Int. J. Pharm. Investigation, 2026; 16(1):225-231.
https://www.jpionline.org

Original Article

Polypharmacy and Probable Drug Interactions in Cardiovascular Patients at a Tertiary Care Hospital

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ABSTRACT

Background: Cardiovascular Disease (CVD) is a general term for conditions affecting the heart or blood vessels. Globally, CVDs are the primary cause of morbidity and mortality. Frequently, treating CVDs requires intricate and comprehensive treatment plans. Heart disease and stroke are predicted to overtake all other causes of mortality and disability globally by 2020. Polypharmacy, the use of multiple medications, is prevalent among CVD patients, managing risk factors and comorbid conditions. However, it raises the risk of adverse drug interactions, necessitating Drug-Drug Interaction (DDI) monitoring to reduce negative medication responses. **Objectives:** We aimed to assess the prevalence of polypharmacy in cardiovascular disease patients. Materials and methods: 170 participants participated in a six-month cross-sectional study conducted at the cardiology department Patients with two or more prescription drugs and a minimum age of 18 were included in the research. A Micromedex drug interaction checker was used to identify and analyze the pattern of probable DDIs. **Results:** The study found that 132 (77.6%) of patients with CVD use 5 to 9 medicines due to multiple disorders. Factors like age, gender, and comorbidities significantly impact polypharmacy, with aspirin and clopidogrel being the most common drug interaction, causing major interactions whereas atorvastatin and clopidogrel cause moderate interaction. **Conclusion:** The study concluded that a high prevalence of polypharmacy in hospitalized cardiac patients is influenced by factors like age, gender, and comorbidities. DDI's were common, with Aspirin and Clopidogrel showing high rates of major interactions while atorvastatin and clopidogrel showed moderate interaction. It emphasizes the need for careful medication management to avoid harmful interactions.

Keywords: CVD, DDI, Polypharmacy Aspirin, Clopidogrel.

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Received: 07-05-2025;
Revised: 16-07-2025;
Accepted: 26-09-2025.

INTRODUCTION

Conditions pertaining to the heart are commonly referred to as cardiovascular disease (CVD). High amounts of fat obstructing the coronary arteries are the cause of heart attacks (American Heart Association, 2024). According to World Health Organization (WHO) projections, the number of deaths globally attributed to cardiovascular disease is estimated to be 17.3 million each year and is projected to rise to 23 million by 2030 (Vilahur *et al*., 2014). Signs and Symptoms of CVD include chest pain, weakness or numb legs and/or arms, breathlessness, tachycardia or bradycardia, or palpitations, feeling dizzy, lightheaded or faint, fatigue, and swollen limbs (British Heart Foundation, 2019).

DOI: 10.5530/ijpi.20260322

Polypharmacy and its Outcome

There are several meanings associated with polypharmacy. It is defined as the prescription of two or more medications at the same time (Veehof *et al*., 2000) or 5-9 drugs (Junius-Walker *et al*., 2006). A definitive definition of "polypharmacy" has not been discovered throughout our literature search. According to the present study, using five to nine different drugs regularly and concurrently may be referred to as "polypharmacy." Taking more than one medication might result in side effects, poor adherence, and inappropriate drug use when taken under prescription (Volpe *et al*., 2010). Polypharmacy, defined as taking more than four medications per day, results in reduced adherence (Rottlaender *et al*., 2007). More generally, polypharmacy may lead to decreased patient compliance because of drug-associated side effects and high frequencies of side effects as a regular consequence of DDI (Queneau, 2006). An aging population makes up one of the greatest segments of individuals with heart disease. This cohort is known to have a number of long-term behaviours that are linked to an increased risk of CVD, such as smoking, physical inactivity, and fat intake. Polypharmacy and difficult therapy are

the outcomes of these variables that impact the development of several additional potential dysfunctions (Vaccaro *et al.*, 1998). In addition to CVD, the most prevalent illnesses that complement it include osteoporosis, cancer, gout, arthritis, and cognitive problems. Multiple medications are needed to adequately address these dysfunctions (Gurwitz, 2004). But in our study, we found the most common comorbidities were Hypertension (HTN), Diabetes Mellitus (DM), and others including Ischemic Heart Disease (IHD), Rheumatic Heart Disease (RHD), old Cerebrovascular Accident (CVA), etc., Because of their comorbidities, patients are obligated to take more than one medicine. For this reason, the use of multiple medication therapy is common in the treatment of many issues. Consequently, the idea of "polypharmacy" is created by multiple-drug treatment.

Due to complex treatment regimens, many prescriptions, severe illnesses, and organ failure, patients hospitalized in Intensive Care Units (ICUs) are susceptible to DDI (Zagli *et al.*, 2008). It has been noted that polypharmacy and the impact of heart disease on medication metabolism attribute patients with CVD to at higher risk of developing drug-related death (Gholami *et al.*, 2008). In order to reduce the possibility of negative medication responses, DDI monitoring is required. When two drugs are taken at the same time and their effects are altered, this is known as DDIs (Hartshorn, 2006). Pharmacokinetic or pharmacodynamic interactions are possible in certain situations. A pharmacokinetic interaction happens when a medicine modifies the way another drug is absorbed, distributed, metabolized, or excreted, hence affecting the way other drugs work. Conversely, pharmacodynamic interaction occurs when the two medications show antagonistic or beneficial interactions throughout their mode of action. Few studies have been done in India to identify possible DDIs in cardiac patients (Patel *et al.*, 2011).

We aimed to investigate the prevalence of polypharmacy (taking 5 to 9 drugs) among cardiac patients. Additionally, our goal was to determine the risk variables that predisposed the patient to polypharmacy as well as the amount of probable DDIs, or medications that interact most frequently to create health concerns.

CVD is a complex condition that, over time, can result in many other illnesses, such as diabetes. Heart disease is primarily associated with age (Lakatta, 2002). Research indicates that at the age of 55, the risk of stroke doubles in a decade (Ramirez-Lassepas, 1998). We assume that older individuals with heart conditions may also exhibit polypharmacy, or the co-occurrence of many illnesses since the number of problems grows with age.

We also hypothesized that the most commonly administered medications for individuals with heart problems are cholesterol-lowering agents and antiplatelet medications. This assumption might be made for two reasons. First of all, the intake of fatty and high-cholesterol foods has caused a shift in eating patterns over time. Secondly, elderly people may have increased cholesterol because they have reduced physical activity.

Heart illnesses were more common in men than in women. Research indicates that among middle-aged adults, men are 2 to 5 times more likely than women to have coronary heart disease (Jousilahti *et al.*, 1999). Males often smoke more than females, which might be one reason for this finding. Furthermore, studies show that cardiac disease is more common in men than in premenopausal women.

We also considered the possibility that patients' comorbidities would inevitably lead to polypharmacy. Cardiologists are eventually influenced by comorbidities to prescribe many medications in a single prescription. Polypharmacy can result in potentially fatal medication interactions, necessitating a lengthier hospital stay. Lastly, we also hypothesized that age, gender, comorbidities, and a few other variables are risk factors linked to polypharmacy. Thus, this study aims to assess the factors affecting polypharmacy in CVD patients.

MATERIALS AND METHODS

Study design

The cross-sectional research was conducted from August 2023 to January 2024. The research comprised 170 patients with CVD diagnosed who were admitted to the cardiology department at Vivekananda General Hospital Hubli, India.

Ethical Considerations

The written informed consent was acquired from each participant after the patients and their families were informed about the study. The KLE College of Pharmacy Ethical Committee gave its approval to the study. The IEC Number: KLECOPH/IEC/2023-24/06.

Study population

Inclusion criteria: All the patients who were diagnosed with CVD, Subjects above 18 years, Subjects of both genders and Subjects with/without comorbid conditions.

Exclusion criteria: Subjects who attended the outpatient department, pregnant, breastfeeding, lactating women, and paediatric patients were excluded.

Statistical Analysis

The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 26.0. The mean was used to display continuous data, while numbers and percentages were used to display categorical variables. Age, gender, and comorbidities with polypharmacy were examined in connection to each other using univariate analysis and one-way

ANOVA. For statistical significance, a *p*-value of less than 0.05 was considered significant.

RESULTS

The study, which aimed to determine the prevalence of polypharmacy among hospitalized cardiac patients at a tertiary care hospital, involved 170 patients in total. Table 1 shows about demographic features: The highest proportion of persons taking more the 4 drugs were observed in the categories of 46-55 years, 56-65 years, 66-75 years age subgroups in male and female. Both genders had the highest polypharmacy level in between 56-65 years as. The average age was 12.09+/-59.23 years. Figure 1 illustrates that of the 170 patients, 106 (62.4%) were male and 64 (37.5%) were female. In the study population, ST Elevation Myocardial Infarction (STEMI) was the most prevalent diagnosis 63 (37.1%), followed by Non-ST Elevation Myocardial Infarction (NSTEMI) 60 (35.3%). The two comorbidities that most frequently impacted the polypharmacy approach for cardiovascular therapy were diabetes mellitus 54 (31.04%) and hypertension 91 (52.3%). Based on a number of drugs prescribed, it is classified into No polypharmacy (1-4 drugs), Polypharmacy (5-9 drugs) and Excessive polypharmacy (≥10 drugs). The majority of patients met the criteria for polypharmacy 132 (77.6%).

The univariate analysis demonstrated that the probability of developing polypharmacy rises with age (p=0.000), gender (p=0.000), Comorbidities (p=0.000), age and comorbidities (p=0.000), gender and comorbidities (p=0.000) are significant in major polypharmacy whereas, in moderate polypharmacy, age (p=0.031), comorbidities (p=0.002) showed significance while gender (p=0.571), Gender and comorbidities (p=0.376), Age and comorbidities (p=0.249) showed insignificant correlation in Table 2.

Out of the 1163 drugs, 972 drug-drug interactions were found in patients. The total number of DDI was classified as probable DDI based on severity that is Major and Moderate interactions as shown in Table 3. For both moderate and major interactions, an ambulatory treatment plan was necessary.

Followed the examination of the medications mainly responsible for severe drug interactions. Out of 63.8% of major interactions, Aspirin+Clopidogrel 158 (25.44%) and Aspirin+Enoxaparin Sodium 107 (17.23%) medications prescribed together may result in the major medication interactions as shown in Figure 2, and out of 36.11% moderate interaction, Atorvastatin+Clopidogrel 134(39.03%) and Aspirin+Metoprolol 121 (34.47%) were highest among moderate interaction as shown in Figure 3.

DISCUSSION

The research, which aimed to determine the incidence of polypharmacy among hospitalized cardiac patients at a tertiary care facility, included a total of 170 patients. The findings revealed that the highest proportion of individuals taking 5 to 9 drugs was in the age subgroups of 46-55 years, 56-65 years, and 66-75 years. The highest levels of polypharmacy were observed in both genders between the ages of 56 and 65 years. The average age was 59.23±12.09 years. Among the 170 patients, 64 (67.5%) were female, and 106 (62.4%) were male. The most common diagnoses in the study population were STEMI 63 (37.1%) and NSTEMI 60 (35.3%), both of which are serious conditions requiring intensive medical treatment. Hypertension 91 (52.3%) and diabetes mellitus 54 (31.04%) were the most common comorbidities influencing polypharmacy for cardiovascular care, as these conditions often required multiple medications to manage effectively. It was categorized as no polypharmacy (1-4 drugs), polypharmacy (5-9 drugs), and excessive polypharmacy (≥10 drugs) based on the quantity of drugs administered. The objective of this investigation was to examine the impact and prevalence of polypharmacy in individuals with Cardiovascular Disease (CVD). According to our predictions, the majority of patients, 132 (77.6%), were using 5-9 medicines, classifying their cases as polypharmacy.

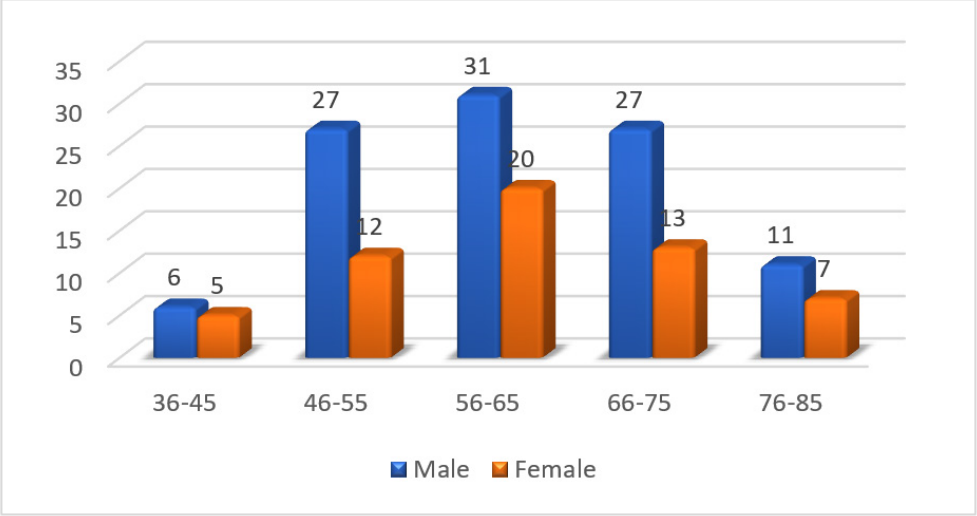

Figure 1: Distribution of Males and Females based on their age.

Table 1: Demographic features of the study population.

Variables	No. of subjects (n)	Percentage (%)
Age		
36-45 years	11	6.5%
46-55 years	44	25.9%
56-65 years	55	32.4%
66-75 years	42	24.7%
76-85 years	18	10.6%
Gender		
Male	106	62.4%
Female	64	37.6%
Comorbidities		
Hypertension	91	52.3%
Diabetes mellitus	54	31.04%
Ischemic heart disease	18	10.35%
Rheumatic heart disease	4	2.3%
Old CVA hemiparesis	3	1.72%
Hypothyroidism	2	1.15%
Pedal oedema	1	0.57%
Atrioventricular block	1	0.57%
Diagnosis		
STEMI	63	37.1%
NSTEMI	60	35.3%
Unstable angina	27	15.9%
Complete Heart Block	4	2.4%
Dilated Cardio Myopathy	6	3.5%
Rheumatic Heart Disease	8	4.7%
Heart Failure	2	1.2%
Number of Drugs Prescribed		
No polypharmacy	11	6.5%
Polypharmacy	132	77.6%
Excessive polypharmacy	27	15.9%

Polypharmacy results from taking many drugs due to the presence of one, two, or more concurrent disorders. The results of the univariate analysis were quite intriguing, highlighting the various factors that influenced the development of polypharmacy. It was clear from the statistical significance levels that age (p=0.000), gender (p=0.000), and comorbidities (p=0.000) all played a significant role in the likelihood of developing polypharmacy. The correlation between age and comorbidities (p=0.000), as well as gender and comorbidities (p=0.000), also showed significant impacts on major polypharmacy. Interestingly, moderate polypharmacy revealed that age (p=0.031) and comorbidities (p=0.002) maintained their significance, while gender (p=0.571), as well as the correlation between gender and comorbidities (p=0.376) and age and comorbidities (p=0.249), showed insignificant correlations. Comparable findings were observed in a study carried out by Md. Mamun Al-Amin *et al.*, 2012. Since the majority of patients with cardiovascular disorders arrived with concurrent problems that necessitated the prescription of many medications, DDIs were a significant concern in the management of these individuals. Compared to other patients, it was noted that cardiac patients were more likely to experience medication interactions (Straubhaar *et al.*, 2006). From insignificant interactions to serious or life-threatening interactions, DDI ranged in severity. A variety of software tools were available to assist in determining and evaluating the DDI pattern. The medication interaction checker utilized in this investigation was the Micromedex drug interaction checker. The combination of aspirin and clopidogrel was shown to cause the greatest medication interactions. Due to their pharmacodynamic synergism, these medications made each other more toxic, raising the risk of bleeding tendencies. Nonetheless, since the combination lowers the risk of further cardiovascular events, low-dose aspirin and clopidogrel were typically administered to cardiac patients. Therefore, when administered for the proper indication and for the right amount of time, the benefits exceeded the hazards (Terpening, 2009). The results of our analysis aligned with a previous investigation that found blood coagulation modifiers to be the most common medication interactions (Smithburger *et al.*, 2010). Since both enhance the toxicity of each other, the Micromedex Drug Interaction Checker advised thorough patient monitoring. The most often reported pharmacological classes that interacted in intensive care units (ICUs) included antithrombotic agents and cardiovascular medicines. (Reis & Cassiani, 2011; Jain *et al.*, 2017). We observed that the majority of interactions were caused by aspirin. It mostly interacted with enoxaparin sodium and clopidogrel. The combinations of aspirin+clopidogrel and aspirin+enoxaparin sodium produced 158 (25.44%) and 107 (17.23%) major interactions, respectively, while the combinations of atorvastatin+clopidogrel and aspirin+metoprolol created 134 (38.17%) and 121 (34.47%) moderate interactions, respectively. Physicians should take into account extra criteria when writing prescriptions in order to reduce the probability of polypharmacy

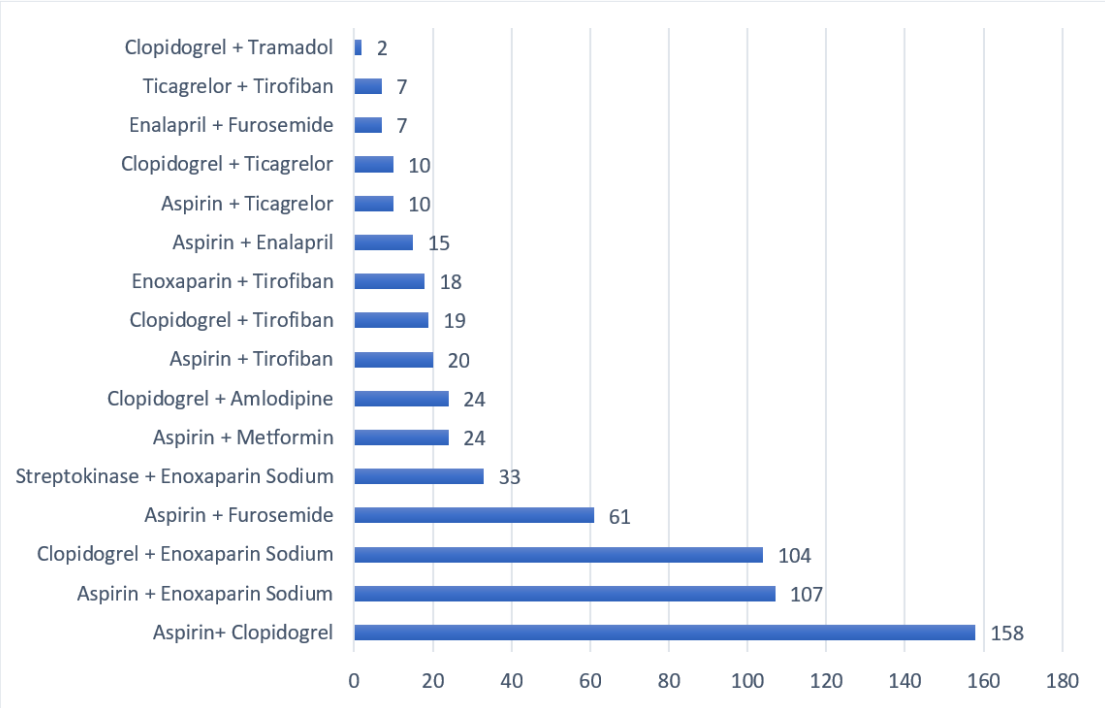

Figure 2: Distribution of drugs based on major interaction.

Table 2: Univariate ANOVA for 2 types of polypharmacy.

Variables	Major polypharmacy		Moderate polypharmacy	
	F value	*p* valve	F value	*p* valve
Age	26.062	0.000*	2.738	0.031*
Gender	19.298	0.000*	0.322	0.571
Comorbidities	26.899	0.000*	6.375	0.002*
Gender* comorbidities	6.754	0.000*	0.984	0.376
Age* comorbidities	12.178	0.000*	1.311	0.249

*Statistically Significant $p<0.05$.

and ensure patient safety. They should regularly check the lists of available drugs and stay updated on the outcomes of prescriptions. The polypill could be an additional option to address these problems. One of the largest solutions in this instance could be advanced dosage forms that incorporate various drugs with varying release patterns. Md. Mamun Al-Amin *et al.*, 2012 carried out a comparable study, and Shipra Jain *et al.*, 2017 revealed similar results. In major interactions, the combination of Clopidogrel+Aspirin caused 158 (25.44%) of DI in CV patients. Pharmacological studies revealed that aspirin, which irreversibly acetylates the cyclooxygenase-1 enzyme, suppressing the production of thromboxane A2 and inhibiting platelet activation and aggregation, and clopidogrel, which blocks the CYP2Y-12 receptor on the platelet membrane, inhibiting ADP-induced platelet activation and aggregation, exhibit antithrombotic action by entirely different mechanisms (Tourmousoglou & Rokkas, 2008). However, their combined action amplified the effects of clopidogrel through pharmacodynamic synergism. Patients using these drugs still experienced problems even though they were effective at preventing thrombosis (Wang, Bhatt, & Topol, 2006). Despite these side effects, clopidogrel and aspirin were combined to provide high-risk cardiac patients with additional benefits (Squizzato *et al.*, 2017). In moderate interaction, aspirin+ atorvastatin is found to be the most common. Aspirin works by preventing the Cyclooxygenase (COX) enzyme from acting, specifically COX-1, which is necessary for the synthesis of thromboxane A2. Thromboxane A2 promotes platelet aggregation, which can lead to the formation of blood clots. By inhibiting thromboxane A2 production, it helps to prevent excessive platelet aggregation and reduces the risk of blood clot formation. The other medication functions by preventing the liver's HMG-CoA reductase enzyme from producing cholesterol.

Table 3: Distribution of probable DDI based on severity.

Based on Severity	Number of Interactions (n)	Percentage (%)
Major	621	63.88%
Moderate	351	36.11%

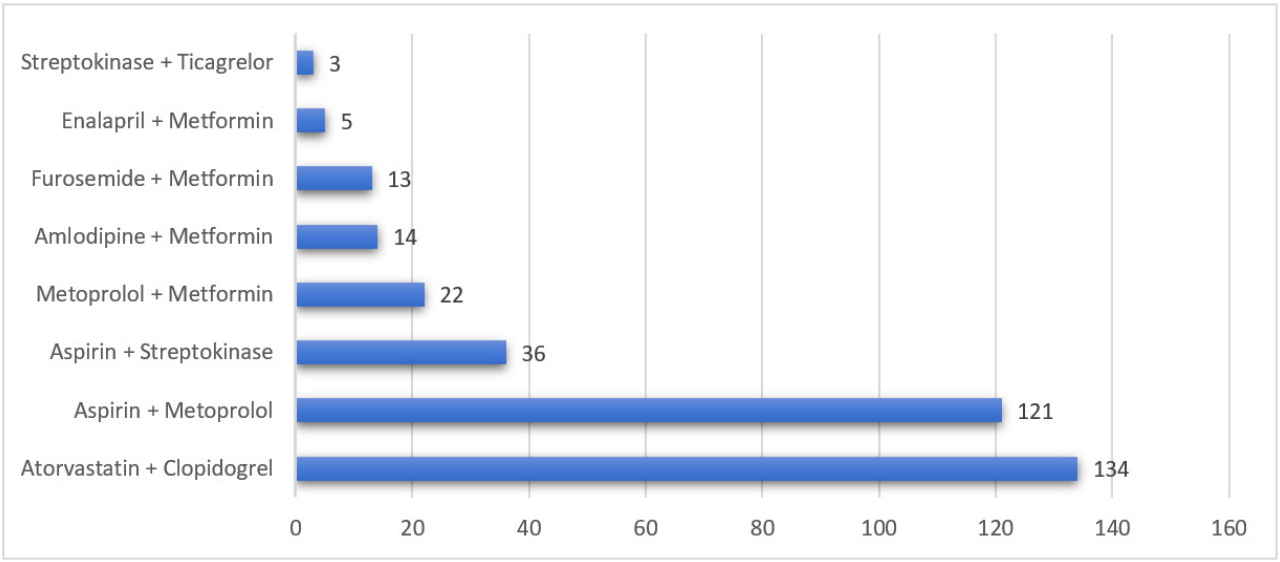

Figure 3: Distribution of drugs based on moderate interaction.

By inhibiting this enzyme, the drug lowers the production of cholesterol, which in turn lowers levels of total and Low-Density Lipoprotein (LDL) cholesterol (MrMed, n.d.).

CONCLUSION

In conclusion, polypharmacy is a common occurrence among patients with cardiovascular diseases, especially in older individuals. The use of multiple medications is often necessary due to comorbidities and complex treatment regimens. Polypharmacy can lead to drug-drug interactions that can have serious consequences. In this study, we observed that the majority of patients with CVD were taking five to nine medications, categorizing them as polypharmacy cases. Age, gender, and comorbidities were significant factors influencing the development of polypharmacy. The most common medications causing major drug interactions were aspirin, clopidogrel, atorvastatin, and metoprolol. Therefore, it is essential for healthcare providers to be vigilant in monitoring and managing polypharmacy in patients with cardiovascular diseases to ensure optimal treatment outcomes and patient safety. Further research and initiatives are needed to address the challenges posed by polypharmacy and drug-drug interactions in this population.

ACKNOWLEDGEMENT

The authors would like to sincerely thank Vivekananda General Hospital Hubli for their outstanding assistance, possibilities for study, cooperation, and facilitation of this research project. Above all, we would like to express our sincere gratitude to each and every patient and family who so kindly allowed and encouraged our study. Their collaboration and desire to work together were essential to the study's effective completion.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CVD: Cardiovascular disease, **DDI:** Drug-drug interaction, **WHO:** World Health Organization, **ICU:** Intensive care units.

AUTHORS' CONTRIBUTION

Each author had equal responsibility for the study's conception, literature review's execution, manuscript writing, and revision. The final draft of the paper has been read and authorized by all writers, who have also promised to take responsibility for the entire project.

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Cite this article: Shetty S, Paladi R, Basavaraj S, Magadum PN, Javali SM, Kittur SA, *et al*. Polypharmacy and Probable Drug Interactions in Cardiovascular Patients at a Tertiary Care Hospital. Int. J. Pharm. Investigation. 2026;16(1):225-31.