



The CACNA1C gene polymorphism and Effect of Some Antihypertensive Medication on Cardiac Function Markers in Hypertension Patients

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ABSTRACT:

The CACNA1C gene affects calcium flow in heart and vessel cells, variants in this gene can alter calcium handling, influencing vascular tone and cardiac contractility, thereby contributing to the development and progression of hypertension. This study aims to evaluate the variation in serum levels of creatine kinase-MB(CK-MB), myoglobin, and cardiac troponin I among hypertensive patients, and to determine whether these levels show a marked difference among individuals receiving antihypertensive therapy in hypertensive patients and untreated healthy controls. It also examines CACNA1C gene variation between HTN patients and healthy explore its potential role in hypertension and cardiac biomarker levels.

The study utilized a cross-sectional design and was conducted at Shahid Dr. Khalid Teaching Hospital in Koya, Erbil. A total of 75 participants were enrolled, including 55 individuals diagnosed with hypertension and 20 healthy controls. The investigation involved measuring cardiac biomarkers such as Troponin I, CK-MB, and Myoglobin. Additionally, PCR amplification of the CACNA1C gene was carried out using DNA extracted from blood samples, prepared with the Beta Bayern Tissue and Blood DNA Preparation Kit, at the research center of Erbil International University. The analysis between groups and diabetes duration was performed through GraphPad Prism 10.

The results showed non-significant difference in troponin I level between the CCB and ARB groups. A significant reduction in myoglobin level was observed in the ARB group compared to the CCB group. Nevertheless, there were non-significant differences between the control group and either the CCB or ARB groups. There were non-significant differences in CK-MB level between any of the groups. This suggests that CK-MB concentrations remained similar regardless of treatment groups. Additionally, genetic result the control group showed no variation in rs1051375 (all G/G), whereas both the CCB and ARB patient groups exhibited SNP variation, including G/A and A/A genotypes. This finding indicates a potential link between the polymorphism and hypertension or its treatment response.

The CACNA1C rs1051375 genotype distribution differed between controls and hypertensive patients, with a shift toward the A allele, especially in those on CCBs. ARB treatment showed greater reduction in myoglobin levels, suggesting better cardio protection. These findings support the role of genetic markers and biomarkers in guiding personalized hypertension therapy.

Keywords: Antihypertensive medication, cTnI, CK-MB, Myoglobin, CACNA1C, ARB, CCB



1 INTRODUCTION

Hypertension continues to be the primary cause of mortality and morbidity globally, considerably outweighing the effects of other occupational, environmental, and lifestyle variables[1]. Hypertension (HTN) impacts more than 1.5 billion individuals globally. It is linked to an elevated danger of CVD events, including coronary heart disease, heart failure, and stroke, as well as mortality[2, 3]. Uncontrolled (HTN) is a major reason of cardiovascular disease [4].There is a link in middle blood pressure (BP) and cardiovascular events [5].

Cardiac markers, also known as biomarkers, are utilized to analyze and monitor heart function, and they are beneficial for early prediction and detection of illness[6]. Creatine kinase (CK), the enzyme that facilitates ATP-dependent vascular

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elasticity also salt keeping, as recently been identified as a novel causes of the risk of developing high blood pressure [7]. Elevated CK Activity could raise the danger of (HTN) and could possibly contribute to the failure of hypertensive treatment [8]. Previous studies have shown that CK-MB is primarily found in the myocardium, while myoglobin is present in both cardiac and skeletal muscle[9]. Myoglobin is a protein that contains iron and plays a crucial role in storing and delivering oxygen to cells for use in cellular respiration[10]. Cardiac troponin (cTn) is a set of myocardial damage biomarkers utilized for diagnosis, prognosis of myocardial infarction. Between the cTn subtypes, cTnI rise is exclusive to myocardial injury [11].

Calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and diuretics are some of the most commonly prescribed hypertension drugs. CCBs are considered some of the most extensively investigated drugs and are frequently recommended as advised as the primary therapy without combination or in mixture regimens[12]. Angiotensin type II receptor blockers (ARBs) are among the highly efficient antihypertensive medications. Accordingly, because hypertension is an extremely common condition and a substantial determinant in cardiovascular related illness and death, ARBs are frequently utilized[13] .CCBs fall into two main classifications: dihydropyridine and non-dihydropyridine[14]. Non-dihydropyridine CCBs act on voltage-dependent L-type calcium channels of cardiac and smooth muscle to reduce muscle contractility [12].Individual reactions to pharmacological therapy are influenced by variations in genes involved in the development of (HTN)[3].

The CACNA1C gene is a putative candidate gene for EH (essential hypertension) development[3]. The CACNA1C gene on chromosome 12p13.3 encodes the α -1 subunit of the CaV1.2 L-type voltage-dependent gated calcium channel (CACNA1C) [15] . Mutations in CACNA1C have been linked more frequently to sudden cardiac death (SCD)[16]. Rare instances of rhabdomyolysis, or the breakdown of skeletal muscle, have been documented in patients with CACNA1C variations, such as those with a particular gain-of-function mutation. These events have resulted in extremely high levels of total CK[16]. While cardiac biomarkers like Troponin, Myoglobin, and CK have been studied in heart disease, their variation in hypertensive patients, especially in relation to CACNA1C gene and medication, is not well understood. This gap limits our knowledge of how genetics and treatment affect heart health in hypertension.

2 METHODOLOGY

STUDY LOCATION AND POPULATION

This cross-sectional study was conducted at Shahid Dr. Khalid Teaching Hospital in Koya, Erbil, in the Kurdistan Region of Iraq. The research involved hypertensive patients divided into two groups, each receiving a different type of antihypertensive medication: calcium channel blockers (CCBs) or angiotensin receptor blockers (ARBs). A total of 55 patients undergoing treatment at the hospital were enrolled for biochemical and cardiac biomarker analysis. Additionally, 20 healthy individuals were included as a control group for comparison.

SAMPLE COLLECTION AND PROCEDURES

A 5 mL venous blood sample was drawn from each participant using a 5cc syringe. The blood was distributed into two different types of collection tubes: a Gel Tube (Clot Activator) for serum separation and an EDTA tube for whole blood, used for DNA extraction. Samples were then stored in a -80°C deep freezer (Germany). Following collection, the gel tubes were centrifuged to isolate the serum for subsequent biochemical testing. The following biochemical analyses were performed on the participant's samples.

1- Measuring Population characteristics

Each participant's age was recorded on a questionnaire sheet, and the average age was calculated using the formula: (minimum age + maximum age) / 2. Body mass index (BMI) was determined using the standard formula: BMI = weight (kg) / height (m²). BP was recorded by using a digital (automatic) blood pressure monitor (mmHg) to identify hypertensive patients. Heart rate (bpm) was also recorded using a pulse oximeter.

2- Cardiac Biomarkers (Troponin I, CK-MB, Myoglobin)

The rapid quantitative test for cTnI, CK-MB, and Myoglobin (ng/mL) was conducted using the Wondfo Finecare Plus diagnostic kit (Netherlands) along with an immunofluorescence-based quantitative analyzer. This assay utilizes fluorescence immunoassay technology, specifically employing a sandwich immunodetection method. The blood sample is added to a detection buffer and thoroughly mixed. The intensity of the fluorescence signal generated by the labeled antibodies is directly proportional to the concentration of the target antigens (cTnI, CK-MB, and Myoglobin). The Finecare TM FIA meter then provides the quantitative results of these biomarkers in the blood specimen.

CHARACTERISTICS OF THE PARTICIPANTS

The study was conducted at a tertiary healthcare facility, Shahid Dr. Khalid Teaching Hospital, and focused on adult male patients aged 40 years and above with a confirmed identification of HTN by specialist physicians. A convenience

sampling technique was employed to recruit the patients. Patients were enrolled consecutively either during routine outpatient follow-up visits or during hospital admissions related to hypertension complications.

SAMPLE SIZE AND SAMPLING TECHNIQUE

A total of 55 patients were chosen through purposive sampling and categorized into two subgroups:

- Group CCBs: 20 Patients diagnosed with hypertension who were using calcium channel blocker (CCB) type antihypertensive drugs.
- Group ARBs: 35 Patients diagnosed with hypertension who were using Angiotensin type II receptor blockers type antihypertensive drugs.

All participants had a confirmed diagnosis of primary hypertension and were under regular follow-up at the hospital. The duration of hypertension was (<1 year). None of the patients had documented comorbidities such as diabetes mellitus, dyslipidemia, chronic kidney disease, ischemic heart disease, or cerebrovascular disease.

Inclusion Criteria

Participants were eligible for inclusion if they met the following criteria:

- Aged 40 years or older.
- Diagnosed with Hypertension for a duration of at least one year.
- Provided informed consent to participate in the study.
- That patients use antihypertensive medication.

Exclusion Criteria

Participants were excluded from the study if they:

- Had Pulmonary Hypertension.
- Were diagnosed with end-stage chronic kidney disease classified as stage 4 or above.
- Were undergoing chemotherapy.
- had hypertension but did not use antihypertensive medication, or used only herbal remedies.

Genotype

Genomic DNA was extracted from whole blood via the Beta Bayern Tissue and Blood DNA extraction Kit (Beta Bayern GmbH, 90453 Bayern, Germany), from 21 patients and 4 healthy controls then, at Erbil International University following the manufacturer's protocol. After breaking down the proteins with proteinase K, 200 μ L of binding solution was mixed in, shaken for 15 seconds, and then left to sit for 10 minutes at 56°C. After that, 200 μ L of absolute ethanol was included, vortexed once more, and centrifuged for a short while. The lysate was loaded onto a spin column, washed with two washing buffers, and the DNA was eluted in 100–200 μ L of Elution Solution.

POLYMERASE CHAIN REACTION (PCR) AMPLIFICATION

PCR amplification was carried out in a total volume of 50 μ l of reaction mixture containing; 2x Taq DNA Polymerase Master Mix (AMPLIQON A/S Stenhuurvej 22), 10 Picomole (pmol) Forward primers, 5'-TCGTCCACCGGCTCCA-3' (16bp), Reverse primer, 5'-CTGAGCTTCCACGCCACCT-3' (19bp). DNase free water (18 μ l) and template DNA concentration (50ng/ μ l), volume (3 μ l) by Bioresearch PTC-200 Gradient thermocycler. Primer code (E44F) Sequence 5'- TCGTCCACCGGCTCCA -3' Amplicon size (16 bp). The temperature profile started with an initial denaturation at 95°C for five minutes. Following that, there were 35 cycles of primer annealing at 54°C for 40 seconds, denaturation at 95°C for 40 seconds, and extension at 72°C for 1 minute. An additional extension at 72°C for five minutes is the final step. Temperature profile begin step one is an initial denaturation at 95 C for 5 min, following step two, 35 cycles of denaturation were performed at 95 °C for 40 seconds, primer annealing at 54 C for 40 seconds, an extension at 72C for 1 min, the process concludes with an extra extension step at 72C for 5 min. Agarose gel electrophoresis is a method employed to separate DNA fragments show in (Fig 1) Based on their molecular weight, this process is an essential component of nearly all standard molecular biology experiments.

AGAROSE GEL ELECTROPHORESIS STAGES

Agarose gel preparation, DNA electrophoresis, and subsequent visualization of the DNA fragments. Preparation of Agarose Gel a 1.0–1.5% agarose solution was prepared in 1X TBE buffer, melted by heating, and stained with a safe dye. After cooling, the gel was cast, solidified, and placed in the electrophoresis chamber. DNA samples were mixed with loading dye, while PCR products using AMPLIQON mix didn't require extra dye. A DNA ladder (1500–100 bp) was loaded, and electrophoresis was run at 50–100 V. The gel was visualized and photographed under UV light.

SEQUENCING OF DNA

The PCR-amplified partial gene fragments were sequenced using the ABI Prism Terminator Sequencing Kit (Applied Biosystems) and processed at Macrogen Molecular Company (Korea). Sequencing chromatograms were examined in detail using FinchTV software to verify base-calling accuracy and to identify any ambiguous peaks. Only high-quality reads were retained for analysis. The obtained nucleotide sequences were compared with reference sequences deposited in the GenBank database using the National Center for Biotechnology Information's (NCBI) Basic Local Alignment Search Tool (BLAST) (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>) to confirm sequence identity and detect potential sequence variations. Sequencing quality was evaluated by monitoring chromatogram clarity and alignment consistency. Genotypes were assigned based on both automated base-calling results and manual inspection of chromatograms to ensure accuracy. The genotype distributions were then tested for compliance with Hardy-Weinberg equilibrium, providing an additional check for sample quality and population representativeness. This step enhances confidence in the molecular findings and minimizes the possibility of genotyping errors.

STATISTICAL ANALYSIS

The Graph pad prism (version 10) is utilized. The data of the current study was expressed as median, interquartile range and Graph pad prism the statistical software is utilized for analyzing the data. Differences in median values among the three groups were analyzed by (Kruskal-Wallis test) because the nonparametric data between the control group and two different therapy groups. Significant at the level of <0.05 . Utilize (one-way ANOVA) for parametric data.

3 RESULT

GENOMIC DNA ISOLATION

Genomic DNA was obtained using the Animal DNA Preparation Kit from Bioscience (Beta Bayern GmbH, 90453 Bayern, Germany. The isolated DNA was electrophorized in 1.5% Agarose gel (Figure 1).

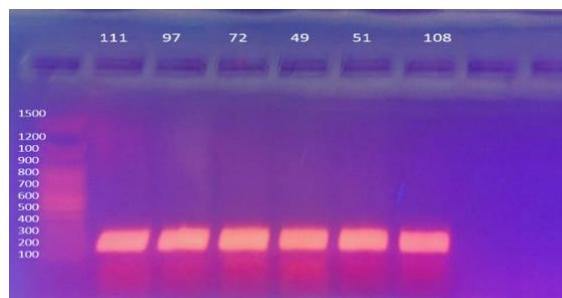


FIGURE 1. DNA segments separated using agarose gel electrophoresis

PCR AMPLIFICATION OF PARTIAL GENES

The primer, which could yield CACNA1C (300 kb), is synthesized by Micro-gene Company (South Korea). A 1.5% agarose gel was used to electrophoresis and visualize the PCR product. The PCR produces as shown in the Fig. 2 and 3.

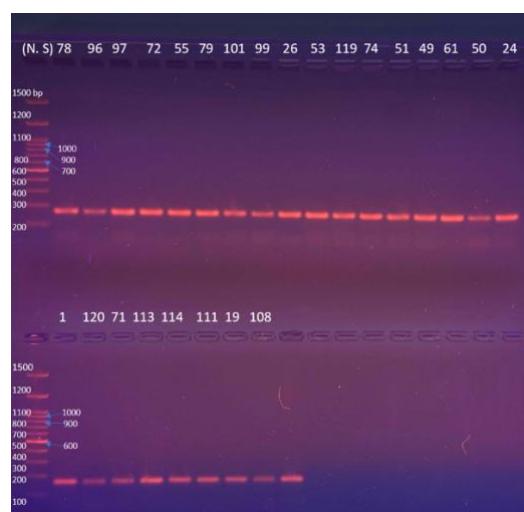


FIGURE 2. PCR amplification of partial CACNA1C gene, wells include M; Ladder (3000-100bp), lane 1-25; gene bands with the size of 550 bp amplified and NC indicates negative control without the band

DETERMINATION OF SINGLE-NUCLEOTIDE POLYMORPHISM IN THE CACNA1C GENE

Table 1. Single-nucleotide Polymorphism in CACNA1C gene in rs1051375

n. Sample	Control	Patient (ARB)	Patient (CCB)
114	GG		
111	GG		
108	GG		
103	GG		
79		GA	
55		AA	
72		AA	
97		AA	
96		AA	
87		GA	
119		GA	
53		GA	
26		AA	
99		AA	
101		GA	
74			AA
51			AA
49			GG
61			GA
50			GA
24			GA
1			AA
120			GA
71			GA

Table 2. Genotype frequency between control and patient in rs1051375

	Control	Patient (ARB)	Patient (CCB)
GG	4	0	1
GA	0	6	5
AA	0	5	3

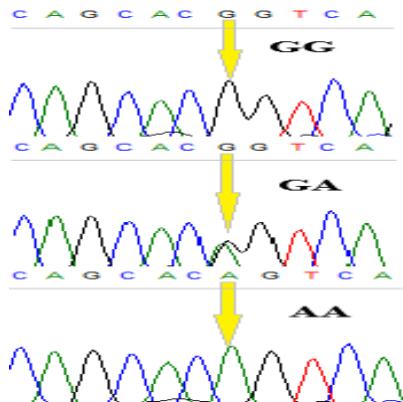


FIGURE 3. Illustrated genotyping of CACNA1C that divided into three genotypes GG is only picogram G present in the locus of rs1051375 nucleotide, genotype, genotype of GA with picogram G the A arise in same locus, in genotype of AA in the locus rs1051375 only picogram A arise instead of G

POPULATION CHARACTERISTIC

Participants ranged in age from 40 to 76 years. The age range was 58 years in each group: CCB (hypertension patients who use Calcium channel blocker antihypertensive medication), ARB (hypertension patients who use Angiotensin II Receptor Blocker antihypertensive medication), and control. A Kruskal-Wallis is a statistical method that was applied to compare BMI among the three groups. The median BMI was 28.16 kg/m² in the CCB group (range: 21.63 to 35.90), 28.70 kg/m² in ARB group (range: 22.53 to 41.01), and 28.16 kg/m² in the control group (range: 20.22 to 35.54). The Kruskal-Wallis test showed no statistically significant difference in BMI between the groups (*p* value = 0.3598). A one-way ANOVA was conducted to differentiate the mean arterial pressure (MAP) among three groups. There was a statistically significant difference in MAP between the groups, *F*(2,77) = 6.122, (*p* value 0.0035). There was no statistically significant difference in pulse rate among the three groups.

Table 3. Age, BMI, Mean Arterial Pressure, and Pulse Rate in controls and hypertension patients

Parameters	CCB Group	ARB Group	Control	P value
Age (Years)	(40.00+76.00)/2	(40.00+76.00)/2	(41.00+75.00)/2	-----
BMI (kg/m²)	21.63 to 35.90	22.53 to 41.01	20.22 to 35.54	0.3598
Mean Arterial Pressure (mmHg)	103.6 ± 9.439	106.6±10.80	97.40 ± 5.603	0.0035
Pulse Rate (bpm)	75.00(70.50-84)	78.00(73.00-86.00)	75.00(70.00-84.75)	0.7722

Range of age = minimum+ maximum/2. result of Blood pressure are express Means ± SD. Result of Pulse Rate are express Median (Q1-Q3), BMI= (Height in meters (m))²Weight in kilograms (kg)

THE EFFECT OF ANTIHYPERTENSIVE MEDICATION ON CARDIAC FUNCTION

The levels of each Cardiac Troponin I, Myoglobin, and CK-MB in hypertension patients and the control group are shown in Table 4. As shown Statistical analysis revealed that the difference between the Control group and both the (CCB) receiving calcium channel blockers and (ARB) angiotensin receptor blocker groups was significant (*p* = >0.9999). However, there was no statistically significant difference in troponin I level between the CCB and ARB groups not significant. A significant decrease in myoglobin levels was noticed in the ARB group compared to the CCB group (*p*=0.0005). Nonetheless, no statistically significant difference was observed between the control group and either the CCB or ARB groups not significant. There were no statistically meaningful differences in CK-MB levels between any of the groups not significant. This suggests that CK-MB concentrations remained similar regardless of the treatment groups. The comparison of CCB and control groups was not significant (*P* = 0.7731), nor was the difference between the ARB and control groups (*P* = 0.3041).

Table 4. Troponin I, Myoglobin, and CK-MB levels in CCB, ARB, and Control groups

Parameter	CCB Group Median (Q1-Q3)	ARB Group Median (Q1-Q3)	Control Group Median (Q1-Q3)	P value
Troponin I (ng/L)	0.1000(0.1000-0.175)	0.1000(0.09000-0.1400)	0.1500(0.1050-0.3150)	0.0009
Myoglobin (ng/mL)	13.44(10.88-17.32)	9.370(8.300-11.94)	11.22(10.03-13.57)	0.0005
CK-MB (ng/mL)	2.760(2.418-3.138)	2.750(2.280-3.170)	2.970(2.745-3.318)	0.2532

Result presented by as median (interquartile range)

4 DISCUSSION

The present study investigated the association between CACNA1C gene polymorphism and the effect of different classes of antihypertensive medications on cardiac function markers including CK-MB, myoglobin, and troponin I in patients with hypertension. Our findings highlight both genetic and pharmacological influences on cardiovascular outcomes.

In our dataset, Heterozygous and homozygous variant alleles were more prevalent in both treatment groups, according to the genotype distribution of rs1051375 in our dataset. Just 11.1% of the CCB group had the wild-type GG genotype, while the GA genotype was more common (55.6%) and followed by AA (33.3%). No GG genotype was found in the ARB group, with GA (54.5%) and AA (45.5%) predominating. Genome-wide association studies have identified numerous loci linked to blood pressure and hypertension, offering potential targets for therapy. Pharmacogenetic research has also demonstrated interindividual variability in drug response and tolerance, often due to genetic variations affecting pharmacokinetics (e.g., transporters, plasma protein binding, metabolism) or pharmacodynamic targets (e.g., receptors, ion channels, enzymes) [17].

CCB is one form of antihypertensive, which works by blocking calcium channels, primarily L-type channels found on cardiac[18]. Dihydropyridine calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs) are both suitable for starting antihypertensive treatment[19]. Amlodipine therapy results range greatly from person to person, mostly because of genetic variations[20]. In the research population, this pattern suggests a high frequency of variant alleles, with complete absence of wild-type homozygotes among ARB-treated individuals. The CACNA1C gene, found on chromosome 12p13.33, produces the alpha-1C subunit, which is extensively expressed in the heart, brain, and smooth muscle, among other tissues. L-type calcium channels are formed as a result, and these channels are essential for muscular contraction, synaptic plasticity, and cardiac and neural excitability[21]. Although the rs1051375 SNP does not directly alter the primary structure of the L-type voltage-gated Ca^{2+} channel, it may function as a methylation site. Studies have shown that this variant can still influence channel function (Kim et al., 2016). A prominent theory suggests that rs1051375 contributes to the epigenetic regulation of *CACNA1C*, and this intronic SNP has also been linked to treatment response in hypertensive patients[22-24]. In this research Sun et al., 2012 show that not all SNPs in the CACNA1C gene affect the effectiveness of CCBs, since the study found no significant differences in blood pressure decrease among patients with the rs1051375 genotype [25].

Our results showed that patients treated with ARBs exhibited a greater reduction in myoglobin levels ($P=0.0005$) compared to the CCB group, whereas CK-MB and troponin I ($P>0.9999$) did not differ significantly between groups. High-pressure treatment weakened hydrophobic and hydrogen bonds but strengthened dipolar interactions in the myoglobin-pepsin complex, improving digestibility. It also exposed aromatic residues and modified the heme-globin linkage, regulating the protein's structure[26]. ARBs exert this benefit by selectively blocking angiotensin II from binding to the AT_1 receptor, thereby counteracting harmful RAAS-mediated processes. Chronic activation of angiotensin II promotes vascular and myocardial inflammation, oxidative stress, fibrosis, and microvascular dysfunction—all of which contribute to myocardial injury. By inhibiting these pathways, ARBs reduce structural and functional damage to the heart, which aligns with our findings and is consistent with the results reported by (Kim et al., 2020). Clinical evidence further supports that ARBs lower the risk of major cardiovascular events, myocardial infarction, and the need for revascularization in high-risk patients[27, 28].

Creatine kinase (CK) is an enzyme composed of two subunits, M and/or B, CK-MB is the heart-specific isoenzyme[29].

The specific mechanism of small CK-MB rise in people with HTN is not totally known, although most authors felt the leakage of CK-MB might result from damage to myocardial damage. In contrast, Gupta et al., 2022 reported opposite findings, classifying individuals into groups with raised versus normal cTnI levels [30]. Despite not being cardiac-specific, myoglobin is incredibly sensitive. After damage, it is released from the cell faster than cardiac troponins or CK-MB. Myoglobin is helpful cardiac diagnostic for early diagnosis of necrosis[31]. Cardiac troponins(cTn), essential for heart muscle contraction, are cardiac-specific proteins and the gold-standard biomarkers for detecting myocardial

injury[32]. This study (Minuzzo et al., 2014) found that the use of ACE inhibitors before hospitalization was linked to Troponin I levels being at or below 0.5 ng/mL[33].

Genotype distribution also appeared to influence biomarker changes in our study. In the ARB group, GA and AA genotypes were associated with lower mean myoglobin levels, whereas no clear genotype–biomarker correlation was observed in the CCB group. These findings align with previous research evaluating the impact of gene polymorphisms on individual responses to ARB therapy [34]. Therefore, our discussion focuses on the influence of genetic variation on drug outcomes, alongside relevant pharmacodynamic and pharmacokinetic mechanisms [17].

ETHICAL STATEMENT

The project received ethical approval from the Local Ethics Committee of the Faculty of Health and Science at Koya University. Furthermore, the project's implementation in the hospitals has been authorized by the Ministry of Health of the Kurdistan Regional Government. Informed consent was obtained from all participating patients. Data anonymity was preserved throughout the entire data processing process.

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CONCLUSION

The genotyping results of the CACNA1C gene at rs1051375 show a clear difference in genotype distribution between the control group and hypertensive patients receiving ARB or CCB treatment. This suggests a shift away from the GG genotype toward GA and AA in hypertensive patients, especially in the CCB group. It may imply that the A allele could be associated with hypertension or its treatment response, particularly with calcium channel blockers. This study indicates significant differential effects of ARB and CCB therapy on cardiac biomarkers in hypertensive individuals, with ARBs demonstrating greater reduction in myoglobin levels. While troponin I and CK-MB levels showed no significant variations between medication groups, the myoglobin data indicate improved cardioprotective effects of ARB therapy. These findings support the use of genetic variables and biomarker profiles to personalize antihypertensive therapy selection and show the potential for precision medicine techniques in hypertension management.

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