Original articles

Pharmacoutilization of statin therapy after acute myocardial infarction. A real practice analysis based on administrative data

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Clinical database; Costs; Myocardial infarction; Outpatient management; Statins.

Background. **Despite randomized and controlled trials indicating continuous treatment with statin therapy as a factor in reducing morbidity and mortality after acute myocardial infarction, records reveal a high percentage of patients at risk who are either not receiving treatment or being treated inadequately.**

Methods. **An administrative database kept by the Local Health Unit of Ravenna and listing patient baseline characteristics, drug prescriptions and hospital admissions was used to perform: 1) an analysis of patients discharged alive from hospital each year between 1996 and 2000 with a diagnosis of acute myocardial infarction, and 2) a retrospective cohort study of drug utilization, and particularly the use of statins, year by year. All prescriptions for statins filled in the 6 months after hospital discharge were considered and used to classify patients in terms of their exposure to statin therapy and of their pharmacoutilization.**

Results. **A total of 2265 subjects were enrolled (446 in 1996, 440 in 1997, 443 in 1998, 443 in 1999, and 493 in 2000). The percentage of patients treated with statins increased each year (from 22.6% in 1996 to 43.8% in 2000) as did the percentage of adequately dosed patients (from 4.3% in 1996 to 23.9% in 2000). The overall cost of dispensed statins amounted to € 10,610 in 1996 and € 45,102 in 2000. The proportion of cost for statins accountable to adequately dosed patients ranged from 36.4% in 1996 to 77.4% in 2000. The average cost per adequately dosed patient ranged from € 203.40 in 1996 to € 296.00 in 2000 and increased year by year.**

Conclusions. **Pharmacoutilization of statin therapy was found to be unsatisfactory in each study year. Interestingly, however, the trend indicated by the study suggests increasing percentages of patients being exposed to the treatment, and of adequately dosed patients. These results may be attributed to a greater awareness of the need for proper treatment, and may be considered as reflecting a significant improvement in drug management.**

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Introduction

Randomized controlled trials have demonstrated that continuous and adequately dosed treatment with statin therapy is a key factor in reducing morbidity and mortality after acute coronary syndromes[1-3]. This effect seems to be independent of the baseline cholesterol levels[4], suggesting that is appropriate to treat these patients with statins. However, recent observational studies have indicated a high percentage of patients interrupting statin therapy or being treated inadequately after acute myocardial infarction (AMI)[5-10]. The implications of an unsatisfactory pharmacoutilization in the case of statins ought to influence the activity both of the prescribing physician, whose task is to improve the clinical outcome for the single patient by way of the therapeutic process, and of the decision-maker, who is entrusted with making the health service accessible to the population by selecting the most effective possible allocation of the available resources. Nonetheless, given the absence of any systematic approach in gathering information through the creation of high-quality clinical databases and the lack of systems for the assessment of the appropriateness of prescription practices by calculating indicators with pharmacological treatment, the process of bringing accountability and assessment into drug utilization has been delayed considerably[11-15].

The present study addresses these issues using information from the healthcare administrative database of the Local Health

Unit (LHU) of Ravenna and calculating therapeutic and economic markers on the basis of the pharmacoutilization of drug treatment. The specific objectives of the study were: 1) to measure the exposure and pharmacoutilization of statin therapy in patients discharged alive with a diagnosis of AMI; 2) to calculate the drug costs attributable to adequately/not adequately dosed patients; 3) to assess the therapeutic and economic markers on the basis of the pharmacoutilization of statin therapy over a 5-year period; and 4) to determine whether the growing evidence in support of the use of statins has helped to increase exposure and to improve pharmacoutilization over time.

Methods

Data source. The study subjects were enrolled among individuals registered with the LHU of Ravenna, Italy (approximately 357 000 inhabitants in 1996 and 359 000 inhabitants in 2000). Being a point of delivery for the National Health System (NHS), the LHU has an information network that routinely measures the volume of expenditure generated by the dispensation of drugs to registered patients. In particular, this administrative/accounting type of archive is conventionally used to record the payments pharmacies are entitled to receive from the LHU by way of refund for drugs reimbursable by the NHS and dispensed free of charge. Since January 1st, 1996, this database has been structured in such a way as to allow patient-oriented searches: the prescriptions recorded are attributed in each case to the patient-recipient. The identification of the patient given by the personal health number, cross-checked with the registry office and hospital database, allows the information (the ATC code[16] of the drug purchased, the number of packs, the number of units per pack, the dosages, the unit cost per pack, and the prescription date) to be integrated with the date of birth, gender and any record of hospitalization (Fig. 1).

Study design and patient population. All subjects registered with the LHU of Ravenna who were discharged alive from hospital with a primary diagnosis of AMI (ICD9[17] code 410) in 1996, 1997, 1998, 1999, and 2000 were enrolled in the study. An analysis of the pharmacoutilization of statins during the 6 months after the discharge date was conducted for each of the study groups. The discharge date was considered as the enrolment date. Those who reported previous hospital admissions for AMI (since January 1st, 1991 to the enrolment date) and those who died or moved away during the 6 months following the enrolment date (follow-up period) were excluded from the study.

Assessment of exposure and pharmacoutilization. All prescriptions for statins (code ATC C10AA) during the follow-up period were processed. The mean daily dose (expressed in tablets) was calculated according to the following formula: the overall number of tablets during the follow-up period divided by the overall number of days in the follow-up period (6 months after the discharge date). The standard equivalent daily dose was arbitrarily taken to be atorvastatin 10 mg, cerivastatin 0.2 mg, fluvastatin 40 mg, pravastatin 20 mg, and simvastatin 20 mg. According to the presence/absence of at least one prescription for statins during the follow-up period, subjects were classified as exposed to treatment/not exposed to treatment. Furthermore, patients exposed to the treatment were defined as adequately/not adequately dosed patients if they took/did not take a mean daily dose ≥ 0.75 tablets.

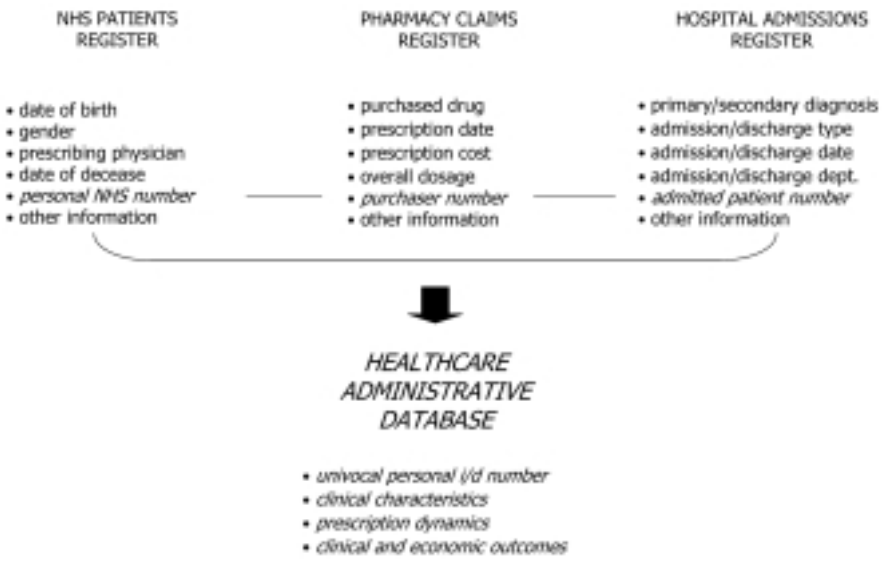

Figure 1. *The Ravenna healthcare administrative database. NHS = National Health System.*

Cost analysis. Only the direct cost of statins was taken into account. Costs were evaluated at Italian NHS purchase prices. The currency reference used was the Euro (€). For the computation of mean values, costs were adjusted to the Italian inflation rate calculated for pharmaceutical products, corresponding to 6.6% in 1997, 4.1% in 1998, 2.7% in 1999, and 2.6% in 2000[18].

Statistical analysis. Continuous variables were expressed as mean values ± SD; costs were presented as mean values ± SE. Differences in baseline characteristics were tested using one-way analysis of variance (ANOVA) for continuous variables and the Pearson's χ^2 test for categorical variables[19]. The trend of the percentage of patients undergoing therapy over the study period and the trend of the fraction of adequately treated patients were adjusted for age and gender using multivariable logistic regression models. Statistical significance in the area of costs was tested using the Kruskal-Wallis test (non-parametric approach). For all analyses, p values < 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS statistical package (SPSS for Windows, version 11.0, SPSS Inc., Chicago, IL, USA).

Results

Patient population characteristics. 3247 patients were enrolled in the study; 2265 of these patients were included (69.8% of the enrolled population) and 982 were excluded (30.2% of the enrolled population) (Fig. 2). Among the excluded patients, 21.7% reported a previous hospital admission for AMI, 0.8% moved and changed their LHU, and 77.5% died during the follow-up period. Among the patients included in the study, 69.4% (1571 patients) were male, with an average age of 66.6 ± 12.3 years (range 21-99 years) and 30.6% (694 patients) were female, with an average age of 74.3 ± 11.6 years (range 38-99 years). The difference in gender and age of the included patients was not statistically significant over the 5 years considered (Table I).

Assessment of exposure and pharmacoutilization. Overall, 779 individuals (34.4% of the included cohort) were exposed to treatment with statins (Table II). Those exposed to the treatment were predominantly male (72.9 vs 67.5%, p < 0.05) and younger than those who were not treated (63.2 ± 10.5 vs 72.0 ± 12.6 years, p < 0.001). The percentage of patients receiving therapy increased, over the study period, from 22.6% in 1996 to

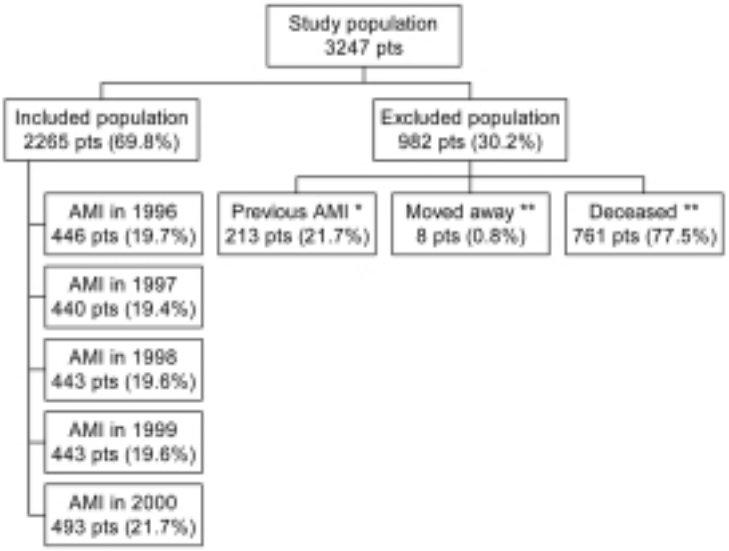

Figure 2. *Flowchart of the enrolled patients. AMI = acute myocardial infarction. * from January 1st, 1991 to enrolment date; ** during the follow-up period.*

Table I. Patient population characteristics.

	1996	1997	1998	1999	2000	Total
No. patients	446	440	443	443	493	2265
Age (years)	68.4 ± 12.2	67.9 ± 12.8	68.9 ± 12.2	69.4 ± 11.8	70.1 ± 13.7	69.0 ± 12.6
Male sex* (%)	70.6	69.3	72.7	70.2	64.5	69.4

* p = NS.

43.8% in 2000 (Table II). After adjusting for age and gender, this trend remained statistically significant ($p < 0.001$). The types of statins prescribed are shown in table III. Among the patients exposed to treatment, 317 (14.0% of the included cohort) were defined as adequately dosed (Table II). Adequately dosed patients were generally younger than not adequately dosed patients (62.1 ± 9.8 vs 64.1 ± 10.9 years, $p < 0.05$). The percentage of adequately dosed patients increased over the study period, from 4.3% in 1996 to 23.9% in 2000 (Table II). Among the patients exposed to statin therapy, the fraction of adequately dosed cases increased progressively over the 5 years of the study, to the point of outstripping that of not adequately dosed patients in 2000 (54.6 vs 45.4% of the patients exposed to treatment) (Fig. 3). Having controlled for age and gender, the progressive increment remained statistically significant ($p < 0.001$).

Cost allocation analysis. The total cost of statins over the 5-year study period was € 130,449, including € 10,610 in 1996, € 15,344 in 1997 (+44.6% compared to 1996), € 23,483 in 1998 (+53.0% compared to 1997), € 35,910 in 1999 (+52.9% compared to 1998) and € 45,102 in 2000 (+25.6% compared to 1999) (Table IV). The overall expenditure on statins for 2000 more than tripled in comparison to the figure for 1996 (+325.1%). A breakdown of the rate of increase suggested that the rising expenditure on statins is attributable mainly to the increase in the cost absorbed by adequately dosed patients (+804.0% compared to 1996) rather than by not adequately dosed patients (+50.8% compared to 1996). The composition of the total cost for statins over the 5-year study period showed that the level of expenditure on adequately dosed patients grew progressively from a minimum of 36.4% in 1996 to a maximum of 77.4% in 2000 (Table IV). The mean cost generated by

Table II. Exposure and pharmacoutilization of statin therapy.

	1996	1997	1998	1999	2000	Total
AMI patients	446 (100%)	440 (100%)	443 (100%)	443 (100%)	493 (100%)	2265 (100%)
Exposed patients	101 (22.6%)	118 (26.8%)	149 (33.6%)	195 (44.0%)	216 (43.8%)	779 (34.4%)
Adequately dosed patients	19 (4.3%)	31 (7.0%)	54 (12.2%)	95 (21.4%)	118 (23.9%)	317 (14.0%)

Table III. Patients exposed to statin therapy by kind of drug.

	1996	1997	1998	1999	2000	Total
Simvastatin	53 (52.4%)	79 (66.9%)	94 (63.1%)	115 (59.0%)	132 (61.1%)	473 (60.7%)
Pravastatin	23 (22.8%)	22 (18.7%)	19 (12.8%)	38 (19.5%)	29 (13.4%)	131 (16.8%)
Fluvastatin	10 (9.9%)	5 (4.3%)	2 (1.3%)	0	0	17 (2.2%)
Atorvastatin	0	1 (0.8%)	13 (8.7%)	21 (10.8%)	25 (11.6%)	60 (7.7%)
Cerivastatin	0	0	2 (1.3%)	3 (1.5%)	3 (1.4%)	8 (1.0%)
≥ 1 statin	15 (14.9%)	11 (9.3%)	19 (12.8%)	18 (9.2%)	27 (12.5%)	90 (11.6%)
Total	101 (100%)	118 (100%)	149 (100%)	195 (100%)	216 (100%)	779 (100%)

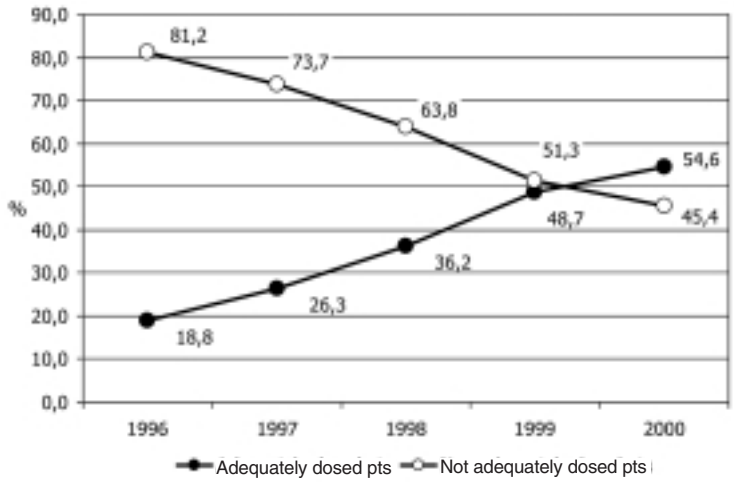

Figure 3. *Adequately/not adequately dosed patients exposed to statin therapy. Percentages are calculated on patients exposed to statin therapy.*

Table IV. Overall cost of statin therapy.

	1996	1997	1998	1999	2000	Total
Adequately dosed patients (1) (€)	3,864	6,432	13,041	25,522	34,930	83,789
Not adequately dosed patients (2) (€)	6,746	8,912	10,442	10,388	10,172	46,660
Exposed patients (1+2) (€)	10,610	15,344	23,483	35,910	45,102	130,449
Rate of increase in adequately dosed patients* (%)	–	+66.5	+102.8	+95.7	+36.9	+804.0**
Rate of increase in not adequately dosed patients* (%)	–	+32.1	+17.2	-0.5	-2.1	+50.8**
Rate of increase in exposed patients* (%)	–	+44.6	+53.0	+52.9	+25.6	+325.1**
Quota for adequately dosed patients [1/(1+2)] (%)	36.4	41.9	55.5	71.1	77.4	64.2
Quota for not adequately dosed patients [2/(1+2)] (%)	63.6	58.1	44.5	28.9	22.6	35.8

* calculated as the increase over the previous year; ** calculated as the increase since 1996.

adequately dosed patients increased progressively over the 5 years of the study, from a minimum of € 203.4 in 1996 to a maximum of € 296.0 in 2000 ($p < 0.001$; Table V). Having discounted the mean values, the difference remained statistically significant ($p < 0.05$; Table V).

Among adequately dosed patients mean daily doses differed significantly during the 5-year study period ($p < 0.05$; Table V).

Discussion

Scrutiny of real practice data from the healthcare database of the Ravenna LHU confirmed that the pharmacoutilization of statin therapy was not adequately achieved in patients with AMI, since a high proportion of the study population was either not treated or was treated inadequately. This underlying situation is repeated in each year of the study period. At the same time, however, the figures show a progressive increase in the rate of appropriate pharmacoutilization of therapy from 1996 to 2000. In particular, the 5-year period in question registered an increase both in the percentage of patients exposed to statin therapy (from 22.6% in 1996 to 43.8% in 2000) and in the percentage of those treated at a dosage deemed to be efficacious (from 4.3% in 1996 to 23.9% in 2000). A first possible explanation for the improvement in the indicators of appropriateness is the growing attention being paid to the question of correct utilization where statins are concerned. Analyses by certain authors show how in recent years, following the publication of important clinical trials on the therapeutic efficacy of statins, the rate of appropriateness of treatment has increased appreciably[7,20-22]. A second and perhaps decisive explanation is discernible in the experience gained by the Ravenna LHU, which since 1996 has been promoting a system of information management based on the creation of a population database, on the epidemiological processing of collected data and on the circulation of scientific evidence to its practitioners and its decision-makers[23]. Given that the indicators of appropriateness show a greater increase in the present study than in other studies[7,10], it could be that the loop established by this process of gathering, processing and interpreting data and circulating the results may have helped to generate the trend.

The economic impact of the level of appropriateness with statin therapy is identifiable, over the short term, in the costs sustained by providing the drug treatment, and, over the long term, in the costs of having to provide hospital services. Our study concentrated on the measurement of drug treatment costs, taking appropriateness or non-appropriateness with the prescribed therapy as the outcome. Though not based on the traditional measurement of an intermediate outcome (level of cholesterol in the blood), or of a final outcome (morbidity and/or mortality), this approach does nonetheless allow the researcher to express an economic evaluation of the resources utilized, and at the same time to verify the appropriateness of drug utilization. From 1996 to 2000, the increase in the overall expenditure on statins was predominantly attributable to the higher costs sustained for appropriately treated patients (+804.0%) rather than for not appropriately treated patients (+50.8%). Moreover, the make-up of the overall expenditure indicated a pro-

Table V. Mean cost of statin therapy among adequately dosed patients.

	1996	1997	1998	1999	2000
Mean daily dose* (tablets)	0.99 ± 0.22	1.08 ± 1.01	0.98 ± 0.19	1.07 ± 0.34	1.21 ± 0.45
Mean cost** (€)	203.4 ± 17.3	207.5 ± 12.6	241.5 ± 6.8	268.7 ± 7.4	296.0 ± 9.0
Disconted mean cost§ (€)	237.7 ± 20.2	227.5 ± 13.8	254.4 ± 7.2	275.5 ± 7.6	296.0 ± 9.0

* $p < 0.05$; ** $p < 0.001$ (Krustal-Wallis test); § costs adjusted to the Italian inflation rate: $p < 0.05$ (Krustal-Wallis test).

gressive shift of resources toward appropriately treated cases (from 36.4% in 1996 to 77.4% in 2000). Although the trend of these indicators may suggest an improvement in the appropriateness of drug utilization, the situation leaves room for further progress. First, resources for secondary prevention are still under-allocated, since the percentage of appropriately treated patients is very low, and whilst in terms of drug expenditure this may appear to represent a cost-saving parameter in the short term, it is likely to become an important factor in the development of other coronary events generating a much higher cost in the future. Second, resources for drug therapy are not being appropriately utilized, with 35.8% of the overall allocation for statins being expended on not appropriately treated patients.

Other concluding considerations are necessary for a proper interpretation of this study. First, administrative databases would appear to provide a suitable tool for the measurement and evaluation of the appropriateness of prescription practices[24,25]. Whilst they provide no meaningful clinical information, being designed for purposes other than epidemiological research, they do on the other hand afford considerable advantages, including a reliably representative picture of the monitored cohorts, the long duration of the observation periods, the widespread applicability of the results obtained, and reasonable utilization costs. Moreover, since administrative databases are mainly set up for accounting purposes (such as refunds to pharmacies in relation to the dispensation of drugs reimbursable by the NHS), the data are carefully checked by the LHU. Second, observational studies should be used as a practical complement to data from experimental studies (randomized controlled trials)[26,27]. Experimental studies represent the "gold standard" for the assessment of the safety and efficacy of pharmaceuticals and are designed to analyze the relationship between treatment processes and outcomes in ideal circumstances. This type of setting is needed to avoid the effects of possible confounders and to settle on the treatment guidelines causally related to the outcomes. Notwithstanding the importance of efficacy studies discussing "how should we treat" given illnesses, the highly controlled conditions of the experimental rationale strongly limit the widespread applicability of their findings in practice, and this has highlighted the need for observational studies to evaluate the appropriateness of medical care in "real world" settings. Such studies serve specifically to establish the accountability and assessability of treatment processes, clinical outcomes and resource allocation in a population under typical care conditions. Discordance between the ideal scenario and the results obtained in practice (non-appropriateness with statins) should increase the awareness of healthcare providers for the need of achieving a better performance and of improving the utilization of resources.

The present study was based on a period of observation of just 6 months following hospitalization for AMI. This is a short interval of time and should certainly be extended. Experimental studies show, in fact, that effects indicating the efficacy of statin therapy tend to be observed after a period of suitable treatment not less than 12 or 24 months in duration. Nonetheless, the study of the first 6 months of observation provided by the healthcare administrative database confirmed the suitability of this information tool in conducting epidemiological and economic investigations. In a forthcoming development of the study, the observation period would be lengthened so as to allow a full definition of the level of appropriateness with statin therapy and an accurate assessment of the cardiovascular outcomes associated with the different patterns of drug utilization (reinfarction, decease).

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