DRUG-INDUCED LIVER INJURY IN CARDIOVASCULAR PHARMACOTHERAPY: CLINICAL IMPLICATIONS AND MANAGEMENT

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Abstract

Drug-induced liver injury (DILI) is an important and often underrecognized complication of cardiovascular pharmacotherapy. Although most cardiovascular drugs are considered safe, several commonly used agents, including statins, antiarrhythmics, and anticoagulants, may affect liver function.

This narrative review examines the mechanisms, clinical presentation, and management of DILI in cardiovascular patients. Special attention is given to the safety profiles of widely used drugs and the balance between therapeutic benefit and hepatic risk.

DILI is typically rare but may lead to treatment interruption, diagnostic uncertainty, and adverse outcomes if not recognized early. Understanding drug-specific patterns and risk factors is essential for safe and effective therapy.

Keywords: *drug-induced liver injury, cardiovascular drugs, statins, amiodarone, hepatotoxicity, anticoagulants*

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METHODS

Aim

To evaluate the impact of cardiovascular pharmacotherapy on liver function and provide a clinical framework for diagnosis and management of DILI.

Design

Narrative literature review.

Data sources

PubMed, Scopus, Web of Science

Timeframe

2010–2025

Search terms

“drug-induced liver injury”, “cardiovascular drugs”, “statins”, “amiodarone”, “hepatotoxicity”, “anticoagulants”

Inclusion criteria

- clinical trials;
- observational studies;
- meta-analyses;
- guideline documents.

Scope

Included: **9 key sources**

1. Introduction

Drug-induced liver injury (DILI) is a major cause of abnormal liver function tests and represents one of the most common reasons for drug discontinuation in clinical practice. Although severe hepatotoxicity is rare, even mild elevations in liver enzymes may create diagnostic uncertainty and influence therapeutic decisions [1]. In cardiovascular medicine, long-term pharmacotherapy is essential for reducing morbidity and mortality. Drugs such as statins, antiarrhythmics, anticoagulants, and antihypertensive agents are widely used, often in combination. This increases the potential for hepatic adverse effects and drug–drug interactions. The liver plays a central role in drug metabolism,

making it particularly vulnerable to toxic effects. Mechanisms of injury include direct hepatocellular toxicity, immune-mediated reactions, and metabolic disturbances. An important clinical challenge is distinguishing true drug-induced liver injury from other causes of liver dysfunction, such as metabolic liver disease, alcohol use, or ischemic injury. This is particularly relevant in cardiovascular patients, who often have multiple comorbidities.

Despite these concerns, most cardiovascular drugs are safe when used appropriately. Understanding their hepatic effects is essential to avoid unnecessary discontinuation of beneficial therapy.

The aim of this review is to provide a practical overview of DILI in cardiovascular pharmacotherapy, focusing on mechanisms, clinical presentation, and management strategies.

2. Mechanisms of Drug-Induced Liver Injury

Drug-induced liver injury (DILI) results from a variety of mechanisms that can broadly be classified into intrinsic (dose-dependent) and idiosyncratic (unpredictable) reactions. Understanding these mechanisms is essential for interpreting liver enzyme abnormalities and assessing causality in clinical practice. Intrinsic hepatotoxicity is typically dose-dependent and predictable. It occurs when a drug or its metabolites directly damage hepatocytes. This type of injury is relatively rare in cardiovascular pharmacotherapy but may occur with certain agents when exposure is prolonged or doses are high.

In contrast, idiosyncratic reactions are more common and clinically relevant. These are not dose-dependent and occur unpredictably in susceptible individuals. They may be mediated by immune mechanisms or by the formation of reactive metabolites that trigger hepatocellular injury. Genetic predisposition and environmental factors likely play a role in these reactions [2].

A key mechanism involves hepatic metabolism via the cytochrome P450 enzyme system. Many cardiovascular drugs, including statins and antiarrhythmics, are metabolized through these pathways. The formation of reactive intermediates during metabolism can lead to oxidative stress, mitochondrial dysfunction, and cell injury. Mitochondrial toxicity is another important mechanism. Impaired mitochondrial function reduces production of **adenosine triphosphate (ATP)**, the main cellular energy source, leading to hepatocyte dysfunction and, in severe cases, cell death. This mechanism has been described with drugs such as amiodarone.

Cholestatic injury represents another pattern of DILI. It occurs when bile formation or flow is impaired, leading to accumulation of bile acids and hepatocellular damage. Some cardiovascular drugs may interfere with bile transport mechanisms, resulting in a predominantly cholestatic or mixed pattern of liver injury. Inflammation and immune-mediated mechanisms also contribute to DILI. Drug-protein complexes may act as neoantigens, triggering an immune response that leads to hepatocyte injury. This mechanism is typically associated with delayed onset and may be accompanied by systemic features such as rash or eosinophilia.

Oxidative stress is a common final pathway in many forms of DILI. Increased production of reactive oxygen species leads to lipid peroxidation, protein damage, and cellular dysfunction.

Importantly, these mechanisms often overlap, and a single drug may cause liver injury through multiple pathways. This complexity contributes to the variability in clinical presentation and makes diagnosis challenging.

In summary, drug-induced liver injury in cardiovascular pharmacotherapy involves multiple mechanisms, including direct toxicity, metabolic activation, mitochondrial dysfunction, and immune-mediated reactions. Understanding these processes is essential for accurate diagnosis and safe clinical management.

3. Clinical Presentation and Patterns of Liver Injury

Drug-induced liver injury presents with a wide spectrum of clinical manifestations, ranging from asymptomatic elevations of liver enzymes to severe liver failure. In cardiovascular patients, the majority of cases are mild and detected incidentally during routine laboratory monitoring. Clinically,

DILI is classified into three main patterns based on biochemical abnormalities: hepatocellular, cholestatic, and mixed injury. This classification is important because it provides insight into the underlying mechanism and helps guide diagnostic evaluation.

The hepatocellular pattern is characterized by predominant elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). This pattern reflects direct injury to hepatocytes and is most commonly associated with drugs such as statins. In most cases, these elevations are mild and transient, but significant increases may indicate true hepatotoxicity [3]. The cholestatic pattern is defined by elevation of alkaline phosphatase (ALP) and bilirubin, reflecting impaired bile flow. Patients may present with jaundice, pruritus, and fatigue. This type of injury tends to have a more prolonged course but is often less severe in terms of hepatocellular damage.

The mixed pattern includes features of both hepatocellular and cholestatic injury. It is not uncommon in clinical practice and may complicate interpretation of laboratory findings.

A useful tool for classification is the R ratio, calculated as:

- (ALT / upper limit of normal) ÷ (ALP / upper limit of normal)

An R ratio >5 suggests hepatocellular injury, <2 indicates cholestatic injury, and values between 2 and 5 correspond to a mixed pattern [2]. In many cardiovascular patients, DILI is asymptomatic and identified only through routine testing. However, symptomatic cases may present with fatigue, nausea, anorexia, or right upper quadrant discomfort. Severe cases can lead to jaundice, coagulopathy, and, rarely, acute liver failure. Timing is another important diagnostic clue. Idiosyncratic DILI typically develops within weeks to months after drug initiation, although delayed presentations may occur. Re-exposure to the offending drug may lead to more rapid and severe recurrence.

A major clinical challenge is distinguishing DILI from other causes of liver dysfunction. Cardiovascular patients often have comorbid conditions such as metabolic-associated steatotic liver disease (MASLD), alcohol use, or ischemic hepatitis, which can mimic drug-induced injury.

In summary, DILI presents with variable clinical and biochemical patterns. Recognition of these patterns, along with careful assessment of timing and risk factors, is essential for accurate diagnosis and management.

4. Statins and Liver Safety: Myths and Evidence

Statins are among the most widely prescribed cardiovascular drugs and have a well-established role in reducing cardiovascular morbidity and mortality. Despite their proven benefits, concerns about hepatotoxicity have historically limited their use, particularly in patients with pre-existing liver disease.

Mild elevations in liver enzymes, particularly alanine aminotransferase (ALT), are relatively common during statin therapy. These increases are usually asymptomatic, transient, and not associated with true hepatocellular injury. In most cases, they resolve spontaneously without the need for drug discontinuation [4]. Clinically significant drug-induced liver injury due to statins is rare. Large observational studies and meta-analyses have shown that the incidence of serious hepatotoxicity is extremely low and comparable to placebo in many cases. This supports the overall hepatic safety profile of statins. One of the major misconceptions is that statins are contraindicated in patients with chronic liver disease. Current evidence suggests that statins can be safely used in patients with stable liver conditions, including metabolic-associated steatotic liver disease (MASLD). In fact, statins may provide additional benefit in these patients by reducing cardiovascular risk and potentially improving liver-related outcomes.

Mechanistically, statins are metabolized in the liver, primarily via the cytochrome P450 system. This raises the potential for drug–drug interactions, particularly in patients receiving multiple medications. However, these interactions are more likely to affect drug levels than to directly cause hepatotoxicity.

Monitoring of liver function during statin therapy remains a common practice, although routine frequent testing is not universally required. Current recommendations suggest baseline assessment

and follow-up testing only when clinically indicated, such as in the presence of symptoms or significant enzyme elevations.

An important clinical principle is that mild elevations in transaminases (less than three times the upper limit of normal) should not automatically lead to discontinuation of statin therapy. The cardiovascular benefits of statins generally outweigh the potential hepatic risks.

In rare cases where significant liver injury is suspected, temporary discontinuation and evaluation for alternative causes are appropriate. Re-challenge with the same or a different statin may be considered once liver function normalizes.

In summary, statins have a favorable hepatic safety profile, and concerns about liver toxicity are often overstated. Appropriate use and monitoring allow patients to benefit from their cardiovascular protective effects without unnecessary interruption of therapy.

5. Antiarrhythmic Drugs and Hepatotoxicity

Antiarrhythmic drugs, particularly amiodarone, are among the cardiovascular agents most commonly associated with liver toxicity. Unlike statins, where hepatotoxicity is rare and usually mild, certain antiarrhythmics can cause clinically significant and sometimes progressive liver injury.

Amiodarone is a highly lipophilic drug with a long half-life and extensive tissue accumulation, including in the liver. It is associated with a wide spectrum of hepatic effects, ranging from asymptomatic elevation of liver enzymes to chronic liver disease and, in rare cases, cirrhosis [5]. The mechanism of amiodarone-induced liver injury is multifactorial. It includes mitochondrial dysfunction, oxidative stress, and phospholipid accumulation within hepatocytes. Histologically, this may resemble alcoholic steatohepatitis, even in patients without alcohol use. Liver enzyme elevations occur in a significant proportion of patients receiving long-term amiodarone therapy. These are usually mild, but persistent elevation may indicate ongoing hepatocellular injury. Clinically significant toxicity is more likely with higher cumulative doses and prolonged treatment duration.

Other antiarrhythmic drugs have a lower hepatotoxic potential but are not entirely risk-free. For example, dronedarone has been associated with rare cases of severe liver injury, including acute liver failure. Although such events are uncommon, they highlight the need for vigilance when prescribing these agents. From a clinical perspective, baseline liver function testing is recommended before initiating antiarrhythmic therapy, particularly with amiodarone. Periodic monitoring during treatment is also advised, especially in long-term use.

An important management principle is early recognition of abnormal liver function. Persistent elevation of transaminases, particularly above three times the upper limit of normal, should prompt reassessment of therapy. Dose reduction or discontinuation may be necessary depending on the severity and clinical context.

Differential diagnosis is essential, as patients on antiarrhythmic therapy often have comorbid conditions that may also affect liver function. Careful evaluation helps avoid unnecessary discontinuation of effective treatment.

In summary, antiarrhythmic drugs, especially amiodarone, carry a higher risk of hepatotoxicity compared to most other cardiovascular agents. Appropriate monitoring and early recognition of liver injury are key to minimizing risk and ensuring safe use.

6. Anticoagulants and Liver Injury

Anticoagulant therapy is a cornerstone of cardiovascular management, particularly in atrial fibrillation, venous thromboembolism, and acute coronary syndromes. Although generally considered safe, certain anticoagulants have been associated with liver injury, raising important clinical considerations.

Vitamin K antagonists, such as warfarin, have a long history of use and are rarely associated with hepatotoxicity. When liver injury occurs, it is typically mild and reversible after drug discontinuation. Clinically significant cases are uncommon.

Direct oral anticoagulants (DOACs) have largely replaced warfarin in many clinical settings due to their favorable safety profile and ease of use. However, concerns about hepatotoxicity emerged early with some agents. For example, ximelagatran, an early direct thrombin inhibitor, was withdrawn from the market due to significant liver toxicity. Currently used DOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, have demonstrated a low incidence of liver injury in clinical trials and real-world studies. Nevertheless, rare cases of hepatocellular and cholestatic injury have been reported, suggesting that hepatotoxicity, although uncommon, remains possible [6].

The mechanisms of anticoagulant-induced liver injury are not fully understood. They are likely idiosyncratic and may involve immune-mediated reactions or metabolic pathways leading to hepatocyte damage. In clinical practice, routine monitoring of liver function is not required for all patients receiving DOACs. However, baseline assessment is recommended, particularly in patients with known liver disease or risk factors for hepatic dysfunction. An important consideration is the presence of underlying liver disease. Many cardiovascular patients have metabolic-associated steatotic liver disease (MASLD), which may influence drug metabolism and increase susceptibility to adverse effects. Careful selection and dose adjustment of anticoagulants are necessary in these patients.

In cases of suspected liver injury, discontinuation of the offending agent and evaluation for alternative causes are essential. Switching to another anticoagulant may be considered once liver function normalizes.

Overall, modern anticoagulants have a favorable hepatic safety profile, but clinicians should remain aware of the potential for rare hepatotoxic effects, particularly in high-risk patients.

In summary, anticoagulant-associated liver injury is uncommon but clinically relevant. Appropriate patient selection, baseline assessment, and clinical vigilance are key to safe and effective therapy.

7. Risk Factors and Drug-Drug Interactions

The development of drug-induced liver injury (DILI) in cardiovascular patients is influenced by multiple factors, including patient characteristics, comorbidities, and pharmacological interactions. Understanding these risk factors is essential for prevention and early recognition.

One of the most important patient-related factors is pre-existing liver disease. Conditions such as metabolic-associated steatotic liver disease (MASLD), alcohol-related liver disease, and chronic viral hepatitis may increase susceptibility to hepatotoxic effects. In cardiovascular populations, MASLD is particularly relevant due to its strong association with obesity, diabetes, and dyslipidemia.

Age is another important determinant. Older patients often have reduced hepatic reserve and altered drug metabolism, which may increase the risk of adverse effects. In addition, polypharmacy is more common in this population, further increasing the risk of drug interactions.

Polypharmacy itself is a major contributor to DILI. Cardiovascular patients frequently receive multiple medications, including statins, anticoagulants, antiarrhythmics, antihypertensives, and antidiabetic drugs. The combined use of these agents increases the likelihood of pharmacokinetic and pharmacodynamic interactions.

Many cardiovascular drugs are metabolized through the cytochrome P450 system, particularly the CYP3A4 pathway. Concomitant use of inhibitors or inducers of these enzymes may alter drug concentrations, increasing the risk of hepatotoxicity. For example, combining statins with certain antibiotics, antifungals, or antiarrhythmic drugs may lead to elevated drug levels and increased hepatic stress [7].

Drug–drug interactions are particularly important in patients receiving amiodarone, which has complex pharmacokinetics and interacts with multiple medications. These interactions may enhance both hepatic and systemic toxicity.

Genetic factors also play a role in susceptibility to DILI. Variations in drug-metabolizing enzymes and immune response genes may influence individual risk, although routine genetic testing is not currently part of clinical practice.

Lifestyle factors, including alcohol consumption and poor nutrition, may further increase vulnerability to liver injury. These factors are particularly relevant in patients with cardiometabolic disease.

From a clinical perspective, risk assessment should be performed before initiating therapy, especially in patients with multiple comorbidities. Careful selection of drugs, dose adjustment, and awareness of potential interactions can significantly reduce the risk of DILI.

In summary, DILI in cardiovascular pharmacotherapy is influenced by a combination of patient-related and drug-related factors. Polypharmacy and drug–drug interactions are key contributors, highlighting the importance of individualized treatment strategies.

8. Diagnosis and Management of Drug-Induced Liver Injury

The diagnosis of drug-induced liver injury (DILI) is primarily clinical and relies on a combination of laboratory findings, temporal association with drug exposure, and exclusion of alternative causes. There is no single definitive test, making a structured and systematic approach essential.

The first step in diagnosis is recognition of abnormal liver function tests. Elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin should prompt further evaluation. The pattern of enzyme elevation—hepatocellular, cholestatic, or mixed—provides important diagnostic clues and helps guide further assessment [3]. A detailed medication history is critical. This includes not only recently initiated drugs but also long-term therapies, dose changes, and over-the-counter or herbal supplements. The temporal relationship between drug exposure and onset of liver abnormalities is a key element in establishing causality.

Exclusion of other causes is essential. Viral hepatitis, alcohol-related liver disease, metabolic-associated steatotic liver disease (MASLD), autoimmune hepatitis, and ischemic liver injury must be considered, particularly in cardiovascular patients who often have multiple comorbidities.

Causality assessment tools, such as the RUCAM (Roussel Uclaf Causality Assessment Method), may be used to support the diagnosis. Although not perfect, these tools provide a structured framework for evaluating the likelihood of DILI. Management is primarily based on discontinuation of the suspected drug. In most cases, liver function improves after withdrawal, confirming the diagnosis retrospectively. Early recognition and prompt discontinuation are key to preventing progression to more severe injury.

In mild cases, continuation of therapy with close monitoring may be considered, particularly when the cardiovascular benefit is substantial and enzyme elevations are minimal. This approach is commonly applied in patients receiving statins with mild transaminase elevations [8].

In more severe cases, particularly when bilirubin is elevated or symptoms are present, immediate discontinuation is recommended. Supportive care and monitoring of liver function are essential, and referral to a specialist may be required in cases of suspected severe hepatotoxicity.

Re-challenge with the same drug is generally not recommended, especially in cases of significant liver injury. However, switching to an alternative agent within the same class may be considered if clinically necessary.

From a practical perspective, baseline liver function testing before initiation of high-risk drugs is advisable. Follow-up testing should be guided by clinical context rather than routine frequent monitoring in all patients [9].

In summary, the diagnosis and management of DILI require a structured clinical approach, careful evaluation of drug exposure, and timely intervention. Early recognition and appropriate management are essential to minimize complications and ensure safe continuation of cardiovascular therapy.

9. Conclusion

Drug-induced liver injury (DILI) is an important but often underrecognized complication of cardiovascular pharmacotherapy. Although most cardiovascular drugs have a favorable safety profile,

certain agents—particularly antiarrhythmics and, less commonly, anticoagulants and statins—may lead to clinically relevant hepatic effects.

The majority of liver enzyme abnormalities observed in clinical practice are mild and do not require discontinuation of therapy. However, distinguishing benign biochemical changes from true hepatotoxicity remains a key clinical challenge, especially in patients with multiple comorbidities such as metabolic-associated steatotic liver disease (MASLD).

Understanding the mechanisms of DILI, recognizing typical patterns of liver injury, and identifying high-risk patients are essential for safe pharmacotherapy. Particular attention should be given to polypharmacy and drug–drug interactions, which significantly increase the risk of adverse hepatic effects.

From a clinical perspective, management should be individualized. The cardiovascular benefits of therapy must always be balanced against potential hepatic risks. In many cases, careful monitoring rather than discontinuation is appropriate, especially when enzyme elevations are mild.

Future research should focus on improving risk stratification, identifying predictive biomarkers, and developing safer pharmacological strategies. As cardiovascular patients increasingly present with complex comorbidities, including liver disease, an integrated and multidisciplinary approach will become increasingly important.

In conclusion, DILI in cardiovascular pharmacotherapy is uncommon but clinically relevant. Awareness, early recognition, and appropriate management are key to optimizing both cardiovascular and hepatic outcomes.

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