INTERNATIONAL JOURNAL OF SOCIAL SCIENCES BULLETIN
ISSN: (E) 3007-1917 (P) 3007-1909
Volume 3, Issue 9, 2025

DRUG-DRUG INTERACTION AND TREATMENT ERRORS IN HYPERTENSIVE PATIENTS

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DOI:https://doi.org/10.5281/zenodo.17293183

Received	Revised	Accepted	Published
25 July 2025	25 August, 2025	07 September 2025	22 September 2025

ABSTRACT

*Hypertension is a prevalent chronic disease often requiring multidrug therapy, which increases the risk of drug–drug interactions (DDIs) and treatment errors. This study aimed to identify the prevalence, types, and clinical implications of DDIs in prescriptions for hypertensive patients in a secondary care hospital in Pakistan. A retrospective review of 124 prescriptions over nine months was conducted, and interactions were analyzed using Medscape software. A total of **535** DDIs were detected. Pharmacodynamic interactions were more common (56%) than pharmacokinetic ones (43.9%). Among pharmacokinetic interactions, metabolism-related changes (57.4%) were most frequent, while synergistic effects (51.1%) dominated pharmacodynamic interactions. Frequently involved drugs included losartan, clopidogrel, bisoprolol, and furosemide, often prescribed alongside NSAIDs, PPIs, and anticoagulants. Notable clinically significant interactions were observed, including ACE inhibitors with NSAIDs and clopidogrel with omeprazole, which may lead to renal impairment, reduced efficacy, or increased bleeding risk. The findings underscore the importance of careful monitoring, dose adjustment, and judicious prescribing to minimize harmful DDIs in hypertensive patients. Strengthening prescribing practices and clinical oversight is essential to improve therapeutic outcomes and patient safety in polypharmacy settings.*

INTRODUCTION

Drug-drug interactions (DDIs) represent a serious problem in medicine, especially when it comes to patients who have long-term illnesses like hypertension (Devarashetty, 2020). High blood pressure, often known as hypertension, is a common cardiovascular condition that dramatically raises the possibility of heart attack, stroke, and various life-threatening illnesses. Using a variety of drugs to address concomitant diseases like diabetes or hyperlipidemia or to regulate blood pressure is a common part of managing hypertension (Kumar, V., et al., 2022). Although essential for all-encompassing therapy, this multi-drug approach also increases the risk of DDIs, which can have a detrimental effect on patient outcomes.

DDIs happen when one medication changes how another works, which can result in increased toxicity, decreased efficacy, or unanticipated adverse effects. DDIs are especially problematic in hypertensive individuals since they can worsen other comorbidities, raise the risk of severe cardiovascular events, and impair blood pressure regulation (Samardžić, I., et al., 2021). As an illustration, some antihypertensive medications may interact with other prescriptions, like non-steroid anti-inflammatory drugs (NSAIDs), resulting in

decreased regulation of blood pressure or harm to the kidneys. Analogously, mixing multiple antihypertensive medication classes without carefully assessing how they interact can lead to hypotension or other issues (Messerli, F. H., et al., 2022).

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Considering the intricacy of managing hypertension and the extensive usage of various drugs in this demographic, comprehending the type and frequency of developmental disabilities is crucial for enhancing therapeutic approaches (Oyetoro, R., et al., 2023). To avoid negative consequences and guarantee proper blood pressure control, healthcare professionals must be aware of the possible interactions between antihypertensive medications and other frequently administered medications.

The goal of this study is to determine and examine the prevalence of medication interactions-related prescription errors in patients with hypertension in this district's various healthcare systems. Comprehending these mistakes is essential to formulating plans to strengthen prescription procedures and, eventually, care for patients in the area.

Objectives of study

a) A retrospective analysis of possible drug-drug interactions

b) To look at the most prevalent ways that anti-hypertensive medications interact with one another and with other drug types.

c) The most often utilized treatment for these medication interactions

Methodology

One of the most common diseases and the main contributor to population-related illnesses, including heart disease, is hypertension (Santangelo et al., 2023). Given that it is a primary cause, treatment is required to stop more complications. For its treatment, a lot of medications are prescribed, which causes polypharmacy and drug-drug interactions. As a result, we have decided to examine prescriptions and look for evidence of drug interactions. Literature reviews were conducted as part of the study's preliminary phase to better understand the conditions that patients with hypertension face. Subsequently, the study involves gathering prescriptions, which are then analyzed to determine which medications were prescribed by the doctor for hypertensive patients in Pakistan and whether any drug interactions occurred (Huynh et al., 2023).

Particular Region

The first study region was Pakistan and a government hospital a secondary care facility was chosen there where patients receive free medical care.

Length of study

The study was conducted over nine months, encompassing winter, spring, and summer, from November to July.

Study Type

The cases for the study were gathered from the general medicine department's medical record room at each hospital using a retrospective methodology. The study involved the presence or absence of pharmacological interactions in the prescriptions written for hypertensive patients, and the data was routinely collected for this purpose.

Inclusion Criteria

All of the medicines that cause hypertension also come with related complications related to age, sex, and other illnesses like renal disease and heart failure.

Exclusive Criteria

Prescriptions with additional parameters, such as pregnancy, were not accepted.

Study parameters

- Prescription drug interactions with each other.
- Antihypertensive patient dose
- Prescription medication strength
- Medication duration
- Frequency of dosing

sample size

A total of 124 prescriptions were gathered to assess drug-drug interactions.

Data Evaluation

We separated the data into two categories;

- The patient's name, age, sex, department, date of admission, date of discharge, diagnosis, and medication chart are all included in the first group.
- The second group comprises information about drug interactions, including frequency, dose, severity, and treatment options.

Data Assessment

Following data analysis, we used various software programs to assess the data. Software (Medscape) was used to investigate medication interactions. MS Excel was used to create the graphs. Different statistical techniques were used to calculate the percentages.

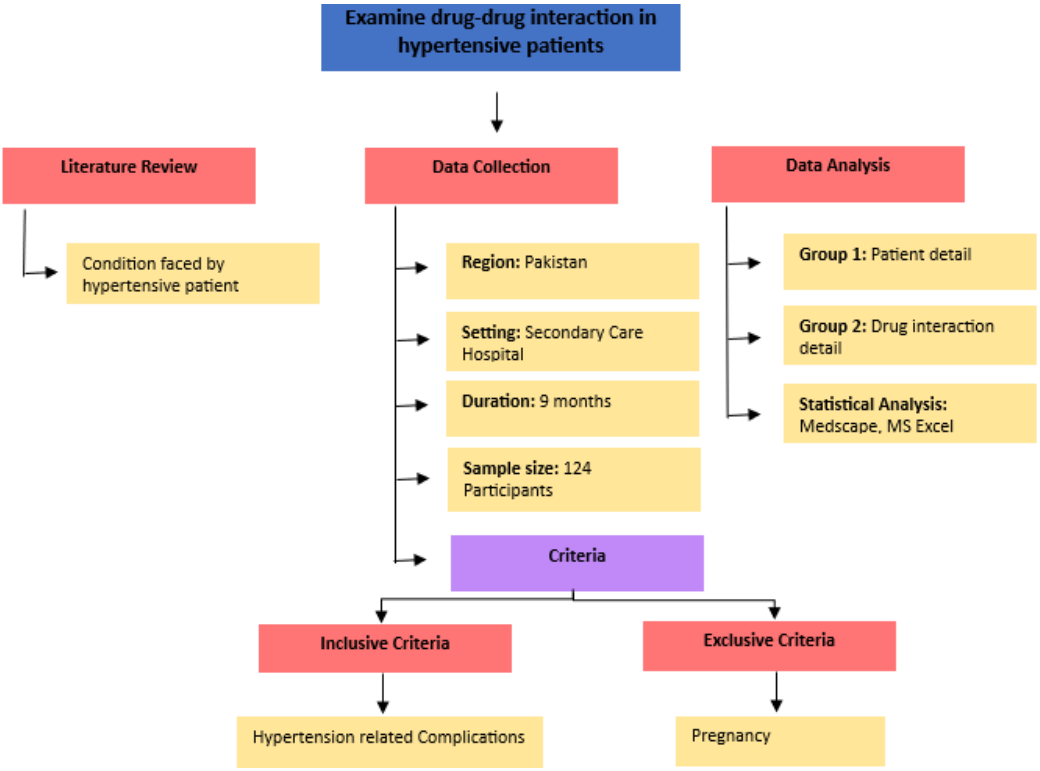


Figure 1- Flow design of methodology

Results and Discussion

The first analysis of drug-drug interactions (DDIs) between antihypertensive medications is this integrative review. Millions of people worldwide suffer from hypertension, which is defined as continuously high blood pressure, with readings frequently above 140/90 mmHg (Islam, Chaudhuri, Islam, & Kamrujjaman, 2023). It is imperative to manage it effectively because it might result in serious complications like ischemic heart disease and stroke (Saceleanu et al., 2023).

Drug interactions between antihypertensive medicines and other medications might result in pharmacokinetic or pharmacodynamic consequences. As (Sun et al., 2023) reveal antihypertensive drugs can have important pharmacokinetic or pharmacodynamic effects when they interact with other medications. These interactions may affect how well drugs are absorbed, distributed, metabolized, or

excreted, which could reduce the effectiveness of treatment or increase toxicity (Xie & Wang, 2023). For instance, taking ACE inhibitors and NSAIDs together may lower renal function, while taking PPIs along with clopidogrel may raise the risk of bleeding in the stomach (Mozaffari, Mousavi, Nikfar, & Abdollahi, 2023).

A total of 535 interactions were observed in the 124 prescriptions for hypertensive patients that we studied. The percentage for pharmacokinetic and pharmacodynamic connections among them is given below in table 1. The table offers a useful summary of several drug interactions, emphasizing their frequency and possible consequences for clinical practice. Pharmacokinetic interactions refer to variations in the way medications are taken in, dispersed, metabolized, or eliminated from the body. They account for 43.9% of instances. Metabolism-related interactions are very common in this group, accounting for 57.4% of occurrences. The cytochrome P450 enzymes in the liver are frequently involved in these interactions, where a medication may either speed up or slow down the metabolism of a different one, sometimes resulting in toxicity or ineffectiveness as a treatment. Protein binding relationships (31.91%) and absorption connections (38%) are noteworthy as well because they can change the bloodstream's active medication concentration, which might lower efficacy or increase the risk of side effects. Clearance interactions (4.25%) are less frequent but important, particularly in individuals with impaired hepatic or renal function, as they might result in subtherapeutic levels or drug buildup.

Contrarily, pharmacodynamic interactions which account for 56% of interactions involve modifications to the way the drug acts on the body as opposed to variations in its concentration. These can be antagonistic (26.6%), when one medicine lessens the effect of another, or synergistic (51.1%) when two treatments work together to generate a bigger effect than the total of their separate effects. This also applies to additive interactions (22.3%), in which the total effect of all the drugs is equal to the sum of their individual effects. These pharmacodynamic connections are especially important when a patient has polypharmacy, which means that the combined consequences of several medications need to be carefully controlled to prevent negative effects (Daunt, Curtin, & O'Mahony, 2024).

All things considered, the table emphasizes how crucial it is to comprehend pharmacokinetic and pharmacodynamic connections in clinical situations. Through identification of these interactions, medical practitioners can improve medication schedules, anticipate possible problems, and protect patient safety.

Type of interaction	**Percentage of interaction**
Pharmacokinetic	**43.9%**
Absorption	38%
Protein binding	31.91%
Metabolism	57.4%
Clearance	4.25%
Pharmacodynamics	**56%**
Synergism	51.1%
P.antagonism	26.6%
Additive	22.3%

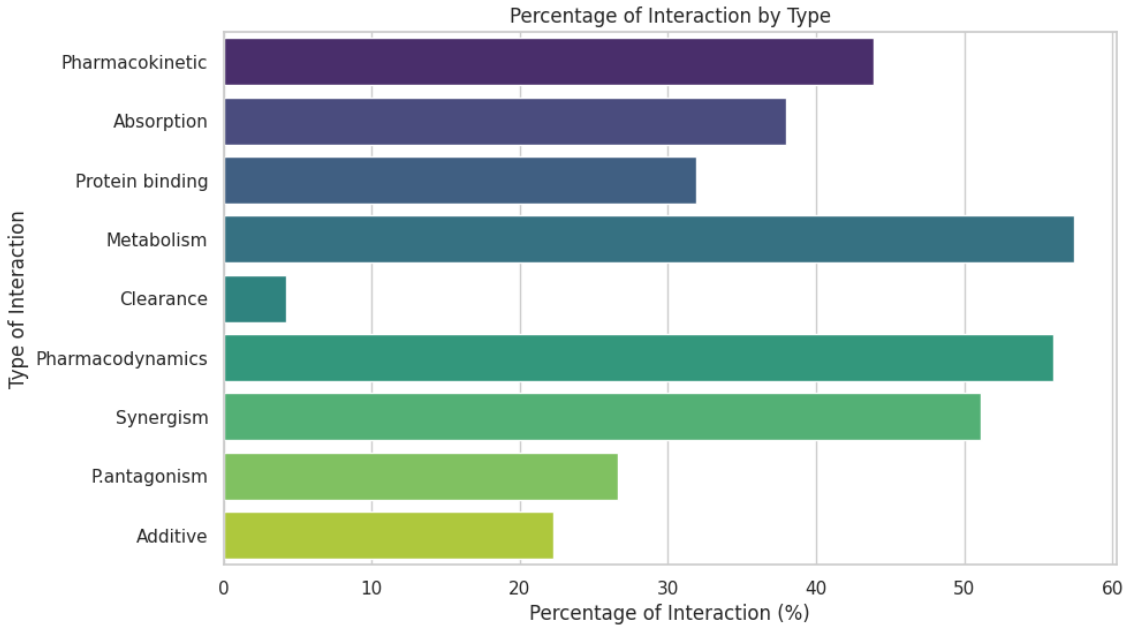


Figure 2- Percentage of interaction by type

(Lockridge, Bennett, & Olyaei, 2023) disclose that azithromycin and enoxaparin, clopidogrel and omeprazole, NSAIDs and ACE inhibitors, and clarithromycin and atorvastatin were found to interact in outstanding ways. Notably, significant interactions between azithromycin and enoxaparin, clopidogrel & omeprazole, NSAIDs plus ACE inhibitors, with clarithromycin and atorvastatin were noted in our research study. Because these interactions have the potential to have serious side effects, care or alternative treatments were often necessary. Like that (Hutman et al., 2023) expose that these interactions often required cautious supervision or alternate treatments due to the possibility of major issues.

The most regularly interacting antihypertensive drugs were losartan, clopidogrel, bisoprolol, and furosemide. These drugs were frequently taken with NSAIDs, PPIs, anticoagulants, and additional antihypertensive tablets. Comprehending these interplays is essential for maximizing the effectiveness of antihypertensive medication and reducing the possibility of side effects. Employing (Stanciu et al., 2023) stated that the most common antihypertensive medications and their interactions are essential for maximizing the therapeutic benefit of antihypertensive medication and lowering the risk of side effects. In the final analysis, careful monitoring of antihypertensive medication interactions is critical to guarantee patient health and therapeutic efficacy, especially in polypharmacy circumstances. As (Mair, Mair, Hilmer, & Kouladjian O'Donnell, 2024) expose Careful observation of interactions between antihypertensive medications is necessary to guarantee the safety of patients and effectiveness in therapy, especially when polypharmacy is involved.

Table 2- Interactions of drugs

SR. No	Antihypertensive drugs	Other drugs	Interactions	Remedy
01	Bisoprolol	Aspirin	Both increase Use caution serum potassium. Aspirin decreases the effect of bisoprolol by pharmacodynamic antagonism.	Use caution
		Valsartan, candesartan, Losartan	Pharmacodynamics synergism Risk of fetal compromised if used in pregnancy.	Use caution
		Furosemide	Bisoprolol increase and Furosemide decrease serum potassium	Use caution
		Amlodipine	Both increase antihypertensive channel blocking	
02	Lisinopril Captopril, Enalpril	Aspirin	Pharmacodynamics antagonism increases toxicity by synergies	Use alternate
03	Clopidogrel	Aspirin, Celecoxib, Ibuprofen	Increase effect by Pharmacodynamic synergism NSAIDS with clopidogrel inhibit platelet aggregation	Monitor closely
		Omeprazole (Serious)	Both increase coagulation by additive effect	
		Enoxaparin, heparin	Enoxaparin increase effect of other by pharmacodynamic synergism and increase risk of hemorrhage	Monitor closely
		Dexamethasone	Dexa increase level of clopidogrel by effecting metabolism	Monitor patient for potential increase in antiplatelet effect

04	Losartan	aspirin, aceclofenac, diclofenac,	All increased serum potassium Increases toxicity may result in renal deterioration. Aspirin and diclofenac increase coagulation. Aspirin decrease effect of losartan by pharmacodynamic antagonism.	
		Hydrochlorothiazide	Increase toxicity may result in renal deterioration. Aspirin and diclofenac increase coagulation. Aspirin decrease effect of losartan by pharmacodynamic antagonism.	Use caution
		Furosemide	Losartan increase and Furosemide decrease serum potassium	
		Spironolactone	Both increase serum potassium	Modify therapy
		Omeprazole	Omeprazole increase level of losartan by effecting metabolism	
		Enoxaparin	Both increase toxicity by pharmacodynamic synergism	
		Amiloride, digoxin	Both increase serum potassium	
		Metoprolol	pharmacodynamic synergism	
		Carvedilol	Both increase serum potassium by pharmacodynamic synergism	

			Risk of fetal compromised if use in pregnancy	
05	Carvedilol	Aspirin	Aspirin decrease effect of carvedilol by pharmacodynamic antagonism	
		Furosemide	Carvedilol increase and Furosemide decrease serum potassium	
06	Spironolactone	Atorvastatin	Spironolactone use caution increase the effect of Atorvastatin by P-glycoprotein efflux transport	Use caution
		Nebivolol, aspirin	Both increase serum potassium	
		Furosemide	Spironolactone increase Furosemide decrease serum potassium	
		Budesonide	Spironolactone will increase the effect of budesonide by P-glycoprotein MDR-1 efflux transporter.	
07	Furosemide	Ceftriaxone	Effect serum potassium level	
		Aspirin	Aspirin decrease the effect of Furosemide by pharmacodynamic antagonism	
		Bambuterol, hydrocortisone, budesonide	Pharmacodynamic synergism results in hypokalemia	
		Nebivolol, bisoprolol	Both Effect serum potassium level	
		Digoxin	Effects serum potassium and Furosemide increases effects of digoxin by pharmacodynamic synergism results in	

			hypokalemia	
		Metformin	Metformin decrease the level of Furosemide by unspecified interaction Furosemide increase the level of metformin by unspecified interactions.	The patient should be closely observed for loss of blood glucose level control.
		Valsartan	Valsartan increase and Furosemide decrease serum potassium	
		Enalapril, Ramipril	Valsartan increase and Furosemide decrease serum potassium	
		Cefixime, ceftazidime, Dexamethasone	Cefixime increase toxicity of Furosemide by pharmacodynamic c synergism Increase risk of nephrotoxicity	
08	Atorvastatin	Valsartan	Valsartan increase the toxicity of Atorvastatin Increase risk of myopathy	
		Azithromycin	Atorvastatin will increase the level and effect of azithromycin by P-glycoprotein efflux transporter	
		Clarithromycin (Serious)	Clarithromycin increases the toxicity of atorvastatin by affecting metabolism	Avoid or use an alternative drug Don't exceed atorvastatin dose of 20mg\day when co administered with Clarithromycin
		Amiodaron budesonide	Amiodarone will increase the level	

			and effects of Atorvastatin by P glycoprotein efflux transporter	
09	Nitroglycerine	Aspirin	Aspirin will increase the effect of nitroglycerine by additive vasodilation	
		Captopril	Both increase effect of each other by pharmacodynamic synergism both decrease blood pressure.	
10	Ramipril	Aspirin (Serious)	Aspirin either increase toxicity of other NSAID diminish Anti-hypertensive effect of ACE inhibitors result in decrease in renal function	
11	Nebivolol metoprolol	Aspirin, Ibuprofen ketorolac	Both increase serum potassium NSAID for Aspirin decrease the effects of nebivolol by pharmacodynamic antagonism NSAID decrease prostaglandin synthesis.	Don't use Aspirin for more than 1 week.
		Amlodipine	Both increase antihypertensive channel blocking	
12	Enoxaparin	Ceftriaxone (Serious)	Increase effect of enoxaparin by anti-coagulation Cephalosporin may decrease prothrombin activity	Avoid or use alternate
		Aspirin	Both increase anti-coagulation sometimes additive effects are intended Increase toxicity	

			of each other by pharmacodynamic synergism	
		Azithromycin (Serious)	Increase effects Use alternate of enoxaparin by decreasing metabolism	Use alternate
		Acetaminophen	Acetaminophen increase effect of enoxaparin	
13	Heparin	Ceftriaxone	Increase the level of heparin by anti-coagulation	Avoid or use alternate
14	Amlodipine	Hydrocortisone	Hydrocortisone decreases effect of Amlodipine by affecting the metabolism	
		Metformin	Amlodipine decrease effect of metformin by pharmacodynamic antagonism	
		Metronidazole	Metronidazole will increase level or effect of Amlodipine by effecting hepatic metabolism	
		Clarithromycin	Increase level or effect of Amlodipine by effecting hepatic metabolism it may lead to hypotension, edema, decrease heart rate, acute kidney injury due to reduced renal blood flow.	
		Dexamethasone	Dexamethasone will decrease the effect of Amlodipine by effecting hepatic enzyme metabolism	
15	Valsartan	Naproxen, celecoxib	Both increase serum potassium, Increase toxicity	

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			of each other, Naproxen decreases the effect of Valsartan by pharmacodynamic antagonism.	
		Humulin	Valsartan increase effects of Humulin by unspecified mechanism of action	Concomitant use of insulin and ARBs may require insulin dosage adjustment and increased glucose monitoring
16	Enalapril	Glimepiride	Enalapril increase effect of glimepiride by pharmacodynamic synergism	
17	Candesartan	Aspirin	Both increase serum potassium	
18	Propranolol	Diazepam	Propranolol increase effect of diazepam by decreasing metabolism	
19	Amiloride	Aspirin	Both increase serum potassium	
20	Hydralazine	Aspirin	Propranolol increase effect of diazepam by decreasing metabolism	

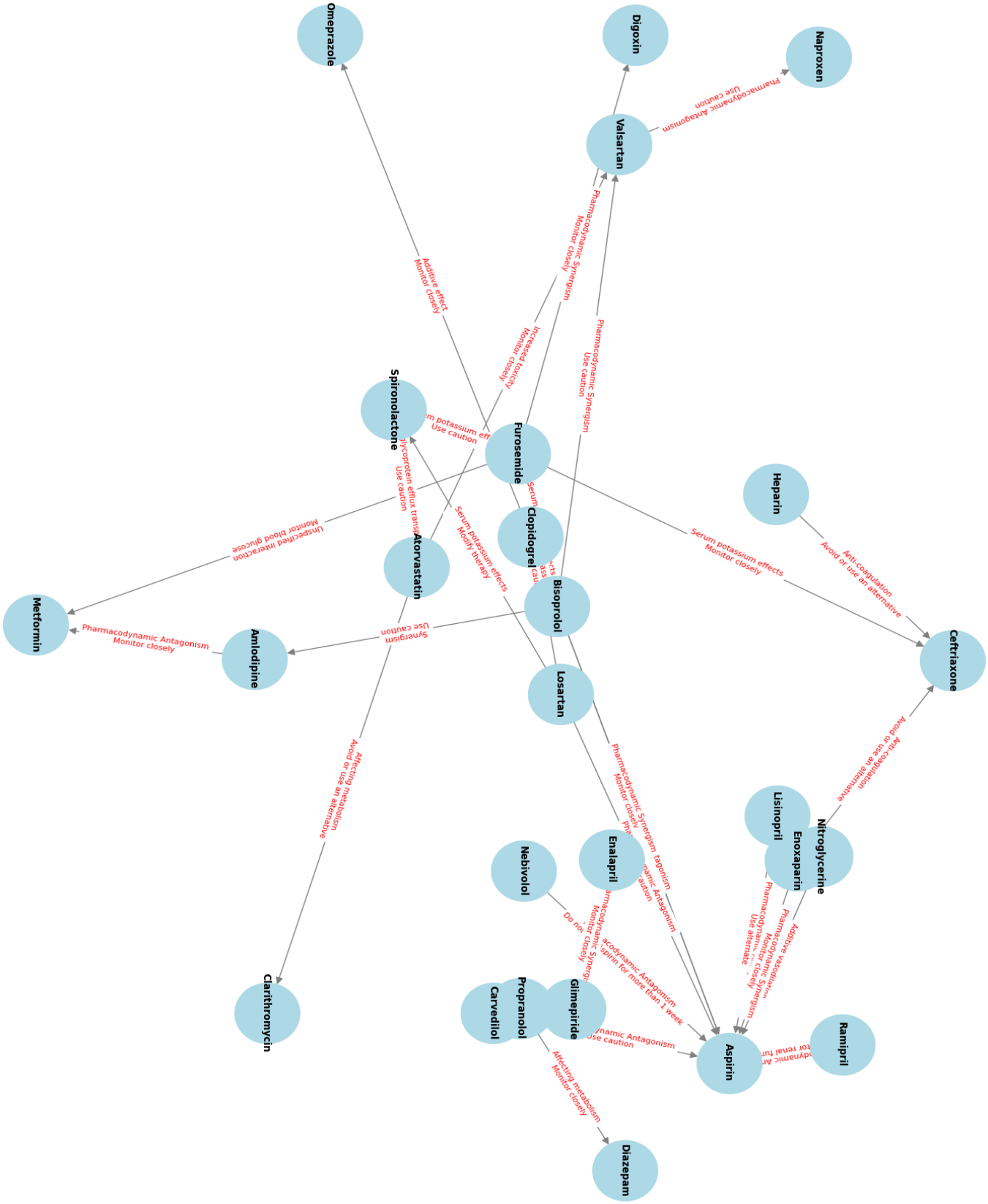


Figure 3- Antihypertensive drugs network interaction

***Nodes-** A node represents any medicine, ***Edges-** We can visualize pharmacological interactions as edges, ***Edge Labels-** The kind of connection and the suggested cure are labeled on each edge.

Conclusion

An analysis of the interactions between anti-hypertensive drugs and prescriptions obtained from the hospital in Pakistan over nine months from August 2017 to July 2018 yielded the following conclusion: of 124 prescriptions, 535 interactions were found to be related to anti-hypertensive medications. Anti-hypertensive drugs could interact with one another or with other classes of drugs; in the future, these interactions can be avoided by adjusting the dosage, using alternatives, exercising caution, monitoring blood pressure, and keeping a close eye on patients in the laboratory, particularly in cases of significant and moderate interactions.

Conflict of interest

We are not obliged to show any conflicts of interest.

Recommendation

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