BMJ Open

Adherence to evidence-based drug therapies after myocardial infarction: is geographic variation related to hospital of discharge or primary care providers? A cross-classified multilevel design

Mirko Di Martino,[1] Michela Alagna,[2] Giovanna Cappai,[1] Francesca Mataloni,[1] Adele Lallo,[1] Carlo Alberto Perucci,[3] Marina Davoli,[1] Danilo Fusco[1]

To cite: Di Martino M, Alagna M, Cappai G, *et al*. Adherence to evidence-based drug therapies after myocardial infarction: is geographic variation related to hospital of discharge or primary care providers? A cross-classified multilevel design. *BMJ Open* 2016;**6**: e010926. doi:10.1136/bmjopen-2015-010926

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2015-010926).

Received 21 December 2015
Revised 23 February 2016
Accepted 16 March 2016

[1]Department of Epidemiology, Lazio Regional Health Service, Roma, Italy
[2]Faculty of Education—Free University of Bolzano, Bolzano, Italy
[3]Senior Epidemiologist Consultant, Roma, Italy

Correspondence to
Dr Mirko Di Martino;
m.dimartino@deplazio.it

ABSTRACT

Objectives: To measure the adherence to polytherapy after myocardial infarction (MI), to compare the proportions of variation attributable to hospitals of discharge and to primary care providers, and to identify determinants of adherence to medications.

Setting: This is a population-based study. Data were obtained from the Information Systems of the Lazio Region, Italy (5 million inhabitants).

Participants: Patients hospitalised with incident MI in 2007–2010.

Outcome measure: The outcome was chronic polytherapy after MI. Adherence was defined as a medication possession ratio ≥0.75 for at least three of the following drugs: antiplatelets, β-blockers, ACEI angiotensin receptor blockers, statins.

Design and analysis: A 2-year cohort study was performed. Cross-classified multilevel models were applied to analyse geographic variation and compare proportions of variability attributable to hospitals of discharge and primary care providers. The variance components were expressed as median ORs MORs. If the MOR is 1.00, there is no variation between clusters. If there is considerable between-cluster variation, the MOR will be large.

Results: A total of 9606 patients were enrolled. About 63% were adherent to chronic polytherapy. Adherence was higher for patients discharged from cardiology wards (OR=1.56 vs other wards, p<0.001) and for patients with general practitioners working in group practice (OR=1.14 vs single-handed, p=0.042). A relevant variation in adherence was detected between local health districts (MOR=1.24, p<0.001). When introducing the hospital of discharge as a cross-classified level, the variation between local health districts decreased (MOR=1.13, p=0.020) and the variability attributable to hospitals of discharge was significantly higher (MOR=1.37, p<0.001).

Conclusions: Secondary prevention pharmacotherapy after MI is not consistent with clinical guidelines. The relevant geographic variation raises equity issues in access to optimal care. Adherence was influenced more by the hospital that discharged the patient than by the primary care providers. Cross-classified models proved to be a useful tool for defining priority areas for more targeted interventions.

Strengths and limitations of this study

- The benefits of chronic polytherapy in reducing cardiovascular disease after myocardial infarction have been clearly shown. However, substantial geographic variation in adherence to guideline recommendations exists and creates equity issues in access to optimal care.
- Cross-classified multilevel models proved to be a useful tool for identifying the priority lines of action to improve adherence and define areas for more targeted healthcare interventions.
- Adherence to drug treatment was estimated on the basis of defined daily doses. Although this is a useful instrument for comparing the results from different studies, misclassification of drug utilisation may have occurred.

INTRODUCTION

Background

Patients who have had an acute myocardial infarction (MI) are at increased risk of repeated MI and death. Evidence-based prevention strategies include changes in lifestyle and drug therapy. International guidelines agree on the use of combinations of drugs belonging to specific anatomical therapeutic chemical (ATC) groups: platelet aggregation inhibitors (antiplatelets), β-blocking agents (β-blockers), agents acting on the renin-angiotensin system (ACEI angiotensin receptor blockers) and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins).[1 2] The benefits of chronic polytherapy in reducing cardiovascular disease have been clearly shown.[3–8]

The gap in clinical practice

However, observational studies reported poor adherence to chronic polytherapy. Therefore, therapies with proven benefit for MI are underused despite strong evidence that their use will result in better patient outcomes.[5 9 10] Moreover, substantial geographic variation exists in the treatment of patients with acute MI, and these gaps between knowledge and practice have important consequences in terms of equity in access to optimal care.[11 12] Unfortunately, from the current scientific evidence, it is not possible to quantify how much of the 'distance from clinical guidelines' is attributable to the patient behaviour, to the therapeutic approach recommended at hospital discharge or to the primary care providers, such as local health districts. The local health district is a body delegated by the National Health System to provide healthcare to a specific area. Each local health district is composed of a well-defined group of general practitioners sharing the same clinical guidelines and participating in the same learning interventions, coordinated by a district director. The analysis of these 'components of variation' may be a useful tool to define areas for more targeted interventions aimed at improving adherence to guidelines and equity in healthcare.

Objectives

The objectives of this study are as follows: to measure the adherence to chronic polytherapy after MI in clinical practice; to quantify and compare the proportions of variation attributable to the hospitals of discharge and to the primary care providers; to identify determinants of adherence to polytherapy.

MATERIALS AND METHODS

Data sources

Our Department has access to regional health information systems that contain mortality, hospital admission and drug claims data. The details of the individual information systems are reported in the online supplementary appendix.

Setting and study cohort

The study was based on the population living in the Lazio region of Italy, which comprises approximately five million persons. Using data from the regional Hospital Information System, the study included a cohort consisting of all patients discharged from hospitals between 1 January 2007 and 31 October 2010 with a diagnosis of MI (index admission). An MI was defined either as a primary diagnosis of International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM) codes 410.xx or as a primary diagnosis of an MI-related condition along with a secondary diagnosis of 410.xx (see online supplementary appendix). Patients aged 35–100 years at discharge were considered for inclusion in the analysis. Patients with hospitalisations for MI or related causes (ie, percutaneous coronary intervention —PCI, bypass, ischaemic heart disease, surgery of the heart and great vessels) in the 9 years before index admission were not considered eligible for the study. Patients who were not registered in the regional health assistance file throughout the whole study period were excluded, because they could not be retrieved from the regional health information system (note that healthcare is offered to all resident citizens without restriction). Patients with a duration of the index admission >21 days (95th centile) were excluded from the analyses as they were considered 'statistical outliers', probably representing extremely complex or unstable patients. Finally, patients who received an outpatient regimen for less than 30 days were excluded, in order to allow a long enough time for consistently estimating the adherence to polytherapy.

Follow-up

Individual follow-up for measuring drug exposure was considered to start on the first day after discharge from the index admission. The end of the observation period was defined as either the end of 2-year follow-up, the time of death or the date of any hospitalisation following discharge from the index admission, whichever occurred first. The last 'censoring' criterion allows one to measure the net impact of the hospital that has discharged the patient without the potential interference of subsequent hospitalisations.

Drug exposure: the adherence to medication

Drug exposure information was collected from the regional registry of all drugs dispensed by public and private pharmacies. All drugs in this study were included in the patients' healthcare plans and were equally available to all residents, in accordance with the universal healthcare coverage provided to residents of Italy. Information about prescriptions of antiplatelets (ATC B01AC04, B01AC05, B01AC06), β-blockers (ATC C07), ACEI/ARBs (ATC C09) and statins (ATC C10AA) were retrieved for all patients. Adherence to medication was measured through the medication possession ratio (MPR), calculated as the number of days of medication supplied during the follow-up on the basis of defined daily doses (DDDs) divided by the number of calendar days in the follow-up. Adherence to individual medications was defined as an MPR≥0.75. Adherence to chronic polytherapy was defined as an MPR ≥0.75 for at least three of the four evidence-based drugs.[8]

Statistical analysis

Continuous variables were presented as the mean value ±SD and/or median value. A map of the Lazio region was produced in order to show and compare the proportions of adherent patients by local health district. The classes used in the maps have been calculated applying the Jenks natural breaks optimisation algorithm,[13] which reduces the variance within classes and maximises the variance between classes.

It is important to note that the data structure is not purely hierarchical. In fact, patients are nested within local health districts and within hospitals of discharge. However, the nesting structure may be less clear when we consider health districts and hospitals of discharge. In other words, we can say that patients are nested within the 'cross-classification of health districts and hospitals'. Therefore, cross-classified logistic multilevel models[14] were performed in order to analyse geographic variation, by measuring and comparing the proportions of variability attributable to hospitals of discharge and primary care providers. After having performed a statistical sensitivity analysis on all potential multilevel models, the standard regression including only the 'local health district' level was compared with the cross-classified model including both the 'local health district' and the 'hospital of discharge' levels. The Akaike Information Criterion (AIC) was used to determine the model that provided the best account of the data. In fact, AIC deals with the trade-off between the goodness of fit of the model and the complexity of the model. The 'best' model is the one with the minimum AIC value.[15] The variance components were expressed in terms of median ORs MORs. The MOR quantifies the variation between clusters by comparing two persons from two randomly chosen different clusters. Consider two persons with the same covariates, chosen randomly from two different clusters. The MOR is the median OR between the person of higher propensity and the person of lower propensity. This measure is always greater than or equal to 1.00. If the MOR is 1.00, there is no variation between clusters. If there is considerable between-cluster variation, the MOR will be large.[16] The MORs were estimated controlling for patients' characteristics. In fact, explanatory variables that are divided very selectively across the groups can often explain a fair amount of group level variance. The interpretation would generally be that this does not reflect a real contextual effect, but rather the unequal composition of the groups.[14] We did not control for general practitioner characteristics in order to measure and emphasize the source of variability attributable to the primary care features.

A cross-classified model was also applied to identify determinants of adherence to polytherapy, properly taking into account the correlation within the specified clusters.[14] In this case, both patient and general practitioner characteristics were included. Determinants of adherence were identified in two steps. First, the following factors were selected based on a priori knowledge:[17 18] gender and age of patient, educational level, discharge ward, length of stay of the index admission, PCI during the index admission, use of antiplatelets, β-blockers, ACEI/ARBs or statins during the 12 months prior to the index admission (defined as at least 2 prescriptions), 15 comorbidities retrieved from the hospital records for both the index admission and the 9 previous years (see online supplementary appendix for details); gender, age and organisational arrangement[19] (none, association, network, group practice) of the general practitioner. Second, the potential determinants were further selected using a bootstrap stepwise procedure to determine which factors were actually associated with the outcome of interest.[20] Using this approach, 1000 replicated bootstrap samples were selected from the original cohort. A bootstrap sample is a sample of the same size as the original data set chosen with a replacement. Thus, a given participant in the original cohort may be selected multiple times, only once or not at all in a specific bootstrap sample. A stepwise procedure, using thresholds of p=0.05 for variable selection and elimination, was applied to each replicated sample and only the factors selected in at least 50% of the procedures were included in the final cross-classified multilevel model. ORs, 95% 95% CIs and p values were reported.

RESULTS

The study cohort

From the initial number of 13 571 patients discharged from hospital with an incident diagnosis of MI, 9606 were enrolled in the cohort (figure 1). Approximately 58% of patients underwent PCI during the index hospitalisation. The prevalence of PCI decreased as age increased: 67% in the age group '35–54', 65% in the group 55–69, 54% in the group 70–84 and 28% in the age group '≥85' years. About 10% of patients were not discharged from cardiology wards. A total of 6532 patients with MI (68%) were men. The mean age was 64 ±12 years for men and 72±12 years for women. Table 1 shows the prevalence of the most frequent comorbidities by age group. The impact of comorbid health conditions increased with age. Hypertension (21%), arrhythmia (16%), vascular diseases (13%) and heart failure (10%) were the most common comorbidities. Overall, more than 50% of patients with MI had at least one concomitant disease. The mean follow-up time was 628 days (95% CI 624 to 632). The median follow-up time was 730 days.

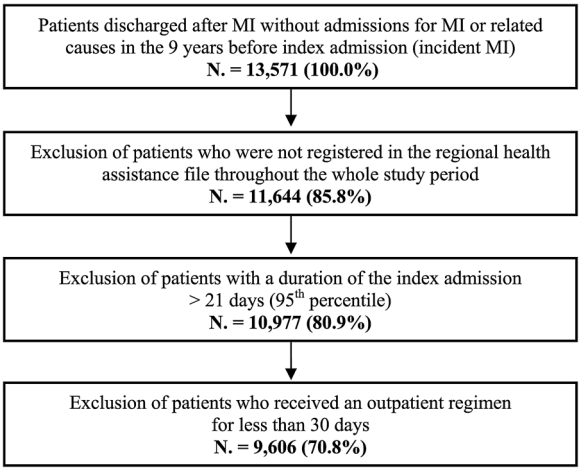

Figure 1 The exclusion criteria flow chart. MI, myocardial infarction.

Table 1 Prevalence of the most frequent comorbidities by age group

Age group (years)	35–54	55–69	70–84	85+	Total
Gastro-oesophageal haemorrhage (%)	0.31	0.56	1.33	1.89	0.91
Chronic liver, pancreas and digestive diseases (%)	4.04	3.51	4.32	3.86	3.93
Haematological diseases (%)	2.04	2.88	7.41	12.40	5.20
Chronic nephropathies (%)	1.24	2.57	7.74	17.34	5.50
Chronic obstructive pulmonary disease (COPD) (%)	1.20	3.62	8.23	11.68	5.53
Conduction disorders (%)	2.31	3.73	8.41	14.29	6.09
Disorders of lipoid metabolism/obesity (%)	5.37	6.70	7.53	6.47	6.72
Malignant neoplasms (%)	1.60	5.43	11.64	12.13	7.52
Cerebrovascular disease (%)	1.20	5.05	13.98	19.50	8.81
Other cardiac diseases (%)	3.95	5.22	12.64	20.75	9.03
Diabetes (%)	3.77	8.04	12.81	13.48	9.43
Heart failure (%)	3.37	5.31	13.58	23.45	9.53
Diseases of arteries, arterioles and capillaries (%)	4.57	9.62	18.91	25.79	13.44
Cardiac dysrhythmias (%)	9.23	11.72	21.43	29.38	16.31
Hypertension (%)	8.43	15.94	28.75	38.10	21.10

Adherence to medication

The adherence to individual evidence-based medications by gender and age group is reported in table 2. As regards the whole cohort, antiplatelets were characterised by the highest adherence (77%), followed by statins (73%), ACEI/ARBs (67%) and β-blockers (53%). It is worth noting that, for both males and females, the adherence to each of the recommended medications decreased markedly, moving from the age group '70–84' to the group '≥85' years. Overall, in the Lazio region, about 63% of patients with MI were adherent to chronic polytherapy, defined as an MPR ≥0.75 for at least three of the four evidence-based drugs. If we consider the full combination therapy (ie, MPR ≥0.75 for all of the four evidence-based drugs), the percentage drops to 28%. The cross-classified logistic multilevel model (table 3) showed that the probability of adherence to chronic polytherapy after MI (at least three out of four drugs) was strongly influenced by the patient and general practitioner characteristics. With regard to patient characteristics, female gender was associated with a lower probability of adherence. The effect of age was not linear: with respect to the reference category (age less than 55 years), the probability of adherence increased significantly in the age class 55–69 years (OR=1.15, p=0.031) and substantially decreased in the older age group (age ≥85 years; OR=0.42, p<0.001). The effect of the educational level was not significant. Moreover, adherence was significantly higher for patients discharged from cardiology wards, for patients with a length of stay longer than 7 days (the median value), for patients who underwent PCI during the index hospitalisation and for patients who were prescribed β-blockers, ACEI/ARBs or statins in the 12 months before

Table 2 Adherence to individual evidence-based medications by gender and age group

Age group (years)	β-Blockers (%)	ACEI/ARBs (%)	Statins (%)	Antiplatelets (%)
Males				
35–54	57.43	60.84	79.21	76.80
55–69	57.79	69.82	81.30	80.25
70–84	49.58	68.69	75.01	81.41
85+	31.87	55.89	47.81	67.90
Total	53.88	66.68	77.17	79.15
Females				
35–54	56.61	56.32	67.24	67.53
55–69	55.35	70.36	71.80	73.71
70–84	52.12	70.40	65.11	74.80
85+	37.06	56.76	41.03	62.21
Total	50.75	66.73	62.87	71.64
Whole cohort				
35–54	57.30	60.14	77.36	75.37
55–69	57.22	69.95	79.08	78.72
70–84	50.64	69.41	70.86	78.64
85+	35.04	56.42	43.67	64.42
Total	52.88	66.69	72.61	76.76

ARBs, angiotensin receptor blockers.

Table 3 Determinants of adherence to chronic polytherapy

Determinants	Reference	OR		95% CI	p Value
Gender of patient	(male)	0.81		0.73 to 0.90	<0.001
Age group (years)	(35–54)	55–69	1.15	1.01 to 1.31	0.031
		70–84	0.99	0.86 to 1.14	0.904
		85+	0.42	0.35 to 0.52	<0.001
Discharge ward: cardiology	(other)	1.56		1.26 to 1.92	<0.001
Length of stay	(≤7 days)	1.11		1.01 to 1.23	0.043
PCI	(absence)	2.60		2.32 to 2.92	<0.001
EB drug use in the 12 months before admission	(≥2 prescriptions)				
β-blockers	(absence)	1.63		1.40 to 1.90	<0.001
ACEI/ARBs	(absence)	1.87		1.69 to 2.07	<0.001
Statins	(absence)	1.30		1.14 to 1.50	<0.001
Antiplatelets	(absence)	1.03		0.90 to 1.17	0.702
Patient comorbidities					
Malignant neoplasms	(absence)	0.85		0.72 to 1.01	0.062
Disorders of lipoid metabolism/obesity	(absence)	0.91		0.75 to 1.11	0.352
Haematological diseases	(absence)	0.69		0.56 to 0.86	0.001
Heart failure	(absence)	0.89		0.75 to 1.03	0.115
Other cardiac diseases	(absence)	0.85		0.72 to 1.00	0.050
Cardiac dysrhythmias	(absence)	0.71		0.63 to 0.81	<0.001
Cerebrovascular disease	(absence)	0.87		0.73 to 1.03	0.102
Diseases of arteries and arterioles	(absence)	0.88		0.76 to 1.02	0.090
Chronic obstructive pulmonary disease	(absence)	0.71		0.58 to 0.87	0.001
Chronic nephropathies	(absence)	0.83		0.67 to 1.02	0.074
Gastro-oesophageal haemorrhage	(absence)	0.54		0.34 to 0.87	0.011
General practitioner characteristics					
Gender	(male)	1.01		0.90 to 1.13	0.923
Age group (years)	(34–49)	50–54	0.99	0.85 to 1.14	0.853
		55–59	0.85	0.73 to 0.98	0.026
		60+	0.86	0.73 to 1.01	0.074
Organisational arrangement	(none)	association	1.05	0.91 to 1.22	0.485
		network	1.13	0.98 to 1.30	0.095
		group practice	1.14	1.01 to 1.29	0.042

ARBs, angiotensin receptor blockers; EB, evidence-based; PCI, percutaneous coronary intervention.

admission. On the other hand, all comorbidities were associated with lower adherence to chronic polytherapy. As regards the general practitioner characteristics, adherence was higher for patients with younger physicians and for patients with general practitioners working in group practice, ie, sharing facilities, electronic patient records, administrative and clinical staff.

The geographic variation

The 'hierarchical' healthcare system was composed as follows: 2156 general practitioners, 55 local health districts and 93 cross-classified hospitals of discharge. A high geographic variation was observed between the local health districts of the region. The percentages of adherence to polytherapy ranged from 49% to 74% (figure 2). In table 4, the proportions of variation attributable to the hospitals of discharge and to the primary care providers were measured and compared. When analysing the variation among primary care providers, after controlling for patients' characteristics, a relevant variation between local health districts was detected (MOR=1.24, p<0.001). However, when introducing the hospital of discharge as a cross-classified level, the variation between local health districts decreased (MOR=1.13, p=0.020). When introducing the hospital level, the variation between local health districts can be seen as the variability between districts as if all patients were discharged from the same hospital. Therefore, a portion of the variability in primary care is attributable to the hospital that has discharged the patient. Moreover, the variability in patient adherence attributable to the hospital of discharge was statistically significant (p<0.001) and substantially higher. In fact, the MOR associated to the hospital of discharge was 1.37, whereas the MOR attributable to the local health district was 1.13. AIC values related to the statistical sensitivity analysis on potential multilevel models were reported in table 5. The variation among general practitioners within the same local health district was not statistically significant (p=0.361).

DISCUSSION

In a study of 9606 patients, we found that after a hospital discharge for MI, only 63% of patients were adherent to

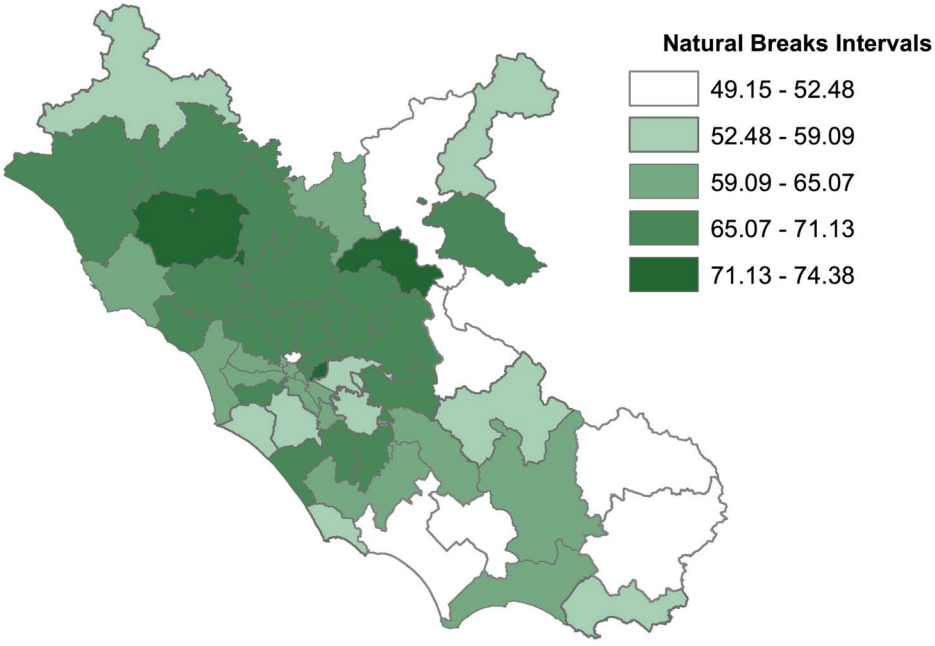

Figure 2 Percentages of adherence to polytherapy by local health district.

polytherapy in the following 2 years. Treatments with proven benefit for MI are underused despite strong evidence that their use will result in better patient outcomes. This result is even more alarming if we consider that our definition of adherence was not restrictive. In fact, adherence to polytherapy was defined as an MPR ≥0.75 for at least three of the four evidence-based drugs. Our findings are consistent with the results of other investigations, which reported unsatisfactory prescribing rates of secondary prevention drugs after MI in different times[10] and in different countries.[17 18 21] Among patient determinants of adherence to polytherapy, we found that older age (≥85 years) and comorbidities played an important negative role. A hypothesis for this finding may be related to the cumbersomeness of therapy, which increases with age and number of comorbidities. The longer and more complex the list of drugs prescribed, the lower the adherence of the patient.[22] The impact of the type of discharge ward was very impressive: patients discharged from cardiology wards were much more likely to be adherent to evidence-based medications. As regards general practitioner determinants, adherence to polytherapy was higher with younger general practitioners and with physicians working in teams, sharing facilities, electronic patient records and clinical staff.

The geographic variation

A relevant geographic variation in adherence to guidelines was observed between the local health districts of the Lazio region. The 'spatial' heterogeneity raises equity concerns in access to optimal care. This kind of unwarranted and avoidable variation in healthcare delivery is not unique to the Italian context.[11 12] This study focuses on the 'trade-off' between hospital and primary care in determining variation. The median ORs estimated by the cross-classified multilevel models are very interesting. They allow one to measure and compare the amount of variation attributable to the 'discharge phase' and to the following 'primary care phase'. The reduction of the variability among local health districts after entering the hospital level in the model proved that the differences we observe in primary care partially 'reproduce' the clinical and organisational approach of the hospital of discharge, whose aims are both the correct

Table 4 The trade-off between hospitals of discharge and primary care providers

	Median OR* (p Value)	
Levels of healthcare system	**Logistic multilevel model including the 'local health district' level**	**Cross-classified model including both the 'local health district' and the 'hospital of discharge' levels**
Local health district	1.24 p<0.001	1.13 p=0.020
Hospital of discharge	–	1.37 p<0.001
AIC	11 500.38	11 431.07

*The analyses were performed controlling for patients' characteristics.
AIC, Akaike Information Criterion.

Table 5 Akaike Information Criterion values related to the statistical sensitivity analysis on potential multilevel models

Multilevel model	Levels of analysis	Explanatory variables	AIC
Two-level regression	(Patient)—GP	Intercept-only	12 617.83
Two-level regression	(Patient)—GP	Patients' characteristics	11 547.13
Three-level regression	(Patient)—GP—LHD	Patients' characteristics	11 502.37
Two-level regression	(Patient)—LHD	Patients' characteristics	11 500.38
Three-level cross-classified regression	(Patient)—LHD/HoD	Patients' characteristics	11 431.07

AIC, Akaike Information Criterion; GP, general practitioner; HoD, hospital of discharge; LHD, local health district.

setting of drug therapy and the planning of the subsequent visits for patient monitoring. Really, adherence to chronic polytherapy in people with previous MI was influenced more by the hospital that discharged the patient (MOR=1.37) than by the primary care providers (MOR=1.13).

The potential 'plans of action'

According to the study results, it is possible to formulate hypotheses about the potential 'plans of action' for health policies aimed at improving adherence to polytherapy, such as (1) to organise prescribing upskilling sessions for general practitioners, focusing on the most recent clinical guidelines; (2) to promote education on doctor–patient relationships, underlining the effectiveness of systematic motivational support; (3) to stimulate association for primary care physicians, in order to improve the continuity of care; (4) to improve the organisational processes within the hospital, in order to discharge patients with MI from specialist wards and plan the subsequent visits for patient monitoring.

Study strengths and limitations

The population-based design, large numbers and robustness of analytical procedures are the main strengths of this study. Moreover, cross-classified multilevel models proved to be a useful tool for identifying the priority lines of action to improve adherence and define areas for more targeted healthcare interventions. However, there are some study limitations to be considered. First, the results come from a single region in Italy and may be not generalisable to other geographic areas. However, our findings are in line with results of other studies carried out in other regions of Italy.[23] Second, our pharmaceutical database does not contain information on the prescribed daily doses and adherence to drug treatment was estimated on the basis of the DDDs. Although this is a useful instrument for comparing the results from different studies,[24] misclassification of drug utilisation may have occurred. Third, although the relative efficiency of using claims databases for studies of adherence in large populations in a 'real-word' setting is highly advantageous, we are unable to determine if patients actually consumed the dispensed medication. Thus, the study results of medication adherence based on claims data may be overestimated and should be interpreted with appropriate caution. Finally, there are some things to keep in mind concerning the use of stepwise procedures for selecting determinants of adherence to polytherapy. The original list of potential determinants was defined on the basis of a priori knowledge.[17 18] Bootstrap stepwise is just a way to improve the efficiency of the statistical model. In fact, this procedure allowed us to identify which of the a priori potential determinants were actually associated with adherence to polytherapy in the specific context of our data. This avoids overparameterisation and improves estimator efficiency.[20]

CONCLUSIONS

In clinical practice, secondary prevention pharmacotherapy after MI is not consistent with clinical guidelines. Moreover, the relevant geographic variation in adherence to polytherapy detected within the Lazio region raises equity issues in access to optimal care. Finally, adherence was influenced more by the hospital that discharged the patient than by the primary care providers. Cross-classified models proved to be a useful tool for identifying the priority lines of action to improve adherence and define areas for more targeted healthcare interventions.

Contributors MDM contributed to the concept and design of the study, the analysis of data and the statistical methodology required for the analytic modelling, the interpretation of results, and the writing of the article. MA contributed to the design of the study, the analysis of data, the interpretation of results and the writing of the article. GC contributed to the design of the study and the acquisition of data from the Lazio regional health information systems. FM and AL contributed to the interpretation of results and the writing of the article. CAP, MD and DF contributed to the concept of the study, the interpretation of results, the writing of the article and the critical revision of the paper for important intellectual content, and they have given their final approval to the version submitted for publication. All authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Funding This work was partially funded by the Italian Ministry of Health. Research project code: GR-2011-02350559.

Competing interests None declared.

Ethics approval This study was approved by the Ethics Committee of the Lazio Regional Health Service.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Prior postings and presentations The preliminary results were presented at the 31st International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Boston, 2015.

REFERENCES

1. National Institute for Clinical Excellence. Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE guidelines [CG172]. Published date: November 2013.
2. Smith SC Jr, Benjamin EJ, Bonow RO, *et al*. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol 2011;58:2432–46.
3. Briffa T, Hickling S, Knuiman M, *et al*. Long term survival after evidence based treatment of acute myocardial infarction and revascularisation: follow-up of population based Perth MONICA cohort, 1984–2005. *BMJ* 2009;338:b36.
4. Gouya G, Reichardt B, Ohrenberger G, *et al*. Survival of patients discharged after acute myocardial infarction and evidence-based drug therapy. *Eur J Epidemiol* 2007;22:145–9.
5. Yan AT, Yan RT, Tan M, *et al*., Canadian ACS Registries Investigators. Optimal medical therapy at discharge in patients with acute coronary syndromes: temporal changes, characteristics, and 1-year outcome. Am Heart J 2007;154:1108–15.
6. Newby LK, LaPointe NM, Chen AY, *et al*. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation* 2006;113:203–12.
7. Mukherjee D, Fang J, Chetcuti S, *et al*. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. *Circulation* 2004;109:745–9.
8. Kirchmayer U, Di Martino M, Agabiti N, *et al*. Effect of evidence-based drug therapy on long-term outcomes in patients discharged after myocardial infarction: a nested case–control study in Italy. *Pharmacoepidemiol Drug Saf* 2013;22:649–57.
9. Gislason GH, Rasmussen JN, Abildstrøm SZ, *et al*. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006;27:1153–8.
10. Kirchmayer U, Agabiti N, Belleudi V, *et al*. Socio-demographic differences in adherence to evidence-based drug therapy after hospital discharge from acute myocardial infarction: a population-based cohort study in Rome, Italy. *J Clin Pharm Ther* 2012;37:37–44.
11. Brooks JM, Cook EA, Chapman CG, *et al*. Geographic variation in statin use for complex acute myocardial infarction patients: evidence of effective care? *Med Care* 2014;52(Suppl 3):S37–44.
12. O'Connor GT, Quinton HB, Traven ND, *et al*. Geographic variation in the treatment of acute myocardial infarction: the Cooperative Cardiovascular Project. *JAMA* 1999;281:627–33.
13. Jenks GF. The Data Model Concept in Statistical Mapping. *Int Yearbook Cartography* 1967;7:186–90.
14. Hox J. *Multilevel analysis: techniques and applications*. Mahwah, New Jersey: Lawrence Erlbaum Associates, 2002:123.
15. Bozdogan H. Akaike's information criterion and recent developments in information complexity. *J Math Psychol* 2000;44:62–91.
16. Larsen K, Merlo J. Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. *Am J Epidemiol* 2005;161:81–8.
17. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;119:3028–35.
18. Mathews R, Wang TY, Honeycutt E, *et al*. TRANSLATE-ACS Study Investigators. Persistence with secondary prevention medications after acute myocardial infarction: insights from the TRANSLATE-ACS study. *Am Heart J* 2015;170:62–9.
19. Fantini MP, Compagni A, Rucci P, *et al*. General practitioners' adherence to evidence-based guidelines: a multilevel analysis. *Health Care Manage Rev* 2012;37:67–76.
20. Austin PC, Tu JV. Automated variable selection methods for logistic regression produced unstable models for predicting acute myocardial infarction mortality. *J Clin Epidemiol* 2004;57:1138–46.
21. Sanfélix-Gimeno G, Peiró S, Ferreros I, *et al*. Adherence to evidence-based therapies after acute coronary syndrome: a retrospective population-based cohort study linking hospital, outpatient, and pharmacy health information systems in Valencia, Spain. *J Manag Care Pharm* 2013;19:247–57.
22. Vik SA, Maxwell CJ, Hogan DB. Measurement, correlates, and health outcomes of medication adherence among seniors. *Ann Pharmacother* 2004;38:303–12.
23. Filippi A, D'Ambrosio G, Giustini SE, *et al*. Pharmacological treatment after acute myocardial infarction from 2001 to 2006: a survey in Italian primary care. *J Cardiovasc Med* 2009;10:714–18.
24. World Health Organization. *Collaborating centre for drug statistics methodology, guidelines for ATC classification and DDD assignment 2013 (16th edition)*. Oslo, Norway: Norwegian Institute of Public Health, 2012.