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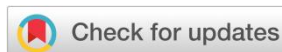
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Review Article

Pharmacovigilance in Cardiology: A Review of Adverse Drug Reactions in Practice

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Abstract

Cardiovascular diseases (CVDs) continue to be the major cause of death worldwide, affecting an estimated 640 million people as of 2021. Treatment success comes a new challenge, a growing population of people living longer with chronic heart issues, often taking multiple medications at once. This makes them more likely to experience adverse drug reactions (ADRs), especially as their health becomes more complex.

Pharmacovigilance plays a crucial role here. According to the World Health Organization, it's the ongoing science and practice of spotting, understanding, and preventing harmful or unexpected effects from medications. Pharmacovigilance fills in the gaps through real-world monitoring.

This review explains side effects tied to commonly used heart drugs, based on research from the last five years. It aims to help clinicians better understand these risks and guide safer prescribing. Some key findings include: bleeding risks with antithrombotics, shifts in electrolyte levels with diuretics and drugs that target the renin-angiotensin system, and organ damage like lung scarring or liver injury with drugs such as amiodarone and statins.

Looking forward, improving drug safety will require stronger reporting systems, better training for healthcare professionals, more advanced tools for analyzing risks, and broader international cooperation.

Keywords: Pharmacovigilance, Adverse Drug Reactions (ADRs), Cardiovascular Drugs, Drug-Drug Interactions, Clinical Monitoring, Therapeutic Innovation.

Introduction

Heart disease has become one of the biggest health threats of this era. In 2021 alone, it caused about 20.5 million deaths worldwide, making it the top cause of death across the world. The number of people living with heart or circulation problems has also doubled since 1993, now reaching nearly 640 million. Two major conditions like ischemic heart disease and stroke are behind most of these deaths.

Over 75% of CVD-related deaths happen in low and middle-income countries, where people often don't have reliable access to healthcare. Over the years, many drugs have proven to be life-saving, helping to prevent serious events like heart attacks and strokes. These treatments target conditions such as high blood pressure, high cholesterol, blood clotting, and weakened heart function that are at the root of heart disease. Advances in medical care have led to increased survival rate for heart attack and stroke, resulting in more individual living with chronic heart conditions. These patients often take multiple medications and deal with other health

problems like kidney or liver disease, which makes them more prone to drug-related side effects. Pharmacovigilance comes from the Greek word *pharmakon* (drug) and the Latin *vigilare*. The World Health Organization defines it as the science and activity of spotting, understanding, and preventing unwanted effects or problems from medications. This initiative was taken after the Thalidomide tragedy in the late 1950s and early 1960s, when thousands of children were born with birth defects due to a drug that hadn't been properly tested. It became apparent that pre-market trail have limitations, including missing rare adverse effect, long term risk or effect in particular patient group. Pharmacovigilance ensures ongoing safety monitoring after approval. It helps to uncover new risks. In heart care, the risk of side effects is especially high. Many patients take five or more drugs at once. This makes drug interactions more likely. Older age, kidney or liver problems, and even genetic differences can change how a person reacts to a medication. These reactions aren't minor, it may leads to cause of emergency visits and hospital stays, costing both lives and money. Nowadays,

cardiology landscape is changing fast. New drug types like ARNIs and SGLT2 inhibitors are becoming standard, and RNA-based therapies are on the horizon. It brings real hope as well as new risks. The aim of this review is clear:

To give a detailed and easy-to-understand summary of recent findings on side effects linked to cardiovascular drugs. This can help healthcare providers use medications more safely and effectively. To do that, the review will:

1. Identify and sort through the most common and serious side effects tied to different classes of heart drugs.
2. Examine the many factors (patient-related, drug-related, and system-level) that affect when and how these side effects occur.
3. Highlight current challenges in drug safety monitoring, like underreporting and figuring out what actually caused a side effect, while also stressing the importance of teamwork among healthcare providers.
4. Explore how new tools like artificial intelligence, real-world data, and patient feedback might shape the future of cardiovascular drug safety.

1. The Landscape of Cardiovascular Disease and the Imperative of Pharmacovigilance

1.1 Background: The Dual Realities of Cardiovascular Disease and its Management

1.1.1 Prevalence and Burden of CVDs Globally and in India

Cardiovascular diseases (CVDs) are one of the biggest public health problems we are facing today. They've become the top cause of death around the world¹. In 2021 alone, they were behind about 20.5 million deaths are roughly one in every three deaths that year^{1,2}. That works out to around 55,000 people dying each day, or one person every 1.5 seconds. The number of people living with heart or circulation problems has also doubled between 1993 and 2021, reaching around 640 million. Two main conditions like ischemic heart disease (IHD) and stroke which make up more than 80% of these deaths¹. The more troubling factor is that one in three of those who die from CVD is under 70^{1,2}. India stands out in this picture. The country is going through a major shift where CVDs are now the top cause of death and long-term illness. Back in 2016, about 54.5 million Indians were living with CVD, and the disease accounted for roughly 27–28% of all deaths in the country³. Moreover, India's death rate from CVD 272 per 100,000 people is much higher than the global average of 235^{2,3}.

1.1.2 Significance of Pharmacotherapy in Managing CVDs

Medications play a key role in today's treatment of cardiovascular disease (CVD). The goal of these treatments is clear that prevent serious events like heart attacks, strokes, or sudden cardiac death by knowing the root causes of heart disease. That means lowering blood pressure, improving cholesterol levels, preventing blood

clots, and helping the heart work better in people with heart failure or irregular rhythms⁴. But success of these drugs has brought new problems. Because more people now survive heart attacks and strokes, there's a growing population of older patients living with long term heart problems. So, even though pharmacotherapy works, it also increases the number of people who could be harmed by the very drugs keeping them alive. Safety checks are now a core part of heart care⁵.

1.1.3 Introduction to Cardiovascular Drug Classes

There's a wide range of medications used to manage heart disease. They're usually classified based on their pharmacological activities. Here are the main ones: Blood Pressure Medicines (Antihypertensives): These help lower blood pressure and include drugs like diuretics, beta-blockers, calcium channel blockers (CCBs), ACE inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs)⁶. Heart Rhythm Medications (Antiarrhythmics): These keep the heart beating at a normal rhythm. They fall into four main types: sodium-channel blockers (Class I), beta-blockers (Class II), potassium-channel blockers like amiodarone (Class III), and certain CCBs (Class IV). Cholesterol-Lowering Drugs (Lipid-Lowering Agents): The go-to group here are statins, but newer options like PCSK9 inhibitors and ezetimibe are being used more often too. Blood Thinners (Antithrombotic Agents): These reduce the risk of clots. Some stop platelets from clumping (like aspirin or clopidogrel), while others are anticoagulants (like warfarin or the newer direct oral anticoagulants)⁷. Drugs for Heart Failure: This group coincides with others but also includes newer classes like ARNIs and SGLT2 inhibitors, which were developed specifically for heart failure⁸.

1.2 Concept of Pharmacovigilance

1.2.1 Importance of Pharmacovigilance in Ensuring Drug Safety

Pharmacovigilance plays a vital role in drug safety, largely because pre-market clinical trials have some pretty significant limitations. While randomized controlled trials (RCTs) are considered the gold standard for figuring out if a drug works and appears safe initially, they don't tell the whole story. These trials are carried out in carefully controlled environments, usually involving a relatively small number of participants who are fairly similar in age and health status—and for only a short period of time⁹. That means there are several safety issues that RCTs often miss: Rare Adverse Reactions: If an adverse event only happens in 1 out of 10,000 patients. Long-Term Effects: Some side effects take years to develop, especially with ongoing use. Effects in Special Populations: Many clinical trials exclude vulnerable groups—like children, the elderly, pregnant women, or people with serious health conditions such as kidney or liver disease. Drug-Drug Interactions: In fields like cardiology, patients are often taking multiple medications at once. Clinical trials will not reflect this complexity, so they can miss harmful interactions between drugs¹⁰. This is where pharmacovigilance steps in. It fills those gaps by offering a system for ongoing

monitoring of drug safety throughout the entire time a drug is on the market. One of its main goals is to detect new "safety signals" essentially, any newly observed links between a drug and an adverse event that hadn't been recognized before or wasn't well understood ¹¹.

1.2.2 Brief Overview of National/International Pharmacovigilance Programs

After the Thalidomide tragedy, countries around the world realized the urgent need for boost drug safety systems and this led to the creation of both national and international pharmacovigilance programs. WHO Programme for International Drug Monitoring (PIDM) and the Uppsala Monitoring Centre (UMC): Back in 1968, the World Health Organization (WHO) launched the PIDM as a way to bring together national pharmacovigilance centers from around the globe. What started with just 10 founding countries has now expanded to more than 170 members. These countries collect reports of adverse drug reactions (ADRs) and submit them as Individual Case Safety Reports (ICSRs) to a central global database called VigiBase. Managed by the Uppsala Monitoring Centre (UMC) in Sweden—which acts as the WHO's Collaborating Centre for International Drug Monitoring—this database has grown into the largest of its kind in the world. With data from millions of patients worldwide, the UMC is able to conduct powerful signal detection analyses. This kind of global collaboration makes it possible to spot rare or unexpected ADRs that would likely go unnoticed within the borders of a single country ¹².

Pharmacovigilance Programme of India (PvPI):

Recognizing its vast population and key role in the global pharmaceutical industry, India launched the Pharmacovigilance Programme of India (PvPI) in 2010. The main goal is to safeguard public health by making sure that the benefits of medicines always outweigh their risks. The Indian Pharmacopoeia Commission (IPC) acts as the National Coordination Centre (NCC), managing a wide network of Adverse Drug Reaction Monitoring Centres (AMCs) set up in hospitals and medical colleges across the country. These centers collect ADR reports from healthcare workers and even directly from patients. Once the data is gathered, it's analyzed by the NCC and used to guide regulatory decisions made by the Central Drugs Standard Control Organization (CDSCO). In a country like India where cardiovascular disease is common, medications are widely accessible, and issues like irrational drug prescribing are still challenges the PvPI is especially vital. It serves as a real-world stress test for the nation's drug safety infrastructure ¹³.

1.3 Adverse Drug Reactions (ADRs) in Cardiovascular Therapy

Pharmacovigilance is important across all medical specialties, but it's critical in cardiology ¹⁴. That's because patients with cardiovascular disease (CVD) are particularly vulnerable to adverse drug reactions (ADRs), and when those reactions occur, the risk can be dangerously high.

1.3.1 Why CVD Patients are Particularly Susceptible to ADRs

The increased risk of ADRs in people with cardiovascular conditions comes from a mix of factors—some related to the patients themselves, others tied to the disease and the medications used to treat it

¹⁵. Comorbidities and Altered Pharmacokinetics/Dynamics: Heart disease often doesn't come alone. It frequently coexists with conditions like chronic kidney disease (CKD), diabetes, or liver dysfunction. For instance, CKD is a common issue in patients with heart failure, it can reduce the body's ability to eliminate drugs such as digoxin, direct oral anticoagulants (DOACs), and ACE inhibitors. If doses aren't properly adjusted, these medications can build up and become toxic. It creates a dangerous cycle: someone with heart failure and diabetes might develop CKD, which in turn increases the risk of drug-related harm (like high potassium levels from an ARNI), which then worsens kidney function even more—leading to a spiral of illness and drug-related injury ¹⁶. Advanced Age: Many heart patients are older adults. With age, the body's ability to metabolize and clear drugs declines due to reduced kidney and liver function, along with other changes like increased body fat and decreased water content. These shifts can make older adults more sensitive to drugs and more prone to side effects. Often, medications stay in their systems longer than expected, raising the risk of toxicity. Genetic Variations (Pharmacogenomics): The genetics can play a big role in how people respond to cardiovascular drugs ¹⁷. For example, some individuals carry a variation in the CYP2C19 gene that prevents the body from properly activating clopidogrel, a key antiplatelet drug. This can reduce the drug's effectiveness, putting the patient at greater risk of blood clots. Similarly, variations in the SLCO1B1 gene can lead to higher levels of simvastatin in the blood, increasing the risk of muscle damage ¹⁸.

1.3.2 General Types of ADRs with Cardiovascular Examples

Adverse drug reactions (ADRs) are generally grouped based on their occurrence, and the most clinically useful way to classify them is into two types: Type A and Type B reactions.

Type A (Augmented) Reactions:

These are the most common kind of ADR which making up about 90% of cases. They're usually predictable, dose-dependent, and essentially just an exaggerated version of the drug's intended effect¹⁹. Bleeding with Antithrombotics: This is a textbook example of a Type A reaction. Anticoagulants like warfarin and DOACs, along with antiplatelets like aspirin, are designed to prevent clots by thinning the blood. But if the blood becomes too thin, the risk of bleeding shoots up. It's a direct result of the drug doing its job a little too well. Bradycardia with Beta-Blockers: Beta-blockers lower your heart rate by blocking β_1 receptors in the heart. If the dose is too strong or the patient is especially sensitive, the heart rate can slow down too much leading to clinically significant bradycardia²⁰.

Again, it's a predictable effect of the drug working too well. Hypotension with Antihypertensives: All blood pressure-lowering drugs can lead to hypotension if the dose is too high or the patient's particularly responsive to them²⁰. It's simply an overextension of their intended effect. Peripheral Edema with Calcium Channel Blockers: Dihydropyridine calcium channel blockers (like amlodipine) are strong vasodilators, especially on arterioles. But because they don't cause equivalent dilation of the veins, pressure builds up in capillaries, pushing fluid into the surrounding tissues. That's what leads to the characteristic swelling, especially in the legs—and it's dose-dependent.

Type B (Bizarre) Reactions:

These are much less common, but far more unpredictable. They're not dose-dependent, and they don't stem from the drug's known pharmacological effects. Instead, they're often driven by unique patient specific factors—like genetic makeup or immune responses. ACE Inhibitor-Induced Cough and Angioedema: These are classic examples of Type B reactions. The dry cough can be persistent and annoying, while the angioedema is potentially life-threatening. Neither of these is due to the blood pressure-lowering effect of ACE inhibitors; instead, they're likely caused by the buildup of substances like bradykinin and substance P, which the enzyme normally helps break down²¹. Statin-Induced Necrotizing Autoimmune Myopathy (SINAM): This is a rare but serious immune reaction. In some individuals, taking a statin can trigger the body to form autoantibodies against the very enzyme the drug is targeting—HMG-CoA reductase. This results in ongoing muscle damage that may continue even after the statin is stopped. It's a striking example of a Type B, immune-mediated ADR. Amiodarone-Induced Pulmonary Toxicity: While amiodarone-related lung damage has some dose related risk, the onset of severe pulmonary fibrosis can be very unpredictable and idiosyncratic²². It involves both direct cell toxicity and immune responses, putting it firmly in the Type B category.

1.3.3 Highlighting the Potential Severity and Impact of Cardiovascular ADRs

Adverse drug reactions in cardiovascular care aren't just minor side effects, they can be seriously dangerous, even deadly. In fact, cardiovascular drugs consistently rank among the top medications linked to emergency department visits and hospital admissions due to ADRs. The clinical consequences can be severe. For example, bleeding from antithrombotic drugs especially when it involves the brain (intracranial hemorrhage) which can lead to permanent disability or even death. Other serious examples include pulmonary fibrosis caused by amiodarone, which can be fatal; angioedema from ACE inhibitors, which can block the airway; and rhabdomyolysis from statins, a condition that breaks down muscle tissue and can lead to acute kidney failure²³.

1.4 Rationale for the Review

Modern cardiology is caught between two competing demands on one side, treatments are advancing

quickly, and on the other, there's a strong need to protect patients. This review aims to explore the three main reasons behind it: heart medications are becoming more involved, the knowledge needed to use them safely has to keep evolving, and using a narrative review is a good way to bring all these pieces together clearly²⁴.

1.4.1 Stating the Increasing Complexity of Cardiovascular Pharmacotherapy

In recent years, doctors have been introduced to brand-new types of medications that have transformed how they care for patients. For example, sacubitril/valsartan, which falls under a newer class called ARNIs, has changed the standard treatment for people with heart failure and reduced ejection fraction. Another group, PCSK9 inhibitors, has helped lower cholesterol levels significantly in people who are at high risk. And SGLT2 inhibitors, once used only for diabetes, are now a standard part of treatment for heart failure, no effecting the patient's ejection fraction²⁵. RNA-based drugs are now on the horizon. Some of these new therapies like small interfering RNA (siRNA) are being developed to help manage conditions such as high blood pressure and cholesterol. Unlike the daily pills most people take, these only need to be given once or twice a year. That's a major change and means doctors will need new ways to think about long-term safety²⁶.

1.4.2 Emphasizing the Need for Updated Knowledge on ADRs

As heart medications keep evolving, so does the need for doctors and nurses to stay current on the possible side effects—also known as adverse drug reactions, or ADRs. When new drugs move from highly controlled trials into everyday use, that's when their full range of effects really starts to show up.

Some side effects that didn't come up in the trials may suddenly appear, and new interactions either with other medications or in specific groups of patients become easier to spot. This means health professionals need solid, up-to-date summaries of what's known about drug safety²⁷. Medical breakthroughs are moving faster than doctors need to stay ahead. This creates a real risk—called a "knowledge-practice gap" where the available safety info hasn't yet made it into daily practice²⁸.

That gap can lead to poor prescribing decisions, missed warning signs, or failure to catch and handle side effects correctly.

1.5 Aim and Objectives of the Review

This review sets out to offer a clear and thoughtful summary of where things currently stand with drug safety in cardiology. The focus is on helping clinicians better understand the risks tied to heart medications and encouraging safer, more informed prescribing choices. Main Aim: To bring together the most recent findings from the past five years on side effects tied to cardiovascular drugs. The goal is to give a well-rounded, narrative-based overview that helps healthcare providers improve how they manage medications in heart care²⁹.

Specific Goals of the Review:

Explore Current Challenges in Drug Monitoring: The review will also take a close look at the hurdles facing pharmacovigilance in heart medicine. This includes the tendency not to report problems and the tricky process of figuring out whether a drug actually caused a specific side effect. It'll also underline how important it is for different healthcare professionals to work together to manage these challenges³⁰. **Discuss What's New and What's Next:** Finally, it will pull in some of the newer tools and approaches that could shake up how drug safety is monitored. Think artificial intelligence, real world data, and input from patients themselves. These emerging methods could help make monitoring more accurate and more responsive moving forward³¹.

2. Adverse Drug Reactions Associated with Major Cardiovascular Drug Classes

Cardiovascular diseases (CVDs) remain the main cause of significant morbidity and mortality worldwide. Drug treatment is an indispensable part of treating various cardiovascular diseases, of optimizing patient outcomes, and of extending life. As with all effective medicines, however, drugs for treating cardiovascular diseases have been associated with a variety of adverse drug reactions (ADRs) from benign and controllable to life-threatening and potentially terminal. It is necessary to comprehend these ADRs and recent accounts (within the past five years, in particular) to optimize patient care, ensure safety, and maximize therapy adherence. This chapter features the most prominent ADRs of major drug classes of drugs for treating cardiovascular diseases, with a focus on those reported in the past five years.

2.1 Antihypertensive Agents

Antihypertensive drugs are a key part of managing high blood pressure. Their main goal is to lower blood pressure and reduce the risk of serious cardiovascular problems such as stroke, myocardial infarction, and heart failure. While these medications are very effective, they can also cause a range of adverse drug reactions (ADRs), many of which are linked to how they work in the body.

2.1.1 Renin-Angiotensin System Inhibitors (ACEIs, ARBs)

Renin-Angiotensin System (RAS) inhibitors—including Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)—are commonly prescribed for hypertension, heart failure, and kidney protection. **Cough:** A persistent, dry cough is one of the most recognized side effects of ACEIs, occurring in about 5% to 20% of patients. A comprehensive systematic review and network meta-analysis published in 2023 confirmed that ACEIs are significantly more likely to cause cough compared to other antihypertensive drugs, including ARBs. The cough usually appears within a few weeks to a few months after starting the medication and typically disappears within days to weeks after stopping it. ARBs, on the other hand, are far less likely to cause this problem³². **Angioedema:** Although less common than cough, angioedema is a more serious and potentially life-

threatening reaction associated with ACEIs. It involves sudden swelling of the face, lips, tongue, glottis, or larynx, which can block the airway³³. Recent data from 2019 to 2022 indicate that 0.1% to 1% of patients taking ACEIs experience angioedema³⁴. The risk is highest during the first month of therapy but can occur at any time. ARBs also have a risk of angioedema, but it is generally lower than that seen with ACEIs³⁵. **Hyperkalemia:** Both ACEIs and ARBs can cause hyperkalemia, or elevated potassium levels in the blood. This is more likely in patients who already have chronic kidney disease (CKD), diabetes, or are taking potassium-sparing diuretics, potassium supplements, or NSAIDs at the same time^{36,37}. A 2022 review highlighted the importance of carefully monitoring potassium levels in patients with these risk factors. Any rise in serum potassium after starting an ARB requires ongoing monitoring³⁸. **Renal Dysfunction:** ACEIs and ARBs can also cause reversible changes in kidney function, such as a mild rise in serum creatinine and a slight drop in glomerular filtration rate (GFR). These effects are more likely in patients with bilateral renal artery stenosis, severe heart failure, or significant dehydration. A small increase in creatinine up to around 30% is usually acceptable and suggests the RAS blockade is working effectively. However, a larger increase should prompt further investigation and may require dose adjustment or stopping the drug. Recent guidelines stress the need to monitor kidney function closely, especially during the first few weeks after starting or increasing the dose³⁹.

2.1.2 Calcium Channel Blockers (CCBs)

Calcium channel blockers are a varied group of drugs that work by reducing calcium entry into vascular smooth muscle cells and cardiac myocytes. This results in vasodilation, as well as decreased cardiac contractility and heart rate. Dihydropyridine CCBs (such as amlodipine and nifedipine) mainly target vascular smooth muscle, whereas non-dihydropyridine CCBs (such as verapamil and diltiazem) have stronger effects on the heart.

Peripheral Edema: Peripheral edema is one of the most frequent and troublesome adverse drug reactions, particularly with dihydropyridine CCBs. It affects anywhere from 5% to 60% of patients, depending on the drug and dose. The edema is typically dose-dependent and appears as pitting swelling in the ankles and lower legs. A review published in early 2025 highlighted its high prevalence and its role in reducing patient adherence⁴⁰. **Headache:** Headaches, often described as throbbing or pulsatile, are another common side effect especially during the early phase of treatment with dihydropyridine CCBs. This occurs because of their strong vasodilatory effect on cerebral blood vessels⁴¹.

Fortunately, these headaches often improve or disappear with continued use. **Constipation:** Constipation is more commonly seen with non-dihydropyridine CCBs, particularly verapamil. This happens because calcium channel blockade reduces the motility of smooth muscles in the gastrointestinal tract, slowing down gut movement⁴². **Bradycardia:** Non-dihydropyridine CCBs, such as verapamil and diltiazem, can slow the heart rate

(bradycardia) by directly suppressing the sinoatrial (SA) node and slowing conduction through the atrioventricular (AV) node. This effect is minimal or absent with dihydropyridine CCBs. Recent clinical evidence continues to emphasize the need to monitor heart rate, particularly when these drugs are used alongside other AV nodal blocking agents⁴³.

2.1.3 Beta-Blockers

Beta-blockers reduce the effects of catecholamines on beta-adrenergic receptors, which leads to a slower heart rate, reduced myocardial contractility, and lower blood pressure.

Bradycardia: A predictable effect of beta-blockers is bradycardia, due to their negative chronotropic action on the heart⁴⁴. In some cases, symptomatic bradycardia can cause dizziness or even fainting. **Fatigue:** Many patients report feeling tired, sluggish, or having reduced exercise tolerance, especially during the first few weeks of therapy⁴⁵. **Bronchospasm:** Non-selective beta-blockers, such as propranolol and nadolol, can trigger bronchospasm and are generally avoided in patients with asthma or severe chronic obstructive pulmonary disease (COPD). **Cardio-selective beta-blockers,** such as metoprolol and bisoprolol, act more specifically on β_1 receptors and are safer at usual doses, but they still require caution in individuals with reactive airway diseases. **Masked Hypoglycemia:** In diabetic patients, beta-blockers can mask the typical adrenergic warning signs of hypoglycemia, such as tremors, palpitations, and rapid heartbeat. However, sweating usually remains as an unmasked symptom, which can help in recognizing low blood sugar.

2.1.4 Diuretics (Thiazide, Loop, K-sparing)

Diuretics help lower blood pressure by promoting the excretion of water and electrolytes, thereby reducing circulating blood volume. They are grouped into thiazide diuretics, loop diuretics, and potassium-sparing diuretics, each acting on different segments of the nephron. **Electrolyte Imbalances:** Electrolyte disturbances are the most common adverse effects of diuretics, and the type of imbalance often depends on the specific drug used. **Hypokalemia:** Thiazide diuretics (e.g., hydrochlorothiazide, chlorthalidone) and loop diuretics (e.g., furosemide, torsemide) frequently cause hypokalemia because they increase potassium excretion⁴⁶. A 2022 review focusing on diuretic therapy in heart failure emphasized that hypokalemia remains a significant clinical concern⁴⁷. **Hyponatremia:** All classes of diuretics can lead to low sodium levels, but thiazides are particularly associated with hyponatremia in older patients or those with underlying fluid balance disorders. A 2022 publication highlighted diuretic-induced hyponatremia as a persistent challenge in clinical management⁴⁸. **Hyperkalemia:** Potassium-sparing diuretics, such as spironolactone, amiloride, and eplerenone, may cause hyperkalemia, especially in patients with chronic kidney disease, those taking ACEIs/ARBs, or those using potassium supplements. A 2024 review provided updated insights into this risk⁴⁹. **Dehydration and Volume Depletion:** Excessive

diuresis can lead to dehydration, which may present as dizziness, orthostatic hypotension, or even acute kidney injury (AKI). This is particularly relevant in patients with heart failure or liver cirrhosis. A 2023 review discussed the delicate balance between achieving fluid removal and avoiding volume depletion⁵⁰. **Ototoxicity:** Loop diuretics, especially when given rapidly intravenously or in high doses, can cause ototoxicity— manifesting as tinnitus, hearing loss (usually reversible), and in rare cases, permanent deafness. The risk is higher in patients with pre-existing renal impairment or those receiving other ototoxic medications⁵¹.

2.2 Antiarrhythmic Drugs

Antiarrhythmic drugs are used to manage cardiac arrhythmias by modifying the heart's electrical properties. However, they have narrow therapeutic windows and can sometimes worsen existing arrhythmias or trigger new ones, making their adverse effect profiles particularly important.

2.2.1 Amiodarone

Amiodarone, a Class III antiarrhythmic, is highly effective and has a broad range of actions. However, its long-term use is limited by multiple systemic adverse effects. This is due to its lipophilic nature, wide tissue distribution, and exceptionally long half-life, which can last for several months⁵². **Pulmonary Fibrosis (Amiodarone-Induced Pulmonary Toxicity – AIPT):** Pulmonary toxicity is one of the most serious and potentially fatal complications of amiodarone, occurring in about 2–18% of patients. The risk increases with cumulative dose and prolonged therapy⁵³. Recent reports continue to stress the diagnostic difficulties, with one 2021 case study describing delayed recognition during the COVID-19 pandemic⁵⁴. **Thyroid Dysfunction:** Amiodarone can cause both hypothyroidism (more common, occurring in 6–25% of patients) and hyperthyroidism (less common, 2–10%), due to its high iodine content and direct effects on thyroid hormone metabolism. A 2022 review highlighted the complexity of diagnosing and managing amiodarone-induced thyroid dysfunction⁵⁵. **Hepatotoxicity:** Liver toxicity can range from mild, transient elevations in liver enzymes (seen in up to 40% of patients) to severe acute hepatitis, cholestasis, or—rarely—chronic liver disease and cirrhosis⁵⁶. This effect is typically dose-dependent. A pharmacovigilance study from early 2025 noted that hepatic adverse events were more frequent with intravenous administration of amiodarone. **Corneal Deposits:** Long-term amiodarone use almost universally leads to corneal microdeposits (yellow-brown spots in the corneal epithelium, known as vortex keratopathy or corneal verticillata)⁵⁷. These changes are usually asymptomatic but may cause visual disturbances like halos, glare, or blurred vision. They are generally reversible after stopping the drug. A case report from April 2025 discussed amiodarone-associated keratopathy.

2.2.2 Beta-Blockers (as antiarrhythmics)

Beta-blockers are widely used as antiarrhythmic agents, particularly for rate control in atrial fibrillation, preventing recurrent supraventricular tachycardias, and

reducing the risk of sudden cardiac death in patients who have had a myocardial infarction or have heart failure. The adverse drug reactions seen with beta-blockers in the antiarrhythmic setting are largely the same as when they are used for hypertension, since they share the same mechanisms of action. Bradycardia: Slowing the heart rate is an expected effect of beta-blockers, but excessive bradycardia or even complete heart block can occur especially in patients with existing conduction abnormalities or when combined with other AV nodal blocking drugs such as non-dihydropyridine CCBs or digoxin⁵⁸. This effect requires closer monitoring when beta-blockers are used for arrhythmia management. Fatigue: As with their use in hypertension, fatigue and reduced exercise tolerance are common complaints during beta-blocker therapy. Bronchospasm: Non-selective beta-blockers can induce bronchospasm in susceptible individuals, such as those with asthma or chronic obstructive pulmonary disease. Masked Hypoglycemia: In diabetic patients, beta-blockers can mask adrenergic warning signs of hypoglycemia—like tremors, palpitations, and tachycardia—making it harder to recognize low blood sugar levels. Other side effects: Additional side effects include cold extremities, dizziness, and sleep disturbances such as insomnia.

2.2.3 Digoxin

Digoxin, a cardiac glycoside, enhances myocardial contractility (positive inotropic effect) while slowing the heart rate and atrioventricular (AV) nodal conduction (negative chronotropic and dromotropic effects). Its narrow therapeutic window makes toxicity a major concern, especially when aggravated by hypokalemia or renal impairment. Arrhythmias: Digoxin toxicity can lead to a wide range of cardiac arrhythmias due to its complex effects on cardiac electrophysiology. These include premature ventricular contractions (PVCs), non-paroxysmal junctional tachycardia, varying degrees of AV block (even complete heart block), and ventricular tachyarrhythmias such as bidirectional ventricular tachycardia^{59,60}. A 2023 review highlighted the broad spectrum of arrhythmic manifestations seen in digoxin toxicity. Nausea and Vomiting: Gastrointestinal symptoms such as nausea, vomiting, and loss of appetite are often the earliest warning signs of toxicity. Visual Disturbances: Classic visual symptoms of digoxin toxicity include blurred vision, yellow-green halos around lights (xanthopsia), scotomas, and altered color perception⁵⁹.

2.3 Lipid-Lowering Agents

Lipid-lowering drugs are essential for managing dyslipidemia and reducing the risk of atherosclerotic cardiovascular disease. They primarily work by lowering low-density lipoprotein cholesterol (LDL-C) levels.

2.3.1 Statins

Statins, or HMG-CoA reductase inhibitors, are the most widely prescribed and effective drugs for lowering LDL cholesterol. Despite their benefits, they are associated with several important adverse effects: Myopathy: Muscle-related side effects are the most frequently reported ADRs. They range from mild myalgia (muscle pain without elevated creatine kinase [CK]) to myositis

(muscle inflammation with CK elevation) and, in rare cases, rhabdomyolysis—a severe form of muscle breakdown that can cause myoglobinuria and acute renal failure^{61,62,63}. Myalgia has been reported in up to 10–29% of patients in observational studies, while rhabdomyolysis is rare, with an estimated incidence of 1.6 cases per 100,000 patient-years. A 2022 review discussed the challenges in diagnosing and managing statin-associated muscle symptoms. Hepatotoxicity: Mild, asymptomatic elevations in liver enzymes (AST/ALT) occur in about 1–3% of patients, usually within the first few months of therapy. However, clinically significant liver injury or severe drug-induced liver injury (DILI) is extremely rare—less than 1 in 100,000 users⁶⁴. New-Onset Diabetes: Statins have been linked to a small but statistically significant increase in the risk of new-onset type 2 diabetes, particularly in patients who already have risk factors for diabetes. A 2022 meta-analysis confirmed this association but emphasized that the absolute risk increase remains modest compared to the cardiovascular benefits⁶⁵.

2.3.2 PCSK9 Inhibitors

PCSK9 inhibitors, such as evolocumab and alirocumab, are monoclonal antibodies that block proprotein convertase subtilisin/kexin type 9 (PCSK9). By preventing PCSK9 from degrading LDL receptors on hepatocytes, they increase receptor availability, leading to a substantial reduction in LDL cholesterol levels. Injection Site Reactions: Since PCSK9 inhibitors are administered subcutaneously (usually every 2–4 weeks), mild local reactions such as pain, redness, swelling, or bruising are the most frequently reported adverse effects^{66,67}. These reactions are generally mild, short-lived, and rarely lead to treatment discontinuation. A March 2025 review confirmed that injection-site reactions remain the most common side effect. Flu-like Symptoms: Some patients report mild, non-specific symptoms resembling the common cold or flu, including nasopharyngitis, upper respiratory tract infections, headaches, and joint pain⁶⁸. These symptoms are typically self-limiting and do not require stopping the medication.

2.4 Antithrombotic Agents (Anticoagulants and Antiplatelets)

Antithrombotic agents prevent the formation or progression of blood clots. Because they interfere with normal hemostasis, bleeding is the most important and common adverse effect across this entire class.

2.4.1 Oral Anticoagulants (Warfarin, DOACs)

Oral anticoagulants include Vitamin K antagonists (VKAs) such as warfarin and Direct Oral Anticoagulants (DOACs), which act as either direct thrombin inhibitors (e.g., dabigatran) or Factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban). Bleeding (Major and Minor): Bleeding is the most significant ADR and directly reflects the intended anticoagulant mechanism^{69,70}. It can range from minor bleeding such as nosebleeds and bruising to serious, life-threatening events like gastrointestinal hemorrhage or intracranial bleeding (69). Large-scale studies and meta-analyses from 2021–

2023 have consistently shown that DOACs generally have a lower risk of intracranial hemorrhage compared to warfarin, but may carry a similar or slightly higher risk of gastrointestinal bleeding⁷¹.

Specific Drug Interactions:

Warfarin: Warfarin has numerous interactions with drugs and foods that can affect its metabolism and vitamin K levels, leading to unpredictable anticoagulant effects. This variability increases the risk of either bleeding or thrombosis⁷². **DOACs:** DOACs have fewer interactions than warfarin but are still affected by potent inhibitors or inducers of P-glycoprotein and CYP3A4 enzymes (e.g., amiodarone, ketoconazole, rifampin)^{73,74}. These interactions can alter DOAC plasma levels, increasing bleeding risk or reducing efficacy.

2.4.2 Antiplatelet Agents (Aspirin, Clopidogrel)

Antiplatelet drugs inhibit platelet aggregation, reducing clot formation.

Bleeding: As with anticoagulants, bleeding is the main adverse effect of antiplatelet therapy, although it is generally less severe than with oral anticoagulants⁷⁵. Common sites include the gastrointestinal tract, skin (bruising), and nose (epistaxis). The risk increases with dual antiplatelet therapy (DAPT) or when combined with anticoagulants. A 2023 systematic review quantified bleeding risks with various antiplatelet regimens⁷⁶. A 2024 report found that about 1 in 100 people on aspirin alone and 2 in 100 on DAPT experience a major bleeding event requiring hospitalization, while minor bleeding is much more common. **Gastrointestinal Upset:** Aspirin is particularly associated with gastrointestinal symptoms, including dyspepsia, nausea, and abdominal pain. It also carries a dose dependent risk of peptic ulcers, erosions, and upper gastrointestinal bleeding⁷⁷. A 2023 review highlighted the mechanisms and clinical management of aspirin-related gastrointestinal injury⁷⁸. Furthermore, a StatPearls article (August 2024) reported that combining aspirin with P2Y12 inhibitors like clopidogrel increases the risk of upper GI bleeding by 2- to 3-fold.

2.5 Other Important Cardiovascular Drugs

Sacubitril/Valsartan (ARNI)

Sacubitril/valsartan is an angiotensin receptor-neprilysin inhibitor (ARNI) approved for the treatment of heart failure with reduced ejection fraction (HFrEF) and, more recently, heart failure with preserved ejection fraction (HFpEF). **Hypotension:** Due to its potent vasodilatory properties, hypotension is a common side effect, particularly when initiating therapy or up-titrating the dose. Symptoms such as dizziness, lightheadedness, or syncope may occur⁷⁹. **Hyperkalemia:** Similar to ACEIs and ARBs, hyperkalemia can occur because of the valsartan component. The risk is higher in patients with renal impairment, diabetes, or those on potassium-sparing diuretics. Real-world data from 2022 confirmed hyperkalemia remains a notable concern⁸⁰. **Renal Impairment:** A reversible rise in serum creatinine and a temporary decline in estimated glomerular filtration rate (eGFR) can be seen, mirroring the effects observed with ACEIs/ARBs. **Angioedema:** While valsartan (an ARB)

carries a lower angioedema risk than ACEIs, sacubitril inhibits neprilysin, leading to bradykinin accumulation, which increases the likelihood of angioedema. Therefore, ARNIs are contraindicated with concurrent ACEI use and should not be given within 36 hours of the last ACEI dose to minimize this risk. A 2023 review specifically addressed the angioedema risk associated with ARNIs⁸¹. **Newer Drugs for Heart Failure (SGLT2 Inhibitors)** Sodium-glucose co-transporter 2 (SGLT2) inhibitors such as dapagliflozin, empagliflozin, and canagliflozin were initially developed for type 2 diabetes but have shown profound cardiovascular and renal benefits in both HFrEF and HFpEF, regardless of diabetes status^{82,83}. Their use in heart failure has expanded significantly in the last five years. **Genitourinary Infections:** There is an increased risk of genital mycotic infections (e.g., vulvovaginal candidiasis, balanitis), affecting about 2–8% of patients, while the association with urinary tract infections (UTIs) is less consistent and often mild and self-limiting. A March 2025 review discussed the genitourinary safety profile of SGLT2 inhibitors in detail⁸⁴. **Volume Depletion:** Because of their osmotic diuretic and natriuretic effects, SGLT2 inhibitors can cause intravascular volume depletion, potentially leading to symptomatic hypotension, dizziness, or orthostatic hypotension. This risk is higher in elderly or frail patients and in those taking other diuretics⁸⁵. A 2023 review emphasized the need for careful fluid status monitoring. **Diabetic Ketoacidosis (DKA):** Although rare, SGLT2 inhibitors can trigger diabetic ketoacidosis, especially in type 1 diabetes (where they are generally contraindicated) or in type 2 diabetic patients under stress, illness, or reduced insulin states. Importantly, they can cause “euglycemic DKA,” where DKA develops despite near-normal blood glucose levels, making it harder to detect⁸⁶. A May 2025 study reported that among over 100,000 adults with type 2 diabetes starting SGLT2 inhibitors between 2013– 2017, about 0.2% developed DKA within 180 days.

This chapter highlights the importance of maintaining an up-to-date understanding of ADRs for both well-established and emerging cardiovascular drug classes. While these therapies have significantly transformed the management of cardiovascular diseases, careful patient selection, routine monitoring, and patient education are essential to minimize risks and maximize therapeutic benefits.

3. Conclusion and Recommendations

This narrative review summarized the key adverse drug reactions of major cardiovascular medications, emphasizing the most recent evidence reported in the last five years. Despite their critical role in improving outcomes and survival, these drugs require thorough knowledge of their ADR profiles to ensure safe and effective use in clinical practice.

3.1 Summary of Key Findings

A review of adverse drug reactions (ADRs) reported over the last five years reveals several common thread and important safety concerns across cardiovascular pharmacotherapy. **Bleeding:** Bleeding remains the most

significant and frequently reported ADR, especially with antithrombotic agents such as oral anticoagulants and antiplatelets. Recent studies have highlighted the ongoing challenge of balancing the reduction in thrombotic risk with the potential for bleeding complications. Comparisons between newer and older agents continue to show differences in bleeding profiles, particularly between warfarin and direct oral anticoagulants (DOACs)^{70,71,76}. **Electrolyte Imbalances:** Disruptions in potassium levels (both hyperkalemia and hypokalemia) and sodium levels (hyponatremia) are common ADRs, most often linked to diuretics and renin-angiotensin system inhibitors. These disturbances can have serious clinical implications, and recent reviews emphasize the importance of vigilant monitoring in high-risk populations^{46,47,49}. **Organ-Specific Toxicities:** Several cardiovascular drugs can cause damage to specific organs. Examples include pulmonary fibrosis with amiodarone, hepatotoxicity with both amiodarone and statins, thyroid dysfunction from amiodarone, and renal impairment associated with RAS inhibitors, ARNIs, and SGLT2 inhibitors^{39,53,55,56,64,79}. **Hemodynamic Alterations:** Adverse effects on blood pressure and heart rate such as hypotension and bradycardia are frequently observed with antihypertensives and antiarrhythmic drugs. These can cause symptoms like dizziness, fatigue impacting patient quality of life and adherence^{40,44,79}. **Metabolic and Endocrine Effects:** New-onset diabetes has been reported with statin therapy⁶⁵. Beta-blockers can also mask hypoglycemia symptoms in diabetic patients, complicating recognition of low blood sugar⁴⁶. Additionally, while SGLT2 inhibitors have major benefits in heart failure, they carry a rare but serious risk of diabetic ketoacidosis (DKA), including euglycemic forms that are harder to detect⁸⁶. **Hypersensitivity Reactions:** Angioedema remains a serious and potentially life-threatening ADR with ACE inhibitors and ARNIs. Prompt recognition and drug discontinuation are crucial to prevent severe outcomes^{33,81}.

Infections: SGLT2 inhibitors are uniquely associated with an increased risk of genitourinary infections, particularly genital mycotic infections⁸⁴. **Muscle -Related Symptoms:** Muscle pain, weakness, and cramps are commonly reported by patients taking statins. While these are often mild, rare but severe cases of rhabdomyolysis can occur and require immediate intervention⁶².

Key Challenges in Managing ADRs:

1. **Balancing Efficacy with Safety:** Clinicians face a constant challenge in achieving therapeutic goals while minimizing adverse effects, especially for drugs with narrow therapeutic windows.
2. **Variability in Patient Response:** Genetics, comorbidities, age, and concurrent medications all affect how patients respond, making individualized risk assessment essential but complex.
3. **Polypharmacy and Drug-Drug Interactions:** Patients with cardiovascular conditions often take multiple medications, raising the risk of significant drug interactions that can either amplify ADRs or reduce drug efficacy.

4. **Early Detection of Rare or Delayed ADRs:** Some ADRs are uncommon or have a delayed onset, making timely recognition difficult during routine care

3.2 Implications for Clinical Practice

The findings of this review carry several critical implications for daily cardiovascular care:

Thorough Patient History and Medication Reconciliation: Before starting any cardiovascular drug, it is essential to obtain a detailed history of comorbidities (e.g., renal or liver disease, diabetes, asthma/COPD, history of angioedema), previous ADRs, and all current medications including over-the counter and herbal supplements. This helps identify potential contraindications, drug-drug interactions, and patient-specific ADR risks, leading to safer prescribing decisions. **Individualized Therapy and Dose Adjustments:** Cardiovascular drug therapy should always be personalized. Clinicians must select the most appropriate drug and dose based on each patient's risk factors, comorbidities, and disease severity. For instance, a patient with ACE inhibitor-induced cough might benefit from switching to an ARB, while a cardio-selective beta-blocker is preferable for someone with mild asthma. Close monitoring of parameters such as blood pressure, heart rate, electrolytes, renal function, and liver enzymes is vital during initiation and dose titration. Prompt dose adjustments or even switching drugs may be necessary if ADRs arise. **Enhanced Patient Education:** Educating patients about their medications and potential ADRs is key to safe and effective therapy.

This education should explain:

What symptoms to watch for

When these symptoms might appear (early vs. delayed)

Which symptoms are mild and manageable vs. those needing immediate attention

Why adherence is important, even if mild side effects occur

When and how to report new or concerning symptoms

Proper patient education improves adherence, sets realistic expectations, and ensures prompt reporting of serious ADRs.

3.3 Recommendations for Future Pharmacovigilance Efforts

To improve patient safety and optimize cardiovascular therapy, future pharmacovigilance should focus on:

1. **Strengthening Reporting Systems:** National and international ADR reporting systems must be easy to use, well-integrated with electronic health records, and actively promoted. Encouraging both healthcare providers and patients to report suspected ADRs regardless of severity it can improve safety data collection and analysis.
2. **Promoting Pharmacovigilance Education:** Comprehensive pharmacovigilance training should be integrated into medical, nursing, and pharmacy curricula, as well as ongoing professional

development. Beyond reporting mechanisms, education should emphasize ADR causality assessment, risk minimization strategies, and proactive harm prevention.

3. Investing in Advanced Analytical Tools: With the growing availability of big healthcare data, advanced technologies such as artificial intelligence (AI), machine learning, and big data analytics can help detect rare ADR patterns. These tools can identify at-risk subgroups, uncover complex drug interactions, and provide early safety signals beyond traditional spontaneous reporting systems.
4. Fostering International Collaboration: ADRs are a global concern. Greater collaboration between regulatory authorities, pharmaceutical companies, academic institutions, and healthcare providers is needed. Harmonizing ADR reporting standards and sharing de-identified safety data worldwide can accelerate the understanding of ADR mechanisms, risk factors, and prevention strategies, especially for newer drugs. The major challenges identified in managing these ADRs include: Balancing Efficacy with Safety: Clinicians constantly navigate the fine line between achieving therapeutic goals and minimizing adverse effects, especially with drugs having narrow therapeutic windows. Variability in Patient Response: Individual patient factors, including genetics, comorbidities, age, and concomitant medications, significantly influence susceptibility to ADRs, making personalized risk assessment complex. Polypharmacy and Drug-Drug Interactions: Patients with cardiovascular diseases often take multiple medications, increasing the complex drug-drug interactions that can exacerbate ADRs or reduce drug efficacy. Early Detection of Rare or Delayed ADRs: Some severe ADRs are rare or have a delayed onset, making their timely identification challenging in routine clinical practice.

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