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Characteristics and Outcome in Acute Coronary Syndrome Patients with and without Established Modifiable Cardiovascular Risk Factors: Insights from the Nationwide AMIS Plus Registry 1997–2010

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Key Words
Acute coronary syndrome · Cerebrovascular events · Myocardial infarction · Re-infarction · Risk factors

Abstract
Objectives: Little is known about patients without known modifiable risk factors presenting initially with acute coronary syndrome (ACS). This study assessed baseline characteristics and outcomes of ACS patients with and without the known modifiable risk factors arterial hypertension, dyslipidemia, obesity, smoking or diabetes. ***Methods:*** All ACS patients enrolled in the AMIS Plus Registry between 1997 and 2010 were analyzed until hospital discharge; a subgroup was re-assessed at the 1-year follow-up. Outcome measures were in-hospital mortality and major adverse cardiac or cerebrovascular events (MACCE) defined as a composite outcome of mortality, re-infarction and cerebrovascular events. ***Results:*** Of 33,306 patients, 2,125 (6.4%) had none of these modifiable risk factors. They were older (males), had less moderate or severe comorbidities and were more frequently in Killip class I on admission. Treatment of ACS patients with or without modifiable risk factors was similar with regard to interventional therapies and use of antiplatelet agents. In-hospital mortality was lower in patients without modifiable risk factors but in-hospital MACCE and 1-year survival was similar. ***Conclusion:*** Lack of modifiable risk factors was an independent predictor of lower in-hospital mortality but not of MACCE in patients who presented with ACS.

Introduction

Cardiovascular disease is the leading cause of death in the Western world and accounts for around 40% of all deaths in Switzerland [1].

The INTERHEART study, a case-control study which was carried out in 52 countries, identified nine potentially modifiable risk factors associated with myocardial infarction (MI) in both male and female patients and in all age groups: among these, abnormal lipid levels, smok-

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ing, hypertension, diabetes and abdominal obesity were found to be the most important modifiable risk factors for MI [2, 3]. However, several previous studies have shown that patients with chest pain may often lack modifiable risk factors [4–6] and some reports have suggested that the presence or absence of modifiable risk factors for coronary artery disease was not clinically helpful in the diagnosis or exclusion of acute MI (AMI) in the emergency department [4]. For the patients presenting to the emergency department, modifiable risk factors do not increase the risk of acute ischemia and convey minimal risk for an acute cardiac event [6, 7]. Use of the cardiac modifiable risk factor burden, defined as the number of risk factors present, is not appropriate for defining the probability of patients with an acute coronary syndrome (ACS), especially in those >40 years [4, 5]. Body et al. [4] reported that 12.2% of emergency room patients with chest pain but without modifiable risk factors had a final diagnosis of AMI.

Little is known about patients without known modifiable risk factors who presented with ACS. Therefore, the aim of this study was to assess baseline characteristics and outcome in patients without known modifiable risk factors admitted with ACS in Switzerland between 1997 and 2010, and compare them to patients with one or more risk factor(s).

Patients and Methods

The AMIS (Acute Myocardial Infarction in Switzerland) Plus project, which was started in 1997, is an ongoing nationwide prospective registry of patients admitted with ACS to hospitals in Switzerland. Details have been published previously [8–11]. Participating centers, ranging from community care institutions to large tertiary care facilities, provide blinded data for each patient through a standardized internet- or paper-based questionnaire. These are checked for plausibility and consistency by the AMIS Plus Data Center in the Institute of Social and Preventive Medicine at the University of Zurich. The registry was approved by the Supra-Regional Ethics Committee for Clinical Studies and the Swiss Board for Data Security, as well as by the cantonal ethics commissions. The AMIS Plus project is officially supported by the Swiss Societies of Cardiology, Internal Medicine and Intensive Care Medicine.

For each patient, a total of 230 items are collected by each hospital, including medical history, co-morbidities, known cardiovascular risk factors, clinical presentation, out-of-hospital management, early in-hospital management, reperfusion therapy, hospital course, diagnostic tests (used or planned), length of hospitalization, discharge medication and discharge destination. Patients are enrolled in the registry on the basis of their final diagnosis. The AMIS Plus registry included all patients with ACS: AMI defined by characteristic symptoms and/or ECG changes and cardiac marker elevation (either total creatine kinase or creatine kinase MB fraction at least twice the upper limit of normal or troponin I or T above individual hospital cutoff levels for MI), and unstable angina (symptoms or ECG changes compatible with ACS and cardiac marker levels lower than cutoff or normal levels) according to the new universal definition of MI [12–14]. Patients were also categorized as having ST-segment elevation MI (STEMI) or non-STEMI (NSTEMI) based on initial ECG findings. Classification of STEMI included evidence of ACS as described above and ST-segment elevation and/or new left bundle branch block on the initial ECG. NSTEMI included patients with ischemic symptoms, ST-segment depression or T-wave abnormalities in the absence of ST-elevation on the initial ECG.

The following modifiable risk factors were included in this study: smoking, dyslipidemia, hypertension, diabetes and obesity. Modifiable risk factors were documented in the patient's medical history: dyslipidemia (defined as a history of dyslipidemia if diagnosed and/or treated by a physician), arterial hypertension (defined as a history of arterial hypertension diagnosed and/or treated by a physician and/or documented blood pressure >140/90 mm Hg) and diabetes (defined as a history of diabetes, regardless of duration of disease if the patient had been treated for diabetes and was previously diagnosed by a physician) [15]. Documentation of the modifiable risk factors provided by the local physicians was accepted as stated. A patient was defined as obese if the body mass index was ≥ 30 kg/m^2 and as smoking if the patient was smoking at the time of the cardiovascular event. In 2005, a question was added to the questionnaire asking patients whether there was a family history of premature heart disease in a first-degree relative <60 years of age. Co-morbidities of the patients were assessed using the Charlson comorbidity index [16].

The primary outcome measure was in-hospital mortality. Secondary outcome measures were the rates of in-hospital major adverse cardiac or cerebrovascular events (MACCE) defined as a composite outcome of mortality, re-infarction and cerebrovascular event as well as 1-year mortality.

Patient Selection

The present analysis included all ACS patients enrolled in AMIS Plus between January 1, 1997, and December 31, 2010. ACS patients were classified as having no modifiable risk factors if they did not have any of the classic modifiable cardiovascular risk factors (arterial hypertension, dyslipidemia, obesity, smoking or diabetes). Furthermore, since 2005, 3- and 12-month follow-ups were carried out with patients who gave their informed consent. This subgroup of AMIS Plus patients was also analyzed in this study.

Statistical Analysis

The results are presented as percentages for categorical variables and analyzed using the non-parametric Pearson χ^2 test or Fisher's exact test as appropriate. Continuous normally distributed variables are expressed as means ± SD and compared using Student's two-tailed unpaired t test. Continuous non-normally distributed variables are expressed as medians and interquartile ranges and analyzed using the Mann-Whitney U test. A probability value of $p < 0.05$ was considered statistically significant. A multivariate logistic regression model based on backward logistic regression methodology was used to determine in-hospital mortality predictors from the following set of variables: age, gen-

der, systolic blood pressure, heart rate, Killip class >2 and the Charlson comorbidity index. Separate univariate logistical models were first fitted for each variable and then backward elimination with a significance level of 0.05 was performed. Odds ratios (OR) were simultaneously adjusted for all other predictors included in the multivariate logistic regression model. SPSS (version 19; SPSS, Chicago, Ill., USA) was used for all statistical analyses.

Results

Between 1997 and 2010, a total of 35,284 patients with a final discharge diagnosis of ACS from 77 Swiss hospitals were enrolled in the AMIS Plus Registry. Of these patients, 51.2% were treated in large teaching centers and 48.8% in smaller regional hospitals. Because of incomplete data on modifiable risk factors, 1,978 (5.6%) patients were excluded from the present analysis. Of the remaining 33,306 patients, 31,181 (93.6%) had one or more modifiable risk factors, and 2,125 (6.4%) had none of the modifiable risk factors (smoking, dyslipidemia, hypertension, diabetes and obesity; fig. 1). Although the annual rate of ACS patients without known modifiable risk factors fluctuated between 4.5 and 7.6% throughout the 14-year period, these fluctuations were not significant ($p = 0.13$; fig. 2). ACS patients without modifiable risk factors were more likely to have STEMI than patients with one or more modifiable risk factors (63.8 vs. 56.9%; $p < 0.001$) and more often presented without prior known coronary artery disease (77.6 vs. 60.2%; $p < 0.001$).

Baseline characteristics of the ACS patients according to the presence of the modifiable risk factors are reported in table 1. ACS patients without modifiable risk factors were on average 2.4 years older (due to males) than those with one or more modifiable risk factors and had less moderate to severe comorbidities (Charlson comorbidity index ≥ 2) and were more frequently in Killip class I on admission. They presented with comparable delay after symptom onset and pain, but they had less frequently dyspnea on admission. For the 14,397 patients for whom this information was available, a positive family history was reported by 26.7% of the patients without modifiable risk factors and by 34.5% of patients with modifiable risk factors ($p < 0.001$).

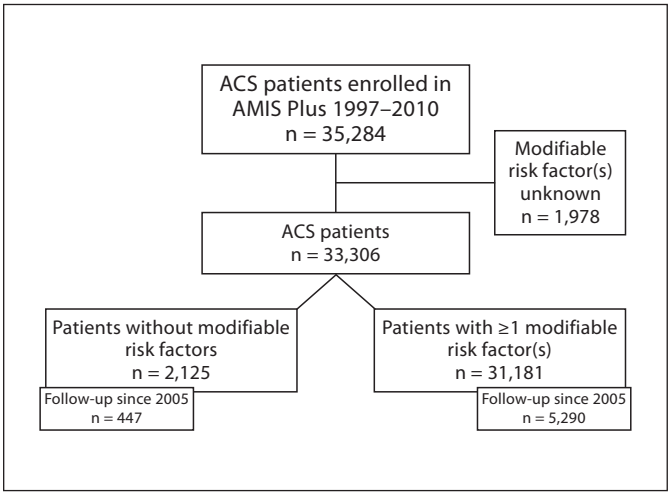

Fig. 1. Flow chart of inclusion data. Modifiable risk factors were smoking, hypertension, dyslipidemia, diabetes and/or obesity.

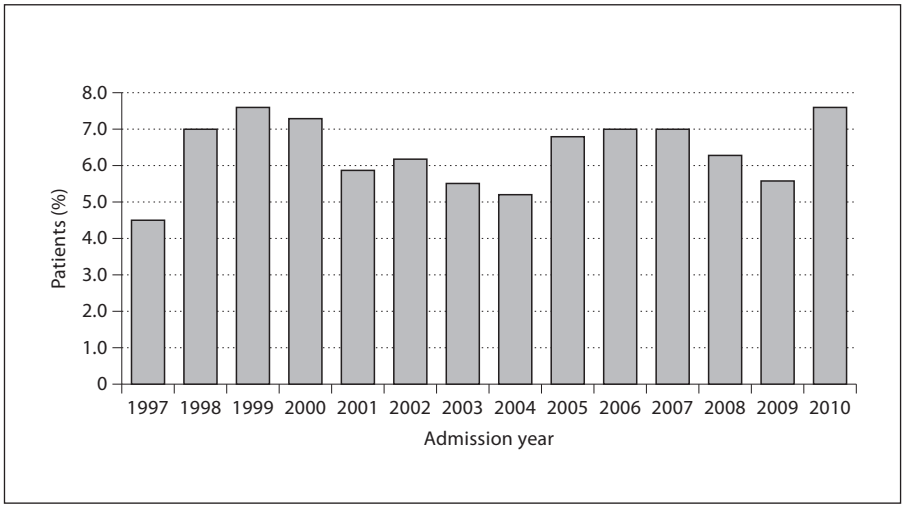

Fig. 2. Percentage of ACS patients without modifiable risk factors according to admission year.

Table 1. Baseline characteristics of the ACS patients (n = 33,306)

	ACS patients without modifiable factors	ACS patients with ≥1 modifiable risk factor	p value
Patients	2,125	31,181	
Males	1,563 (74%)	22,683 (73%)	0.43
Age, years (mean ± SD)			
All	67.3 ± 13.0	65.7 ± 13.2	<0.001
Males	65.9 ± 12.6	63.5 ± 12.9	<0.001
Females	71.3 ± 13.4	71.4 ± 12.3	0.81
Delay, h:min			
Median	3:50	4:00	0.32
Interquartile range	1:55 to 11:30	2:00 to 11:45	
Resuscitation prior to admission			
Cardiopulmonary resuscitation	69/2,082 (3.3%)	1,015/30,415 (3.3%)	0.99
Cardioversion/defibrillation	71/2,082 (3.4%)	1,024/30,284 (3.4%)	0.96
Symptoms on admission			
Pain	1,793/2,088 (85.9%)	25,660/30,324 (84.6%)	0.13
Dyspnea	488/2,023 (24.1%)	7,959/28,375 (28.0%)	<0.001
Vital signs on admission (mean ± SD)			
Systolic blood pressure, mm Hg	133 ± 25	137 ± 28	<0.001
Diastolic blood pressure, mm Hg	79 ± 16	80 ± 18	0.003
Heart rate, beats/min	78 ± 21	79 ± 20	0.012
ECG on admission			
ST-elevation	1,304/2,123 (61.4%)	16,542/31,075 (53.2%)	<0.001
ST-depression	463/2,073 (22.3%)	7,737/30,090 (25.7%)	0.001
Left bundle branch block	71/2,122 (3.3%)	1,525/31,058 (4.9%)	0.001
Q-waves	343/2,122 (16.2%)	5,256/31,074 (16.9%)	0.39
Killip class	n = 2,114	n = 30,845	0.004
I	1,717 (81.2%)	24,044 (78.0%)	
II	273 (12.9%)	4,668 (15.1%)	
III	82 (3.9%)	1,312 (4.3%)	
IV	42 (2.0%)	821 (2.7%)	
Type of ACS	n = 2,125	n = 31,109	<0.001
STEMI	1,354 (63.7%)	17,701 (56.9%)	
NSTEMI	688 (32.4%)	11,665 (37.5%)	
UA	83 (3.9%)	1,743 (5.6%)	
History of coronary artery disease	443/1,929 (22.4%)	11,409/28,651 (39.8%)	<0.001
Modifiable risk factors			
Smoking		12,437/29,177 (42.6%)	
Dyslipidemia		17,679/28,059 (63.0%)	
Hypertension		19,669/30,082 (65.4%)	
Diabetes		6,791/30,172 (22.5%)	
Obesity		5,585/25,368 (22.0%)	
Family history (since 2005)	280/1,048 (26.7%)	4,611/13,349 (34.5%)	<0.001
Number of risk factors (mean ± SD)	0	2.1 ± 0.9	<0.001
Charlson comorbidity index ≥2 (since 2002)	202/1,563 (12.9%)	5,709/22,834 (25.0%)	<0.001

Unless indicated otherwise, numbers of patients are shown. p values for Killip class and ACS type indicate trends.

Treatment of ACS patients with or without modifiable risk factors was similar with regard to interventional therapies and use of antiplatelet agents such as thienopyridine and GPIIb/IIIa inhibitors. Patients with modifiable risk factors were more likely to receive angiotensin-converting enzyme inhibitors and/or angiotensin II antagonists and statins but less likely to receive aspirin and heparins (table 2).

Complications and overall outcome were comparable between these two patient groups (fig. 3). Crude in-hospi-

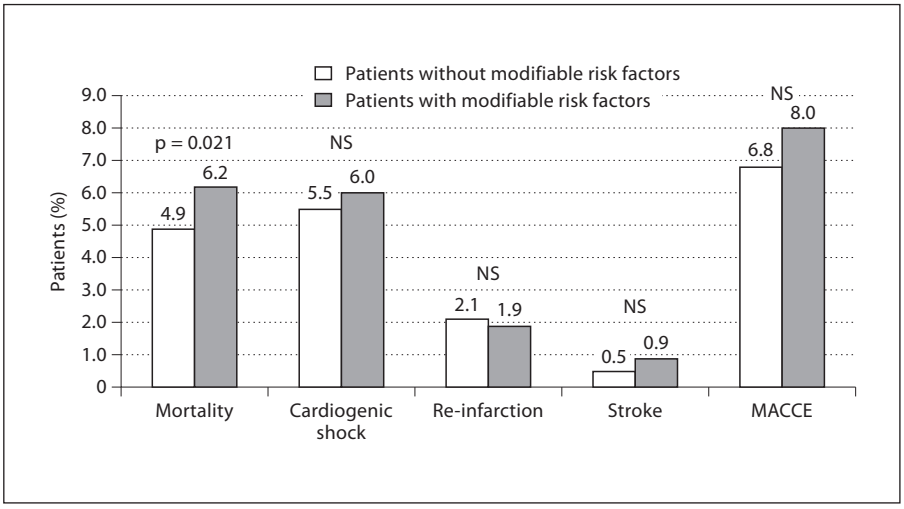

Fig. 3. In-hospital outcome of ACS patients. Modifiable risk factors were smoking, hypertension, dyslipidemia, diabetes and/or obesity. NS = Not significant.

Table 2. Pharmacological treatment and reperfusion according to modifiable risk factors (n = 33,306)

	ACS patients without modifiable risk factors	ACS patients with ≥1 modifiable risk factor	p value
Patients	2,125	31,181	
Immediate drug therapy			
Aspirin	2,045/2,120 (96.3%)	29,385/31,069 (94.6%)	0.001
Thienopyridine	1,272/2,115 (60.1%)	18,282/30,917 (59.1%)	0.37
GPIIb/IIIa antagonist	5,935/1,817 (32.7%)	8,089/26,262 (30.8%)	0.08
Heparin	1,928/2,118 (91.0%)	27,556/31,009 (88.9%)	0.002
β-Blocker	1,426/2,109 (67.6%)	21,414/30,891 (69.3%)	0.10
ACEI/AT antagonist	862/2,109 (41.3%)	15,226/30,725 (49.6%)	<0.001
Statin	1,158/1,606 (72.1%)	17,574/23,505 (74.8%)	0.019
Reperfusion			
Any PCI (all patients)	1,326/1,853 (71.6%)	19,223/27,018 (71.1%)	0.73
Reperfusion in STEMI			
Thrombolysis	246/1,354 (18.2%)	3,089/17,671 (17.5%)	0.53
Primary PCI	741/1,354 (54.7%)	9,715/17,696 (54.9%)	0.91

Modifiable risk factors were smoking, dyslipidemia, hypertension, diabetes and obesity. Unless indicated otherwise, numbers of patients are shown. ACEI = Angiotensin-converting enzyme inhibitor; AT = angiotensin II receptor; PCI = percutaneous coronary intervention.

tal mortality was lower in patients without modifiable risk factors (OR 0.79; 95% confidence interval, CI, 0.65–0.96, p = 0.021). However, the risk for MACCE was similar in the two groups (unadjusted OR 0.85; 95% CI 0.71–1.01, p = 0.059). Lack of the modifiable risk factors smoking, dyslipidemia, hypertension, diabetes and obesity in patients admitted with ACS was an independent predictor of lower in-hospital mortality, but failed to reach a statistically significant level as a predictor of MACCE (table 3).

After the acute event, 5,737 ACS patients were followed up after a median of 384 days (interquartile range 370–404 days). A total of 3.3% of patients with one or several and 2.9% of patients without any of the modifiable risk factors studied died during the follow-up period. The adjusted OR for mortality for patients without modifiable risk factors was 0.82 (95% CI 0.46–1.46; p = 0.49).

Table 3. Independent predictors of in-hospital mortality and in-hospital MACCE

	In-hospital mortality			In-hospital MACCE		
	OR	95% CI	p	OR	95% CI	p
No modifiable risk factors	0.69	0.52–0.92	0.012	0.79	0.61–1.02	0.065
Age per additional year	1.07	1.06–1.07	<0.001	1.05	1.05–1.06	<0.001
Female gender	1.04	0.91–1.19	0.58	1.09	0.96–1.23	0.17
Killip class >II	4.54	3.89–5.30	<0.001	4.13	3.57–4.77	<0.001
Charlson comorbidity index >2	1.60	1.40–1.83	<0.001	1.62	1.44–1.83	<0.001
Systolic blood pressure (per mm Hg)	0.98	0.97–0.98	<0.001	0.98	0.98–0.98	<0.001
Heart rate (per beat/min)	1.01	1.01–1.02	<0.001	1.01	1.00–1.01	<0.001

Modifiable risk factors were smoking, dyslipidemia, hypertension, diabetes and obesity.

Discussion

In this study, 6.4% of the patients with a final diagnosis of ACS had none of the classic modifiable cardiac risk factors. This is in accordance with the results from Body et al. [4] who found that 7.4% of patients diagnosed with AMI in the emergency department had no modifiable risk factors.

The pathophysiology of the atherosclerotic process has been a topic in cardiovascular research and recent results showed that even in the absence of significant coronary artery disease and conventional modifiable risk factors, chronic inflammation may be associated with severe abnormalities of the coronary microcirculation [17, 18]. In previous reports, the coronary microcirculation plays a crucial role in the outcome of patients with STEMI [19].

For risk assessment in individual patients, several algorithms have been developed, but their implementation in clinical practice is poor [20].

The absence of any modifiable risk factors carried a negative likelihood ratio of 0.61 for the diagnosis of MI [4]. However, a lack of modifiable risk factors for coronary artery disease should not prevent physicians from seeking to rule out acute MI.

Assessing a patient's cardiovascular risk is one of the important goals and may help to target individual patients who are asymptomatic but at sufficiently high risk for the development of cardiovascular disease and could therefore benefit from preventive interventions [21]. The risk of atherosclerotic cardiovascular disease for those with a severe modifiable risk factor burden has been reported to be as high as 52% for men and 31% for women at 50 years of age [22].

In this study, patients hospitalized for ACS without one of the modifiable risk factors recorded in their chart did not differ in outcome from patients with known modifiable risk factors. Although patients without modifiable risk factors were older and more frequently admitted for STEMI than patients with one or more modifiable risk factors, their in-hospital mortality was statistically significantly lower. However, mortality in the sub-group of patients followed for a median of 384 days after the initial ACS was similar for patients with or without these risk factors. Hierarchy and impact of clinical risk factors on admission to hospital, such as age and hemodynamic parameters, played a role in both groups with no change in major cardiovascular events, indicating the great importance of clinical risk stratification on admission.

Differences in baseline characteristics between the patients with and without established modifiable cardiovascular risk factors were assessed regarding the presence of moderate or severe comorbidities, dyspnea on admission and the severity of heart failure expressed in Killip classes. Male patients without modifiable risk factors in this study were on average 2.4 years older than those with one or more modifiable risk factors. It could be speculated that such patients have later onset of an acute ischemic event. In a study by Han et al. [5] in patients presenting to the emergency department with suspected ACS, predominantly in young (<40 years) but not in older patients, the odds of ACS being present increased with increasing number of cardiac risk factors identified. However, in both populations of our study, only 2% of the patients were <40 years of age.

Patients admitted with ACS without known risk factors were treated with an early invasive strategy and with thienopyridine and GPIIb/IIIa inhibitors in a similar way

to those patients with one or more risk factors. Overall outcome in hospital as well as 1-year survival was similar for both patient groups. Studies on the validation of the Thrombolysis in Myocardial Infarction (TIMI) risk score have found that the presence of at least three of the five modifiable risk factors helps to predict the development of early adverse cardiac events [23, 24]. In this study, however, the number of patients followed for approximately 1 year after the initial ACS event was probably too low to show differences in cumulative MACCE or mortality according to the presence or absence of modifiable risk factors.

Limitations

Participation in the AMIS Plus registry is voluntary, the number of hospitals varied and might therefore not be entirely representative of all hospitals in the country despite the permanent involvement of >70% of all hospitals treating patients with ACS. Usual selection bias and confounding parameters of such non-randomized and uncontrolled studies should be taken into account in the interpretation of the data. The possibility of inaccuracies in data entry cannot be totally ruled out and may thus create unrecognized biases. Individual on-site auditing at the participating centers was only performed sporadically up until 2010. Since then, external auditing has been performed regularly. However, the AMIS Plus database is very large and represents hospitals of various sizes and equipment over a substantial period of time. Data questionnaires were always carefully checked by the data management center.

All variables were classified based on the assessment of the local investigators. The modifiable risk factors were treated as dichotomous variables, which is not physiologically accurate due to the spectrum of disease severity. A total of 1,978 patients (5.6%) were excluded from these analyses due to missing data on one or several risk factors. Furthermore, there were no data stating how long the patients had the modifiable risk factors. There were no assessments of clinical eligibility for each drug and thus failure in the use of certain drugs may reflect contraindication for their use.

Conclusion

Patients without any of the classic modifiable risk factors such as smoking, dyslipidemia, obesity, hypertension and diabetes who suffered an ACS were comparable with ACS patients with one or more of these modifiable risk factors. The differences in baseline characteristics showed that ACS patients without modifiable risk factors were less likely to have moderate or severe comorbidities, dyspnea or Killip class II/III on admission, and male patients were significantly older. There were no differences in gender, age of female patients, delay or resuscitation prior to admission. In addition, coronary reperfusion and antiplatelet therapies were similarly used in patients with or without modifiable risk factors. Lack of modifiable risk factors was an independent predictor of lower in-hospital mortality but not an independent predictor of the composite outcome of re-infarction, stroke and death or 1-year survival in patients who presented with ACS.

Appendix

Centers Participating in AMIS Plus 1997–2010

The authors would like to express their gratitude to the teams of the following hospitals (listed in alphabetical order with the name of the local principal investigator): Aarau: Kantonsspital (P. Lessing); Affoltern am Albis: Bezirkspital (F. Hess); Altdorf: Kantonsspital (R. Simon); Altstätten: Kantonales Spital (P.J. Hangartner); Baden: Kantonsspital (U. Hufschmid); Basel: Kantonsspital (P. Hunziker), St. Claraspital (C. Grädel); Bern: Beau-Site Klinik (A. Schönfelder), Inselspital (S. Windecker); Biel: Spitalzentrum (H. Schläpfer); Brig-Glis: Oberwalliser Kreisspital (D. Evéquoz); Bülach: Spital (G. Mang); Burgdorf: Regionalspital Emmental (D. Ryser); Chur: Rätisches Kantons- und Regionalspital (P. Müller), Kreuzspital (R. Jecker); Davos: Spital (W. Kistler); Dornach: Spital (A. Droll/T. Hongler); Einsiedeln: Regionalspital (S. Stäuble); Flawil: Spital (G. Freiwald); Frauenfeld: Kantonsspital (H.P. Schmid); Fribourg: Hôpital cantonal (J.C. Stauffer/S. Cook); Frutigen: Spital (K. Bietenhard); Genève: Hôpitaux universitaires (J.M. Gaspoz/P.F. Keller); Glarus: Kantonsspital (W. Wojtyna); Grenchen: Spital (B. Oertli/R. Schönenberger); Grosshöchstetten: Bezirksspital (C. Simonin); Heiden: Kantonales Spital (R. Waldburger); Herisau: Kantonales Spital (M. Schmidli); Interlaken: Spital (E.M. Weiss); Jegenstorf: Spital (H. Marty); Kreuzlingen: Herzzentrum Bodensee (K. Weber); La Chaux-de-Fonds: Hôpital (H. Zender); Lachen: Regionalspital (C. Steffen); Langnau im Emmental: Regionalspital (A. Hugi); Laufenburg: Gesundheitszentrum Fricktal (J. Frei/E. Koltai); Lugano: Cardiocentro Ticino (G. Pedrazzini); Luzern: Kantonsspital Luzern (P. Erne), Kantonsspital Sursee (S. Yoon), Kantonsspital Wolhusen (M. Peter); Männedorf: Kreisspital (T. Heimes); Martigny: Hôpital régional (B. Jordan); Mendrisio: Ospedale regionale (A. Pagnamenta); Meyrin: Hôpital de la Tour (P. Urban); Monthey: Hôpital du Chablais (P. Feraud); Montreux: Hôpital de Zone (E. Beretta); Moutier: Hôpital du Jura bernois (C. Stettler); Münsingen: Regionales Spital Zentrum (F. Repond); Münsterlingen: Kantonsspital (F. Widmer); Muri: Kreisspital für das Freiamt (C. Heimgartner); Nyon: Groupement hospitalier de l'Ouest lémanique (R. Polikar); Olten: Kantonsspital (S. Bassetti); Rheinfelden: Gesundheitszentrum Fricktal (H.U. Iselin); Rorschach: Kantonales Spital (M. Giger); Samedan: Spital Oberengadin (P. Egger); Sarnen: Kantonsspital Obwalden (T. Kaeslin); Schaffhausen: Kantonsspital

(A. Fischer); Schlieren: Spital Limmattal (T. Herren/B. Caduff); Schwyz: Spital (P. Eichhorn); Scuol: Ospidal d'Engiadina Bassa (C. Neumeier/G. Flury); Solothurn: Bürgerspital Solothurn (A. Grêt/R. Schönenberger); St. Gallen: Kantonsspital (H. Rickli); Tiefenau: Tiefenauspital (P. Loretan); Thun: Spital (U. Stoller); Thusis: Krankenhaus (U.P. Veragut); Uster: Spital (E. Bächli); Uznach: Kantonales Spital (A. Weber); Wädenswil: Schwerpunktspital Zimmerberg-Horgen (B. Federspiel); Walenstadt: Kantonales Spital (D. Schmidt/J. Hellermann); Wetzikon: GZO Spital (M. Graber); Winterthur: Kantonsspital (T. Fischer); Wolhusen: Kantonales Spital (M. Peter); Zofingen: Spital (S. Gasser); Zollikerberg: Spital (R. Fatio); Zug: Kantonsspital (M. Vogt/D. Ramsay); Zürich: Klinik im Park (O. Bertel), Universitätsspital Zürich (M. Maggiorini), Stadtspital Triemli (F. Eberli), Stadtspital Waid (M. Fischler/S. Christen).

Acknowledgments/Conflict of Interest

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Conflict of Interest: The sponsors did not play any role in the design, data collection, analysis or interpretation of the registry.

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