



Symptomatic Bradycardia Associated with Beta-Blocker Therapy: Clinical Recognition, Risk Factors, Management and Pharmacovigilance-A Narrative Review

*Ayesha Batool, Asma Anjum and Fouzia Khan

Department of Pharmacy, Deccan School of Pharmacy, Hyderabad, Telangana, India

*Corresponding author: Dr Ayesha Batool, Doctor of Pharmacy Graduate, Deccan school of Pharmacy, Hyderabad, Telangana 500001. Email: asma.18110@gmail.com

Article Info

Received: 17.08.2026
Accepted: 20.09.2026
Published: 10.10.2026



© 2026 by the authors. The terms and conditions of the Creative Commons Attribution (CC BY) license

ABSTRACT

Beta-adrenergic blockers are widely used in cardiovascular medicine because of their negative chronotropic, negative inotropic, and anti-ischemic effects. Although these agents provide substantial therapeutic benefits in conditions such as acute coronary syndrome, heart failure, hypertension, and cardiac arrhythmias, clinically significant bradycardia remains an important adverse drug reaction. The clinical significance of beta-blocker-associated bradycardia depends on the degree of heart-rate reduction, associated symptoms, hemodynamic status, underlying cardiac disease, concomitant medications, and potentially reversible causes. Metoprolol is a commonly prescribed cardio selective beta-blocker whose effects may be influenced by dose, drug interactions, organ function, and pharmacogenetic variability. This narrative review discusses the pharmacological basis of beta-blocker-associated bradycardia, clinical risk factors, differential diagnosis, medication-related contributors, drug interactions, diagnostic assessment, management principles, dechallenge, pharmacovigilance, and the role of clinical pharmacists. Evidence from pharmacovigilance databases and clinical studies indicates that beta-blocker-associated bradyarrhythmias can result in clinically important outcomes, including treatment discontinuation and, in selected patients, additional cardiac interventions. Current guidelines emphasize assessment of reversible causes and careful consideration of medication-related bradycardia. Pharmacogenetic evidence also indicates that CYP2D6 phenotype may influence metoprolol exposure and heart-rate response. Early recognition, structured medication reconciliation, ECG assessment, monitoring, and individualized treatment modification are therefore essential for safe beta-blocker therapy.

Keywords Beta-blockers, Metoprolol, Bradycardia, Clinical pharmacy, Bradyarrhythmia.

INTRODUCTION

Beta-adrenergic receptor blockers are an important class of cardiovascular medicines used in the management of hypertension, ischemic heart disease, heart failure, tachyarrhythmias, and other cardiovascular conditions [1]. Their therapeutic actions are primarily mediated through inhibition of beta-adrenergic receptor stimulation, resulting in reductions in heart rate, myocardial contractility, and sympathetic activity. The reduction in heart rate is therapeutically desirable in many cardiovascular conditions because it decreases myocardial oxygen demand and may improve myocardial perfusion. In patients with acute coronary syndromes, current guidelines recommend early oral beta-blocker therapy when there are no contraindications [2]. However, the same pharmacological

effects may produce clinically significant bradycardia in susceptible individuals.

Bradycardia may range from an asymptomatic reduction in heart rate to symptomatic sinus bradycardia, sinus pauses, atrioventricular conduction abnormalities, hypotension, dizziness, syncope, and, in severe situations, hemodynamic compromise [1,3]. The occurrence of bradycardia therefore requires clinical interpretation rather than assessment solely on the basis of a numerical heart-rate threshold. The evaluation of a patient with suspected medication-associated bradycardia should include a detailed history, physical examination, ECG assessment, medication reconciliation, and investigation of potentially reversible causes. The ACC/AHA/HRS guideline specifically identifies beta-blockers and other negative

chronotropic medications among drugs that can induce or exacerbate bradycardia and conduction disorders [3]. This narrative review summarizes the clinical and pharmacological aspects of beta-blocker-associated bradycardia, with particular emphasis on metoprolol, risk factors, drug interactions, diagnostic evaluation, management, pharmacovigilance, and the role of clinical pharmacists.

Pharmacological Basis of Beta-Blocker-Associated Bradycardia

Beta-blockers inhibit beta-adrenergic receptor-mediated sympathetic stimulation. In the cardiovascular system, this produces negative chronotropic and negative inotropic effects and may slow atrioventricular nodal conduction [3]. The reduction in sinoatrial-node activity decreases spontaneous pacemaker activity and consequently lowers the resting heart rate. In addition, inhibition of atrioventricular nodal conduction can be clinically relevant in patients with pre-existing conduction disease or in patients receiving other rate-limiting medications. The pharmacological effect is dose-dependent but is also influenced by individual patient characteristics. Age, cardiovascular disease, renal and hepatic function, concomitant medications, autonomic status, and genetic differences in drug metabolism may influence the magnitude of the response. Therefore, a heart-rate reduction following beta-blocker administration is not necessarily an adverse drug reaction. It becomes clinically important when it is associated with symptoms, hypotension, impaired perfusion, conduction abnormalities, or other clinically significant consequences.

Clinical Significance of Bradycardia

Bradycardia should be interpreted in the context of the individual patient rather than by a single numerical value. A patient may tolerate a relatively low heart rate without symptoms, whereas another patient may develop dizziness, weakness, presyncope, syncope, or hypotension with a more modest reduction. The ACC/AHA/HRS guideline emphasizes the importance of correlating symptoms with documented bradycardia and evaluating potentially reversible causes [3]. This approach is particularly important in patients receiving medications with negative chronotropic effects. Clinically important manifestations may include: Dizziness, generalized weakness, Fatigue, Exercise intolerance, Presyncope, Syncope, Hypotension, worsening ischemic symptoms, altered mental status in severe cases, Sinus pauses, Atrioventricular conduction abnormalities. The presence of symptoms or hemodynamic compromise should prompt immediate clinical assessment.

Beta-Blocker-Associated Bradyarrhythmia

Beta-blocker-associated bradyarrhythmia is a recognized adverse effect of therapy. A 2024 analysis of the Japanese Adverse Drug Event Report database evaluated beta-blocker-induced bradyarrhythmias and highlighted bradycardia, atrioventricular block, and hypotension as important adverse events associated with beta-blocker therapy [1]. The authors also noted that bradycardia may result in discontinuation of beta-blocker therapy or, in some cases, pacemaker implantation [1]. These findings emphasize that beta-blocker-associated bradycardia is not merely a pharmacological laboratory finding but can have clinically important consequences. A retrospective study of 596 patients admitted with symptomatic bradyarrhythmia found that beta-blocker use was associated with several bradyarrhythmic presentations, including slow atrial fibrillation, sick sinus syndrome, and sinus bradycardia or

pauses [4]. These observations reinforce the importance of considering beta-blocker therapy when evaluating a patient presenting with symptomatic bradyarrhythmia.

Metoprolol and Bradycardia

Metoprolol is a cardioselective beta-1 adrenergic receptor blocker widely used in cardiovascular medicine. Its therapeutic effects include reduction of heart rate, myocardial contractility, and sympathetic cardiac activity. Because metoprolol is primarily metabolized through CYP2D6, its systemic exposure may be influenced by genetic differences in CYP2D6 activity and by concomitant medications that inhibit the enzyme. The clinical importance of this interaction is illustrated by a published report of severe sinus bradycardia associated with concomitant metoprolol and terbinafine therapy. Terbinafine inhibits CYP2D6 and may reduce metoprolol clearance, resulting in increased metoprolol exposure [5]. This example demonstrates why medication reconciliation should extend beyond cardiovascular medications. Drugs prescribed for unrelated conditions may significantly alter beta-blocker exposure. Several patient- and treatment-related factors may increase the likelihood of clinically important beta-blocker-associated bradycardia. Older adults may be more susceptible to adverse cardiovascular effects because of age-related changes in cardiac conduction, pharmacokinetics, pharmacodynamics, and comorbidity burden. Patients with sinus-node dysfunction or atrioventricular conduction disease may experience worsening bradycardia following administration of negative chronotropic drugs [3]. Acute myocardial ischemia may itself influence cardiac conduction and autonomic activity. Consequently, bradycardia occurring in an acute coronary syndrome patient should not automatically be attributed to beta-blocker therapy. Organ dysfunction may alter drug exposure and increase susceptibility to adverse drug reactions depending on the pharmacokinetic properties of the specific beta-blocker and its metabolites.

Concomitant Rate-Limiting Drugs

Concomitant medications can produce additive negative chronotropic or dromotropic effects. Important examples include: Non-dihydropyridine calcium-channel blockers, Digoxin, Amiodarone, Ivabradine, Certain antiarrhythmic drugs, Other beta-blockers. The ACC/AHA/HRS guideline lists beta-blockers, non-dihydropyridine calcium-channel blockers, digoxin, amiodarone, and several other medications among drugs that may induce or exacerbate bradycardia or conduction disorders [3]. Hypothyroidism, electrolyte abnormalities, hypothermia, hypoxemia, and other systemic disturbances may contribute to bradycardia [3].

Metoprolol and CYP2D6 Inhibitors

Metoprolol is substantially metabolized through CYP2D6. Inhibition of this pathway can increase metoprolol exposure. The metoprolol-terbinafine interaction provides a clinically relevant example. A patient receiving metoprolol developed marked sinus bradycardia after terbinafine therapy, and the interaction was attributed to CYP2D6 inhibition and reduced metoprolol clearance [5].

Other Rate-Limiting Cardiovascular Drugs

The simultaneous use of beta-blockers with other negative chronotropic agents may increase the risk of clinically significant bradycardia. Particular caution is warranted when

beta-blockers are combined with: Verapamil, Diltiazem, Digoxin, Amiodarone, Ivabradine, Other beta-blockers. The possibility of additive effects should be considered whenever bradycardia develops following medication changes [3].

Differential Diagnosis of Bradycardia

When a patient receiving beta-blocker therapy develops bradycardia, clinicians should consider alternative causes before concluding that the medication is solely responsible. Important differential diagnoses include: Excessive beta-adrenergic blockade, Acute myocardial ischemia or infarction, Sinus-node dysfunction, Atrioventricular conduction disease, Electrolyte abnormalities, Hypothyroidism, Hypothermia, Hypoxemia, Drug-drug interactions, Increased drug exposure, Autonomic disturbances, Other negative chronotropic medications. The ACC/AHA/HRS guideline specifically recommends consideration of reversible causes, including medication-related causes, when evaluating bradycardia [3].

Symptomatic Bradycardia

When bradycardia is accompanied by dizziness, syncope, hypotension, weakness, or other clinically important manifestations, prompt assessment is required. If a nonessential medication is responsible, withdrawal or dose reduction may improve heart rate and symptoms [3].

Hemodynamic Instability

Patients with severe bradycardia and hemodynamic compromise require urgent cardiovascular management. In beta-blocker toxicity or overdose, supportive treatment is directed toward restoring hemodynamic stability. The ACC/AHA/HRS guideline identifies glucagon and high-dose insulin therapy as reasonable options in selected patients with beta-blocker or calcium-channel-blocker overdose associated with symptomatic or hemodynamically significant bradycardia [6]. Treatment should therefore be guided by severity and the clinical context rather than by heart rate alone.

Dechallenge and Rechallenge

Dechallenge refers to improvement in an adverse event following withdrawal or dose reduction of the suspected drug. In beta-blocker-associated bradycardia, improvement in heart rate and symptoms following withdrawal can support a suspected drug-related association. However, dechallenge does not independently establish causality because heart rate may change as a result of resolution of ischemia, changes in autonomic tone, alterations in concomitant therapy, or other clinical factors. Rechallenge involves reintroducing the suspected drug. Rechallenge should not be performed simply to establish causality when there is a significant risk of recurrent harm. If beta-blocker therapy remains clinically indicated, reintroduction should be individualized and undertaken with appropriate monitoring.

Pharmacovigilance Perspective

Pharmacovigilance involves the detection, assessment, understanding, and prevention of adverse effects or other drug-related problems. Beta-blocker-associated bradyarrhythmia represents an important pharmacovigilance concern because it can be clinically significant and may lead to treatment modification or additional interventions [1].

Pharmacogenetic Considerations

Genetic variation may contribute to interindividual differences in beta-blocker response. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline reviewed evidence involving CYP2D6 and several pharmacodynamic genes in relation to beta-blocker therapy [7]. The evidence is particularly relevant to metoprolol because CYP2D6 genetic variation influences metoprolol exposure and heart-rate response. CYP2D6 poor metabolizers may have greater metoprolol exposure and a greater reduction in heart rate compared with individuals who are not poor metabolizers [7]. These findings provide a pharmacological explanation for some interindividual differences in metoprolol response. However, pharmacogenetic information should be interpreted together with clinical factors, drug interactions, dose, comorbidities, and other patient characteristics.

Beta-Blockers in Acute Coronary Syndrome

Beta-blockers remain an important component of cardiovascular therapy in selected patients with acute coronary syndromes. The 2025 ACC/AHA/ACEP/NAEMSP/SCAI guideline recommends early oral beta-blocker therapy in patients with ACS who do not have contraindications [2]. The therapeutic benefit is related partly to reductions in heart rate, blood pressure, and myocardial oxygen demand [2]. However, clinicians should assess for contraindications and clinical instability before initiation or continuation. Bradycardia, hypotension, significant conduction abnormalities, and other clinical factors may affect the appropriateness of therapy. Therefore, the occurrence of bradycardia should lead to individualized reassessment rather than an automatic assumption that beta-blockers are inappropriate in all patients. Patients receiving beta-blocker therapy may benefit from structured monitoring, particularly following treatment initiation or dose escalation.

Evidence From Clinical and Pharmacovigilance Studies

Available evidence demonstrates that beta-blocker-associated bradycardia occurs across different clinical settings. Motoishi et al. analyzed the Japanese Adverse Drug Event Report database and evaluated beta-blocker-associated bradyarrhythmias, emphasizing the clinical importance of these adverse events [1]. Marcu et al. evaluated 596 patients with symptomatic bradyarrhythmia and found that beta-blocker use was associated with specific bradyarrhythmic presentations, including slow atrial fibrillation, sick sinus syndrome, and sinus bradycardia or pauses [4]. Drug interaction evidence further demonstrates that pharmacokinetic mechanisms may contribute to clinically significant events. The metoprolol-terbinafine case demonstrated marked sinus bradycardia associated with CYP2D6 inhibition [5]. Together, these findings support a multidimensional approach to beta-blocker-associated bradycardia that considers pharmacology, patient factors, drug interactions, ECG findings, and pharmacogenetic variability.

CONCLUSION

Beta-blockers remain important medications in cardiovascular medicine, including the management of selected patients with acute coronary syndromes, heart failure, hypertension, and arrhythmias. However, clinically significant bradycardia is a recognized adverse effect that requires appropriate clinical assessment. The risk of beta-blocker-associated bradycardia is influenced by drug dose, patient characteristics, underlying conduction disease, acute cardiovascular conditions,

concomitant medications, drug interactions, and pharmacogenetic variability. Metoprolol is particularly relevant because CYP2D6 activity can influence drug exposure and heart-rate response. A structured approach involving medication reconciliation, ECG assessment, evaluation of reversible causes, monitoring, individualized dose adjustment, and pharmacovigilance can improve the recognition and management of this adverse drug reaction. Clinical pharmacists have an important role in identifying medication-related risk factors and preventing avoidable adverse events. Future research should focus on individualized risk prediction, pharmacogenetic implementation, clinically meaningful pharmacovigilance signals, and integration of medication-related risk assessment into routine cardiovascular care.

ACKNOWLEDGMENT

The authors express sincere thanks to the Head Deccan School of Pharmacy, Hyderabad, Telangana, India for the facilities provided to carry out this research work.

CONFLICT OF INTERESTS

This manuscript the authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

FUNDING

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on based on their request

REFERENCES

1. Motoishi H, Uesawa Y, Ishii-Nozawa R. Evaluation of β -blocker-induced bradyarrhythmia using an analysis of the Japanese Adverse Drug Event Report database. *Biol Pharm Bull.* 2024;47(10):1668-1674. doi:10.1248/bpb.b24-00305.
2. Rao SV, O'Donoghue ML, Ruel M, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI guideline for the management of patients with acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2025. doi:10.1161/CIR.0000000000001309.
3. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2019;140(8). doi:10.1161/CIR.0000000000000628.
4. Marcu DTM, Adam CA, Dorobanțu DM, Șalaru DL, Sascău RA, Balasanian MO, et al. Beta-blocker-related atrioventricular conduction disorders—a single tertiary referral center experience. *Medicina (Kaunas).* 2022;58(2):320. doi:10.3390/medicina58020320.
5. Bebawi E, Jouni SS, Tessier AA, Frenette AJ, Brindamour D, Doré M. A metoprolol-terbinafine combination induced bradycardia. *Eur J Drug Metab Pharmacokinet.* 2015;40(3):295-299. doi:10.1007/s13318-014-0205-x.
6. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Circulation.* 2019;140(8). doi:10.1161/CIR.0000000000000628.
7. Johnson JA, Cavallari LH, Beitelshes AL, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6, ADRB1, ADRB2, ADRA2C, GRK4, and GRK5 genotypes and beta-blocker therapy. *Clin Pharmacol Ther.* 2024;116(4):939-947. doi:10.1002/cpt.3351.