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Original Article

Inpatient versus outpatient onsets of acute myocardial infarction☆

Paul Erne [a,b], Osmund Bertel [c], Philip Urban [d], Giovanni Pedrazzini [e], Thomas F. Lüscher [f], Dragana Radovanovic [g,*], on behalf of the AMIS Plus Investigators

[a] AMIS Plus, Hirschengraben 84, CH-8001 Zurich, Switzerland
[b] Department of Cardiology, Cardiology Clinic, University Hospital Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland
[c] Cardiology Center, Klinik im Park, Seestrasse 220, CH-8027 Zurich, Switzerland
[d] Cardiovascular Department, La Tour Hospital, 3, avenue J.-D. Maillard, CH-1217 Geneva, Switzerland
[e] Division of Cardiology, Cardiocentro Ticino, Via Tesserete 48, CH-6900 Lugano, Switzerland
[f] University Heart Center, Department of Cardiology, University Hospital Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland
[g] AMIS Plus Data Center, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Hirschengraben 84, CH-8001 Zurich, Switzerland

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ABSTRACT

Background: There are few studies on patients suffering acute myocardial infarction (AMI) when already in hospital for other reasons; therefore, this study aimed to compare patients with in-hospital-onset AMI admitted for either medical or surgical reasons versus patients with outpatient-onset AMI.
Methods: Patients enrolled in the AMIS Plus registry from 2002 to 2014 were analyzed. The main endpoint was in-hospital mortality.
Results: Among 35,394 AMI patients, 356 (1%) had inpatient-onset AMI following hospital admission due to other pathologies (surgical 175, non-surgical 181). These patients were older (74 vs. 66 years; $P < 0.001$), more often female (35% vs. 27%; $P < 0.001$), had less frequently ST-elevation myocardial infarction (35.5% vs. 55.5%; $P < 0.001$), but higher risk profiles: hypertension (83% vs. 62%; $P < 0.001$), diabetes (28% vs. 20%; $P = 0.001$), known coronary artery disease (54% vs. 35%; $P < 0.001$), and more comorbidities (Charlson Comorbidity Index above 1 in 51% vs. 22%; $P < 0.001$) than those with outpatient-onset AMI. Percutaneous coronary intervention was less frequently applied (OR 0.45; 95% CI 0.36–0.57), and they were less likely to be treated with aspirin (OR 0.43; 95% CI 0.37–0.59), P2Y12 blockers (OR 0.42; 0.34–0.52) or statins (OR 0.51; 95% CI 0.41–0.63). Crude mortality was higher (14.3% vs. 5.5%; $P < 0.001$) and inpatient-onset AMI was an independent predictor of in-hospital mortality (OR 2.35; 95% CI 1.63–3.39; $P < 0.001$).
Conclusions: Patients with in-hospital-onset AMI were at greater risk of death than those with outpatient-onset AMI. More work is needed to improve the identification of hospitalized patients at risk of AMI in order to provide the appropriate management.

1. Introduction

There are very few studies on patients suffering acute myocardial infarction (AMI) when already hospitalized for other reasons [1,2]. In particular, prospective data are lacking in this patient population, and the magnitude of the problem has not been appropriately examined.

Of the studies available, the majority come from the surgical field. Annually, more than 200 million patients undergo surgical procedures [1], and for such patients, AMI is the most common major perioperative vascular complication [3]. Of the patients undergoing non-cardiac, non-neurological surgery, 0.24% developed Q-wave AMI within 30 days post surgery [4]. A cohort study of 8351 patients who underwent non-cardiac surgery in 190 centers of 23 countries noted an AMI incidence of 5.0% within 30 days [5]. However, patients experiencing an AMI after non-cardiac surgery have a hospital mortality rate of 15%–25% [6].

Cardiovascular complications including AMI can occur during the acute phases of many diseases, during pregnancy [7], or during medical procedures, and little is known on the incidence and outcome of AMI developing during hospitalizations for other than surgical reasons. Therefore, the aim of this study was to compare the baseline characteristics, treatments, and outcomes of patients prospectively enrolled in the AMIS Plus registry with in-hospital-onset AMI admitted for either medical or surgical reasons versus those patients with outpatient-onset AMI.

2. Methods

The AMIS Plus project is an ongoing nationwide prospective registry of patients admitted with acute coronary syndromes (ACS) to hospitals in Switzerland. It was founded by the Swiss Societies of Cardiology,

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* Corresponding author. Tel.: +41 44 634 48 34; fax: +41 44 634 49 86.
E-mail address: dragana.radovanovic@uzh.ch (D. Radovanovic).

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Internal Medicine and Intensive Care Medicine in 1997 with the goal to understand the transfer, use, and practicability of knowledge gained from randomized trials in the real world of daily clinical practice. Details have been previously published [8–12]. From 106 hospitals treating ACS in Switzerland, 82 hospitals temporarily or continuously enrolled patients in AMIS Plus. Participating centers, ranging from community institutions to large tertiary facilities, provided blinded data for each patient through standardized Internet- or paper-based questionnaires. All data were checked for completeness, plausibility, and consistency by the AMIS Plus Data Center in the Epidemiology, Biostatistics and Prevention Institute at the University of Zurich and treating physicians or study nurses were queried when necessary. External monitoring has been carried out regularly since 2010 in randomly selected hospitals using randomly selected cases. The registry was approved by the Supra-Regional Ethics Committee for Clinical Studies, the Swiss Board for Data Security, and the Cantonal Ethics Commissions.

The questionnaire comprised items addressing medical history, comorbidities, known cardiovascular risk factors, clinical presentation, out-of-hospital management, early in-hospital management, reperfusion therapy, hospital course, used or planned diagnostic tests, length of stay, discharge medication, and discharge destination. Patients were enrolled on the basis of their final discharge diagnosis.

Information on known risk factors was obtained from the patient's medical history. Dyslipidemia, arterial hypertension, and diabetes were considered if the patient had been previously treated for such a condition and/or diagnosed by a physician. Patients were defined as obese if the body mass index was ≥30 kg/m^2 and as smokers if the patient was smoking at the time of the cardiovascular event. Patient comorbidities were assessed using the Charlson Index [13,14]. Immediate drug therapy was defined if administrated within 24 hours after admission. Bleeding complications were recorded if deemed clinically relevant by the individual physician caring for the patient, without the use of a classification system. Reinfarction was defined as clinical signs or symptoms of ischemia with ECG changes indicative of new ischemia (new ST-changes or new LBBB) and a re-rise of biomarkers following the initial infarction. A stroke was defined as any event due to ischemic, thrombotic, or hemorrhagic disturbances confirmed by a neurologist or imaging modality.

The primary outcome measure was in-hospital mortality. Secondary outcome measures were the rates of in-hospital major adverse cardiac or cerebrovascular events (MACCE) defined as a composite endpoint of mortality, reinfarction, and cerebrovascular events. An additional outcome measure in a subgroup of patients was 1-year mortality.

2.1. Patient selection

The present analysis included all patients enrolled in AMIS Plus between January 2002 and September 2014. AMI was defined by characteristic symptoms and/or ECG changes and cardiac marker elevation (creatinine kinase MB fraction at least twice the upper limit of normal or troponin I or T above individual hospital cut-off levels for AMI). Patients with unstable angina were excluded.

The patients with in-hospital-onset AMI were additionally divided into three groups according to the primary admission reasons: surgery, internal medicine diseases (including gastric, urological, pulmonary, neurological, oncological, dermatological, and ophthalmological diseases), and diagnostic procedures.

Subgroup analyses for 1-year mortality after discharge were performed using patients enrolled from 2006 to 2014, who had signed an informed consent form for follow-up participation.

2.2. Statistical analysis

The results are presented as percentages for categorical variables and analyzed using the non-parametric Pearson chi-square test or Fisher's exact test as appropriate. Continuous normally distributed variables are expressed as means ± 1 standard deviation (SD) and compared using the Student's two-tailed unpaired t-test. Continuous non-normally distributed variables are expressed as median and interquartile ranges and analyzed using the Mann–Whitney *U* test. The differences in immediate and discharge therapies between the groups, the odd ratios (OR) were additionally adjusted for age and gender. A univariate analysis was carried out using all available variables and calculated only for patients with no missing variables. To determine in-hospital independent mortality predictors, a multivariate logistic regression model was applied for the same population using the following variables: inpatient-onset AMI, age, sex, Killip class >2, the risk factors dyslipidemia, hypertension, and diabetes as well as a Charlson comorbidity weighted index >1. The results of logistic regression are reported as OR with a 95% confidence interval (95% CI). A probability value of $P < 0.05$ was considered significant. SPSS software (version 22, SPSS Inc, Chicago, Illinois, USA) was used for all other statistical analyses.

3. Results

Between 2002 and 2014, 35,394 patients with AMI from 68 Swiss hospitals were enrolled in the AMIS Plus Registry. From these, 356 (1%) suffered in-hospital-onset AMI: 121 patients (34%) were hospitalized for various internal medicine diseases, such as gastric (6.7%), pulmonary (5.1%), urological (6.7%), neurological (6.2%), oncological (3.7%), or other medical disorders (ophthalmological or dermatological conditions, infections or delivery; 3.9%), 175 (49.2%) for surgery (orthopedic, visceral, or vascular), and 60 (16.9%) patients were hospitalized for diagnostic procedures.

Inpatient-onset AMI patients were older, more often female, hypertensive or diabetic with more moderate to severe comorbidities than those with outpatient-onset AMI. Chest pain was less frequently the leading symptom for AMI in patients admitted for other indications (Table 1).

Patients who suffered in-hospital-onset AMI underwent less frequently percutaneous coronary interventions, and if performed then considerably later with a median of 24 hours after symptom onset. These patients were less likely to immediately receive drugs such as aspirin, P2Y12 blockers, or statins even after adjusting for gender and age (Table 2).

Table 1
Baseline characteristics of patients according to AMI-onset location.

	Outpatient-onset AMI	Inpatient-onset AMI	P value
Number of patients	35,038	356	
Sex female	9406/35,038 (26.8)	123/356 (34.6)	0.001
Age in years, mean (SD)	66.1 (13.3)	74.0 (10.6)	<0.001
Symptoms			
Pain	28,597/33,264 (86.0)	207/308 (67.2)	<0.001
Dyspnea	9329/30,895 (30.2)	104/303 (34.3)	0.13
ST-elevation myocardial infarction	19,359/34,875 (55.5)	126/355 (35.5)	<0.001
Killip classes 3/4 at presentation	2426/34,837 (7.0)	51/351 (14.5)	<0.001
Risk factors			
Smoking	12,145/31,623 (38.4)	84/287 (29.3)	0.002
Dyslipidemia	17,878/30,796 (58.1)	211/312 (67.6)	0.001
Hypertension	20,460/33,132 (61.8)	278/336 (82.7)	<0.001
Obesity (BMI≥30)	6243/29,751 (21.0)	62/311 (19.9)	0.72
Diabetes	6753/33,513 (20.2)	95/344 (27.6)	0.001
Coronary artery disease	11891/34,448 (34.5)	188/347 (54.2)	<0.001
Charlson Comorbidity Index>1	7723/35,038 (22.0)	182/356 (51.1)	<0.001

n/N (%)

Table 2
Immediate therapies of patients according to AMI-onset location.

	Outpatient-onset AMI	Inpatient-onset AMI	P value	OR adjusted for age and gender (95% CI)
Number of patients	35,038	356		
Aspirin	33,282/34,899 (95.4)	309/354 (87.3)	<0.001	0.43 (0.37–0.59)
P2Y12 blocker	28124/34,829 (80.7)	201/349 (57.6)	<0.001	0.42 (0.34–0.52)
Heparin	30,149/34,778 (86.7)	287/352 (81.5)	0.006	0.77 (0.59–1.00)
Beta-blocker	21,367/33,883 (63.1)	178/347 (51.3)	<0.001	0.66 (0.53–0.81)
ACEI/ARB	18,044/33,890 (53.2)	153/350 (43.7)	<0.001	0.68 (0.55–0.84)
Statin	25,659/33,932 (75.6)	198/349 (56.7)	<0.001	0.51 (0.41–0.63)
PCI (any)	27,565/33,976 (81.1)	193/341 (56.6)	<0.001	0.45 (0.36–0.57)
Time to PCI (median in min; IQR)	91 (31, 335)	1654 (207, 5620)	<0.001	

n/N (%);
P2Y12 blocker—clopidogrel, prasugrel, or ticagrelor
ACEI/ARB—angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, PCI—percutaneous coronary intervention

At discharge, these patients less frequently received guideline-recommended drug therapy for secondary prevention, such as aspirin, P2Y12 blockers, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin II receptor antagonists (ARB), beta-blockers or statins, even after adjusting for gender and age (Table 3).

Overall outcome was worse for patients with inpatient-onset AMI compared to those with outpatient-onset AMI; they more frequently developed cardiogenic shock during hospitalization (9.0% vs. 3.8%; $P < 0.001$), and bleeding (4.8% vs. 2.6%; $P = 0.023$). Stroke and re-infarction rates in hospital were similar for both groups (1.7% vs. 1.0%; $P = 0.18$ and 1.1% vs. 0.7%; $P = 0.31$, respectively) but length of stay was significantly longer for patients with in-hospital-onset AMI [median 12 days (IQR 6, 21 days) versus 5 days (IQR 2, 8 days); $P < 0.001$] and these patients also had a higher crude in-hospital mortality (14.3% vs. 5.5%; $P < 0.001$) and MACCE (15.8% vs. 6.6%, $P < 0.001$).

Logistic regression analysis showed that even after adjusting for baseline differences including the comorbidity score, inpatient-onset AMI remained an independent predictor of in-hospital mortality (OR 2.35, 95% CI 1.63–3.39; $P < 0.001$). (Table 4)

Outcome analyses of the primary hospitalization reasons of patients with in-hospital AMI onset showed that those with internal medicine diseases had worse in-hospital outcomes, albeit not significant, compared to patients hospitalized for surgical and diagnostic procedures. (Fig. 1)

From 2006 to 2014, 8,310 AMI patients were followed up after a median duration of 386 days after the event (IQR 370, 409 days). From 71 patients who suffered inpatient-onset AMI and were followed thereafter, 7 died (9.9%) during the follow-up period versus 3.6% of patients with outpatient-onset AMI ($P = 0.014$). Patients admitted for somatic diseases with in-hospital-onset AMI had significantly higher mortality 1 year after discharge than patients admitted for surgery (25.0% vs. 7.5%; $P = 0.049$).

4. Discussion

Our study has several key findings. First, patients with inpatient-onset AMI differed in their baseline characteristics compared to those with outpatient-onset AMI: they were more often female, sicker, and older. Second, these patients were less likely to receive guideline-recommended drugs and interventions for the treatment of acute AMI, and third, they were at higher risk of death, both during their index hospital stay as well as during the 1-year follow-up period. The most common reason for the initial hospitalization in our study was surgery. The causes of AMI in surgical patients have already been thoroughly addressed by others [2,5,6].

The incidence of AMI in patients undergoing surgery has been reported as less than 1% [15] to above 10%. For instance, from the patients who underwent laparoscopic sigmoid resection for diverticular disease, 1.14% had cardiac complications [16], while 11.2% patients suffered an AMI after colorectal surgery [17]. Patients undergoing head and neck surgery had an AMI rate of 0.3% [18]. In studies where patients were actively monitored for perioperative AMI, the incidence was markedly higher [5], suggesting that cardiac damage in the perioperative period is often overlooked by the treating physicians. Of note, however, most patients with perioperative AMI were asymptomatic [5]. Two studies regarded routine monitoring of cardiac biomarkers after surgery as essential, irrespective of whether the patient experiences ischemic symptoms or not [5,19]. Risk assessment of AMI should be considered particularly during the first 6 weeks after total hip replacement or during the first 2 weeks after knee replacement surgery [20].

In our patient population, 49.2% of the patients suffered in-hospital-onset AMI while undergoing a surgical procedure. Our results are in accordance with a large study on inpatient-onset ST-elevation MI using the California State Inpatient Database [2]. Indeed, it is known that most postoperative AMIs occur within the first 48 hours after surgery [5]. Of note, patients undergoing non-cardiac surgery who suffered a perioperative AMI had a 5-fold higher 30-day crude mortality rate irrespective of ischemic symptoms [5]. In our study, the crude in-hospital mortality rate of surgical patients was 13.7 % and lower than for patients suffering AMI when already in hospital for internal medicine diseases (19.0%). The number of follow-up patients was too small to allow further conclusions. Kaul et al. analyzed 3068 patients with STEMI while hospitalized for non-ACS conditions. They found the risk was lowest in patients with no procedures and highest in patients undergoing cardiac surgery [2].

Table 3
Discharge therapies of patients according to AMI-onset location.

	Outpatient-onset AMI	Inpatient-onset AMI	P value	OR adjusted for age and gender (95% CI)
Number of patients	33,116	305		
Aspirin	31,664/32,990 (96.0)	273/305 (89.5)	<0.001	0.50 (0.34–0.72)
P2Y12 blocker	27,744/32,937 (84.2)	194/302 (64.2)	<0.001	0.46 (0.36–0.59)
Beta-blocker	26,191/32,886 (79.6)	220/305 (72.1)	0.001	0.71 (0.55–0.91)
ACEI/ARB	25,435/32,871 (77.4)	214/304 (70.4)	0.004	0.66 (0.54–0.88)
Statin	25,661/28,474 (90.1)	229/286 (80.1)	<0.001	0.60 (0.44–0.81)

n/N(%)
P2Y12 blocker—clopidogrel, prasugrel, or ticagrelor
ACEI/ARB—angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist

Table 4
Univariate and independent predictors of in-hospital mortality.

	All patients (n = 29,589)				Patients with AMI in hospital (n = 301)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
AMI in hospital	3.88 (2.80–5.38)	<0.001	2.35 (1.63–3.39)	<0.001				
Female gender	1.69 (1.50–1.90)	<0.001	1.10 (0.96–1.25)	0.16	1.40 (0.71–2.73)	0.33	1.38 (0.66–2.87)	0.39
Age (per additional year)	1.07 (1.06–1.08)	<0.001	1.06 (1.05–1.07)	<0.001	1.07 (1.03–1.11)	0.001	1.05 (1.01–1.09)	0.014
Diabetes	1.83 (1.62–2.7)	<0.001	1.16 (1.00–1.34)	0.046	1.16 (0.57–2.36)	0.67	1.13 (0.49–2.59)	0.77
Hypertension	1.39 (1.23–1.57)	<0.001	0.78 (0.68–0.90)	<0.001	0.88 (0.38–2.02)	0.75	0.99 (0.39–2.52)	0.96
Dyslipidemia	0.66 (0.59–0.74)	<0.001	0.71 (0.63–0.81)	<0.001	0.40 (0.21–0.77)	0.006	0.49 (0.22–1.07)	0.072
Coronary artery disease	1.28 (1.14–1.43)	<0.001	0.83 (0.73–0.95)	0.007	0.48 (0.25–0.92)	0.027	0.58 (0.27–1.25)	0.17
Charlson Comorbidity Index>1	3.42 (3.05–3.84)	<0.001	1.96 (1.71–2.26)	<0.001	1.93 (0.98–3.77)	0.056	2.20 (1.00–4.84)	0.049
Killip class>2	11.9 (10.4–13.5)	<0.001	8.90 (7.77–10.2)	<0.001	4.13 (1.95–8.73)	<0.001	3.72 (1.66–8.35)	0.001

In a previous study, a substantial proportion of patients with perioperative AMI were treated with secondary prophylaxis cardiac interventions known to be beneficial, such as statins or ACEIs [5]. In our study population, ACEI and/or ARB antagonists were prescribed in patients with AMI in hospital more frequently than in patients with out-of-hospital AMI, but statins and aspirin, unfortunately, were not. Physicians are possibly reticent of prescribing aspirin in the perioperative period. Special attention should be paid to patients with coronary stents who require non-cardiac surgery [21]. Indeed, the use of double antiplatelet treatment with aspirin and clopidogrel in patients undergoing coronary artery bypass grafting up to the time of surgery is associated with an increased risk of postoperative AMI [22].

In a large prospective multicenter study of patients undergoing non-cardiac surgery, seven predictors of perioperative MACCE in non-cardiac surgery were evaluated, i.e., the presence of coronary artery disease, heart failure, kidney disease, cerebrovascular disease, abnormal ECG, intraoperative hypotension, and blood transfusion [23]. From the American Surgeons' 2007 database, which included 211,410 patients, 5 predictors of perioperative MI were identified: type of surgery, dependent functional status, abnormal creatinine levels (>1.5 mg/dL), and increasing age [15]. In our patient population, only age and a Killip class >2 were independent predictors of in-hospital mortality.

Furthermore, internal medicine patients had worse outcomes than surgery patients. To our knowledge, this is the first cardiological study investigating the clinical characteristics and outcomes of patients suffering an AMI during hospitalizations not only for surgical but also for other reasons.

There are many case reports regarding AMI as an in-hospital complication of patients treated for conditions, such as endocarditis [24,25], acute pancreatitis [26], rheumatoid arthritis [27], venous thromboembolism [28], diabetes mellitus [29], antiphospholipid syndrome [30], ovarian hyperstimulation syndrome [31], anorexia nervosa [32], anaphylaxis [33], and blunt chest trauma [34]. Among the 121 patients with somatic conditions in this study (n = 121), the most frequent diagnosis was gastrointestinal (25%), followed by urological (20%) and neurological (18%) diseases. Furthermore, AMI can, albeit rarely, occur at all stages of pregnancy with an incidence of 0.7 per 100,000 maternities [7]. Spontaneous coronary artery dissection appears to be more common in postpartum women [35]. In our study, one patient (0.8%) had an AMI during childbirth.

Chemotherapy for different cancers is also associated with increased cardiovascular risk. The incidence of AMI during chemotherapy for testicular cancer was estimated at 0.24% [36]. In our patient population, 4% of patients suffered AMI during a hospital stay for chemotherapy and/or other oncological reasons.

We assume that similar factors such as stress might be involved both for patients admitted for other than cardiologic reasons and for surgical patients, which could facilitate AMI. Thus, there is a need to teach the dangers of AMI in other units and to check if ECGs are widely used since indicators of ischemia might be altered and are not essential for the diagnosis of AMI.

Moreover, in-hospital AMI may develop during or after various diagnostic procedures [37,38]. In this study, 60 patients developed chest pain while undergoing diagnostic procedures and were discharged with an AMI diagnosis. These patients had a favorable in-hospital as well as long-term outcome compared with patients who suffered inpatient-onset AMI during hospitalizations for internal medicine or surgical reasons.

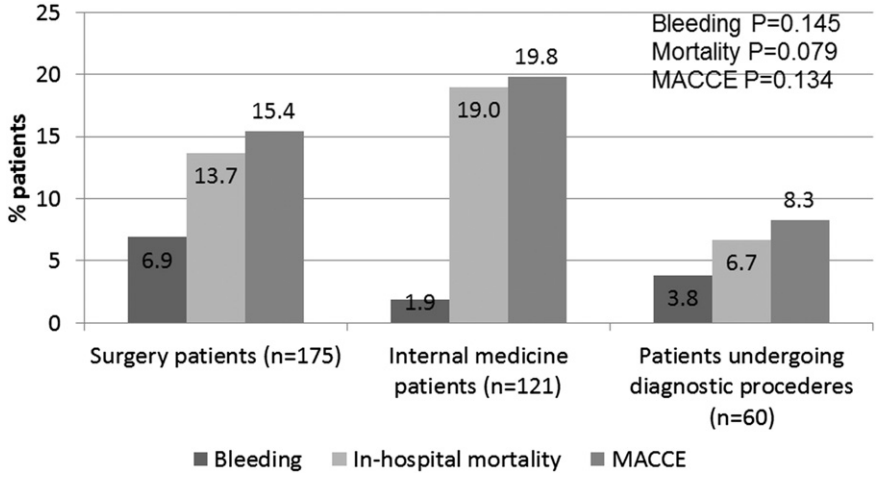

Fig. 1. In-hospital outcome of patients with AMI in hospital according to reason of primary hospitalization. Surgery patients (orthopedic, visceral, or vascular surgery); internal medicine patients (gastric, pulmonary urological, oncological diseases, or other medical disorders). MACCE—major adverse cardiac or cerebrovascular events, defined as a composite endpoint of mortality, reinfarction, and cerebrovascular event.

4.1. Limitations

Our study should be interpreted in the context of the following limitations. First, the weaknesses of AMIS Plus are common to all registries. Participation is voluntary, the number of participating hospitals varied and might therefore not be entirely representative of all-comers to all hospitals in the country despite the permanent involvement of more than 70% of all hospitals treating AMI. Second, patients who suffered an AMI in hospital may not have been systematically included in AMIS Plus, and therefore, the true incidence of this type of AMI may be higher than reported. Further, the data of the primary diagnosis and clinical course were not extensively reported. Third, the choice of drugs and interventions was at the discretion of the treating physicians and hence reflects common practice in Switzerland. Although the multivariable model used included a number of factors, it is likely that other parameters may explain some of the differences between patients with inpatient-onset AMI versus those with outpatient-onset AMI. Furthermore, we cannot be certain how often the diagnosis of AMI was overlooked since typical chest pain or dyspnea is infrequent in patients hospitalized for a non-AMI diagnosis and for some patients with poor prognoses, physicians may have decided against a full diagnostic work-up or specific therapy. Another limitation is the low number of follow-up patients which does not allow a conclusive answer, but it does show possible differences, which should be borne in mind when these patients leave hospital and they need to be continuously controlled in terms of secondary prevention. However, this study arises from the AMIS Plus registry with a large number of patients and continuous data collection, which allows a contemporary view of this insufficiently investigated patient population.

5. Conclusions

Patients suffering AMI when already in hospital for other reasons had a worse prognosis than patients with out-of-hospital AMI. The most frequent reasons for primary hospitalization were various surgical procedures or internal medicine diseases, but there were also other conditions involved. Due to the different clinical presentations of such AMI patients, the diagnosis may often be overlooked and therefore the number of patients who suffered an AMI in hospital might be much higher than reported here. Based on their previous medication, it is likely that these patients had known heart disease and thus would have needed special care during hospitalization due to somatic illnesses, diagnostic procedures, or prior to surgery. Therefore, a cardiologist should always be involved when patients with known coronary heart disease are hospitalized for other reasons. However, further work is needed to improve the identification of hospitalized patients at risk of AMI and to provide proper management.

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AMIS Plus Participants 2002–2014

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Conflict of interests

The authors state that they have no conflicts of interest.

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