over the same calendar year were sampled. The diagnosis of ACS included all patients with acute or rapidly worsening symptoms thought to be due to coronary artery disease (CAD) at the time of hospitalization

Abbreviations and Acronyms

ACS	= acute coronary syndromes
AMI	= acute myocardial infarction
CAD	= coronary artery disease
CPK	= creatine phosphokinase
HF	= heart failure
HR	= hazard ratio
NYHA	= New York Heart Association
PCI	= percutaneous coronary intervention

and included patients with ST-elevation acute myocardial infarction, non–ST-elevation myocardial infarction, and patients with unstable angina. Myocardial infarction (AMI) was recorded when total creatine phosphokinase (CPK) was ≥2× the upper limit of normal. Unstable angina was diagnosed in patients on clinical grounds when study criteria for AMI were lacking but total CPK was above the upper limit of normal, electrocardiographic changes consistent with acute myocardial ischemia were present, or in the absence of enzyme or electrocardiographic findings when patient complaints suggested an ACS. In the majority of patients in whom unstable angina was diagnosed, there was elevated total CPK or historical or angiographic evidence of CAD (276 of 363, 80.8%). Record was made of interventional procedures, and in-hospital outcomes and symptomatic status of survivors was assessed at 16 ± 4 months and survival at 24 ± 4 months. Interventional procedures were sometimes performed after the primary period of hospitalization due either to an initial physician instigated strategy of medical therapy; to patient indecision; or to waiting lists, particularly for surgical procedures. The definitive therapy was considered to be interventional if performed within the calendar year of the registry or no later than one month after discharge in patients hospitalized in the last month of the registry period. Survival status was obtained for all patients through governmental records or direct patient inquiry by a structured telephone interview. Assessment was made of functional capacity (New York Heart Association [NYHA] classification) and of overall patient well-being. Patient well-being was defined as worse, same, better, or much better than in the week before index hospitalization. Patient recollection of repeat hospitalizations was found to be unreliable, and repeat hospitalizations in internal medicine, cardiology, or cardiac surgery departments were recorded from health insurance administrative databases. These databases included >90% of all hospitalizations, but over-reporting of hospitalization could occur due to classification of some elective day hospital visits and emergency room visits as full hospitalizations and registration of repeat hospitalization after weekend home leave.

Statistical methods. Baseline characteristics in the two groups were examined and compared using 2 × 2 tables and chi-squared tests for categorical variables and Student *t* test for continuous variables. Difference in time to event distributions (death and death or repeat hospitalization) was examined using Kaplan-Meier curves and tested using the log-rank test. Hazard ratios (HR) were estimated using the Cox proportional hazards model. Two-year survival rates and 16-month hospitalization-free rates were estimated using the Kaplan-Meier method. Binary outcomes were examined by logistic regression. Results were summarized using odds ratios and 95% confidence intervals (CI). Model building techniques were used to model the distribution of time to event from the set of predictors. Due to a large number of predictor variables, the stepwise multivariate procedure with forward selection was chosen. Initial variables included significant univariate predictors of outcome and important clinical and laboratory variables. Model fit statistics of the final model were examined as well as the proportional hazards assumption (7). A two-tailed probability of <0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics. Baseline characteristics of the two patient cohorts are given in Table 1. Mean age was 74.3 ± 2.7 years in group 1 and 84.1 ± 4.0 years in group 2. Risk factors for CAD (hypertension, diabetes mellitus) were less prevalent in patients in group 2, and the total cholesterol/high-density lipoprotein ratio was lower. The older patient cohort had undergone less prior revascularization. On the other hand, the prevalence of adverse acute admission characteristics such as heart failure (HF) on admission, renal failure on admission, and AMI (total CPK ≥2× the upper limit of normal) was greater. The majority of patients in both cohorts were classified as non–ST-elevation ACS and were mostly in Braunwald class 3B, but there was a higher prevalence of noncardiac causes of angina in the older cohort (Braunwald class A).

Interventional procedures. Coronary angiography was performed in 110 (43.8%) of group 1 patients and in 58 (29.3%) of group 2 (p = 0.002). Selection for coronary angiography was based on clinical status and the clinical judgment of the attending internists and/or cardiologists. Patients selected for angiography were younger (Table 2), more frequently male, and more frequently diabetic. More had undergone previous PCI. Patients with HF were catheterized less often. Although undergoing angiography less frequently, group 2 patients were more likely to undergo revascularization after angiography (45, 77.6% vs. 61, 55.5%, p = 0.005) so that overall revascularization rates were similar in the 2 groups (Table 1). There was a tendency to a greater use of percutaneous interventional strategies rather than bypass surgery in group 2 patients, with more surgical revascularization in the younger cohort despite a tendency to a lower incidence of triple-vessel disease and less left main CAD (Table 1).

Immediate and late outcomes. In-hospital mortality was 2 (0.8%) in group 1 and 12 (6.1%) in group 2 (p = 0.001).

JACC Vol. 43, No. 3, 2004
February 4, 2004:346–52

Table 1. Baseline Characteristics and Revascularization Data

	70–79 Years Group 1	≥80 Years Group 2	p Value
n	251	198	
Age (SD)	74.3 ± 2.7	84.1 ± 4.0	
Hypertension (%)	183 (73.5)	129 (65.5)	0.07
Diabetes mellitus (%)	83 (33.4)	50 (25.5)	0.07
Total cholesterol/HDL-C (SD)	4.7 ± 1.2	4.4 ± 1.1	0.04
Prior revascularization (%)	88 (35.1)	44 (22.2)	0.003
Prior CVA/TIA (%)	19 (7.6)	24 (12.1)	NS
Heart failure at index hospitalization (%)	48 (19.4)	66 (33.3)	< 0.001
Renal failure* (SD)	30 (12.3)	41 (21.6)	0.01
AMI† at index hospitalization (%)	23 (9.2)	63 (31.8)	< 0.0001
ST elevation AMI	10 (4.0)	19 (9.6)	0.016
Fibrinolytic therapy	6 (2.4)	8 (4.0)	NS
Classification of non–ST-elevation ACS (Braunwald)‡			
I (%)	4 (1.8)	1 (0.6)	
II (%)	30 (13.8)	11 (6.7)	
III (%)	183 (84.3)	151 (92.6)	0.047
A (%)	16 (7.4)	26 (16.0)	
B (%)	199 (91.7)	133 (82.2)	
C (%)	2 (0.9)	3 (1.9)	0.02
Extent of coronary artery disease‡			
Coronary angiography performed (%)	110 (43.8)	58 (29.3)	0.002
1-vessel disease (%)	20 (19.6)	10 (17.2)	NS
2-vessel disease (%)	26 (25.5)	10 (17.2)	NS
3-vessel disease (%)	44 (43.1)	33 (56.9)	0.09
Left main coronary artery stenosis (%)	6 (5.9)	9 (16.1)	0.04
Revascularization (% of patients undergoing angiography)	61 (55.5)	45 (77.6)	0.005
Revascularization (% of total patients)	61 (24.3)	45 (22.7)	NS
Percutaneous revascularization (% of revascularization)	38 (62.3)	35 (77.8)	0.09

*Serum creatinine ≥1.6 mg/100 ml; †total creatine phosphokinase ≥2× upper limit of normal; ‡some data lacking.
ACS = acute coronary syndrome; AMI = acute myocardial infarction; CVA = cerebrovascular accident; HDL-C = high-density lipoprotein cholesterol; TIA = transient ischemic attack.

Kaplan-Meier survival curves and hospitalization-free survival curves are shown in Figures 1A and 1B, respectively, and 2-year survival rates and hospitalization-free survival at 16 months are given in Table 3. Estimated survival at 2 years for the group as a whole (76.5 ± 2%) and survival free of repeat hospitalization at 16 months (41.3 ± 2%) were low. Survival rate was lower in the older age group (HR 2.3; 95% CI 1.6 to 3.5; $p < 0.0001$). Repeat hospitalization was similar in both groups, but survival free of rehospitalization was poorer in the older group. Functional capacity (NYHA) at follow-up was similar in both age groups, although overall well-being improved to a greater extent in group 2 (in relation to that before hospitalization).

Table 2. Characteristics of Patients Undergoing and Not Undergoing Angiography

	Angiography (n = 168)	No Angiography (n = 281)	p Value
Age	77.0 ± 4.9	79.6 ± 6.2	< 0.0001
Male	110 (65.5%)	145 (51.6%)	0.004
Heart failure	26 (15.5%)	88 (31.3%)	0.0002
AMI	34 (20.2%)	52 (18.5%)	NS
Diabetes mellitus	59 (35.5%)	74 (26.6%)	0.047
Hypertension	113 (67.7%)	199 (71.3%)	NS
Prior CABG	29 (17.5%)	50 (17.9%)	NS
Prior PCI	36 (21.6%)	33 (11.8%)	0.006
Serum creatinine	1.25 ± 0.55	1.32 ± 0.56	0.16
Total cholesterol/ HDL-C	4.52 ± 1.14	4.63 ± 1.15	NS

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; HDL-C = high-density lipoprotein cholesterol; PCI = percutaneous coronary intervention.

Outcomes in relation to treatment modality (medical or revascularization) and age group are shown in Table 3. In patients treated medically, the older cohort had a significantly poorer survival than the younger (HR 2.5; 95% CI 1.6 to 3.9; $p < 0.0001$), but, in patients treated by revascularization, the difference was smaller and not statistically significant (HR 1.6; 95% CI 0.65 to 4.0; $p = 0.3$). However, the difference in hazard rates between the revascularization and medically treated cohorts was not significant ($p = 0.52$). Rates of repeat hospitalization were similar between treatment groups. A greater proportion of surviving patients in the older cohort reported improvement in overall well-being irrespective of treatment modality (Table 3).

Determinants of clinical outcome. Patients selected for angiography were found to be an a priori low-risk group. They had a higher rate of survival during follow-up irrespective of whether revascularization was performed (esti-

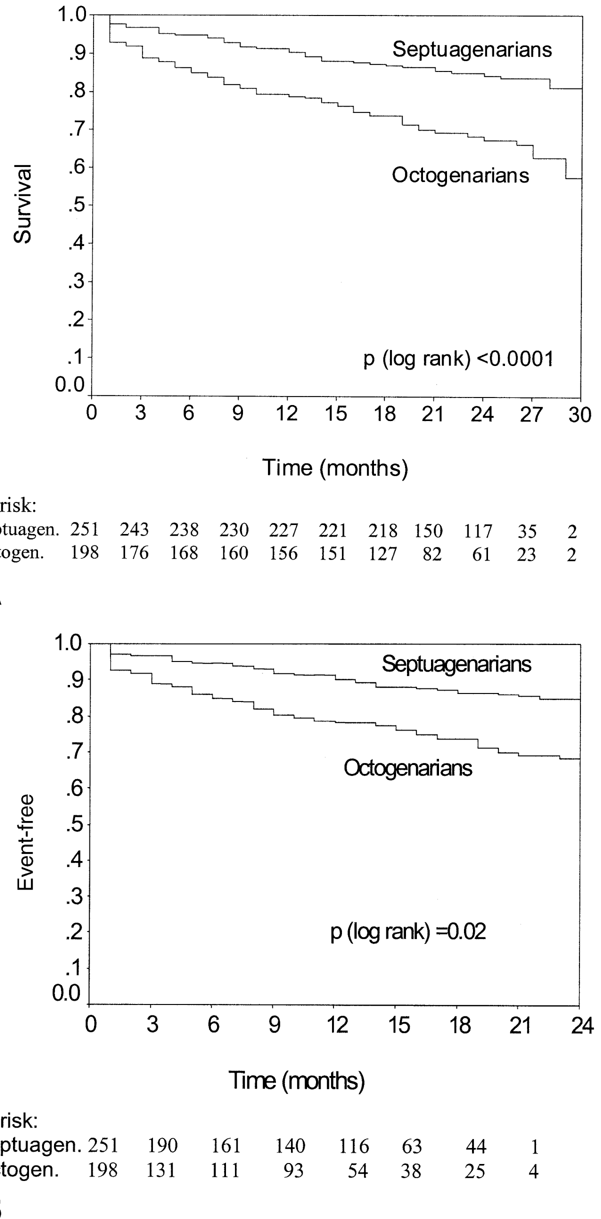

Figure 1. Kaplan-Meier curves of **(A)** survival and **(B)** survival free of hospitalization for septuagenarian and octogenarian patients.

mated two-year survival 84.6 ± 2% in those selected for angiography vs. 71.6 ± 2% for those not selected, p = 0.007). In patients undergoing diagnostic angiography without subsequent revascularization, two-year survival rate was 88.7 ± 4% (p = 0.016 vs. patients not selected for angiography). Overall survival rate after revascularization was not significantly different from that in medically treated patients (74.7 ± 2% in patients treated medically vs. 82.3 ± 4%, p = 0.18).

Univariate predictors of death and death or repeat hospitalization are shown as HRs and 95% CIs in Figures 2A and 2B, respectively. Heart failure on admission (two-year survival rate, 51 ± 5% vs. 85.1 ± 2%; p < 0.0001) and higher serum creatinine (60.3 ± 6% two-year survival rate

Table 3. Outcomes in Relation to Treatment Modality

	Overall Group				Revascularization				Medical Therapy				
	70–79 yrs	≥80 yrs	p Value	HR/OR* (95% CI)	70–79 yrs	≥80 yrs	p Value	HR/OR (95% CI)	70–79 yrs	≥80 yrs	p Value	HR/OR (95% CI)	p for Interaction
n	251	198			61	45			190	153			
Survival rate (%) (2 yrs)	83.5 ± 2.5	67.4 ± 3.5	< 0.0001	2.3 (1.6–3.5)	86.9 ± 4.3	75.2 ± 7.3	0.3	1.6 (0.65–4.0)	82.3 ± 3.0	64.8 ± 4.1	< 0.0001	2.5 (1.6–3.9)	0.52
Hospitalization-free survival rate (%)†	45.3 ± 3.2	36.1 ± 3.7	0.02	1.3 (1.0–1.7)	49.0 ± 6.4	37.2 ± 7.3	0.14	1.5 (0.88–2.4)	44.0 ± 3.8	35.8 ± 4.2	0.07	1.3 (0.98–1.7)	0.70
Repeat hospitalization, n (%)	121 (48.2)	105 (53.0)	0.31	0.82 (0.60–1.2)	26 (42.6)	24 (53.3)	0.28	0.65 (0.3–1.4)	86 (45.3)	81 (52.9)	0.16	0.74 (0.48–1.1)	0.79
Improved/class 1 (NYHA), n (%)‡	91 (45.5)	56 (39.7)	0.29	1.3 (0.82–2.0)	29 (60.4)	11 (32.4)	0.01	3.2 (1.3–8.0)	62 (40.8)	45 (42.1)	0.83	0.95 (0.56–1.6)	0.02
Improved well-being, n (%)	95 (46.3)	84 (60.0)	0.01	0.59 (0.37–0.91)	30 (61.2)	29 (76.3)	0.14	2.0 (0.80–5.2)	65 (41.7)	55 (53.9)	0.05	0.61 (0.37–1.0)	0.69
Deteriorated well-being, n (%)	65 (31.7)	22 (15.7)	< 0.001	2.5 (1.4–4.3)	13 (26.5)	0 (0)	< 0.001	—	52 (33.3)	22 (21.6)	0.04	1.8 (1.0–3.2)	—

*Hazard ratio for survival/event-free survival rates, odds ratio for binary outcomes (elderly vs. very elderly); †at 16 months; ‡proportion of live patients available for follow-up.
CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association; OR = odds ratio.

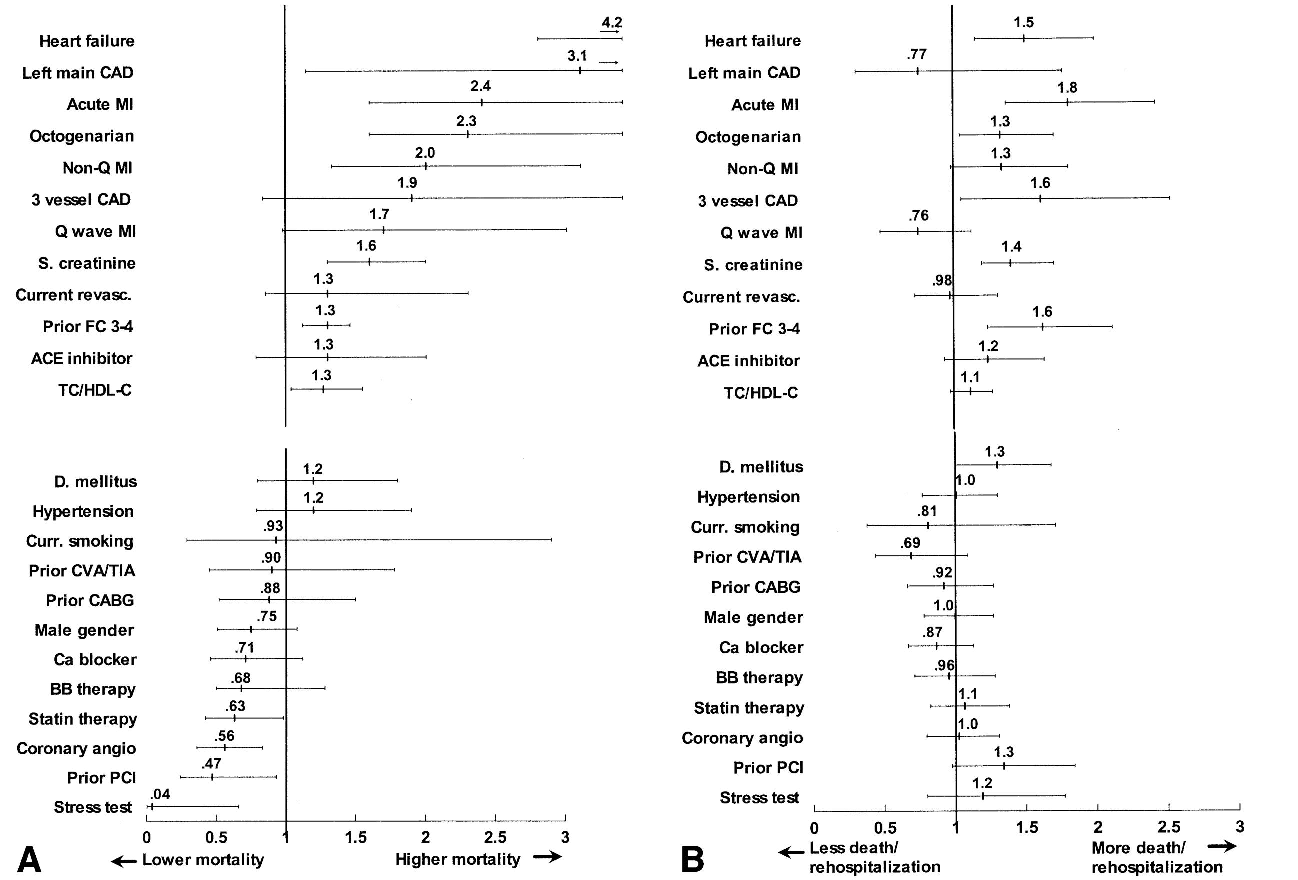

Figure 2. Univariate predictors of **(A)** death (24 months) and **(B)** death/repeat hospitalization (16 months) (hazard ratios ± 95% confidence intervals). ACE = angiotensin-converting enzyme; BB = beta blocker; Ca = calcium; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CVA/TIA = cerebrovascular accident/transient ischemic attack; FC (NYHA) = functional capacity (New York Heart Association classification); HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; revasc = revascularization; TC = total cholesterol.

for patients with serum creatinine >1.5 mg% vs. 78.7 ± 2% with creatinine ≤1.5 mg%, $p = 0.001$) and AMI predicted poorer two-year survival rate (AMI 60.4 ± 6% vs. 80.3 ± 2%, $p < 0.0001$). This was most apparent in the younger cohort in which two-year survival rate was 65.2 ± 10% in patients with AMI compared with 85.4 ± 3% in those without ($p = 0.003$) and directionally similar in the older cohort in which two-year survival rate was 58.3 ± 7% in patients with AMI and 71.7 ± 4% in those without ($p = 0.08$). The interaction of AMI with age tended to significance ($p = 0.15$); AMI on admission was a predictor of poorer survival in both the revascularization and the medically treated cohorts. In the revascularization cohort, survival rate was 57.7 ± 7% in patients with AMI on admission versus 78.2 ± 3% in those without AMI ($p = 0.03$), and in patients treated medically alone 66.8 ± 9% in patients with AMI on admission versus 88.3 ± 4% in those without ($p < 0.0001$). There was no interaction of revascularization with AMI ($p = 0.76$). The increased overall risk in patients with AMI was primarily the result of poorer survival in the first six months after the acute event, whereas, during later follow-up, the increased risk diminishes considerably. Survival rate was higher in patients discharged on statin therapy (two-year survival 82.7 ± 3% vs. 75.2 ± 3%, $p = 0.04$), those selected for treadmill testing (100 ± 0% vs. 74.1 ± 2%, $p = 0.0005$) or coronary angiography (as reported above), and those who had undergone previous percutaneous coronary intervention (PCI) (86.7 ± 4% vs. 74.5 ± 2%, $p = 0.02$).

A multivariate regression model was constructed to examine predictors of death and included the univariate predictors of death: older age, HF on admission, admission serum creatinine, AMI, poorer functional capacity (NYHA) before admission, lack of selection for exercise stress test, and lack of selection for coronary angiography. Also included were clinical variables such as sex, diabetes mellitus, history of hypertension, prior revascularization, and current revascularization therapy. Predictors of death in the final model were older age group (HR 2.1; 95% CI 1.4 to 3.1; $p = 0.001$), admission HF (HR 3.2; 95% CI 2.1 to 4.8; $p < 0.001$) and poorer functional capacity (NYHA) before hospital admission (HR 1.5 for each grade of functional capacity; 95% CI 1.1 to 2.0; p for trend 0.006), and lack of selection for exercise stress testing (100% survival in patients selected for test). An additional similar model examined independent predictors of death or repeat hospitalization.

Acute myocardial infarction (HR 1.7; 95% CI 1.3 to 2.3; $p = 0.001$), poorer prior functional capacity (HR 1.4 per grade; 95% CI 1.2 to 1.7; p for trend <0.001), and diabetes mellitus (odds ratio 1.3; 95% CI 1.0 to 1.7; $p = 0.03$) were significant in the final model.

Verification of the proportional hazards assumption with regard to the identified risk factors was established using time-dependent covariates (7). Global (overall) chi-squared statistic of the final model for survival was 92.99 and for hospitalization-free survival 29.723 with 4 degrees of freedom for both ($p < 0.0001$ for both models), indicating that the identified risk factors can be used to predict survival time.

DISCUSSION

This study focused on the contrasts between elderly (septuagenarians) and very elderly (octogenarians and older) patients hospitalized for ACS. An increase of 10 years of age was associated with a doubling of mortality rate at 24 months (33% vs. 17%, $p < 0.001$). Although at the time of hospitalization octogenarians were more ill than the septuagenarians, a low-risk subgroup of octogenarians was selected for coronary angiography with a two-year survival rate of 76 ± 6% (75 ± 7% in those undergoing revascularization) approaching that of the younger cohort not selected for angiography (79 ± 4% two-year survival rate). Symptomatic improvement was experienced by the majority of patients in both age groups selected for intervention but in much fewer of those not selected (Table 3). Few studies have directly compared age substrata within a group of elderly patients. The American College of Cardiology-National Cardiovascular Data Registry showed that, among octogenarians undergoing PCI, age was a progressive predictor of adverse outcome (8,9) as in other nomograms predicting outcome (10,11). The present study had the advantage of examining an unselected cohort of consecutive elderly patients in a registry rather than those selected for interventions or selected by stringent inclusion/exclusion criteria (3). As a single-center study, it was possible to ensure that all elderly patients with ACS hospitalized within a given time period were included, thus avoiding selection bias, which may play a role with the less exact reporting that may occur in multicenter registries.

Patients presenting with ACS in their 80s were sicker on admission to hospital as manifested by a greater prevalence of HF, AMI, renal failure, and, in those undergoing angiography, more extensive coronary disease (three-vessel, left main coronary disease). Similar findings were described in elderly patients in both percutaneously and surgically treated patients (8,12–14). Surviving patients in the older cohort experienced a greater improvement in overall well-being, and this was in keeping with two other studies (3,15).

In the American College of Cardiology National Cardiovascular Data Registry, octogenarians undergoing PCI within a week of AMI had higher in-hospital mortality than those without AMI (7). The present study also found a higher overall late mortality in patients presenting with AMI both in the revascularization and medically treated cohorts. In a comparison of cohorts of elderly patients after AMI with a high and low intervention rate, one-year mortality was similar (16). A recent trial selecting patients at high risk for bypass surgery for randomization to PCI or surgery (including age >70 years as one high-risk criterion) (17) found almost identical survival rates in the two treatment cohorts at 36 months. Longer postoperative hospitalization was reported in elderly patients (18). A report of bypass surgery in 11 nonagenarians reported an in-hospital survival of 82% with improvement in quality of life in survivors but high in-hospital morbidity (19). In the present study, mortality was not significantly different in patients treated medically or undergoing revascularization. Among patients undergoing revascularization, late mortality was similar after PCI or bypass surgery.

Lack of selection for exercise testing (and for angiography) were independent predictors of mortality. Also significant as an independent predictor of death or repeat hospitalization was a poorer functional capacity before the acute event leading to hospitalization. These data confirm the importance of straightforward clinical assessment and sound clinical judgment as predictors of mortality and as correlates of outcome in elderly patients.

The study has the limitations of a single-center registry in that findings may be influenced by local patient referral and physician practice patterns and, therefore, need to be confirmed in additional patient cohorts. A registry study does have the advantage of representing real world clinical practice, and the findings of the study are probably applicable to a large number of tertiary health care facilities. Serum troponin was not available at the time of the study. If available, this would have allowed better definition of the acute characteristics of the patient cohorts because a considerable proportion of patients with normal total CPK values would probably have been troponin-positive. There have been some changes in emphasis in treatment options since the registry data were recorded. A relatively small proportion of patients had ST-elevation myocardial infarction (partially due to referral bias), and the number treated with fibrinolytic therapy was relatively small due to very late arrival in some patients. Primary angioplasty was not performed in this patient cohort (although percutaneous rescue interventions were). Primary angioplasty is more frequently performed at the present time.

Summary. The registry provides a picture of the characteristics and outcomes in unselected elderly and very elderly patients with ACS. The elderly are sicker on admission and have poorer outcome, but a subgroup selected for angiography and possible intervention have two-year outcomes similar to their younger counterparts.

Acknowledgment

The authors acknowledge the expert statistical advice of Ofra Barnett, PhD.

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