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Metoprolol Therapy and *CYP2D6* Genotype

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Introduction

Metoprolol is a beta-blocker indicated for the treatment of various cardiovascular diseases, including hypertension, arrhythmias, angina, myocardial infarction, and heart failure (HF). Metoprolol selectively blocks beta$_1$-adrenoreceptors, which are expressed predominantly in cardiac tissue. The primary therapeutic effect resulting from the blockade of these receptors is a reduction in heart rate and a decrease in the force of heart contractions.

Metoprolol is metabolized extensively by the hepatic CYP2D6 enzyme. Approximately 8% of Caucasians and 2% of most other populations have absent CYP2D6 activity and are known as "CYP2D6 poor metabolizers (PM)." In addition, several drugs inhibit CYP2D6 activity, such as bupropion, quinidine, fluoxetine, paroxetine, and propafenone.

The FDA-approved drug label for metoprolol states that CYP2D6 PM and normal metabolizers (NM) who concomitantly take drugs that inhibit CYP2D6 will have increased metoprolol blood levels, decreasing metoprolol's cardioselectivity; co-medication with CYP2D6 inhibitors warrants close monitoring (1). (Table 1) Beta-blockers, such as metoprolol, have been demonstrated in several large clinical trials to be safe and effective for the treatment of individuals with cardiovascular disease. As a mainstay of therapy associated with improvements in quality of life, hospitalization rates, and survival (2, 3), clinical care pathways that might lead to the underutilization of beta-blockers require scrutiny. It is common clinical practice to adjust the dose of metoprolol according to individual heart rate until either the target or maximum tolerated dose is reached. The FDA does not specifically comment on the role of genetic testing for initiating therapy.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that CYP2D6 PM should initiate metoprolol therapy at the lowest recommended starting dose, and titration should be performed with care and close monitoring for bradycardia. (Table 2) Standard dosing and care are recommended for intermediate metabolizers (IM) and NM of CYP2D6, but no recommendation is made for ultrarapid metabolizers (UM) given the limited data on this phenotype and beta-blocker response. (4)

The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Pharmacists Association (KNMP) has also published metoprolol dosing recommendations based on *CYP2D6* genotype. For individuals who have a *CYP2D6* gene variation that reduces the conversion of metoprolol to inactive metabolites (namely, the IM and PM phenotype), DPWG states that the clinical consequences are limited mainly to the occurrence of

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asymptomatic bradycardia. For CYP2D6 PM or IM, if a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia, DPWG recommends increasing the dose of metoprolol in smaller steps, prescribing no more than 25% (PM) or 50% (IM) of the standard dose, or both. For CYP2D6 UM, DPWG indicates that clinical response is hardly decreased at a dose of 200 mg/day. However, if efficacy is insufficient at this maximum dose, the DPWG recommends increasing the dose based on effectiveness and side effects up to a maximum of 2.5 times the normal dose, or selecting an alternative. (Table 3) (5).

Table 1: Statement on CYP2D6-based Interactions with Metoprolol from the Food and Drug Administration (FDA)

Interaction	Effect	Recommendation
CYP2D6 inhibition by other medication(s)	Strong inhibitors of CYP2D6 were shown to double metoprolol concentrations; increases in plasma concentration decrease the cardioselectivity of metoprolol	Monitor individuals closely when the combination cannot be avoided.
CYP2D6 poor metabolizers	Will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.	(None)

Table adapted from (1)

Table 2: Recommendations from the Clinical Pharmacogenetic Implementation Consortium (CPIC) for Beta-Blocker Therapy by Genotype

CYP2D6 phenotype	Implications[a]	Recommendation	Classification of recommendation[b]
Ultrarapid metabolizer	Increased metabolism of metoprolol leading to decreased drug concentrations; however, it is unclear whether this results in clinically significant changes in heart rate, blood pressure, or clinical outcomes.	No recommendation for metoprolol therapy due to insufficient evidence regarding diminished metoprolol effectiveness clinically.	No recommendation
Normal metabolizer	Normal metabolism of metoprolol	Initiate standard dosing	Strong
Intermediate metabolizer	Decreased metabolism of metoprolol leading to increased drug concentrations; however, this does not appear to translate into clinically significant changes in heart rate, blood pressure, or clinical outcomes.	Initiate standard dosing	Moderate
Poor metabolizer	Decreased metabolism of metoprolol leading to markedly increased drug concentrations; this leads to greater heart rate and blood pressure reductions. The effect on clinical outcomes is unclear.	Initiate therapy with lowest recommended starting dose. Carefully titrate dose upward to clinical effect or guideline-recommended dose; monitor more closely for bradycardia. Alternatively, consider selecting another beta-blocker.	Moderate
Indeterminate	n/a	No recommendation	No recommendation

n/a, not applicable. Indeterminate: Genotype data for *CYP2D6* is either unavailable or cannot be converted to a metabolizer phenotype due to unknown or uncertain allele function.
[a] Metoprolol has no known active metabolites formed by CYP2D6.
[b] No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice. Moderate: There is a close or uncertain balance as to whether the evidence is high quality, and the desirable effects clearly outweigh the undesirable effects. Strong: The evidence is high quality, and the desirable effects clearly outweigh the undesirable effects.
Table adapted from (4).

Table 3: Recommendations for Metoprolol and CYP2D6 Phenotype from the Dutch Pharmacogenetics Working Group (DPWG)

CYP2D6 phenotype	Effect	Recommendation
UM	Increases the conversion of metoprolol to inactive metabolites. This can increase the dose requirement. However, with a target dose of 200 mg/day, there was no effect on the blood pressure and hardly any effect on the reduction of the heart rate.	Use the maximum dose for the relevant indication as a target dose. If the effectiveness is still insufficient: increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative. Possible alternatives include: -Heart failure: bisoprolol or carvedilol. -Other indications: atenolol or bisoprolol.
IM	Reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia	If a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia: use smaller steps in dose titration, prescribe no more than 50% of the standard dose or both. Other cases: no action required.
PM	Reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia	If a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia: use smaller steps in dose titration, prescribe no more than 25% of the standard dose or both. Other cases: no action required.

UM: Ultrarapid metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer
Table adapted from (5).

Drug: Metoprolol

Metoprolol is a commonly prescribed drug that belongs to the drug class of beta-adrenoreceptor antagonists, also known as "beta-blockers". Metoprolol is indicated to treat hypertension, angina, myocardial infarction, and HF (stable, symptomatic [New York Heart Association Class II or III] HF). Metoprolol selectively blocks the $beta_1$-adrenoreceptor (1). Beta-blockers are a recommended first-line therapy for cardiac conditions, including various arrhythmias, and as second-line therapy for hypertension by professional medical societies in the US and Europe (6, 7, 8).

There are 2 main types of adrenoreceptors, alpha and beta, each of which has numbered subtypes. The beta adrenoreceptors have 3 subtypes: $beta_1$, $beta_2$, and $beta_3$. All 3 subtypes are coupled to the G_s protein, which in turn activates adenylate cyclase, an enzyme that catalyzes the production of cyclic adenosine monophosphate (cAMP) from ATP. The binding of an agonist, such as the catecholamines adrenaline and noradrenaline, to beta receptors leads to a rise in the intracellular concentration of cAMP, which triggers signaling pathways via protein kinase A (9). Stimulation of the $beta_1$ receptor, which is predominantly expressed in cardiac tissue, leads to an increase in heart rate and the contractility of the atria and ventricles. It also leads to the increased secretion of hormones from other tissues, including renin (from the kidneys), ghrelin (from the stomach), and amylase (from the salivary glands).

Metoprolol exerts its therapeutic effects by reducing the impact of catecholamine stimulation. Metoprolol reduces heart rate, improves contractile function by stimulating the upregulation of $beta_1$ receptors, reduces vasoconstriction, and possibly also reduces the risk of arrhythmias (2, 10, 11, 12). In the treatment of HF, certain beta-blockers, such as extended-release metoprolol succinate, are thought to protect the heart from increased catecholamine stimulation. In the short term, adrenergic activation can help the heart maintain cardiac performance, but over time, continued activation can be detrimental. Harmful effects include a persistently increased heart rate, down-regulation and impaired functioning of the beta receptors, and myocyte hypertrophy and death, which lead to adverse remodeling of heart tissue (10, 13).

Metoprolol is a racemic mixture of R- and S-enantiomers (in equal amounts). S-metoprolol has a higher affinity for the $beta_2$ receptors than the R-enantiomer (14). R-metoprolol is predominantly metabolized by O-

demethylation, whereas S-metoprolol primarily undergoes alpha-hydroxylation (15, 16, 17). Both pathways are metabolized extensively by CYP2D6, though CYP2D6 seems to metabolize R-metoprolol more efficiently (18). The CYP2D6 enzyme is absent in approximately 8% of Caucasians (PM) and approximately 2% of most other populations. Individuals who lack CYP2D6 activity will have plasma concentrations of metoprolol roughly 5 times higher and may be at an increased risk of side effects (18, 19, 20, 21). Individuals with hepatic or renal failure have also been reported to experience elevated plasma levels of metoprolol and increased exposure (22). Metoprolol has a relatively low (approximately 12%) albumin-bound fraction in plasma, can cross the blood-brain barrier, and shows a dose-related increase in bioavailability, though this increase is not directly proportional (1). At higher plasma concentrations, metoprolol is less cardioselective. Metoprolol can inhibit $beta_2$ receptors, which are mainly located in the bronchial and vascular musculature. The FDA-approved drug label advises that individuals with bronchospastic disease should not take beta-blockers, except for individuals who cannot tolerate another antihypertensive treatment; in such cases, the lowest possible dose should be used (1).

In a geriatric population, plasma levels of metoprolol above the median were associated with an increased risk of falls; however, this association was not seen for non-selective beta-blockers (23). The drug label in Canada and the FDA label for metoprolol tartrate recommend lower starting and maintenance doses, as well as safety monitoring in geriatric individuals on metoprolol therapy (24, 25).

The safety and effectiveness of metoprolol have not been established in individuals under 6 years of age, according to the FDA-approved label (1). Metoprolol has not been authorized for pediatric use in Canada (24). Even though beta-blockers are typically not recommended for use in pediatric individuals, off-label use in pediatric heart failure does occur (26). The few studies available provide conflicting outcomes regarding the benefit of beta-blockers in a pediatric HF population. Although this pharmacologic management approach did not appear to cause a significant rate of adverse events, more studies are needed to determine the efficacy of beta-blockers for pediatric HF (26). Much of the use of beta-blockers in a pediatric population is extrapolated from experiences in adults, and CPIC states that their recommendations can, with caution, be extrapolated from adult to pediatric use (4, 27). Changes in gene expression over the lifespan of an individual can impact drug responses; the primary metabolic enzyme for metoprolol, CYP2D6, is absent in fetal development but reaches mature expression within the first several post-natal weeks of life. Less is known regarding the beta-adrenergic receptors (27).

Metoprolol can cross the placenta and is secreted in breast milk (28). There are notable risks to a pregnant mother with untreated hypertension during pregnancy, including pre-eclampsia, gestational diabetes, premature delivery and delivery complications. Likewise, hypertension also increases the risk of adverse fetal outcomes (1). Observational studies have not definitively established nor excluded any drug-associated risk of major congenital malformations during pregnancy for metoprolol tartrate or succinate (1, 25). The combined levels of metoprolol and the alpha-OH-metoprolol metabolite secreted into breast milk are reported to be low (less than 2% of the mother's weight-adjusted dose), and the amounts ingested by the infant are not expected to cause adverse effects, with studies to date finding no adverse reactions in breastfed infants (29). Changes in gene expression or metabolism can occur during pregnancy; an increase in the clearance rate of metoprolol has been reported during mid and late pregnancy, which may require changes in medication selection or dosing (30). However, the use of metoprolol during pregnancy or nursing is not recommended by Health Canada (24), and the US FDA advises monitoring of a breastfed infant for bradycardia or listlessness (signs of beta-blockade) (1).

Gene: *CYP2D6*

The CYP450s are a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The *CYP450* genes are polymorphic and can result in decreased, absent,

or increased enzyme activity. One prominent CYP450 member, CYP2D6, is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers.

The *CYP2D6* Alleles

The *CYP2D6* gene is highly polymorphic, as over 170 star (*) alleles have been described and cataloged at the Pharmacogene Variation (PharmVar) Consortium, and each allele is associated with either normal, decreased, or absent enzyme function (Table 4) (31, 32). Star alleles are defined by the variants detected on one chromosome (haplotype).

The combination of *CYP2D6* haplotypes that a person has is used to determine their diplotype (for example, *CYP2D6 *4/*4*). Based on their impact on enzyme function, each allele can be assigned an activity score from 0 to 1, which is then used to assign a phenotype (for example, CYP2D6 PM). To promote harmonization, the CPIC and DPWG standardized their *CYP2D6* genotype-to-phenotype methods in October 2019, creating a consensus activity scoring guideline. The CYP2D6 phenotype is predicted from the diplotype activity score, defined by the sum of the allele score values, which usually ranges from 0 to 3.0. (33)

- An UM has an activity score greater than 2.25
- A NM phenotype has an activity score of 1.25–2.25
- An IM has an activity score of >0–<1.25
- A PM has an activity score of 0

Table 4. Activity Status of Selected CYP2D6 Alleles

Allele type	*CYP2D6* alleles	Activity score
Normal function	**1, *2, *27, *33*	1
Decreased function	**17, *41, *49*	0.5
Strongly decreased function	**10*	0.25
No function	**3, *4, *5, *6, *36*	0

For a comprehensive list of *CYP2D6* alleles, please See the Pharmacogene Variation Consortium . Activity scores from (34).

The *CYP2D6*1* allele is the wild-type allele when no variants are detected and is associated with normal enzyme activity and the NM phenotype. The *CYP2D6*2*, **27*, and **33* alleles are also considered to have near-normal activity.

Other *CYP2D6* alleles include variants that produce a non-functioning enzyme (for example, **3*, **4*, and **6*) (35, 36, 37) or an enzyme with decreased activity (for example, **10*, **17*, and **41*) (32, 38) (see Table 4). There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **6*, and **41* being more common in individuals with European ancestry, **17* more common in those with African ancestry, and **10* more common in individuals with Asian ancestry. (39)

Larger structural variants at the *CYP2D6* locus have also been described, including gene duplications, deletions, tandem alleles, gene hybrids (namely, *CYP2D6-CYP2D7*), and gene conversions. The *CYP2D6* gene deletions result in a no-function allele (for example, the **5* allele is a deletion). Duplications have been reported for alleles with both normal and decreased function. For allele duplications, the activity scores for the full complement of *CYP2D6* alleles are summed to determine the predicted metabolizer phenotype. Additional details on structural variants are available from PharmVar (see the document Structural Variation for CYP2D6) (40).

The frequency of *CYP2D6* star alleles with altered function varies across global populations, resulting in different frequencies of the resulting metabolizer phenotypes. Given CYP2D6's role in the metabolism of many drugs, the

literature on allele and phenotype frequency is expansive. Most populations have a high frequency of normal-function star alleles, and thus a high proportion of the population are NMs. However, reduced-function alleles like *CYP2D6*10* are highly prevalent in East Asian populations, leading to a higher proportion of IM phenotype individuals in this ancestral group. Many groups in sub-Saharan Africa have higher frequencies of decreased-function alleles like *CYP2D6*17* and **29*, which can correlate with lower metabolizer scores in these individuals. More details regarding published allele and phenotype frequencies are available in the CYP2D6 supplemental chapter.

Pharmacologic Conversion of CYP2D6 Phenotype

Factors other than genotype can affect CYP2D6 enzyme activity and, thus, the metabolizer phenotype of any individual. Administration of an interacting medication can lead to phenoconversion, whereby an individual with one metabolizer genotype can exhibit the enzymatic activity of a different metabolizer group (higher or lower, depending on the medications). The enzymatic activity of CYP2D6 can be inhibited or reduced by medications, including but not limited to strong inhibitors such as paroxetine, fluoxetine, bupropion, and quinidine, and moderate inhibitors such as duloxetine (24, 41, 42, 43). This can potentially result in NMs or IMs responding to medications as if they were PMs, depending on the strength of the enzyme inhibition. Strong inhibitors can completely inhibit CYP2D6, while moderate inhibitors can reduce activity by 50%. Thus, co-medication with multiple CYP2D6 strong or moderate inhibitors may result in reduced metabolism of drug substrates, as has been observed in psychiatric pharmacotherapy (44, 45 2023). In contrast, discontinuing a concomitant CYP2D6 inhibitor can then revert the individual's CYP2D6 activity back to the genetically predicted baseline phenotype. Coadministration of metoprolol and amiodarone has shown a significant increase in metoprolol concentrations and lower heart rate, despite no significant changes in metoprolol doses (46). The product monograph reviewed by Health Canada for metoprolol states that "strong inhibition of CYP2D6 would result in the change of phenotype into poor metabolizer… caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol" (24). The metoprolol tartrate drug labeling approved by the FDA states that strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, and propafenone) have been shown to double metoprolol concentrations (25). Integration of CYP2D6 phenoconversion into clinical practice requires knowledge of multiple clinical factors, and tools have been developed to support clinicians (47).

Other Genes of Interest: *ADRB1, ADRB2, OR10P1, SNX9, GRK5*

The beta-adrenergic receptors mediate signaling via coupled G-protein signaling. In the heart, beta$_1$-adrenergic receptors are the primary target for beta-blockers and represent the major adrenergic receptor (27). Encoded by *ADRB1* on chromosome 10q25, the beta$_1$-adrenergic receptor is a 7-transmembrane domain protein with intracellular and extracellular portions that facilitate ligand and G-protein binding (48, 49). Binding of a ligand to the receptor induces a conformational change that allows the G-alpha subunit to activate adenylyl cyclase, creating cAMP signaling molecules, which in turn leads to increased intracellular calcium ion levels. Calcium influx drives increased contractility and heart rate, as well as increased electrical automaticity (27).

There are known polymorphisms in *ADRB1* that have been associated with disease and altered drug response in some studies. The 2 commonly studied variants are ADRB1 p.Ser49Gly (rs1801252, c.145A>G) and p.Arg389Gly (rs1801253, c.1165G>C). The p.389 residue falls within the G-protein binding intracellular loop, and the p.49 residue occurs in an extracellular loop (27). The C>G single nucleotide polymorphism (SNP) at rs1801253 (p.Arg389Gly) has been reported to occur at a frequency of 27% in individuals of European descent, 40–42% in those of African descent, 32–41% in individuals of Asian descent, and 19–32% in individuals of Latin American descent (50, 51). The variation at p.49 of ADRB1 (c.145A>G, rs1801252) occurs less frequently: 10–12.5% in Asian populations, 13% in European populations, 20–25% in African and African descent populations, and 17–24% in Latin American populations. These 2 variants are in negative linkage disequilibrium, such that it is

unlikely for an individual to have a Gly49-Gly389 allele (27). Individuals homozygous for arginine at p.389 have been reported to have an increased risk of hypertension (50), and this variation may interact with other variants in the G-protein signaling pathway to negatively impact survival, particularly in individuals of African ancestry (52).

The beta$_2$-adrenergic receptor, encoded by *ADRB2* and located on chromosome 5q32, has been associated with nocturnal asthma, obesity, type 2 diabetes, cardiovascular disease, and Parkinson's disease risk (53). The ADRB2 protein is abundantly expressed in bronchial smooth muscle cells, where activation of the receptor leads to bronchodilation (54). It is also expressed, to a lesser extent, in the cardiac myocytes and vascular smooth muscle cells, contributing to increased heart rate and contractility following adrenergic stimulation (54). There are 2 common variants in *ADRB2* that encode amino acid changes: rs1042713 (p.Gly16Arg) and rs1042714 (p.Glu27Gln, c.79G>C), with the minor allele frequencies ranging between 40–50% (54). The Gly16 protein isoform is more susceptible to agonist-stimulated downregulation in vitro (54). The Gln27 variant has been associated with increases in systolic blood pressure and reduced response to isoproterenol (54). A third variant, rs1800888 (p.Thr164Ile), is relatively rare, with a minor allele frequency range of ~1–2% in individuals of European or African ancestry, and it is not detected in Chinese populations (54). This rare allele is associated with reduced response to beta$_2$-agonists such as salmeterol or albuterol (54, 55).

A genome-wide association study found that *OR10P1* and *SNX9*-linked variants were associated with changes in heart rate in response to beta-blocker therapy for individuals classified as 'Black' in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) and PEAR-2 studies (56). The variants g.56022983T>G (rs17117817, near the olfactory receptor family 10 subfamily-p-member 1 gene *OR10P1*) or rs2364349 c.1648+912G>A (rs2364349) (linked to the sorting nexin-9 gene *SNX9*) were associated with a decreased heart rate-lowering response in this population. These loci were found to yield significant association signals in 'White' study participants as well (56). There is evidence that OR10P1 is expressed in cardiac tissue and may indirectly interact with ADRB2, though the specific mechanism by which olfactory receptors impact heart rate is unknown. Sorting nexin-9 is associated with endocytosis of transmembrane signaling proteins and may be involved in regulating the endocytosis of ADRB2.

One study also found a connection between *GRK5* variation and improved survival in HF. p.Gln41Leu (c.122A>T) in the G-protein-coupled receptor kinase 5 protein (rs17098707, now rs2230345) was reported to be more common in individuals of African ancestry than in Caucasians and may attenuate beta-adrenergic signaling, similar to beta-blocker medication (57). This same allele was examined in a Chinese population with an allele frequency of 0.008, but it was not associated with differences in systolic HF mortality compared with the reference allele (58).

Linking *CYP2D6* and *ADRB1/2* Genetic Variation with Treatment Response

Genetic variants of the *CYP2D6* gene have been found to influence the ratio of enantiomers, the dose and dose titration of metoprolol, and heart rate—CYP2D6 PM have an increased risk of bradycardia (59, 60, 61, 62, 63, 64). However, in one study, *CYP2D6* did not appear to influence the efficacy of metoprolol when used to treat hypertension (65). Reduced function of CYP2D6 enzyme alters the pharmacokinetics of metoprolol, resulting in increased exposure (measured by plasma area under the concentration-time curve levels) in PMs and IMs (*10/*10) and this is correlated with a higher risk of bradycardia in PMs (66). In a genome-wide association biobank study using 'white' (self-reported) study participants, metoprolol and alpha-OH-metoprolol concentrations were significantly associated with genetic variation located only in the *CYP2D6* locus (67).

A meta-analysis of 21 studies reported a significant difference in the BP-lowering effects of metoprolol between CYP2D6 PMs and all other phenotypes (68). At similar doses, individuals with a PM CYP2D6 phenotype

experienced a larger decrease in heart rate (measured in beats per minute, BPM), blood pressure (both systolic and diastolic), and more cases of bradycardia (heart rate of less than 60 BPM) across the relevant studies (68).

Variants within the $beta_1$ receptor have also been found to influence the treatment response to specific beta-blockers. The most studied is a reduced-function variant, p.Gly389Arg (rs1801253), which leads to reduced levels of cAMP and diminished $beta_1$ receptor signaling cascades (69). Individuals who are homozygous p.Arg389 may have a more favorable response to metoprolol treatment than individuals who are homozygous for the reference sequence p.Gly389 (69, 70, 71, 72, 73). The p.Ser49Gly (rs1801252) variant has been reported to be associated with increased ventricular ectopic beats and favorable beta-blocker response in a cohort study of hypertrophic cardiomyopathy (HCM), though the p.Gly389Arg polymorphism did not show significant impacts on beta-blocker response in this HCM cohort (74). The *ADRB1* p.Gly389Arg (rs1801253) variant, which was associated with decreased response to beta-blockers, was detected in roughly half the cohort from the Alabama Genomic Health Initiative that had a prescription for one of the affected medicines, including metoprolol (75). One study found that individuals with HF and a variant allele (p.389Arg) at rs1801253 benefited from higher doses of beta-blockers (76). In a separate study, p.389Arg homozygous individuals had greater improvement in left ventricular ejection fraction compared with individuals with the homozygous reference allele (77). However, the CPIC guideline writing committee found the data insufficient to issue recommendations regarding genetic variations in *ADRB1* and beta-blocker therapy, citing a need for additional research to refute or confirm the reported findings to date (4).

Additional studies have examined the role of $beta_2$ receptor variants and heart rate responses to beta-blockers (78). The PEAR-2 trial examined variants in metoprolol response for individuals with hypertension, finding a significant association of a more pronounced heart rate-lowering response with *ADRB2* rs1042714 C/C genotype (encoding Gln at p.27) and a "trending toward significant" association with rs1042713 A-allele in *ADRB2* (78). In contrast, the p.27Glu genotype was associated with longer survival for individuals with HF who were taking beta-blockers, and no association was observed with the p.Arg16Gly variants and clinical outcomes (76). This literature was also insufficient to justify clinical recommendations from the CPIC writing committee for beta-blockers and *ADRB2* variation (4).

Other studies have failed to find associations between *ADRB1* or *ADRB2* common variants and blood pressure responses to beta-blockers (79), though it is unclear if the underlying cardiac disorder may impact the specific drug response (or lack of response) associated with genetic variants.

Genetic Testing

The NIH's Genetic Testing Registry provides examples of the genetic tests available for metoprolol response and the CYP2D6 gene.

The available *CYP2D6* tests include targeted single-gene tests as well as multi-gene panels. In addition, variant *CYP2D6* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (AMP) (80). For *CYP2D6*, the AMP recommends that the minimum panel of variant alleles should include *2, *3, *4, *5, *6, *9, *10, *17, *29, *41, and a copy number interrogation. Results are reported as a diplotype, such as *CYP2D6 *1/*1*; however, copy number testing is crucial when interpreting *CYP2D6* results (81). When individuals have more than 2 copies of *CYP2D6*, the copies of the allele are denoted by an "xN", where the "N" can either be quantified or unquantified (for example, *CYP2D6 *1/*2x2* or *CYP2D6 *1/*2xN*). Some laboratories also use the notation of duplication ("DUP") to indicate an increase in copy number, but the report does not always specify the number of duplications or the allele that has been duplicated due to technical limitations. The test results may include an interpretation of the individual's predicted metabolizer phenotype, which can be confirmed by checking the diplotype and calculating the *CYP2D6* activity score, as described in the "*CYP2D6* Alleles" section above.

Multiple studies have reported successful implementation of pharmacogenetic testing to guide medication selection or dosing in real-world clinical settings (82, 83, 84). Of particular concern are cases where individuals are prescribed multiple medications for chronic health conditions, where gene-drug or gene-drug-drug interactions may negatively impact the individual's response to medications (85).

The *CYP2D6* Gene Interactions with Medications Used for Additional Indications

The CYP family of enzymes is involved in the metabolism of many substances, and CYP2D6 has been implicated in altered pharmacologic responses for many compounds. The drugs can be categorized into many different classes:

- Antipsychotics—for example, aripiprazole, risperidone, and thioridazine, and to a lesser extent, clozapine, are metabolized by CYP2D6. According to the FDA, aripiprazole dosage should be reduced for PMs, and thioridazine is contraindicated for individuals known to have reduced CYP2D6 activity due to an increased risk of potentially fatal side effects. The UMs may have a decreased plasma concentration of risperidone.

- Tricyclic antidepressants—for example, amitriptyline and imipramine may require dosage adjustments, potentially guided by therapeutic drug monitoring, to achieve the desired therapeutic range in UMs or PMs. Ultimately, tricyclic antidepressants may be ineffective in CYP2D6 UMs.

- Serotonin and norepinephrine reuptake inhibitors, for example atomoxetine and venlafaxine may have reduced efficacy in UMs at standard doses, while PMs are at risk of elevated plasma concentrations for both medications. The DPWG advises against the use of venlafaxine in CYP2D6 PMs and IMs.

- Antimalarial medications—for example, primaquine is activated by CYP2D6 and CYP450 Nicotinamide Adenine Dinucleotide Phosphate oxidoreductase.

- Anticancer medications—for example, tamoxifen is activated by CYP2D6, and IMs or PMs may have reduced benefit from tamoxifen therapy.

- Pain management—for example, codeine and tramadol are pro-drugs that require activation by CYP2D6 to achieve the desired analgesic effect.

- Various therapies for genetic disorders, for example, eliglustat used in the treatment of Gaucher disease, and deutetrabenazine, used in the treatment of Huntington disease, have reduced dose recommendations for CYP2D6 PMs. The CYP2D6 UMs may not achieve adequate concentrations of eliglustat, and therefore *CYP2D6* genotyping is required before initiating eliglustat therapy.

It is important to note that *CYP2D6* is the most common biomarker in drug responses for FDA drug labels. The lists provided here is by no means exhaustive. Additional information on gene-drug interactions for *CYP2D6* is available from PharmGKB, CPIC, and the FDA (search for "CYP2D6").

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2024 Statement from the US Food and Drug Administration (FDA):

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

CYP2D6 Inhibitors are likely to increase metoprolol concentration. […] Drugs that are strong inhibitors of CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone were shown to double metoprolol concentrations. While there is no information about moderate or weak inhibitors, these too are likely to increase metoprolol concentration. Increases in plasma concentration decrease the cardioselectivity of metoprolol … Monitor patients closely when the combination cannot be avoided.

[…]

Drug Interactions

CYP2D6

Metoprolol is metabolized predominantly by CYP2D6. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg, a potent CYP2D6 inhibitor, and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life.

[…]

CYP2D6 is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by several drugs. Poor metabolizers of CYP2D6 will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.

Please review the complete therapeutic recommendations that are located here: (1)

2024 Summary of recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC):

The evidence supporting the association of CYP2D6 genotype with metoprolol exposure and response included participants with a variety of health statuses (e.g., healthy, hypertension, heart failure, etc.). Therefore, it may be reasonable to assume that the pharmacokinetic effects of CYP2D6 variation would affect clinical metoprolol response similarly across a variety of indications, and the dosing recommendations provided could be utilized for most cardiovascular indications …

Recommendations primarily focus on minimizing the risk of adverse effects in CYP2D6 poor metabolizers related to the greater observed reductions in heart rate and blood pressure stemming from increased metoprolol systemic exposure. In addition, the maximally tolerated metoprolol dose may be lower in poor metabolizers compared with normal metabolizers due to these pharmacokinetic differences… We found insufficient evidence to support recommendations related to CYP2D6 genotype and other clinical outcomes.

While the evidence suggests metoprolol plasma concentrations are also increased in CYP2D6 intermediate metabolizers compared with normal metabolizers, these effects appear smaller in magnitude than those observed with poor metabolizers, and there was insufficient evidence to clarify whether these smaller pharmacokinetic differences significantly affect clinical response.

… Most of the data available regarding associations between CYP2D6 genotype and metoprolol response are related to oral formulations; limited evidence exists regarding pharmacogenetic effects with intravenous formulations.

….

CYP2D6 normal and intermediate metabolizers: Recommendations: Initiate standard dosing.

CYP2D6 poor metabolizers: Recommendations: Initiate therapy with lowest recommended starting dose. Carefully titrate dose upward to clinical effect or guideline-recommended dose; monitor more closely for bradycardia. Alternatively, consider selecting another beta-blocker.

CYP2D6 ultrarapid metabolizers: No recommendation for metoprolol therapy due to insufficient evidence regarding diminished metoprolol effectiveness clinically.

Please review the complete therapeutic recommendations that are located here: (4)

2022 Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP):

CYP2D6 Poor Metabolizers:

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

If a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia:

1. Use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose

Other cases:

1 No action required

CYP2D6 Intermediate Metabolizers:

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

If a gradual reduction in heart rate is desired, or in the event of symptomatic bradycardia:

1. Use smaller steps in dose titration and/or prescribe no more than 50% of the standard dose.

Other cases:

1. No action required

CYP2D6 Ultrarapid Metabolizers:

The gene variation increases the conversion of metoprolol to inactive metabolites. This can increase the dose requirement. However, with a target dose of 200 mg/day, there was no effect on the blood pressure and hardly any effect on the reduction of the heart rate.

Recommendation:

1. Use the maximum dose for the relevant indication as a target dose

2. If the effectiveness is still insufficient: increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative

Possible alternatives include:

- Heart failure: bisoprolol or carvedilol. Bisoprolol: advantage: not metabolised by CYP2D6; disadvantage: elimination depends on the kidney function. Carvedilol: advantage: elimination does not depend on the kidney function; disadvantage: is metabolised (to a lesser extent than metoprolol) by CYP2D6.
- Other indications: atenolol or bisoprolol. Neither is metabolised by CYP2D6.

Please review the complete therapeutic recommendations that are located here: (5)

Nomenclature of Selected *CYP2D6* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
CYP2D6*2	2851C>T	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*3	2550delA	NM_000106.6:c.775del	NP_000097.3:p.Arg259fs	rs35742686
CYP2D6*4	1846G>A	NM_000106.6:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
CYP2D6*5	Gene deletion			
CYP2D6*6	1707 del T	NM_000106.6:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
CYP2D6*10	100C>T	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*17	1022C>T	NM_000106.6:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2851C>T	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*27	3854G>A	NM_000106.6:c.1228G>A	NP_000097.3:p.Glu410Lys	rs769157652
CYP2D6*31	2851C>T	NM_000106.6:c.886C>T	NP_000097.3:p.Arg296Cys	rs16947
	4043G>A	NM_000106.6:c.1319G>A	NP_000097.3:p.Arg440His	rs267608319
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*36[1]	100C>T	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4129C>G	NM_000106.6:c.1405C>G	NP_000097.3:p.Pro469Ala	rs1135833
	4132A>G	NM_000106.6:c.1408A>G	NP_000097.3:p.Thr470Ala	rs1135835
	4156C>T+4157A>C	NM_000106.6:c.1432C>T+ NM_000106.6:c.1433A>C	NP_000097.3:p.His47Ser	rs28371735+ rs766507177
	4159G>C	NM_000106.6:c.1435G>C	NP_00097.3:p.Gly479Arg	
	4165T>G	NM_000106.6:c.1441T>G	NP_00097.3:p.Phe481Val	
	4168G>A+4169C>G	NM_000106.6:c.1444G>A+ NM_000106.6:c.1445C>G	NP_000097.3:p.Ala482Ser	rs74478221+ rs75467367
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*41	2851C>T	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2989G>A	NM_000106.6:c.985+39G>A	Variant occurs in a non-coding region (impacts slicing).	rs28371725
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
CYP2D6*49	100C>T	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	1612T>A	NM_00106.6:c.358T>A	NP_000097.3:p.Phe120Ile	rs1135822
	4181G>	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

[1] CYP2D6*36 is a gene conversion with CYP2D7; variants provided here are from the Pharmacogene Variation Consortium.
Alleles described in this table are selected based on discussion in the text above. This is not intended to be an exhaustive description of known alleles.
Nomenclature for Cytochrome P450 enzymes is available from PharmVar (28).

Nomenclature of Selected *ADRB1* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
Ser49Gly	ADRB1 Ser49Gly	NM_000684.3:c.145A>G	NP_000675.1:p.Ser49Gly	rs1801252
Arg389Gly	ADRB1 Arg389Gly	NM_000684.3:c.1165G>C	NP_000675.1:p.Gly389Arg	rs1801253

Nomenclature of Selected *ADRB2* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
Gly16Arg	ADRB2 Gly16Arg	NM_000024.6:c.46G>A	NP_000015.2:p.Gly16Arg	rs1042713
Glu27Gln	ADRB2 Glu27Gln	NM_000024.6:c.79G>C	NP_000015.2:p.Glu27Gln	rs1042714

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

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Version History

The April 4, 2017 version (1.0) of this chapter is available as a PDF here.

Version 2.0 published on September 19, 2024 encompasses new recommendations from CPIC that were not previously available as well as expanded recommendations from DPWG that include dosing adjustment guidelines for CYP2D6 IM and UM individuals. Language from the FDA-approved drug label discussing drug-drug interactions via CYP metabolism is also included in version 2.0. Updated *CYP2D6* allele information, activity scores and translation from genotype-based activity scores to predicted metabolizer phenotype are also provided in this version based on harmonized international standards. The Genetic Testing section also includes the recommendations from AMP regarding Tier 1 and Tier 2 alleles for *CYP2D6* pharmacogenetic testing.

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