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REVIEW article

Optimizing antihypertensive drug metabolism through pharmacogenomics by understanding CYP2D6 and CYP3A5 polymorphism

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Abstract: Hypertension is a major cause of cardiovascular diseases, with significant morbidity and mortality worldwide. While many effective antihypertensive drugs are on the market, patients respond variably to these drugs because of genetic variations in drug metabolism. Pharmacogenomics-the analysis of how genetic variation affects drug response-provides a tailored method for optimizing antihypertensive treatment. This review examines the impact of polymorphisms in the CYP2D6 and CYP3A5 enzymes on the metabolism of commonly prescribed beta-blockers and calcium channel blockers. Polymorphisms in CYP2D6 can have a dramatic impact on the degradation of beta-blockers, influencing drug clearance and leading to variable therapeutic effects. Poor metabolizers may develop higher drug levels, increasing the potential for side effects such as bradycardia and hypotension. Conversely, ultra-rapid metabolizers can clear the drug too rapidly, decreasing its efficacy. Likewise, CYP3A5 polymorphisms influence the metabolism of calcium channel blockers. Those who express CYP3A5 metabolize the drugs more rapidly and potentially need greater doses, whereas non-expressers metabolize them more slowly, raising the potential for drug build-up and toxicity. Pharmacogenomic testing incorporated into everyday practice can allow for individualized antihypertensive treatment according to an individual's genotype. This precision strategy increases treatment efficiency, reduces side effects, and enhances patient compliance. A transformation from a general to a personalized treatment paradigm by pharmacogenomics has the potential to transform the management of hypertension and enhance cardiovascular outcomes.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide and accounts for 17 million deaths every year [1]. Of all its most serious and modifiable risk factors, hypertension (HPT) is one whose prevalence across the world keeps increasing consistently [2]. The most common condition to be encountered in primary healthcare, HPT, if not diagnosed or inadequately treated, may result in very serious complications like heart attack, stroke, kidney failure, and even mortality [3]. Current data indicate that more than 116.4 million people are affected by HPT, contributing to about 2,303 daily deaths due to CVD [4, 5]. Projections suggest that within the next two decades, the number of individuals living with HPT will increase by 60.0%, reaching over 1.5 billion worldwide [2]. Notwithstanding increased public knowledge of HPT and its risks, blood pressure control (<140/90 mmHg) is still suboptimal in many treated patients [1, 6, 7]. Several reasons account for these poor results, including nonadherence to medication-typically secondary to side effects or cost and,

genetic variation in drug response [1, 8]. Clinical practice has shown that patients tend to respond differently to antihypertensive drugs [9]. This difference is usually determined by a mix of demographic, environmental, clinical, and genetic factors [10]. Genetic variation, specifically, plays an important role in how individuals react to the six primary categories of antihypertensive medication: calcium channel blockers (CCBs), diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists, and beta-blockers. Beta-blockers produce their antihypertensive impact through their effect on the renin-angiotensin-aldosterone system, hence reducing elevated blood pressure, **Figure 1**, [11]. The cytochrome P450 (CYP) enzyme system, which includes CYP2D6 and CYP3A5, is responsible for the metabolism of most antihypertensive drugs. Genetic variations in these enzymes can result in substantial variability in drug efficacy and clearance. Elucidation of the relationship between genetic variation (genotype) and drug response (phenotype) is necessary to maximize personalized HPT therapy [12]. Pharmacogenomics is the discipline that seeks to define the genetic causes of drug action and guide tailored medicine by aligning drug choice and dosage with an individual's genetic makeup. Pharmacogenomics also identifies those individuals who require increased monitoring. This strategy, central to precision medicine, looks to enhance treatment response by augmenting drug effectiveness and safety via stratification on the basis of genetic variation [10].

CYP2D6 polymorphisms and antihypertensive drug metabolism: CYP2D6, one of the most important enzymes in the cytochrome P450 family, has a heme-binding domain that is crucial for its function in drug metabolism. Its structural characteristic enables it to catalyse the oxidation of a wide range of drug agents. CYP2D6 participates in the metabolism of about 25.0% of all clinically prescribed drugs, such as adrenergic antagonists and angiotensin receptor blockers (ARBs) [13]. Interestingly, this enzyme shows considerable genetic polymorphism, leading to extensive interindividual variability in metabolic activity. These genetic variations can affect the efficiency with which drugs are metabolized, with a direct effect on therapeutic response, drug efficacy, and adverse effect risk [14].

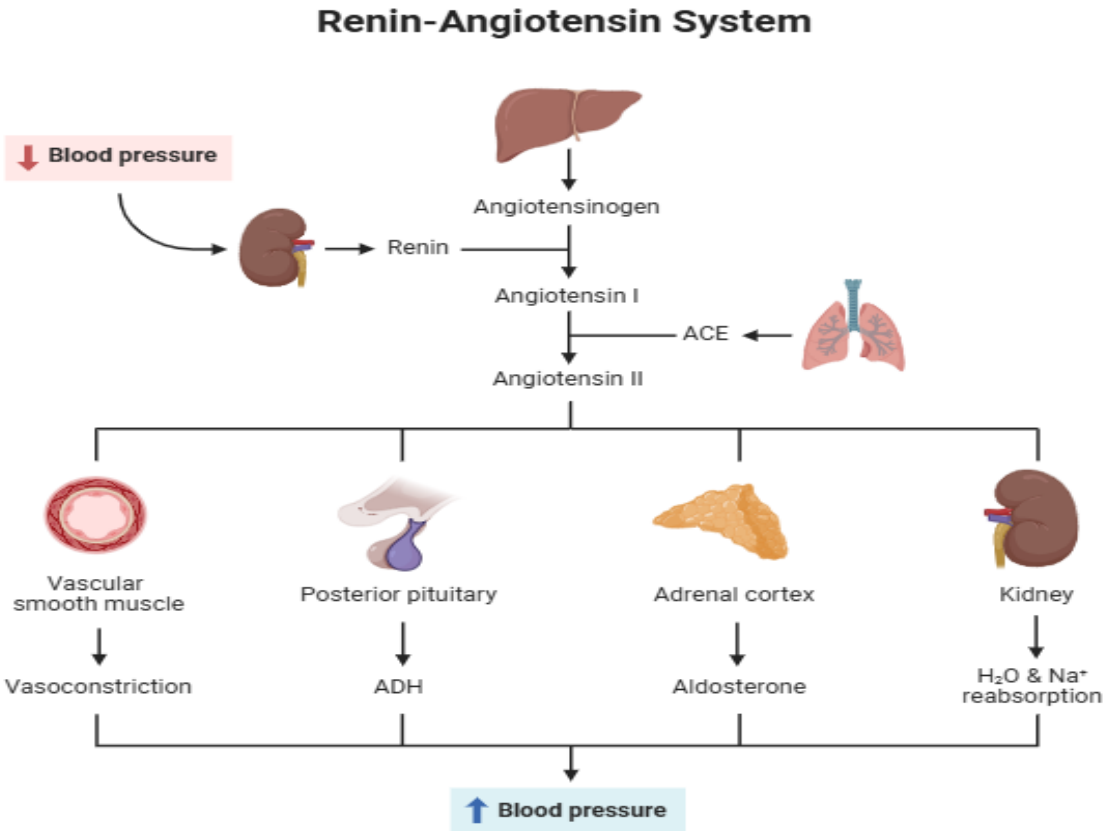

Figure 1: Renin-angiotensin-aldosterone system

Poor metabolizers: Patients who are designated as CYP2D6 Poor Metabolizers (PMs) have little or no enzyme activity owing to genetic polymorphisms, which lead to production of non-functioning or not present CYP2D6 enzymes [15]. This greatly hampers their potential to metabolize some drugs. For instance, metoprolol, a beta-blocker that is most often used to treat conditions like HPT, arrhythmias, angina, myocardial infarction, and heart failure, acts by selectively blocking beta1-adrenergic receptors, which occur mainly in the heart. By doing so, it decreases heart rate and the force of cardiac contractions. Metoprolol is metabolized extensively in the liver by the CYP2D6 enzyme (**Figure 2**). Based on its FDA-approved labelling, patients who are CYP2D6 PMs or normal metabolizers and taking CYP2D6 inhibitors concomitantly might have increased plasma levels of metoprolol. This could result in intensified pharmacologic effects and increased risks of adverse events like bradycardia, HPT, and fatigue. These complications can be avoided by advising dose reduction or the use of other beta-blockers that are not predominantly metabolized by CYP2D6.

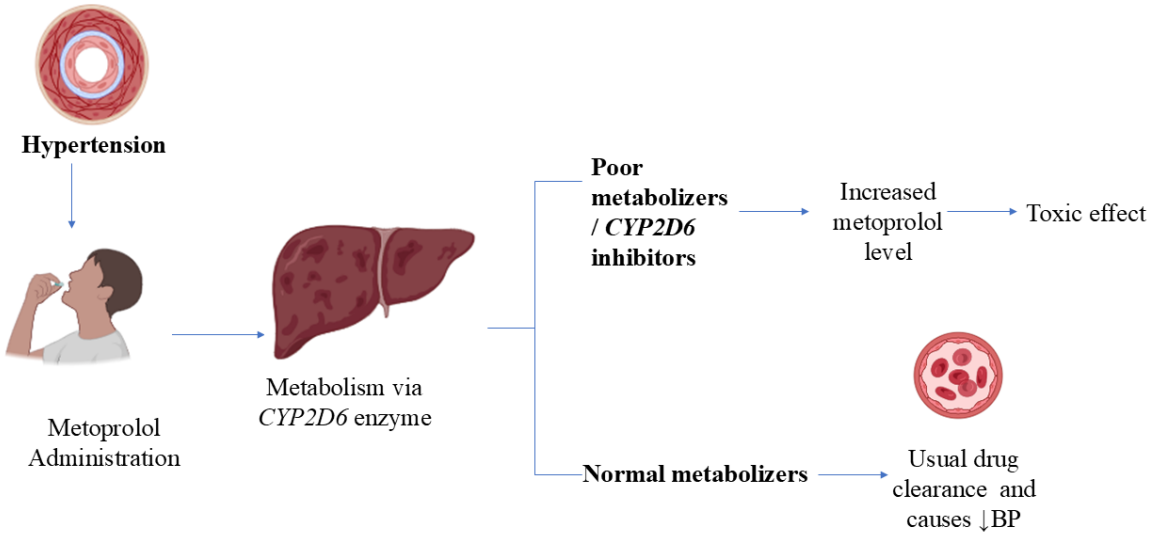

Figure 2: Impact of CYP2D6 metabolism on metoprolol clearance and toxicity in hypertension treatment

Intermediate metabolizers: People having the intermediate metabolizer (IM) phenotype have a genetic make-up that features either two reduced-function alleles or one non-functional allele and an allele with decreased activity. Consequently, CYP2D6 enzyme activity is partially compromised [16]. Nebivolol, which is a beta1-selective adrenergic blocker, is mainly metabolized by CYP2D6. In patients with reduced CYP2D6 activity - i.e., Ims- and PMs- the drug is more slowly cleared from the body. This decreased clearance can result in increased plasma levels, increased therapeutic effects, and an extended duration of action. As a result, patients may develop increased risks of adverse effects like excessive bradycardia, hypotension, and fatigue. To reduce such risks, PMs and IMs might need lower doses of Nebivolol. In a few instances, it might be more appropriate to switch to other beta-blockers such as atenolol or bisoprolol that are not significantly metabolized by CYP2D6 [17].

Extensive Metabolizers: Individuals who fall under the category of Extensive Metabolizers (EMs) have normal CYP2D6 enzymatic activity, leading to usual drug metabolism and clearance rates [18]. Alprenolol, which is a non-selective beta-blocker, is extensively metabolized with, most of its metabolites being eliminated in the urine. Its metabolism is characterized by three major pathways: aromatic hydroxylation, N-dealkylation (largely through CYP2D6), and direct glucuronidation [19].

Ultra-rapid Metabolizers: Ultrarapid Metabolizers (UMs) have genotypes related to highly increased CYP2D6 enzyme activity, typically secondary to gene duplications or multiplications [20]. Such increased enzyme function has a major impact on the pharmacokinetics of beta-blockers and can result in reduced therapeutic effect and modified dosing needs [15]. For instance, carvedilol, an antihypertensive non-selective

beta-blocker, is mainly metabolized via CYP2D6. In UMs, the heightened enzymatic activity leads to faster drug metabolism, which translates into decreased plasma levels. This reduces the efficacy of the drug in managing blood pressure (**Figure 3**). Clinicians might be required to escalate the dose or switch to a different antihypertensive drug that does not depend mainly on CYP2D6 metabolism [21].

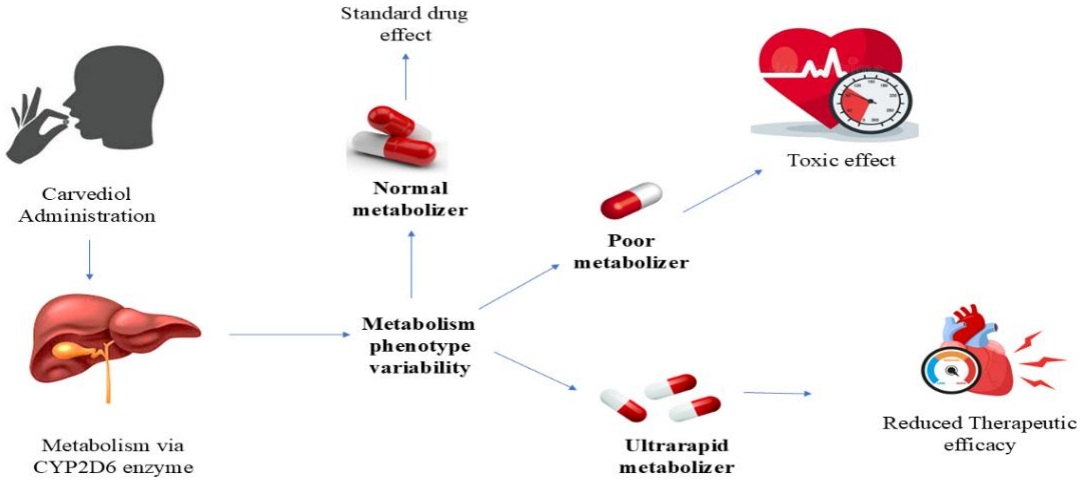

Figure 3: Impact of CYP2D6 metabolism variability on carvedilol therapeutic outcomes

CYP3A5 polymorphisms and metabolism of antihypertensive drugs: CYP3A5 belongs to the CYP3A subfamily and is found in the liver and small intestine of all people, where there is very high expression in the kidneys. The most commonly found CYP3A5*3 allele has a mutation in intron 3, which interferes with normal mRNA splicing and leads to a truncated, nonfunctional protein. The CYP3A5*1 allele, on the other hand, codes for a fully functional enzyme [22]. Recent studies indicate that CYP3A5 polymorphisms could be implicated in blood pressure regulation and potentially be a genetic risk factor for the onset of HPT. CYP3A enzymes are also involved in metabolizing cortisol to 6β-hydroxycortisol, a substance with a physiological role in regulating sodium transport across renal epithelial cells [23]. The existence of functional kidney CYP3A5 and resultant enhanced 6β-hydroxycortisol production is potentially able to augment sodium and water reabsorption by the kidneys, leading to elevated blood pressure. Therefore, genetic polymorphisms in CYP3A5 expression-particularly in the kidney-could influence blood pressure control and predispose individuals to HPT, **Figure 4**, [24].

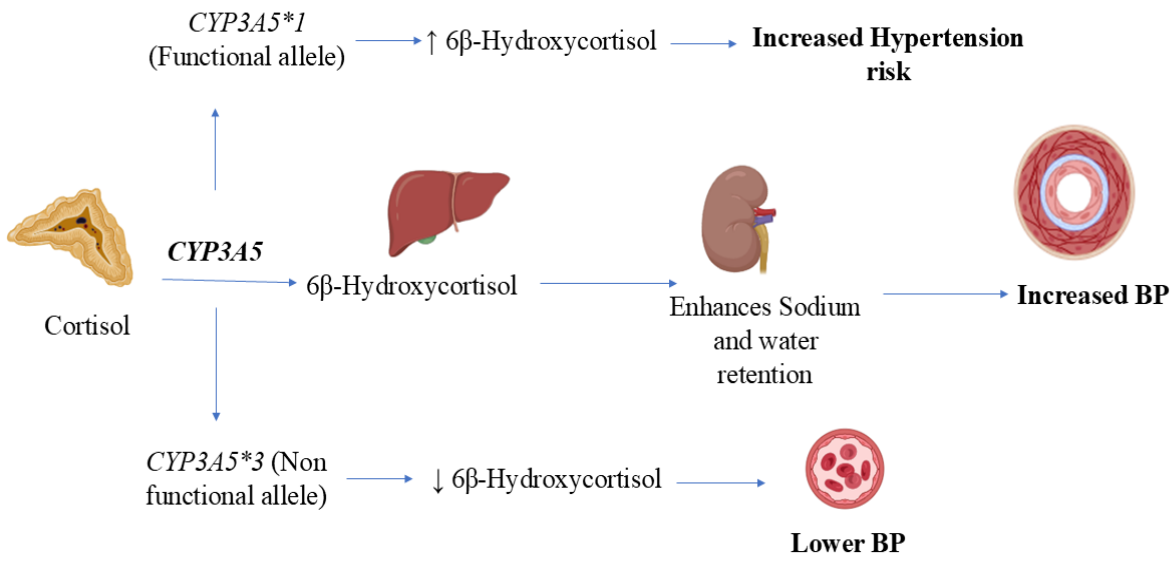

Figure 4: Impact of CYP3A5 genetic variants on cortisol metabolism and blood pressure regulation

CYP3A 4/5 enzyme activity and metabolism of calcium channel blockers: The enzymatic action of CYP3A4 and CYP3A5 is important in the metabolism of amlodipine, one of the most commonly used first-line long-acting calcium channel blockers (CCB). Amlodipine is effective by blocking the entry of calcium via L-type calcium channels in vascular smooth muscle cells, with decreased vasoconstriction and enhanced blood flow [2]. Polymorphisms for enzymes that carry out the metabolism of amlodipine, specifically to its biologically inactive pyridine metabolite (M9), influence drug response. Such polymorphic differences would potentially change the drug plasma level and, accordingly, the response to antihypertension of the patient [2]. Verapamil, another calcium channel blocker employed in the treatment of HPT, angina, and cardiac arrhythmia, is also a substrate of CYP3A enzymes. Variability among individuals in the expression of CYP3A, particularly CYP3A5, may result in variability in the metabolism of verapamil. Carriers of at least one CYP3A5 function allele usually have an increased metabolic capacity for verapamil that can decrease its plasma concentration and therapeutic effect, **Figure 5**, [25].

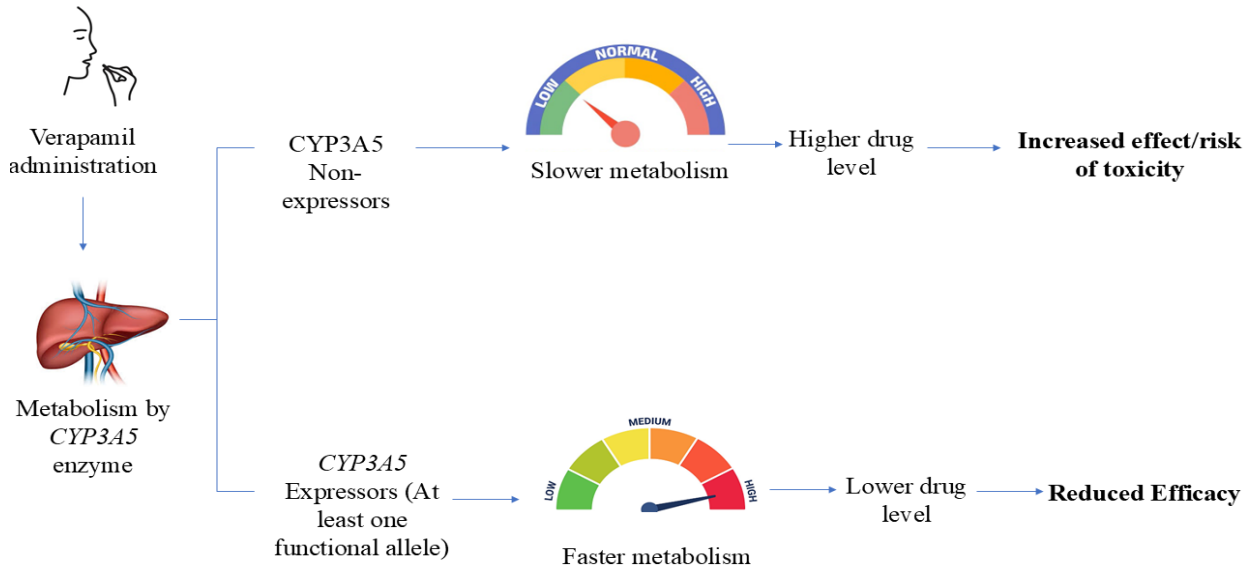

Figure 5: Effect of CYP3A5 genetic variability on verapamil metabolism and drug response

Persons with the CYP3A5 *1/*1 or 1/3 genotypes are expressors because they have active CYP3A5 enzymes. This leads to increased enzymatic activity, which causes drugs metabolized by CYP3A5 to be metabolized at a faster rate. Consequently, such persons will have lower plasma drug levels and reduced therapeutic effects [23]. Individuals with the CYP3A5 3/3 genotype are referred to as non-expressors, since this allele leads to non-functional enzymes. They have little or no CYP3A5 activity, leading to reduced drug metabolism. Therefore, they can have increased drug exposure, extended drug action, and a higher risk of side effects [26]. In the case of calcium channel blockers such as amlodipine, expressor patients could need increased doses to achieve therapeutic concentrations because drug clearance is more rapid. Conversely, non-expressor patients might need reduced doses in order to prevent drug accumulation and toxicity because the drug is cleared more slowly [27].

Pharmacogenomics-guided antihypertensive therapy: Antihypertensive drugs have been an established first line of treatment for reducing blood pressure to normal values and preventing organ damage due to HPT for many years [28]. First-line drugs are usually thiazide diuretics, CCBs, ACEIs, and ARBs, frequently in combination if necessary [29]. Of note, ACEIs and ARBs must not be combined because of the potential for harmful drug interactions [29]. Despite the existence of efficient drugs, non-adherence by patients, most times due to side effects, is a major hindrance, leading to the world's problem of uncontrolled HPT [29]. Compounding treatment outcomes are also issues like prescribing at an inappropriate level due to insufficient clinical experience and drug resistance [28]. The introduction of individualized treatment plans will

significantly improve the efficacy and safety of drugs, hence minimize the burden of HPT for society [29]. Pharmacogenomics (PGx) is concerned with comprehending how genetic differences shape an individual's reaction to drugs. In contrast to classical genetic screening that aims to find connections between gene mutations and disease, PGx determines how DNA variations impact drug metabolism, efficacy, and the likelihood of adverse effects- allowing for a tailored method of treatment [30]. Pharmacogenomics encompasses pharmacokinetics (how the body influences a drug through absorption, distribution, metabolism, and excretion) and pharmacodynamics (how the drug influences the body). These factors influence together a drug's therapeutic effect and toxicity [31]. Most drugs are metabolized in the liver by P450 (CYP) enzymes, whose genes encode particular gene families (e.g., CYP2C9). Apart from metabolizing enzymes, receptors, and transporters also play a crucial role in determining the response to drugs [32]. Technological advancements in genomic sequencing continue to discover new pharmacogenes that affect drug safety and efficacy, rendering pharmacogenomics an ever-changing and fast-paced field [28]. PGx-guided prescribing holds enormous potential in personalizing CVD treatment through reducing adverse drug reactions and enhancing therapeutic outcomes. Research indicates that it's more often combinations of gene variants, instead of one mutation, that control how patients respond to HPT medication [30]. For instance, the RIGHT (Right Drug, Right Dose, Right Time) trial examined five core pharmacogenes (CYP3A5, SLCO1B1, CYP2C19, CYP2C9, VKORC1, and CYP2D6), of which four are of relevance to HPT therapy. Interestingly, 58.0% of the study participants had clinically relevant genetic variants present in three or more of the above genes, demonstrating unequivocally an opportunity for PGx to dictate the choice of drug and dosage in a significant manner [30].

CYP2D6 & beta-blockers: The CYP2D6 enzyme is essential in the metabolism of beta-blockers, either activating or deactivating the medication based on the course of metabolism. Polymorphisms in the gene for CYP2D6 affect the ability of an individual to effectively rid the body of beta-blockers and directly impact the therapeutic effect and risk of side effects [15-19].

Table 1: Impact of CYP2D6 phenotype on drug metabolism and dosing recommendations

CYP2D6 Phenotype	Impact on drug metabolism	Recommendation
Poor Metabolizer	↓ Drug Clearance → increased risk of bradycardia, hypotension	Consider lower dose or switch to Atenolol (not CYP2D6 dependent)
Intermediate Metabolizer	Moderate ↓ metabolism → Increased Drug Levels	Monitor for side effects, titrate dose if necessary
Extensive/Normal Metabolizer	Normal metabolism	Standard dosing
Ultra-Rapid Metabolizer	Rapid clearance → decreased efficacy	Increase dose or change to different beta-blocker

CYP3A5 & calcium channel blockers: The CYP3A5 enzyme metabolizes calcium channel blockers like amlodipine and verapamil into their inactive states. Genetic polymorphisms in the CYP3A5 gene have been shown to significantly influence how these drugs are metabolized, with differences in plasma drug levels and antihypertensive response [25-27].

Table 2: Impact of CYP3A5 phenotype on drug metabolism and dosing recommendations

CYP3A5 phenotype	Effect on drug metabolism	Recommendation
Expressers (CYP3A5*1 carriers)	Faster metabolism → lower drug levels → reduced efficacy	Increased doses might be required
Non-Expressers (CYP3A5 3/3)	Slower metabolism → higher drug levels → increased risk of side effects	Consider a lower dose to avoid toxicity

Clinical evidence has emphasized the heterogeneity of patient responses to antihypertensive drugs. This interindividual variability can be partly explained by genetic polymorphisms and pharmacokinetic considerations. Increasing evidence supports the use of personalized pharmacotherapy that includes an individual's genetic makeup to inform treatment [28]. Consequently, genetically directed therapy is expected to be a key approach in the future treatment of HPT, especially for those patients who do not respond well to conventional therapy. This strategy seeks to determine the most effective and cost-effective antihypertensive drugs for an individual [28]. So far, genetic studies in HPT have been concerned with the identification of genes for high blood pressure, including the ACE I/D polymorphism and ATP2B1 gene variant, which have been implicated in the pathogenesis of HPT [28]. By means of pharmacogenomic testing, physicians can tailor antihypertensive therapy by identifying genetic variants that influence drug metabolism and therapeutic response. This approach enables maximized drug choice, optimized dosing, and a decrease in adverse effects, ultimately enhancing patient outcomes [2].

CYP2D6 and beta-blocker metabolism: CYP2D6 is an important liver enzyme involved in the metabolism of beta-blockers, which are widely used in the treatment of HPT, arrhythmias, and heart failure. Nonetheless, because of genetic polymorphisms, individuals metabolize beta-blockers at various rates, which affects their effectiveness and potential side effects. PMs have greatly decreased CYP2D6 activity, resulting in drug buildup and increased risk of bradycardia, hypotension, and fatigue. To prevent toxicity, a reduced dose or a different beta-blocker such as atenolol (not CYP2D6-dependent) is advisable. IIMs have moderately decreased metabolism, resulting in increased plasma drug levels, necessitating cautious dose adjustments and monitoring of side effects. EM/NMs process beta-blockers at a normal rate and generally need standard dosing. Conversely, UMs eliminate beta-blockers very rapidly, decreasing their effect, which may require increased doses or other medications. One of the best examples of CYP2D6-mediated metabolism is metoprolol, a beta-1 selective antagonist. PMs and IMs slowly metabolize metoprolol, causing elevated plasma drug levels and a higher risk of bradycardia and hypotension. In contrast, UMs over-metabolize the drug, resulting in decreased efficacy. In patients with marked CYP2D6 variations, atenolol or bisoprolol is a better choice, as these drugs are not mainly metabolized by CYP2D6 and provide more predictable action.

CYP3A5 and calcium channel blocker metabolism: CYP3A5 plays a major role in the metabolism of CCBs Amlodipine and Verapamil that reduce blood pressure through the induction of vascular smooth muscle relaxation. Drug metabolism is considerably affected by CYP3A5 genetic polymorphisms, resulting in differences in drug treatment response between individuals. People who are CYP3A5 expressers (CYP3A5*1 carriers) possess higher enzymatic activity, causing drug metabolism to occur more quickly and with reduced plasma levels of CCBs. This causes decreased efficacy, or the need for higher doses to achieve adequate blood pressure control. On the other hand, CYP3A5 non-expressers metabolize CCBs more slowly, which results in elevated plasma drug concentrations and increased risk of side effects like dizziness, hypotension, and peripheral oedema. To avoid toxicity, CCBs might require lower doses in these patients. For example, amlodipine is metabolized by CYP3A5 to inactive metabolites. CYP3A5 expressers metabolize amlodipine more rapidly, resulting in decreased drug levels and diminished antihypertensive action, necessitating greater doses to obtain the desired blood pressure reduction. CYP3A5 non-expressers have slower metabolism, with greater drug levels and increased risk of side effects, requiring dosing adjustments to prevent complications. Knowledge of CYP3A5 polymorphisms enables clinicians to individualize calcium channel blocker therapy, thereby optimizing dosing and reducing side effects. The potential of pharmacogenomic-guided antihypertensive therapy is in further developing knowledge about genetic variations that affect drug metabolism. As additional genetic polymorphisms associated with antihypertensive medication, including CYP2D6 and CYP3A5, come to light, treatment will continue to become more individualized. More sophisticated pharmacogenomic testing will enable physicians to prescribe medications based on a patient's genetic profile, with the best medicines selected with the least number of adverse effects. By incorporating pharmacogenetic information into everyday clinical practice, health professionals can enhance patient

outcomes, decrease drug resistance, and decrease non-adherence caused by side effects [8]. The personalized strategy will likely greatly increase the safety and effectiveness of antihypertensive therapy, making it more effective for a wide range of patients. Aside from genetic testing, the future will involve integrating pharmacogenomics into global treatment regimens that take into account other variables like environmental factors, lifestyle, and underlying medical conditions [33, 34]. As pharmacogenomic databases grow, predictive algorithms based on a person's entire genetic code could become the norm. These developments may facilitate a more comprehensive and personalized method of treating HPT, lowering healthcare expenditures, and enhancing long-term outcomes. With advancements in the field of pharmacogenomics, more accurate and effective treatments are potentially available that will eventually revolutionize HPT management, as well as the treatment of other diseases.

Conclusion: Hypertension is one of the leading risk factors for cardiovascular diseases. Despite the existence of potent antihypertensive drugs, patients respond differently to treatment. One of the principal reasons for such variability is genetic variation in drug metabolism, CYP2D6 and CYP3A5 polymorphism, which influences the way antihypertensive drugs are metabolized in the body. Pharmacogenomics, the analysis of how genes affect drug response, holds the promise of personalized therapy. Through the identification of genetic differences, clinicians can customize treatments, changing doses or medications to achieve the best blood pressure control while reducing the risk of side effects.

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تحسين استقلاب الأدوية الخافضة للضغط من خلال علم الصيدلة الجينية من خلال فهم تعدد أشكال CYP2D6 وCYP3A5

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*** الكاتب الذي يجب توجيه المراسلات إليه**

ملخص: يُعد ارتفاع ضغط الدم سببًا رئيسيًا لأمراض القلب والأوعية الدموية، مع معدلات اعتلال ووفيات مرتفعة عالميًا. على الرغم من توفر العديد من الأدوية الفعالة لخفض ضغط الدم في السوق، إلا أن استجابة المرضى لهذه الأدوية تختلف باختلاف الجينات في استقلاب الدواء. يوفر علم الصيدلة الجيني - وهو تحليل كيفية تأثير التباين الجيني على استجابة الدواء - طريقة مُصممة خصيصًا لتحسين علاج ارتفاع ضغط الدم. تدرس هذه المراجعة تأثير تعدد الأشكال في إنزيمي CYP2D6 وCYP3A5 على استقلاب حاصرات بيتا وحاصرات قنوات الكالسيوم الموصوفة عادةً. يمكن أن يكون لتعدد الأشكال في CYP2D6 تأثير كبير على تحلل حاصرات بيتا، مما يؤثر على تصفية الدواء ويؤدي إلى تأثيرات علاجية متفاوتة. قد ترتفع مستويات الدواء لدى الأشخاص الذين يعانون من ضعف في عملية الأيض، مما يزيد من احتمالية ظهور آثار جانبية مثل بطء القلب وانخفاض ضغط الدم. في المقابل، يمكن للأشخاص الذين يعانون من سرعة الأيض العالية أن يتخلصوا من الدواء بسرعة كبيرة، مما يقلل من فعاليته. وبالمثل، تؤثر تعدد أشكال CYP3A5 على استقلاب حاصرات قنوات الكالسيوم. أولئك الذين يُعبّرون عن CYP3A5 يستقلبون الأدوية بسرعة أكبر، وقد يحتاجون إلى جرعات أكبر، بينما يستقلبها غير المُعبّرين عنها ببطء، مما يزيد من احتمالية تراكم الدواء وسميته. يمكن للاختبارات الدوائية الجينية المُدمجة في الممارسة اليومية أن تُتيح علاجًا فرديًا لارتفاع ضغط الدم وفقًا للنمط الجيني لكل فرد. تزيد هذه الاستراتيجية الدقيقة من فعالية العلاج، وتقلل من الآثار الجانبية، وتعزز التزام المريض. ومن شأن التحول من نموذج علاجي عام إلى نموذج علاجي شخصي من خلال علم الصيدلة الجينية أن يُحدث نقلة نوعية في إدارة ارتفاع ضغط الدم، ويُحسّن نتائج علاج أمراض القلب والأوعية الدموية.