Summary

Background: Acute coronary syndrome (ACS) encompasses ST-segment elevation myocardial infarction (STEMI), non-ST-segment myocardial infarction (NSTEMI) and unstable angina (UA). Although initially a syndrome with a poor prognosis, the advent of acute percutaneous coronary intervention (PCI), with novel stents and anticoagulation therapy, as well as the establishment of acute chest pain units, has to a great extent improved the outcome for patients with ACS.

Objective: The aim of the present study was to assess the 30-day outcome for patients with ACS admitted to the University Hospital of Zurich, and to compare the data, particularly for in-hospital death, with results from various other registries, such as the international Global Registry of Acute Coronary Events (GRACE).

Methods: Between 2007 and 2010, we included consecutive patients with a diagnosis of ACS, examined in-hospital death and major adverse cardiac events (MACE) at 30-days, and compared our results with the esteemed GRACE-Registry.

Results: During these 4 years, 1,787 consecutive patients were diagnosed with ACS. Of these, 55.8% (n = 998) had STEMI, 35.3% (n = 631) NSTEMI and 8.8% (n = 158) UA. In contrast, in the GRACE, out of 11,543 patients 30% (n = 3419) had STEMI, 25% (n = 2893) NSTEMI and 38% (n = 4397) UA. The in-hospital death rate in our study group was 5.7% with STEMI, 2.5% with NSTEMI and 1.3% with UA (p = 0.001). Hospital case fatality rates for STEMI, NSTEMI and UA from the GRACE were 7%, 5% and 3%, respectively (p < 0.01). At the University Hospital of Zurich, myocardial infarction occurred in 1.6%, 0.5% and 1.3% of the STEMI, NSTEMI and UA groups, respectively (p = 0.120), compared with 3% with STEMI and 2% with NSTEMI in the GRACE (data for UA not available). Cardiogenic shock was present in 8.7%, 5.4% and 0.6% (p < 0.001) at the University Hospital of Zurich compared with 7%, 5%, and 2% (p < 0.01) in patients from the GRACE for STEMI, NSTEMI and UA, respectively. Kaplan-Meier survival analysis including MACE revealed that patients with STEMI had the most unfavourable outcome when compared with NSTEMI and UA (p = 0.018).

Conclusions: Our results indicate that patients with ACS from the “real-world” Zurich registry show a higher rate of STEMI and yet lower event rates for adverse cardiovascular complications and in-hospital death when compared with the GRACE, which may be explained by the high standard of healthcare at this institution and implementation of novel therapeutic strategies.

Key words: acute coronary syndrome; outcome; registry

Introduction

Acute coronary syndrome (ACS) constitutes a spectrum of clinical presentations such as ST-segment elevation myocardial infarction (STEMI), non-ST-segment myocardial infarction (NSTEMI) and unstable angina (UA) [1]. ACS is most commonly caused by rupture of a vulnerable atherosclerotic plaques [2], al-
though ulceration, fissuring, erosion or dissection with intraluminal thrombus formation may also be involved. All these presentations are referred to as myocardial infarction (MI) type 1 according to the European Society of Cardiology classification by Thygessen et al. [3]. Advances in medical therapy, and large clinical trials and the guidelines established in consequence, have substantially improved the treatment of ACS over recent past decades. Nonetheless, ACS remains the leading cause of morbidity and mortality worldwide and such cardiovascular disease accounts for 17.3 million deaths per year [4].

Attempts have been made to evaluate hospital management and clinical outcomes using registries in order to monitor and improve the quality of care [5]. It is noteworthy that, in spite of available guidelines [6] on the management of ACS, current practice differs between hospitals and countries; as a consequence, differences in outcomes for patients with ACS between centres and countries have been noted [7]. Furthermore, although randomised clinical trials are the gold standard of evidence-based medicine, the patient population in clinical trials may not truly represent “real life” patients [8]. Indeed, Steg et al. found that ineligible patients in randomised controlled trials had the highest mortality, while eligible participants showed the lowest mortality [9]. Similarly, Bosch and colleagues reported that patients who were excluded from a randomised trial assessing the outcome of NSTEMI had a worse risk profile, more comorbidities and a nearly three-fold higher mortality rate compared with eligible patients [10]. Consequently, registries are of significant importance in outcome evaluation of ACS.

The Global Registry of Acute Coronary Events (GRACE) is a prospective, multinational study of patients with ACS which was launched in 1999, and which currently includes 30 participating countries and over 100,000 patients [11, 12]. However, even in such registries, the real world may not be fully reflected, as patients with shock are often not included.

Here, we present the acute and short-term outcome for all consecutive patients with ACS enrolled in the Zurich-Acute Coronary Syndrome Registry (Z-ACS), within a 4-year period. Thus, this patient cohort truly represents the real-world population seen in an urban tertiary centre, including sudden-death survivors and patients in cardiogenic shock. Furthermore, we compared in-hospital death and major adverse cardiovascular events (MACE) at 30 days, as outcome measures of this single-centre registry with those of the international GRACE registry.

**Methods**

**Data collection**

From 2007 to 2010, we included consecutive patients who were admitted with a diagnosis of ACS to the University Hospital of Zurich and who underwent coronary angiography. As at this institution thrombolysis has been abandoned and all ACS patients are referred for angiography, this represents the true ACS population. All patients enrolled in this registry were at least 18 years of age. The time period of the inclusion of patients in our registry covered three redefinitions of myocardial infarction [13, 14]. However, because of the retrospective nature of the study we used the current definition of myocardial infarction of 2012 [15]. Retrospectively, data were collected using KISIM® (Klinik Informations System Innere Medizin), an in-hospital software system. The data included baseline characteristics such as cardiovascular risk factors, patients’ cardiovascular medication on admission and laboratory values. Coronary artery disease (CAD) was classified as single vessel or multivessel disease, and the culprit lesion was documented and categorised in the following manner: left main artery, left ascending artery, circumflex artery, right coronary artery or bypass graft disease. Furthermore we recorded haemodynamic parameters such as blood pressure, heart rate, left ventricular enddiastolic pressure and left ventricular ejection fraction. Data were retrospectively analysed as part of the quality control at the University Hospital of Zürich.

**Short-term follow-up**

The occurrence of MACE, including in-hospital death, revascularization, coronary artery bypass graft (CABG), nonfatal myocardial infarction, stent thrombosis, cardiogenic shock, stroke and septic shock, was assessed at the 30-day follow-up. ACS was defined as typical angina, elevated cardiac enzymes and/or typical ECG changes. Stroke was recorded after the case was reviewed independently by a neurologist and was defined as focal neurologic deficits lasting longer than 24 hours with a clinically relevant lesion on brain imaging. The second endpoint included in-hospital death.

**Statistical analysis**

Baseline characteristics and outcomes for the three patient groups were summarised using frequency tables with count and proportion for each category, or mean with the standard deviation (SD) or standard error of the mean (SEM) as appropriate. Differences between groups were tested using Chi-square or Fisher’s exact test for nominal endpoints, or the Kruskal-Wallis tests for continuous endpoints. Survival analysis for the three groups STEMI, NSTEMI and UA at 30-day follow-up was performed using the Kaplan Meier-Method for the combined endpoint of MACE. The curves were compared using the logrank-sum test. SPSS software (Chicago, Illinois; Version 20.0) was used for all statistical analysis. A p-value <0.05 was considered as significant. Data are shown as percentages.
Results

Baseline characteristics

A total of 1,787 patients were included in the Zurich-Acute Coronary Syndromes Registry. Among them, 55.8% (n = 998) had STEMI, 35.3% (n = 631) NSTEMI and 8.8% (n = 158) had UA. The baseline demographic and clinical characteristics are given in table 1.

Patients with STEMI (mean age ± SD = 62.4 ± 12.5 years) were younger than patients with NSTEMI (65.3 ± 12.2 years) and UA (64.3 ± 12.3 years) (p <0.001) (table 1 and fig. 1), and had fewer cardiovascular risk factors than the patients with NSTEMI and UA. Only smoking was more prevalent in patients with STEMI. A significant difference in cardiovascular risk factors was observed for the three groups of ACS, except for obesity (p = 0.831) and a known family history for ACS (p = 0.053) (table 1).

Of note, patients with UA were pretreated more aggressively, with preventive medication such as aspirin, beta-blockers and statins, compared to patients with NSTEMI and STEMI. The proportion of patients receiving aspirin was 59.5% (n = 94) in patients with UA, 43.9% (n = 277) in the NSTEMI group and 26.6% (n = 265) in the STEMI group (p <0.001). Similarly, pretreatment with beta-blockers was more common among patients with UA (43.7%; n = 69) when compared with those with NSTEMI (35.2%; n = 222) or STEMI (20.0%, n = 200) (p <0.001). Finally, patients with UA were also more likely to take statins (51.3%; n = 81) than those with NSTEMI (37.4%, n = 236) or STEMI (19.5%, n = 195) (p <0.001). All cardiovascular medications taken prior to admission are summarised in table 1.

After admission, patients with STEMI were more frequently treated with vasopressors (11.0%, n = 110) compared with those with NSTEMI (4.9%, n = 31) or UA (1.3%, n = 2) (p <0.001), and were more often intubated, resuscitated or treated with glycoprotein IIb/
BNP) values on admission and peak values were higher in the NSTEMI group compared with the STEMI and UA patients (p <0.001). All laboratory values are shown in table 3.

Short-term follow-up
The in-hospital mortality rate was 5.7% (n = 57) in the STEMI group, 2.5% (n = 16) in the NSTEMI group and lowest at 1.3% (n = 2) with UA (p = 0.001, fig. 2).

Unplanned revascularisations after discharge were more common in patients with UA (5.7%, n = 9) than in those with NSTEMI (2.2%, n = 14) or STEMI (2.5%, n = 25) (p = 0.047). CABG was not different between the three groups (p-value not significant).

No difference was found in re-infarction rates between the three groups (STEMI 1.6%, n = 16; NSTEMI 0.5%, n = 3; UA 1.3%; n = 2; p = 0.120). Stent thrombosis occurred in 1.1% (n = 11) of the STEMI group, and 0.2% (n = 1) of the NSTEMI group and 0.6% (n = 1) with UA (p = 0.091).

Cardiogenic shock was significantly more common in the STEMI group (8.7%, n = 87) than with NSTEMI (5.4%, n = 34) or UA (0.6%, n = 1) (p <0.001). Cardiac

IIIa-inhibitors. In addition, an intra-aortic balloon pump was implanted substantially more often in STEMI patients (12.6%, n = 126) than in those with NSTEMI (8.1%, n = 51) or UA (2.5%, n = 4) (p <0.001). These findings were mirrored by the haemodynamic parameters: patients with STEMI exhibited the lowest systolic blood pressure (p <0.001) and highest heart rate (p = 0.001). This was in line with the clinical finding that 13.9% (n = 139) of patients with STEMI were in an unstable condition, compared with only 6.8% (n = 43) of the NSTEMI and 1.3% (n = 2) of the UA patients (p <0.001). Table 2 summarises the acute medication, emergency procedures, haemodynamic parameters and findings at coronary angiography.

Patients with STEMI exhibited the highest plasma total cholesterol levels (p = 0.017) and white blood cell counts on admission (p <0.001). C-reactive protein (CRP) on admission was highest in the NSTEMI group, whereas patients with STEMI had the highest peak values. Troponin, creatinine kinase (CK), CK-MB and plasma myoglobin levels were highest in the STEMI group, reflecting more extensive myocardial damage. N-terminales probrain natriuretic peptide (NT-pro-BNP) values on admission and peak values were higher in the NSTEMI group compared with the STEMI and UA patients (p <0.001). All laboratory values are shown in table 3.

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tamponade was rare and numerically more common in the STEMI group (0.6%, n = 6) but was not statistically different from the other groups (0.2% (n = 1) with NSTEMI and 0% (n = 0) with UA). For septic shock (p = 0.513) and stroke (p = 0.612), there was no statistically significant difference between the three groups (fig. 3).

Table 3
Laboratory values (mean ± standard deviation).

<table>
<thead>
<tr>
<th></th>
<th>STEMI (55.8%)</th>
<th>NSTEMI (35.3%)</th>
<th>UA (8.8%)</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>4.9 (± 0.05)</td>
<td>4.7 (± 0.07)</td>
<td>4.6 (± 0.14)</td>
<td>4.8 (± 0.04)</td>
<td>0.017</td>
</tr>
<tr>
<td>HDL</td>
<td>1.1 (± 0.02)</td>
<td>1.1 (± 0.02)</td>
<td>1.1 (± 0.05)</td>
<td>1.1 (± 0.01)</td>
<td>0.838</td>
</tr>
<tr>
<td>LDL</td>
<td>3.3 (± 0.06)</td>
<td>3.0 (± 0.07)</td>
<td>2.8 (± 0.15)</td>
<td>3.1 (± 0.04)</td>
<td>0.002</td>
</tr>
<tr>
<td>TG</td>
<td>1.4 (± 0.04)</td>
<td>1.5 (± 0.06)</td>
<td>1.5 (± 0.10)</td>
<td>1.4 (± 0.03)</td>
<td>0.014</td>
</tr>
<tr>
<td>CRP on admission</td>
<td>15.7 (± 1.25)</td>
<td>18.3 (± 1.66)</td>
<td>9.5 (± 2.04)</td>
<td>16 (± 0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP maximum</td>
<td>60.8 (± 3.17)</td>
<td>58.7 (± 3.94)</td>
<td>33.1 (± 5.27)</td>
<td>57.7 (± 2.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC on admission</td>
<td>12.2 (± 0.15)</td>
<td>10.0 (± 0.16)</td>
<td>8.6 (± 0.25)</td>
<td>11.1 (± 0.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC maximum</td>
<td>13.7 (± 0.17)</td>
<td>11.5 (± 0.20)</td>
<td>9.9 (± 0.35)</td>
<td>12.6 (± 0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK on admission</td>
<td>926.5 (± 53.70)</td>
<td>445.6 (± 27.68)</td>
<td>167.0 (± 24.87)</td>
<td>693.7 (± 32.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK maximum</td>
<td>2386.5 (± 86.96)</td>
<td>870.7 (± 51.43)</td>
<td>317.2 (± 45.20)</td>
<td>1680.8 (± 56.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK-MB on admission</td>
<td>114.0 (± 5.53)</td>
<td>62.2 (± 3.84)</td>
<td>28.0 (± 2.88)</td>
<td>88.6 (± 3.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK-MB maximum</td>
<td>235.7 (± 8.57)</td>
<td>100.1 (± 5.31)</td>
<td>45.1 (± 5.26)</td>
<td>172.1 (± 5.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myoglobin on admission</td>
<td>745.7 (± 44.02)</td>
<td>257.6 (± 17.96)</td>
<td>163.6 (± 51.30)</td>
<td>532.2 (± 27.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myoglobin maximum</td>
<td>1284.1 (± 71.71)</td>
<td>522.2 (± 56.98)</td>
<td>323.2 (± 89.04)</td>
<td>945.4 (± 47.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin T on admission</td>
<td>2.0 (± 0.16)</td>
<td>0.9 (± 0.09)</td>
<td>0.2 (± 0.09)</td>
<td>1.5 (± 0.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin T maximum</td>
<td>6.1 (± 0.27)</td>
<td>2.2 (± 0.15)</td>
<td>4.1 (± 3.49)</td>
<td>4.5 (± 0.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP on admission</td>
<td>1758.7 (± 183.06)</td>
<td>2535.5 (± 253.78)</td>
<td>1895.9 (± 571.62)</td>
<td>2027.9 (± 144.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP maximum</td>
<td>3370.5 (± 245.68)</td>
<td>3928.3 (± 376.26)</td>
<td>2210.7 (± 580.05)</td>
<td>3456.9 (± 196.65)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment myocardial infarction; UA = unstable angina; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides; CRP = C-reactive protein; WBC = white blood count; CK = creatinine-kinase; BNP = brain-natriuretic peptide.

At the 30-day follow-up, the rate of MACE was 9.0% (n = 160) for the total study population. The prevalence of MACE was higher in the STEMI group (10.6%, n = 106) than with NSTEMI (6.7%, n = 42) or UA (7.6%, n = 12) (p = 0.020). Moreover, the Kaplan-Meier survival analysis revealed that the outcomes of STEMI, NSTEMI and UA were indeed substantially different (logrank test p = 0.018), in particular for the first days; after approximately 13 days, the survival curves ran in parallel (fig. 4).

Discussion
Our results reveal that overall ACS patients enrolled in the Z-ACS registry had a lower 30-day MACE rate and in-hospital mortality compared with the established international GRACE registry [5], which reflects the high quality of the management of this patient population in this tertiary centre.

Our in-hospital mortality rates for STEMI are comparable to the OPERA Registry and Swiss registry of acute coronary syndrome (4.6% and 4.8% for STEMI, respectively) [16, 17], but significantly lower than in the PL-ACS Registry Pilot Group, which revealed an in-hospital mortality rate of 11.6% for STEMI and 8.7% for NSTEMI [18]. We also noted that patients with NSTEMI or UA had a more favourable outcome than patients with STEMI, as frequently reported previ-
Hospital mortality, were most commonly pretreated with aspirin, statins and/or beta-blockers on admission. This suggests that when a plaque rupture occurs, patients pretreated with aspirin may develop a smaller clot that is less likely to occlude a major coronary artery, while statin pretreatment may lead to smaller cholesterol cores within the vulnerable lesion resulting in smaller cavities after rupture of a plaque. In line with the latter interpretation, total cholesterol and LDL values were significantly lower in patients with UA, as compared with STEMI and NSTEMI. Of note, optical coherence tomography (OCT) studies have shown that STEMI patients have larger cavities than those with NSTEMI [19]. A previously published study from the GRACE has also demonstrated that preventive cardiovascular premedication can influence the type of ACS presentation [20] and therefore might modulate clinical outcome.

Although difficult to assess in a registry setting, several factors may have contributed to the low complication rates in the Z-ACS registry, including optimal management of ACS patients in a high volume centre with experienced operators. Indeed, volume and operator experience markedly influence ACS outcome [21, 22]. Furthermore, the Zurich metropolitan area is rather small and hospitals are easy to reach. The Zurich area also has a very efficient ambulance system, which further contributes to short-time periods from symptom onset to treatment. Other factors that may have contributed are those that are patient-related, such as age, a major determinant of outcome in ACS [23, 24]. The Z-ACS patients were somewhat younger (mean age for STEMI 62 years, NSTEMI 65 years, UA 64 years) than the GRACE population (STEMI 64 years, NSTEMI 68 years, UA 66 years) [5]. Indeed, in the Z-ACS registry, patients with STEMI were younger, and in the age group below 55 years the rate of STEMI was 28.3%, whereas in the age group over 75 years, only 20.4% presented with STEMI. An increasing frequency of patients with NSTEMI was observed with advanced age, while the frequency of UA was stable over the various age groups. These observations are very similar to the GRACE [5].

Our results are the more impressive because in most trials, and also registries, patients in very poor health with comorbidities and in particular those with cardiogenic shock are usually excluded, which obviously changes reported patient outcomes [25–27]). In the Z-ACS registry, 6.8% of the patients presented in cardiogenic shock, whereas in trials commonly less than 2% of patients exhibited cardiogenic shock. Of note, cardiogenic shock complicates myocardial infarction and accounts for 50%–60% of in-hospital mortality among all age groups [28]. In line with these data, exclusion of patients with cardiogenic shock in the Z-ACS registry would have led to an overall in-hospital mortality of only 1.4%. Similarly, the MACE rate would

| Figure 3 |
| Distribution of complications including, revascularisation, CABG, myocardial infarction, stent thrombosis, cardiac shock, cardiac tamponade, stroke and septic shock between the three groups of ACS. CABG = coronary artery bypass graft; ACS = acute coronary syndrome. |

| Figure 4 |
| Kaplan Meier survival curves for 30-day MACE rate of the three groups of ACS (STEMI, NSTEMI and UA). MACE = major adverse cardiac events; ACS = acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment myocardial infarction; UA = unstable angina. |
have been 4.7% under these conditions. Thus, real-world registries reflect the real world only if all patients with cardiogenic shock or out-of-hospital cardiac arrest are included in the analysis. Furthermore, metropolitan areas with suboptimal ambulance systems may underestimate their true mortality in ACS as many patients may not reach the hospital in time. Be that as it may, our results again demonstrate that there is still room for improvement in the management of patients with cardiogenic shock. who represent a highest risk subset. These patients would benefit most from new treatment strategies.

It is important to note that our patient cohort only included patients from one tertiary care centre with a high quality medical service. However, the GRACE registry contains a total of 18 cluster sites in 14 countries including newly industrialised countries. Unfortunately, healthcare disparities affect the infrastructure and lead to inferior outcomes, in this case pertaining to cardiovascular disease. Switzerland has one of the best healthcare systems in the world, which translates into high-quality care, as demonstrated by the Deloitte Centre for Health Solutions 2010 survey “Health care consumers in Switzerland 2010”. For instance, with the advent of drug-eluting stents (DES), studies have shown that patients with STEMI undergoing primary angioplasty have better long-term outcomes for up to 4 years as compared with those receiving bare-metal stents. In this regard, it is of interest that in Switzerland, DES were utilised in 91% of all patients in 2007 [29]. A recent randomised trial of Swiss centres comparing biolimus-eluting and bare metal stents in patients with STEMI indeed showed that DES are associated with better outcome [27]. At our institution, the use of DES based quality report was between 2007 and 2010 above 80%.

Furthermore, appropriate medical pretreatment may affect outcome. Indeed, a report published by Stauffer et al., using data from the Acute Myocardial Infarction Swiss-Plus (AMIS Plus) registry, found, as in a similar Austrian study [30], that patients pretreated with combination of clopidogrel and percutaneous coronary intervention (PCI) had significantly lower morbidity and mortality, which may not be the case in settings with limited access to resources [31].

One limitation of our single-centre study was the retrospective and observational nature. However, the allcomer design potentially minimised selection bias. In this regard, many prospective, randomised, controlled trials do not enrol all consecutive patients owing to exclusion criteria or missing informed consent. Here we present a reliable, allcomer registry in which all in-hospital events were carefully reported. However, data on long-term follow-up are lacking and only limited information on medical assessments such as door-to-balloon time, percentage of TIMI flow and rate of multivessel PCIs was available.

In summary, registries can serve as effective tools for evaluating outcomes and clinical practice. They are able to demonstrate to what degree the highest standards of evidence-based care are used and what impact they have on outcome. Our results provide such an insight and strongly suggest that outcome must particularly be improved in patients with cardiogenic shock, who contribute the most to morbidity and mortality in ACS. Furthermore, they strongly suggest that preventive medication with aspirin, stents and beta-blockers may protect from STEMI, the clinical presentation with the worst outcome.

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