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

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Article Info	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)

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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.
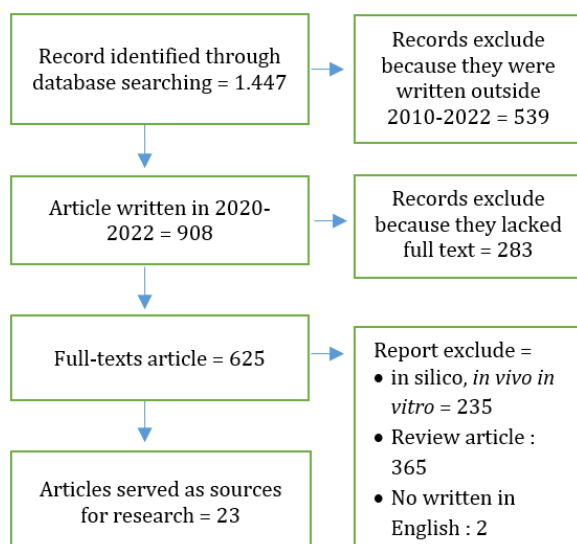

Figure 1. Search strategy for articles to be used for narrative review.

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 amlodipine 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 tylerdipine hydrochloride revealed that subjects with the *CYP3A5*3/*3* genotype had a t1/2 that was 1.35 fold longer than the *CYP3A5*1/*1* group. Additionally, the t1/2 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 *CYP3A*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.

	Author	Subject	CCB drug name	The genes that are thought to affect CCB	Gene polymorphism	Effect on CCB
1	(Han *et al.*, 2020)	healthy male subjects	amlodipine	*POR*, *CYP3A4*, *CYP3A5*	*POR* g.57332T>C, *POR* g.56551G>A, *CYP3A4*1G* and *CYP3A5*3*	Cmax was higher in T allele carriers than CC genotype of POR g.57332T>C and wild-type POR g.56551G>A allele. No significant effects of *CYP3A4* and *CYP3A5* polymorphisms
2	(Do *et al.*, 2016)	Essential hypertensive patients	amlodipine	*AGTR1*, *FVII*	*AGTR1* rs275653, *FVII* rs762637	*AGTR1* rs275653 and *FVII* rs6046 affect amlodipine response in reducing diastolic blood pressure (DBP)
3	(Zhang *et al.*, 2017)	Essential hypertensive patients	amlodipine	*PRKCH*	*PRKCH* rs2230500 for GG, GA, and AA	No significant difference in blood pressure reduction between *PRKCH* rs2230500 (GG vs GA/AA) genotypes in the amlodipine group
4	(Zhang *et al.*, 2016)	Essential hypertensive patients	amlodipine	*GNB3*	*GNB3* C825T	No difference in SBP, DBP and MAP in C825T between before and after amlodipine treatment
5	(He *et al.*, 2020)	Essential hypertensive patients	felodipine	*TRIB3*	rs6037475	*TRIB3* rs6037475 CC genotype had significantly higher mean SBP, DBP and MAP than those with TT genotype in the felodipine treatment group
6	(Lynch *et al.*, 2013)	Essential hypertensive patients	amlodipine	*RYR3*	rs877087	rs877087 had a higher risk of heart failure when randomized to amlodipine, compared to other treatment
7	(Xiang *et al.*, 2017)	Healthy subject	felodipine	*CYP3A4*, *CYP3A5*, *BCRP*	*CYP3A4*18B*, *CYP3A5*3*, *BCRPC421A*	AUC $_{(0-72)}$ infuenced by *BCRP C421A* and *CYP3A5*3/*3*. No statistically significant difference between *CYP3A4*1/*1* vs *CYP3A4*1/*18B* in the value of AUC$_{(0-72)}$
8	(Haas *et al.*, 2013)	Pregnant women	nifedipine	*CYP3A4*, *CYP3A5*	*CYP3A4*1B*; *CYP3A5* alleles (*1*3,*6, or *7*)	*CYP3A4*1B* and the haplotype combination (*CYP3A4*1B* + *CYP3A5*1*) were significantly correlated with the level of CL/F
9	(Sugimoto *et al.*, 2010)	Hypertensive patients with type 2 diabetes	azelnidipine	*RGS2*	*RGS2* A-638G (rs2746071)	A-638G was significantly associated with changes in blood pressure
10	(Kamide *et al.*, 2013)	Essential hipertensive patients	Calcium channel blocker	*PICALM*, *TANC2*, *NUMA1*, *APCDD1*	rs588076, rs2429427, rs10898815, rs564991	SNPs in *PICALM*, *TANC2*, *NUMA1* and *APCDD1* were found to be associated with CCB responses
11	(Zuo *et al.*, 2014)	Essential Hypertensive patients	amlodipine	*ABCB1*, *CYP3A4*, *CYP3A5*, *POR*	*ABCB1* C3435T, *CYP3A4*1G*, *CYP3A5*3*, *POR*28*	*ABCB1* 3435CC, or CT genotype have greater decreases in blood pressure. No significant effect of *CYP3A4*1G*, *CYP3A5*3*, *POR*2*
12	(Zhou *et al.*, 2019)	Healthy subject	Tylerdipine hydrochloride	*CYP3A4*, *CYP3A5*	*CYP3A4*1G* and *CYP3A5*3*	*CYP3A5*3* and *CYP3A4*1G* influence tylerdipine pharmacokinetics (AUC$_{(0-24)}$, t1/2)

Table I. A summary of the result of the gene polymorphism that have influenced calcium channel blocker.

	Author	Subject	CCB drug name	The genes that are thought to affect CCB	Gene polymorphism	Effect on CCB
13	(Bhatnagar *et al.*, 2010)	Hypertensive patients with renal disease	amlodipine	*CYP3A4, CYP3A5*	*CYP3A4* (A−392G and T16090C) and *CYP3A5* (A6986G) gene	*CYP3A4* T16090C SNP was significantly associated with blood pressure responses. CYP3A5 A6986G was not associated with blood pressure response
14	(F. He *et al.*, 2013)	Essential hipertensive patients	Azelnidipine & nitrendipine	*hERG* or *KCNH2*	*KCNH2* (1956, C.T)	*KCNH2* (1956, C.T) was statistically significant interactions with DBP and MAP change on azelnidipine or nitrendipine therapy
15	(Punzallan *et al.*, 2022)	Essential hypertensive patients	Calcium channel blocker	*FGF 5*	rs1458038	rs1458038 showed a significant association with poor blood pressure-lowering response
16	(Zhou *et al.*, 2016)	adult kidney transplant patients	diltiazem	*CYP3A4, CYP3A5*	*CYP3A4*1G* and *CYP3A5*3.*	*CYP3A4*1G* and *CYP3A5*3* are significantly related to diltiazem's trough concentration/dose ratio.
17	(Xu *et al.*, 2012)	Essential hypertensive patients	Lercanidipine	*MTHFR*	*MTHFR* C677T	*MTHFR* C677T did not affect the antihypertensive effects of the lercanidipine treatment but had associated with the vascular protective effects of short-term lercanidipine treatment
18	(Guo *et al.*, 2015)	Essential hypertensive patients	amlodipine	*CYP3A4, CYP3A5, POR* and *MDR1*	*POR* A503V, *CYP3A4*1G, CYP3A5*3, MDR1* C3435T	C3435T of *MDR1* affected amlodipine plasma concentration but did not affect its antihypertensive activity. There was no effect of *CYP3A4*1G, CYP3A5*3* and *POR* A503V on amlodipine plasma concentrations or efficacy.
19	(Niu *et al.*, 2010)	Hypertensive patients with coronary artery disease	verapamil	*CACNB2*	rs2357928	rs2357928 was found to have significant interaction with treatment strategy for adverse cardiovascular outcomes
20	(Huang *et al.*, 2017)	hypertension following renal transplantation	amlodipine	*CYP3A4, CYP3A5, MDR1*	*CYP3A4*1G, CYP3A5*3,* and *MDR1* C3435T	CYP3A5*3 polymorphism affects the efficacy of amlodipine in Chinese hypertensive patients after kidney transplantation.
21	(Zhou *et al.*, 2019)	Essential hypertensive patients	azelnidipine/nitrendipine	Tribbles homolog 3 (*TRIB3*) mediating	*TRIB3* (251, A > G, rs2295490)	Azelnidipine or nitrendipine had a better antihypertensive effect on *TRIB3* (251, A > G) AA genotype carriers than on AG/GG genotype carriers.
22	(Sychev *et al.*, 2018)	Essential hypertensive patients	amlodipine	*ABCB1 (MDR1)*	*ABCB1 (MDR1)* rs1045642	The TT group showed the most substantial antihypertensive impact and the lowest rate of side effects.
23	(Türkmen *et al.*, 2022)	Essential hypertensive patients	Dihydro-pyridines (dCCB)	*CYP3A5, RYR3, NUMA1,*	(*RYR3*) rs8777087, *CYP3A5* rs776746, *NUMA1* rs10898815	Patients with common genetic variants in *NUMA1, CYP3A5* and *RYR3* had increased adverse clinical outcomes.

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 AUC0–24h 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 diltiazem 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 7Q11.23. 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). This 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

CYP3A4 and *CYP3A5* expressors (Han *et al.*, 2020). The g.57332T > C SNP is located in the intron region, which is not typically involved in protein synthesis. However, research in these areas is possible because intron regions can potentially affect mRNA splicing as well as protein expression and activity (Raponi & Baralle, 2010).

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, rs2231142). East Asian populations have a higher prevalence of the *ABCG2* c.421 C > A allele (30-60%) than African-American and Caucasian populations (5-10%). In addition to these allele variants, SNP *ABCG2* c34G > 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).

Variants of the breast cancer-related protein transporter gene (*BCRP*) with AA alleles have a higher mean felodipine AUC than those with *BCRP*421 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.

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 *CYP3A4/5* regarding substrate specificity (Wolking *et al.*, 2015).

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 1.50-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 intrahepatocellular 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 azelnidipine 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 $\alpha 1$ subunit, which is coded by *CACNA1C* or *CACNA1D*, the auxiliary β-subunits (Cav$\beta 2$), which is encoded by *CACNB2*, then $\alpha_2\delta$, 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 $\alpha 1$ subunit in cell membranes (Q. Zhang *et al.*, 2018)

The Ca$_v\beta$ and $\alpha_2\delta$ subunits synergize with the voltage gated Ca^{2+} (Ca$_v$1 dan Ca$_v$2) channels that constitute the $\alpha 1$ subunit. The Ca$_v\beta$ 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 $\alpha 1$ subunit region (Dolphin, 2009). This binding promotes channel folding and protects the channels from the endoplasmic reticulum (ER)-associated proteasomal degradation. While Ca$_v\beta$ and $\alpha_2\delta$ increase the expression of Ca$_v$1 and Ca$_v$2 channels, in the absence of Ca$_v\beta$, $\alpha_2\delta$ is less effective (Dolphin, 2016).

The *CACNB2* gene encodes the Ca$_v\beta$ 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 per cent CI, 1.19 to 4.66; P = 0.014), whereas the AG genotype had no adverse events (HR, 1.16; 95 per cent CI, 0.75 to 1.79; P = 0.69) or in the AA genotype group (HR, 0.63; 95 per cent 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 I (*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 amlodipine 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 amlodipine 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 incidence 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 diastolic blood pressure (DBP), 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: Gα, Gβ, and Gγ. G protein β3 subunit is a protein that is involved in GPCR signalling and Ca^{2+} 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 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 effect 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

Ca^{2+} is primarily stored in the endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR)

(SR). The Ca^{2+} release channel comprises of four Ryanodine receptors (RyRs) or four protein inositol triphosphate receptors (IP3Rs) that regulate the release of Ca^{2+} 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 Ca^{2+} from the extracellular area by opening L-type voltage-gated calcium channels. Furthermore, Ca^{2+} binds to the RyR receptor, resulting in the opening of calcium channels in the sarcoplasmic reticulum (SR) and the subsequent release of Ca^{2+} 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 $G\alpha_q$ activity. The GTPase activating protein (GAP), also known as the regulator of G protein signalling 2, is the specific inhibitor of the $G\alpha_q$ 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 comprises 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 azeldinipine patients azeldinipine (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*: K897T (Lys897Thr); rs1805123; *KCNH2*: 1670A > C and K*CNH2*: 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 (AIGF), 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 amlodipine 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 aaantihypertensive effects and the fewest adverse effect. 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.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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