# The role of pharmacogenomics in predicting metoprolol response in patients with cardiovascular disease: review article

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**Abstract**

**Background:** Recently the issue of individual variability in response to pharmacological agents in a variety of medical condition has been extensively discussed in published medical articles. Metoprolol is one of the major pharmacological agents used to control cardiovascular events by cardiologist and tailoring the dose of the drug according to patients has been suggested by significant number of authors in order to get optimum response based on gene polymorphism studies.

**Aim of the study:** To assess the role of pharmacogenomics in predicting metoprolol response in patients with cardiovascular disease**.**

**Materials and methods:** The current review was done in College of Medicine/ University of Al-Qadisiyah and involved the search in the Google search engine about the following key words: pharmacogenomics, heart failure, metoprolol. The studies that were published with this respect during the last 20 years were enrolled. Any article dealing with use of metoprolol for other indications other than heart failure was excluded.

**Results:** One previous meta-analysis has shown that "CYP2D6 PM have a greater reduction in HR compared to non-PM by >3 beats/min when treated with metoprolol". It is suggested that greater risk of bradycardia is expected in PM individuals. The clinical advantages of lowering resting heart rate have also been shown following post-myocardial infarction intervention, particularly when beta-blockers have been used.

**Conclusion:** individualization of the dose o metoprolol is required because response of the patients varies considerably based on gene polymorphism in a number of genes.

**Key words:** pharmacogenomics, metoprolol, cardiovascular disease

## Introduction

Cardiovascular disorders are important causes of mortality and morbidity worldwide (1). The pathophysiology of these disorders varies considerably with some representing congenital defects and others acquired during postnatal life (2). These cardiovascular disorders may be due diseases affecting cardiac valves, disorders of conductive system of the heart, diseases of pericardium, disorders of myocardium or of endocardium (3-5). Ischemic heart diseases resulting from diseases of coronary arteries are by far the most common cardiac abnormalities globally and annually cause significant morbidity and mortality (6).

Ischemic heart disease may result in sudden cardiac death, in chronic ischemic heart disease or in acute coronary syndrome manifestations such as unstable angina and acute myocardial infarction (7-9). Heart failure may be caused by a variety of cause in addition to ischemia such as cardiomyopathy and valvular heart disease (10). Arrhythmias are among the common manifestation of cardiac disorders worldwide such as atrial fibrillation and supraventricular tachycardia (11). Beta blockers are one of the most familiar drug classes that are used to control

manifestations of cardiovascular disorders such as hypertension, arrhythmias and heart failure (12). One of the most common beta blockers is the cardioselective agent metoprolol (13). Response to metoprolol has been shown by a variety of studies to vary from person to person and that genetic polymorphism of number of genes can predict such response variation (14).

The current review was aiming at assessment of the role of pharmacogenomics in predicting metoprolol response in patients with cardiovascular disease**.**

## Materials and methods

The current review was done in College of Medicine/ University of Al-Qadisiyah and involved the search in the Google search engine about the following key words: pharmacogenomics, heart failure, metoprolol. The studies that were published with this respect during the last 20 years were enrolled. Any article dealing with use of metoprolol for other indications other than heart failure was excluded.

## Results and discussion

The used of beta blockers in heart failure patients is associated with reduction of the risk of mortality (15). It is estimated that approximately 80 % of metoprolol is metabolized by the enzyme CYP2D6 (16) and previous studies have shown that pharmacokinetics of metoprolol are significantly affected by the CYP2D6 genotype (17). One previous meta-analysis has shown that "CYP2D6 PM have a greater reduction in HR compared to non-PM by >3 beats/min when treated with metoprolol" (18).It is suggested that greater risk of bradycardia is expected in PM individuals (18).The clinical advantages of lowering resting heart rate have also been shown following post-myocardial infarction intervention, particularly when beta-blockers have been used (19).

Thus PM individuals are at risk of bradycardia. In line with that, previous authors have shown than the use of fixed doses of metoprolol in patients with cardiovascular disease, greater plasma concentrations were observed in PM persons compared to non-PM persons (20). Furthermore, the amount of reduction in blood pressure in PM group was greater than that seen in non-PM group (20). It will be justified therefore to use higher doses of metoprolol in patients on non-PM phenotype or shifting to other forms of agents that are not metabolized by CYP2D6. In one trial, the doses of metoprolol to achieve the same reduction in heart rate were significantly higher in EM phenotype in comparison with PM phenotype (21). In addition, the results of Bijl et al (22) also confirmed the findings that bradycardia is more associated with PM phenotype than EM phenotype.

Metoprolol and other beta-blockers are known to have a mild blood pressure-lowering impact (23) (8). Evidence indicates that a population-wide DBP reduction of just 2 mmHg would result in a 15% reduction in stroke (24) (47). The incidence of coronary heart disease, stroke, and heart failure events would all be dramatically reduced annually with an equally small SBP reduction, according to recent projections (25) (48).

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