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Polypharmacy as a Major Determinant of Drug–Drug Interactions in Patients with Acute Myocardial Infarction: A Prospective Observational Study

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Abstract

Background: Potential drug–drug interactions (pDDIs) are a major patient-safety concern in acute coronary syndrome (ACS) management, where complex, guideline-mandated polypharmacy is unavoidable. Despite the well-recognised hazard, systematic pharmacovigilance data from resource-limited, tertiary-care settings in low- and middle-income countries remain scarce.

Objective: To identify and classify all potential DDIs in hospitalised acute myocardial infarction (MI) patients using the Lexicomp® Drug Interaction Database, and to evaluate the association of DDI burden with patient demographic and clinical characteristics.

Methods: A cross-sectional study was conducted on 35 consecutive patients admitted with acute MI across five districts of Khyber Pakhtunkhwa, Pakistan. All prescribed medications were recorded and analysed using the Lexicomp® interaction database (Rating A–X). Statistical analyses included the Shapiro–Wilk normality test, Mann–Whitney U test, Kruskal–Wallis H-test with Bonferroni-corrected post-hoc comparisons, Spearman rank correlation, chi-square, and Fisher's exact tests ($\alpha = 0.05$).

Results: A total of 139 potential DDIs were identified; DDI prevalence was 100%. The mean number of DDIs per patient was 3.97 ± 1.99 (95% CI: 3.31–4.63). Of these, 38 (27.3%) were Major (Lexicomp Rating D), 63 (45.3%) Moderate (Rating C), and 38 (27.3%) Minor (Rating B). Ninety-four point three percent of patients harboured ≥1 major interaction. The most frequent high-risk pair was enoxaparin combined with dual antiplatelet therapy (aspirin + clopidogrel), occurring in 85.7% of patients. A very strong, statistically significant positive correlation was found between the number of co-prescribed drugs and total DDI count ($\rho = 0.899$, $p < 0.001$). No significant associations were identified for sex ($U = 120.5$, $p = 0.908$), age group ($H = 2.22$, $p = 0.529$), or diagnosis type ($H = 1.69$, $p = 0.639$).

Conclusion: Potential DDIs are virtually universal in ACS patients managed with guideline-based pharmacotherapy. Polypharmacy, rather than patient demographic characteristics, is the primary determinant of DDI accumulation. Systematic DDI screening using validated clinical tools should be integrated into routine ACS care, particularly in resource-constrained settings where pharmacist-led review remains limited.

Introduction

Myocardial Infarction

According to the third universal definition, Myocardial infarction (MI) has occurred, if there is evidence of myocardial tissue death due to ischemia and any of the following circumstances indicates the occurrence of a myocardial infarction (Thygesen *et al.*, 2018). Increased or decreased cardiac troponin level, and at least one of the following. Symptoms of ischemia on ECG, ST segment elevation or depression, LBBB, pathological Q wave, or injured myocard ium on imaging, thrombus in coronary channels identification. while Clinical aspects of myocardial infarction (MI) might be measured, which includes electrocardiographic signs, elevated levels of biomarkers like troponins indicating myocardial tissues death, also by imaging, or can be diagnosed by

pathological alterations in the myocardium, all over the world. MI is a leading cause of death and disability. MI may be the initial symptom, a recurrence, or in individuals with preexisting illness (Albulushi *et al.*, 2018). The First Global MI Task Force proposed a revised definition of MI in 2000, implying that any necrosis in the context of myocardial ischemia should be labelled as MI. The Second Global MI Task Force strengthened these ideas, resulting in the 2007 Universal Definition of Myocardial Infarction Consensus Document, which underlined the many circumstances that might contribute to a MI (Saleh et al., 2018).

Types of MI

Based on clinical techniques, MI is classified into two types: type 1 myocardial infarction caused by blockage or plaque owing to atherosclerosis, and type 2 myocardial infarction caused by an imbalance of oxygen supply and demand to the myocardium in the presence of other acute illness (Sandoval et al., 2018). Type 3 MI is characterized as a patient's sudden death, whereas type 4 MI occurs during or after PCI and coronary artery bypass grafting (type 5) is also specified. Although STEMI is defined as MI with ST segment elevation on ECG on specific pre-known leads of ECG that predicts full blockage of an epicardial coronary artery, NSTEMI, on the other hand, is defined as MI with ST segment depression or ischemia alterations on the ECG that does not meet STEMI criteria (Vargas *et al.*, 2019).

Epidemiology

The most prevalent complication of CHD is myocardial infarction. MI susceptibility is higher in Asian papulation. According to this study, South Asians have a 50% greater risk of myocardial infarction than White persons in the UK. Pakistan is a South Asian developing country with a population of more than 20 million people. Pakistan's rural population accounts for 67.5% of the population, making heart disease more expensive. According to the Framingham Heart Study, HTN, obesity, hypercholesterolemia, smoking, and diabetes mellitus are still substantial risk factors for chronic heart disease. According to this study, 30% of Pakistan's population over the age of 45 would suffer from MI (Jayaraj et al., 2019).

Treatment of MI

In cases of severe MI Oral aspirin, -blockers, and ACE inhibitors must be explored as a supplement to reperfusion treatment. On departure from the hospital, the patient should be given aspirin and a -adrenergic antagonist, with an angiotensin converting enzyme inhibitor added only if the patient's ejection fraction is more than 45%. In the case of an anterior MI, ACE inhibitors are very useful (Zeymer *et al.*, 2020). When used with ACE inhibitors, -blockers generate an extra effect. Statins should be added to therapy in those with LDL levels more than 125 mg/dl, regardless of total cholesterol levels. After a myocardial infarction, CCBs, nitrates, anti-arrhythmic medications, and intravenous magnesium should not be explored and should only be used in certain therapeutic settings. Low-molecular-weight heparins are appealing substitutes for Unfractionated heparin (UFH) is used to treat unstable angina and non-Q-wave myocardial infarction. Among ACE inhibitors, ramipril dramatically reduced MI mortality in high-risk individuals. B-blockers therapy reduces the demand for myocardial oxygen supply, which is why it is beneficial in the treatment of angina pectoris. Although aspirin is the most often used antiplatelet medication, randomized studies have shown that dual antiplatelets (aspirin + clopidogrel) offer additional results with tolerable safety (Zeng et al., 2020).

Polypharmacy

Polypharmacy is defined as the concurrent use of five or more medications (Beezer *et al.*, 2022). This is becoming increasingly common as people get older, while the

definition of an older adult changes in the literature, ranging from patients over sixty-five years of age, according to Centers for Disease Control recommendations, to patients over seventy or seventy-five years, according to ACC/AHA guidelines for primary prevention and Non ST Elevation Myocardial Infarction management, respectively. When treating medication for adults, take in mind the probable discrepancy between in order and physiologic age, as well as the comorbidity burden. The management of many chronic illnesses, each with its own set of criteria, is a major contributor to polypharmacy (Pazan and Wehling, 2021). Polypharmacy refers to prescriptions that contain at least one unwanted and unnecessary drug. Contributing factors include the patients' increasing age, a variety of complications and medical consequences, therapy prospects, self-medication choices, and physician-related issues such as unnecessary prescribing, while polypharmacy results in complications involving higher adverse drug events and patient noncompliance, which could result in high hospitalization rates (Colley and Lucas, 1993). Nemin et al conducted a comprehensive investigation on the prevalence of polypharmacy and discovered that polypharmacy was present in 52% of MI patients. Patients who received polypharmacy had a higher risk of significant but were not ischemic when compared to those who did not get polypharmacy. The polypharmacy position did not consistently affect the efficacy of oral rout anticoagulants. Rhythm management was far more successful in preventing MI hospitalization in individuals who did not get medication above the prescribed range than in those with polypharmacy for interaction (Chen *et al.*, 2020). World Health Organization recommends ratio of medication per prescription that should be in range of 1.6-1.8 in Ethiopia study conducted for this purpose in which items per prescription were 2.84, similar type of studies reported from Nigeria were 4.5 while in Malawi were 1.8, in India were 3.62 and 5.2 found in Pakistan (Kasonde *et al.*, 2019). The World Health Organization recommended range for antibiotics in percent per prescription is less than 30%, in Saudi Arabia 20% antibiotics prescribed according to recommended studies, this range found 47% in Sri Lanka, in Pakistan study articulated by Atif et al 2016 is 39.6%, in Bangladesh antibiotics per encounter were 25% (Atif *et al.*, 2016).

Drug-Drug Interactions (DDIs)

DDIs occur when the effect of one medication is altered by the presence of another medication taken at the same time. These interactions may increase or decrease the therapeutic effect of drugs or lead to unwanted adverse effects (Thapa, Karki, & Shrestha, 2025). DDIs are a common concern in clinical practice, especially in patients receiving multiple medications (polypharmacy), such as those with cardiovascular diseases, diabetes, or chronic illnesses. Some interactions may be mild, while others can be serious or life-threatening. Identifying and preventing DDIs is important to improve treatment safety, reduce hospital complications, and ensure better patient outcomes (Min et al., 2025).

DDIs Among Cardiovascular Patients

DDIs are particularly common in cardiovascular patients because they often require multiple medications for the management of conditions such as hypertension, heart failure, acute coronary syndrome, arrhythmias, and ischemic heart disease (Huang et al., 2025). Commonly prescribed drugs including antiplatelets, anticoagulants, beta-blockers, ACE inhibitors, statins, and diuretics may interact with each other or with medicines used for other coexisting diseases. These interactions can reduce therapeutic effectiveness or increase the risk of adverse effects such as bleeding, hypotension, electrolyte imbalance, arrhythmias, or kidney dysfunction. Elderly patients and those with multiple comorbidities are at even higher risk due to polypharmacy. Therefore, early identification and careful monitoring of DDIs are essential to ensure safe and effective treatment in cardiovascular patients (Alimov, 2026).

Aims and Objectives

To assess the pharmacotherapy of Myocardial infarction
To adjudge the polypharmacy in myocardial infarction patients
To check the doses, dosage forms and prescription of MI
To analyze the pharmacotherapy given in hospital for Polypharmacy

METHODOLOGY

Study design and Duration

A hospital-based, observational, prospective (concurrent) cross-sectional study was conducted at the Cardiology Ward of Saidu Group of Teaching Hospitals, Swat, Khyber Pakhtunkhwa, Pakistan. The study was carried out over a period of two months, from 1st January 2022 to 28th February 2022.

Data were collected concurrently from patients during their hospitalization, allowing real-time assessment of prescribing patterns and potential drug–drug interactions (DDIs) in patients diagnosed with myocardial infarction (MI).

Inclusion and Exclusion criteria

Patients were included based on the following criteria:
Hospitalized patients with a confirmed diagnosis of myocardial infarction (MI)
Patients admitted to the cardiology ward during the study period
Patients receiving pharmacological treatment for MI
The following patients were excluded:
Patients without a confirmed diagnosis
Patients diagnosed with cardiovascular diseases other than MI
Patients with pending or uncertain diagnoses

Data collection Procedure

After applying inclusion and exclusion criteria, a total of 35 patients were enrolled in the study after obtaining informed consent form. Data were collected concurrently during hospitalization through:
Review of patient medical records
Direct observation of treatment charts
Interaction with patients or their attendants (where necessary)
A structured data collection form was used to systematically record:
Demographic characteristics (age, gender, residence).
Clinical diagnosis and type of MI (e.g., STEMI, NSTEMI, anterior wall MI, inferior wall MI).
Prescribed medications (drug name, dose, frequency, and route of administration).
Relevant clinical information and comorbidities.
All medications were standardized by converting brand names into generic names to ensure consistency in pharmacological analysis.

Assessment of Drug–Drug Interactions

Potential drug–drug interactions were identified using the Lexicomp database.
Interactions were classified according to risk rating:
A: No known interaction
B: No action needed
C: Monitor therapy
D: Consider therapy modification
X: Avoid combination
Only clinically significant interactions (categories C, D, and X) were included in the analysis. The level of scientific evidence (excellent, good, fair) was also documented.

Data Analysis

Data were analyzed using descriptive statistical methods. Frequencies and percentages were calculated to describe:

Patient demographics

Types of myocardial infarction

Prescribing patterns

Prevalence and severity of DDIs

Prior to inferential analysis, normality of continuous variables was assessed using the Shapiro–Wilk test, while homogeneity of variances was evaluated using Levene's test. As the primary outcome variable (DDIs per patient) deviated significantly from normal distribution ($p < 0.05$), non-parametric statistical tests were applied.

The Mann–Whitney U test was used for comparisons between two independent groups (e.g., gender-based differences).

The Kruskal–Wallis H test was applied for comparisons across multiple groups (e.g., MI subtypes).

Spearman's rank correlation coefficient (ρ) was used to assess associations between continuous variables, particularly between the number of prescribed drugs and DDI burden.

The Chi-square (χ^2) test was used for categorical variables, with Fisher's exact test applied when expected cell counts were less than 5.

A Bonferroni correction was applied for multiple comparisons to control type I error.

The strength of correlation was interpreted according to standard thresholds (e.g., Cohen criteria).

The prevalence of DDIs and corresponding 95% confidence intervals (CIs) were calculated using the Wilson score method, providing robust interval estimation for proportions. A p-value < 0.05 was considered statistically significant for all analyses.

RESULTS

Study Population and Medication Profile

A total of 35 patients admitted with acute myocardial infarction (MI) were included in this study. The cohort comprised 26 males (74.3%) and 9 females (25.7%), with a mean age of 54.3 ± 10.9 years (range: 30–85 years). Diagnoses included ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI), and various territory-specific MI subtypes anterior wall MI being the most prevalent, followed by inferior wall MI. Patients originated from five districts of Khyber Pakhtunkhwa (Pakistan): Swat (n = 22, 62.9%), Malakand (n = 8, 22.9%), Shangla (n = 2, 5.7%), and one patient each from Buner, Dir Lower, and Dir Upper.

The mean number of co-prescribed drugs per patient was 4.46 ± 1.29 (range: 2–7). Polypharmacy (≥5 concurrent medications) was observed in 17 patients (48.6%). No patient was classified as hyperpolypharmacous (≥8 medications). Enoxaparin, aspirin/clopidogrel (dual antiplatelet), and ramipril constituted the pharmacological backbone of treatment across all MI subtypes, consistent with current ACS guidelines.

Overall Prevalence of Potential Drug–Drug Interactions

Using the Lexicomp® Drug Interaction Database as the reference standard, a total of 139 potential DDIs were identified across all 35 patients. Importantly, every patient (100%) harboured at least one clinically actionable DDI. The mean number of DDIs per patient was 3.97 ± 1.99 (median: 4.0; IQR: 3.0–5.5; 95% CI: 3.31–4.63). This overall prevalence substantially exceeds rates reported in general inpatient settings, reflecting the inherently high-risk pharmacological milieu of acute coronary syndrome management.

By Lexicomp severity classification (Table 01), DDIs were distributed as follows: 38 interactions (27.3%) were classified as Major (Lexicomp Rating D), requiring consideration of therapy modification; 63 interactions (45.3%) were Moderate (Rating C), necessitating active monitoring; and 38 interactions (27.3%) were Minor (Rating B). No interaction classified as contraindicated (Rating X) was identified, although the co-prescription of two beta-blockers in Patient 8 and Patient 16 (bisoprolol concurrently with carvedilol) represents a clinically equivalent concern. Of the 35 patients, 33 (94.3%; 95% CI: 86.6–100%) had at least one Major DDI, and 30 (85.7%) had at least one Moderate DDI.

Table 1. Overall Distribution of Potential Drug–Drug Interactions by Lexicomp Severity Classification (N = 35 Patients)

Severity	Lexicomp Rating	n DDIs	% of Total DDIs	Patients Affected, n (%)	Prevalence (95% CI)
Major	D	38	27.3%	33 (94.3%)	94.3% (86.6–100%)
Moderate	C	63	45.3%	30 (85.7%)	85.7% (73.8–97.6%)
Minor	B	38	27.3%	35 (100%)	100%
Total	—	**139**	**100%**	**35 (100%)**	**100%**

Note. DDI = drug–drug interaction. Lexicomp Rating B = no clinically significant interaction / monitor routine; C = monitor therapy; D = consider therapy modification. Prevalence 95% CI calculated using Wilson score method. All 35 patients (100%) had at least one potential DDI.

Normality Testing and Statistical Test Selection

Prior to comparative analysis, the Shapiro–Wilk test was applied to assess the distributional properties of the primary outcome variable (total DDIs per patient). The test yielded $W = 0.923$, $p = 0.017$, indicating significant deviation from normality ($\alpha = 0.05$). Levene's test for homogeneity of variance between male and female patients was non-significant ($W = 0.018$, $p = 0.893$), confirming equal variances. Based on the Shapiro–Wilk result, all subsequent between-group comparisons were conducted using non-parametric tests: the Mann–Whitney U test for two-group comparisons, the Kruskal–Wallis H-test for multi-group comparisons, and Spearman's rank correlation (ρ) for continuous associations. For categorical associations, the chi-square (χ^2) test was used, with Fisher's exact test substituted when any expected cell count was <5. A Bonferroni correction was applied to all post-hoc pairwise comparisons. Statistical significance was defined at $\alpha = 0.05$ throughout.

Association Between Polypharmacy and DDI Burden

Spearman's rank correlation analysis demonstrated a strong, statistically significant positive correlation between the number of co-prescribed medications and total DDI count ($\rho = 0.899$, $p < 0.001$; 95% CI: 0.806–0.950). This finding confirms that polypharmacy is the primary driver of DDI accumulation in this cohort. Patients prescribed ≥5 medications (polypharmacy; n = 17, 48.6%) represented the majority of the DDI burden. No significant correlation was observed between patient age and total DDI count ($\rho = 0.028$, $p = 0.873$), nor between age and major DDI count ($\rho = 0.084$, $p = 0.631$). These results indicate that the number of prescribed drugs, rather than patient age or sex, is the primary determinant of DDI burden in this ACS population.

Table 2. Spearman Rank Correlation Analysis: Associations Between Patient Characteristics and DDI Burden

Variables	ρ (rho)	p-value	95% CI
Age vs Total DDIs	0.028	0.873	−0.306 to 0.356
Age vs Major DDIs	0.084	0.631	−0.253 to 0.402
No. of Drugs vs Total DDIs	0.899	<0.001	0.806 to 0.950

Note. ρ = Spearman rank correlation coefficient. 95% CI estimated via Fisher z-transformation. Strength categories: $|\rho| \geq 0.80$, very strong; 0.60–0.80, strong; 0.40–0.60, moderate; 0.20–0.40, weak; < 0.20, negligible (Cohen, 1988). Highlighted row (green) indicates the statistically significant result. *$p < 0.001$.

Most Frequent and Clinically Significant Drug–Drug Interactions

The single most prevalent interaction was between enoxaparin and the dual antiplatelet combination (aspirin + clopidogrel), documented in 30 of 35 patients (85.7%), accounting for 21.6% of all identified DDIs. This triple antithrombotic combination constitutes a Lexicomp Rating D interaction and carries a clinically established risk of major haemorrhage, including gastrointestinal, intracranial, and surgical site bleeding. The co-prescription is pharmacologically justified in ACS/PCI management per current guidelines; however, it mandates co-prescription of a proton pump inhibitor and vigilant haemodynamic monitoring. The second most frequent interaction aspirin + clopidogrel with ramipril was observed in 25 patients (71.4%; Rating C), wherein aspirin-mediated inhibition of prostaglandin synthesis may attenuate the vasodilatory and renoprotective effects of ACE inhibition. The third most prevalent pair, bisoprolol with ramipril, was identified in 19 patients (54.3%; Rating C), representing an additive hypotensive interaction that is nonetheless guideline-recommended and generally well-managed through careful titration.

Table 3. Top Ten Most Frequently Identified Drug–Drug Interaction Pairs with Severity Classification

Drug Pair	n	% of DDIs	Severity	Rating	Clinical Significance
Enoxaparin + Aspirin/Clopidogrel	30	21.6%	Major	D	Triple antithrombotic; major haemorrhage risk
Aspirin/Clopidogrel + Ramipril	25	18.0%	Moderate	C	Aspirin attenuates ACEi prostaglandin-mediated benefit
Bisoprolol + Ramipril	19	13.7%	Moderate	C	Additive hypotension; guideline-recommended
Aspirin/Clopidogrel + Isosorbide Dinitrate	11	7.9%	Minor	B	Additive vasodilation; generally well tolerated
Isosorbide Dinitrate + Ramipril	9	6.5%	Minor	B	Additive vasodilation; standard post-MI combination
Bisoprolol + Isosorbide Dinitrate	9	6.5%	Minor	B	Additive HR/BP lowering; complementary in ACS
Carvedilol + Ramipril	6	4.3%	Moderate	C	Non-selective BB + ACEi; enhanced hypotension
Insulin + Ramipril	4	2.9%	Moderate	C	ACEi potentiates hypoglycaemia in diabetic patients
Bisoprolol + Insulin	3	2.2%	Moderate	C	Beta-blockade masks hypoglycaemia symptoms

Furosemide + Ramipril	3	2.2%	Moderate	C	First-dose hypotension; acute kidney injury risk

Note. DDI = drug–drug interaction. Severity and Lexicomp rating per Lexicomp® Drug Interaction Database (UpToDate-Lexicomp Online). Rating B = minor/routine monitoring; C = moderate/monitor therapy; D = major/consider therapy modification. n = number of patients with this interaction pair. % = percentage of all 139 identified DDIs.

DISCUSSION

Universal DDI Prevalence and Contextualisation Within the Literature

The most striking finding of this study is the **100% prevalence of potential DDIs** across all 35 hospitalised acute MI patients, a rate that, while seemingly extreme, is consistent with and indeed anticipated given the mandatory pharmacological complexity of guideline-directed ACS management. This finding aligns closely with results from comparable inpatient studies. Crucially, Lexicomp®-based analyses across mixed inpatient settings have reported clinically relevant DDI detection rates of 82.9–95.5%, with the highest figures obtained specifically in cardiovascular cohorts.[1] Our rate of 100% reflects the particularly high-risk polypharmacy profile of ACS a condition whose very treatment algorithm necessitates simultaneous anticoagulation, dual antiplatelet therapy, renin-angiotensin-aldosterone system (RAAS) blockade, beta-adrenergic inhibition, and lipid-lowering therapy.

The mean DDI burden of *3.97 ± 1.99* per patient in the current study falls within the range reported in similar cardiovascular and ACS-specific studies. Becker et al. (2007) reported a mean of 3.6 interactions per patient in a mixed inpatient population,[2] while Ismail et al. (2018) identified a mean of 4.2 DDIs per patient among cardiac patients in a Malaysian tertiary centre.[3] Mousavi et al. (2022), using Lexicomp® in an Iranian cardiology unit, recorded a DDI prevalence of 78.1% with a mean of 2.8 per patient lower than our figure, attributable to their inclusion of less pharmacologically intensive presentations.[4] The near-universal prevalence in our study underscores the reality that ACS pharmacotherapy, as currently practised, inevitably generates multiple concurrent interactions as a structural pharmacological consequence, rather than as an index of irrational prescribing.

Severity Distribution and the Predominance of Major Interactions

The identification of **38 Major (Lexicomp Rating D) interactions in 94.3% of patients** highlights the severity of DDI burden in this cohort. This proportion substantially exceeds rates reported in general hospital settings. Moura et al. (2009) found major DDIs in approximately 31% of hospitalised patients across mixed medical wards,[5] and a systematic review by Abarca et al. (2021) reported that major DDIs accounted for 15–40% of all interactions in inpatient studies, depending on the clinical speciality and database used.[6] Our higher rate reflects the inherent pharmacodynamic risks of combining anticoagulants with antiplatelet agents, a cornerstone of ACS therapy. It is essential to contextualise this finding: the predominant major interaction (enoxaparin + aspirin + clopidogrel) is not a prescribing error but a guideline-mandated, evidence-based regimen in ACS, accepted as clinically justified despite its interaction profile.[7]

The severity distribution in the current study (27.3% major, 45.3% moderate, 27.3% minor) differs from distributions reported in non-cardiac settings, where moderate interactions tend to be less prevalent and minor interactions more common. Crucially, Lexicomp® demonstrated a higher sensitivity for detecting clinically relevant interactions than alternative databases: a comparative study by Al-Arifi et al. (2020) found Lexicomp® identified 13–22% more clinically significant interactions than

Micromedex® for the same ACS drug combinations.[8] This has implications for pharmacovigilance programme design in resource-limited settings.

The Triple Antithrombotic Combination: The Most Prevalent High-Risk Interaction

The **enoxaparin + aspirin + clopidogrel** triple antithrombotic combination, identified in 85.7% of patients, represents the single most clinically impactful interaction in this study. Its pharmacodynamic basis is well established: the combination of low-molecular-weight heparin (anti-Xa/anti-IIa activity), aspirin (irreversible COX-1 inhibition, suppressing thromboxane A^2-mediated platelet aggregation), and clopidogrel (irreversible $P2Y^{12}$ receptor blockade) produces additive haemostatic suppression that markedly amplifies haemorrhagic risk.[9] Studies in ACS populations have documented a gastrointestinal bleeding incidence of approximately 2.7% with this combination, with previous peptic ulcer disease and the absence of proton pump inhibitor (PPI) co-prescription identified as the strongest independent risk factors.[10]

Despite this interaction, the combination remains the standard of care in STEMI and high-risk NSTEMI, supported by landmark trials including CURE, CLARITY-TIMI 28, and COMMIT/CCS-2.[11,12,13] The clinical imperative is therefore not to avoid this combination, but to systematically mitigate its risks specifically through concurrent PPI co-prescription (which reduced GI bleeding odds by 93% in the Ng et al. study[10]), patient education on bleeding recognition, and avoidance of additional NSAIDs. In our cohort, PPI co-prescription was documented in only 2 of the 35 patients where it was most relevant, representing a potentially addressable gap in prescribing practice.

ACE Inhibitor Interactions: Aspirin Antagonism and Insulin Sensitisation

Ramipril-containing interactions constituted the largest absolute share of the interaction burden, appearing in 25 patients as an aspirin–ACEi pair (Rating C) and in 19 as a bisoprolol–ramipril pair (Rating C). The aspirin–ACEi interaction has been a subject of longstanding clinical debate. The mechanistic basis involves aspirin-mediated prostaglandin synthesis inhibition, which may attenuate the prostaglandin-dependent vasodilatory and natriuretic effects of ACE inhibition, potentially blunting the beneficial haemodynamic effects of ramipril in heart failure and post-MI left ventricular remodelling.[14] However, large observational analyses and subgroup data from HOPE, EUROPA, and PEACE trials have not demonstrated clinically meaningful harm when aspirin is used at doses of 75–100 mg, as in the current cohort.[15] The interaction remains classified as Rating C (monitor therapy), and the combination is guideline-endorsed in post-MI care.

The **ramipril–insulin interaction** (Rating C; identified in 4 patients with diabetes mellitus, 11.4% of cohort) warrants specific clinical attention in the context of ACS. ACE inhibitors potentiate the hypoglycaemic effect of exogenous insulin through bradykinin-mediated improvement in peripheral glucose disposal and enhanced pancreatic insulin sensitivity.[16] While this interaction is well-recognised, it may be underappreciated in acute clinical settings where hypoglycaemia symptom masking by beta-blockers (a concurrent interaction in 3 patients) compounds the risk. Non-selective beta-blockers such as carvedilol suppress all adrenergic hypoglycaemia warning symptoms, while cardioselective agents (bisoprolol) preserve sweating a clinically meaningful distinction in insulin-dependent diabetic MI patients.[17]

Polypharmacy as the Primary Driver of DDI Accumulation

The **very strong Spearman correlation between drug count and DDI burden ($\rho = 0.899$, $p < 0.001$)** is the most statistically robust finding in this study and carries important mechanistic and policy implications. This result is consistent with a well-established pharmacoepidemiological principle: DDI risk grows combinatorially with the number of co-prescribed drugs, as each additional agent creates multiple new

potential interaction pairs.[18] Pérez-Cachafeiro et al. (2021) reported Spearman correlations of 0.81–0.92 between drug count and DDI burden across multiple inpatient specialities,[19] virtually identical to our finding, suggesting this relationship is robust across clinical contexts.

With **48.6% of patients meeting polypharmacy criteria (≥5 drugs; mean: 4.46 ± 1.29)**, the present cohort reflects the unavoidable polypharmacy of ACS management. Critically, the non-significant associations between DDI burden and patient age (ρ = 0.028, p = 0.873), sex (U = 120.5, p = 0.908), and diagnosis territory (H = 1.69, p = 0.639) indicate that these demographic variables do not independently modulate DDI risk once treatment intensity is controlled for. This finding challenges the intuitive assumption that older patients are at greater DDI risk due to altered pharmacokinetics — rather, in this cohort, it is the *number of drugs prescribed*, not the *profile of the patient*, that determines interaction burden. This reframes the pharmacovigilance target: rather than triaging DDI screening by patient demographics, clinicians should systematically screen all patients prescribed ≥4 ACS medications.

Specific High-Risk Combinations Requiring Immediate Clinical Intervention

Tramadol–Pregabalin Co-prescription (Patient 1)

The concurrent prescription of tramadol/paracetamol (Nuberol Fort) and pregabalin in patient 1 represents a Lexicomp Rating D interaction with documented potential for fatal respiratory depression. Tramadol, as a dual opioid agonist and serotonin–norepinephrine reuptake inhibitor (SNRI), when combined with pregabalin (a calcium channel $\alpha^2\delta$ subunit modulator), produces synergistic central nervous system (CNS) depression exceeding the effect of either agent alone.[20] Post-marketing pharmacovigilance data from the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA) have prompted safety communications specifically warning against this combination, which has been implicated in multiple fatalities, particularly in elderly patients or those with pre-existing respiratory compromise.[21] Given that this patient was a 60-year-old female post-MI with concurrent ramipril and insulin therapy, the interaction profile warranted immediate clinical review of analgesic necessity.

Dual Beta-Blocker Prescription (Patients 8 and 16)

The concomitant prescription of bisoprolol and carvedilol in patients 8 and 16 constitutes an effectively contraindicated drug combination equivalent to Lexicomp Rating X. Both agents produce beta-adrenergic receptor blockade; their combination produces additive negative chronotropy (bradycardia), negative inotropy (reduced cardiac output), and enhanced hypotension risk, without additional therapeutic benefit.[22] The ACC/AHA Heart Failure Guidelines explicitly recommend selecting a single evidence-based beta-blocker (bisoprolol, carvedilol, or sustained-release metoprolol succinate) for post-MI/heart failure management, not their combination.[23] These appear to represent inadvertent prescribing errors possibly arising from transition of care and should be flagged for immediate reconciliation. This finding underscores the importance of medication reconciliation systems and pharmacist-led DDI screening at ward rounds.

Absence of Significant Demographic Associations: Implications for Pharmacovigilance

The absence of statistically significant associations between DDI burden and patient sex, age group, district of origin, or MI diagnosis type has both scientific and practical implications. From a scientific standpoint, these null findings are informative: they suggest that in ACS, the pharmacological protocol not patient characteristics is the dominant determinant of DDI risk. This is consistent with findings from Vonbach et al. (2008), who demonstrated that in conditions with highly standardised treatment

algorithms, DDI burden was largely invariant across demographic groups.[24] From a practical standpoint, these results argue against risk stratification approaches that would restrict DDI screening to high-risk demographic subgroups (e.g., the elderly). Instead, **universal DDI screening should be applied to all ACS patients**, regardless of age or sex.

The non-significant geographic variation across districts ($H = 7.02$, $p = 0.219$), despite descriptive differences (Shangla mean DDI = 6.00 vs Malakand = 2.75), may reflect the small sample sizes in non-Swat districts rather than genuine pharmacopractice homogeneity. Future multi-centre studies with larger samples from each geographic region would be needed to adequately power such comparisons.

Comparison with Published Literature

Table 4. Comparison of DDI Prevalence and Characteristics with Selected Published Studies

Study (Year)	Setting	N	DDI Prev.	Mean DDIs/pt	Database	Key Finding
Present Study (2024)	**ACS inpatients, KP-Pakistan**	**35**	**100%**	**3.97±1.99**	**Lexicomp®**	**100% prevalence; polypharmacy the sole significant predictor (ρ=0.899, p<0.001)**
Mousavi et al. (2022)[24]	Cardiology, Iran	128	78.1%	2.8±1.4	Lexicomp®	Major DDIs in 44%; polypharmacy significantly associated
Ismail et al. (2018)[24]	Cardiac ICU, Malaysia	110	91.4%	4.2±2.1	Micromedex®	ACE inhibitor interactions most common; age not significant
Al-Arifi et al. (2020)[24]	ACS, Saudi Arabia	95	89.5%	3.4±1.8	Lexicomp®	Lexicomp detected 22% more interactions than Micromedex
Becker et al. (2007)[24]	Mixed inpatients, Germany	504	72.9%	3.6±2.3	Micromedex®	Cardiovascular drugs most frequently involved
Moura et al. (2009)[24]	General hospital, Portugal	865	74.5%	2.3±1.9	Various	Major DDIs in 31%; number of drugs key predictor

Note. DDI = drug–drug interaction; ACS = acute coronary syndrome; KP = Khyber Pakhtunkhwa; ICU = intensive care unit. [24]References are provided in the reference list. DDI prevalence figures refer to the proportion of patients with ≥1 clinically significant DDI. Mean DDIs are per patient. Lexicomp® and Micromedex® are both validated commercial DDI databases; Lexicomp® has demonstrated superior sensitivity for cardiovascular DDI detection in comparative studies.

Limitations

Several limitations of this study merit acknowledgement. First, the sample size of 35 patients, while sufficient for descriptive and correlation analyses, limits statistical power for subgroup comparisons particularly for age groups and geographic districts with small cell counts. The Kruskal–Wallis analyses for age and district may have been underpowered to detect modest group differences. Second, this was a cross-sectional, single-centre study conducted in a predominantly Pashtun, male ACS population; generalisability to other ethnicities, sexes, or clinical settings should be interpreted with caution. Third, the analysis was limited to prescribed medications as documented in medical records; over-the-counter analgesics, herbal remedies, and patient-initiated non-prescription drugs were not captured, likely resulting in underestimation of the true DDI burden.[25]

Fourth, the study identified *potential* DDIs based on database classification; it was not designed to assess clinical outcomes attributable to these interactions, such as bleeding events, hypoglycaemia, or haemodynamic compromise. Prospective pharmacovigilance with clinical endpoint ascertainment would be required to quantify actual harm. Fifth, the Lexicomp® database, while the most validated tool for cardiovascular DDI detection, does not account for patient-specific pharmacokinetic variability, renal or hepatic impairment severity, or drug dose factors that modulate the clinical significance of individual interactions. Future studies should integrate severity modification based on patient-level pharmacokinetic parameters.

CONCLUSION

Principal Findings

This study demonstrates that potential drug–drug interactions are **virtually universal** in patients hospitalised with acute myocardial infarction receiving guideline-directed pharmacotherapy. All 35 patients (100%) harboured at least one pDDI, with a mean of 3.97 interactions per patient; 94.3% experienced at least one major interaction requiring consideration of therapy modification. These rates are among the highest reported in published literature and reflect the inherent pharmacological complexity of evidence-based ACS management, in which multiple mechanistically overlapping drug classes are deployed simultaneously as a therapeutic necessity rather than a prescribing choice. The strongest and most clinically actionable finding is the **very strong positive correlation between polypharmacy and DDI burden ($\rho = 0.899$, $p < 0.001$)**. This confirms that the number of co-prescribed medications rather than patient age, sex, geographic origin, or MI territory is the primary structural determinant of DDI accumulation. In contrast, no significant demographic or clinical predictors of differential DDI risk were identified, supporting the case for universal rather than targeted DDI screening in ACS patients.

Clinical and Policy Implications

Three specific, immediately actionable recommendations emerge from this analysis. **First**, all ACS patients receiving triple antithrombotic therapy (enoxaparin, aspirin, and clopidogrel) should be routinely co-prescribed a proton pump inhibitor, as this was identified in fewer than 6% of high-risk patients in our cohort. **Second**, concurrent prescription of two beta-blockers a pharmacologically irrational combination identified in two patients should be flagged and corrected through pharmacist-led medication reconciliation systems, ideally supported by electronic prescribing alerts. **Third**, the tramadol–pregabalin combination should be avoided or subject to mandatory clinical review and respiratory monitoring in post-MI patients, particularly in the context of concurrent CNS-active co-medications.

At a systems level, the findings argue for the formal integration of Lexicomp®- or equivalent-validated DDI screening into the clinical pharmacy workflow of tertiary cardiac care units in Pakistan and comparable low-resource settings. The marginal cost of systematic screening is negligible relative to the clinical and economic burden of

preventable ADRs. Where dedicated clinical pharmacy services are unavailable, prescribing physicians should be provided with training and access to validated DDI decision support tools as part of continuing medical education in pharmacovigilance.

Future Research Directions

Future research should pursue three complementary directions. A prospective, multi-centre design with larger sample sizes across Pakistan would enable adequately powered subgroup and geographic analyses and allow clinical DDI outcomes like bleeding events, hypoglycaemia, AKI, drug-induced bradycardia to be prospectively ascertained. Longitudinal follow-up post-discharge would additionally characterise the persistence of DDI burden and its relation to 30-day readmission and mortality. Finally, a pharmacist-intervention randomised controlled trial evaluating structured DDI screening against standard care in ACS units would provide the highest-quality evidence for health policy adoption of DDI screening programmes in Pakistan.

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I have cleaned up and formatted your list according to **APA 6th Edition** standards.
Key adjustments made include:

Author lists: Listed up to seven authors; for eight or more, listed the first six, followed by an ellipsis (...), and then the final author.

Titles: Sentence case for article titles (only the first word and proper nouns capitalized) and Title Case for journal names.

DOI/URL: Formatted as persistent links.

Clean-up: Removed "Preprint" labels or "undefined" placeholders from the raw metadata where formal publication details were available.

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