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# Patterns of practice for acute myocardial infarction in a population from ten countries

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**Abstract** *Background*: There is conclusive evidence from large scale randomized clinical trials (RCTs) that several treatments administered in the acute phase of a myocardial infarction (AMI) reduce mortality. However, only a minority of patients admitted with AMI receives at the appropriate treatments.
*Objectives*: This study aims at (1) describe the utilization patterns for AMI; (2) determine the appropriateness of prescribing, measured as adherence to the ACC/AHA guidelines; and (3) determine which factors are associated with the administration of thrombolytic agents.
*Methods*: The study was a multi-center survey carried out in ten countries (nine European and one Canadian province) over a 3-month period. Data were prospectively collected by clinical pharmacists. All consecutive patients admitted to the participating hospitals during the study period with a diagnosis of suspected AMI were included in the study. Rates of use were calculated as "overall utilization" and "adjusted utilization" (e.g., accounting for eligibility).
*Results*: Data were available on 1976 patients from 56 participating centers. The mean age of the patients was 65 years (range 25–95, SD = 12.6) and 29.7% were women. Adjusted utilization rates were 63.7% for thrombolysis, 88% for aspirin, and 65.9% for β-adrenergic blocking agents. The most utilized thrombolytic agent was streptokinase (65.9%). The main reasons given by physicians for not administering thrombolysis was the delay from chest pain onset to admission. Patients admitted to teaching hospitals were less likely to receive aspirin than patients admitted to general hospitals (adjusted rate 90.1% vs 86%, $P = 0.007$), but they were more likely to undergo a primary invasive procedure (11.0% vs 2.5% $P = 0.001$). Multivariate analysis showed that age greater than 74 years, delay, prior myocardial infarction, and Killip scale were correlated with the non-utilization of thrombolysis.
*Conclusion*: Recommended treatments are still underutilized in patients with AMI. Increased utilization is required, particularly for elderly people. There is a wide variability among hospitals with different affiliations (teaching vs non teaching), demonstrating the different patterns of practice in various settings.

**Key words** myocardial infarction · drug utilization · thrombolytic therapy · aspirin · beta-adrenergic blocking agents · pharmacists

## Introduction

In the last decade the management of acute myocardial infarction (AMI) has changed dramatically. Numerous large-scale, randomized controlled trials (RCTs) have presented conclusive evidence of the beneficial effects of certain medical therapies. Thus, thrombolysis [1, 2] and aspirin [2] administered on arrival at the emergency department, as well as β-adrenergic blocking agents [3] and angiotensin-converting enzyme (ACE) inhibitors [4, 5] during the first 24 h of hospitalization, are well-recognized lifesaving treatments in patients without contraindications [6], because of their beneficial effects in decreasing mortality in this patient population. National and international evidence-based guidelines for the management of patients with AMI have been published [6, 7]. The issue of representativeness of patients in RCTs often justifies the difficulties in the transferability of the trials' results to routine practice [8]. In the case of

On behalf of the S.I.F.O./E.S.C.P. Study Group on Acute Myocardial Infarction Management (see Appendix)

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AMI, many large-scale trials were designed to resemble routine daily practice, with no strict inclusion criteria. However, specific subpopulations (e.g., the elderly) are still underrepresented [9]. Several examples of the impact of trials' results on clinical practice have been published in the international literature [10, 11].

Given the substantial reduction in mortality, few question the value of the routine use of these treatments in all eligible patients admitted with AMI. However, failure to administer recommended treatments in a portion of the eligible population is attested by several reports. Accordingly, it is of considerable importance to determine whether all eligible patients receive the treatments. While the oldest studies relied on administrative claims or registry data, [10, 12] and for this reason were not able to examine the reasons for withholding recommended treatments, three recent studies carried out in different countries and care settings have analyzed the rates of utilization based on eligibility criteria [13–15]. In a European study, it was estimated that 20% of the patients apparently eligible for thrombolysis did not receive the treatment [13]. In a study carried out in New Zealand, 49.7% of the admitted patients were eligible for thrombolysis, and 43.5% received it [15]. In a recent US based study, the degree of adherence to the national guidelines [6] for AMI management was evaluated. The proportion of eligible patients not receiving recommended treatment was 28% for thrombolytic agents, 47% for β-adrenergic blocking agents and 12% for aspirin [14].

Another important and interesting issue in the management of AMI is the variability of treatment practices. The influence that the practice setting may have in taking the decision to perform certain procedures and to administer pharmacological treatments was tested and confirmed in several reports. Differences in management and practice patterns were found in populations from different countries [16], among physicians with different specialties [17], or simply among patients admitted to different hospitals [18].

As part of their duties, hospital pharmacists routinely evaluate the prescribing behavior of physicians in their hospitals. However, of the published studies on AMI treatment utilization, very few employed hospital pharmacists as monitors of clinical practice [19], even though the importance of hospital pharmacists in drug use evaluations in MI has been emphasized [20].

The following analysis will describe the utilization of treatments in a population with suspected AMI admitted to a sample of hospitals in ten different countries. The objectives of this analysis are threefold:

1. To describe utilization patterns for AMI management
2. To determine the appropriateness of prescribing measured as adherence to the American college of cardiology/American Heart Association (ACC/AHA) guidelines
3. To determine which factors are associated with administration of thrombolytic agents

## Materials and methods

### Study sample

All consecutive patients admitted to the participating hospitals with a diagnosis of suspected AMI during a 3-month period in 1996 were included in the study. The suggested diagnosis of suspected AMI followed the WHO definition [21]. However, the treating clinician's diagnosis of AMI was accepted without revision, since the main objective was to analyze practice patterns made on the basis of that diagnosis.

### Participating hospitals

The study involved patients from ten countries, both in Europe and in North America. This investigation was generated from a collaboration between the Italian Society of Hospital Pharmacy (SIFO) and the European Society of Clinical Pharmacy (ESCP). Thus, participating hospital pharmacists were identified through the SIFO/ESCP pharmacists' network. A pharmacist from each country was selected as coordinator. The main responsibility of the country coordinators was to serve as a link between the coordinating center and the participating hospitals in their country. Each country coordinator was mainly responsible for the identification of the participating hospitals (e.g., contact of hospital pharmacists known to be interested in the cardiology field and in collaborating in a pharmacoepidemiological survey), the exchange of information among the participating centers, in order to assure the continuity and quality of the data collection, and the sending of the forms to the coordinating center.

### Data collection

In each participating hospital, the pharmacist(s) in charge of the study prospectively collected information on all patients admitted consecutively to their hospital with a diagnosis of suspected AMI. The sources of information were the patient's chart and the direct involvement of the physicians and nurses in charge of the patients. Standard data collection forms were used in all centers. The forms included information on:

1. The patient's demographics (age, gender, race)
2. Clinical profile on admission (delay from onset of symptoms to hospital arrival, Killip scale, methods of MI diagnosis, infarct location, clinical history)
3. Pharmacological treatments and additional procedures administered in the acute phase, with required explanation when the treatments were not administered
4. Clinical events and complications during hospitalization
5. intrahospital outcome and date of outcome
6. drugs prescribed on discharge

Furthermore, general information on the hospital (e.g., geographical location, number of beds, presence of guidelines for AMI management) was retrieved. Forms were checked for completeness at the coordinating center before data entry. Country coordinators were contacted in the case of missing data. In the final analysis the proportion of missing data was very low, and was mainly due to a lack of routine collection of some clinical variables in several centers (e.g., Killip scale, delay from onset of symptoms to hospital arrival).

### Eligibility for recommended treatments

In the case of failure of administration of recommended treatments, (e.g., thrombolytics, aspirin, and β-adrenergic blocking agents), the pharmacist was required to collect adequate information to explain the reason for not administering such treatments, and was responsible for interviewing the physician in charge or checking the information in the patient chart. Absolute and relative contrain-

dications for recommended treatments (thrombolysis, aspirin, and β-adrenergic blocking agents) were derived from the "ACC/AHA guidelines for the management of patients with acute myocardial infarction" (Table 1) [6]. Using these data, patients were classified as having or not having absolute or relative contraindications for these treatments. Furthermore, for thrombolysis, performance of primary percutaneous transluminal coronary angioplasty (PTCA) or bypass was considered a documented reason for not giving thrombolytic therapy. For ACE inhibitors, for simplicity of the data collection form, no questions were asked about reasons for not administering the agents or the presence of specific contraindications to the treatment. However, the results from the major large-scale RCTs on ACE inhibitors in AMI patients [4, 5] suggest that early treatment (e.g., within 24 h) significantly reduces mortality, and that the subgroup of patients who benefit most are those with an anterior infarction. Thus, for ACE inhibitors, an analysis was performed to verify whether the subgroup that would benefit most received the treatment.

Following the analysis of eligibility, patients who did not receive the treatments were divided as follows: patients with a documented contraindication [e.g., a contraindication recognized by the (ACC/AHA) guidelines], patients with a non-documented contraindication (e.g., a contraindication not recognized by the guidelines) and patients for whom the reason for not administering the therapy was unknown. Both absolute and relative contraindications were considered as documented. Furthermore, the utilization rates for recommended treatments were given as:

1. *Overall utilization rate*, calculated as the number of patients receiving the therapy during the first 24 h, divided by the total number of patients admitted with suspected AMI
2. *Adjusted utilization rate*, calculated as the number of patients receiving the therapy during the first 24 h, divided by the patients potentially eligible (e.g., taking into consideration relative and absolute contraindications).

### Factors associated with recommended treatments utilization

A multivariate analysis in the patient population potentially eligible for thrombolytic treatment was conducted. Age, gender, delay from onset of symptoms, presence of previous MI and Killip scale were used as explanatory variables. Results are expressed as odds ratios and 95% confidence intervals.

### Statistical analysis

The $\chi^2$ square test was utilized for testing differences in the distributions of categorical variables. ANOVA was used to test differ-

**Table 1** List of absolute and relative contraindications for recommended treatments (ACC/AHA Guidelines) [6]. *ACC* American college of cardiology, *AHA* American Heart Association

| |
|---|
| **Thrombolytic agents** |
| Contraindications: clinical profile at presentation |
| Time to admission > 12 h |
| Lack of ECG criteria |
| Medical contraindications |
| Previous hemorrhagic stroke at any time |
| Other strokes or cerebrovascular events within 1 year |
| Intracranial neoplasm |
| Active internal bleeding (does not include menses) |
| Suspected aortic dissection |
| Cautions – relative contraindications |
| Severe uncontrolled hypertension on presentation (BP > 180/110 mmHg) |
| History of prior cerebrovascular accident or known intracerebral pathology not covered in contraindications |
| Current use of anticoagulants in therapeutic doses |
| Recent trauma (within 2–4 weeks) including: |
| head trauma |
| traumatic or prolonged (> 10 min) cardiopulmonary resuscitation |
| major surgery (< 3 weeks) |
| Noncompressible vascular punctures |
| Recent (within 2–4 weeks) internal bleeding |
| For streptokinase/anistreplase: prior exposure or prior allergic reaction |
| Pregnancy |
| Active peptic ulcer |
| History of chronic severe hypertension |
| **Oral aspirin** |
| Absolute contraindications |
| Known hypersensitivity |
| Gastrointestinal bleeding |
| Cautions – relative contraindications |
| Blood dyscrasias |
| Severe hepatic disease |
| History of bleeding peptic ulcer |
| **β-Adrenergic blocking agents** |
| Contraindications |
| Heart rate less than 60 bpm |
| Systolic arterial pressure less than 100 mmHg |
| Moderate or severe left ventricular failure |
| Signs of peripheral hypoperfusion |
| AV conduction abnormalities |
| Severe chronic obstructive pulmonary disease |
| History of asthma |
| Severe peripheral vascular disease |
| Insulin-dependent diabetes mellitus |

ences in the mean of continuous variables. The chosen level of significance was 0.05. Multiple logistic regression technique was used to assess the relative likelihood of receiving thrombolysis based on a set of clinical characteristics. Data were analyzed using the SAS System for Windows [22].

## Results

### Characteristics of the sample

During the study period, 1976 patients were recruited from 56 hospitals. Patients were admitted to an average of 5.6 hospitals per country (range 1–12). Sample size per country ranged from 84 (Norway) to 451 patients (Italy; Table 2). Patients were 29.7% female, and the mean age with (SD) was 65 (12.6). Women were older than men (Fig. 1): 70% of the female sample was >65 years old, while the same age group made up 42.1% of the male patient population. The sample differed significantly among countries regarding mean age and gender distribution (Table 2). The proportion of female patients ranged from 17.2% (Spain) to 39.6% (United Kingdom, UK), while the average age ranged from 58.4 years (Turkey) to 70.3 (Norway). Table 3 lists the general characteristics of the sample. About 21% of the population was older than 74 years, 60% of the patients reached the hospital within 6 h from the onset of chest pain, and their clinical history included diabetes for 24% and a previous MI for 23%. Two hundred and thirteen patients (10.8%) died during hospitalization.

### Use of recommended treatments

The overall utilization rate for thrombolytic therapy was 39.5%. The rate varied among countries ranging from 10.7% (Norway) to 81.5% (UK; Table 4 and Fig. 2a). After adjusting the utilization rate for patient eligibility, the proportion of treated patients was 63.7% (range 22.0% Norway, to 95.2% UK). The agent most frequently used was streptokinase ($n = 514$, 65.7%), followed by rt-PA ($n = 253$, 32.6%), anistreplase ($n = 10$, 1.3%) and urokinase ($n = 3$, 0.4%). Streptokinase was the preferred agent in almost all countries, with the exception of Canada, Italy and Germany. For the majority of the patients treated with rt-PA the drug administration followed the "global utilization of streptokinase and tPA for occluded coronary arteriesn" (GUSTO) schedule (84.9% [23]). Primary PTCA was performed in 107 patients (5.4%), while bypass was performed in 26 patients (1.3%). The eligibility-adjusted utilization rate for thrombolysis was 53.0% for women versus 67.5% for men [odds ratio (OR) 0.542, $P = 0.0001$, 95% CI = 0.42–0.70]. When the rate was adjusted for age, the difference was not significant anymore (OR = 0.76, $P$ = NS, 95% Cl = 0.58–1.0).

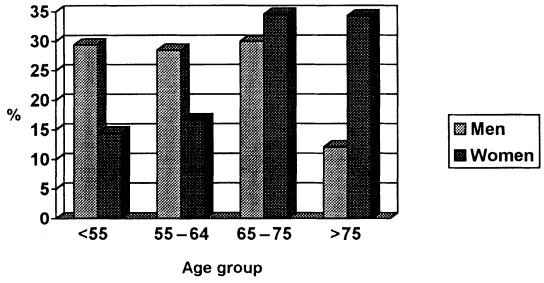



**Fig. 1** Distribution of the sample by gender and age (proportion within each gender)

The reasons stated by physicians for withholding recommended treatments were classified according to the ACC/AHA guidelines reported in Table 1. Out of the 1195 patients who did not receive thrombolysis, for 426 (35.6%) physicians reported a non-documented contraindication, while for 20 (1.7%) the reason was unknown (Table 5). Among the documented contraindications, delay from onset of symptoms to admission was the most frequent justification, followed by lack of ECG criteria.

The overall rate of utilization of aspirin during the first 24 h was 82.6%, with a range among countries from 37.9% (Yugoslavia) to 96.5% (UK; Table 4). This rate reached 88% when it was adjusted by eligibility. The only country with an obvious difference in the utilization

**Table 2** Distribution of the sample and demographic characteristics by country

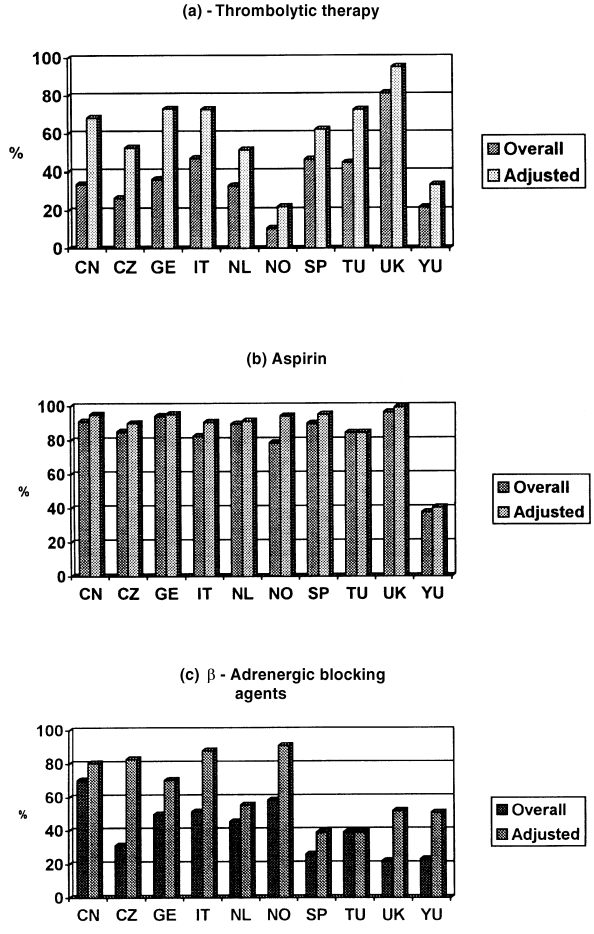
| Country/state | Number of centers | Number of patients | Average age (SD, years) | Gender (% female) |
|---|---|---|---|---|
| Canada (Ontario) | 4 | 128 | 67.5 (13.0) | 38.1% |
| Czech Republic | 12 | 385 | 67.0 (11.8) | 36.4% |
| Germany | 6 | 105 | 63.3 (14.4) | 35.2% |
| Italy | 11 | 451 | 65.1 (13.2) | 24.6% |
| Norway | 1 | 84 | 70.3 (10.8) | 39.3% |
| Spain | 6 | 274 | 64.5 (13.0) | 17.2% |
| The Netherlands | 4 | 106 | 62.9 (12.8) | 28.9% |
| Turkey | 5 | 136 | 58.4 (10.9) | 25.7% |
| United Kingdom | 2 | 146 | 65.4 (11.3) | 39.6% |
| Yugoslavia | 5 | 161 | 63.9 (11.1) | 29.8% |
| Total | 56 | 1976 | 65.1 (12.6) | 29.7% |

Chi-square for gender among countries = 51.68, $df = 9$, $P = 0.001$.
ANOVA for age among countries, $F = 8.27$, $P = 0.0001$

**Table 3** General characteristics of the sample. *MI* myocardial infarction

| | Number of patients (%) ($n$ = 1976) |
|---|---|
| Age[a] (years) | |
| < 55 | 468 (23.7%) |
| 55–64 | 455 (23.0%) |
| 65–74 | 633 (32.0%) |
| > 74 | 409 (20.7%) |
| Gender[b] | |
| Male | 1384 (70.0%) |
| Female | 586 (29.7%) |
| Hours from onset of symptoms[c] | |
| < 1 | 280 (14.2%) |
| 1–3 | 641 (32.4%) |
| 3–6 | 296 (15.0%) |
| 6–12 | 218 (11.0%) |
| 12–24 | 221 (11.2%) |
| > 24 | 229 (11.6%) |
| Infarct location | |
| Inferior | 850 (43.0%) |
| Killip scale[d] | |
| I | 1283 (64.9%) |
| II | 350 (17.7%) |
| III | 123 (6.2%) |
| IV | 61 (3.1%) |
| Previous MI[e] | |
| Yes | 455 (23.0%) |
| No | 1517 (76.8%) |
| Diabetes[f] | |
| Yes | 475 (24.0%) |
| No | 1497 (75.8%) |
| Events during hospitalization | |
| Reinfarction[g] | 82 (4.5%) |
| Post-Ml angina[h] | 258 (13.1%) |
| In-hospital mortality rate[i] | 213 (10.8%) |

[a] 11 missing values (0.6%)
[b] 6 missing values (0.4%)
[c] 91 missing values (4.6%)
[d] 159 missing values (8.0%)
[e] 4 missing values (0.2%)
[f] 4 missing values (0.2%)
[g] 166 missing values (8.4%)
[h] 166 missing values (8.4%)
[i] 11 missing values (0.6%)




CN=Canada; CZ=Czech Republic; GE=Germany; IT=Italy; NL=The Netherlands; NO=Norway; SP=Spain; TU=Turkey; UK=United Kingdom; YU=Yugoslavia.

**Fig. 2** Utilization rates (overall and adjusted) of recommended treatments by country. *CN* Canada, *CZ* Czech Republic, *GE* Germany, *IT* Italy, *NL* Netherlands, *NO* Norway, *SP* Spain, *TU* Turkey, *UK* United Kingdom, *YU* Yugoslavia

of aspirin was Yugoslavia (Fig. 2b), while the rates for all the other countries were around 80% or above. For the majority of patients who did not receive aspirin during the first 24 h, physicians reported non-documented contraindications (60.9%, 204/335). History of bleeding peptic ulcer was the most frequent justification for not administering aspirin (Table 5).

β-Adrenergic blocking agents (either oral or intravenous) were administered to 783 patients (39.6% overall rate, 65.9% adjusted rate). In this instance, Norway had the highest adjusted utilization rate (90.7%) followed by Italy and Czech Republic (Fig. 2c). The majority of patients who did not receive β-adrenergic blocking agents had a contraindication to the drugs (788/1193, 66%, Table 5). Left ventricular failure, bradycardia and low systolic arterial pressure were the most common reasons.

Teaching and general hospitals differed significantly in the adjusted prescription rate of aspirin, while the rates of thrombolysis and β-adrenergic blocking agent utilization did not reach statistical significance (Table 6). Patients admitted to a teaching hospital were more likely to receive a primary invasive procedure [(e.g., PTCA and bypass) general hospitals 25/992, 2.5%, vs teaching hospitals 108/979, 11.0%, $P = 0.001$].

**Table 4** Utilization rates of recommended treatments during the first 24 h of hospitalization. *ACE* angiotensin converting enzyme

| Treatment | Overall utilization rate | Range among countries | Adjusted utilization rate | Range among countries |
|---|---|---|---|---|
| Thrombolylic agents | 39.5% (781) | 10.7%–81.5% | 63.7% | 22.0%–95.2% |
| Aspirin | 82.6% (1632) | 37.9%–96.5% | 88.0% | 40.4%–99.3% |
| β-Adrenergic blocking agents | 39.6% (783) | 21.9%–70.3% | 65.9% | 39.0%–90.7% |
| ACE inhibitors | 26.6% (526) | 11.0%–40.6% | – | – |

**Table 5** Reasons for not administering recommended therapies[a]. *PTCA* percutaneous transluminal coronary angioplasty

| Reason | Number of patients not receiving the therapy | Proportion |
|---|---|---|
| **Thrombolysis** | $n = 1195$ | |
| Documented contraindications | 749 | 62.7% |
| Time to admission >12 h or unknown | 491 | |
| Primary PTCA or bypass | 133 | |
| No initial ECG criteria | 96 | |
| Absolute medical contraindications | 35 | |
| Cautions – relative medical contraindications | 81 | |
| Non-documented contraindications | 426 | 35.6% |
| Unknown reasons | 20 | 1.7% |
| **Aspirin** | $n = 335$ | |
| Documented contraindications | 113 | 33.7% |
| Absolute contraindications | 32 | |
| Hypersensitivity | 22 | |
| Active gastrointestinal bleeding | 10 | |
| Cautions – relative contraindications | | |
| History of bleeding ulcer | 81 | |
| Non-documented contraindications | 204 | 60.9% |
| Unknown reasons | 18 | 5.4% |
| **β-Adrenergic blocking agents** | $n = 1193$ | |
| Documented contraindications | 788 | 66.0% |
| Moderate or severe left ventricular failure | 265 | |
| Heart rate less than 60 bpm | 190 | |
| Systolic arterial pressure less than 100 mmHg | 174 | |
| Severe chronic obstructive pulmonary disease or asthma | 146 | |
| AV conduction abnormalities | 94 | |
| Insulin-dependent diabetes mellitus | 68 | |
| Signs of peripheral hypoperfusion | 47 | |
| Severe peripheral vascular disease | 86 | |
| Non-documented contraindication | 374 | 31.4% |
| Unknown reason | 31 | 2.6% |

[a] Patients who did not receive each of the three recommended therapies are divided into three groups: "documented contraindication", "non-documented contraindication" and "unknown reason". Within the documented contraindications a patient may be counted more than once if he/she has more than one contraindication. Thus, the subtotals of the documented contraindications may be higher than the number of patients because of multiple answers

ACE inhibitors were administered to 524 patients (26.5%). With regard to infarct location, 32.7% (215/658) of patients with anterior infarction received an ACE inhibitor, versus 23.7% (309/1306) of patients with any other infarct location ($P = 0.001$).

### Factors associated with thrombolysis utilization

In the multivariate analysis (Table 7), older age, delay from onset of symptoms, prior myocardial infarction, and Killip scale, all emerged as independent variables correlated with the non-utilization of thrombolytic therapy in potentially eligible patients. In particular, the odds of receiving thrombolytic therapy for a patient older than 74 years were 0.18 times the odds of an individual younger than 55. Patients presenting between 1 to 6 h from onset of symptoms were 44% less likely to receive the treatment compared with patients arriving during the "golden hour". This likelihood decreased by 78% when the delay was greater than 6 h. Patients with a history of previous infarction were 41% less likely to receive thrombolysis versus individuals without MI in their history.

**Table 6** Adjusted utilization rates of recommended treatments by hospital type. *NS* not significant

| Treatment | Adjusted utilization rates | | *P*-value |
|---|---|---|---|
| | Teaching hospitals | General hospitals | |
| Thrombolytics | 378/604 (62.6%) | 403/623 (64.7%) | NS |
| Aspirin | 797/927 (86%) | 835/927 (90.1%) | 0.007 |
| β-Adrenergic blocking agents | 430/640 (67.2%) | 353/548 (64.4%) | NS |

## Discussion

The main objective of this study was to describe the utilization patterns for AMI management in a sample of hospitals in diverse settings of care. Utilization studies on this matter often analyze prescribing patterns in a single institution [24] or in a limited number of hospitals [16]. The peculiarity of this study was to have available data collected with a standard procedure in a sample of hospitals in ten countries, utilizing clinical pharmacists as monitors.

**Table 7** Multiple logistic regression model for predicting the use of thrombolysis in patients potentially eligible. *MI* myocardial infarction

| Explanatory variable | Parameter estimate | Standard error | *P* | Odds ratio | 95% Confidence interval |
|---|---|---|---|---|---|
| Intercept | 2.3172 | 0.2578 | 0.0001 | | |
| Age (years) | | | | | |
| < 55 | | | | 1 | |
| 55–64 | −0.2320 | 0.2037 | NS | 0.79 | 0.53–1.18 |
| 65–74 | −0.5640 | 0.1903 | 0.0030 | 0.57 | 0.39–0.83 |
| > 74 | −1.7026 | 0.2248 | 0.0001 | 0.18 | 0.12–0.28 |
| Gender | | | | | |
| Male | | | | 1 | |
| Female | −0.2460 | 0.1585 | NS | 0.78 | 0.57–1.07 |
| Delay from symptoms | | | | | |
| ≤1 h | | | | 1 | |
| 1–6 h | −0.6212 | 0.1965 | 0.0016 | 0.54 | 0.37–0.79 |
| > 6 h | −1.5359 | 0.2370 | 0.0001 | 0.22 | 0.14–0.34 |
| Previous MI | | | | | |
| No | | | | 1 | |
| Yes | −0.6752 | 0.1633 | 0.0001 | 0.51 | 0.37–0.70 |
| Killip | −0.2244 | 0.0928 | 0.0156 | 0.80 | 0.67–0.96 |

Number of observations = 1112; $\chi^2$ test for covariates: 194.471, $df$ = 8 ($P$ = 0.0001). Association of predicted probabilities and observed responses: concordant = 72.6%; discordant = 24.6%; tied = 2.8%; and Somer's D = 0.481

Despite wide recognition that several treatments are life-saving if administered in patients with AMI, a large proportion still do not receive them in clinical practice. Even after adjusting the utilization rate by patient eligibility, there is still a fraction of eligible patients who do not receive thrombolysis (36.3%), aspirin (12%) and β-adrenergic blocking agents (34.1%). Regarding aspirin and β-adrenergic blocking agents, the proportion of patients is very similar to the findings of a recent US study [14]. However, several other studies found lower utilization rates for aspirin [25, 26]. The adjusted rate for thrombolysis is very close to the most recent European-based study [13], higher if compared with a nationwide French survey [27], while it is low compared with studies conducted in the US and New Zealand [15, 24].

Older age (> 74 years) and a later arrival at the hospital (6–12 h) continue to be the greatest risk factors for not receiving thrombolysis, despite the very consistent findings of major trials and of meta-analysis that the benefit of treatment in these subpopulations is very well established [28, 29]. Regarding age, encouraging trends in the use of thrombolytics in older patients were reported in a study conducted in Massachussets [30]. However, despite these encouraging trends, elderly patients are still significantly less likely to receive thrombolytic therapy.

The early debates on the optimal time window for obtaining a patent artery and the adoption of the narrower time limit in some major trials may have influenced the attitudes of clinicians, already inclined to be more interested and aggressive in younger and more acute patients. The low transferability of the controlled evidence for this important and at risk fraction of the AMI population is a major iatrogenic and avoidable variable for the outcome of AMI patients. A similar (though less impressive) observation applies (with no obvious explanation at hand) to other at risk groups such as patients with previous MI and those with signs of ventricular dysfunction (Killip > 1). Regarding delay, since decision time (e.g., the time that the patient spends in deciding to seek help) is 50-fold higher in patients presenting after 12 h versus patients presenting at the hospital within 2 h [31], patient education covering the most evident signs and symptoms of an AMI might reduce this delay and improve treatments and, consequently, the outcome. As far as the age bias is concerned, women are particularly disadvantaged due to older age at presentation, as confirmed in previous studies [32].

Variability in prescribing habits among care settings was another important result of the present study. While there was no significant difference in the administration rate of thrombolysis and β-adrenergic blocking agents between teaching and general hospitals, a simple treatment like aspirin was administered more frequently to patients admitted to general hospitals, while invasive procedures were performed more frequently in patients admitted to teaching hospitals. While there is no conclusive explanation for the difference found for aspirin, the higher performance of revascularization procedures in teaching hospitals is to be expected, since it requires facilities and specialist personnel that might not be present in general hospitals.

The unbalanced samples from different countries do not allow an in-depth discussion of the differences in AMI management among countries. However, some macroscopic behavior may be highlighted and proposed as hypothesis testing in further studies. For example, huge differences in the prescription of recommended treatments may be an indicator of the influence of cultural and organizational issues on the transferability of trials' results. Many patients admitted to Yugoslavian hospitals did not receive thrombolytic treatment because of lack of availability of the drugs, rather than because of any other plausible contraindication to the treatment,

and this fact explains the low utilization rate for thrombolysis. On the other hand, the low aspirin usage in Yugoslavia is probably due to a lack of routine practice. In the same way, the high utilization rate of thrombolytics in Italy may be easily correlated to the long tradition of research in the AMI field, with RCTs involving a high proportion of Italian hospitals [1, 4, 33]. Among all the countries, Norway and the UK present very unique utilization patterns. However, due to the low number of centers participating in the study from these countries, any hypothesis or assumption on these results may be misleading.

The results of the present study can only be considered in light of the limitations associated with the study design. First, the representativeness of the sample is questionable. We collected data from hospitals in ten countries, but the wide variability in sample size among countries as well as the small number of centers and patients recruited for certain countries do not allow us to claim that the samples are representative of the prescribing situation in each country. This might be asserted for countries like Italy, with a centralized government-based health care system, for which a large population is available, with a typical mix of urban and rural settings and of teaching and non-teaching hospitals. The same argument is hard to support for countries like Norway or UK, for which we collected data from just one and two hospitals, respectively. Thus, the generalization of the results to the whole situation and pattern of practice of these countries is arguable.

A common issue that characterizes multicenter studies is the completeness of the data. The present study was designed with a coordinator in each country, in order to be able to strictly control for missing data. Despite the difficulties in communication among pharmacists and coordinators from different countries, the missing data in the final sample are very limited compared with previous studies involving clinical pharmacists as monitors [19], and they concern specific clinical information that are not routinely collected by clinicians in some hospitals. On the other hand, when the information was missing for many patients (e.g., the left ventricular ejection fraction, originally included in the data form to assess the appropriateness of use of ACE inhibitors), the variables in question were not included in the analysis. In light of all these considerations, the peculiarity of the study was to allow a standard data collection on current practice patterns in several countries though the network of hospital pharmacists belonging to very diverse settings and situations of care.

In conclusions, the current study has shown that several proven efficacious therapies for AMI are underutilized in a sample of European and North-American hospitals. Analysis of practice patterns is a very important step in the clinical quality improvement process. This kind of activity will facilitate the involvement of hospital pharmacists in the clinical management of the patients in those countries in which this task is not a routine part of pharmacists' activities.

## Appendix: S.I.F.O./E.S.C.P. Study Group on Acute Myocardial Infarction Management
## S.I.F.O. = Societa' Italiana di farmacia Ospedaliera
## E.S.C.P. = European Society of Clinical Pharmacy

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