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Impact of comorbidities on clinical presentation, management and outcome of patients with acute coronary syndrome

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Summary

Background: Most randomised controlled trials (RCT) for acute coronary syndrome (ACS) exclude patients with significant comorbidities. This may lead to misconceptions regarding applicable treatment modalities and hospital outcomes. The objective of the present analysis was to assess the importance of major comorbidities in patients admitted with ACS.

Methods and results: We used the Charlson comorbidity Index (CCI) to evaluate the impact of chronic comorbidities in 19 496 patients included in the AMIS Plus registry following admission for ACS to 63 Swiss hospitals between 2002 and 2008. Among the studied population, 3881 (19.9%) had at least one comorbidity which would exclude them from most RCT for ACS. When compared to patients with a CCI score of 0, those with higher CCI scores were older, more frequently females, and had higher rates of hypertension, dyslipidaemia and obesity. They were less often treated with guideline-recommended drugs and eligible patients underwent acute reperfusion therapy less frequently. The CCI was associated with an increased rate of in-hospital mortality (3.0%, 5.6%, 8.1% and 13.7% respectively for a CCI score of 0, 1, 2, and 3 or more, p <0.001), and remained a powerful predictor of hospital mortality by multivariate analysis. For 3323 patients with long term follow-up, mortality 1 year after discharge was similarly correlated with the CCI (1.6%, 2.7%, 8.4%, and 16.0% respectively for a CCI score of 0, 1, 2, and 3 or more, p <0.001).

Conclusions: Comorbidities have a major impact on clinical presentation, management and outcome of patients admitted to hospital for ACS. This should be taken into account when transposing results obtained from RCT into the "real world".

Introduction

Current management of acute coronary syndrome (ACS) is based on guidelines issued by major cardiology societies, established on the basis of results obtained from randomised controlled trials (RCT) [1–4]. However, a notable limitation of the applicability of the results obtained in RCT for ACS is that these studies exclude many patients who are commonly encountered in daily clinical practice, in particular patients with multiple comorbidities, whose treatment can prove to be

There is no conflict of interest.

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challenging and whose outcome may markedly depend on the comorbid conditions [5–9].

We used the opportunity offered by AMIS Plus (acute myocardial infarction and unstable angina in Switzerland), a large prospective multicentre registry of patients admitted with ACS in Switzerland, to assess the impact of comorbidities on clinical presentation, management and outcome of all patients who presented with ACS.

Methods

The AMIS Plus registry

The AMIS Plus registry is a nationwide prospective registry of patients with ACS admitted to hospitals in Switzerland. The registry was started in 1997 and patient inclusion has been ongoing since. The structure and design of the registry have been previously reported [10–12]. Briefly, at the time of the present publication, 63 hospitals (listed below) participate using paper or electronic data capture to collect information on patients admitted for acute coronary syndrome. Data is entered by dedicated research personnel or by junior physicians. Definitions of the main parameters are available online in pop-up menus, for use during data capture. Data checks for completeness, consistency and plausibility are carried out systematically at the central data center (Institute of Social and Preventive Medicine, University of Zurich), and queries are made to local investigators as needed. Since March 2005, a subset of 49 hospitals has collected individual follow-up information at 3 and 12 months from the patient, their relatives or the referring physician.

Table 1
Prevalence of conditions composing the Charlson comorbidity index and their assigned weight.

Comorbid condition	Weight	n patients	% of population
History of prior myocardial infarction	1	3554	18.2
Heart failure	1	765	3.9
Peripheral vascular disease	1	1056	5.4
Cerebrovascular disease	1	1165	6.0
Dementia	1	366	1.9
Chronic lung disease	1	1184	6.1
Connective tissue disease	1	185	0.9
Peptic ulcer disease	1	453	2.3
Diabetes without target organ damage	1	2964	15.2
Mild liver disease	1	154	0.8
Hemiplegia	2	167	0.9
Diabetes with target organ damage	2	747	3.8
Moderate to severe renal disease	2	1288	6.6
Malignant neoplasm	2	820	4.2
Leukaemia	2	55	0.3
Lymphoma	2	80	0.4
Moderate to severe liver disease	3	112	0.6
Metastatic solid tumour	6	175	0.9
Acquired immunodeficiency syndrome	6	33	0.2

The AMIS Plus project is supported by the Swiss Societies of Cardiology, Internal Medicine, and Intensive Care Medicine and is sponsored by unrestricted grants from the Swiss Heart Foundation as well as a number of pharmaceutical and medical device companies (listed above). The registry was approved by the regional Ethical Committees for clinical studies and the Swiss Board for Data Security. Furthermore, the present study complies with the Declaration of Helsinki.

Charlson index of comorbidities

The Charlson comorbidity index (CCI) is a scoring system that involves weighting factors on the basis of disease severity. The definitions used for each comorbid condition have been described previously [13]. The system was originally developed as a prognostic indicator in patients admitted to a general medical service with a variety of medical conditions, and was then validated in several cohorts of patients [14–17]. Since 2002, the CCI was included in the AMIS Plus questionnaire.

Patients

The present analysis included all patients included in the AMIS Plus registry from January 2002 to December 2008 with valid data on CCI.

Statistical analysis

Data are presented as numbers (percentages) of valid cases for discrete variables and as means (standard deviation) or medians for continuous variables. Group differences were compared using chi square analysis of variance or the Student t test, as appropriate. A probability value of $p < 0.05$ was considered significant.

A multivariate logistic regression model was used to determine predictors of in-hospital mortality from the following set of variables available at admission: age, sex, hypertension, dyslipidemia, smoking at time of admission, obesity, Killip class (class I as reference category), CCI (CCI score of 0 as reference category), pre-hospital cardio-pulmonary resuscitation, ST elevation and/or left bundle branch block (LBBB) on admission ECG. Since diabetes is a component of the CCI, it was not included in the regression model. However, in order to determine the prognostic value of the CCI independently from the impact of diabetes, we repeated the regression model after excluding diabetes from the CCI and including it as an independent variable.

SPSS (version 15.0, SPSS Inc., Chicago, IL) was used for all statistical analyses.

Results

From the 20 252 patients included in the AMIS Plus registry during the study period, 19 496 (96%) had valid data on CCI and hospital outcome. Follow-up information was obtained from 4256 patients at 3 months (96.0% of those who consented and were eligible) and 3323 patients at 12 months (96.8% of those who consented and were eligible).

The prevalence of each comorbidity composing the CCI, as well as the assigned weight of each condition, are shown in table 1. The most common comorbidities

Table 2
Baseline characteristics.

	CCI = 0	CCI = 1	CCI = 2	CCI ≥3	p
Patients, n (%)	10367 (53.2)	4447 (22.8)	2176 (11.2)	2506 (12.9)	
Male gender (%)	7792 (75.2)	3196 (71.9)	1469 (67.5)	1693 (67.6)	<0.001
Mean age (SD), years Median	61.9 (13) 61	67.2 (13) 68	71.5 (12) 73	74.3 (11) 76	<0.001
History of CAD (%)*	2259/10305 (22.9)	2423/4427 (54.7)	1265/2161 (58.5)	1682/2493 (67.5)	<0.001
Diabetes mellitus (%)†	217/10005 (2.2)†	1441/4308 (33.4)	846/2117 (40.0)	1254/2426 (51.7)	<0.001
Hypertension (%)	4820/9886 (48.8)	2907/4237 (68.6)	1587/2087 (76.0)	1916/2402 (79.8)	<0.001
Dyslipidaemia (%)	4883/9277 (52.6)	2566/3945 (65.0)	1261/1911 (66.0)	1385/2158 (64.2)	<0.001
Smoking (current) (%)	4374/9863 (44.3)	1383/4138 (33.4)	500/1998 (25.0)	526/2236 (23.5)	<0.001
Obesity (BMI ≥30 kg/m^2) (%)	1552/8911 (17.4)	834/3736 (22.3)	416/1817 (22.9)	463/2082 (22.2)	<0.001
Pain to door median delay in min interquartile range 25,75	222 111, 619	225 110, 643	240 120,713	285 125, 784	0.110
Clinical presentation					
Typical symptoms (%)	5750/6446 (89.2)	2315/2640 (87.7)	1081/1305 (82.8)	1172/1538 (76.2)	<0.001
Chest pain (%)	8508/10146 (83.9)	3495/4351 (80.3)	1665/2113 (78.8)	1742/2433 (71.6)	<0.001
Dyspnoea (%)	1954/9741 (20.1)	1125/4198 (26.8)	711/2048 (34.7)	1120/2381 (47.0)	<0.001
Killip class (n patients)	10313	4426	2164	2499	<0.001
Killip class I (%)	9014 (87.4)	3503 (79.1)	1507 (69.6)	1421 (56.9)	
Killip class II (%)	927 (9.0)	650 (14.7)	459 (21.2)	723 (28.9)	
Killip class III (%)	150 (1.5)	154 (3.5)	143 (6.6)	267 (10.7)	
Killip class IV (%)	222 (2.2)	119 (2.7)	55 (2.5)	88 (3.5)	
Out of hospital management					
CPR (%)	303/10033 (3.0)	112/4321 (2.6)	43/2089 (2.1)	65/2423 (2.7)	0.078
Cardioversion/defibrillation (%)	400/10035 (4.0)	129/4302 (3.0)	49/2089 (2.3)	54/2423 (2.2)	<0.001
ECG at admission					
Sinus rhythm (%)	9728/10325 (94.2)	3991/4414 (90.4)	1922/2161 (88.9)	2017/2480 (81.3)	<0.001
Atrial fibrillation (%)	303/10325 (2.9)	238/4414 (5.4)	149/2161 (6.9)	299/2480 (12.1)	<0.001
ST-elevation (%)	6174/10354 (59.6)	2143/4438 (48.3)	876/2170 (40.4)	909/2499 (36.4)	<0.001
LBBB (%)	252/10350 (2.4)	232/4437 (5.2)	153/2169 (7.1)	252/2498 (10.1)	<0.001
Q wave (%)	1044/10352 (10.1)	619/4437 (14.0)	260/2170 (12.0)	363/3499 (14.5)	<0.001

CCI, Charlson comorbidity index; SD, standard deviation; CAD, coronary artery disease; BMI, body mass index; CPR, cardio-pulmonary resuscitation; LBBB, left bundle branch block. *Includes angina pectoris, myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention. †In the AMIS Plus registry, patients diagnosed with diabetes before hospitalisation who remained untreated or had diabetes detected in hospital were considered as diabetics. For the CCI, a patient was considered as diabetic only if he was taking oral antidiabetic medication or insulin before hospitalisation.

Table 3
Drug therapy during acute phase (first 24 hours after admission) and at discharge.

Number of patients/N (%)	CCI = 0	CCI = 1	CCI = 2	CCI ≥ 3	p
Acute phase					
Aspirin	9995/10 338 96.7%	4164/4433 93.9%	2004/2169 92.4%	2194/2492 88.0%	<0.001
Clopidogrel	7830/10 309 76.0%	3113/4402 70.4%	1291/2157 59.9%	1302/2485 52.4%	<0.001
Beta blocker	7446/10 263 72.6%	3123/4414 70.8%	1490/2159 69.0%	1566/2485 63.0%	<0.001
Statin	8068/10 278 78.5%	3295/4412 74.7%	1521/2160 70.4%	1585/2479 63.9%	<0.001
ACEI/ARB	4979/10 250 48.6%	2282/4407 51.8%	1171/2158 54.3%	1319/2490 53.0%	<0.001
At discharge					
Aspirin	9696/10 021 96.8%	3952/4181 94.5%	1838/1992 92.3%	1845/2155 85.6%	<0.001
Clopidogrel	8344/10 002 83.4%	3220/4166 77.3%	1307/1989 65.7%	1210/2157 56.5%	<0.001
Beta blocker	8505/9990 85.1%	3532/4173 84.6%	1651/1990 83.0%	1686/2160 78.1%	<0.001
Statin	9221/10 002 92.2%	3708/4173 88.9%	1679/1992 84.3%	1711/2155 79.4%	<0.001
ACEI/ARB	7103/9969 71.3%	3158/4170 75.7%	1498/1990 75.3%	1642/2156 76.2%	<0.001

CCI: Charlson comorbidity index; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 4
Reperfusion for patients with ST elevation myocardial infarction or left bundle branch block on admission.

	CCI = 0	CCI = 1	CCI = 2	CCI ≥3	p
n patients	6354	2340	1005	1125	
No reperfusion (%)	929 (14.6)	590 (25.2)	389 (38.7)	600 (53.3)	<0.001
Thrombolysis (%)	636 (10.0)	188 (8.0)	63 (6.3)	43 (3.8)	<0.001
Primary PCI (%)	4789 (75.4)	1562 (66.8)	553 (55.0)	482 (42.8)	<0.001

CCI: Charlson comorbidity index; PCI: percutaneous coronary intervention.

reported were a history of a previous myocardial infarction, diabetes mellitus, moderate to severe renal disease, chronic lung disease and cerebrovascular disease. More precisely, 3881 (19.9%) patients suffered from at least one of the following comorbidities which were considered as exclusion criteria in several major RCT of ACS: cerebrovascular disease, hemiplegia, dementia, connective tissue disease, peptic ulcer disease, moderate to severe liver disease, moderate to severe renal disease, solid malignant tumour, leukaemia, lymphoma, metastatic solid tumour and acquired immune deficiency syndrome (AIDS) [18–20].

The overall mean CCI score was 1.01 ± 1.59. CCI scores of 1, 2 and 3 or more applied respectively to 22.8%, 11.2% and 12.9% of the patient population, while approximately half (53.2%) of the patient population did not have any condition included in the CCI, reported as a CCI score of zero (table 2).

When considering baseline characteristics, patients with higher CCI scores were older, more often female and had higher rates of cardiovascular risk factors such as hypertension, dyslipidaemia and obesity. However, there was also a lower proportion of active smokers among these patients.

With regard to clinical parameters, the patients with higher CCI scores were admitted with higher degrees of haemodynamic instability (according to Killip class), while their symptoms at admission time were less typical than in patients with lower rates of comorbidities. Furthermore, the admission ECG of patients with higher CCI scores showed ST elevation less frequently, whereas Q waves were found more often.

Prescription of several guideline-recommended drugs (including aspirin, clopidogrel, beta-blockers, and statins) during the acute phase and at discharge was significantly less frequent for patients with higher degrees of comorbidities, but angiotensin converting enzyme inhibitors and angiotensin II receptor blockers showed an opposite trend (table 3).

Among the subgroup of patients admitted with ST elevation myocardial infarction (STEMI) or LBBB (n = 10 824, 55.5%), reperfusion either with primary percutaneous coronary intervention (PCI) or thrombolysis was less frequently applied to patients with higher comorbid conditions (table 4). Patients who did not undergo reperfusion had a mean CCI score of 1.6, whereas the mean CCI score of patients who underwent primary PCI and thrombolysis was 0.6 and 0.5, respectively (p <0.001 across all 3 treatment modalities).

A higher CCI score was associated with an increased rate in-hospital of major adverse cardiac and cerebral events (MACCE), which include re-infarction, cardiogenic shock, cerebrovascular events and to death (table 5). Among the subset of patients with long-term follow-up information, mortality remained higher after 3 and 12 months for patients with a higher CCI score.

Increased CCI scores were powerful predictors of in-hospital mortality by multivariate analysis (table 6).

Table 5
Outcome.

	CCI = 0	CCI = 1	CCI = 2	CCI ≥ 3	p
Patients (%)	10367 (53.2)	4447 (22.8)	2176 (11.2)	2506 (12.9)	
In hospital outcome and hospital stay					
Cardiogenic shock (%)	3.4	4.4	5.6	9.2	<0.001
Re-infarction (%)	0.8	1.6	2.4	2.2	<0.001
Cerebrovascular insult (%)	0.5	0.9	0.8	1.7	<0.001
In-hospital mortality (%)	3.0	5.6	8.1	13.7	<0.001
MACCE* (%)	4.0	7.1	10.0	16.1	<0.001
Median hospital stay (days) interquartile range 25,75	5 2, 8	6 2, 10	7 3, 12	8 4, 14	<0.001
Out of hospital outcome					
3 months mortality (n/N) % 0.7 0.9 3.7 6.4	(18/2466)	(8/909)	(16/430)	(29/451)	<0.001
1 year mortality (n/N) % 1.6 2.7 8.4 16.0	(31/1924)	(19/699)	(30/356)	(55/344)	<0.001

CCI: Charlson comorbidity index; MACCE: major adverse cardiac and cerebral events.
*Defined as re-infarction, cardiogenic shock, cerebrovascular event and death.

Table 6
Multivariate predictors of in-hospital mortality.

	p	OR	95 % CI for OR
CCI = 1	<0.05	1.51	1.07–2.14
CCI = 2	<0.001	2.62	1.79–3.83
CCI ≥ 3	<0.001	3.08	2.18–4.35
Age (1 year increase)	<0.001	1.07	1.06–1.09
Killip Class II	<0.001	2.49	1.84–3.37
Killip Class III	<0.001	4.38	2.87–6.70
Killip Class IV	<0.001	15.94	10.26–24.75
Hypertension	<0.05	0.72	0.54–0.94
Prehospital CPR	<0.001	4.7	2.90–7.44

OR: odds ratio; CI: confidence interval; CCI: Charlson comorbidity index; CPR: cardio-pulmonary resuscitation; LBBB: left bundle branch block.

Other major independent predictors at admission were age, Killip class, pre-hospital CPR and ST segment elevation on the first ECG. Furthermore, since diabetes is one of the major components of the CCI and also a major risk factor for ACS, we repeated the multivariate analysis after exclusion of diabetes from the CCI score, in order to determine if the prognostic value of the CCI is merely a reflection of the impact of diabetes: CCI scores of 1, 2 and 3 or more remained significant predictors of in-hospital mortality (odds ratio [OR] of 1.63 [95% confidence interval {CI} 1.17–2.28], 2.20 [95% CI 1.50–3.23] and 3.02 [95% CI 2.13–4.27], respectively). This analysis also showed that diabetes was not a significant predictor for in-hospital death (OR 1.28, 95% CI 0.95–1.71).

Discussion

Previous studies have shown the importance of comorbid conditions in patients admitted with ACS. However, these studies were either focused on acute conditions only, were monocentric or were based on small populations [15, 21–23]. To our knowledge, the present analysis is the largest multicentric study focusing on the importance of chronic comorbid conditions among patients admitted with ACS. Our results confirm those from previous studies, showing that chronic comorbidities are frequently encountered in patients admitted for ACS in daily clinical practice. They also show that patients with multiple comorbid conditions differ significantly from those with few or no comorbidities in terms of clinical presentation, treatment and outcome. Indeed, patients with a higher CCI were typically older, more often females and had higher rates of hypertension, dyslipidaemia and obesity. Furthermore, these patients were admitted more often with non-ST elevation myocardial infarction than patients with lower CCI scores who presented more frequently with STEMI. Interestingly, active smoking was less often encountered among patients with higher CCI scores. This finding concurs with the suspected origin of the "smoker's paradox", where smokers have better outcomes than non-smokers following acute myocardial infarction, likely because of their younger age and lower risk profile [24, 25]. Moreover, the fact that there was no positive effect of active smoking on survival after adjustment for the CCI score in our multivariate analysis is consistent with this hypothesis.

In our series, the presence of comorbidities was associated with a reduced use of most guideline-recommended drugs as well as reperfusion therapies in eligible patients. Fear of increased risk for adverse drug and procedure related events among this population is probably the main reason for this finding [7]. For instance, the lower use of Aspirin, Clopidogrel and reperfusion therapies in patients with higher CCI scores was possibly related to an increased haemorrhagic risk. Nevertheless, the appropriateness of withholding such therapies is difficult to assess precisely since evidence-

based guidelines are not available for these clinical situations. Furthermore, higher CCI scores were associated with an increased risk of in-hospital mortality and MACCE as well as mortality at follow-up. While this poorer prognosis may be related to some extent to the comorbidities themselves, underuse of guideline recommended therapies for ACS, whether justified or not, may also have contributed to this finding.

As several chronic diseases impact on the management and outcome of patients suffering from a given disease, and thus increase the background "noise" of events, RCT usually have strict criteria which exclude many patients with significant comorbidities in order to increase the likelihood of identifying a significant difference between the selected treatment arms [7]. The drawback of this, however, is that RCT only partly reflect daily clinical practice, due to patients' selection and untoward bias. Therefore, results from RCT can be difficult to apply in a "real world" setting since the patient population encountered may have been excluded from these trials. In other words, guidelines mainly established on the basis of RCT may be difficult to apply as demonstrated in our study. Another important caveat may concern registries. Indeed, adjusting for baseline characteristics is increasingly used in numerous registries when embarking upon comparisons between different sub-groups [26–29]. However, without proper assessment of comorbidities, such adjustment may be of only limited value. Our data support the contention that all registries should account for a broad spectrum of comorbid conditions, to allow identification of confounding factors encountered in daily clinical practice.

Limitations

The Charlson index was designed over 20 years ago, and although it has become the most widely used instrument to quantify chronic comorbidities for patients admitted to hospital for an acute major complaint, it was not designed specifically for patients with ACS. It gives a high score to certain items that have now become rare in Switzerland, such as AIDS, while other problems, such as conditions associated with increased haemorrhagic or thrombotic risk, human immunodeficiency virus status or transplant recipient on immunosuppressant drugs, might be of greater interest at the present time.

The post-discharge follow-up was only available for a subset of patients, and the numbers are still small, in particular for the 12 month follow-up point. Larger numbers will be required to confirm the long-term prognostic value of the CCI score at admission for ACS patients.

Conclusions

Chronic comorbidities have a major impact on clinical presentation, management and outcome of patients admitted with ACS. The overall comorbidity burden is independently associated with higher rates of in-hospital mortality. The excess mortality appears to persist at 3 and 12 months follow-up.

Despite being among the most difficult patients to manage, the sub-group of those with comorbid conditions is poorly described in current literature and guidelines, and many of them are excluded from standard RCT.

In order to improve management of these patients, further efforts are warranted to include these patients in RCTs on ACS and also take into account the effect of comorbidities in major registries.

Participating centres

The following hospitals participated in the AMIS Plus registry from 2002 to 2008 (in alphabetical order): Kantonsspital, Aarau; Bezirksspital, Affoltern am Albis; Kantonsspital, Altdorf; Kantonales Spital, Altstätten; Kantonsspital, Baden; Kantonsspital, Basel; Beau-Site Klinik, Bern; Inselspital, Bern; Spital Tiefenau, Bern; Spitalzentrum, Biel; Oberwalliser Kreisspital, Brig-Glis; Spital, Bülach; Regionalspital, Einsiedeln; Regionalspital Emmental, Burgdorf; Kreuzspital, Chur; Spital, Davos Platz; Spital, Dornach; Kantonales Spital, Flawil; Kantonsspital, Frauenfeld; Hôpital cantonal, Fribourg; Spital, Frutigen; Hôpitaux universitaires, Genève; Kantonsspital, Glarus; Spital, Grenchen; Kantonales Spital, Herisau; Spital, Interlaken; Hôpital, La Chaux-de-Fonds; Regionalsspital, Lachen; Regionalspital, Langnau im Emmental; GZF Regionalspital, Laufenburg; Cardiocentro Ticino, Lugano; Kantonsspital, Luzern; Kreisspital, Männedorf; Ospedale regionale, Mendrisio; Hôpital de la Tour, Meyrin; Hôpital du Jura bernois, Moutier; Regionales Spital Zentrum, Münsingen; Kantonsspital, Münsterlingen; Kreisspital für das Freiamt, Muri; Group. Hosp. Ouest lémanique, Nyon; Kantonsspital, Olten; GZF Regionalspital, Rheinfelden; Kantonales Spital, Rorschach; Spital Oberengadin, Samedan; Kantonsspital Obwalden, Sarnen; Kantonsspital, Schaffhausen; Spital Limmattal, Schlieren; Spital, Schwyz; Ospidal d'Engiadina Bassa, Scuol; Bürgerspital, Solothurn; Kantonsspital, St. Gallen; Spital, Sursee; Spital, Thun; Spital, Uster; Schwerpunktspital Zimmerberg-Horgen, Wädenswil; Kantonales Spital, Walenstadt; GZO Spital, Wetzikon; Kantonsspital, Winterthur; Kantonales Spital Wolhusen, Wolhlusen; Spital, Zofingen; Spital, Zollikerberg; Universitätsspital, Zürich; Stadtspital Triemli, Zürich; Stadtspital Waid, Zürich.

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