Comparison of In-Hospital Mortality for Acute Myocardial Infarction in Switzerland With Admission During Routine Duty Hours Versus Admission During Out of Hours (Insight Into the AMIS Plus Registry)

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To improve long-term survival, prompt revascularization of the infarct-related artery should be done in patients with acute myocardial infarction (AMI); therefore, a large proportion of these patients would be hospitalized during out of hours. The clinical effects of out-of-hours AMI management were already questioned, with conflicting results. The purpose of this investigation was to compare the in-hospital outcome of patients admitted for AMI during out of hours and working hours. All patients with AMI included in the AMIS Plus Registry from January 1, 1997, to March 30, 2006, were analyzed. The working-hours group included patients admitted from 7 A.M. to 7 P.M. on weekdays, and the out-of-hours group included patients admitted from 7 P.M. to 7 A.M. on weekdays or weekends. Major cardiac events were defined as cardiovascular death, reinfarction, and stroke. The study primary end points were in-hospital death and major adverse cardiac event (MACE) rates. A total of 12,480 patients met the inclusion criteria, with 52% admitted during normal working hours, and 48%, during out of hours. Patients admitted during weekdays included more women (28.1% vs 26%; $p = 0.009$), older patients (65.5 ± 13 vs 64.1 ± 13 years; $p = 0.0011$), less current smokers (40.1% vs 43.5%; $p < 0.001$), and less patients with a history of ischemic heart disease (31.5% vs 34.5%; $p = 0.001$). A significantly higher proportion of patients admitted during out of hours had Killip's class III and IV. No differences in terms of in-hospital survival rates between the 2 groups (91.5% vs 91.2%; $p = 0.633$) or MACE-free survival rates (both 88.5%; $p = 1.000$) were noted. In conclusion, the outcome of patients with AMI admitted out of hours was the same compared with those with a weekday admission. Of predictors for in-hospital outcome, timing of admission had no significant influence on mortality and/or MACE incidence. **(Am J Cardiol 2008;101:422–427)**

Acute myocardial infarctions (AMIs) need prompt revascularization of the infarct-related artery to preserve cardiac function and improve long-term survival. Because of the close relation between time-dependant AMI management and long-term outcome, these patients need to be admitted and treated with the shortest delay. Additionally, variations in sympathetic nervous system activity, platelet aggregation reactivity, fibrinogen, and antithrombin were described, leading to a peak in early-morning hours of AMI onset.[1–3] Subsequently, a large proportion of patients with AMI will be hospitalized during weekends and weeknights. The clinical effect of out-of-hours management was already questioned. Historically, increased weekend neonatal mortality was the first to be described.[4–11] In adult populations, many factors, including nurse and medical staffing, medical level of education, logistics (number of beds), severity of disease, and coexisting illness, were associated with mortality variations.[12–14] Surprisingly few studies focused on out-of-hours care of patients with AMI. Available investigations included relatively few patients and were limited to out-

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A list of participating hospitals in the Acute Myocardial Infarction and Unstable Angina in Switzerland (AMIS Plus) appears in the Appendix.

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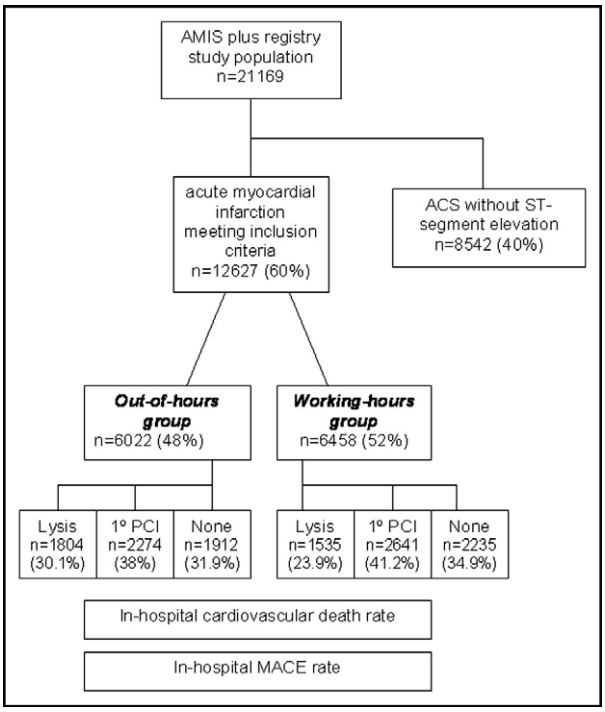

Figure 1. Patient disposition in the study. ACS = acute coronary syndrome.

come after percutaneous coronary revascularization. The purpose of our investigation is to compare the in-hospital outcome of patients admitted for AMI during out of hours and working hours.

Methods

The Acute Myocardial Infarction in Switzerland (AMIS) Registry, including patients with AMI, was started in 1997 and substituted by the AMIS Plus Registry in 2000, with additional inclusion of patients with acute coronary syndromes without ST-segment elevation. Of 106 hospitals treating patients with acute ischemic heart disease in Switzerland, 66 centers are participating centers enrolling patients, ranging from community institutions to large tertiary facilities. Of these, 11 centers offer around-the-clock (24-hour/24-hour) catheterization laboratory availability. All centers provide blinded data for each patient through a standardized Internet- or paper-based questionnaire. Data are centralized at the institute of Social and Preventive Medicine at the University of Zurich, where data are checked for plausibility and consistency before being analyzed. The registry was approved by the regional ethical committees for clinical studies and the Swiss Board for Data Security.

All patients included in the registry from January 1, 1997, to March 30, 2006, meeting the criteria for AMI of acute chest pain lasting <12 hours with new ST-segment elevation by >1 mm in 2 contiguous leads or new left branch bundle block and cardiac enzymes (total creatinine kinase [CK] or CK-MB) at least twice the upper limit of normal range were analyzed. Patients were included in the out-of-hours group if admitted between 7 P.M. and 7 A.M. or during the weekend. The working-hours group included patients admitted during routine duty hours between 7 A.M. to 7 P.M. on weekdays.

Table 1
Baseline characteristics

Variable	On-Hours Group (n = 6,458; 51.7%)	Off-Hours Group (n = 6,022; 48.3%)	p Value
Men	4,646 (71.9%)	4,457 (74.0%)	
Women	1,812 (28.1%)	1,565 (26.0%)	0.009
Killip's classification			0.005
I	4,808 (75.5%)	4,419 (74.7%)	
II	1,130 (17.7%)	1,002 (16.9%)	
III	257 (4.0%)	305 (5.2%)	
IV	173 (2.7%)	192 (3.2%)	
Cardiogenic shock	612 (9.6%)	611 (10.3%)	0.205
Reinfarction	201 (3.2%)	180 (3.1%)	0.715
Cerebrovascular event	76 (1.2%)	71 (1.2%)	1.000
Systemic hypertension	3,220 (52.0%)	2,998 (52.2%)	0.855
Dyslipidemia	3,202 (55.1%)	3,044 (56.2%)	0.217
Diabetes mellitus	1,170 (18.7%)	1,138 (19.6%)	0.220
Smoking (current)	2,451 (40.1%)	2,482 (43.5%)	0.000
Overweight (BMI $\geq$25 kg/m^2)	3,138 (61.8%)	2,878 (62.8%)	0.303
Previous myocardial infarction or stable angina pectoris	1,715 (31.5%)	1,752 (34.5%)	0.001

BMI = body mass index.

The AMIS Plus questionnaire includes 140 items for each patient and is filled in by the coordinator of each institution. Major adverse in-hospital cardiac events were defined as cardiovascular death, reinfarction, or stroke. Myocardial reinfarction was defined as the occurrence of new Q waves and/or increase in CK more than twice the upper limit of normal range and increased by >50% over the previous value. Stroke was diagnosed using an imaging study and expert neurologist opinion. The study primary end points were in-hospital cardiovascular death and combined incidence of cardiovascular death, reinfarction, or stroke.

Continuous variables were expressed as mean ± SD, and discrete variables, as count and percentage. In univariate tests, chi-square and Fischer's exact *t* test were used for categorical variables, and Student's *t* test or U test was used for continuous variables. Multivariate stepwise logistic regression, including working time and variables (age >65 years, history of coronary heart disease, arterial hypertension, dyslipidemia, diabetes, current smoking, overweight, Killip's classification at hospital admission, delay from symptom onset to admission to hospital >6 hours, and working time) achieving statistical significance at univariate logistic regression, was then performed. A p value <0.05 was considered statistically significant. SPSS (version 13.0; SPSS Inc., Chicago, Illinois) was used for all statistical analyses.

Results

Of 21,169 patients included in the registry from January 1, 1997, to March 30, 2006, a total of 12,667 patients met the

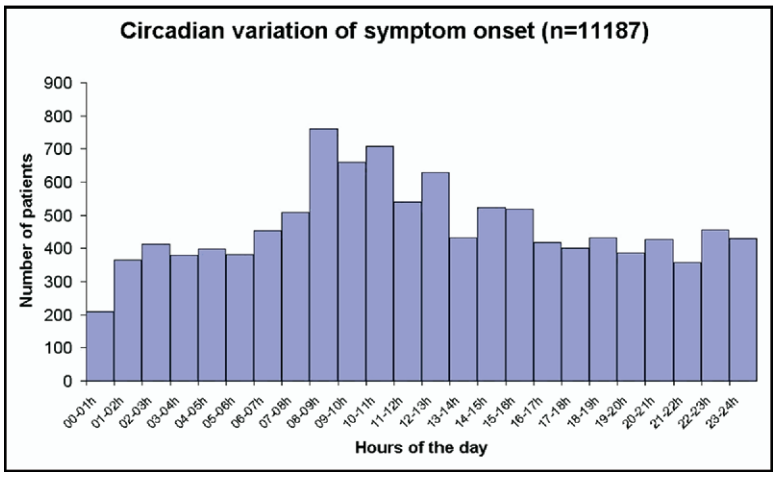

Figure 2. Circadian variation of symptom onset.

Table 2
Time delays

	On-Hours Group (n = 6,458; 51.7%)	Off-Hours Group (n = 6,022; 48.3%)	p Value
Median delay (h:min)	4:00	3:02	0.001
Reperfusion groups			
Thrombolysis	1,535 (23.9%)	1,804 (30.1%)	0.001
Delay	n = 1,482	n = 1,721	
	2:44	2:30	0.02
Door-to-needle time	n = 1,255	n = 1,526	
	0:30	0:30	NS
Primary PCI	2,641 (41.2%)	2,274 (38.0%)	0.025
Delay	n = 2,347	n = 2,071	
	3:30	3:00	0.001
Door-to-balloon time	n = 2,051	n = 1,775	
	1:05	1:15	NS
No reperfusion	2,235 (34.9%)	1,912 (31.9%)	0.025
Delay	n = 1,792	n = 15,72	
	10:20	5:34	0.001

Table 3
Medications

Variable	On-Hours Group (n = 6,458; 51.7%)	Off-Hours Group (n = 6,022; 48.3%)	p Value
Immediate drug therapy			
Aspirin	6,089 (94.6%)	5,687 (94.8%)	0.660
Clopidogrel	2,807 (43.9%)	2,674 (44.8%)	0.293
Unfractionated heparin	4,763 (74.1%)	4,673 (78.0%)	0.000
Low-molecular-weight heparin	1,420 (30.5%)	1,131 (26.6%)	0.000
β Blocker	4,567 (71.2%)	4,201 (70.2%)	0.206
Angiotensin-converting enzyme inhibitor	2,702 (42.7%)	2,493 (42.3%)	0.634
Angiotensin receptor II antagonist	165 (3.7%)	152 (3.7%)	1.000
Calcium channel blocker	293 (4.6%)	287 (4.8%)	0.551
Nitrate	4,244 (66.2%)	4,139 (69.3%)	0.000
Lipid-lowering drug	2,584 (70.2%)	2,470 (72.3%)	0.055
Glycoprotein antagonist	1,717 (36.8%)	1,681 (39.4%)	0.011
Reperfusion			0.000
Thrombolysis	1,535 (23.9%)	1,804 (30.1%)	0.001
Primary PCI	2,641 (41.2%)	2,274 (38.0%)	0.025
No reperfusion	2,235 (34.9%)	1,912 (31.9%)	0.025

inclusion criteria for AMI, and 12,480 patients were analyzed in the present study because of 147 patients missing data. As shown in Figure 1, 52% were admitted during normal working days (n = 6,458), and 48%, during out of hours (n = 6,022). Table 1 lists baseline characteristics according to time of admission. Patients admitted during weekdays included more women (28.1% vs 26%; p = 0.009), older patients (65.5 ± 13 vs 64.1 ± 13 years; p = 0.0011), less current smokers (40.1% vs 43.5%; p <0.001), and less patients with a history of ischemic heart disease (31.5% vs 34.5%; p = 0.001). A significantly higher proportion of patients admitted during out of hours had Killip's classification III and IV.

Figure 2 shows the circadian variation in symptom onset in the entire population. Hospital length of stay was longer when the patient was hospitalized during out of hours than during normal working days (median 8 vs 9 days; p = 0.04). Details for time delays are listed in Table 2, and for medications, in Table 3.

Figure 3 shows reperfusion strategies according to the availability of a catheterization laboratory. Thrombolysis was administered to 3,339 patients (27%), mainly during out of hours (30.1% vs 23.9%; p = 0.001). Use of thrombolytics increased in hospitals without a catheterization laboratory (37.0%) compared with hospitals with catheterization laboratory facilities (16.0%). Primary percutaneous coronary intervention (PCI) was performed more often during working days (41.2% vs 38%; p = 0.025). A proportion of patients did not undergo reperfusion because of either medical decision not to perform reperfusion because of contraindications or changes in clinical or electrocardiographic criteria between inclusion and time of treatment administration. Patients admitted during working hours more often did not undergo reperfusion compared with those with out-of-hours admission (34.9% vs 31.9%; p = 0.025).

No difference in terms of in-hospital survival rates between the 2 groups (91.5% vs 91.2%; p = 0.633) or major adverse cardiac event (MACE)-free survival rates (both

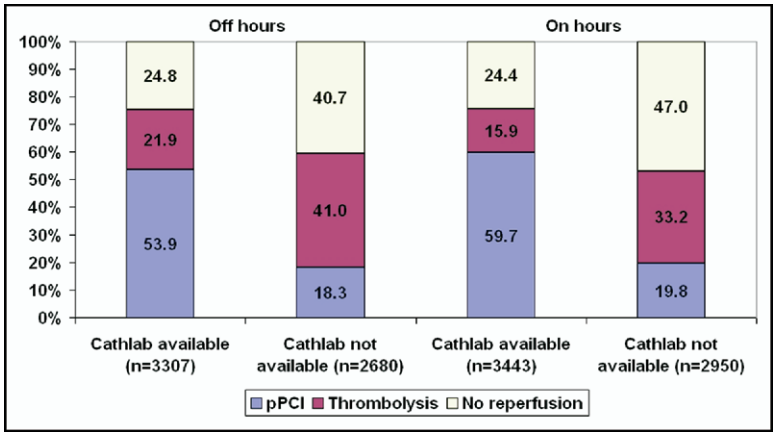

Figure 3. Reperfusion strategies according to the availability of PCI facilities. Cathlab = catheterization laboratory; pPCI = primary PCI.

Table 4
Details of outcome according to reperfusion strategies

Variable	On-Hours Group (n = 6,458; 51.7%)	Off-Hours Group (n = 6,022; 48.3%)	p Value
Outcome (%)			
Reinfarction	3.2%	3.1%	0.715
Cerebrovascular event	1.2%	1.2%	1.000
Death	8.5%	8.8%	0.633
MACE	11.5%	11.5%	1.000
Reperfusion groups			
Thrombolysis	1,535 (23.9%)	1,804 (30.1%)	0.001
Reinfarction	4.2%	3.7%	0.419
Cerebrovascular event	1.6%	1.1%	0.289
Death	6.4%	5.5%	0.273
Primary PCI	2,641 (41.2%)	2,274 (38.0%)	0.025
Reinfarction	1.5%	1.3%	0.462
Cerebrovascular event	0.9%	0.9%	1.000
Death	3.6%	4.2%	0.292
No reperfusion	2,235 (34.9%)	1,912 (31.9%)	0.025
Reinfarction	4.5%	4.7%	0.821
Cerebrovascular event	1.3%	1.7%	0.434
Death	15.8%	17.6%	0.135

88.5%; p = 1.0) were noted. Details for deaths and MACE rates according to each reperfusion strategy are listed in Table 4. Unexpectedly, better outcome was related to patients undergoing primary PCI regardless of admission time (Figure 4). As listed in Table 5, multivariate analysis showed that timing of admission had no significant influence on survival rates.

Discussion

The AMIS Plus Registry allows a real-world picture of AMI management in Switzerland and gives the opportunity to assess daily practice in a large population of ischemic patients. International guidelines recommended that patients with AMI undergo revascularization as soon as possible, but such specific application as out-of-hours management was scarce. We report that out-of-hours AMI management had the same outcome compared with weekdays, and whenever admitted, patient treated using primary angioplasty had better outcomes, with a 2.5-fold decrease in MACE rates compared with the rest of the population. Of predictors for in-hospital outcome, timing of admission had no significant influence on mortality and/or the composite end point of reinfarction, stroke, and death.

Conflicting results emerged from the available data comparing outcomes related to weekends or weekdays admissions. Bell and Redelmeier[15] analyzed acute-care admissions from emergency departments in Canada in what is by far the largest study available, with nearly 4 million patients included during a 9-year period (1988 to 1997). Several acute diagnoses were associated with increased in-hospital mortality. However, the analysis was not able to determine whether weekend patients were sicker that their weekday counterparts, and staffing problems, postulated to be the cause of those findings, could not be proved. Additional investigations corroborated an increased risk of dying during out-of-hours. Cram et al[16] analyzed 650,000 admissions in California for 50 common medical diagnoses. They found a 3% increase in risk-adjusted mortality for weekend admissions compared with weekdays. Two studies of intensive care unit admissions supported these conclusions, even after adjustment for severity of illness. The retrospective cohort from the Cleveland Health Quality Choice program included >150,000 intensive care unit admissions and analysis of 23,000 consecutive emergency admissions in 18 intensive care units in Finland.[17,18] Conversely, Schmulewitz et al[19] analyzed 3,244 hospital admissions in Edinburgh for 6 predetermined medical diagnoses and showed that weekend admissions were not associated with significantly higher in-hospital mortality, readmission rates, or increased hospital lengths of stay. Two additional investigations supported no compromise in emergency care during out of hours.[20,21]

Regarding data for AMI, a recent publication identified a higher mortality rate in patients with AMI admitted during weekends.[22] We extended the analysis by inclusion of nighttime admissions because we believed that speculations about less access to care and a lower rate of primary PCIs during weekends were also likely during nights. In addition, Garot et al[23] analyzed the outcome of primary PCI in 288 patients according to time of admission and showed that in-hospital outcome was similar between the on- and off-hour groups (7% vs 6%; p = NS). Furthermore, a retro-

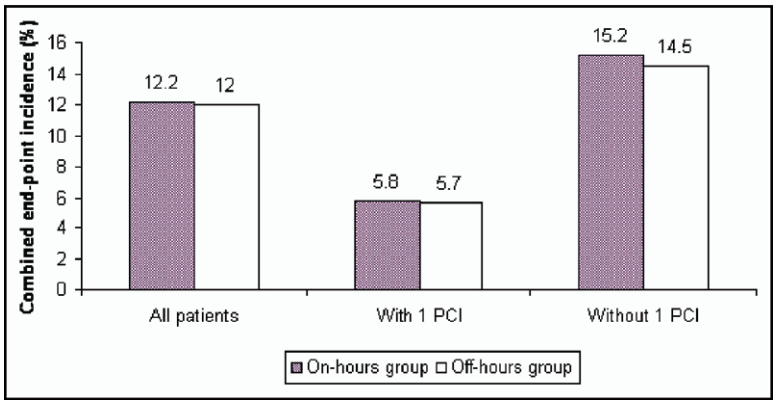

Figure 4. MACE rate according to the use of primary PCI.

Table 5
In-hospital mortality predictors at multivariate analysis

	Odds Ratio	95% Confidence Interval
Age>65 yrs	3.8	2.8–5.0
Killip's classification II	2.1	1.6–2.7
Killip's classification III	2.7	1.9–3.96
Killip's classification IV	3.5	2.3–5.3
Time of admission	0.96	0.77–1.2

spective analysis of 491 patients included in the maximal individual therapy in acute myocardial infarction (MITRA) study noted no in-hospital mortality difference in patients treated from 8 P.M. to 8 A.M. compared with 8 A.M. to 8 P.M. (8.7% vs 5.3%; $p = 0.238$).[24] Data with longer follow-up were also available. Beohar et al[25] included 220 consecutive patients undergoing primary PCI within 12 hours of ST-segment elevation myocardial infarction. No significant difference in MACE incidence was noted according to the time of the intervention after a median follow-up of 20 months. Sadeghi et al[26] evaluated the impact of delays resulting from off-hours management in the 2,036 patients included in the controlled abciximab and device investigation to lower late angioplasty complications (CADILLAC) trial. Despite increased delays during off hours, 1-year mortality was similar to that of patients presenting during daily working days. We also described in a previous work that the long-term outcome of patients with AMI after primary angioplasty was not dependant on the timing of management.[27] Conversely, 2 publications described worse outcomes in off-hours treatment. A short report by Saleem et al[28] of 1,050 patients noted a higher incidence of in-hospital death for patients presenting during off hours (7 P.M. to 7 A.M.; 5.8% vs 3.2%; $p < 0.05$). Henriques et al[29] published a post hoc analysis of 1,702 patients with ST-segment elevation myocardial infarction treated using primary PCI. They found a higher incidence of death at 30 days in the population treated during off-hours that was strongly linked with failure to achieve successful reperfusion.

Even if our study did not give definitive conclusions about AMI management during out of hours, it gave additional indication for Swiss AMI care by showing no difference in survival whether the patient is admitted during on or off hours.

Several limitations should be mentioned. By essence, the AMIS Plus is an observational study; patients were not randomly assigned to institution with or without cardiac catheterization facilities. It was recorded on a voluntary basis, and some baseline characteristics of patients were not available and may have caused unrecognized bias. The collection and controlling of data has much improved since 2000, which is why we decided to focus on the most recent years (1997 to 2006) to minimize bias caused by uncontrollable variables. Finally, all our results were limited by design to the in-hospital period. Whether longer follow-up would have changed results is not known.

Appendix

STEERING COMMITTEE: P. Erne, President, Luzern; F.W. Amann, Zürich; O. Bertel, Zürich; E. Camenzind, Genève; F.R. Eberli, Zürich; J.-M Gaspoz, Genève; F. Gutzwiller, Zürich; P. Hunziker, Basel; M. Maggiorini, Zürich; B. Quartenoud, Fribourg; H. Rickli, St. Gallen; J. Schilling, Zürich; P. Siegrist, Zürich; J.-Ch. Stauffer, Lausanne; P. Urban, Genève; and S. Windecker, Bern.

DATA MANAGEMENT CENTER: D. Radovanovic, N. Duvoisin, J. Piket, E. Hollinger, and C. Baumgartner.

PARTICIPATING CENTERS: The following hospitals participated in the AMIS Registry, on which this report from 1997 to 2006 was based (in alphabetical order): Kantonsspital, Altdorf (Dr. R. Simon), Kantonales Spital Altstätten, Altstätten (Dr. P.-J. Hangartner), Kantonsspital, Basel (PD Dr. P. Hunziker), St. Claraspital, Basel (Dr. C. Grädel), Inselspital, Bern (Prof. B. Meier/PD Dr. S. Windecker), Spitalzentrum Biel, Biel (Dr. H. Schläpfer), Oberwalliser Kreisspital, Brig-Glis (Dr. D. Evéquoz), Spital Bülach, Bülach (Dr. R. Pampaluchi/Dr. A. Ciurea), Rätisches Kantons- und Regionalspital Chur, Chur (Dr. P. Müller), Kreuzspital, Chur (Dr. V. Wüscher), Spital Davos, Davos Platz (Dr. G. Niedermaier), Spital Dornach, Dornach (Dr. A. Koelz), Kantonsspital Frauenfeld, Frauenfeld (Dr. H.P. Schmid), Hôpital Cantonal Fribourg, Fribourg (Dr. B. Quartenoud), Spital Frutigen, Frutigen (Dr. S. Moser), HUG, Genève (Dr. J.-M. Gaspoz), Kantonsspital, Glarus (Dr. W. Wojtyna), Spital Grenchen, Grenchen (Dr. P. Schlup/Dr. A. Oestmann), Bezirksspital Grosshöchstetten, Grosshöchstet-

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