

Review

Influence of *CYP2C9* Genetic Polymorphisms on the Pharmacokinetics of Losartan and Its Active Metabolite E-3174: A Systematic Review and Meta-Analysis

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Abstract: This study aimed to investigate the influence of *CYP2C9* genetic polymorphisms on the pharmacokinetics of losartan and its active metabolite, E-3174, through a systematic review and meta-analysis. Eight studies published before March 2021 were included in this study. We used PubMed, the Cochrane Library, EMBASE, and Web of Science, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The data analysis was conducted through Review Manager (RevMan), version 5.3, and R software. We found that healthy volunteers with *CYP2C9**2 or *3 carriers had higher area under the curve ($AUC_{0-\infty}$) of losartan (mean difference (MD) 0.17 $\mu\text{g}\cdot\text{h}/\text{mL}$; 95% confidence intervals (CI): 0.04, 0.29) and lower $AUC_{0-\infty}$ of E-3174 (MD $-0.35 \mu\text{g}\cdot\text{h}/\text{mL}$; 95% CI: $-0.62, -0.08$) than those with *CYP2C9**1/*1. Subjects with *CYP2C9**2 or *3 carriers showed lower maximum concentration (C_{max}) of E-3174 than those with *CYP2C9**1/*1 (MD $-0.13 \mu\text{g}/\text{mL}$; 95% CI: $-0.17, -0.09$). For half-life, subjects with *CYP2C9**2 or *3 carriers had longer half-lives of losartan and E-3174 than those with *CYP2C9**1/*1 (MD 0.47 h; 95% CI: 0.32, 0.61 and MD 0.68 h; 95% CI: 0.44, 0.92, respectively). This meta-analysis suggests that the pharmacokinetics of losartan and E-3174 are associated with the *CYP2C9* polymorphisms

Keywords: losartan; E-3174; *CYP2C9*; polymorphism; pharmacokinetics



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1. Introduction

Losartan is an angiotensin II receptor blocker (ARB) that is widely used for hypertension, heart failure, and diabetic nephropathy. It blocks the angiotensin II type 1 (AT1) receptor. It is absorbed from the gastrointestinal tract after oral administration and undergoes substantial first-pass metabolism, resulting in a systematic bioavailability of approximately 33%. It is metabolized to an active carboxylic acid metabolite E-3174, which has up to 40 times greater pharmacological activity than losartan [1,2].

Cytochrome P450 (CYP) 2C9 comprises approximately 20% of CYP enzymes in the human liver, where it metabolizes more than 100 clinical drugs, including losartan [3]. *CYP2C9* metabolizes losartan to E-3174 by oxidation of the C5-hydroxymethyl on the imidazole ring of the 5-carboxylic acid. *CYP2C9* is highly polymorphic, with at least 30 different variants. Among them, *CYP2C9**2 (430T > C, Arg144Cys) and *CYP2C9**3 (1075A > C, Ile359Leu) are the two most well-studied alleles. These alleles reportedly decrease the activity of *CYP2C9* [3].

As the *CYP2C9* gene plays an important role in losartan pharmacokinetics, there are several studies on the effects of *CYP2C9* polymorphisms on losartan pharmacokinetic parameters, such as the area under the curve ($AUC_{0-\infty}$), maximum concentration (C_{max}), and half-life. Individuals with *CYP2C9**2 or *3 alleles reportedly undergo poorer metabolism than those with *CYP2C9**1/*1 [4]. *CYP2C9**2 or *3 carriers have a higher ratio of plasma $AUC_{0-\infty}$ of losartan to $AUC_{0-\infty}$ of E-3174 than those with *CYP2C9**1/*1 [3]. In contrast,

Burnier et al. reported that the $AUC_{0-\infty}$ of E-3174 in individuals with $CYP2C9^*1/^*3$ was not significantly lower than those with $CYP2C9^*1/^*1$ [5].

Safe and effective drug therapy requires an understanding of a drug's pharmacokinetic, pharmacodynamic, and pharmacogenomic interrelationships [6]. Drug response and adverse events can be predicted using pharmacokinetic parameters [7]. Genetic polymorphisms can affect drug concentrations and effectiveness. However, the association between $CYP2C9$ gene polymorphisms and losartan pharmacokinetic parameters has been inconsistent, possibly due to small sample sizes [8–11]. This study aimed to investigate the effects of the $CYP2C9$ polymorphisms on the pharmacokinetic characteristics of losartan and E-3174 through systematic review and meta-analysis.

2. Methods

The paper was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

2.1. Search Strategy

Two investigators independently conducted a systemic search for all studies published before 4 March 2021, using PubMed, Cochrane Library, EMBASE, and Web of Science. The following search terms were included: (losartan OR (losartan potassium) OR Cozaar) AND (($CYP2C9^*$) OR (cytochrome p450 2C9) OR (cytochrome p 450 2C9)) AND (polymorph* OR variant* OR mutation* OR genotyp* OR phenotyp* OR haplotyp* OR allele* OR SNP* OR pharmacogen*).

2.2. Selection Criteria and Data Extraction

Studies were selected if they (1) compared the pharmacokinetic characteristics of subjects with $CYP2C9^*2$ or $*3$ alleles to those with $CYP2C9^*1/^*1$ after oral administration of losartan; (2) included healthy adults who received a single dose of 50 mg losartan; and (3) were randomized, controlled trials (RCT) or cohort studies.

Studies were excluded if they (1) were editorials, notes, abstracts, reviews, news, letters, posters, or comments; (2) were in vitro or animal studies; (3) did not include blood sample data; (4) had concomitant medications with losartan; or (5) were unable to extract outcome data. If there were overlapping data, only the most recent and comprehensive data were included in the meta-analysis.

The following parameters were extracted independently by two investigators: name of the first author, year of publication, nation, studied polymorphisms, age, number of subjects, body mass index (BMI), genotyping methods, and quantitative methods. The $AUC_{0-\infty}$ (primary outcome), C_{max} , and half-life (secondary outcomes) of losartan and E-3174 were also extracted from each study.

Study quality was assessed by the Newcastle-Ottawa scale (NOS) tool [13]. The NOS tool assessment is based on three primary domains, including selection of subjects (0–4 points), comparability of study groups (0–2 points), and determination of outcomes of interest (0–3 points).

2.3. Statistical Analysis

The mean difference (MD) with 95% confidence intervals (CIs) was calculated to compare $AUC_{0-\infty}$, C_{max} , and half-life. $CYP2C9^*2$ or $*3$ carriers were compared with $CYP2C9^*1/^*1$. We also compared the two groups ($CYP2C9^*3$ carriers and $CYP2C9^*1/^*1$). Heterogeneity was evaluated by Cochrane's Q statistic and Higgins' I^2 statistics [14]. The random-effects model was applied when heterogeneity existed ($I^2 > 50\%$); otherwise, the fixed-effects model was applied.

We performed a subgroup analysis by ethnicity and conducted a sensitivity analysis, using sequential omission of each study, to validate the robustness of the results. Begg's rank correlation test and Egger's regression test were used to detect publication bias. Statistical analyses were performed using Review Manager (RevMan) version 5.3

(The Cochrane Collaboration, Copenhagen, Denmark) and R software (version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria). A p -value < 0.05 was considered statistically significant.

3. Results

The literature search resulted in 490 articles, 294 of which remained after duplicates were removed, and 234 of which were excluded based on the title and abstract. We excluded 52 articles for the following reasons: (1) not original articles ($n = 10$); (2) no losartan administration ($n = 4$); (3) subjects administered other drugs concomitantly ($n = 21$); (4) no blood sample data ($n = 9$); (5) no original pharmacokinetic data ($n = 4$); (6) studies on other genotypes ($n = 2$); and (7) not extractable data ($n = 2$). Eight articles remained after assessing full-text articles (Figure 1). The characteristics of these studies are presented in Table 1 [8,15–21]. Five studies were published in Asia, two studies were conducted in Europe, and one study was in the United States. The studies were published between 2002 and 2021. The NOS ranged from 6 to 7 (Table 1).

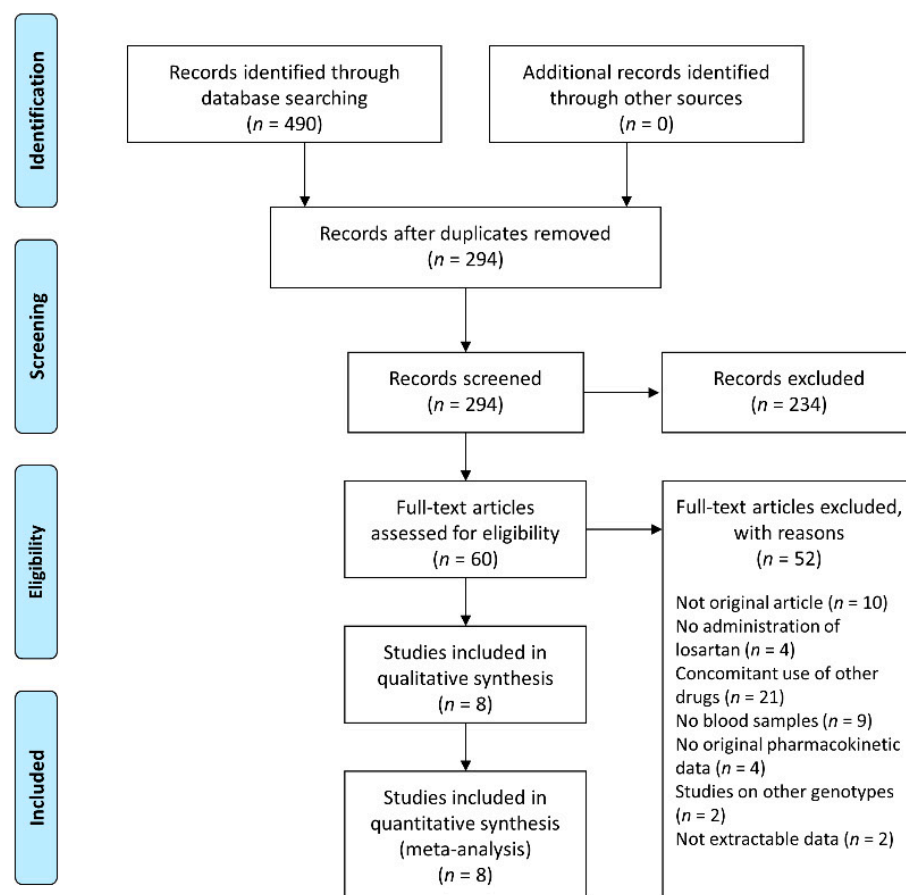


Figure 1. Flow diagram of study selection.

Based on the seven studies in Figure 2, subjects with $CYP2C9^*2$ or $*3$ carriers showed higher $AUC_{0-\infty}$ of losartan than those with $CYP2C9^*1/*1$ (MD $0.17 \mu\text{g}\cdot\text{h}/\text{mL}$; 95% CI: 0.04, 0.29) (Figure 2a). Heterogeneity was detected among the studies ($I^2 = 64\%$; $p = 0.01$). In contrast, subjects with $CYP2C9^*2$ or $*3$ carriers showed significantly lower $AUC_{0-\infty}$ of E-3174 compared to those with $CYP2C9^*1/*1$ (MD $-0.35 \mu\text{g}\cdot\text{h}/\text{mL}$; 95% CI: $-0.62, -0.08$), with low heterogeneity ($I^2 = 6\%$) (Figure 2b).

Table 1. Characteristics of studies included.

First Author, Year	Nation	Studied Polymorphisms	Age	n (Male Percent, %)	BMI (kg/m ²) (SD)	Genotyping Methods	Quantitative Methods	Total NOS
Bae et al. 2012 [15]	Korea	CYP2C9*3	22.6 (1.5 ^b)	13 (N/A)	22.6 (2.3 ^b)	PCR-RFLP	HPLC-FLU	7
Cabaleiro et al. 2013 [16]	Spain	CYP2C9*2 CYP2C9*3	22.6 (1.6 ^b)	36 (50.0)	72.1 c (6.2 ^{b,c})	RT-PCR	HPLC-MS/MS	6
Han 2009 et al. [17]	China	CYP2C9*3	21.9 (2.6 ^b)	12 (100.0)	24.6 (4.9 ^b)	PCR-RFLP	HPLC-MS	7
Huang 2021 et al. [18]	China	CYP2C9*3	23.0 (N/A ^b)	11 (N/A)	19.6 (N/A ^b)	PCR-RFLP	HPLC-MS	7
Lee 2003 et al. [8]	United States	CYP2C9*2 CYP2C9*3	24.0 (5.0 ^b)	15 (47.0)	79.0 c (18.0 ^{b,c})	N/A	HPLC-FLU	7
Li 2009 et al. [19]	China	CYP2C9*3	20.1 (1.9 ^b)	16 (100.0)	17.0–19.0 ^a	PCR-RFLP	HPLC-MS/MS	6
Yang 2018 et al. [20]	China	CYP2C9*2	21–25 ^a	14 (50.0)	17.4–24.8 ^a	PCR-RFLP	HPLC-FLU	7
Yasar 2002 et al. [21]	Sweden	CYP2C9*2 CYP2C9*3	25–54 ^a	22 (50.0)	52–91 ^{a,c}	PCR-RFLP	HPLC-FLU	7

Index; BMI: body mass index; HPLC-FLU: high performance liquid chromatography with fluorescence; HPLC-MS/MS: high performance liquid chromatography with tandem mass spectrometry; N/A: Not Available; NOS: Newcastle-Ottawa score; PCR-RFLP: polymerase chain reaction–restriction fragment length polymorphism; RT-PCR: real time-polymerase chain reaction; SD: standard deviation. ^a range, ^b standard deviation, ^c weight (kg).

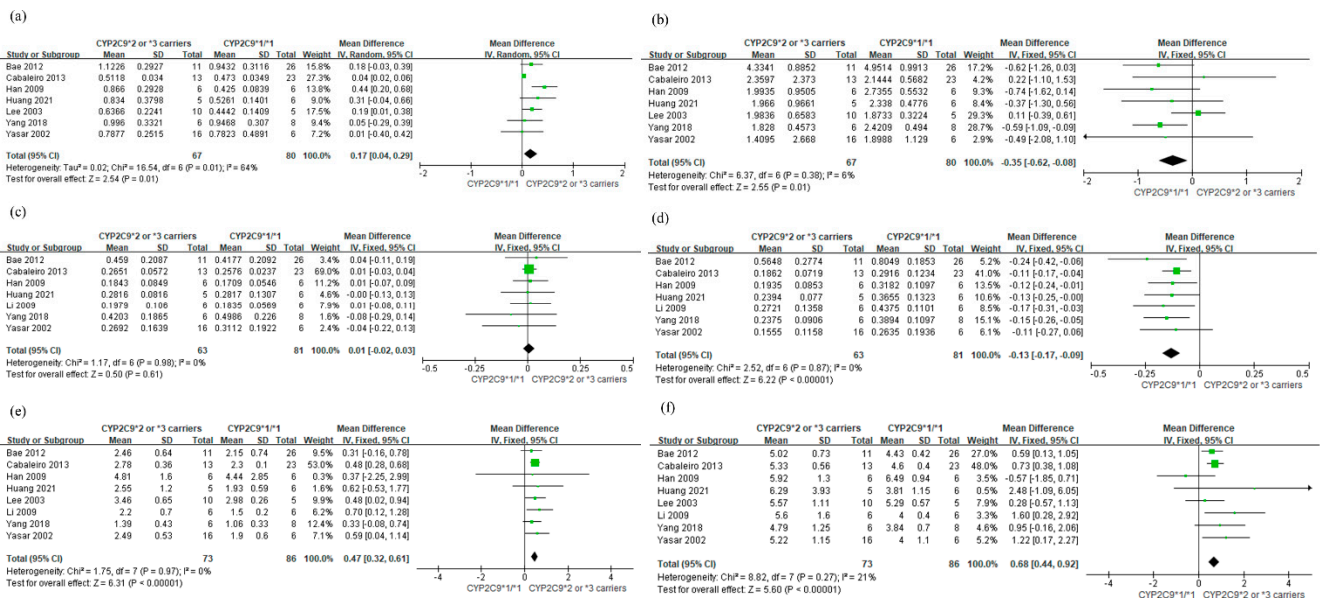


Figure 2. Forest plot comparing the mean difference between CYP2C9*2 or *3 carriers and CYP2C9*1/*1. (a) AUC_{0-∞} of losartan (µg·h/mL), (b) AUC_{0-∞} of E-3174 (µg·h/mL), (c) C_{max} of losartan (µg/mL), (d) C_{max} of E-3174 (µg/mL), (e) half-life of losartan (h), (f) half-life of E-3174 (h).

For C_{max} of losartan, there was no significant difference between subjects with CYP2C9*2 or *3 alleles and those with CYP2C9*1/*1 (MD 0.01 µg/mL; 95% CI: −0.02, 0.03) (Figure 2c). Heterogeneity was not detected among the studies (I² = 0%). However, subjects with CYP2C9*2 or *3 variants showed lower C_{max} of E-3174 than those with CYP2C9*1/*1 (MD −0.13 µg/mL; 95% CI: −0.17, −0.09) (Figure 2d), with no heterogeneity (I² = 0%). Subjects with the CYP2C9*2 or *3 carriers showed significantly longer half-lives of losartan and E-3174 than those with the CYP2C9*1 carrier (MD 0.47 h; 95% CI: 0.32, 0.61 and MD 0.68 h; 95% CI: 0.44, 0.92, respectively) (Figure 2e,f). Neither Begg’s test nor Egger’s test showed significant publication bias for all analyses.

In a comparison between CYP2C9*3 carriers and CYP2C9*1/*1 (Figure 3), the analysis results were similar to that between CYP2C9*2 or 3 carriers and CYP2C9*1/*1 (Figure 2). Additionally, a subgroup analysis was conducted by ethnicity (Figure 4). There was a significant difference in the AUC_{0-∞} of losartan (p = 0.04) and AUC_{0-∞} of E-3174 (p = 0.02) depending on the ethnic subgroup. In the Asian subgroup, subjects with CYP2C9*2 or *3 car-

riers had a higher $AUC_{0-\infty}$ of losartan than those with $CYP2C9^*1/*1$ (MD 0.25 $\mu\text{g}/\text{mL}$; 95% CI: 0.09, 0.42). In contrast, the $AUC_{0-\infty}$ of losartan was not significantly different between those with $CYP2C9^*2$ or $*3$ alleles and with $CYP2C9^*1/*1$ in the Caucasian subgroup (MD 0.06 $\mu\text{g}/\text{mL}$; 95% CI $-0.02, 0.15$). The MD of $AUC_{0-\infty}$ of E-3174 between $CYP2C9^*2$ or $*3$ genotypes and $CYP2C9^*1/*1$ for Asians and Caucasians were -0.59 (95% CI $-0.93, -0.26$) and 0.08 (95% CI $-0.37, 0.52$), respectively.

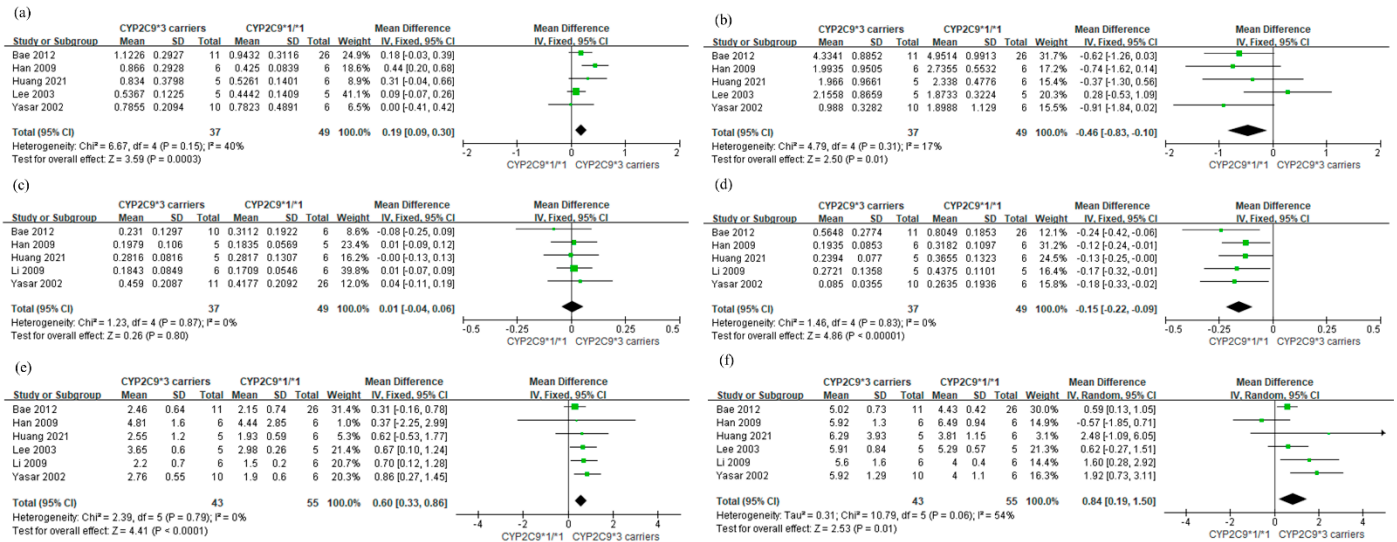


Figure 3. Forest plot comparing the mean difference between $CYP2C9^*3$ carriers and $CYP2C9^*1/*1$. (a) $AUC_{0-\infty}$ of losartan ($\mu\text{g}\cdot\text{h}/\text{mL}$), (b) $AUC_{0-\infty}$ of E-3174 ($\mu\text{g}\cdot\text{h}/\text{mL}$), (c) C_{max} of losartan ($\mu\text{g}/\text{mL}$), (d) C_{max} of E-3174 ($\mu\text{g}/\text{mL}$), (e) half-life of losartan (h), (f) half-life of E-3174 (h).

Sensitivity Analysis

To assess the stability of the results, a sensitivity analysis was performed by sequentially excluding each study. Sensitivity analysis of $AUC_{0-\infty}$ of losartan and E-3174 showed similar results to the main analysis; MD between $CYP2C9^*2$ or $*3$ carriers and $CYP2C9^*1/*1$ ranged from 0.09 to 0.22 for $AUC_{0-\infty}$ of losartan and -0.54 to -0.25 for $AUC_{0-\infty}$ of E-3174, respectively. When the study by Cabaleiro et al. was eliminated, the heterogeneity of losartan $AUC_{0-\infty}$ decreased from 64% to 11% [16].

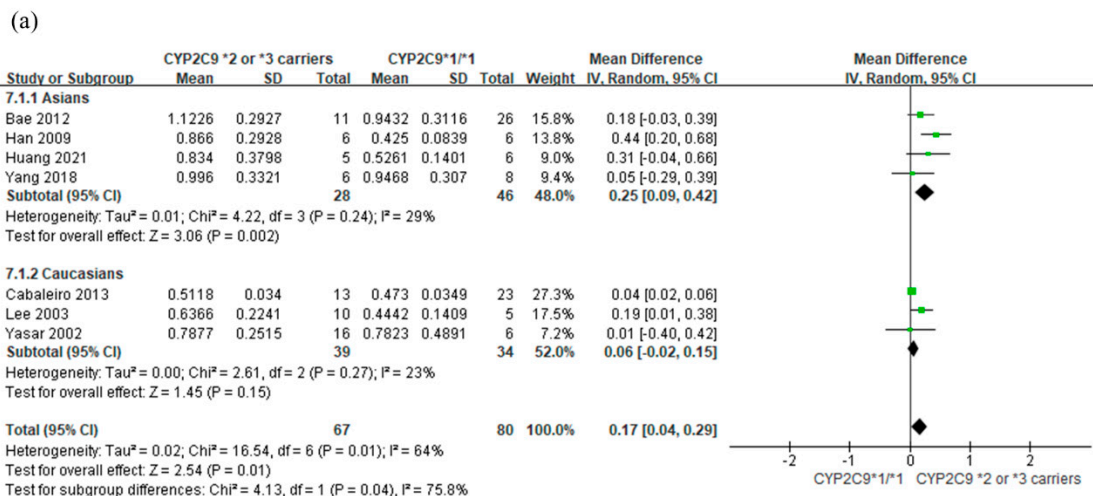


Figure 4. Cont.

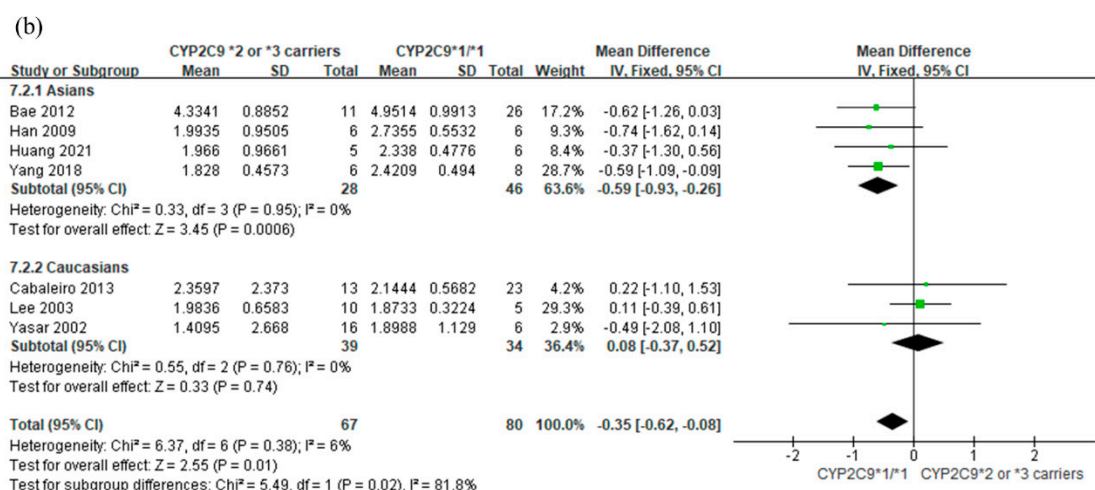


Figure 4. Forest plot with subgroups of Asians and Caucasians for comparing the mean difference between CYP2C9*2 or *3 carriers and CYP2C9*1/*1. (a) AUC_{0-∞} (μg·h/mL) of losartan and (b) AUC_{0-∞} (μg·h/mL) of E-3174.

4. Discussion

This is the first meta-analysis to evaluate the effect of CYP2C9 gene polymorphisms on the pharmacokinetic properties of losartan. The results showed that CYP2C9*2 or *3 carriers had a higher AUC_{0-∞} of losartan and lower AUC_{0-∞} of E-3174 than those with CYP2C9*1/*1. There was no significant difference in the C_{max} of losartan between subjects with CYP2C9*2 or *3 and CYP2C9*1/*1, whereas the subjects with CYP2C9*2 or *3 carriers had lower C_{max} of E-3174 than those with CYP2C9*1/*1. The half-lives of both losartan and E-3174 were longer in CYP2C9*2 or *3 carriers than CYP2C9*1/*1. Similar results were obtained in the comparison between CYP2C9*1/*1 and CYP2C9*3 carriers. There was an ethnic difference in the effects of CYP2C9 gene polymorphisms on the AUC_{0-∞} values of losartan and E-3174 between Asians and Caucasians.

There are several studies on the effect of CYP2C9 inhibitors, such as fluconazole, bucolome, and ticlopidine, on the pharmacokinetic parameters of losartan. An in vitro study revealed that the C_{max} and AUC_{0-∞} of E-3174 significantly decreased to 30% and 47% by fluconazole, respectively, compared to the control group [22]. Kobayashi et al. reported that concomitant use of losartan and bucolome resulted in the significant decrease of AUC_{0-∞} of E-3174 and increase of AUC_{0-∞} of losartan in healthy male volunteers [23]. There was also a report that ticlopidine increased the AUC_{0-∞} of losartan in rats [24]. The aforementioned studies indicate that the CYP2C9 enzyme was a significant metabolizer of losartan.

The pharmacokinetic properties of losartan can affect its response. One study found that the CYP2C9*3 variant reduces losartan metabolism and its hypotensive effect after oral administration of losartan [25]. In this study, the C_{max} of E-3174 in the CYP2C9*1/*3 group was 30% lower than that in the CYP2C9*1/*1 group. Subjects with CYP2C9*1/*3 had a less hypotensive effect in the diastolic blood pressure (DBP) at 10 h and 12 h post-dosing than those with CYP2C9*1/*1. The CYP2C9*1/*1 group had a more significant decrease in the systolic blood pressure (SBP) from 1 h to 12 h than the CYP2C9*1/*3 group.

CYP2C9 polymorphism may differently affect the ARB drug responses. Losartan has lower efficiency in CYP2C9*2 or *3 carriers, despite an increased concentration of losartan. The low efficiency in CYP2C9*2 or *3 carriers was attributed to the decreased AUC_{0-∞} of E-3174, which has more potent activity than losartan. In contrast, in the case of irbesartan, the CYP2C9*1/*3 genotype carriers showed both a higher concentration of irbesartan and greater DBP responses compared to the CYP2C9*1/*1 genotype carriers; this was possibly because the metabolite has no pharmacological activity [26]. Chen et al. also showed that subjects with the CYP2C9*1/*3 genotype had significantly higher plasma irbesartan concentrations compared with those with the CYP2C9*1/*1 genotype [27].

We further investigated the effect of the complex heterozygous genotype of *CYP2C9**2 and *CYP2C9**3 on losartan pharmacokinetics or pharmacodynamics. There was only one study to examine the pharmacokinetic difference between patients with both *CYP2C9**2 and *CYP2C9**3 alleles and those with *CYP2C9**1/*1 [11]. Subjects with the complex heterozygous genotype of *CYP2C9**2 and *CYP2C9**3 had a significantly higher C_{max} and AUC of E-3174 than those with *CYP2C9**1/*1 (179 vs. 603 nmol/L and 2134 vs. 4346 nmol/L·h, respectively). However, in the case of losartan, the C_{max} and AUC did not show a statistically significant difference between *CYP2C9**2/*3 and *CYP2C9**1/*1 (635 vs. 675 nmol/L and 1697 vs. 2006 nmol/L·h, respectively).

*CYP2C9**2 and *3 frequencies are higher in Caucasians than in Asians [4,28,29]. In the *CYP2C9* polymorphisms in Asians, the *CYP2C9**3 frequencies are more dominant than *CYP2C9**2 (3.55% vs. 0.25%) [29]. Among Caucasians, the *CYP2C9**2 allele is more frequent than the *CYP2C9**3 allele (8.0% vs. 6.0%) [4]. Overall, in this study, a higher MD of the $AUC_{0-\infty}$ of losartan was observed in the Asian subgroup than in the Caucasian subgroup (0.25 $\mu\text{g}\cdot\text{h}/\text{mL}$ vs. 0.06 $\mu\text{g}\cdot\text{h}/\text{mL}$). The *CYP2C9* polymorphisms in Asians were mostly *CYP2C9**1/*3 in this study. On the contrary, in the Caucasian subgroup, the *CYP2C9**2 carriers, such as *CYP2C9**1/*2 and *CYP2C9**2/*2, were more common than in the Asian subgroup. The ethnic difference in the MD by *CYP2C9* polymorphisms is possibly due to different distributions of *2 and *3, considering that the *CYP2C9**3 allele has lower enzyme activity than the *CYP2C9**2 allele [30].

Polymorphisms of *CYP2C9* should be considered in the case of antihypertensive drug polytherapy, because other hypertensive agents, such as carvedilol, torsemide, and indapamide, are also known to be *CYP2C9* substrates [31]. According to Pan et al., *CYP2C9* variants decreased the intrinsic clearance of carvedilol [32]. For torsemide, it was shown that *CYP2C9**3 resulted in lower oral clearance and metabolite formation clearance [33]. In the study of Wang et al., patients with homozygous variants of *CYP2C9* rs4918758, which showed lowered *CYP2C9* activity, had higher C_{max} and AUC and lower clearance of indapamide [34]. As *CYP2C9* is involved in the metabolism of several antihypertensive agents, *CYP2C9* loss-of-function alleles may increase the parent drug level. There are some limitations to this meta-analysis that should be considered when interpreting the results. First, the limited number of studies may lead to low statistical power in detecting differences or heterogeneity. However, according to Herbison et al., meta-analyses with as few as four or five studies could produce robust results that are consistent with long-term results [35]. Second, some potential confounder variables, which could be associated with pharmacokinetics (e.g., kidney and liver functions), could not be adjusted due to a lack of information from individual studies. Third, only healthy volunteers were involved in this study, indicating that the results may not be applicable to patients. Fourth, other *CYP2C9* genotypes, such as *CYP2C9**13, were not included in this meta-analysis because of low frequencies. Fifth, we could not conduct a meta-analysis comparing *CYP2C9**2 carriers with *CYP2C9**1/*1 carriers due to a lack of studies.

Despite these drawbacks, this study is the first systematic review and meta-analysis to evaluate the association between *CYP2C9* genotypes and pharmacokinetic characteristics of losartan and its active metabolite. By combining the results of several studies, this study suggests that *CYP2C9**2 or *3 alleles may be significantly associated with the pharmacokinetics of losartan and its active metabolite.

In conclusion, we found that *CYP2C9**2 or *3 carriers showed higher $AUC_{0-\infty}$ of losartan and lower $AUC_{0-\infty}$ of E-3174 compared to those with *CYP2C9**1/*1. As altered pharmacokinetics can affect the therapeutic responses of losartan, genotyping *CYP2C9* may be useful in understanding individual pharmacokinetic and pharmacodynamic differences.

Author Contributions: All the authors have made substantial contributions to the conception of the study. H.-Y.Y., J.Y. and H.-S.G. contributed to designing the study. Y.-A.P. and Y.-b.S. contributed to acquisition and analysis of data. Y.-A.P. and H.-S.G. contributed to the interpretation of data. Y.-A.P. and H.-S.G. contributed to drafting of the manuscript. J.Y. and H.-S.G. contributed to critical revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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