A Prior Myocardial Infarction: How Does it Affect Management and Outcomes in Recurrent Acute Coronary Syndromes?

Address for correspondence:
Kim A. Eagle, MD
University of Michigan
Cardiovascular Center
300 North Ingalls, 8B02
Ann Arbor, MI 48109-0477, USA
keagle@umich.edu

Apurva A. Motivala, MD, Umesh Tamhane, MD, Vijay S. Ramanath, MD, Fadi Saab, MD, Daniel G. Montgomery, BS, Jianming Fang, MS, Eva Kline-Rogers, RN, Niquole May, Garry Ng, James Froehlich, MD, Hitinder Gurm, MD, Kim A. Eagle, MD
Division of Cardiovascular Medicine, Department of Internal Medicine and the Cardiovascular Center, University of Michigan Health System, Ann Arbor, Michigan, USA

ABSTRACT

Background: Despite improved secondary prevention efforts, acute coronary syndrome (ACS) recurrence among patients with prior history of coronary events remains high. The differences in presentation, management, and subsequent clinical outcomes in patients with and without a prior myocardial infarction (MI) and presenting with another episode of ACS remain unexplored.

Methods: A total of 3,624 consecutive patients admitted to the University of Michigan with ACS from January 1999 to June 2006 were studied retrospectively. In-hospital management, outcomes, and postdischarge outcomes such as death, stroke, and reinfarction in patients with and without a prior MI were compared.

Results: Patients with a prior MI were more likely to be older and have a higher incidence of diabetes mellitus, hypertension, hyperlipidemia, and peripheral vascular disease. In-hospital outcomes were not significantly different in the 2 groups, except for a higher incidence of cardiac arrest (4.3% versus 2.5%, $p<0.01$) and cardiogenic shock (5.7% versus 3.9%, $p=0.01$) among patients without a prior MI. However, at 6 mo postdischarge, the incidences of death (8.0% versus 4.5%, $p<0.0001$) and recurrent MI (10.0% versus 5.1%, $p<0.0001$) were significantly higher in patients with a prior history of MI compared with those without.

Conclusion: Patients with prior MI with recurrent ACS remain at a higher risk of major adverse events on follow-up. This may be partly explained by the patients not being on optimal medications at presentation, as well as disease progression. Increased efforts must be directed at prevention of recurrent ACS, as well as further risk stratification of these patients to improve their overall outcomes.

Key words: recurrent acute coronary syndrome, outcomes, prior myocardial infarction

Introduction

Patients who present with an acute coronary syndrome (ACS) continue to represent a major health concern. Secondary prevention measures improve long-term morbidity and mortality after an initial acute myocardial infarction (MI). As a result, more than 1 million individuals survive an MI annually in the US. Despite our best efforts at secondary prevention, the rate of ACS recurrence in this group remains relatively high. It is well-known that these patients with a recurrent ACS have worse outcomes; however, the timing of these adverse outcomes, as well as the contributing factors, remain unexplored. In this study, we sought to compare the differences in the presenting characteristics, in-hospital management, and subsequent clinical outcomes of patients with and without a prior MI and presenting with an ACS.

Methods

The study cohort comprised of 3,624 consecutive patients who presented between January 1999 and June 2006 and were admitted to the University of Michigan Medical Center (Ann Arbor, Mich., USA) with a diagnosis of acute coronary syndrome (ACS). All patients were initially identified by a discharge diagnosis of unstable angina (UA), ST-segment elevation myocardial infarction (STEMI), or non-ST-segment elevation myocardial infarction (NSTEMI). Identified charts were reviewed by nurses or physicians for entry criteria. Inclusion into the study required symptoms consistent with acute coronary insufficiency, along with 1 or more of the following: a documented history of coronary artery disease; electrocardiographic changes suggestive of ischemia, such as transient ST-segment elevations of $\geq$1 mm, ST-segment depressions of $\geq$1 mm, new T-wave inversions of $\geq$1 mm, pseudonormalization of previously inverted T-waves, new Q-waves, new R-wave >S-wave in lead V_1, or a new left bundle branch block [CK] evidence of coronary artery disease by cardiac catheterization; and/or elevated cardiac biomarkers (creatin kinase-[CK]-MB >2 times the upper limit of normal and/or troponin I >0.39 ng/ml). Clinical, demographic, treatment, and outcome data were abstracted from medical charts by trained abstractors (physicians and/or cardiology research nurses). Data were collected on a 6-page form and then forwarded

Clin. Cardiol. 31, 12, 590–596 (2008)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20356

Received: September 24, 2007
Accepted with revision: November 27, 2007

abstractors (physicians and/or cardiology research nurses). Data were collected on a 6-page form and then forwarded to a database service for dual data entry after review for face validity. Demographic variables included age and sex. Comorbidities included prior history of heart disease including angina, congestive heart failure (CHF), myocardial infarction (MI), coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), diabetes mellitus (DM), smoking, hyperlipidemia, and hypertension. Electrocardiogram (ECG) changes and initial laboratory data were recorded. Procedures and complications during the ACS hospitalization were documented. These patients were then followed-up by telephone 6 mo after their discharge, at which point outcomes and medication adherence were noted. The protocol was approved by the institutional review board at the University of Michigan and informed consent was obtained from all patients.

Patients were divided into 2 groups: Group 1 (n = 1,508) had a prior documented MI by history (either STEMI or NSTEMI) and Group 2 (n = 2,116) had no prior documented history of MI. Univariate comparisons between the 2 groups were performed using Pearson's chi-square test and Fisher's exact test for categorical variables, and a Student *t* test for continuous variables. Multivariable logistic regression modeling was performed to derive the independent association of clinical outcomes at 6 mo postdischarge with a prior history of MI. We compared in-hospital outcomes including death, reinfarction, stroke, cardiogenic shock, pulmonary edema, cardiac arrest, atrial fibrillation/flutter, and the composite of major adverse cardiac events (MACE) (i.e., death, stroke, and reinfarction). Reinfarction was defined as re-elevation of CK-MB to above the upper limits of normal and increased by at least 50% over the previous value. Stroke, either embolic and/or hemorrhagic, was defined as the onset of focal neurological signs or symptoms; for example, loss or slurring of speech, with confirmation by either computed tomography or magnetic resonance imaging. Cardiogenic shock was defined as the presence of pulmonary edema and hypoperfusion characterized by systolic blood pressure <80 mm Hg. We also compared rates of death, recurrent MI, unscheduled revascularization, stroke, and a composite of these at 6 mo postdischarge. Statistical Analysis Software (SAS) 8.2 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

This study included 3,624 patients, 1,508 patients with a prior MI and 2,116 without, who presented with an ACS. As shown in Table 1, patients with a prior history of MI were older and (mean age: 65.3 y versus 62.3 y, p<0.0001), and had a higher incidence of DM (37.5% versus 26.1%, p<0.0001), hypertension (79.5% versus 62.8%, p<0.0001), hyperlipidemia (77.1% versus 53.2%, p<0.0001), peripheral vascular disease (19.3% versus 10.0%, p<0.0001), and other

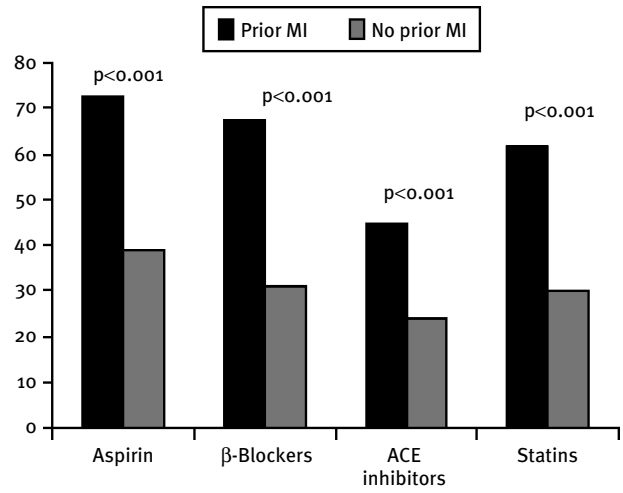

Figure 1: Chronic medications.

cardiovascular history. These patients had lower systolic blood pressures (138±29 versus 142±31 mm Hg, p<0.001) and lower initial serum low-density lipoprotein (LDL) cholesterol levels (90±37 versus 109±42 mg/dl, p<0.0001) than those without (Table 1). As one would expect, patients with a prior MI were more frequently on chronic β-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, and aspirin than those without at presentation with recurrent ACS (Figure 1). These patients were more likely to present in Killip class II heart failure (13.5% versus 7.9%, p<0.0001), and were generally a higher risk group based on their average risk scores during hospitalization (Table 1).

Although the in-hospital usage of statins was higher in this higher risk group (76.2% versus 71.6%, p<0.01), the use of thienopyridines (54.9% versus 60.9%, p<0.001), antithrombotics (86.9% versus 89.5%, p = 0.01), and glycoprotein IIb/IIIa inhibitors (20.0% versus 32.0%, p<0.0001) was significantly less. Also, the use of coronary revascularization procedures was significantly less in ACS patients with a prior MI (Table 2).

In-hospital adverse clinical events were not significantly different in the 2 groups, except for the incidence of cardiac arrest, which was higher in patients without a prior history of MI (4.3% versus 2.5%, p<0.01) (Table 3). Moreover, patients in this group were more likely to develop cardiogenic shock (5.7% versus 3.9%, p = 0.01), and were more likely to require the use of pulmonary artery (PA) catheters (10.3% versus 6.9%, p<0.001) and intra-aortic balloon pumps (IABP) (6.2% versus 4.0%, p<0.01). However, at 6 mo postdischarge, the unadjusted rates of death, recurrent MI, stroke, and unscheduled revascularization were significantly higher in patients with a prior history of MI compared with those without (Table 4). Multivariate logistic regression analysis showed that a history of prior MI remained a significant independent risk factor for MACE at 6 mo postdischarge

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20356

TABLE 1: Baseline patient characteristics

Characteristics	Prior MI n = 1,508 (41.6%)	No Prior MI n = 2,116 (58.4%)	p-value
Age (mean SD)	65 (14)	62 (13)	<0.0001
Male, sex	533 (35.3)	748 (35)	0.5
Body mass index (kg/m²) (mean SD)*	29.3 (8.9)	29.6 (11.3)	0.4
Cardiovascular History			
Angina	852 (56.8)	769 (36.4)	<0.0001
Transient ischemic attack/stroke	230 (15.3)	164 (7.8)	<0.0001
Congestive heart failure	489 (32.6)	204 (9.6)	<0.0001
Percutaneous intervention	758 (50.4)	272 (12.9)	<0.0001
CABG surgery	554 (36.9)	228 (10.8)	<0.0001
Risk Factors			
Smoking history	957 (63.5)	1257 (59.6)	0.02
Diabetes mellitus	564 (37.5)	552 (26.1)	<0.0001
Hypertension	1,192 (79.5)	1,327 (62.8)	<0.0001
Hyperlipidemia	1,159 (77.1)	1,122 (53.2)	<0.0001
Peripheral vascular disease	290 (19.3)	210 (10)	<0.0001
Systolic blood pressure (mean SD, mm Hg)	138 (29)	142 (31)	<0.001
Initial serum LDL cholesterol (mean SD, mg/dl)	90 (37)	109 (42)	<0.0001
Fasting serum glucose (mean SD mg/dl)	123±61	116±44	0.01
LVEF % (mean SD)	47 (17)	53 (14)	<0.0001
Presentation diagnosis			
Unstable angina	468 (31)	375 (17.7)	<0.0001
Non-ST-elevation myocardial infarction	870 (57.7)	1,174 (55.5)	0.2
ST-segment elevation myocardial infarction	170 (11.3)	567 (26.8)	<0.0001
Mean GRACE score (SD)	118 (36)	93 (34)	<0.0001

*Body mass index was calculated as weight in kilograms divided by the square of height in meters. *Abbreviations*: CABG = coronary artery bypass graft; GRAC = global registry of acute coronary events;[11] LVEF = left ventricular ejection fraction; MI = myocardial infarction; SD = standard deviation.

after adjusting for age, gender, and the presence or absence of DM, hypertension, hyperlipidemia, peripheral vascular disease, CHF, renal insufficiency, angina history, stroke, ejection fraction (EF) at presentation, renal insufficiency, and in-hospital therapies with an odds ratio (OR) of 1.41 (95% confidence interval [CI]: 1.029–1.94; $p < 0.05$).

Discussion

The principal findings of our study are 3-fold. First, the patients with a prior history of MI represented a significant portion of all patients (approximately 40%) presenting with an ACS and were clearly at higher risk in terms of comorbid conditions. Patients in this group were more likely to be on aspirin, β-blockers, statins, and ACE inhibitors upon presentation and were more likely to receive statins during their hospitalization. However, the use of in-hospital thienopyridines, antithrombotics, glycoprotein IIb/IIIa inhibitors, and coronary revascularization was significantly less in this group. Second, in spite of worse comorbidities, the in-hospital outcomes in this group were

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20356

TABLE 2: In-hospital management

Characteristics	Prior MI n = 1,508 (41.6%)	No Prior MI n = 2,116 (58.4%)	p-value
Aspirin	1,455 (96.5)	2,038 (96.3)	NS
β-blockers	1,374 (91.1)	1,939 (91.6)	NS
ACE inhibitor	1,001 (66.4)	1,417 (67.0)	NS
Statins	1,149 (76.2)	1,515 (71.6)	0.002
Thienopyridines	828 (54.9)	1,288 (60.9)	<0.001
Unfractionated heparin/LMWH	1,310 (86.9)	1,894 (89.5)	0.01
Glycoprotein IIb/IIIa inhibitor	303 (20.1)	677 (32.0)	<0.0001
Thrombolytics	39 (2.6)	152 (7.2)	<0.0001
Percutaneous coronary intervention	526 (34.9)	1,090 (51.5)	<0.0001
Coronary artery bypass grafting	91 (6.0)	243 (11.5)	<0.0001

Abbreviations: ACE = angiotensin-converting enzyme; LMWH = low molecular weight heparin; MI = myocardial infarction.

TABLE 3: In-hospital outcomes

Variable	Prior MI n = 1,508 (41.6%)	No Prior MI n = 1,781 (%)	p-value
Death	49 (3.2)	90 (4.3)	0.12
Cardiac arrest	38 (2.5)	91 (4.3)	0.004
CHF/Pulmonary edema	133 (8.8)	209 (9.9)	0.29
Cardiogenic shock	59 (3.9)	121 (5.7)	0.01
Atrial fibrillation/flutter	91 (6.1)	154 (7.3)	0.15
Sustained VF/VT	45 (3.0)	87 (4.1)	0.07
AV block	14 (0.9)	29 (1.4)	0.22
MI/Reinfarction	79 (5.3)	101 (4.8)	0.52
Stroke	8 (0.5)	20 (0.9)	0.16
Major bleeding	90 (6.0)	116 (5.5)	0.53
MACE	127 (8.4)	192 (9.1)	0.5

Abbreviations: AV = atrio-ventricular; CHF = congestive heart failure; MACE = major acute coronary events; MI = myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.

similar to those without a prior MI. Third, patients in this group were more likely to be discharged on statins and were more likely to adhere to their ACE inhibitors 6 mo postdischarge. Nevertheless, the rates of death, recurrent MI, and MACE at 6 mo postdischarge remained significantly higher in this group.

As expected, patients with a prior history of MI had higher rates of cardiovascular risk factors and were more likely to be on medications for these at the time of their hospital presentation (Table 1, Figure 1). Encouragingly, they had more favorable systolic blood pressures and lipid profiles during their recurrent ACS presentation. However, patients in this group had higher levels of fasting blood glucose levels and lower left ventricular EFs at presentation. There were no significant differences in the use of in-hospital aspirin, β-blockers, or ACE inhibitors among

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20356

TABLE 4: Follow-up outcomes

Variable	Prior MI n = 1,508 (41.6%)	No Prior MI n = 2,116 (58.4%)	p-value
1 mo after discharge			
Death	28 (2.1%)	30 (1.7%)	0.32
6 mo after discharge			
Death	105 (8.0%)	81 (4.5%)	<0.0001
MI	91 (10.0%)	66 (5.1%)	<0.0001
Stroke	13 (1.2%)	18 (1.1%)	0.89
Unscheduled revascularization	80 (7.7%)	101 (6.8%)	0.38
MACE	199 (15.0%)	158 (8.6%)	<0.0001

Abbreviations: MACE = major adverse cardiac event; MI = myocardial infarction.

the 2 groups. However, the use of in-hospital thienopyridines, glycoprotein IIb/IIIa inhibitors, antithrombotics, and coronary revascularization was significantly less in patients with a prior MI. While this may be attributed to differences in their hospital presentation, observations from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation (CRUSADE) registry suggest that the use of guideline-based acute recommendations and invasive cardiac procedures is lower in higher risk presenters with non-ST-elevation ACS.[1]

Interestingly, this group of patients, which was clearly at a higher risk, did not have worse in-hospital outcomes during their recurrent ACS episode. Moreover, the rates of postdischarge death did not differ significantly between the 2 groups, even in the immediate postdischarge period (Table 4, Figure 4). While this may be due to our analysis being underpowered to detect this difference, this finding is consistent with a previous report by the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial investigators who showed that the history of prior MI does not appear to affect outcomes in ACS for up to 1 mo after hospital discharge.[2] In-hospital and short-term outcomes in ACS have been previously shown to be determined less by the patient's risk factors and chronic medication use, and more by the clinical features of their presentation, such as Killip class, age, blood pressure, heart rate, elevations in biomarkers, creatinine level, ST-segment deviation, heart rate, and the resulting immediate therapies provided to them.[3,4,5] However, at 6 mo postdischarge, patients with a prior history of an MI who presented with a recurrent ACS were clearly more likely to experience death and recurrent MI than those without a prior MI. Rates of MACE at 6 mo remained higher in this group, even after a multivariate adjustment for underlying comorbidities. This occurred in spite of an

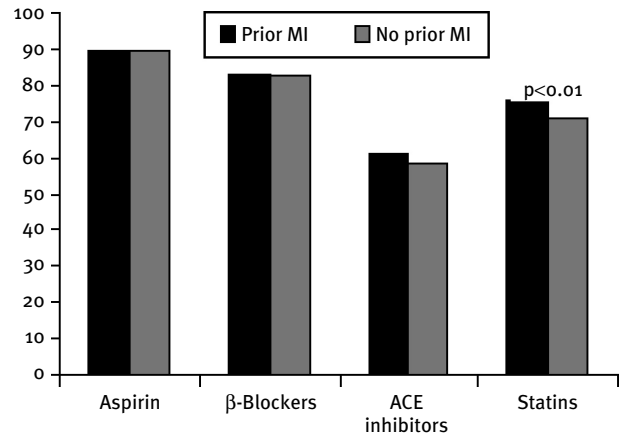

Figure 2: Discharge medications.

increased number of patients in this higher risk group being discharged on statins (Figure 2), and adhering to their ACE inhibitors and β-blockers at 6 mo postdischarge (Figure 2). A lower left ventricular EF in this group, as previously established, remained an independent predictor of worse 6 mo outcomes in the prior MI group.[6,7,8] However, the history of a prior MI predicted worse 6 mo outcomes even after adjusting for EF.

Interestingly, patients with no prior coronary artery disease (but no prior MI) had better follow-up survival as compared with those with prior MI in spite of no in-hospital differences in the use of aspirin, statins, β-blockers, and ACE inhibitors during their ACS. We suspect that the explanation for our findings include both a greater burden of coronary artery disease and greater progression, despite increased efforts at secondary prevention by the physician as well as patients. However, in our study many patients who had a prior MI did not appear to be on optimal medical therapy

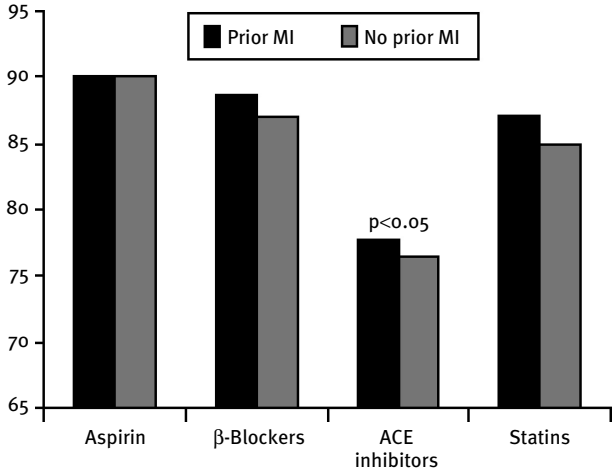

Figure 3: Six-mo medication adherence.

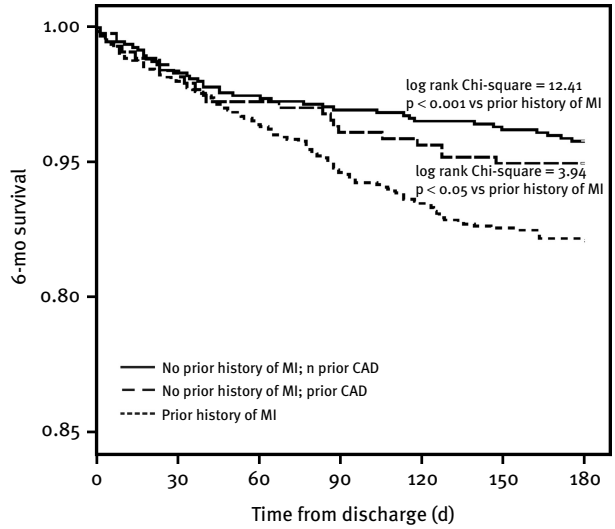

Figure 4: Unadjusted postdischarge survival. *Abbreviation:* CAD = coronary artery disease.

(aspirin, statins, β-blockers, and ACE inhibitors) at the time of presentation with their recurrent ACS (Figure 1). This may explain part of the reason so many of these patients present with a recurrent ACS. Additionally, these higher risk patients were less likely to receive antithrombotic or antiplatelet agents during their hospitalization. This did not seem to be responsible for their worse follow-up outcomes on multivariate analysis. However, coronary revascularization procedures (PCI and CABG) were also significantly underused in this group and this seems to be partly responsible for their worse outcomes at 6 mo. We speculate that the subsequent additive loss of myocardium in a heart that is already previously damaged may be the reason why these patients did poorly upon discharge.

Certainly, greater emphasis must be placed on long-term prevention of a recurrent ACS by ensuring timely initiation and subsequent adherence to optimal lifestyle and evidence-based pharmacologic therapies after the first MI. Recent studies have shown that risk stratification after ACS remains suboptimal, regardless of presenting characteristics.[9,10] Perhaps identification of higher risk patients with recurrent ACS and implementation of in-hospital guideline-based care, as well as multifaceted postdischarge interventions, may improve their long-term outcomes.

Limitations

Our study should be interpreted in the context of several limitations. The study was retrospective and lacked data on the type, management, and timing of the previous MI. Further, because of the small sample size we were unable to adjust for other comorbid conditions, such as anemia, chronic liver diseases, and pulmonary diseases, which may have influenced mortality in our study population. Moreover, other secondary prevention measures, such as diet, exercise, and smoking cessation, could not be compared in our database and may be partly responsible for this difference. The results of our study should therefore be interpreted as generating a hypothesis, and needs to be confirmed in larger registries and with clinical trials.

Conclusion

Our data reflect that patients with previous MI represent approximately 40% of those coming into our medical center with an ACS. These patients have similar in-hospital outcomes as those presenting without a prior MI history, but have substantially higher rates of recurrent events by 6 mo. Increased efforts must be directed at prevention of recurrent ACS, and better risk stratification and long-term medical management with more intense follow-up of these patients may improve their overall outcomes.

Acknowledgements

The study was partially supported by an unrestricted grant from the Mardigian Fund. The sponsor had no role in design, data analysis or interpretation, or manuscript preparation.

References

1. Roe MT, Peterson ED, Newby LK, Chen AY, Pollack CV Jr, et al.: The influence of risk status on guideline adherence for patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2006;151(6):1205–1213
2. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, et al.: Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9,461 patients. The PURSUIT Investigators. *Circulation* 2000;101(22):2557–2567
3. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, et al.: A validated prediction model for all forms of acute coronary syndrome. *JAMA* 2004;291:2727–2733

4. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle Ka, et al.: Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163(19):2345–2353
5. Szygula-Jurkiewicz B, Wojnicz R, Trzeciak P, Niklewski T, Zembala M, et al.: Clinical characteristics, in-hospital outcomes and predictors of in-hospital mortality in patients with acute coronary syndromes without persistent ST-segment elevation assigned to early invasive treatment strategy. *Przegl Lek* 2005;62(5): 265–269
6. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR Jr, et al.: Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. *Circulation* 1994;90:2645–2657
7. Brezinski D, Stone PH, Muller JE, Tofler GH, Davis V, et al.: Prognostic significance of the Karnofsky performance status score in patients with acute myocardial infarction: Comparison with the left ventricular ejection fraction and the exercise treadmill test performance. The MILIS study group. *Am Heart J* 1991;121:1374–1381
8. Bosch X, Theroux P; Left ventricular ejection fraction to predict early mortality in patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2005;150(2):215–220
9. Devlin G, Anderson FA, Heald S, Lopez-Sendon J, Avezum A, et al.: Management and outcomes of lower risk patients presenting with acute coronary syndromes in a multinational observational registry. *Heart* 2005;91(11):1394–1399
10. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, et al.: Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: Results from an international trial of 41,021 patients. *Circulation* 1995;91:1659–1668
11. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, et al.: A validated prediction model for all forms of acute coronary syndrome: Estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;291:2727–2733