Clinical pharmacist intervention reduces mortality in patients with acute myocardial infarction: a propensity score matched analysis

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ABSTRACT

Background Is it possible that the mortality rate from acute myocardial infarction (AMI) may decline after interventions by pharmacists?

Objective To evaluate the impact of clinical pharmacist on the mortality of AMI.

Methods Clinical pharmacists did not perform any interventions during phase 1 (pre-intervention), and consulted with physicians to address drug related problems (DRPs) during phase 2 (post-intervention). The main outcome was a decrease in mortality from AMI. The two phases were compared using propensity score matching (PSM).

Results 1388 interventions were suggested by clinical pharmacists during phase 2, of which 1239 (89.2%) were accepted. Logistic regression analysis demonstrated that interventions of clinical pharmacists were significantly associated with a reduced mortality in patients with both ST segment elevation myocardial infarction (STEMI) (OR 0.449; 95% CI 0.296 to 0.680) and non-ST segment elevation myocardial infarction (NSTEMI) (OR 0.268; 95% CI 0.125 to 0.572). Using PSM analysis, mortality reduced from 6.8% to 4.3% in STEMI patients (P=0.0034) and from 3.2% to 0.7% in NSTEMI patients (P=0.0202) after the interventions.

Conclusions DRPs that caused or contributed to possible mortality were detected by clinical pharmacists in patients with AMI. Correcting these DRPs after pharmacists' interventions could result in a significant decrease in mortality.

INTRODUCTION

Increased use of evidence based therapies and lifestyle changes have spurred a considerable reduction in mortality from coronary heart disease in recent decades.[1] However, acute myocardial infarction (AMI) retains a substantial footprint on global health, affecting more than 7 million individuals worldwide each year.[2] AMI can be divided into ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI). Since the mid-1990s, there has been a steady decline in the proportion of STEMI, and a smaller increase in NSTEMI, leading to an overall decline in AMI. Today, NSTEMI comprises 60–75% of all AMI.[2]Inhospital mortality of AMI has decreased from 29% in 1969 to <7% today. The progress is the result of several major trends, including improvement in risk stratification, more widespread usage of invasive strategy, implementation of immediate revascularisation via percutaneous coronary intervention, advances in antiplatelet agents and anticoagulants, and greater use of statins, ACE inhibitors (ACEI) and β-blockers.[3] Despite considerable improvement in prophylaxis and treatment, AMI remains a common life threatening disease and an enormous burden on healthcare systems, suggesting an opportunity for improvement.

Drug related problems (DRPs) are defined as circumstances related to drug therapy that potentially interfere with the desired health outcomes.[4]Fatal adverse drug events (FADEs) are events associated with a patient's death.[5] Preventable FADEs are events that have occurred that could have been preventable with interventions. Ameliorable FADEs are events that have occurred but could have been ameliorated with interventions.[6] A study demonstrated that there were 133 FADEs among 732 deaths in the internal medicine department over a 2 year period, and half of the FADEs were judged to be related to DRPs.[7] Drugs that were suspected to cause or contribute to mortality were aspirin, warfarin, heparin, diuretics, nitrates, ACEI, calcium channel blockers, cardiac glycoside, terbutaline and theophylline, which were often used to treat AMI and its complications.[7]

Patients with AMI are at a significant risk of DRPs due to the combination of multiple drugs.[8] Also, the disproportionate use of medications and changes in pharmacokinetics and pharmacodynamics related to age and disease may lead to a higher risk of DRPs in these fragile patients.[9] In addition, nosocomial infections in patients with AMI are related to factors such as old age, heart failure, invasive procedures, concomitant diseases and inappropriate use of antimicrobial agents. These infections also ultimately increase the risk of death for these patients.[10]

Currently, clinical pharmacists play a key role in the cardiovascular care team, and are engaged with medical practices for correcting substantial DRPs.[11] However, the effects of clinical pharmacists' interventions on mortality are limited. Thus it is necessary to evaluate the impact of the clinical pharmacist on the mortality of AMI.

It is best if clinical pharmacists can discuss DRPs with physicians face to face.[12] In brief, cases can be reviewed by clinical pharmacists and DRPs found. In addition, clinical pharmacists could also play an important role via improvement in antibiotic regimens, dosing and frequency.[13] These can prompt the physician to change the treatment strategy in time to avert an FADE.[14] In such situations, the mortality rate of hospitalised AMI patients may decline further.

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METHODS

A two phased study design was carried out in a 60 bed cardiology ward in a teaching hospital (Renji Hospital, School of Medicine, Shanghai Jiaotong University). Patients whose primary diagnoses were STEMI or NSTEMI were included. During phase 1 (no intervention phase, 1 January 2010 to 30 April 2012), no pharmacists were involved. Baseline data of all AMI patients was collected, and the improper use of medications in the absence of interventions were also recorded.

During phase 2 (intervention phase, 1 January 2013 to 30 April 2016), clinical pharmacists' services were provided for about 40 hours per week in the cardiology ward, and possible DRPs were identified for all patients with AMI who died. Pharmacists then discussed these DRPs with the cardiologists face to face. Finally, cardiologists agreed on ameliorable FADEs and reached a consensus on DRPs that physicians had a duty to amend in principle. All of the pharmacists' recommendations were documented, whether or not the physician chose to accept them. The role and actions of the clinical pharmacists are described in detail for three typical cases. The ratio of pharmacists to patients was approximately 1:30. The ratios of nurses and physicians were similar during the two study phases.

Approval for the study by the local institutional review board was not required because it was a non-invasive and retrospective study. All patients provided written informed consent.

Data collection

Patient characteristics (demographics and discharge diagnosis) were recorded by reviewing the medical charts and hospital information system. Chronic comorbidities were frequently encountered in patients with AMI and have a high impact on patient outcome.[15 16] The Charlson Comorbidity Index (CCI) provides a way to quantify this impact on survival and is also used as a prognostic comorbidity index in AMI populations.[17 18] The comorbidities were weighted by Charlson *et al* using a point system. According to the point system, patients without comorbidities have a CCI score of 0, and those with only one comorbidity a CCI score of 1. Patients have a CCI score of 2 when there are two comorbidities weighted as 1, or one comorbidity weighted as 2. Patients have a CCI score ≥3 if the sum of the weighted points of comorbidities is 3 or more.

The types of interventions and corresponding actions taken by the medical team were recorded as follows: (1) identification of medication contraindications and recommendation of optimal treatment when necessary; (2) identification of incompatibilities in solution; (3) discovery of harmful drug–drug interaction; (4) clarification of medication dosage or frequency; (5) discovery of incorrect indications; and (6) identification of inappropriate antibiotics use.

Outcome measures

Two measures were used to assess the impact of pharmacists' interventions: (1) numbers of DRPs and acceptance recommended by clinical pharmacists; and (2) comparison of mortality during phase 1 and phase 2.

Statistical analysis

We analysed the data by employing propensity score matching (PSM) to correct the differences in patient characteristics between phase 1 and phase 2.[19] In brief, logistic regression was used to yield a propensity score and the score included the corrected variables (age, sex, CCI and primary discharge diagnosis). The greedy matching algorithm was used to identify matched pairs (a patient in phase 1 and a patient in phase 2).[20] In addition, logistic regression analysis was performed using a backward selection model in the following order: (1) the presence of clinical pharmacists' interventions; and (2) risk factors including age, gender and CCI.[21] Dichotomous variables were expressed as counts (percentage) and were analysed using the χ^2test or Fisher's exact test. Continuous variables are presented as mean (SD) and were tested using a grouped t test or Wilcoxon rank sum test. All statistical analysis was performed using SAS V.9.3 (SAS Institute Inc, Cary, North Carolina, USA).[22]

RESULTS

Typical cases in phase 2

Case No 1

An 86-year-old man with acute inferior MI, atrial fibrillation, grade 3 hypertension and diabetes mellitus was admitted to the coronary care unit. The patient died 2 hours later despite aggressive rescue. Subsequent evaluation of the treatment protocol by clinical pharmacists focused on several issues. First, according to the guidelines, patients with AMI should avoid straining at stool, and the use of morphine might sharpen constipation. Second, ACEI can significantly reduce mortality in AMI patients with acute left heart failure (ALHF), and its relative contraindications are low blood pressure and high serum creatinine (>265 μmol/L). Thirdly, dyphylline should not be used in AMI patients with ALHF because it could increase heart rate and myocardial oxygen consumption. Torsemide may increase the pharmacological effects of dyphylline. Thus the risk of serious arrhythmias would be increased. Fourthly, the antiplatelet effect of clopidogrel would be reduced with the combination of esomeprazole. In total, five DRPs were identified: (1) incorrect indications for laxatives in AMI patients and the use of morphine; (2) incorrect indications for ACEI; (3) incorrect indications for dyphylline; (4) one harmful interaction between dyphylline and torsemide; and (5) a second harmful interaction between esomeprazole and clopidogrel.

Case No 2

An 81-year-old man was admitted to hospital due to unstable angina and hypertension. The patient died of respiratory failure as well as heart failure despite positive rescue. This patient with severe infection had not been treated with antibacterial drugs, which may have induced respiratory failure and increased cardiac load. Furthermore, if the use of antibiotics is not effective after 3 days, timely adjustment of antimicrobial agents should be considered. One DRP was identified in this case—namely, irrational and inadequate usage of antibiotics.

Case No 3

An 83-year-old man with a history of percutaneous coronary intervention for AMI was admitted to the cardiology ward due to recurrent acute anterior MI (Killip III), hypertension (grade 3), chronic obstructive pulmonary diseases and pulmonary infection. The patient stopped breathing suddenly with ventricular fibrillation and died despite aggressive rescue. Several issues should be considered in this case. First, the amiodarone information insert states that (1) it is prohibited in combination with moxifloxacin because the risk of ventricular arrhythmias may be increased for more prolonged QT interval and (2) it is suitable for supraventricular or ventricular arrhythmias. Second, the morphine information insert states that it is contraindicated in bronchial asthma or decompensated chronic obstructive pulmonary diseases. Thirdly, according to the guidelines, ACEI should

Table 1 Drug related problems identified by the pharmacists in phase 2 of the study

Drug related problem	Intervention times (n (% of total))	Accepted by cardiologists (n (% of total Intervention times))
Violation of contraindications	425 (30.6)	375 (27.0)
Violation of incompatibilities	116 (8.4)	116 (8.4)
Patient experienced a harmful Interaction	359 (25.9)	302 (21.8)
Dose/frequency inappropriate	166 (12.0)	151 (10.9)
Incorrect indications	199 (14.3)	182 (13.1)
Irrational usage of antibiotics	123 (8.9)	113 (8.1)
Total	1388 (100)	1239 (89.2)

be used within the first 24 hours of AMI and (or) clinical heart failure despite high creatinine (>265 mmol/L) or low systolic blood pressure (<90 mm Hg). In total, four DRPs were identified: (1) one harmful interaction between amiodarone and moxifloxacin; (2) violation of the medication contraindications regarding morphine; (3) incorrect indications for amiodarone; and (4) incorrect indications for ACEI.

Interventions of clinical pharmacists

A total of 1388 interventions were provided by clinical pharmacists in phase 2, 1239 (89.2%) of which were accepted. The types of interventions are presented in table 1. Violation of incompatibilities had the highest percentage of acceptance.

Impact of clinical pharmacists' interventions in reducing mortality

A total of 2120 patients with STEMI (phase 1, 842 patients; phase 2, 1278 patients) and 2422 patients with NSTEMI (phase 1, 407; phase 2, 2015) were enrolled in the study. As shown in table 2 and table 3, the characteristics of the patients were comparable, with the exception of CCI (CCI 0 and CCI ≥4 in STEMI; CCI ≥4 in NSTEMI). After PSM, 770 patients with STEMI and 407 patients with NSTEMI were retained, and none of these differences was statistically significant. Mortality was reduced from 6.8% to 4.5% in STEMI patients (P=0.036) after the interventions. Similarly, in NSTEMI patients, the mortality rate reduced from 3.2% to 0.8% (P=0.0003). Using PSM, mortality reduced from 6.8% to 4.3% in STEMI patients (P=0.0034) and from 3.2% to 0.7% in NSTEMI patients (P=0.0202) after the interventions (table 4).

In addition, logistic regression analysis demonstrated that age and CCI were associated with an increased risk of mortality in patients with STEMI and NSTEMI. Conversely, the presence of clinical pharmacists' interventions were associated with a reduced risk of mortality in patients with STEMI (OR 0.449; 95% CI 0.296 to 0.680) and NSTEMI (OR 0.268; 95% CI 0.125 to 0.572) (table 5).

Table 2 Characteristics of ST segment elevation myocardial infarction in phase 1 and phase 2, before and after propensity score matching

	Before PSM		After PSM	
	Phase 1 (n (%))	Phase 2 (n (%))	Phase 1 (n (%))	Phase 2 (n (%))
Characteristic	(n=842)	(n=1278)	(n=770)	(n=770)
Age (years)	63.0±12.2	63.4±12.0	63.0±12.3	63.4±12.2
Men	678 (80.5)	1048 (82.0)	619 (80.4)	630 (81.8)
Women	164 (19.5)	230 (18.0)	151 (19.6)	140 (18.2)
CCI (%)				
0	423 (50.2)	545 (42.6)*	389 (50.5)	341 (44.3)
1	276 (32.8)	433 (33.9)	252 (32.5)	260 (33.8)
2	104 (12.3)	190 (14.9)	93 (12.1)	120 (15.6)
3	33 (3.9)	64 (5.0)	30 (3.9)	34 (4.4)
≥4	6 (0.7)	46 (3.6)**	6 (0.8)	15 (1.9)

*P<0.05; **P<0.001.
CCI, Charlson Comorbidity Index; PSM, propensity score matching.

Table 3 Characteristics of non-ST segment elevation myocardial infarction in phase 1 and phase 2, before and after propensity score matching

	Before PSM		After PSM	
	Phase 1 (n (%))	Phase 2 (n (%))	Phase 1 (n (%))	Phase 2 (n (%))
Characteristic	(n=407)	(n=2015)	(n=407)	(n=407)
Age (years)	65.5±11.5	65.4±10.2	65.5±11.5	64.6±10.2
Men	299 (73.5)	1475 (73.2)	299 (73.5)	295 (72.5)
Women	108 (26.5)	540 (26.8)	108 (26.5)	112 (27.5)
CCI (%)				
0	198 (48.6)	995 (49.4)	198 (48.6)	213 (52.3)
1	130 (31.9)	616 (30.6)	130 (31.9)	115 (28.2)
2	54 (13.3)	230 (11.4)	54 (13.3)	47 (11.5)
3	19 (4.7)	104 (5.2)	19 (4.7)	20 (4.9)
≥4	6 (1.5)	70 (3.5)*	6 (1.5)	12 (2.9)

*P<0.05.
CCI, Charlson Comorbidity Index, PSM, propensity score matching.

DISCUSSION

Studies have shown that critically ill patients with AMI are more vulnerable to develop FADEs due to the presence of DRPs.[23 24] In the present study, we focused on DRPs that caused or contributed to the mortality of patients with AMI, and identified inappropriate use of medications. Recommendations for optimal therapy were suggested. The major finding of this study was that clinical pharmacists' interventions can have positive effects in reducing mortality in patients with AMI.

In principle, the recommendations of clinical pharmacists should be complied with. However, in certain clinical settings, pharmacists' recommendations were not able to be followed due to extenuating clinical circumstances. The main reason was the great necessity of the original treatment in spite of the presence of contraindications. Also, even if the patient was suffering a

Table 4 All cause mortality of ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction before and after propensity score matching

	Before PSM			After PSM		
	Phase 1 (n (%))	Phase 2 (n (%))	P value	Phase 1 (n (%))	Phase 2 (n (%))	P value
No of patients (STEMI)	842	1278	0.0360	770	770	0.0340
Fatalities	57 (6.8)	58 (4.5)		52 (6.8)	33 (4.3)	
No of patients (NSTEMI)	407	2015	0.0003	407	407	0.0202
Fatalities	13 (3.2)	17 (0.8)		13 (3.2)	3 (0.7)	

NSTEMI, non-ST segment elevation myocardial infarction; PSM, Propensity Score Matching; STEMI, ST segment elevation myocardial infarction.

Table 5 Logistic regression analysis of inhospital mortality in patients with ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction

	STEMI			NSTEMI		
Variable	Adjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Age	1.061	1.041 to 1.082	<0.0001	1.102	1.053 to 1.152	<0.0001
CCI	1.719	1.503 to 1.965	<0.0001	1.625	1.305 to 2.024	<0.0001
Presence of clinical pharmacists' interventions	0.449	0.296 to 0.680	0.0002	0.268	0.125 to 0.572	0.0007

CCI, Charlson Comorbidity Index, NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.

harmful drug–drug interaction, the indications were very definite. In other situations, although the dose of the drug was not correct according to the regulations, the cardiologist regarded the dose as accurate according to the patient's specific conditions. Furthermore, the efficacy and safety of the treatment should be balanced in certain patients. Finally, despite the obvious improper use of antibiotics based on the consensus, the cardiologist considered that it was reasonable when considering the condition of the infection.

In an attempt to adjust for confounding factors, PSM was performed. We applied PSM to match each patient in phase 1 with a patient in phase 2. After PSM, patient characteristics were similar between phase 1 and phase 2. All cause mortality showed a significant decrease after the interventions of the clinical pharmacists, regardless of STEMI or NSTEMI. The stepwise logistic regression model for mortality also revealed that clinical pharmacists' interventions were associated with a reduced mortality in patients with STEMI and NSTEMI. A report from the National Cardiovascular Data Registry (NCDR) demonstrated that the range of mean mortality was 4.9–7.0% in STEMI and 3.3–4.9% in NSTEMI.[25] All cause mortality in the present study was 6.8% in STEMI patients and 3.2% in NSTEMI patients during phase 1, in agreement with the results of the NCDR. The clinical pharmacists proposed 1388 recommendations, of which 1239 were accepted. We assumed that this led to a reduction in mortality of 4.5% in STEMI patients and 0.8% in NSTEMI patients during phase 2 with statistical significance.

Our result demonstrated that the presence of clinical pharmacists, who identified all possible DRPs, was associated with a reduced mortality in patients with STEMI and NSTEMI in a university affiliated hospital. This pattern may also apply to other departments and other hospitals.

Study limitations

Several limitations are worth mentioning. First, the study was not randomised. In fact, randomisation was not feasible because it would have interfered with the normal hospital process. Second, blinding was not feasible in our study owing to the presence of the pharmacists. Thus, as is inherent in observational studies, interventions were not comparable because of the different baseline characteristics . For reducing confounding bias, PSM was used to adjust the imbalance between the two phases, and the results were consistent before and after PSM. However, it should be noted that many other variables (socioeconomic status, education, total number of medications, recent healthcare utilisation, specific comorbidities, GRACE risk score, etc) were not included in the present study, which may have led to certain biases. In addition, PSM only included a very small sample of patient characteristics. Therefore, further study and randomised controlled trials are needed to confirm our results.

CONCLUSIONS

The presence of clinical pharmacists can bring about positive effects in reducing mortality in patients with acute myocardial infarction. This pattern may also apply to other departments and other hospitals.

Statements

The present study has added to our previous work in terms of patient characteristics, intervention period, comparison method and outcomes.[26] Inclusion of all cardiac diseases, similar to our previous study, may lead to selective bias due to different characteristics in different diseases. The focus of AMI in the present study confirmed the results of the clinical pharmacist's role. The results showed that the mortality rate of patients with STEMI was 6.8% in phase 1 and 4.3% in phase 2 after PSM. These data translate to a number needed to treat of 40, implying that 40 patients exposed to clinical pharmacists' interventions could prevent death in 1 patient compared with those without the intervention. The study period of the present study was not in line with our previous study. To correct for differences in patient characteristics, we used the PSM method, which is a popular way to balance differences within two comparable groups. As an adjusted variable, CCI compared with the nursing acuity score in the previous study, provides a more effective way to quantify the impact of comorbidities on survival and is also used as a prognostic comorbidity index in the AMI population. Collectively, the present study provides a relatively precise result for the clinical pharmacist's role.

What this paper adds

What is already known on this subject?

- Clinical pharmacists play a key role in the cardiovascular care team.
- Clinical pharmacists engage with medical practices for correcting substantial drug related problems.

What this study adds?

- The presence of clinical pharmacists can bring about positive effects in reducing mortality in patients with acute myocardial infarction.
- This pattern may also apply to other departments and other hospitals.

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