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Early Drug Therapy and In-Hospital Mortality following Acute Myocardial Infarction

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Key Words
Drug therapy · Acute myocardial infarction · In-hospital mortality

Abstract
Background: Early drug therapy in patients with ST-elevation infarction is essential for improved short- and long-term outcomes. Most of the drugs used currently have been extensively studied in the era prior to reperfusion therapies, and thus it is important to assess the value of these drugs in today's clinical practice and compare the results with those of randomized trials. ***Objectives:*** The study assessed the effects of age, gender, risk factors, reperfusion therapy and early drug therapy in patients with acute myocardial infarction with ST elevation or new left bundle-branch block on in-hospital mortality. ***Methods:*** The analysis of drug administration and in-hospital mortality is based on the AMIS Plus project, a registry of acute coronary syndromes in Switzerland since 1997. Data from 7,279 patients admitted to participating hospitals between 1997 and 2002 were analyzed, and the effect of factors and drug therapies on in-hospital mortality was assessed by logistic regression analysis. ***Results:*** Age and diabetes were identified as factors associated with a higher likelihood of in-hospital mortality, while a significant and important reduction of in-hospital mortality was due to the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) [relative risk reduction (RRR) of 31%, odds ratio (OR) and 95% confidence interval: 0.69; 0.54–0.87; p = 0.002 for thrombolysis, RRR of 34%; OR 0.66; 0.44–0.99; p = 0.044 for PCI]. Early administration of aspirin or ADP antagonists is associated with a risk reduction of in-hospital mortality by 36% (OR 0.63; 0.45–0.89; p = 0.009) and 50% (OR 0.49; 0.35–0.70; $p < 0.001$), respectively. The use of unfractionated heparin did not reduce in-hospital mortality. Administration of ACE inhibitors, nitrates or beta-blockers reduced the relative risk of in-hospital death by 40% (OR 0.60; 0.49–0.75; p = 0.009), 42% (OR 0.58; 0.46–0.72; $p < 0.001$) and 54% (OR 0.46; 0.37–0.57; $p < 0.001$), respectively. Less frequent use of reperfusion therapies and beta-blockers was documented for older patients. Gender was not a determining factor for in-hospital survival. ***Conclusion:*** Early administration of aspirin or ADP inhibition with ticlopidine or clopidogrel as well as the

[1] Acute Myocardial Infarction and Unstable Angina in Switzerland (AMIS Plus). List of participating hospitals in the 'Appendix'.

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early use of beta-blockers, nitrates and ACE inhibitors had a beneficial effect on in-hospital mortality in the reperfusion era with either thrombolytics or PCI. The association of a beneficial effect of ADP inhibition was more pronounced than that found in randomized trials for non-ST-elevation infarction. However, it cannot be excluded that patients with a lower risk for in-hospital death who were selected for early invasive assessment received more frequently ADP inhibitors and that this influenced this beneficial effect. Diabetes and age had negative effects on in-hospital mortality, and both reperfusion therapy and beta-blockers were much less frequently used in elderly patients.

Introduction

The management of acute myocardial infarction (MI) in patients with ST elevation was recently reviewed by the Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology [1]. Many drug therapies such as aspirin, beta-blockers, heparins and nitrates, once cornerstones of therapy and heralded as major advances in the treatment of patients with MI, need to be reassessed in the context of thrombolysis and percutaneous coronary interventions (PCI) as revascularization strategies. The treatment of acute MI underwent a remarkable evolution over the past decade [2]. The effectiveness of aspirin was convincingly evidenced by the ISIS-2 trial [3] and its clinical value documented in large meta-analyses [4, 5]. The beneficial use of heparins in addition to aspirin was documented by the ISIS-3 trial [6]. Although there is substantial evidence that starting therapy with ACE inhibitors on the 1st day of MI can reduce mortality by a small but significant amount [7, 8], other studies failed to show a benefit [9]. A large number of trials carried out in the prethrombolytic era demonstrated a reduction in mortality and reinfarction by beta-blockers. The beneficial effects of beta-blockade were documented in subgroups [10], but careful meta-analysis indicated that early administration of beta-blockers has a positive effect on both short- and long-term outcomes after MI [11]. A significant reduction of mortality due to nitrates was shown in a meta-analysis [12], but this positive effect could not be demonstrated in large randomized trials [7, 8].

Prospective, randomized trials do not necessarily reflect the wider-range patient population, nor do they necessarily reflect a transfer of findings to clinical practice. Registries of defined populations have some important limitations. However, they do offer the opportunity to study the impact of new evidence, to evaluate adherence to guidelines and to assess the impact of therapies in an unselected group of patients [2]. They also offer the possibility of improving compliance to therapy as shown for the use of aspirin [13–15] and beta-blockers [16, 17] following MI. In Switzerland, we initiated a registry on acute MI in 1997 and we now report on the impact of early drug therapy on in-hospital mortality in patients with acute MI.

Methods

The AMIS Plus Registry

In 1997 the Swiss Societies of Cardiology, Internal Medicine and Intensive Care initiated a registry to assess the diagnostic and therapeutic measures in patients with acute MI in Switzerland (AMIS). Participating hospitals provide blinded data on these patients to a Data Center through an Internet- and paper-based questionnaire of 140 questions. The Data Center checks the data for plausibility and cross-checks in case of queries. In 2000, unstable angina was added to this Registry and the Data Center was transferred from Geneva to Zurich (AMIS Plus). The project is led by a Steering Committee comprised of members of the founding societies. The Registry was approved by the Above-Regional Ethical Committee for Clinical Studies and the Swiss Board for Data Security.

Patients

The AMIS Plus Registry documented data from 11,845 patients admitted to hospital for acute coronary syndrome between 1997 and 2002. In the present analysis, data from 7,279 patients with ST elevation or new left bundle-branch block (LBBB) were analyzed. The characteristics of these patients are summarized in table 1. The most dominant risk factors were overweight, dyslipidemia and hypertension. We analyzed the drugs administered within 48 h of symptom onset and their impact on in-hospital mortality. Reinfarction, cerebrovascular insult and death were defined as major cardiac events.

Statistical Analyses

Data are presented as percentages for discrete variables and as mean ± SD and median for continuous variables. The nonparametric Mann-Whitney rank sum test was used for group comparisons. A p value of <0.05 was considered significant.

To predict hospital mortality, a multivariate logistic regression analysis was conducted using the following variables: age, gender, Killip class admission (Killip class 1 as a reference category with an odds ratio, OR, of 1.0), history of hypertension, diabetes, drugs administered within 48 h after symptom onset (aspirin, beta-blocker, ticlopidine or clopidogrel, standard heparin, ACE inhibitor, and nitrates). Angiotensin II antagonists, low-molecular-weight heparin and statins were excluded from analysis in order to increase the sample size in the multivariate analysis.

SPSS (Chicago, Ill., USA) for Windows XP (version 11.5) was used for all statistical analyses.

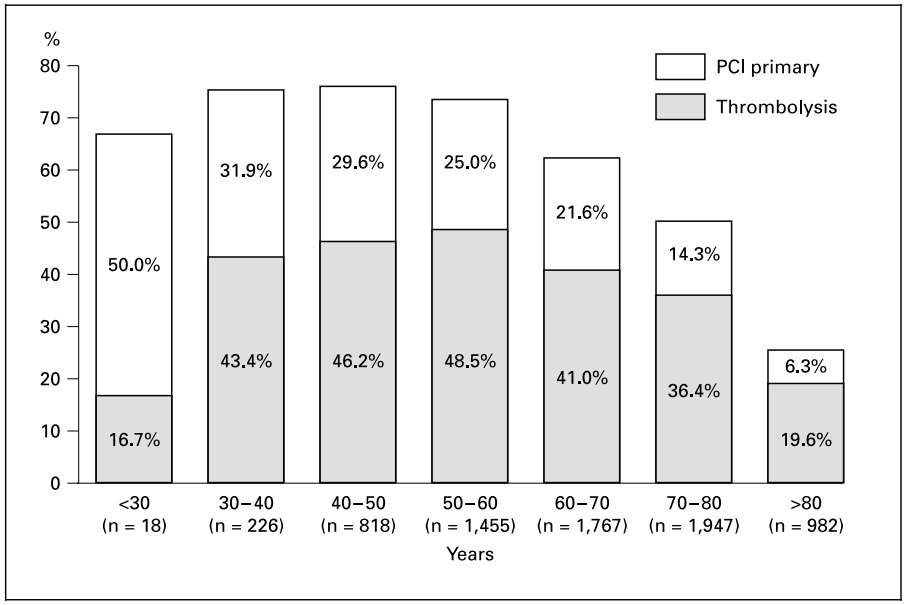

Fig. 1. Reperfusion therapies in patients with ST elevation and/or LBBB.

Table 1. Characteristics of the study population (n = 7,279)

	Cases	
Sex	7,177	
Male		73%
Female		27%
Age	7,217	
Range		23–100 years
Mean ± SD		65.3 ± 13.3 years
Median		66 years
Killip class	7,083	
Killip class I		72%
Killip class II		19%
Killip class III		6%
Killip class IV		3%
Past medical history		
Coronary artery disease	5,258	36%
Hypertension	6,995	50%
Hyperlipidemia	6,619	54%
Diabetes	7,042	20%
Smoking (current)	6,875	43%
Overweight (BMI ≥25)	4,800	62%
Delay (median)	6,570	3.45 h

Results

Reperfusion Therapy in Patients with ST Elevation or New LBBB

In most patients, reperfusion therapy was carried out, although this therapy did not exceed 80% in any of the patient groups and was less frequently used in patients older than 60 years (fig. 1). Primary PCI was the preferred therapeutic strategy in the very young patient group, and the older the patient the less this therapy was applied. There is a definitely increasing temporal trend for PCI, this strategy being used in 8% of patients in 1997 and in almost 43% of patients in 2002.

Early Drug Therapy in Patients with ST Elevation or New LBBB

Early drug therapy was defined as the administration of drugs within 48 h of symptom onset. In table 2, the frequency of administration within the various age groups is summarized. Aspirin, unfractionated heparin and nitrates were most frequently administered in all age groups. Beta-blockers were more frequently used in younger age groups and ACE inhibitors in elderly patients. Inhibitors of ADP-induced platelet aggregation, ticlopidine and clopidogrel, were administered in those age groups with more frequent PCIs. ADP inhibitors were applied to 1,839 patients (25.6%), 968 of these patients underwent primary PCI, while in 871 patients with ADP inhibitors PCI was not performed as the primary revascu-

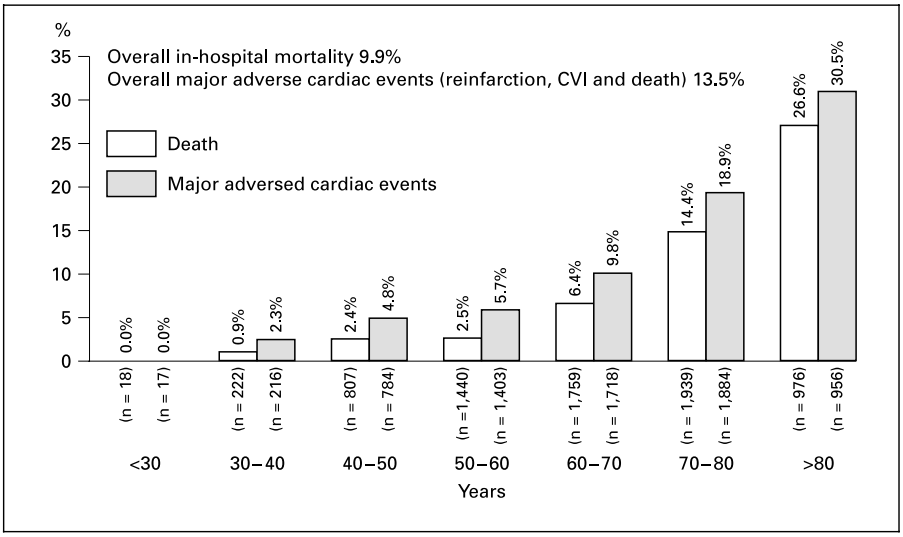

Fig. 2. Outcome in patients with ST elevation and/or LBBB.

Table 2. Early drug therapy in patients with ST elevation and/or LBBB (%)

	Age groups, years						
	<30	30–40	40–50	50–60	60–70	70–80	>80
Aspirin (n = 7,088)	94.4	94.2	96.4	96.3	94.4	92.8	89.6
Ticlopidine, clopidogrel (n = 7,019)	66.7	33.9	37.7	32.4	26.0	21.4	11.1
Unfractionated heparin (n = 7,089)	77.8	83.6	89.3	88.5	86.9	85.8	76.8
Low-molecular-weight heparin (n = 3,460)	25.0	19.2	17.4	20.5	20.8	19.6	32.0
Beta-blocker (n = 7,069)	66.7	82.7	82.5	80.5	71.5	63.2	47.1
ACE inhibitor (n = 6,915)	27.8	34.3	36.6	36.7	40.1	43.9	43.5
Angiotensin II antagonist (n = 3,281)	0.0	0.0	1.9	1.9	2.8	4.7	4.3
Ca channel blocker (n = 7,026)	0.0	3.1	3.3	2.6	4.1	6.3	7.2
Nitrate (n = 7,069)	77.8	70.2	77.6	77.0	74.5	75.6	76.3
Lipid-lowering drug (n = 1,620)	80.0	62.5	70.1	66.8	62.6	59.0	30.4

larization strategy. Calcium channel blockers and the more recent angiotensin II antagonists were infrequently used in acute MI (less than 5% of patients) and were thus excluded from further analysis.

In-Hospital Mortality and Major Adverse Cardiac Events

An overall hospital mortality of 9.9% (n = 717) and an incidence of major adverse cardiac events (MACE) of 13.5% (n = 949) were documented. In figure 2, the age-associated increases in in-hospital mortality and incidence of MACE, as well as maximal mortality (26.6%) and incidence of MACE (30.5%) in patients older than 80 years are shown. In table 3, the result of the logistic regression analysis, odds ratios, and confidence limit with regard to in-hospital mortality in this patient population, is summarized. Age and the Killip class were the important determinants of increased mortality, while gender had no significant association and effect on in-hospital mortality. In-hospital mortality increased by 6% per year of age. While diabetes had a negative effect, hypertension had no significant effect on in-hospital mortality. Both thrombolysis and PCI reperfusion strategies reduced the risk of in-hospital mortality by more than 30%. The use of unfractionated heparin did not affect in-hospital mortality, whereas the use of aspirin, inhibition of ADP-platelet

Table 3. Multivariate logistic regression model for predicting in-hospital mortality at admission (n = 6,306)

	OR	95.0% confidence interval for OR		p value
		lower	upper	
Age (per year)	1.064	1.05	1.08	0.000
Gender	0.85	0.69	1.05	0.13
Killip class 1	1.00			–
Killip class 2	2.13	1.68	2.69	0.000
Killip class 3	4.32	3.19	5.84	0.000
Killip class 4	13.63	8.96	20.71	0.000
Diabetes	1.34	1.07	1.67	0.011
Hypertension	1.12	0.91	1.38	0.279
Aspirin[1]	0.63	0.45	0.89	0.009
Beta-blocker[1]	0.46	0.37	0.57	0.000
Ticlopidine, clopidogrel[1]	0.49	0.35	0.70	0.000
Standard heparin[1]	1.13	0.86	1.49	0.393
ACE inhibitor[1]	0.60	0.49	0.75	0.000
Nitrate[1]	0.58	0.46	0.73	0.000
Thrombolysis	0.69	0.54	0.87	0.002
Primary PCI	0.66	0.44	0.99	0.044

[1] Medication within 48 h after chest pain began (including emergency medication).

aggregation, beta-blockers and ACE inhibitors was associated with a risk reduction of in-hospital death by 37, 50, 54 and 39%, respectively.

Study Limitation

The number of participating hospitals during the time of this data collection varied, ranging from 18 to 52 (from rural to university) of the 106 hospitals treating acute MI in Switzerland. Therefore, the participating hospitals may not be representative of all Swiss hospitals. However, no differences were documented on early drug treatments between the different categories of hospitals with the exception of the use of GP IIb/IIIa antagonists, which were more frequently applied early in hospitals with direct cath lab facilities (data not shown). On-site validation of data collection was only periodic and there were no checks for consistency between data-base entries and medical chart notes. There were no assessments of clinical eligibility for each medication, and thus failure in the use of certain medications may reflect contraindication to their use. Furthermore, there was no follow-up after hospital discharge since the Ethical Committee and Board for Data Security restricted the registry to the collection of anonymous data.

Discussion

The AMIS Plus project is a registry of patients admitted with unstable angina or acute MI in Switzerland. Its purpose is to enable assessment of temporal changes in the epidemiology of patients, and in diagnostic and therapeutic measures. Another purpose is to facilitate the control of compliance of evidence from randomized trials and the evolution of guidelines [1, 18] in the treatment of MI and unstable angina. Registries are valuable means of documenting potential under- or overuse of diagnostic procedures, of defining how new information from evidence-based medicine is transferred to clinical practice, and also of documenting effects not addressed in clinical trials [16].

This study focused on the in-hospital mortality of patients with ST-elevation MI as a strong outcome measure and confirms the already documented importance of age and diabetes for higher in-hospital mortality. Furthermore, as documented in other registries [2] and studies [19], we report a reduced reperfusion therapy in older patients. Moreover, this study has found that reperfusion therapy is highly effective and provides a relative overall risk reduction of more than 30% on in-hospital mortality. As in studies on patients with severe coronary artery disease [20], but in contrast to the present investigation in MI, beta-blockers were more widely used in a younger patient population while ACE inhibitors were more frequently used in older patients. Based on this result, it might be concluded that elderly patients are less likely to receive guideline-indicated therapies. The less frequent use of therapies is most obvious for acute reperfusion for both thrombolytic therapy and primary angioplasty, while aspirin is evenly administered to patients of all age groups.

The administration of aspirin in the acute phase of MI resulted in a 34% reduction of in-hospital mortality and it was postulated that it is of utmost importance to give aspirin to all patients as soon as the diagnosis of acute MI is deemed probable [1]. This is clearly taken into account by the participating hospitals. We cannot exclude a bias in the sense that patients with MI who did not receive aspirin suffered from other serious conditions such as bleeding disorders or recent surgery, which did not allow administration of aspirin, and that these conditions might have influenced the incidence of MACE and in-hospital deaths. In patients who were treated by ADP inhibition, a similar but more pronounced association of risk reduction (50%) has been documented irrespective of whether the patients underwent angioplasty as a primary treat-

ment strategy. However, it cannot be excluded that ADP inhibition was more frequently used in patients who were managed with the option of early percutaneous intervention. This association of ADP inhibition was also greater than the relative risk reduction (31%) found with clopidogrel in the CURE trial, in which patients with non-ST elevation were treated [21]. Although the beneficial effect of heparin was documented in a large randomized trial [6], this study found the use of unfractionated heparin to be associated with a trend, albeit not significant, toward increased in-hospital mortality. We do not know if the participating hospitals monitored the effect of heparin and adjusted the dose to values for partial thromboplastin time, since values over 70 s increase the likelihood of mortality [22].

Apart from hypotension, renal failure and angioneurotic edema, it is now generally agreed that there are no major contraindications for starting ACE inhibitors early, in particular in patients with impaired ejection fraction or patients who experienced heart failure in the early phase [23]. However, in an unselected patient population of variable reduction of ejection fraction, the overall effect might be small but nevertheless significant. In this trial of patients cared for in daily routine practice, we could document an important 39% relative risk reduction on in-hospital mortality. A similarly unexpected and important association with reduced in-hospital mortality for early use of nitrates was also documented in this trial. However, this positive association may emerge from a more common use of nitrates to reduce ischemic burden, which would contrast with randomized studies in which nitrates were administered independently of chest pain [7].

Early intravenous administration of beta-blockers was convincingly documented prior to the use of fibrinolytic agents or PCI [24]. However, a post hoc analysis of the GUSTO-I trial [25] did not support the routine early intravenous use of beta-blockers in today's care of patients by revascularizations. On the other hand, it is widely agreed that early oral administration of beta-blockers is beneficial for both short- and long-term outcome of MI, and this study documented an impressive association to relative risk reduction of 54% on in-hospital mortality.

In summary, this study based on a large patient population in a registry of acute coronary syndromes demonstrates an outstanding association for the early administration of beta-blockers, ACE inhibitors and nitrates in patients with ST elevation in an era where drug or interventional revascularization was frequently used. These results suggest that under these circumstances, the beneficial effects of platelet inhibition by aspirin and ADP antagonism on in-hospital mortality were even larger than in studies on patients with non-ST elevation. Overall, we documented a high rate of mortality in association with age and diabetes but also a very low rate of reperfusion therapy provision to older patients.

Appendix

Funding and Participants

The AMIS Plus Registry is funded by grants from (in alphabetical order): Astra-Zeneca, Switzerland, Biotronik, Switzerland, Bristol-Myers Squibb, Switzerland, Guidant AG, Switzerland, Johnson & Johnson, Switzerland, Jomed AG, Switzerland, Medtronic AG, Switzerland, A. Menarini AG, Switzerland, Merck Sharp Dohme Chibret, Switzerland, Pfizer AG, Switzerland, Rahn Foundation, Switzerland, Roche Pharma, Switzerland, Swiss Heart Foundation. Their support is gratefully acknowledged. The supporting institutions did not play any role in the design of the Registry, Data Collection, Analysis or Interpretation.

Steering Committee: P. Erne, President, Luzern, F.W. Amann, Zürich, W. Angehrn, St. Gallen, O. Bertel, Zürich, J.-M. Gaspoz, Genève, S. Dehler, Zürich, F.R. Eberli, Zürich, F. Gutzwiller, Zürich, P. Hunziker, Basel, M. Maggiorini, Zürich, B. Quartenoud, Fribourg, J. Schilling, Zürich, P. Siegrist, Zollikerberg, J.-Ch. Stauffer, Lausanne, P. Urban, Genève and S. Windecker, Bern.

The following hospitals participated in the AMIS Registry on which this report is based from 1997–2002 (in alphabetical order): Kantonsspital, Altdorf (Dr. R. Simon), Kantonales Spital Altstätten, Altstätten (Dr. P.-J. Hangartner), Kantonsspital Basel, Basel (PD Dr. P. Hunziker), St. Claraspital, Basel (Dr. C. Grädel), Inselspital, Bern (Prof. B. Meier), 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), Hôpital cantonal Fribourg, Fribourg (Dr. B. Quartenoud), Spital Frutigen, Frutigen (Dr. S. Moser), HUG, Genève (Dr. J.-M. Gaspoz), Kantonsspital Glarus, Glarus (Dr. W. Wojtyna), Spital Grenchen, Grenchen (Dr. P. Schlup/Dr. A. Oestmann), Bezirksspital Grosshöchstetten, Grosshöchstetten (Dr. C. Simonin), Kantonales Spital, Heiden (Dr. R. Waldburger), Kantonales Spital, Herisau (Dr. P. Staub), Spital Interlaken, Interlaken (Dr. P. Sula), Spital Jegensdorf, Jegenstorf (Dr. H. Marty), Hôpital La Chaux-de-Fonds, La Chaux-de-Fonds (Dr. H. Zender), Spital Lachen, Lachen (Dr. I. Poepping), Kantonsspital, Luzern (Prof. P. Erne), Hôpital régional, Martigny (Dr. B. Jordan), Hôpital de la Tour, Meyrin (PD Dr. P. Urban), Hôpital du Chablis, Monthey (Dr. P. Feraud), Hôpital de Zone, Montreux (Dr. E. Beretta), Hôpital du Jura bernois, Moutier (Dr. Ch. Stettler), Regionales Spital Zentrum, Münsingen (Dr. F. Repond), Kreisspital für das Freiamt, Muri (Dr. A. Spillmann), Group Hosp. Ouest lémanique, Nyon (Dr. R. Polikar), Gesundheitszentrum Fricktal, Regionalspital Rheinfelden, Rheinfelden (Dr. H.-U. Iselin), Kantonales Spital, Rorschach (Dr. M. Pfister), Kantonsspital Obwalden, Sarnen (Dr. T. Kaeslin), Kantonsspital Schaffhausen, Schaffhausen (Dr. R. Frey), Spital Limmattal, Schlieren (Dr. B. Risti), Spital Schwyz, Schwyz (Dr. P. Eichhorn), Ospidal d'Engiadina Bassa, Scuol (Dr. G. Flury/Dr. C. Neumeier), Bürgerspital, Solothurn (Dr. P. Hil-

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