Impact of Gene Polymorphism on Pharmacokinetics and Pharmacodynamics of Calcium Channel Blockers: A Narrative Review

Sarah Puspita Atmaja1, Dwi Aris Agung Nugrahaningsih2, Ellsya Angeline Rawar1, Ani Kristiyani1, Ahmad Hamim Sadewa3 and Dita Maria Virginia4

1. Faculty of Pharmacy, Universitas Kristen Immanuel. Jl. Ukrim no. km 11, Kalasan, Sleman 55571, Yogyakarta, Indonesia
2. Department of Pharmacology and Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Sekip Utara 55281, Yogyakarta, Indonesia
3. Department of Biochemistry, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Sekip Utara 55281, Yogyakarta, Indonesia
4. Division of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Sanata Dharma, Yogyakarta, Indonesia

ABSTRACT

A class of drugs known as calcium channel blockers (CCBs) is used to treat hypertension, angina, and arrhythmias. There are two subcategories of this medication class: dihydropyridines and non-dihydropyridines. Studies on CYP3A5*3, AGTR1 rs275653, ABCB1 (MDR1) rs1045642, and POR*28 A503V have all investigated the effects of SNPs on CCBs. In this study, further research will be conducted to determine which SNPs most influence the efficacy of CCBs. The narrative reviews in this article come from a variety of sources. We performed searches in PubMed, ScienceDirect, and Google Scholar using the terms "calcium channel blocker," "efficacy," "blood pressure response," "pharmacokinetic," and "polymorphism" OR "genetic" OR "genomic" to find relevant articles. When prescribing antihypertensive drugs, especially calcium channel blockers, it is essential to consider specific gene variants, for example, CYP3A5*3/*3, CYP3A4 *1G/*1G, MDR1 C3435T, RyR3 gene rs877087, because of their significant effects.

Keywords: calcium channel blocker, gene polymorphism, efficacy

INTRODUCTION

Calcium channel blockers (CCBs) are a class of drugs used to treat hypertension, angina, and arrhythmias (Sica, 2005). CCBs bind to and inhibit L-type calcium channels by preventing calcium entry into smooth muscle cells of the heart and blood vessels, resulting in vasodilation that lowers vascular resistance and arterial blood pressure (Laurent, 2017). For the initial treatment of preventing stroke and myocardial infarction, the meta-analysis revealed that using a calcium channel blocker may be superior to an angiotensin II receptor blocker (Wu et al., 2014). In another study, CCB was more effective than hydrochlorothiazide in preventing end-stage renal disease (Bakris et al., 2010). This class of drugs is divided into two subclasses: dihydropyridines and non-dihydropyridines. Dihydropyridines have a more significant vasodilating effect than non-dihydropyridines (Chandra & Ramesh, 2013). Amlodipine, nifedipine, and felodipine are examples of CCBs belonging to the dihydropyridine class, whereas verapamil and diltiazem are non-dihydropyridines.

Most calcium channel blockers are extensively metabolized by CYP3A4/5 (Zisaki et al., 2014). Single-nucleotide polymorphisms (SNPs) in cytochrome P450 CYP3A5 can increase the rate of metabolism of dihydropyridine CCBs (Bhatnagar et al., 2010). Amlodipine, a dihydropyridine, is known to be a substrate of ATP-binding cassette subfamily B member 1 (ABCB1). Polymorphism of the transporter gene may affect the bioavailability of amlodipine (Johnson et al., 2019). Other gene variants that affect blood pressure control with calcium channel blockers include ryanodine receptor 3 (RYR) (Lynch et al., 2013).
Several studies have investigated the impact of SNPs on CCBs, including CYP3A5*3, AGTR1 rs275653, ABCB1 (MDR1) rs1045642, and POR*28 A503V (Guo et al., 2015; Do et al., 2016; Xiang et al., 2017; Sychev et al., 2018). However, which gene has the most significant impact on CCB or how genetic variations interact is unknown. Therefore, this review will further investigate which SNPs have the most significant impact on CCB efficacy.

MATERIALS AND METHODS

Search Technique

This article is a compilation of narrative reviews from several sources. Using the terms ‘calcium channel blocker’, ‘efficacy’ OR ‘blood pressure response’ OR ‘pharmacokinetic’, and ‘polymorphism’ OR ‘genetic’ OR ‘genomic’, we searched PubMed, ScienceDirect, and Google Scholar for relevant literature. The search was restricted to literature published between 2010 and 2022.

Criteria for Inclusion and Exclusion

Inclusion criteria for the article search included: (1) articles published between 2010 and 2022; (2) articles discussing the effect of gene variations on the pharmacokinetics, efficacy, or blood pressure control of calcium channel blocker antihypertensives; (3) original research; and (4) articles written in English. Articles with an in-silico, in-vitro, or in-vivo research design and review articles will be excluded.

Search Outcomes

The search returned 1,447 articles from three different databases. The remaining articles were chosen based on inclusion and exclusion criteria after 283 articles were eliminated because they lacked the full text. The remaining 23 articles served as sources for research (Figure 1).

Data Extraction

Each article's information is organized into several distinct sections: (1) authors, (2) year of publication, (3) subjects of the study, (4) types of CCB drugs, (5) gene polymorphisms, and (6) results obtained. The results of each article's extraction will be tabulated in a table (Table I), along with a description of each gene polymorphism and its effect on CCB.

RESULTS AND DISCUSSION

This review will examine all gene polymorphisms that have influenced the pharmacokinetic profile and control of blood pressure-lowering antihypertensive calcium channel blockers over the past 12 years (2010–2022).

Calcium Channel Blocker

Calcium channel blockers work by inhibiting calcium influx by blocking L-type calcium channels, thereby preventing depolarization in vascular smooth muscle cells, cardiac myocytes, and sinoatrial and atrioventricular nodes (Laurent, 2017). The ultimate effect of this mechanism is vasodilation, which can lower blood pressure (Sica, 2005). The dihydropyridine calcium blocker group has more significant vasodilating potential than the non-dihydropyridine calcium blocker group. It is safer for patients with heart failure because it has fewer adverse inotropic effects (Chandra & Ramesh, 2013). Amlodipine, one of the dihydropyridine drugs, is metabolized by multiple CYP pathways, including CYP3A4. Similarly, CYP3A4 converts the non-dihydropyridine group in verapamil to the nor verapamil form. Verapamil is also known to be a P-glycoprotein substrate (Ueno & Sato, 2012). The half-life of amloidine is greater than 44 hours, while that of nifedipine is between 0.2-1 hour (Elliott & Ram, 2011).

CYP3A5 gene polymorphism and the effect on CCB

Human chromosome 7q22.1 contains the CYP3A subfamily, which consists of four isoforms: CYP3A4, CYP3A5, CYP3A7, and CYP3A43. CYP3A4
is required to metabolize nearly half of all clinically administered drugs. The structural similarity between CYP3A5 and CYP3A4 results in overlapping substrates (Tornio & Backman, 2018). The expression of the CYP3A5 gene is highly polymorphic, with 25 allele variants. The CYP3A5*3 allele is the most common allele found in the population and has been extensively studied (Lamba et al., 2016). People in America, Europe, East Asia, and South Asia are most likely to have this variant, with 80%, 94%, 71%, and 67%, respectively (Y. Zhou et al., 2017).

Individuals with CYP3A5*3/*3 have a poor metabolizer phenotype, while those with CYP3A5*1/*3 have an intermediate metabolizer phenotype, and those with CYP3A5*1/*1 have a normal metabolizer phenotype (Tornio & Backman, 2018). This was demonstrated in studies examining the effect of CYP3A5*3 on drug-level changes. Simvastatin levels were higher in people with CYP3A5*3/*3 than in those with CYP3A5*1/*3 or *1/*1 (Kitzmiller et al., 2014). Furthermore, research on tacrolimus therapy revealed that CYP35 *1/*1 and *1/*3 individuals required more time to reach steady-state concentrations than CYP35 *3/*3 individuals (Durand et al., 2013).

In a study of antihypertensive drugs in the calcium channel blocker class, the same changes in pharmacokinetic profile occurred. Individuals with CYP3A5*3/*3 had a higher mean Area Under the Curve (AUC) for felodipine than those with CYP3A5*1/*3 (Xiang et al., 2017). Similarly, the pharmacokinetic study of tlyceridine hydrochloride revealed that subjects with CYP3A5*3/*3 genotype had a 1.35 fold longer than the CYP3A5*1/*1 group. Additionally, the 1/2 of CYP3A5*3 carriers was a 1.32-fold increase in length compared to the wild-type group (S. Zhou et al., 2019). The maximum levels (C-max) and AUC of diltiazem were significantly higher in subjects with CYP3A5*3/*3 than in those with CYP3A5*1/*1 or CYP3A5*1/*3 (L. Y. Zhou et al., 2016). Oral clearance of nifedipine was lower in subjects with CYP3A5*3 than in subjects with CYP3A4*1 (M et al., 2014). However, the variation of CYP3A5*3 does not affect the variation of amlodipine levels and pharmacokinetic profiles (Guo et al., 2015; Han et al., 2020).

In terms of clinical outcome, the efficacy of amlodipine was significantly higher in patients with the CYP3A5*3/*3 genotype than in patients with other CYP3A5 genotypes (p<0.05). In addition, the decrease in diastolic blood pressure (DBP) in patients with the CYP3A5*3/*3 genotype was more significant than in patients with other CYP3A5 genotypes (p<0.05) (Huang et al., 2017). However, Bhatnagar et al. (2010) found no correlation between CYP3A5 and amlodipine’s effectiveness (Bhatnagar et al., 2010). In a study by Türkmen et al. (2022), the incidence of chronic renal failure in patients receiving dihydropyridine and without a history of chronic renal failure was 12.3%, 6.6%, and 6.8%, respectively, in patients with CYP3A5*3 TT homozygous, heterozygous, and homozygous CC (Türkmen et al., 2022).

### CYP3A4 gene polymorphism and the effect on CCB

Cytochrome 450 3A4 (CYP3A4) is a large group of endogenous and exogenous cytochrome metabolizers encoded by the CYP3A4 gene. The CYP3A4 gene is part of the cytochrome P450 gene family, found on chromosome 7q22.1 (L. P. Zhou et al., 2013). There are more than 139 CYP3A4 variants that have been characterized. CYP3A4*1A is a wild type, whereas CYP3A4*1B is a -392A>G mutation in the 5’UTR region. CYP3A4*1G is found in intron 10 of the CYP3A4 gene, which has been studied extensively in Asian populations (Saiz-Rodríguez et al., 2020). CYP3A4*22 is one of the widely studied single nucleotide polymorphisms (SNPs) because these SNPs are located in introns and are associated with decreased CYP3A4 activity (Werk & Cascorbi, 2014). CYP3A4*2, CYP3A4*12 and CYP3A4*17 gene variants are rare, and their effects are unknown (Saiz-Rodríguez et al., 2020). CYP3A4*1G/*1G variant in Fentanyl-using patients revealed that patients require less fentanyl than those with CYP3A4*1/*1 and CYP3A4*1/*1G (W. Zhang et al., 2010). In addition, studies employing sufentanil have confirmed this result (H. Zhang et al., 2017). Individuals with CYP3A4*3, CYP3A4*20, and CYP3A4*22 have a greater Area Under the Curve (AUC) for fentanyl, imatinib, and quetiapine (Saiz-Rodríguez et al., 2020).

Variations in the CYP3A4 gene have been reported to affect several calcium channel blockers used to treat hypertension. In a study by Xiang et al. (2017) on felodipine-taking patients with the CYP3A4 gene variant, the CYP3A4*1/*1 carriers displayed trends of higher AUC (0–72) compared to the CYP3A4*1/*18B carriers. However, the difference was insignificant (P = 0.38) (Xiang et al., 2017). In contrast, in the study of the effect of CYP3A4*1B gene variation, a significant relationship was found between CYP3A4*1B and increased nifedipine clearance in patients with these gene variations.
Table I. A summary of the result of the gene polymorphism that have influenced calcium channel blocker.

<table>
<thead>
<tr>
<th>Author</th>
<th>Subject</th>
<th>CCB drug name</th>
<th>The genes that are thought to affect CCB</th>
<th>Gene polymorphism</th>
<th>Effect on CCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Han et al., 2020)</td>
<td>Healthy male subjects</td>
<td>amlodipine</td>
<td>POR, CYP3A4, CYP3A5</td>
<td>POR g.57332T&gt;C, POR g.56551G&gt;A, CYP3A4<em>1G and CYP3A5</em>3</td>
<td>Cmax was higher in T allele carriers than CC genotype of POR g.57332T&gt;C and wild-type POR g.56551G&gt;A allele. No significant effects of CYP3A4 and CYP3A5 polymorphisms</td>
</tr>
<tr>
<td>2 (Do et al., 2016)</td>
<td>Essential hypertensive patients</td>
<td>amlodipine</td>
<td>AGTR1, FVII</td>
<td>AGTR1 rs275653, FVII rs762637</td>
<td>No significant difference in blood pressure reduction between AGTR1 rs275653 and FVII rs6046 affect amlodipine response in reducing diastolic blood pressure (DBP)</td>
</tr>
<tr>
<td>3 (Zhang et al., 2017)</td>
<td>Essential hypertensive patients</td>
<td>amlodipine</td>
<td>PRKCH</td>
<td>PRKCH rs2230500 for GG, GA, and AA</td>
<td>No significant difference in blood pressure reduction between PRKCH rs2230500 (GG vs GA/AA) genotypes in the amlodipine group</td>
</tr>
<tr>
<td>4 (Zhang et al., 2016)</td>
<td>Essential hypertensive patients</td>
<td>amlodipine</td>
<td>GNB3</td>
<td>GNB3 G825T</td>
<td>No difference in SBP, DBP and MAP in G825T between before and after amlodipine treatment</td>
</tr>
<tr>
<td>5 (He et al., 2020)</td>
<td>Essential hypertensive patients</td>
<td>felodipine</td>
<td>TRIB3</td>
<td>rs6037475</td>
<td>TRIB3 rs6037475 CC genotype had significantly higher mean SBP, DBP and MAP than those with TT genotype in the felodipine treatment group.</td>
</tr>
<tr>
<td>6 (Lynch et al., 2013)</td>
<td>Essential hypertensive patients</td>
<td>amlodipine</td>
<td>RYR3</td>
<td>rs877087</td>
<td>RYR3 rs877087 had a higher risk of heart failure when randomized to amlodipine, compared to other treatment</td>
</tr>
<tr>
<td>7 (Xiang et al., 2017)</td>
<td>Healthy subject</td>
<td>felodipine</td>
<td>CYP3A4, CYP3A5, BCRP</td>
<td>CYP3A4<em>1B, CYP3A5</em>3, BCRPC421A</td>
<td>No statistically significant difference between CYP3A4*1/<em>1 vs CYP3A4</em>1/<em>18B in the value of AUC(0-72) influenced by BCRP C421A and CYP3A5</em>3/*3. No statistically significant differences were associated with changes in blood pressure</td>
</tr>
<tr>
<td>8 (Haas et al., 2013)</td>
<td>Pregnant women</td>
<td>nifedipine</td>
<td>CYP3A4, CYP3A5</td>
<td>CYP3A4*1B, CYP3A5 alleles (*1, *3, *6, or *7)</td>
<td>CYP3A4<em>1B and the haplotype combination (CYP3A4</em>1B + CYP3A5*1) were significantly correlated with the level of CL/F A-638G was significantly associated with changes in blood pressure</td>
</tr>
<tr>
<td>9 (Sugimoto et al., 2010)</td>
<td>Hypertensive patients with type 2 diabetes</td>
<td>azelnidipine</td>
<td>RGS2</td>
<td>RGS2 A-638G (rs2746071)</td>
<td>SNPs in PICALM, TAN2, NUMA1 and APCDD1 were found to be associated with CCB responses</td>
</tr>
<tr>
<td>10 (Kamide et al., 2013)</td>
<td>Essential hypertensive patients</td>
<td>Calcium channel blocker</td>
<td>PICALM, TANC2, NUMA1, APCDD1</td>
<td>rs588076, rs2429427, rs10898815, rs564991</td>
<td>SNPs in PICALM, TANC2, NUMA1 and APCDD1 were found to be associated with CCB responses</td>
</tr>
<tr>
<td>11 (Zuo et al., 2014)</td>
<td>Hypertensive patients</td>
<td>amlodipine</td>
<td>ABCB1, CYP3A4, CYP3A5, ABCB1 C3435T, CYP3A5, POR</td>
<td>ABCB1 3435CC, or CT genotype have greater decreases in blood pressure. No significant effect of CYP3A4<em>1G, CYP3A5</em>3, POR<em>2 CYP3A5</em>3 and CYP3A4*1G influence tylerdipine pharmacokinetics (AUC0-24, t1/2)</td>
<td></td>
</tr>
<tr>
<td>12 (Zhou et al., 2019)</td>
<td>Healthy subject</td>
<td>tylerdipine hydrochloride</td>
<td>CYP3A4, CYP3A5</td>
<td>CYP3A4<em>1G and CYP3A5</em>3</td>
<td>ABCB1 3435CC, or CT genotype have greater decreases in blood pressure. No significant effect of CYP3A4<em>1G, CYP3A5</em>3, POR<em>2 CYP3A5</em>3 and CYP3A4*1G influence tylerdipine pharmacokinetics (AUC(0-24), t1/2)</td>
</tr>
</tbody>
</table>
Table I. A summary of the result of the gene polymorphism that have influenced calcium channel blocker.

<table>
<thead>
<tr>
<th>Author</th>
<th>Subject</th>
<th>CCB drug name</th>
<th>The genes that are thought to affect CCB</th>
<th>Gene polymorphism</th>
<th>Effect on CCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatnagar et al, 2010</td>
<td>Hypertensive patients with renal disease</td>
<td>amlodipine</td>
<td>CYP3A4, CYP3A5</td>
<td>CYP3A4 T16090C SNP was significantly associated with blood pressure responses. CYP3A5 A6986G was not associated with blood pressure response.</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>F. He et al, 2013</td>
<td>Essential hypertensive patients</td>
<td>Azelnidipine &amp; nitrendipine</td>
<td>hERG or KCNH2</td>
<td>KCNH2 (1956, C.T) was statistically significant interactions with DBP and MAP change on azelnidipine or nitrendipine therapy</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>Punzallan et al, 2022</td>
<td>Essential hypertensive patients</td>
<td>Calcium channel blocker</td>
<td>FGF 5</td>
<td>rs1458038</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>Zhou et al, 2016</td>
<td>Adult kidney transplant patients</td>
<td>Diltiazem</td>
<td>CYP3A4, CYP3A5</td>
<td>CYP3A4<em>1G and CYP3A5</em>3, CYP3A5*3.</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>Xu et al, 2012</td>
<td>Essential hypertensive patients</td>
<td>Lercanidine</td>
<td>MTHFR</td>
<td>MTHFR C677T did not affect the antihypertensive effects of the lercanidine treatment but had associated with the vascular protective effects of short-term lercanidine treatment</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>Guo et al, 2015</td>
<td>Essential hypertensive patients</td>
<td>Amlodipine</td>
<td>CYP3A4, CYP3A5, POR and MDR1</td>
<td>POR A503V, CYP3A4<em>1G, CYP3A5</em>3, MDR1 C3435T</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>Niu et al, 2010</td>
<td>Hypertensive verapamil patients with coronary artery disease</td>
<td>Verapamil</td>
<td>CACNB2</td>
<td>rs2357928</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>Huang et al, 2017</td>
<td>Hypertension following renal transplantatin on</td>
<td>Amlodipine</td>
<td>CYP3A4, CYP3A5, MDR1</td>
<td>CYP3A4<em>1G, CYP3A5</em>3, MDR1 C3435T</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>Zhou et al, 2019</td>
<td>Essential azelnidipine/nitrendipine patients</td>
<td>Tribbles homolog 3</td>
<td>TRIB3 (251, A &gt; G, rs2295490)</td>
<td>Azelnidipine or nitrendipine had a better antihypertensive effect on TRIB3 (251, A &gt; G) AA genotype carriers than on AG/GG genotype carriers.</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>Sychev et al, 2018</td>
<td>Essential hypertensive patients</td>
<td>Amlodipine</td>
<td>ABCB1 (MDR1)</td>
<td>ABCB1 (MDR1) rs1045642</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
<tr>
<td>Türkmken et al, 2022</td>
<td>Essential hypertensive patients</td>
<td>Dihydropyridines</td>
<td>CYP3A5, RYR3, NUMA1, (RYR3) rs8777087, CYP3A5 rs776746, NUMA1 rs10898815</td>
<td>Patients with common genetic variants in NUMA1, CYP3A5 and RYR3 had increased adverse clinical outcomes.</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
</tr>
</tbody>
</table>
Furthermore, subjects with the haplotype combination (CYP3A4*1B+CYP3A5*1) were significantly associated with higher clearance (Haas et al., 2013). On the other hand, the CYP3A4*1B gene variation study did not affect changes in the pharmacokinetic profile of amlodipine (Zuo et al., 2014). The discrepancy in these results may be due to the different conditions of the subjects; in a study conducted by Haas et al. (2013), they observed the effect of these gene variations on nifedipine in pregnant women. Pregnant women may experience metabolic shifts. Pregnancy-related hormones (PRH) increase the concentration of CYP3A4 during pregnancy, which can also increase nifedipine metabolism (Khatri et al., 2021).

Amlodipine concentration changes were unaffected by the CYP3A4*1G gene polymorphism (Guo et al., 2015). However, this is distinct from the findings of other studies. The effect of CYP3A4 gene variation revealed that in the wild-type group, the mean dose-corrected AUCO–24h of tylerdipine hydrochloride was 1.35-fold longer than in CYP3A4*1G carriers (p = 0.018) (S. Zhou et al., 2019). These findings support the findings of Zhou et al. (2016), who discovered that patients with the CYP3A4*1/*1 genotype had higher diiltiazem concentrations than those with the CYP3A4*1G*1G variant. Variations in the CYP3A4 gene also have an impact on blood pressure control. Individuals with a C/C or T/C genotype were twice as likely to achieve a target MAP of 107 mm Hg compared to those with a T/T genotype: 2.04 (1.17–3.56; adjusted p = 0.01) (Bhatnagar et al., 2010). Another study found that patients with the CYP3A4*1G*1G genotype had a significantly higher reduction in diastolic blood pressure (DBP) than patients with other CYP3A4 genotypes (p=0.005) (Huang et al., 2017). Since CYP3A4 is the most abundant metabolizing enzyme in the body, its effect on drug metabolism, in this case, calcium channel blockers, cannot be overlooked. In addition, the CYP3A5 genotype is closely related to the CYP3A4 haplotype, and the substrates of CYP3A4 and CYP3A5 overlap, so it would be ideal if the study examined the effects of these haplotypes.

**POR gene polymorphism and the effect on CCB**

The POR gene is involved in the production of the enzyme Cytochrome P450 Oxidoreductase, which is involved in drug and steroid metabolism. POR transports electrons from Nicotinamide Adenine Dinucleotide Phosphate (NADPH) to all Cytochrome P450 microsomal in the endoplasmic reticulum (Pandey & Sproll, 2014). In humans, the POR gene is located on chromosome 7Q1.2.3. It consists of one non-coding exon region and 15 exon codes of protein that encodes the protein-bound membrane having 680 amino acids. The gene is 78-KDa in size and is made up of Flavin Adenine Dinucleotide (FAD) and Flavin Mononucleotide (FMN) moieties (Miller et al., 2009).

The level of variation of this POR gene is very high. One hundred forty single nucleotide polymorphisms were present in >1% of African-American, Caucasian-American, Mexican-American, and Asian (Han Chinese) American populations. The most prevalent polymorphism is A503V, which changes the 503rd amino acid from alanine to valine (Miller et al., 2011).

The structure of the POR gene consists of an NADPH-binding site, FAD in one lobe, FMN in the other, and a P-450 interacting domain. Several steps are required for the POR gene to provide electrons to the CYP450 enzyme. First, electrons are transferred from NADPH to FAD to FMN to P450 (Agrawal et al., 2010). It suggests that variations in POR will affect the activity of CYP enzymes. The POR A287P mutation found in European populations reduces CYP3A4 enzyme activity by 75% (Nicolo et al., 2010). Meanwhile, populations with POR variants A503V, G504R, R316W, and G413S had the same activity level as populations with wild-type genotypes (Flück et al., 2010).

Three studies investigating the influence of variants in the POR*28 A503V gene on the pharmacokinetics profile of amlodipine found that the gene variation did not affect changes in amlodipine levels (Zuo et al., 2014; Guo et al., 2015; Han et al., 2020). The effect of POR variation on CYP3A4 is dependent on the specific substrates (Burkhard et al., 2017), as demonstrated by the variation of POR*28 A503V, where the impact of lowered CYP3A4 activity is 61 per cent - 77 per cent of wild-type with testosterone and midazolam substrates. These versions have the same activity as the wild-type due to the use of quinidine and erythromycin substrates (Agrawal et al., 2010). In addition, Han et al. (2020) obtained SNP candidates from POR, specifically g. 57332T > C, which influences changes in the maximum level of amlodipine. Carriers of the g.57332T > C, T-allele had a C-max that was 21% higher than those with the CC genotype (p = 0.007). Furthermore, g.57332T > C was significantly associated with a 1.3-fold increase in C-max value in T-allele carriers compared to subjects with the CC genotype in
**BCRP/ABCG2 gene polymorphism and the effect on CCB**

The breast cancer resistance protein (BCRP) encoded by the *ABCG2* gene is the second member of the G subfamily of the ATP binding cassette (ABC) efflux transporter superfamily. In normal tissue, BCRP transporters can be identified in intestinal mucosal cells, hepatocytes, the placenta, endothelial microvesicles in microvascularization of the brain, and proximal tubular tubular cells in the kidneys. In the gastrointestinal tract, BCRP limits the absorption of drugs and toxins, whereas in the liver and kidneys, it aids in eliminating drugs and xenobiotics (Mao & Unadkat, 2015). There are 80 single nucleotide polymorphisms (SNPs) in the *ABCG2* gene, with the most significant nonsynonymous variant being *ABCG2* c.421 C > A, which converts glutamine to lysine (Q141K). East Asian populations have a higher prevalence of the *ABCG2* c.A21 C > A allele (30-60%) than African-American and Caucasian populations (5-10%). In addition to these allele variants, SNP *ABCG2* c.34G > A is prevalent in Asian populations, whereas *ABCG2* c.376 C > T and c.10000 G > T have a low frequency across all ethnic groups. Several studies indicate that the *ABCG2 c421 C > A* variant is a polymorphism with a clinical effect (Hira & Terada, 2018). When compared to wild-type mice, the absence of the *ABCG2* gene in genetically modified mice (*Mdr1a*/Mdr1b-/+/*Bcrp-/-* (triple knockout) group resulted in increased plasma levels of rivaroxaban and a significant decrease in clearance (Gong et al., 2013). This demonstrates that variations in the *BCRP* gene can affect its function as a xenobiotic efflux transporter, thereby altering a drug’s pharmacokinetic profile. *ABCG2* polymorphisms are known to influence the efficacy of chemotherapy drugs such as imatinib and sunitinib, which may contribute to the side effects of thrombocytopenia and hand-foot syndrome in sunitinib users (Koo et al., 2015; Sun et al., 2021). In addition, subjects with the A allele in the *ABCG2* gene variant 421 C > A had significantly higher peak levels than those with the CC genotype (Song et al., 2022).

**ABCB1/MDR1 gene polymorphism and the effect on CCB**

The *MDR1* gene encodes P-glycoprotein (P-gp), a transmembrane transporter. The transporter functions as an efflux pump dependent on adenosine triphosphate (ATP). It was found in the epithelium of the small and large intestines, adrenal glands, placenta (trophoblasts), kidney (the brush border of the renal tubule), liver (the canalicular membrane of the hepatocyte), pancreas (pancreatic duct cell), and liver endothelial capillary cells (Ieiri et al., 2004). According to an in vivo study using knockout mice (Kim et al., 1998), P-glycoprotein plays a vital role in the excretion of xenobiotics and endogenous substrates through the hepatocyte canalicular membrane into the bile, through the brush border membrane of enterocytes into the intestinal lumen, and through the brush border membrane of proximal tubules into the urine (Mayer et al., 1996). *BCB1 (MDR1)* is one of several adenosine triphosphate (ATP)-binding cassette (ABC) genes in subfamily B (MDR/TAP). The *ABCB1* gene contains 29 exons in a 209.6 kb genomic region, including two 5’ untranslated exons. The translation of these genes results in the production of 1280 amino acids known as P-glycoprotein (P-gp) (Hodges et al., 2012). Immunosuppressants (cyclosporine, tacrolimus), digoxin, antibiotics (erythromycin, levofloxacin), and calcium channel blockers are known to be P-glycoprotein substrates (diltiazem, verapamil). It is well known that the substrate of P-glycoprotein substantially overlaps with *CYP3A4* regarding substrate specificity (Wolking et al., 2015).

Variants of the breast cancer-related protein transporter gene (*BCRP*) with AA alleles have a higher mean felodipine AUC than those with *BCRP* CC or CA genotypes. In addition, *BCRP* C421A was significantly correlated with AUC (0-72) values (Xiang et al., 2017). According to the author’s review of the relevant literature, no studies have examined the effect of *BCRP* on other types of calcium channel blocker antihypertensives. No research has been done on how the haplotypes of the metabolizing genes (*CYP3A4* and *CYP3A5*) and the *BCRP* gene affect the pharmacokinetic profile of calcium channel blockers and their effect on lowering patients’ blood pressure. Therefore, there is still room for further research.
The most common MDR1 variant found in different ethnic groups is C3435T, with the 3435C allele frequency ranging from 34 to 90 per cent across populations (Hodges et al., 2012). Its effect on altering the pharmacokinetic profile was demonstrated in a study conducted by Zuo et al. (2014), who found that patients with the ABCB1 3435 TT genotype had 1.5-fold higher oral clearance of amlodipine than subjects with the ABCB1 3435 CT or 3435 CC genotype (Zuo et al., 2014). This finding was confirmed by Guo et al. (2014), who discovered that the plasma concentrations of patients with the MDR1 C3435T TT genotype were lower than those of the CC and CT genotypes. However, these gene variations did not affect antihypertensive efficacy (Guo et al., 2015). Clinical studies on the Caucasian race discovered that patients with the TT genotype had the highest antihypertensive effect and the lowest incidence of side effects. In contrast, patients with the CC genotype had a low antihypertensive effect and a high incidence of side effects (Sychev et al., 2018). Individuals with the ABCB1 gene variations 3435 CC and 3435 CT will express more P-gp than those with variant 3435 TT. Reduced P-gp activity in the liver increases intrahepatic drug absorption, which increases the metabolism of drugs that are co-substrates of CYP3A and P-gp by CYP3A4 in the liver (Meibohm et al., 2002).

**TRIB3 gene polymorphism and the effect on CCB**

Homologous tribble 3 (TRIB3), also known as NIPK/Skip3/TRB3, is located on chromosome 20p13-p12.2 and belongs to the 'tribbles' pseudokinase family. There are three distinct types of genes in mammals, namely TRIB1, TRIB2, and TRIB3. TRIB3 contains four exons that codify 358 amino acid proteins (Prudente & Trischitta, 2015). TRIB3 plays a role in insulin signalling, insulin secretory capacity, adipose and muscle cell differentiation, and endoplasmic reticulum stress (Prudente et al., 2012). The interaction between TRIB3 and Akt contributes to the physiological processes of blood vessels. This is because Akt mediates the phosphatidylinositol 30-kinase protein kinase B-endothelial nitric oxide (NO) synthase (PI3K-AKT-eNOS)-dependent pathway in cardiovascular cells. This pathway is crucial for NO synthase activation, which increases NO production, vasodilation, and blood flow (Yu et al., 2011).

TRIB3 Q84R (251, A > G, rs2295490) is a TRIB3 gene variant that has been studied both in vitro and in vivo. The gene polymorphism is located in exon 2. It is a missense mutation because it replaces glutamine (Q) at position 84 with arginine (R), thereby strengthening the Akt bond and reducing Akt phosphorylation (Fischer et al., 2017). Prudente et al. (2005) were the first to report the effect of the TRIB3 Q84R variant; the single nucleotide polymorphism (SNP) gene is associated with insulin resistance and cardiovascular risk in Caucasian races (Prudente et al., 2005). A subsequent study found that TRIB3 Q84R affected the incidence of obesity, particularly in glucose metabolism, diabetic nephropathy, polycystic ovarian syndrome and increased left ventricular mass in white nondiabetic individuals (X. Zhang et al., 2011; W. Zhang et al., 2015; Mannino et al., 2021).

Tribbles homolog 3 in the TRIB3 gene variation (251, A > G, rs2295490) decreased systolic and diastolic blood pressure and mean arterial pressure (MAP) in patients with essential hypertension taking amlodipine or nitrendipine. Patients with the AA genotype had a significantly better antihypertensive effect than those with the AG/GG genotype (J. Zhou et al., 2019). This is possible because the amino acid Glutamine, produced by the translation of the cytosine (C)-Adenine (A)-Guanine (G) codon sequence, has a weaker bond with Akt than the amino acid Arginine, produced by the translation of the TRIB3 A > G gene variation, which increases vasodilation and thus has a synergistic effect with calcium channel blockers.

Single nucleotide polymorphisms (SNPs) of tribbles homolog 3 (TRIB3) rs6037475 significantly decreased systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) in the felodipine group versus placebo in an open-label study of 830 hypertensive patients. The genotype group exhibiting the most significant reduction in blood pressure was the TT genotype group. The decrease in blood pressure was also affected by the TRIB3 variants rs2295490, rs11470129, and rs4815567, but the P-value did not indicate statistical significance. This gene variant changes felodipine’s ability to control blood pressure, possibly by changing how TRIB3 is expressed or by affecting how NO is released (F. He et al, 2020).

**CACNB2 gene polymorphism and the effect on CCB**

Voltage-gated calcium channels (VGCC/CaVs) are ion channel proteins that selectively deliver calcium ions across the cell
membrane in response to membrane potential changes during depolarization. Calcium channels were first classified as high-voltage-activated (HVA) and low-voltage-activated (LVA), with HVA having sensitivity to 1,4 dihydropyridine antagonists and agonists and thus being known as DHP channels or L-type (LTCC) (Feng et al., 2012). The LTCC located in the heart consists of 4 subunits, namely the α1 subunit, which is coded by CACNA1C or CACNA1D, the auxiliary β-subunits (Cavβ2), which is encoded by CACNB2, then αδ, which is coded by CACNA2D, and finally the subunit γ which is coded by CACNG. The auxiliary β can improve calcium status by regulating the expression of the α1 subunit in cell membranes (Q. Zhang et al., 2018).

The Caβ and αδ subunits synergize with the voltage-gated Ca2+ (Ca.1 and Ca.2) channels that constitute the α1 subunit. The Caβ subunit can increase traffic in the channel to the plasma membrane by binding via a guanylate kinase (GK)-like domain to the interaction domain (AID) in the α1 subunit region (Dolphin, 2009). This binding promotes channel folding and protects the channels from the endoplasmic reticulum (ER)-associated proteasomal degradation. While Caβ and αδ increase the expression of Ca.1 and Ca.2 channels, in the absence of Caβ, αδ is less effective (Dolphin, 2016).

The CACNB2 gene encodes the Caβ subunit's 600 amino acids. The gene comprises 14 exons measuring 421 kb on chromosome 10p12 (Hedley et al., 2009). Brugada syndrome (BrS) type 4 is known to be caused by CACNB2 mutations. Brugada syndrome is an inherited cardiac arrhythmic syndrome that results in ventricular fibrillation when structural heart defects are absent (Q. Zhang et al., 2018). In a case-control study (Lin et al., 2011), variations in CACNB2 increased the risk of hypertension in the Han Chinese population and the She ethnic minority of China (Hong et al., 2013).

The white population with the CACNB2 rs2357928 GG (minor allele homozygote) variation had more adverse events than the beta-blocker group (95 percent CI, 1.19 to 4.66; \(P = 0.014\)), whereas the AG genotype had no adverse events (HR, 1.16; 95 percent CI, 0.75 to 1.79; \(P = 0.69\)) or in the AA genotype group (HR, 0.63; 95 percent CI, 0.36 to 1.11). Furthermore, 1 SNP promoter in CACNB2 rs2357928 was found to be significantly associated with SNP and treatment in the white population, implying that minor allele homozygous patients receiving CCB treatment had a significantly increased risk of side effects when compared to atenolol-based treatment. Furthermore, the risk outcomes for CCBs and beta blockers were comparable in people with AA and AG (Niu et al., 2010).

**AGTR1 gene polymorphism and the effect on CCB**

Angiotensin II (AngII) is a hormone that regulates vascular contraction, renal tubular sodium transport, and aldosterone secretion through the Ang II Type 1 Receptor (AT-1 receptor). This receptor is encoded by the Angiotensin receptor type 1 (AGTR1) gene, located on chromosome 3 (q22 band). The AGTR1 gene has five exons and four introns (Baudin, 2005). SNP rs5186 at position 1166 in the 3′ untranslated gene region causes A/C transversion, making it one of the most studied polymorphisms. This polymorphism has been linked to an increased risk of developing essential hypertension (Parchwani et al., 2018; Semianiv et al., 2021). Several studies have shown that these gene variations affect Irbesartan’s response to blood pressure reduction and the clinical outcome of patients with acute coronary syndrome who use captopril (Jiang et al., 2011; Ghafil et al., 2019).

Another polymorphism is rs275653, which changes the nitrogenous base adenine to guanine at position 153 of the promoter region. After the age of 55, the AGTR1 153G allele has an additional effect on the occurrence of aortic stiffness (Lajemi et al., 2001). Do et al. (2016) discovered that this gene variation significantly affected the amiodipine response in lowering diastolic blood pressure (DBP) in the African American population. Patients with alleles AA, AG, and GG had a greater response to a decrease in diastolic blood pressure, with values of -9.83 mmHg, -7.95 mmHg, and -6.07 mmHg, respectively (Do et al., 2016). These findings differ from previous research, but the study identified AGTR1 A1166C (rs17231380) and discovered that this variation was not related to the response to lowering blood pressure with azelnidipine (Sugimoto et al., 2010).

**FVII gene polymorphism and the effect on CCB**

Clotting factor VII (FVII) participates in the extrinsic coagulation pathway, which converts to factor VIIa, which then activates fibrin, causing platelet aggregation, and blood clots to form. Polymorphisms in factor VII (FVII) gene R353Q (rs6046) can raise the level of coagulation factor VII in the blood (Smith et al., 2011). This gene
variation was found in exon 8 of the FVII gene, where there was a missense replacement of the amino acid arginine (R) by glutamine (Q), resulting in up/down-regulation of gene expression and a close relationship with a lower risk of coronary heart disease in Asian populations (Smith et al., 2011; F. Li et al., 2020; Yyan Li et al., 2021).

The FVII polymorphism also influences the response to blood pressure reduction. The use of anlodipine resulted in a decrease in diastolic blood pressure in patients with FVII rs6046. Patients with the GG, GA, and AA alleles had blood pressure responses of -9.70 mmHg, -6.45 mmHg, and -3.20 mmHg, respectively. Furthermore, in individuals carrying the F7 rs762637 variation, this gene variation affects the systolic blood pressure response to lisinopril (Do et al., 2016).

**PRKCH gene polymorphism and the effect on CCB**

Protein kinase C (PKC) is a serine/threonine protein kinase that regulates several crucial cellular processes, including apoptosis, differentiation, and proliferation (Singh et al., 2017). PKC consists of three families with distinct cofactor requirements: The conventional or classical (c)PKCs: α, βI, βII and γ, the novel (n)PKCs:δ, ε, η and θ, and the atypical (a) PKCs: ζ and λ (L. Zeng et al., 2012). The PRKCH gene, which encodes PKCη, is located on chromosomes 14q22-q23, is approximately 229.1 kb in length and contains 14 exons. It was discovered that a nonsynonymous SNP (1425G/A) increased PKC activity and was closely related to the occurrence of lacunar infarction in the Japanese population (Cheng et al., 2009).

Overexpression of PRKCH in monocyte cells can increase nitric oxide (NO). NO can cause blood vessel dilation and muscle relaxation, which can increase blood pressure. Yamada (2008) discovered that the PRKCH 1425G/A polymorphism was associated with increased diastolic blood pressure in women (Yamada et al., 2008). In a study of the effect of this gene polymorphism on CCB blood pressure control in 136 patients with essential hypertension, there was no significant difference in the reduction of mean arterial pressure (MAP), systolic blood pressure (SBP), or mean arterial pressure (MAP) in patients with the PRKCH 1425G/A genotype who received amlodipine. However, subjects with the GA/AA genotype demonstrated superior antihypertensive effects when using telmisartan compared to those with the GG genotype (Zhang et al., 2017). Additional research is needed to confirm these findings.

**GNB3 gene and the effect on CCB.**

The function of heterotrimeric guanine-binding proteins (G proteins) is to transmit signals from the cell surface to the intracellular signalling cascade. Each G protein comprises three letters: Ga, Gβ, and Gγ. G protein β3 subunit is a protein that is involved in GPCR signalling and Ca²⁺ regulation. GNB3 (G-protein polypeptide 3) encodes the protein found on chromosome 12p13 and has a length of 7.5 kb with 11 exons and ten introns (Weinstein et al., 2006; Klenke & Siffert, 2011).

One of the identified GNB3 polymorphisms is GNB3 C825T (rs5443), which changes the nucleotide base at position 825 of exon ten from C to T. This polymorphism induces a splice variant, specifically the deletion of nucleotides 498-620 in exon 9, resulting in the loss of 41 amino acids along with exon 9 with the fourth Tryptophan-aspartate (W-D) repeat in a sequence of seven WD repeats, thereby altering the β-propeller structure. In Caucasian and Chinese populations, these alterations are associated with elevated G-protein activity and essential hypertension (Rosskopf et al., 2000) (Zheng et al., 2013). Another polymorphism in the 3’-UTR region is C1429T, which is strongly linked to the C825T polymorphism (Rosskopf et al., 2000). Furthermore, six new polymorphisms have been discovered: G76A, G1906T, G2906A, A38882C, G5177A, and G5249A (Rosskopf et al., 2002).

The GNB3 C825T variant in the Chinese population was not associated with amlodipine blood pressure control. However, this study discovered that patients with GNB3 825 TT had a lower decrease in diastolic blood pressure and mean arterial pressure (MAP) than patients with the 825C allele (Z. L. Zhang et al., 2016). The study of the impact of this gene variant on other antihypertensive groups revealed contradictory results. Patients with hypertension who carry the 825T allele respond better to thiazide antihypertensives and antihypertensives in general (Turner et al., 2001; Schelleman et al., 2006). Patients with at least one GNB3 825T allele respond less effectively to beta blockers in lowering blood pressure than patients with other alleles (Filigheddu et al., 2004).

**RYR3 gene and the effect on CCB**

Ca²⁺ is primarily stored in the endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR)
The Ca²⁺ release channel comprises of four Ryanodine receptors (RyRs) or four protein inositol triphosphate receptors (IP3Rs) that regulate the release of Ca²⁺ from intracellular storage. There are three RyR isoforms in mammals: RyR1, RyR2, and RyR3, which are encoded by different genes on different chromosomes (Fill & Copello, 2012). RyR1 isoforms are highly abundant in skeletal muscle, RyR2 isoforms are highly abundant in cardiac muscle and Purkinje cells. Meanwhile, RyR3 is dispersed throughout diverse tissues (skeletal muscle, brain, vascular smooth muscle, etc.). (Lanner et al., 2010).

The RyR1 gene is located on chromosome 19q13.2 and consists of 104 exons. The RyR2 gene, located on chromosome 1q43, has 102 exons. The RyR3 gene is located on chromosome 15q13.3–14 and contains 103 exons (Lanner et al., 2010). Depolarization causes an influx of Ca²⁺ from the extracellular area by opening L-type voltage-gated calcium channels. Furthermore, Ca²⁺ binds to the RyR receptor, resulting in the opening of calcium channels in the sarcoplasmic reticulum (SR) and the subsequent release of Ca²⁺ from the SR, which causes the contraction of vascular smooth muscle (Van Petegem, 2012; Amberg & Navedo, 2013).

The variation of the RyR3 gene rs877087 was found to have pharmacogenetic effects on the incidence of heart failure in patients taking amlodipine compared to other drugs, with a p-value of 0.0005. (Lynch et al., 2013). The research by Türkmen et al. (2022) confirmed this, demonstrating that patients treated with the calcium channel blocker dihydropyridine (dCCB) developed heart failure during the follow-up period. Compared to homozygous CC, this diagnosis was observed in patients with homozygous RyR3 rs8777087 TT and heterozygous CT. In addition, it was discovered that the incidence of heart failure could be reduced by 9.2% if patients with the T allele who received dCCB switched to other antihypertensive drugs. Patients with RyR rs8777087 had no association with the incidence of heart failure in those who had never received dCCB (Türkmen et al., 2022).

It is known that the RyR3 gene variant rs8037864 is associated with hypertension incidence. In comparison to the T/G and T/T genotypes, the expression of the homozygous gene for the GG genotype was statistically significant in causing fibroblast changes, according to an in-silico study (S. Gong et al., 2018).

**RGS2 gene and the effect on CCB.**

Blood pressure is controlled by vasoactive substances that activate G protein-coupled receptors (GPCRs) that coexist with one or more heterotrimeric G protein families with different subunit types (Gs, Gq/11, Gi/o, and G12/13) (Osei-Owusu & Blumer, 2015). Hypertension is known to be caused by increased Gaq activity. The GTPase activating protein (GAP), also known as the regulator of G protein signalling 2, is the specific inhibitor of the Gaq subunit (RGS2). The function of the RGS protein is to activate GAP, which can accelerate the hydrolysis of the G subunit; thereby inhibiting signal transduction (Nance et al., 2013; Osei-Owusu & Blumer, 2015).

RGS2 is found in various tissues related to cardiovascular regulation, the immune system, bone formation, and cancer (P. Zhang & Mende, 2014). The Rgs2 gene, which codes for this protein, is located on chromosome 1 and is comprised of five exons (Osei-Owusu & Blumer, 2015). According to studies conducted on mice, the absence of the RGS2 gene can increase blood pressure in female mice (Luu et al., 2022). Previously, it was known that the RGS2 C1114G (rs4606) polymorphism increased the risk of postnatal hypertension (Kvehaugen et al., 2014). In contrast, a meta-analysis examining the association between hypertension and other variations of the RGS2 gene, specifically the RGS2 G638A polymorphism, revealed that this variation had no association with the risk of hypertension (Zhang et al., 2013).

The ATTEST study found that the RGS2 A-638G polymorphism with changes in nitrogen base in the promoter region was associated with changes in blood pressure in azelidinepine patients azelidine (Δsystolic BP: AA – 28.0 ± 10.1 mmHg, AG – 15.5 ± 12.6 mmHg, GG – 7.0 ± 12.2 mmHg, P=.0013; Δdiastolic BP: AA – 17.2 ± 9.8 mmHg, AG – 8.1 ± 9.0 mmHg, GG – 4.0 ± 11.0 mmHg, P=.067). This relationship, however, was not discovered in patients taking temocapril (Sugimoto et al., 2010). The mechanism by which these variations affect calcium channel blocker blood pressure control is unknown.

**hERG or KCNH2 gene and the effect on CCB.**

The human ether-a-go-go-related gene (hERG or KCNH2) encodes the pore-forming subunit of the potassium-selective hERG1 channel, also known as Kv11.1. These channels are
responsible for activating the delayed-rectifier current (IKr), which is involved in cardiomyocyte membrane repolarization (Miranda et al., 2020). The hERG potassium channel is expressed in cardiac muscle, smooth muscle, liver, pancreas, nervous tissue, and tumour tissue, with cardiac muscle being the most abundant (F. Z. He et al., 2013). In humans, the KCNH2 gene is located on chromosome 7q35-36 and consists of 16 exons totalling 34 kb in length (Sanguinetti, 2010). These gene polymorphisms can result in tumours, schizophrenia, cardiovascular disease, epilepsy, short QT syndrome, and long QT syndrome (F. Z. He et al., 2013). The most studied variations are KCNH2: K977T (Lys977Thr); rs1005123; KCNH2: 1670A > C and KCNH2: R1047L (Arg1047Leu); rs36210421; KCNH2: 2120G > T, which is known to cause Long QT syndrome (Oshiroa et al., 2010). Furthermore, it is known that KCNH2 A2690C variations (change of amino acid lysine 897 to threonine) contribute to the occurrence of aldosteronoma, which is the primary cause of hyperaldosteronism in humans (Sarzani et al., 2006). The renin-angiotensin-aldosterone system (RAAS), which regulates fluid and electrolyte homeostasis, is affected by increased aldosterone. Because this system is the primary regulator of blood pressure, interference from one of its components, namely aldosterone, can cause hypertension (Tomaschitz et al., 2010). It is possible that variations in the KCNH2 gene can cause hypertension.

Variations in KCNH2 (2690, A > C) were not associated with the hypotensive effect of antihypertensive drugs, according to studies on the association of KCNH2 polymorphisms on blood pressure control of calcium channel blockers. In patients receiving azelnidipine or nitrendipine, KCNH2 variation (1956, C > T) had a significant association with changes in DBP and MAP. However, there was no significant difference in drug response across all KCNH2 genotypes (1956, C > T) in patients receiving imidapril, candesartan, and irbesartan (F. He et al., 2013). Patients with the T allele respond better to blood pressure medication than the wild type. The nonsense mutation KCNH2 (2690, A > C) produces the same amino acid as tyrosine, but the change in nitrogen base results in a stop codon (F. He et al., 2013).

**FGF5 gene and the effect on CCB**

In the human embryonic phase, fibroblast growth factors (FGFs) play a role in cell proliferation and morphogenesis. FGFs are thought to play a role in nervous system control, tissue repair, wound healing, and tumour angiogenesis once they reach adulthood. FGFs have 22 members, namely FGF1, FGF2, FGF3 (INT2), FGF4, FGF5, FGF6, FGF7 (KGF), FGF8 (AGF), FGF9, FGF10, FGF11, FGF12, FGF13, FGF14, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22, and FGF23 (Yun et al., 2010). Twenty-two genes encoding FGF have been identified, including FGF16 located on chromosomes (Ornitz & Itoh, 2001). The FGF gene subfamily consists of seven members, one for each subfamily. The FGF1 gene subfamily includes FGF1 and FGF2; the FGF4 gene subfamily includes FGF4, FGF5 and FGF6; the FGF7 gene subfamily includes FGF3, FGF7, FGF10 and FGF22; the FGF8 gene subfamily includes FGF8 and FGF17; the FGF9 gene subfamily includes FGF9, FGF16 and FGF20; the FGF15/19 gene subfamily (endocrine FGFs) includes FGF (Ornitz & Itoh, 2015).

FGF5 was linked to hypertension in the GWAS study (Newton-Cheh et al., 2009). In addition, a second study found that patients with the FGF5 gene variant rs1458038 and increased body mass index were susceptible to hypertension (J. Li et al., 2015). Another study found a positive correlation between rs16998073 T/A variants and diastolic and systolic blood pressure (Ren et al., 2018). In the Filipino population, rs1458038 variation was associated with a lower response to lowering blood pressure in the calcium channel blocker group (CT genotype: adjusted OR 3.41, P =.001; TT genotype: adjusted OR 6.01, P =.001) (Punzallan et al., 2022). More research can be done to determine the mechanism of the FGF5 gene variant’s influence on the CCB blood pressure response.

**NuMA1 gene and the effect on CCB**

The Nuclear Mitotic Apparatus Protein is a 240 kDa protein that plays a role in the preparation and stabilization of the polishing spindle from the onset of mitosis until the beginning of anaphase (C. Zeng, 2000). During interphase, NuMA accumulates in the nucleus of human cell cultures. During mitosis, it moves to the spindle poles and cell cortex (Kiyomitsu & Boerner, 2021). Five types of NuMA exist, including NuMA 1, NuMA 2, the centrosome (CE), middle body (MB), and F-centromere (CENP-F) (Bradwell et al., 2007). The NuMA1 gene is located on chromosome 11q13, a region that promotes ovarian cancer development (Spark et al., 1993). NuMA levels were significantly elevated in epithelial ovarian cancer (Brüning-Richardson et al., 2012).
The variation of the *NuMA1* gene rs10898815 was associated with the response to CCB blood pressure control, particularly in reducing diastolic blood pressure, according to studies examining the association between antihypertensive treatment and *NuMA* gene polymorphisms (Kamide et al., 2013). A cohort study revealed that using CCBs in patients with the *NuMA1* variant rs10898815 was associated with the necessity of treatment switching. Patients with homozygous mutant AA are more likely to switch treatments than patients with homozygous wild-type GG (Türkmen et al., 2022).

**PICALM gene and the effect on CCB**

*PICALM* (Phosphatidylinositol binding clathrin assembly protein) is a protein involved in endocytosis mediated by clathrin. These proteins are expressed in various tissues, mostly microvessels (Baig et al., 2010). In humans, the *PICALM* gene is located on chromosome 11q14 and plays a role in developing several diseases. *PICALM* was discovered to be a translocation partner of the AF10 transcription factor gene (10p12), which causes leukemia and lymphoma (Huh et al., 2010). A single nucleotide polymorphism (SNP) in the *PICALM* gene has also been associated with Alzheimer’s disease (Ferrari et al., 2012).

Patients who use CCB and have variations in the *PICALM* gene rs588076 with the GG genotype have lower blood pressure than patients with other genotypes (Kamide et al., 2013). A cohort study of 82,107 hypertensive patients revealed that CCBs could help prevent dementia. After ten years of monitoring, the CCB group had a lower risk of developing dementia than the comparison group (C. L. Wu & Wen, 2016)(Hussain et al., 2018). However, other systematic review studies have not confirmed whether CCBs increase or decrease the risk of dementia (Peters et al., 2014). The protective effects of these CCBs may vary based on the effects of gene variations, such as those affecting the *PICALM* gene.

**MTHFR gene and the effect on CCB**

*Methylenetetrahydrofolate reductase* (MTHFR) is an enzyme that acts as a catalyst in the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a necessary enzymatic process in folate metabolism, as well as in the remethylation of homocysteine (Hcy) into methionine. The enzyme gene is located on chromosome 1 (1p36.3) (Liew & Gupta, 2015). The single nucleotide polymorphisms (SNPs) that are frequently studied are C677T and A1298C. The *MTHFR* C677T polymorphism causes a change from a C nucleotide base to a T nucleotide base at position 677 in the exon region. This changes the 222nd amino acid from alanine to valine.

The homozygous *MTHFR* 677TT genotype possesses thermolabile enzyme properties, resulting in a decrease in activity that decreases folate concentration and increases plasma Hcy concentration. These polymorphisms have been linked to an increased risk of myocardial infarction and essential hypertension (Xuan et al, 2011)(Y. Le Wu et al., 2014). In a cross-sectional study of an adult Chinese population, an increase in serum homocysteine was found to be closely related to an increase in SBP and DBP (H. Wu et al., 2018). However, the *MTHFR* C677T gene polymorphism was not linked to lercanidipine's antihypertensive effect (Xu et al., 2012).

Interestingly, a randomized, placebo-controlled clinical trial examining the blood pressure response to the addition of riboflavin supplementation in hypertensive patients (including those on calcium channel blockers) with the *MTHFR* 677TT genotype found that riboflavin supplementation in the treatment of hypertension provided blood pressure target achievement compared to antihypertensive treatment alone (Wilson et al., 2013). These findings were confirmed by a 4-year follow-up of riboflavin use in a population with variations in *MTHFR* C677T and a decrease in systolic (-9.2 ± 12.8 mm Hg; P = 0.001) and diastolic (-6.0 ± 9.9 mm Hg; P = 0.003) blood pressure (Wilson et al., 2012).

**CONCLUSION**

This review could not find the most essential CCB pharmacokinetic and pharmacodynamic SNPs. However, several SNPs in some genes can influence CCBs’ pharmacokinetics and pharmacodynamics, affecting the clinical efficacy and safety in the clinical setting. Individuals with the CYP3A5*3/*3 genotype had considerably greater amlopidine efficacy than those with other CYP3A5 genotypes. This is made possible because CYP3A5*3/*3, a poor metabolizer of CCB drugs (Tornio & Backman, 2018), causes active drug levels to rise in the body, increasing the drug’s capacity to lower blood pressure. CYP3A4 gene variations also impact the control of blood pressure. Compared to people with CYP3A4 *1G/*1G, those with CYP3A4 *1/*1 or *1/*1G were twice as likely to reach a target MAP 107 mmHg. In vivo and in vitro studies explain that increased metabolic activity and CYP3A4 protein...
concentration are linked to the CYP3A4*1G allele (Fohner et al., 2021). This allows individuals with the CYP3A4*1/*1 genotype to have higher drug concentrations than CYP3A4*1G/*1G. Patients with the MDR1 C3435 TT genotype had the greatest antihypertensive effects and the fewest adverse effects. In contrast, patients with CC genotype experience a low antihypertensive effect and a higher incidence of side effects. In patients using amlodipine, the RyR3 gene variant rs877087 was discovered to have pharmacogenetic implications on the prevalence of heart failure.

Therefore, when prescribing CCB, it is crucial to consider specific gene variants, for example, CYP3A5*3/*3, CYP3A4*1G/*1G, MDR1 C3435, RyR3 gene rs877087, because of their considerable effects.

ACKNOWLEDGMENTS

We would like to express our gratitude to the Ministry of Education and Culture of the Republic of Indonesia for supporting the research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES


Impact of Gene Polymorphism on Pharmacokinetics and Pharmacodynamics

on blood-pressure response to treatment among treatment-naïve hypertensive African Americans in the GenHAT study. 30(9), 549–554. https://doi.org/10.1038/jhj.2015.121.
Polymorphisms Within RYR3 Gene Are Associated With Risk and Age at Onset of Hypertension, Diabetes, and Alzheimer’s Disease. 31(July). https://doi.org/10.1093/ahj/hpy046


https://doi.org/10.1002/humu.21066

Volume 34 Issue 3 (2023) 387
Impact of Gene Polymorphism on Pharmacokinetics and Pharmacodynamics


Nance, M. R., Kreutz, B., Tesmer, V. M., Sterne-Marr,
Impact of Gene Polymorphism on Pharmacokinetics and Pharmacodynamics


Impact of Gene Polymorphism on Pharmacokinetics and Pharmacodynamics


