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Evaluation of clinical pharmacy services in patients receiving antithrombotic treatment in a randomized controlled trial

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Patients receiving antithrombotic therapy are at increased risk of drug-related problems (DRPs) due to the complexity of their regimens and high-risk pharmacological profiles. Clinical pharmacists, through structured medication reviews and active collaboration with the healthcare team, have been shown to optimise pharmacotherapy, reduce medication errors, and improve patient safety outcomes. This study aimed to evaluate the impact of clinical pharmacy services on the identification and prevention of DRPs in hospitalised cardiology patients receiving antithrombotic drugs. A prospective, randomised controlled trial was conducted between November 2021 and November 2022 in the cardiology ward of a tertiary-care university hospital in Istanbul, Türkiye. Four hundred adult patients prescribed at least one antithrombotic agent (ATC group B01) were randomly assigned (1:1) to a control group, in which patients were monitored without intervention, or an intervention group, in which a clinical pharmacist performed a structured medication review using the Pharmaceutical Care Network Europe (PCNE) classification v9.1. Recommendations for resolving clinically significant DRPs were directly communicated to the physician in charge during multidisciplinary ward rounds. Patients were followed for unplanned readmissions at 1- and 3-months post-discharge. In the control group, the mean age was 67.2 ± 12.2 years, while in the intervention group it was 67.8 ± 12.3 years. Coronary artery disease and hypertension were the most prevalent comorbidities in both groups. A total of 561 DRPs were identified in the control group and 497 in the intervention group, with treatment safety and treatment effectiveness being the most common problem categories. Drug selection and dose selection were the leading causes of DRPs. In the intervention group, 248 recommendations for 266 clinically significant DRPs were made for 126 patients (63% of the group), of which 94.76% were accepted by physicians. The most frequent drug-level interventions were dose adjustments (29.65%) and initiation of new therapy (28.49%). The mean number of clinically significant DRPs per patient was significantly lower in the intervention group compared with the control group ($p < 0.05$). Active involvement of a clinical pharmacist within a multidisciplinary hospital team significantly reduced clinically significant DRPs in patients receiving antithrombotic therapy. These findings underscore the value of integrating clinical pharmacists into inpatient care to optimise pharmacotherapy and improve medication safety outcomes.

Keywords Clinical pharmacy, Pharmacists, Drug-related problem cardiology, Antithrombins, Pharmaceutical care services, PCNE

Cardiovascular disease (CVD) remains the leading cause of adult mortality worldwide[1]. According to the World Health Organization, CVD-related deaths are projected to exceed 23 million annually by 2030[1,2]. Thrombosis is a major contributor to CVD morbidity and mortality, underscoring the importance of effective antithrombotic

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therapy in treatment success[3]. Although antithrombotic therapy is highly effective in preventing and managing thrombotic events, these agents are categorised as high-risk medicines[4,5]. Their use is closely linked to the occurrence of serious adverse drug events, even when treatment is delivered in accordance with established clinical practice guidelines[6,7]. Among these, bleeding complications are the most common and frequently lead to discontinuation of therapy, reported in up to half of all patients[8]. Furthermore, individuals treated with antithrombotics face a substantially elevated risk of intracranial haemorrhage, with some studies indicating up to an eight-fold increase compared to non-users[9]. Beyond bleeding, challenges such as inappropriate dosing, poor adherence, and clinically relevant drug–drug interactions further complicate antithrombotic therapy, underlining the necessity for vigilant monitoring and collaborative management to ensure both safety and therapeutic effectiveness. However, the widespread use of antithrombotic drugs also means that patients on these therapies are especially vulnerable to drug-related problems (DRPs)[10].

The Pharmaceutical Care Network Europe (PCNE) defines a DRP as any event involving drug therapy that actually or potentially interferes with desired health outcomes[11]. Adverse drug events (ADEs) constitute only a subset of DRPs; other issues include medication errors, overdose, drug dependence, non-adherence, and therapeutic failures[12]. Patients with CVD often receive high-risk medications (such as antithrombotics) and thus face a heightened risk of ADEs and medication errors. Importantly, studies have shown that proactive measures to prevent medication-related adverse events and errors can significantly improve patient outcomes[13,14]. Given the high risk of ADEs and DRPs associated with these agents, targeted clinical pharmacy services are particularly relevant in patients receiving antithrombotic therapy. Clinical pharmacists are uniquely positioned to support physicians through expert dosing adjustments, monitoring of therapeutic efficacy and safety, identification and management of drug–drug interactions, and patient education and follow-up. Recent evidence from a multicentre study demonstrated that pharmacist-led interventions significantly improved the appropriateness of anticoagulant prescriptions and reduced the incidence of medication-related adverse events, thereby providing measurable improvements in the safety of anticoagulant use[15]. Systematic reviews confirmed that pharmacist-provided care in hospitals has a positive impact on clinical outcomes, including reduced medication errors, fewer drug-related problems and adverse reactions, improved appropriateness of therapy, shorter hospital stays, and decreased readmission rates, thereby validating the role of targeted interventions in such high-risk patient populations[15–18].

These findings provide robust evidence that integrating clinical pharmacists into inpatient care not only reduces ADEs and medication errors but also enhances continuity of care after discharge. Comprehensive pharmacist-led services such as medication review, reconciliation, and counselling have been consistently associated with fewer hospital readmissions and better overall treatment outcomes. Collectively, these data underscore the essential role of clinical pharmacists in ensuring safe and effective management of complex therapies such as antithrombotics[19,20].

This study aims to evaluate the impact of clinical pharmacy services on patients receiving antithrombotic treatment, with a focus on improving prescribing quality, preventing drug-related problems, and enhancing clinical outcomes through pharmacist–physician collaboration.

Materials and methods

Study design, participants and setting

A prospective, randomised controlled study was conducted on patients admitted to the cardiology ward and receiving antithrombotic therapy for indications such as acute coronary syndrome, atrial fibrillation, venous thromboembolism, heart failure, or other cardiovascular conditions requiring antithrombotic treatment at a tertiary-care university hospital in Istanbul, Türkiye, between November 2021 and November 2022. Inclusion criteria were age ≥ 18 years and confirmed use of at least one antithrombotic medication (ATC Group: B01), including agents such as acetylsalicylic acid, clopidogrel, ticagrelor, prasugrel, enoxaparin, warfarin, apixaban, rivaroxaban, and dabigatran. All participants provided written informed consent. Patients were excluded if they had incomplete biochemistry and haematology results, incomplete two-day medication records, or if they did not complete the scheduled follow-up visits (at the 1st and 3rd months) required for medication reviews. In addition, patients with dementia, cancer, pregnancy, or those unable to provide informed consent by themselves were also excluded. The study design and eligibility criteria were developed to comprehensively evaluate the impact of clinical pharmacist interventions on the clinical outcomes of patients prescribed antithrombotic medications.

Randomisation was conducted using a simple randomisation method via an algorithm generated by Research Randomizer® software, assigning patients to either the control group or the intervention group in a 1:1 ratio. A clinical pharmacist on the study team developed a concealed allocation schedule to minimise selection bias. This schedule, stratified by study groups, generated two random allocation sequences linked to a consecutive series of participant identification numbers. Upon enrolment, each eligible participant was assigned the next available identification number in the sequence by the clinical pharmacist, thereby determining their allocation to the control or intervention group. Allocation concealment was maintained until the point of assignment.

In the intervention group (IG), the clinical pharmacist conducted structured medication reviews, identified DRPs, and communicated recommendations directly to the physician in charge during multidisciplinary ward rounds. In the control group (CG), the clinical pharmacist also performed structured medication reviews and documented DRPs; however, no recommendations were communicated to the physician in charge, in order to serve as a comparator group. Both groups underwent the same baseline assessment and structured follow-up at discharge, 1 month, and 3 months post-discharge. Clinical outcomes included hospital readmissions and the occurrence of drug-related problems (such as adverse drug events and medication errors), ensuring that outcome assessments were conducted consistently across both groups.

Data collection

During the study, records were maintained with confidentiality, encompassing contact information, medical history, medication history, current medications, laboratory findings, and physical examination records. These details were carefully documented to ensure the highest level of privacy and compliance with ethical standards. The characteristics of the patients in the control and intervention groups were recorded through the hospital electronic record system. The evaluation and classification of DRPs were carried out by following five steps: (i) Recording the sociodemographic and hospitalization day information of the patients: Age, gender, disease, comorbid conditions, admission diagnoses, laboratory data during hospitalization (creatinine, blood glucose, AST, etc.). (ii) The medications (active substance, dose, route, time, frequency of drug administration, duration of treatment) previously used and prescribed during hospitalization were recorded. Topicals such as ointments, pomades and maintenance fluids were excluded. (iii) Assessment of patients' medications during hospitalization: The evaluation was based on current diagnostic and therapeutic guidelines (e.g. European Society of Cardiology, American Heart Association), health practice guidelines, clinical decision support systems and current literature (e.g. UpToDate®, RxMediaPharma® interactive drug information resource, IBM Micromedex drug reference®, Medscape®, Lexicomp®, Sanford Guide®). In the current study, these well-established guidelines collectively formed the basis for ensuring the appropriateness and adherence to best practices in antithrombotic therapy for patients prescribed antithrombotic medication. *(iv)* Assessment of existing or potential drug-drug interactions: The Lexicomp® Drug Interactions application was used for this purpose. *(v)* Identification and classification of DRPs: The European Pharmaceutical Care Network's DRPs classification (v9.1) was used.

The study also delved into DRPs, encompassing their causes, clinical pharmacist recommendations for resolution, and physicians' subsequent acceptance and implementation. The Turkish version of the Pharmaceutical Care Network Europe Association (PCNE) Classification scheme for Drug-Related Problems v9.1 was employed to identify DRPs. This version, validated by the PCNE working group, features a comprehensive classification system consisting of primary domains for problems, causes, planned interventions, level of acceptance (of interventions), and the status of the problem. On a more detailed level, the scheme comprises grouped sub-domains, providing explanatory granularity for the principal domains. The validated PCNE classification scheme offers a robust framework for systematically categorizing and addressing DRPs in the study context (https://www.pcne.org/upload/files/417_PCNE_ classification _V9-1_ final.pdf).

This study has been reported according to recommendations of Consolidated Standards of Reporting Trials (CONSORT) [21].

Ethics approval

The studies involving human participants were reviewed and approved by the local Ethics Committee of Clinical Research with decision number 19/5. This study protocol has been retrospectively registered on 05/01/2024 at ClinicalTrials.gov (NCT06193473).

Clinical interventions

The data of patients admitted to the cardiology ward with a prescription of antithrombotic (AT) medication were meticulously recorded during their hospitalization. During patients' hospital stay, a multidisciplinary team evaluated the patients' treatment regimen and medications. The clinical pharmacist played an integral role in this process, closely monitoring patients and their treatment adjustments and identifying DRPs through a comprehensive assessment of their medication information.

The clinical pharmacist, together with the responsible physician and other health workers, attended daily ward visits on weekdays, conducted medication reviews and provided interventions for patients with DRPs in the intervention group. These interventions were face-to-face, verbal recommendations to the health workers in the team. Recommendations were made at the time of admission to the ward, during the hospital stay and at discharge.

In the intervention group, the clinical pharmacist provided face-to-face recommendations for DRPs to the attending physician. An experienced multidisciplinary team containing a clinical pharmacist jointly assessed the clinical significance of identified DRPs. The interventions were designed to detect and prevent DRPs, thereby addressing concerns in patients hospitalized with antithrombotic medication. Recommendations included additions to the patient's treatment regimen, discontinuation of off-label or inappropriate medications (e.g., unnecessary dual antiplatelet therapy or continued dual antiplatelet treatment despite a high bleeding risk), proposing alternative agents, changing the route of administration (e.g., switching from oral anticoagulants to low molecular weight heparin in patients unable to take oral therapy), suggesting therapeutic drug monitoring, advising dose adjustments, managing drug-drug interactions, and optimizing the duration of treatment. The clinical pharmacist provided advice on drug selection, addition, discontinuation, follow-up, dose adjustment, management of side effects, and potential drug-drug interactions. To analyse medications and evaluate potential drug-drug interactions (pDDIs), the Lexicomp® (Wolters Kluwer Health Inc.) database was utilized. The X (contraindicated) and D (drug change considered) levels, which are important levels for potential drug-drug interactions, were assessed. Among these, recommendations were made for those deemed clinically important. The drugs used by the patients from hospitalization to discharge and the agents responsible for DRPs were compared between the two groups. In addition, the groups were evaluated in terms of whether the patients were readmitted to hospital within 1 and 3 months post-discharge. The LACE index was utilised solely to assess the risk of 30-day readmissions. The LACE index, a validated risk score composed of length of stay, acuity of admission, comorbidities, and emergency department visits, was used to estimate the 30-day risk of readmission or death, with higher scores reflecting greater risk. Outcomes at three months were obtained independently from follow-up data and were not predicted using the LACE index. The index was applied at baseline to support the homogenisation of patient characteristics between the study groups and to evaluate its association with 30-day

readmissions. While the relationship between baseline LACE scores and 3-month readmissions was explored in correlation analyses, this was not an intended predictive application of the index[22].

Main outcome measure

The primary outcomes of the study were defined as follows: (i) the identification and classification of DRPs according to the PCNE classification system; (ii) the acceptance rate of recommendations provided by the clinical pharmacist to the treating physicians; and (iii) the rate of re-hospitalisations occurring within both 30 and 90 days after discharge in the control and intervention groups. The secondary outcomes included a comparison of the control and intervention groups with respect to rehospitalisation rates and overall clinical course, aiming to identify potential differences in clinical progression and healthcare utilisation attributable to clinical pharmacist involvement.

Sample size

The sample size calculation for the study was conducted based on data from the literature[23]. According to our sample size calculations based on drug-related problems to determine the number of participants needed, the effect size (d) was calculated as 0.5540. Based on an alpha level of 0.05, at least 135 participants should be included in each group, and the power of the study was calculated as 0.95.

Statistical analysis

Analyses were performed using SPSS (Statistical Package for Social Sciences) Windows 11.0 program. The results were evaluated at 95% confidence interval and significance at $p < 0.05$ level. Demographic data were expressed as percentages, continuous and discrete variables were expressed as mean, standard deviation, median, interquartile range, and drug-related problems were expressed as percentages and numerical values. Normality of the data was assessed using the Kolmogorov–Smirnov test. For variables with a normal distribution, differences between the two groups were analysed using Student's t-test, while the Mann–Whitney U test was applied for non-normally distributed variables. For categorical (discrete) variables, comparisons were performed using the Chi-square test or Fisher's exact test, as appropriate. Correlation analyses between results were conducted using Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation coefficient for non-normally distributed variables. $P < 0.05$ was accepted as the level of statistical significance.

Results

Demographics, medications and hospital admission

A total of 400 patients met the inclusion criteria and were enrolled in the study, with 200 allocated to the control group and 200 to the intervention group (Fig. 1). The mean age was 67.20 ± 12.20 years in the control group and 67.80 ± 12.30 years in the intervention group. The mean number of comorbid conditions per patient was

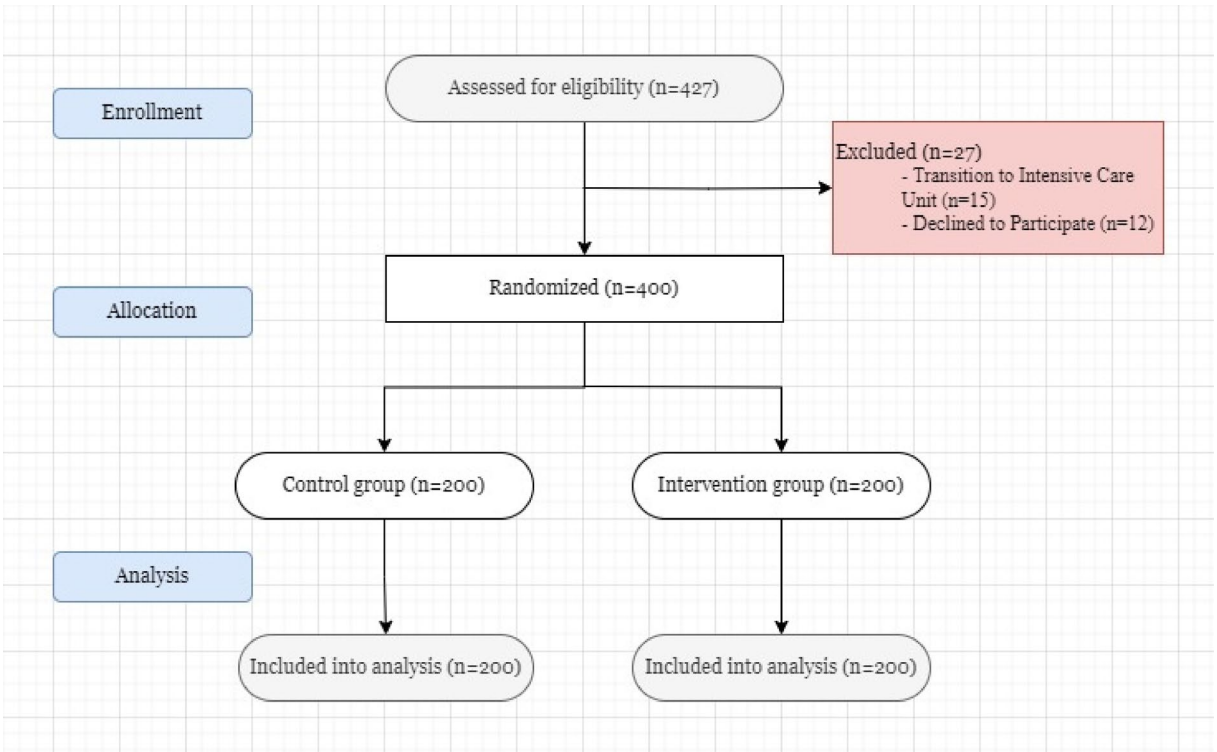


Fig. 1. Flowchart of the study.

4.74 ± 1.88 in the control group and 4.77 ± 2.04 in the intervention group. Across both groups, the number of comorbidities ranged from a minimum of 1 to a maximum of 10 per patient.

Coronary artery disease was the most prevalent condition, present in 149 patients (74.50%) in each group. Hypertension was the second most common comorbidity, affecting 141 patients (70.50%) in the control group and 140 patients (70.00%) in the intervention group. The third most common diagnosis differed between groups: diabetes mellitus was observed in 99 patients (49.50%) in the control group, whereas heart failure was recorded in 96 patients (48.00%) in the intervention group. Acute coronary syndrome was reported in more than 40% of patients in both groups, affecting 88 patients (44.00%) in the control group and 87 patients (43.50%) in the intervention group. Atrial fibrillation (AF) and other rhythm disturbances were identified in 68 patients (34.00%) in the control group and 76 patients (38.00%) in the intervention group (Table 1).

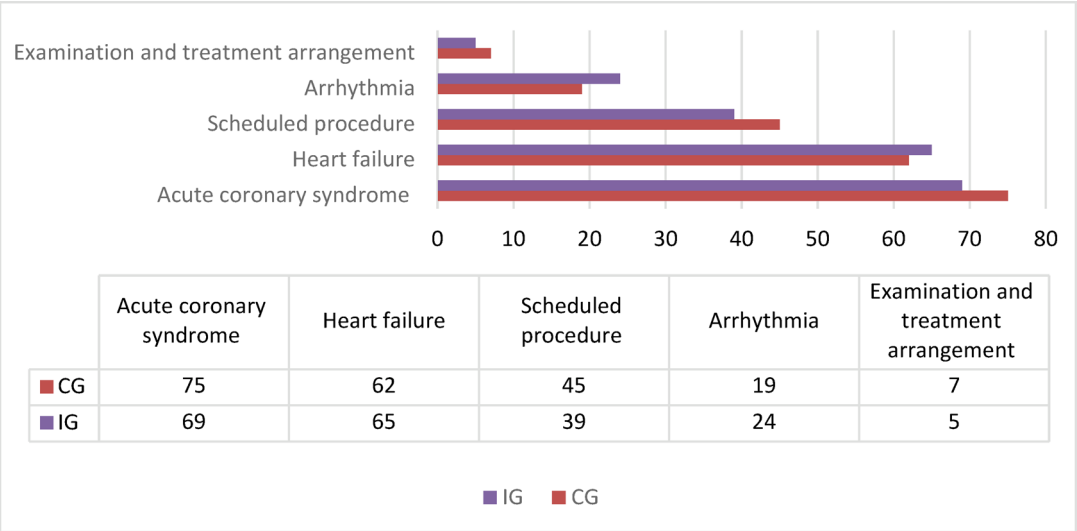
In both the control group and intervention group, the majority of patients were referred to the cardiology service from the emergency department, accounting for 52% of admissions in the control group and 51.50% in the intervention group. The second most frequent source of referral was from the outpatient clinic to the ward, representing 47.50% of admissions in the control group and 43.50% in the intervention group. The primary reasons for hospitalisation, along with the corresponding diagnoses for each group, are presented in Fig. 2.

The five most frequently utilised ATC classification groups in both the control group and intervention group were as follows: cardiovascular system (C), digestive system and metabolism (A), blood and blood-forming organs (B), nervous system (N), and respiratory system (R) (Fig. 3). With regard to antithrombotic therapy, acetylsalicylic acid was the most commonly prescribed antiplatelet agent, administered to 71.00% of patients in the control group and 67.50% in the intervention group. The most frequently prescribed anticoagulant was enoxaparin, which was given to 44.00% of patients in the control group and 53.00% in the intervention group.

No statistically significant difference was observed between the groups with respect to the LACE index scores ($p > 0.05$). Likewise, there were no significant differences between the control group and IG regarding emergency readmissions or unplanned hospitalisations within 1 and 3 months following discharge. Although these

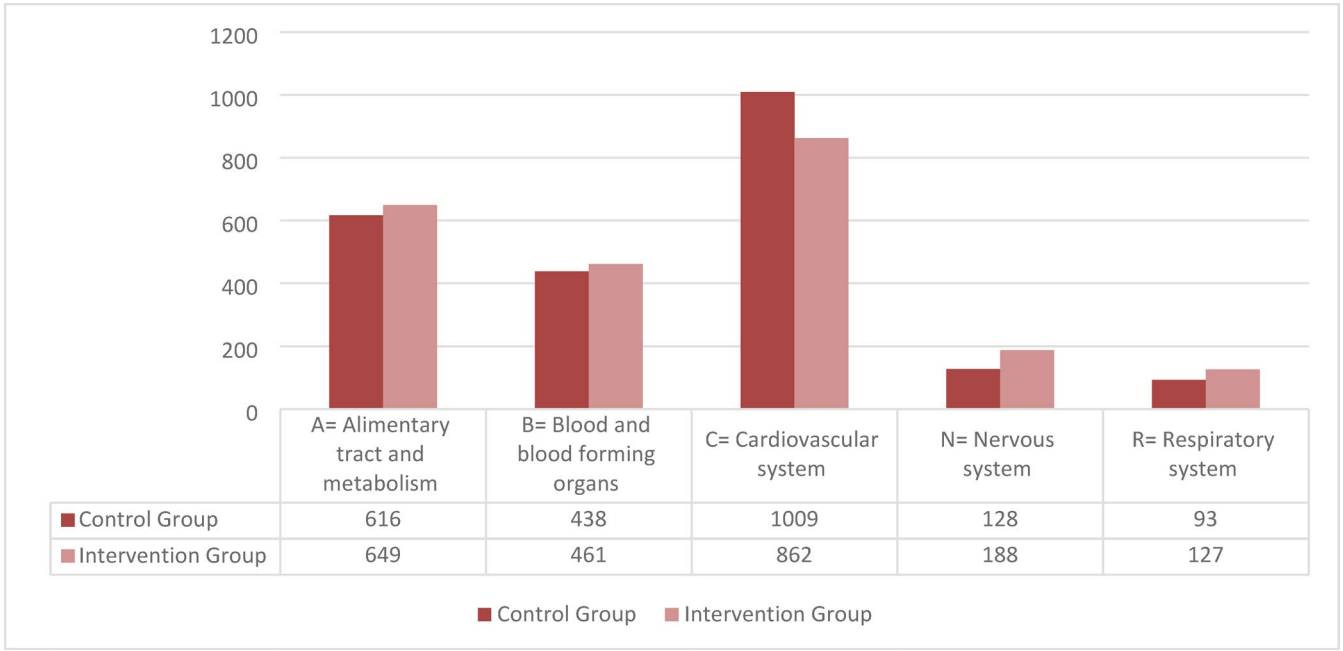
Baseline characteristics of patients	Control group ($n = 200$)	Intervention group ($n = 200$)	p
Sex *(n, %)*			0.26#
Female *(n, %)*	85 (42.5%)	74 (37%)	
Male *(n, %)*	115 (57.5%)	126 (63%)	
Age (mean ± SD)	67.2 ± 12.2	67.8 ± 12.3	0.93*
Weight (kg) (mean ± SD)	79.8 ± 18.1	78.3 ± 12.5	0.79*
BMI (mean ± SD)	28.9 ± 6.07	28.2 ± 4.61	0.17*
No of comorbidities (mean ± SD)	4.74 ± 1.88	4.77 ± 2.04	0.94*
1 (n)	2	3	
2 (n)	19	20	
3 (n)	36	34	
4 (n)	47	45	
5 (n)	29	38	
6 (n)	27	25	
7 (n)	24	9	
8 (n)	9	11	
Most common 10 diseases and comorbidities (n, %)			
Heart valve disease	55 (27.5%)	50 (25%)	
Arrhythmia	68 (34%)	76 (38%)	
Atrial fibrillation/ flutter (AF/AFL)	58 (29%)	60 (30%)	
Arrhythmia without AF/ AFL	10 (5%)	16 (8%)	
Cerebrovascular disease/ Transient ischemic attack	25 (12.5%)	16 (8%)	
Coronary artery disease	149 (74.5%)	149 (74.5%)	
Acute coronary syndrome	88 (44%)	87 (43.5%)	
Percutaneous coronary intervention	70 (35%)	63 (31.5%)	
Coronary artery bypass graft surgery	34 (17%)	29 (14.5%)	
Hypertension	141 (70.5%)	140 (70%)	
Heart failure	86 (43%)	97 (48.5%)	
Chronic kidney disease	28 (14%)	24 (12%)	
Diabetes mellitus	99 (49.5%)	96 (48%)	
Thyroid diseases	15 (7.5%)	25 (12.5%)	
Asthma/ Chronic obstructive pulmonary disease	29 (14.5%)	39 (19.5%)	

Table 1. Demographic characteristics of patients. *Mann–Whitney U test, #Chi-Square test, SD, standard derivation.



	Acute coronary syndrome	Heart failure	Scheduled procedure	Arrhythmia	Examination and treatment arrangement
CG	75	62	45	19	7
IG	69	65	39	24	5

Fig. 2. The most common hospitalization reasons and diagnoses of patients.



	A= Alimentary tract and metabolism	B= Blood and blood forming organs	C= Cardiovascular system	N= Nervous system	R= Respiratory system
Control Group	616	438	1009	128	93
Intervention Group	649	461	862	188	127

Fig. 3. ATC classes of the most commonly used drugs in the groups.

differences did not reach statistical significance, both readmission and rehospitalisation rates were numerically higher in the control group compared with the intervention group (Table 2).

Drug-related problems and pharmacist interventions

According to the Pharmaceutical Care Network Europe (PCNE) classification, the clinical pharmacist identified 561 potential DRPs in 166 patients (83.00%) in the control group and 497 potential DRPs in 153 patients (76.50%) in the intervention group. The majority of identified DRPs in both groups were related to treatment safety, accounting for 413 (73.62%) in the control group and 369 (74.25%) in the intervention group. Problems related to treatment effectiveness comprised 135 (24.06%) in the control group and 115 (23.14%) in the intervention group.

The most frequent cause of DRPs was drug selection in both groups, representing 81.11% of problems in the control group and 80.88% in the intervention group. The second most common cause was dose selection, which accounted for 107 cases (19.08%) in the control group and 80 cases (16.10%) in the intervention group. Within the dose selection category, 'low dose' and 'high dose' issues were identified in 58 (10.34%) and 35 (6.24%)

Data	Control group ($n=200$)	Intervention group ($n=200$)	p
Number of drugs (mean ± SD)	11.8 ± 5.52	12.6 ± 5.82	0.14*
Length of stay (mean ± SD)	3.83 ± 3.41	4.04 ± 3.08	0.28*
LACE Index for readmission (mean ± SD)	7.25 ± 2.87	7.15 ± 2.70	0.95*
Unplanned rehospitalization within 1 month (n)	12	6	0.16#
Unplanned rehospitalization within 3 month (n)	26	22	0.60#
The number of emergency and unplanned readmissions within 3 months (mean ± SD)	0.454 ± 0.955	0.38 ± 0.703	0.96*
Total number of DRPs, n	561	497	0.15*
Number of possible drug-drug interactions per patient (mean ± SD)	1.78 ± 1.95	1.58 ± 1.71	0.53*
Number of clinically significant DRPs per patient (mean ± SD)	2.81 ± 2.87	1.33 ± 2.11	***< 0.001****
Accepted interventions, n (%)	–	235 (94.76%)	–
Unaccepted interventions, n (%)	–	13 (5.24%)	–

Table 2. Patient's hospitalization information and drug-related problems identified. *Mann–Whitney U test, # Chi-Square test, SD, standard derivation. Data presented as percentage. Significant values are in [bolditalic].

Problems (also potential)	CG	%	IG	%	Causes	CG	%	IG	%
P1. Treatment effectiveness	135	24.06%	115	23.14%	C3.1 Drug dose too low	58	10.34%	35	7.04%
P1.1 No effect of drug treatment despite correct use	–	–	1	0.20%	C3.2 Drug dose of a single active ingredient too high	35	6.24%	17	3.42%
P1.2 Effect of drug treatment not optimal	99	17.64%	72	14.49%	C3.3 Dosage regimen not frequent enough	13	2.32%	14	2.82%
P1.3 Untreated symptoms or indication	36	6.42%	42	8.45%	C3.4 Dosage regimen too frequent	1	0.18%	11	2.21%
P2. Treatment safety	413	73.62%	369	74.25%	C3.5 Dose timing instructions wrong, unclear or missing	–	–	3	0.60%
P2.1 Adverse drug event (possibly) occurring	413	73.62%	369	74.25%	C4. Treatment duration	–	–	**2**	0.40%
P3. Other	13	2.32%	13	2.61%	C4.2 Duration of treatment too long		–	2	0.40%
P3.1 Unnecessary drug-treatment	12	2.14%	7	1.41%	C5. Dispensing	–	–	**3**	0.60%
P3.2 Unclear problem/complaint. Further clarification necessary	1	0.18%	6	1.20%	C5.1 Prescribed drug not available		–	2	0.40%
Causes					C5.4 Wrong drug or strength dispensed		–	1	0.20%
C1. Drug selection	**455**	81.11%	**402**	80.88%	C6. Drug use process	–	–	**3**	0.60%
C1.1 Inappropriate drug according to guidelines/formulary	54	9.63%	30	6.04%	C6.1 Inappropriate timing of administration or dosing intervals by a health professional		–	3	0.60%
C1.2 No indication for drug	1	0.18%	4	0.80%	C7. Patient related	–	–	**3**	0.60%
C1.3 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	359	64.00%	320	64.39%	C7.2 Patient uses/takes more drug than prescribed		–	1	0.20%
C1.4 Inappropriate duplication of therapeutic group or active ingredient	2	0.36%	3	0.60%	C7.4 Patient decides to use unnecessary drug		-	2	0.40%
C1.5 No or incomplete drug treatment in spite of existing indication	39	6.94%	44	8.85%	C8. Patient transfer related	**11**	1.96%	**22**	4.43%
C1.6 Too many different drugs/active ingredients prescribed for indication	–	–	1	0.20%	C8.1 Medication reconciliation problem	11	1.96%	22	4.43%
C2. Drug form	–	–	**2**	0.40%	C9 Other	**1**	0.18%	**11**	2.21%
C2.1 Inappropriate drug form/formulation (for this patient)	–	–	2	0.40%	C9.1 No or inappropriate outcome monitoring (including TDM)	-		1	0.20%
C3. Dose selection	**107**	19.08%	**80**	16.10%	C9.2 Other cause; specify	1	0.18%	10	2.01%

Table 3. Classification of drug-related problems according to PCNE v9.1. CG, control group, IG, intervention group, %, percentage. Significant values are in [bold].

patients in the control group, and in 35 (7.04%) and 17 (3.42%) patients in the intervention group, respectively (Table 3).

Most pharmacist interventions were implemented at the prescriber level (214; 86.29%) and at the drug level (172; 69.35%) (Table 4). Interventions classified under the 'other' category primarily addressed pDDIs monitored during therapy, such as QTc prolongation risk, the need for serum level monitoring of agents such as warfarin, or other clinically significant concerns.

In the control group, 356 pDDIs were identified in 130 patients (65.00%), whereas 317 pDDIs were identified in 128 patients (64.00%) in the intervention group. In the intervention group, the majority of pDDIs were not considered clinically significant, as they involved intentionally co-prescribed medicines for specific indications, where concomitant use was clinically justified and closely monitored by the pharmacist. Consequently, no action was taken to avoid such combinations. After excluding these, the clinical pharmacist identified 86 pDDIs (27.13%) in the intervention group as clinically significant. The total number of clinically significant DRPs in the

	Number of recommendations ($n = 248$)	Percent
Level of Interventions*		
I1. At prescriber level	214	86.29%
I2. At patient level	3	1.21%
I3. At drug level	172	69.35%
I4. Other	81	32.66%
Intervention Acceptance		
A1. Intervention accepted	235	94.76%
A1.1 Intervention accepted and fully implemented	129	52.02%
A1.2 Intervention accepted, partially implemented	47	18.95%
A1.3 Intervention accepted but not implemented	57	22.98%
A1.4 Intervention accepted, implementation unknown	2	0.81%
A2. Intervention not accepted	13	5.24%
A2.2 Intervention not accepted: no agreement	6	2.42%
A2.3 Intervention not accepted: other reason (specify)	4	1.61%
A2.4 Intervention not accepted: unknown reason	3	1.21%
Status of Interventions		
O0. Problem status unknown	3	1.21%
O1. Problem solved	140	56.45%
O2. Problem partially solved	87	35.08%

Table 4. Level, acceptance and status of interventions. *Percentage over the total number of interventions ($n = 248$). Data presented as percentage.

Variable	LACE index score	Length of stay (Day)	Number of DRPs
Number of comorbidities	r:0.459***	r:0.317***	r:0.348***
Number of drugs	r:0.478***	r:0.602***	r:0.621***
Number of possible drug-drug interactions	r:0.378***	r:0.363***	r:0.882***
Age	r:0.156**	r:0.251***	r:0.177***
CRP mg/dl	r:0.218***	r:0.322***	r:0.322***
Urea mg/dl	r:0.271***	r:0.366***	r:0.272***
eGFR mL/min/1.73 m^2	r:– 0.289***	r:– 0.303***	r:– 0.259***
Calcium mg/dL	r:– 0.184***	r:– 0.342***	r:– 0.153**
Sodium mmol/L	r:– 0.143**	r:– 0.103*	r:– 0.154**
Neutrophil/lymphocyte absolute count	r:0.258***	r:0.307***	r:0.233***
HGB *g/dl*	r:– 0.246***	r:– 0.365***	r:– 0.245***
BNP *ng/l*	r:0.228***	r:0.388***	r:0.127*
Readmissions within 1 month	r:0.155**	r:0.111*	–
Readmissions within 3 month	r:0.112*	r:0.127***	–

Table 5. Correlation matrix of associated factors with hospitalizations and DRPs. r: Correlation Coefficient; p: significance level, *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; HGB, hemoglobin; BNP, brain natriuretic peptide. Data presented as percentage.

intervention group, reflecting the pharmacist's direct involvement, was therefore 266. A statistically significant reduction in clinically significant DRPs was observed in the intervention group compared with the control group ($p < 0.01$) (Table 2).

During hospitalisation, the clinical pharmacist in the intervention group made 248 recommendations (93.23%) for 126 patients (63.00%) regarding the 266 clinically significant DRPs. Of these, 235 (94.76%) were accepted by the healthcare team, and 91.53% of the problems were fully resolved (Table 2). Correlation analysis demonstrated that higher LACE scores were positively associated with both the number of drug-related problems (DRPs) and longer hospital stays. In addition, a significant association was observed between hospital length of stay and readmissions at both 1 month and 3 months post-discharge. The strongest correlation was identified between pDDIs and total DRPs (Table 5).

Across both groups, the most common drug classes associated with DRPs were those used in the blood and blood-forming organs, the digestive system and metabolism, the cardiovascular system, anti-infectives, and the nervous system (Fig. 4). Correspondingly, these drug classes accounted for the majority of pharmacist

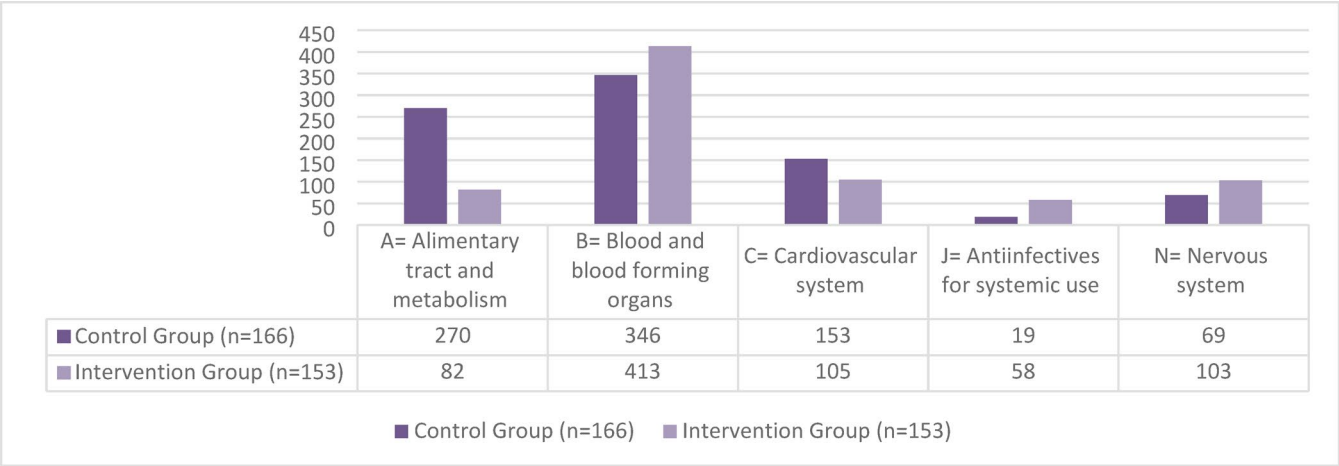


Fig. 4. ATC classes most responsible for DRPs in the control and intervention groups.

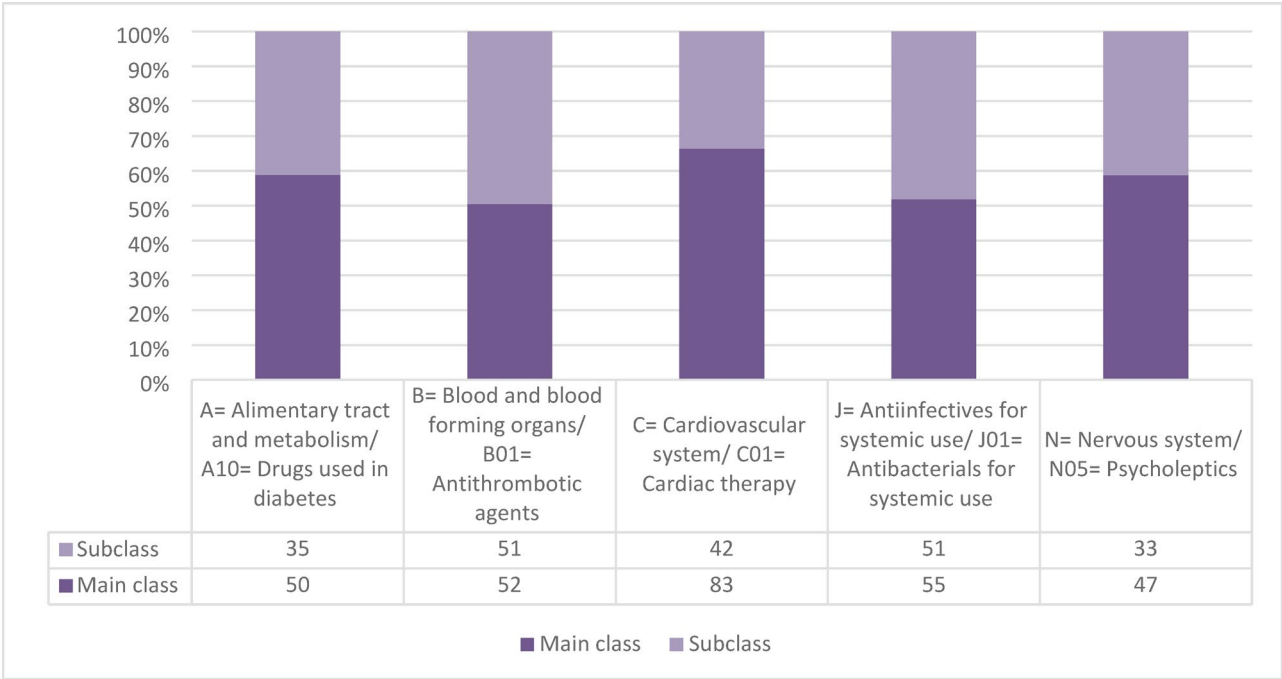


Fig. 5. The most intervened ATC classes and drug subclasses.

interventions. The most frequently targeted specific agents included systemic antibacterials, antithrombotics, cardiovascular drugs, antidiabetic medications, and psycholeptics (Fig. 5).

Among antithrombotic agents, enoxaparin, acetylsalicylic acid, and clopidogrel were the most frequent contributors to drug-related problems in both groups. The agents that most often required clinical pharmacist intervention were enoxaparin, apixaban, and warfarin (Fig. 6). Examples of interventions for these drugs commonly involved prophylaxis-to-treatment dose adjustments, renal function-based dose optimisation, modifications related to administration route (e.g., nasogastric use), and, in the case of warfarin, INR-guided dosing and management of clinically relevant drug–drug interactions.

Discussion

In our study, coronary artery disease was the most frequent diagnosis in both groups, reflecting the inclusion of patients on antithrombotic therapy. Hypertension was the second most common, while diabetes predominated in the control group,while heart failure predominated in the intervention group. These findings are consistent with earlier reports by Patel et al. and Greeshma et al., who also identified hypertension and diabetes as the leading comorbidities[24,25]. The high prevalence of coronary artery disease and hypertension, together with

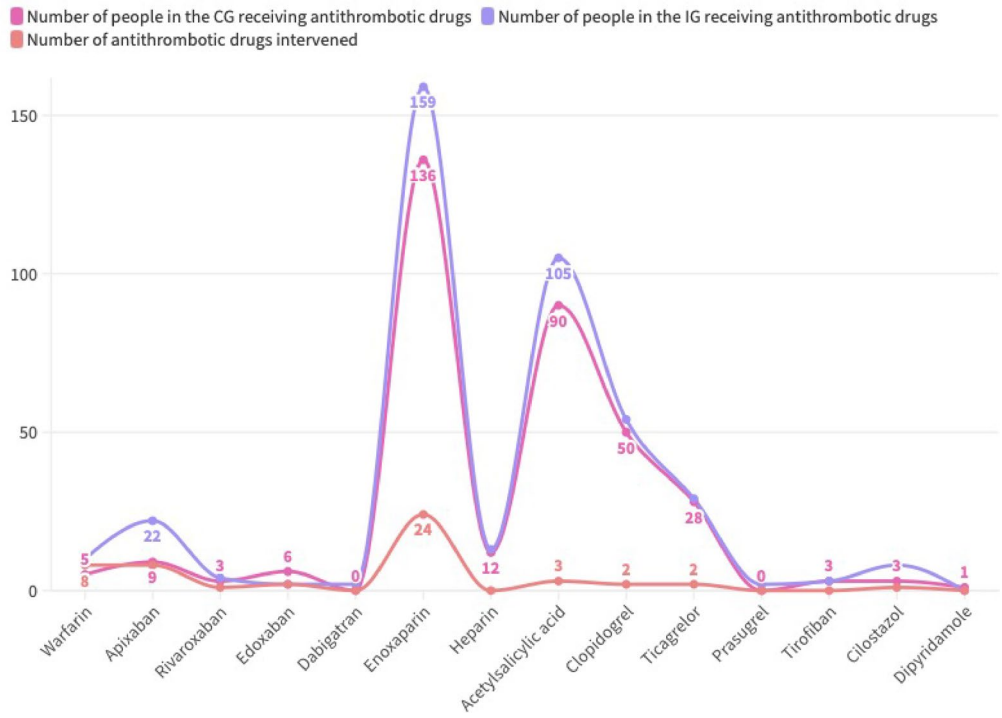


Fig. 6. Distribution of patients in the groups receiving the most frequent antithrombotic drugs and the most frequently intervened antithrombotic drugs.

multiple comorbidities, likely contributed to the observed DRP burden. Advanced age and multimorbidity are confounding factors that increase susceptibility to inappropriate prescribing and adverse outcomes.

Clinical pharmacists have been shown to improve the use of high-risk medicines through comprehensive medication reviews, ensuring the accuracy and appropriateness of regimens, particularly in older patients[26–28]. In our study, the mean age was 67 years in both groups, and all patient's medications were carefully assessed by the clinical pharmacist. Prior studies have shown that adults over 60 face a threefold higher risk of DRPs[29], largely due to age-related renal and hepatic decline, comorbidity burden, and polypharmacy. These factors increase the likelihood of dosing errors, drug interactions, adverse effects, and poor adherence. Consistent with this, Bektay et al. reported significant associations between DRPs, comorbidities, and medication count[23], while Niriayo et al. found that polypharmacy tripled DRP risk by worsening adherence challenges, interactions, and adverse effects[30]. The frequent involvement of cardiovascular, metabolic, and blood-related drugs may reflect their high baseline use rather than solely the effect of pharmacist interventions, representing an inherent confounder in antithrombotic studies.

In our study, the number of DRPs correlated positively with age ($r = 0.177$, $p < 0.001$), comorbidities ($r = 0.348$, $p < 0.001$), and medication count ($r = 0.621$, $p < 0.001$). Over 75% of patients experienced DRPs, mainly driven by pDDIs arising from frequent antithrombotic combinations. Literature likewise shows that cardiovascular, metabolic, and blood-related drugs account for most DRPs[31], which was consistent with our findings. In the intervention group, the clinical pharmacist played a pivotal role in managing these high-risk medicines safely and effectively. Renal impairment was common and strongly associated with DRPs, highlighting impaired kidney function as a key confounder complicating dose optimisation, particularly for enoxaparin and apixaban.

Wang et al. reported that DRPs were most frequently related to treatment efficacy (53.71%), followed by treatment safety (33.90%)[32], whereas Albayrak et al. found treatment safety to be the predominant concern[33]. In our study, treatment safety emerged as the most common issue in both the control (73.62%) and intervention (74.25%) groups, followed by treatment efficacy (24.06%; 23.14%). Given the high prevalence of adverse drug effects in the cardiology ward, these findings underscore the necessity for comprehensive safety evaluations in such settings.

In terms of underlying causes, the literature identifies drug selection (51.41%), dose selection (11.62%), patient-related factors (10.70%), and other causes (5.73%) as the leading contributors to DRPs[31]. Our findings were similar, with drug selection (81.11%; 80.88%) and dose selection (19.08%; 16.10%) predominating. Within dose selection issues, low dosing (10.34%; 6.24%) and high dosing (7.04%; 3.42%) were most frequent. Notably, we observed significant correlations between DRPs and elevated urea ($r = 0.272$, $p < 0.001$), blood urea nitrogen ($r = 0.266$, $p < 0.001$), and creatinine ($r = 0.186$, $p < 0.001$) levels, highlighting the association between DRPs and renal function. These results reinforce the importance of heightened vigilance by clinical pharmacists in patients with impaired kidney function. At the medication level, 46.51% of pharmacist-recommended interventions involved dose modification or discontinuation/interruption, most often necessitated by acute, chronic, or acute-on-chronic kidney dysfunction. In addition, DRPs involving medicines such as enoxaparin

and apixaban required weight-based dosing adjustments. All recommendations made by the clinical pharmacist were accepted, underlining their clinical value. In line with the literature, inappropriate drug selection, no or incomplete drug treatment despite a current indication[34–36,37,3839,40], and inappropriate drug combinations[41,42] have been reported as frequent causes of drug selection-related problems. In our study, inappropriate drug selection or drug combination (N1.3) emerged as the most common cause within the drug selection category, largely because level D and X pDDIs accounted for the majority of DRPs identified using the PCNE classification. Notably, previous research has indicated that interventions addressing drug interactions are less frequently implemented compared with other types of interventions[42,43]. Similarly, in our study, the clinical pharmacist intervened only in cases deemed clinically significant, resulting in fewer interventions than the total number of pDDIs identified. Specifically, pDDIs for which no intervention was performed constituted 92.77% of the problems without intervention, representing 46.48% of all potential or actual problems and 72.87% of the total pDDIs identified. These observations reinforce that, in cardiology wards, patient care must be multidimensional, taking into account individual characteristics, comorbidities, and dynamic clinical changes.

A large proportion of the non-intervened pDDIs—about half of all identified—were not clinically significant, as many reflected guideline-recommended combinations, such as anticoagulant–antiplatelet therapy in acute coronary syndrome. When these clinically justified cases were excluded, the number of significant DRPs in the intervention group decreased from 497 to 266, a statistically significant reduction compared with controls ($p < 0.001$). Most remaining pDDIs requiring intervention involved clinically important combinations, often linked to QTc prolongation or altered drug levels, for which the pharmacist recommended targeted monitoring. These results highlight how pharmacist involvement enhances the safe and appropriate management of complex therapies.

According to PCNE, all clinically significant pDDIs are classified as inappropriate drug combinations under the drug selection domain. However, this approach can overestimate DRPs, as it also includes guideline-recommended therapies prescribed for legitimate clinical indications. Refining the system by adding subcategories for interventions such as drug preparation and monitoring, and tailoring versions to ward-specific contexts, could enhance its accuracy and practical use. Addressing these limitations is crucial for broader and more effective application of PCNE in hospital practice.

Several studies have explored the effect of clinical pharmacists on readmission rates, with mixed results. O'Dell et al. reported a significantly lower rate of 30-day cardiac readmissions in intervention patients[44] whereas another study found no significant differences in mortality or hospitalisation[45]. In our study, readmissions within three months were numerically lower in the intervention group but not statistically significant. This outcome may have been influenced by unmeasured factors such as post-discharge adherence. Notably, a weak yet significant correlation between LACE scores and readmissions suggests that, with adaptation, this tool could help predict longer-term readmission risk. Admission pathways also posed a confounder, as over half of patients were admitted via the emergency department with acute conditions such as ACS or arrhythmias, which may have independently increased prescribing changes and DRPs.

Harrison et al. reported antihypertensives, antibiotics, analgesics, antiplatelets, and antidiabetics as common contributors to DRPs[46]. In line with this, our most frequent interventions involved antibacterials (15.45%), antithrombotics (15.45%), cardiac agents (12.73%), and antidiabetics (10.61%). Acheampong et al. identified anticoagulants as the leading cause of DRPs[47], which was also reflected in our findings, where enoxaparin (47.06%), apixaban (15.69%), and warfarin (15.69%) were the main agents requiring intervention. Enoxaparin, in particular, accounted for many DRPs due to its frequent use as parenteral therapy without routine laboratory monitoring. These findings highlight the essential role of clinical pharmacists in optimising both traditional and newer antithrombotic treatments.

Stuhec et al. reported that one-third of pharmacist interventions involved cardiovascular therapies[48]. Consistently, cardiovascular medicines accounted for the largest share in our study (25.15%), reflecting the burden of underlying conditions and the benefits of interprofessional collaboration in this area. Anti-infectives formed the second most frequent group (16.66%), mainly antibacterials, which is consistent with Harrison et al.[46]. Their high involvement may relate to the increased risk of secondary infections such as pneumonia in patients with cardiovascular disease. Drugs affecting the digestive system and metabolism were the third most common group (15.16%), with antidiabetics (10.61%) highlighting another key area where pharmacists contribute substantially to optimising care.

The prominence of DRPs and interventions involving antithrombotics in our study highlights the need for dedicated clinical pharmacy services for these high-risk patients. The broad range of drug classes requiring intervention further demonstrates how pharmacists enhance care quality through multidisciplinary collaboration. These findings suggest that clinical pharmacists could develop specialised expertise in areas such as cardiovascular, internal, and infectious diseases, while training programmes should be refined to address ward-specific challenges like antithrombotic management and electrolyte disturbances. The high acceptance of these interventions further reinforces their relevance, demonstrating that clinical pharmacists not only identify and resolve DRPs but also provide practical, evidence-based solutions readily adopted in routine care.

Acceptance rates for pharmacist interventions in the literature range from 70% to 97%[44,49,50]. In our study, the acceptance rate was 94.76%, supported by the pharmacist's active role in prescribing, provision of evidence-based recommendations, and direct communication with physicians. The medical team's familiarity with clinical pharmacy services likely further enhanced acceptance. Overall, both our findings and previous evidence emphasise the central role of clinical pharmacists within multidisciplinary teams in optimising pharmacotherapy and improving patient outcomes.

Limitations of the study

The limitations of our study include the fact that randomization was performed at a single center; therefore the results could not be generalized. Other limitations include not knowing patient's drug regimens and other factors during the three-month follow-up after discharge. These factors, when evaluated in terms of hospital admission and hospitalization, are independent of the clinical pharmacist. The low turnover of physicians in the team means the clinical pharmacist could not be completely isolated from both groups; team collaboration may influence results, which poses a risk of contamination.

Conclusion

This study demonstrates that integrating a clinical pharmacist into the multidisciplinary cardiology care team significantly enhances the identification, evaluation, and resolution of clinically relevant DRPs, particularly among patients receiving antithrombotic therapy. The clinical pharmacist's interventions—most frequently addressing inappropriate drug selection, dose optimisation, and management of pDDIs—were highly accepted by physicians, reflecting both their clinical relevance and the value of face-to-face collaboration.

The strong correlations observed between DRPs and factors such as age, polypharmacy, comorbidity burden, and impaired renal function underscore the importance of targeted pharmaceutical care in high-risk patient populations. Although the reduction in readmission rates did not reach statistical significance, the findings support the role of the clinical pharmacist in optimising pharmacotherapy, enhancing medication safety, and contributing to improved care quality in cardiology wards. Future research should explore multi-centre, longer-term evaluations to confirm these benefits and to further refine classification systems such as PCNE for better applicability in clinical practice.

Data availability

The data will be made available upon request from the corresponding author.

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Author contributions

Conceptualization, DS, MYB; methodology, DS, MYB, FVI; software, DS, MYB; validation, DS, MYB; formal analysis, DS, MYB; investigation, DS, MYB; resources, DS, MYB, NA, and FVI; data curation, DS; writing—original draft preparation, DS, MYB; writing—review and editing, DS, MYB, NA, and FVI; visualization, DS, MYB; supervision, MYB and FVI; project administration, DS, MYB; All authors have read and agreed to the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The study received ethical approval from the Clinical Research Ethics Committee (Decision No: 19/5), and written informed consent was obtained from all participants. All procedures adhered to the ethical standards of the University of Siena and the principles of the 1964 Helsinki Declaration and its later amendments. This study protocol has been registered on 05/01/2024 at ClinicalTrials.gov (NCT06193473).

Additional information
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