Journal of Community Health Provision
Vol. 6, Issue 2, 2026
Page 626-643
DOI: https://doi.org/10.55885/jchp.v6i2.1040

Pharmacogenomic Interactions in Antihypertensive Drug Polypharmacy and their Association with Intradialytic Complications in Chronic Kidney Disease Patients Undergoing Hemodialysis

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Abstract. *This study aims to synthesize scientific evidence on pharmacogenomic interactions in antihypertensive drug polypharmacy and their association with intradialytic complications in patients with chronic kidney disease (CKD) undergoing hemodialysis through a Systematic Literature Review (SLR) approach. A systematic search of PubMed, Scopus, Web of Science Core Collection, Google Scholar, and Wiley Online Library was conducted for studies published from 2017 to 2025. The review was reported in accordance with PRISMA 2020, although the protocol was not prospectively registered. Evidence from maintenance hemodialysis populations was synthesized separately from contextual pharmacogenomic evidence derived from non-dialysis or mixed CKD populations. A total of 30 articles met the inclusion criteria and were synthesized narratively. The review findings indicate that antihypertensive polypharmacy is highly prevalent in the hemodialysis population, with an average use of ≥5–10 medications. The most frequently reported pharmacogenomic interactions involve phase I drug-metabolizing genes, particularly CYP2D6 and CYP2C9, which influence responses to beta-blockers and angiotensin receptor blockers (ARBs). Drug–drug–gene interactions under intensive polypharmacy conditions increase the risk of intradialytic hypotension, intradialytic hypertension, bradycardia, electrolyte disturbances, and reduced quality of life. This synthesis confirms that intradialytic complications are influenced not only by drug class or timing of administration, but also by the combination of genetic factors, kidney function, and medication burden. The integration of pharmacogenomic approaches, polypharmacy evaluation, and the involvement of clinical pharmacists has the potential to improve patient safety and hemodynamic stability in hemodialysis patients.*

Keywords: *Pharmacogenomics, Polypharmacy, Antihypertensive Drugs, Hemodialysis, Intradialytic Complications*

Received: June 8, 2026 Received in Revised: July 16, 2026 Accepted: August 5, 2026

INTRODUCTION

Hypertension is a very common comorbidity among patients with chronic kidney disease (CKD) undergoing hemodialysis and is associated with left ventricular hypertrophy, cardiovascular events, and mortality (Law et al., 2023; Clemmer et al., 2022; Georgianos & Agarwal, 2016; Loutradis & Sarafidis, 2019; Sarafidis et al., 2017). Blood pressure control in this population is rarely sufficient with a single drug, making antihypertensive polypharmacy a common therapeutic pattern in dialysis services. Drug choices usually include RAAS inhibitors

(ACE inhibitors/ARBs), beta-blockers, calcium channel blockers, and other agents according to the patient's clinical profile (Diaconu et al., 2021). However, when several drugs are administered simultaneously, patient responses are not always uniform; some patients remain stable, while others experience blood pressure fluctuations that interfere with treatment quality and safety during hemodialysis sessions.

During hemodialysis, changes in intravascular volume and hemodynamic responses may trigger intradialytic complications, particularly intradialytic hypotension (IDH) and intradialytic hypertension (Timofte et al., 2021; Kanbay et al., 2020; Iatridi et al., 2022; Bradshaw, 2014). IDH has been reported to occur in approximately 5–30% of hemodialysis sessions, depending on the definition used and patient characteristics, and is associated with unfavorable outcomes such as organ ischemia, heart failure, vascular access problems, increased cardiovascular events, and mortality (Kanbay et al., 2020). Intradialytic hypertension is also a concern because it is related to sodium/volume overload, sympathetic activation, and increased cardiovascular risk; some clinical literature highlights the need to avoid highly dialyzable antihypertensive drugs in patients prone to this phenomenon (Siddiqi & Shatat, 2020).

The relationship between antihypertensive drugs and IDH has long been the basis for the practice of "taking medication at night and withholding it on the morning of dialysis" in some patients. Research evidence, however, does not always point in the same direction. The TAKE-HOLD study evaluated the effect of "taking versus withholding" blood pressure medication before hemodialysis on IDH and showed that the issue of medication timing requires more careful interpretation, rather than merely following routine practice (Chang et al., 2021). The AHA review also emphasized that the evidence is still developing and that clinical decisions need to consider both the risk of hypotension during dialysis and blood pressure control between sessions (Jentzer et al., 2020).

Differences across studies become clear when IDH risk is compared by drug class. A randomized trial emulation study among incident hemodialysis patients reported that, compared with calcium channel blockers, the use of beta/alpha-beta blockers, ACE inhibitors/ARBs, and diuretics was associated with a higher likelihood of IDH (Zoccali et al., 2024). Conversely, another study specifically comparing antihypertensive classes and IDH risk reported more "neutral" findings for ACE inhibitors/ARBs and beta-blockers, while dihydropyridine calcium channel blockers and alpha-blockers may reduce IDH risk under certain definitions (Chen et al., 2025). Differences in IDH definitions, methods of defining drug exposure, duration of use, and patient characteristics, such as new versus long-term dialysis patients, play a major role in producing inconsistent conclusions (Iatridi et al., 2025).

Beyond clinical factors, genetic variation also shapes antihypertensive response and susceptibility to adverse effects. For beta-blockers such as metoprolol, CYP2D6 variation affects drug levels and the risk of adverse effects such as bradycardia, hypotension, and syncope; evidence-based guidelines for metoprolol–CYP2D6 are available and emphasize dose adjustment/titration in certain metabolizer groups and in drug–gene or drug–drug–gene conditions (Dean & Kane, 2025). In CKD patients, pharmacokinetic issues are not limited to kidney function; reduced non-renal clearance, including CYP2D6 and CYP3A pathways, may occur, increasing drug exposure even when the drug is not primarily excreted by the kidneys (Liabeuf et al., 2025). This means that hemodialysis patients may experience altered drug exposure due to the combination of kidney status, genotype, and concomitant medications.

Pharmacogenomic evidence in the RAAS pathway has also developed. Oosthuizen & Sturrock (2022) showed that ACE I/D polymorphism may be associated with renal protective responses to ACE inhibitors in proteinuric nephropathy, although findings across populations are not always consistent and some earlier studies were limited by small sample sizes and follow-up duration. In dialysis populations, studies on ACE I/D have also suggested associations with cardiovascular outcomes or mortality, although their focus has not been specifically on intradialytic complications during hemodialysis sessions (Uchiyama et al., 2021). In the field of

hypertension pharmacogenomics in CKD, Tomson et al. (2021) showed the potential for changes in hypertension control after PGx information was provided, but the outcomes assessed were more often blood pressure control or general therapy adjustment, rather than acute hemodynamic events during dialysis.

This is where the evidence gap becomes apparent. The literature on IDH often discusses drug class, dialyzability, and timing of administration, while the pharmacogenomic literature discusses variations in drug response, adverse-effect risk, and the potential for therapy optimization. A synthesis that connects both areas pharmacogenomic interactions, including drug–gene and drug–drug–gene interactions in antihypertensive polypharmacy, and directly links them to intradialytic complications such as IDH and intradialytic hypertension remains rarely presented systematically (Knežević et al., 2024; Le et al., 2025; Altoum et al., 2023).

In fact, polypharmacy is the most common situation encountered in hemodialysis patients, and phenomena such as CYP2D6 phenoconversion in the presence of strong inhibitors may alter the risk profile of hypotension/bradycardia when beta-blockers are used together with other drugs (Wolf, 2024). Without a well-organized evidence map, clinical decisions may still rely on habitual drug withholding or general drug-class selection, while genetic variation and drug interactions may be important explanations for why responses differ between patients.

Based on this need, this study is designed using a Systematic Literature Review (SLR) approach to collect, appraise, and synthesize scientific evidence related to pharmacogenomic interactions in antihypertensive polypharmacy and their relationship with intradialytic complications in CKD patients undergoing hemodialysis. The SLR is expected to produce a map of the most frequently reported genes/variants, dominant drug–gene pairs, such as CYP2D6–beta-blockers, and also highlight differences in outcome definitions, variations in study designs, and the need for more targeted primary research in hemodialysis populations.

This study aims to systematically synthesize and evaluate scientific evidence regarding pharmacogenomic interactions in the use of antihypertensive polypharmacy and their relationship with intradialytic complications in patients with chronic kidney disease undergoing hemodialysis. It examines the types and patterns of the most frequently reported drug–gene and drug–drug–gene interactions, genes or genetic variations associated with changes in antihypertensive response and adverse effects, and the relationship between these pharmacogenomic findings and intradialytic hypotension and intradialytic hypertension. Through a Systematic Literature Review approach, this study is also directed at identifying differences in outcome definitions and study designs in previous research, while mapping existing evidence gaps as a basis for developing further research and formulating a more measurable direction for antihypertensive therapy management in the hemodialysis population.

METHODS

This study employed a systematic literature review to identify and synthesize evidence concerning pharmacogenomic interactions in antihypertensive polypharmacy and their association with intradialytic complications among patients with chronic kidney disease undergoing hemodialysis. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) statement. The review protocol was not prospectively registered in PROSPERO, the Open Science Framework, or another public repository; therefore, the absence of protocol registration is acknowledged as a methodological limitation. The review question was developed using the Population, Intervention/Exposure, Comparison, and Outcome framework. The principal population consisted of adults with advanced CKD or end-stage kidney disease undergoing maintenance hemodialysis. Studies involving non-dialysis CKD or mixed dialysis and non-dialysis populations were included only as contextual pharmacogenomic evidence and were analyzed separately from studies reporting direct intradialytic outcomes.

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

Table 1. PICO Research Framework

PICO Components	Description
Population (P)	Adults aged ≥18 years with advanced CKD or end-stage kidney disease undergoing maintenance hemodialysis. Non-dialysis or mixed CKD populations were used only as contextual evidence.
Intervention (I)	Antihypertensive polypharmacy, primarily defined as the concurrent use of ≥5 medications, involving drug–gene or drug–drug–gene interactions.
Comparison (C)	Different genotypes, metabolizer phenotypes, medication burdens, antihypertensive regimens, or no formal comparator.
Outcome (O)	Intradialytic hypotension, intradialytic hypertension, bradycardia, arrhythmia, electrolyte disturbances, adverse drug events, and altered therapeutic response.

Based on the PICO framework, three research questions were formulated to guide article selection, data extraction, and narrative synthesis.

Table 2. Research Questions

Code	Research Questions	Focus of Analysis
RQ1	What are the characteristics of antihypertensive polypharmacy among adult patients undergoing hemodialysis?	Medication number, drug classes, and clinical context
RQ2	What pharmacogenomic drug–gene and drug–drug–gene interactions are reported in antihypertensive therapy among CKD patients?	Genes, variants, metabolizer phenotypes, and mechanisms
RQ3	How are pharmacogenomic interactions and antihypertensive polypharmacy associated with intradialytic complications?	Intradialytic hypotension, hypertension, bradycardia, arrhythmia, and adverse effects

A systematic search was conducted in PubMed, Scopus, Web of Science Core Collection, Google Scholar, and Wiley Online Library for articles published between January 2017 and December 2025. PubMed, Scopus, and Web of Science were treated as the principal bibliographic databases. Wiley Online Library was used as a supplementary publisher platform to identify relevant nephrology, pharmacology, and pharmacogenomic publications. The final search was conducted on. The search strategy combined controlled vocabulary and free-text terms related to CKD, hemodialysis, antihypertensive therapy, polypharmacy, pharmacogenomics, and intradialytic complications. The complete PubMed search strategy was:

> ("Renal Insufficiency, Chronic"[MeSH] OR "Kidney Failure, Chronic"[MeSH] OR "chronic kidney disease"[Title/Abstract] OR CKD[Title/Abstract] OR ESRD[Title/Abstract]) AND ("Renal Dialysis"[MeSH] OR hemodialysis[Title/Abstract] OR haemodialysis[Title/Abstract]) AND ("Antihypertensive Agents"[MeSH] OR antihypertensive*[Title/Abstract] OR polypharmacy[Title/Abstract]) AND ("Pharmacogenetics"[MeSH] OR pharmacogenomic*[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR "drug-gene interaction*"[Title/Abstract] OR "drug-drug-gene interaction*"[Title/Abstract] OR CYP2D6[Title/Abstract] OR CYP2C9[Title/Abstract]) AND (intradialytic[Title/Abstract] OR hypotension[Title/Abstract] OR hypertension[Title/Abstract] OR bradycardia[Title/Abstract] OR arrhythmia*[Title/Abstract]).

The strategy was adapted to the syntax and field restrictions of Scopus, Web of Science, and Wiley Online Library, with the complete strategies provided in Supplementary Table S1. For Google Scholar, the first 170 records ranked by relevance were screened because the platform produces dynamically ranked and potentially extensive results.

Table 3. Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Publication Type	Peer-reviewed primary studies and relevant systematic or clinical reviews	Editorials, letters, theses, books, protocols, and conference abstracts
Population	Adults with CKD undergoing maintenance hemodialysis	Pediatric patients, non-CKD populations, acute kidney injury, and peritoneal dialysis-only populations
Contextual population	Non-dialysis or mixed CKD populations reporting relevant pharmacogenomic evidence	Non-dialysis studies without relevant antihypertensive pharmacogenomic findings
Exposure	Antihypertensive polypharmacy, drug–gene interactions, or drug–drug–gene interactions	Exclusively non-pharmacological interventions
Outcomes	Intradialytic complications, adverse drug events, altered drug exposure, or therapeutic response	Studies without relevant clinical or pharmacogenomic outcomes
Publication period	2017–2025	Published before 2017
Study model	Human studies	Animal or exclusively *in vitro* studies

All records were imported into Mendeley. Duplicate records were identified using DOI, title, authors, journal, and publication year, followed by manual verification. The search identified 642 records: 168 from PubMed, 134 from Scopus, 96 from Web of Science, 74 from Wiley Online Library, and 170 from Google Scholar. After removing 52 duplicates, 590 records were screened. A total of 160 full-text articles were assessed, of which 30 were included in the final narrative synthesis.

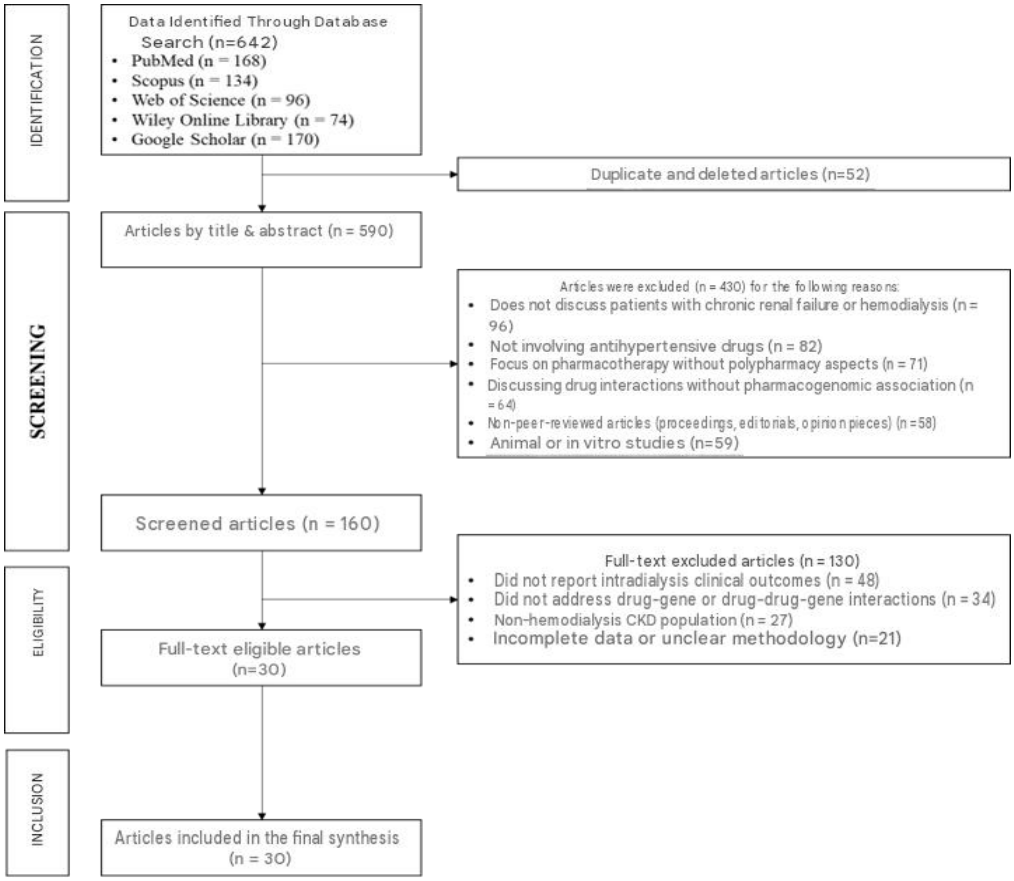

Figure 1. Research PRISMA Diagram

Evidence obtained from maintenance hemodialysis populations was treated as direct evidence of intradialytic outcomes. Studies involving non-dialysis or mixed CKD populations were classified as contextual evidence and used only to explain relevant pharmacogenomic mechanisms. Data were synthesized narratively according to polypharmacy characteristics, genes and metabolizer phenotypes, drug–gene and drug–drug–gene interactions, and reported intradialytic outcomes. Meta-analysis was not performed because of heterogeneity in dialysis status, study design, medication exposure, pharmacogenomic assessment, and outcome definitions.

RESULT AND DISCUSSION

A total of 30 articles were included in the narrative synthesis. The included literature showed substantial variation in publication year, study design, population characteristics, therapeutic focus, type of interaction assessed, and clinical outcomes. This heterogeneity was important because the available studies did not provide an equally direct assessment of pharmacogenomic interactions and intradialytic complications. Studies conducted exclusively in maintenance hemodialysis populations provided more direct evidence regarding intradialytic outcomes, whereas studies involving non-dialysis CKD or mixed populations primarily contributed contextual evidence on drug metabolism, pharmacogenomic variation, medication burden, and antihypertensive response.

Table 4. Characteristics of Articles Included in the SLR (N = 30)

Characteristics	Category	Frequency (n=30)	Percentage (%)
Publication Year	2017–2019	4	13,3
	2020–2022	10	33,3
	2023–2025	16	53,4
Research Design	Narrative review / Clinical review	11	36,7
	Systematic review / Meta-analysis	7	23,3
	Observasional (cross-sectional/retrospektif)	7	23,3
	Prospective cohort/PGx intervention	5	16,7
Population	Non-dialysis CKD	6	20,0
	CKD with hemodialysis	15	50,0
	Mixed CKD (dialysis & non-dialysis)	9	30,0
Focus Therapy	Polypharmacy in general (≥5 drugs)	12	40,0
	Antihypertensives in CKD	9	30,0
	Farmakogenomik (drug–gene / PGx)	6	20,0
	Drug interactions (DDIs)	3	10,0
Types of Interactions Studied	Drug–drug interaction (DDI)	13	43,3
	Drug–gene interaction (DGI)	8	26,7
	Drug–drug–gene interaction	4	13,3
	Non-specific (conceptual/general)	5	16,7
Clinical Outcomes	Intradialysis complications / hemodynamic effects	7	23,3
	Side effects / ADR / drug safety	8	26,7
	Blood pressure control	6	20,0
	Mortality / prognosis / QoL	5	16,7
	General pharmacotherapy outcomes	4	13,3

More than half of the included articles were published between 2023 and 2025, indicating increasing interest in pharmacogenomics and medication optimization in CKD. Nevertheless, publication recency should not be interpreted as evidence maturity. Narrative and clinical reviews represented 36.7% of the included literature, while systematic reviews and meta-analyses accounted for another 23.3%. Consequently, approximately three-fifths of the evidence consisted of secondary literature rather than prospective studies directly evaluating genotype, antihypertensive exposure, and intradialytic outcomes within the same population.

Only five studies were classified as prospective cohort or pharmacogenomic intervention studies. This imbalance limits causal interpretation because review articles may summarize overlapping primary studies and may reproduce the same underlying evidence. Observational studies are also vulnerable to confounding by indication, comorbidity burden, residual kidney function, dialysis prescription, volume status, and clinicians' selection of antihypertensive drugs. Therefore, the findings should be interpreted as an evidence map identifying plausible pharmacogenomic and pharmacological mechanisms rather than definitive proof that a particular genotype causes an intradialytic complication.

Differences According to Study Population and Dialysis Status

The included studies differed substantially in their study populations. Fifteen articles focused on patients undergoing hemodialysis, six involved non-dialysis CKD populations, and nine included mixed dialysis and non-dialysis populations. These groups should not be treated as clinically equivalent. Hemodialysis causes rapid changes in intravascular volume, electrolyte concentration, sympathetic activity, vascular resistance, and drug concentration. These changes are not experienced in the same manner by patients with non-dialysis CKD.

Medication burden also tends to be greater in maintenance hemodialysis populations because antihypertensive drugs are commonly administered with phosphate binders, erythropoiesis-stimulating agents, iron preparations, antidiabetic drugs, statins, antiplatelet drugs, proton-pump inhibitors, and medications for CKD-related symptoms. Westergaard et al. (2024) reported a higher medication burden among dialysis patients than among non-dialysis CKD patients, while Oosting et al. (2024) found that polypharmacy was highly prevalent across CKD populations. However, evidence from non-dialysis CKD primarily informs the biological plausibility of drug–gene associations and cannot independently establish an association with intradialytic hypotension or hypertension.

Differences may also arise between incident and long-term maintenance hemodialysis patients. Incident patients may have unstable dry-weight estimates, changing residual kidney function, recent modification of antihypertensive regimens, and greater variation in dialysis prescriptions. Long-term patients may have more established treatment patterns but greater cardiovascular remodeling, autonomic dysfunction, vascular stiffness, and cumulative medication exposure. Consequently, associations observed in one dialysis subgroup may not be directly generalizable to another.

Variation in Polypharmacy Definitions and Medication Exposure

The definition of polypharmacy was inconsistent across the included studies. Most studies defined polypharmacy as the concurrent use of five or more medications, whereas others used different thresholds, counted only regularly prescribed medications, or distinguished severe polypharmacy as ten or more medications. Some studies evaluated the total medication burden, while others focused only on the number of antihypertensive agents. These definitions measure different clinical constructs.

A patient taking five medications from different therapeutic classes may have a different risk profile from a patient receiving four antihypertensive drugs with additive blood pressure-lowering effects. Therefore, the number of medications alone does not fully represent interaction risk. Drug class, dose, administration time, dialysis removal, enzyme inhibition,

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

pharmacogenomic phenotype, and the clinical necessity of each medication are equally important.

The clinical relevance of non-essential medication burden should also be considered. Kitamura et al. (2021) reported that non-essential medications may be more strongly associated with poor outcomes than the total number of medications. This suggests that indiscriminate medication counting may obscure the distinction between necessary multidrug treatment and potentially inappropriate polypharmacy. The present synthesis therefore supports medication review based not only on a numerical threshold but also on therapeutic indication, interaction potential, dialyzability, and patient-specific risk.

Differences in Antihypertensive Classes, Timing, and Dialyzability

Associations between antihypertensive treatment and intradialytic complications varied according to drug class. Beta-blockers may increase susceptibility to bradycardia and may impair compensatory tachycardia during ultrafiltration, particularly when exposure is increased. Calcium channel blockers primarily reduce vascular resistance, but their hemodynamic effects differ between dihydropyridine and non-dihydropyridine agents. ACE inhibitors and ARBs alter the renin–angiotensin–aldosterone system, whereas diuretics have limited effectiveness in anuric patients but may remain relevant in patients with residual urine production. Comparisons across studies may therefore yield different results when broad class labels are used without distinguishing individual drugs. Even within the beta-blocker class, agents differ in CYP2D6 dependence, protein binding, dialyzability, receptor selectivity, and elimination pathways. Similar heterogeneity exists among ACE inhibitors, ARBs, and calcium channel blockers.

Medication timing is another source of variation. The effect of administering antihypertensive drugs before dialysis differs from that of evening or post-dialysis administration. Chang et al. (2021) demonstrated that routinely withholding all antihypertensive medications before dialysis should not be considered universally appropriate because this practice may reduce intradialytic hypotension in some patients but worsen pre-dialysis or interdialytic blood pressure control in others. The relevant clinical question is therefore not simply whether medication was taken, but which drug was taken, at what dose, how long before dialysis, and whether the drug or its active metabolites were removed during the session.

Drug dialyzability further modifies exposure. Highly dialyzable drugs may show reduced concentrations during or after hemodialysis, potentially contributing to inadequate blood pressure control or intradialytic hypertension in susceptible patients. Poorly dialyzable drugs may maintain their effect throughout dialysis and may contribute to hypotension when combined with rapid ultrafiltration or other vasodilatory agents. Dialyzability is primarily a pharmacokinetic property and should not be described as a pharmacogenomic interaction unless a relevant genetic factor has also been measured.

Differences in Definitions of Intradialytic Complications

The reported frequency and predictors of intradialytic hypotension varied because the included studies did not uniformly define the outcome. Some studies used a decrease in systolic blood pressure from the pre-dialysis value, whereas others required an absolute nadir, symptoms, nursing intervention, saline administration, ultrafiltration reduction, or premature termination of dialysis. A definition based solely on a numerical decline may identify events that are clinically tolerated, while a symptom- or intervention-based definition may identify fewer but more clinically significant events.

Variation in outcome definition can alter the apparent relationship between antihypertensive classes and intradialytic hypotension. A drug may appear associated with IDH under a broad blood pressure-based definition but not under a definition requiring symptoms or clinical intervention. Differences in dialysis duration, ultrafiltration rate, dialysate temperature, dialysate sodium, food intake, and pre-dialysis blood pressure may further modify the observed association (Kanbay et al., 2020; Chen et al., 2025).

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

Intradialytic hypertension was also defined inconsistently. Some studies focused on any increase in blood pressure during dialysis, whereas others required a recurrent increase across several sessions. A single intradialytic increase may reflect temporary volume or sympathetic changes, while recurrent intradialytic hypertension may represent a more stable clinical phenotype. These distinctions reduce comparability across studies and prevent the direct pooling of results.

Pharmacogenomic Interactions in Antihypertensive Therapy

The pharmacogenomic findings were concentrated mainly on CYP2D6 and CYP2C9, although the strength of evidence differed by drug and outcome. The included studies more commonly reported metabolizer categories or clinically actionable drug–gene pairs than consistent estimates for individual variants. Therefore, the synthesis distinguishes phenotype-level findings from specific allelic findings and avoids assigning a particular variant when it was not explicitly reported in the primary study.

Table 5. Mechanistic Classification of Pharmacogenomic and Pharmacological Interactions

Drug or exposure	Gene, phenotype, or pathway	Mechanism	Potential clinical implication	Interpretation
Metoprolol	CYP2D6 poor, intermediate, normal, or ultrarapid metabolizer phenotype	Inherited variation in CYP2D6-mediated metabolism	Poor or intermediate metabolism may increase exposure and susceptibility to bradycardia or hypotension; ultrarapid metabolism may reduce therapeutic response	Relevant drug–gene relationship, but direct evidence for intradialytic events remains limited
Carvedilol	CYP2D6 phenotype	Partial influence on oxidative metabolism	Differences in exposure and hemodynamic response may occur	Effect may be less predictable because carvedilol has multiple metabolic pathways
Metoprolol combined with a CYP2D6 inhibitor	CYP2D6 phenoconversion	Enzyme inhibition produces a functional poor-metabolizer state despite the inherited genotype	Increased beta-blocker exposure, bradycardia, fatigue, or hypotension	Drug–drug–gene mechanism; should not be equated with an inherited poor-metabolizer genotype
Losartan	CYP2C9 reduced-function phenotype or variants when reported	Reduced conversion of losartan to its more active metabolite	Reduced antihypertensive effect and persistent hypertension	Potential explanation for therapeutic failure, but not necessarily for drug accumulation

ACE inhibitors	ACE insertion/deletion polymorphism and related RAAS pathways	Pharmacodynamic variation in treatment response	Heterogeneous blood pressure or renoprotective response	Evidence is population-dependent and not specific to intradialytic outcomes
ARBs	AGTR1 and related RAAS variants	Variation at the pharmacological target	Differences in antihypertensive response	Findings require validation across ethnic groups and dialysis populations
Calcium channel blockers	ABCB1, NOS3, or related pathways	Variation in drug transport or vascular response	Differences in plasma exposure or vasodilatory response	Evidence remains exploratory and drug-specific
Advanced CKD or ESKD	No single genetic variant required	Reduced kidney-related non-renal clearance and altered hepatic enzyme activity	Increased exposure to some non-renally eliminated drugs	Disease-related pharmacokinetic alteration, not a pharmacogenomic interaction
Multiple antihypertensives	No genotype required	Additive or synergistic pharmacodynamic effects	Hypotension, bradycardia, dizziness, or impaired compensatory responses	Pharmacodynamic drug–drug interaction unless a genetic factor is directly demonstrated
Dialyzable or non-dialyzable drug exposure	Drug-specific physicochemical properties	Drug removal or persistence during hemodialysis	Loss of efficacy or prolonged hypotensive effect	Pharmacokinetic dialysis effect, not inherently pharmacogenomic
PPI or other CYP2C19 substrate/inhibitor	CYP2C19 only when supported by a specific drug pair	Drug-specific metabolism or inhibition	Possible alteration in exposure of relevant CYP2C19 substrates	CYP2C19 should not be presented as a principal beta-blocker pathway without direct drug-specific evidence

CYP2D6-Mediated Metabolism and Phenoconversion

The strongest and most clinically interpretable pharmacogenomic relationship concerned CYP2D6 and metoprolol. CYP2D6 activity can be categorized into poor, intermediate, normal, and ultrarapid metabolizer phenotypes. Poor and some intermediate metabolizers may experience greater metoprolol exposure, increasing susceptibility to bradycardia, fatigue, hypotension, or syncope. Ultrarapid metabolizers may have lower exposure and an inadequate antihypertensive or heart-rate response (Eadon et al., 2022; Dean & Kane, 2025).

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

However, inherited CYP2D6 phenotype should be distinguished from phenoconversion. Phenoconversion occurs when a patient with a genetically normal or intermediate phenotype receives a strong CYP2D6 inhibitor and consequently develops functional enzyme activity resembling that of a poor metabolizer. For example, combining metoprolol with a CYP2D6-inhibiting antidepressant may increase metoprolol exposure despite the absence of a poor-metabolizer genotype. This is clinically relevant in polypharmacy because treatment decisions based only on genotype may underestimate the actual metabolic phenotype.

CYP2D6 variation should also not be treated as interchangeable with reduced non-renal clearance associated with advanced CKD. CKD-related changes may reduce hepatic or intestinal drug metabolism through uremic toxins, inflammation, altered protein binding, and changes in enzyme or transporter activity. These disease-related effects may increase drug exposure regardless of inherited genotype. A patient may therefore have an inherited normal-metabolizer phenotype but still experience increased exposure because of enzyme inhibition, advanced kidney disease, or both. The effect of CYP2D6 also differs between beta-blockers. Metoprolol has a well-recognized dependence on CYP2D6, whereas carvedilol undergoes metabolism through multiple pathways. Consequently, findings for metoprolol should not automatically be generalized to all beta-blockers.

CYP2C9 and Losartan Response

CYP2C9 findings require a different interpretation. Losartan is converted to a more active metabolite, and reduced CYP2C9 activity may decrease the formation of this metabolite. The expected consequence is therefore more commonly reduced antihypertensive effectiveness rather than accumulation-related hypotension (Reddy et al., 2025; Verzicco et al., 2022). Patients with reduced-function CYP2C9 phenotypes may remain hypertensive despite treatment, potentially leading clinicians to increase the dose or add another antihypertensive drug.

This mechanism differs from CYP2D6-related metoprolol overexposure. Reduced CYP2D6 metabolism of metoprolol may increase parent-drug exposure, whereas reduced CYP2C9 conversion of losartan may decrease formation of an active metabolite and reduce effectiveness. These mechanisms should not be summarized collectively as "slow metabolism causing drug accumulation" because they have opposing clinical implications.

The combination of losartan, a diuretic, and an NSAID should also not automatically be classified as a CYP2C9-mediated drug–drug–gene interaction. Its major clinical concern is impaired renal autoregulation through simultaneous effects on the RAAS, circulating volume, and prostaglandin pathways. A pharmacogenomic designation is appropriate only when a CYP2C9 genotype or phenotype was measured and shown to modify the interaction.

CYP2C19 and Beta-Blocker Therapy

The previous presentation of CYP2C19 as a principal beta-blocker biotransformation pathway was not sufficiently drug-specific. CYP2C19 should therefore be removed from the main beta-blocker pathway unless an included primary study directly evaluates a defined CYP2C19–beta-blocker pair. CYP2C19 may remain relevant to other concomitant medications, including certain proton-pump inhibitors or antiplatelet drugs, but such interactions should not be interpreted as evidence that CYP2C19 broadly determines beta-blocker response.

Similarly, PPI-associated hypomagnesemia is primarily a drug-related electrolyte effect. It should not be classified as a CYP2C19-mediated antihypertensive pharmacogenomic interaction unless a study directly demonstrates genotype-dependent PPI exposure and a subsequent effect on intradialytic outcomes.

Association with Intradialytic Complications

The included literature suggested that intradialytic complications arise from multiple interacting factors rather than a single pharmacogenomic mechanism. The relationship among genotype, medication burden, and dialysis outcomes is biologically plausible, but direct evidence

remained limited because few studies simultaneously measured genotype, actual drug exposure, dialysis parameters, and intradialytic outcomes.

Table 6. Interpretation of Evidence Linking Pharmacogenomics, Polypharmacy, and Intradialytic Complications

Exposure or mechanism	Potential complication	Factors modifying the association	Directness of evidence
CYP2D6 poor or intermediate metabolism with metoprolol	Bradycardia or intradialytic hypotension	Dose, administration timing, CYP2D6 inhibitors, heart rate, autonomic function, and dialyzability	Pharmacogenomically plausible; limited direct hemodialysis-specific evidence
CYP2D6 phenoconversion caused by enzyme inhibitors	Bradycardia, dizziness, fatigue, or hypotension	Inhibitor strength, dose, treatment duration, and inherited CYP2D6 phenotype	Drug–drug–gene evidence is plausible but mainly contextual
Reduced CYP2C9-mediated activation of losartan	Inadequate blood pressure control or possible intradialytic hypertension	Genotype, adherence, dose, sodium and volume status, and concomitant medication	Primarily contextual evidence; not direct proof of intradialytic hypertension
Multiple antihypertensive drugs with additive effects	Intradialytic hypotension or syncope	Drug class, dose, pre-dialysis administration, ultrafiltration rate, and pre-dialysis blood pressure	Supported by hemodialysis studies, although confounding remains substantial
Highly dialyzable antihypertensive drugs	Reduced effect during dialysis or intradialytic/interdialytic hypertension	Dialysis membrane, blood flow, treatment duration, dose timing, and protein binding	Direct pharmacokinetic relevance, but not a pharmacogenomic mechanism
Poorly dialyzable drugs with persistent activity	Prolonged blood pressure reduction during ultrafiltration	Drug half-life, dose, cardiovascular function, and concomitant vasodilators	Clinically plausible and drug-specific
Diuretics and electrolyte-modifying regimens	Cramps, arrhythmia, or hemodynamic instability	Residual kidney function, dialysate composition, electrolyte status, and ultrafiltration	Primarily pharmacodynamic and physiological evidence
Non-essential polypharmacy	Adverse drug events, non-adherence, symptom burden, and reduced quality of life	Frailty, age, comorbidities, regimen complexity, and medication appropriateness	Supported mainly by observational and review evidence
Pharmacogenomic-guided treatment	Improved medication selection or blood pressure control	Panel composition, ancestry, actionable guidelines, pharmacist involvement, and follow-up	Promising but supported by few prospective studies

Intradialytic hypotension was the most frequently discussed complication, but its occurrence cannot be attributed solely to antihypertensive drug exposure or genotype. Ultrafiltration rate, dry-weight estimation, cardiac function, autonomic dysfunction, meal intake, dialysate temperature, dialysate sodium, vascular stiffness, and pre-dialysis blood pressure

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

remain major determinants. Pharmacogenomic variation may modify susceptibility by altering drug exposure or therapeutic response, but the magnitude of this contribution remains uncertain.

Beta-blockers illustrate this complexity. Increased metoprolol exposure in a CYP2D6 poor metabolizer or in a patient experiencing phenoconversion may impair heart-rate compensation during ultrafiltration. Nevertheless, the same clinical event may also occur in a normal metabolizer receiving a high dose shortly before dialysis or taking other negative chronotropic drugs. Thus, genotype is one component of a broader exposure–response relationship.

Intradialytic hypertension also has multiple possible explanations. Reduced response to losartan in patients with reduced CYP2C9 activity may contribute to inadequate blood pressure control, but intradialytic hypertension is also strongly influenced by extracellular volume excess, sodium loading, sympathetic activation, endothelial dysfunction, and removal of dialyzable antihypertensive drugs. Therefore, persistent or recurrent intradialytic hypertension should not be interpreted as evidence of a drug–gene mismatch without genotyping, medication adherence assessment, and evaluation of dialysis-related factors.

Influence of Ethnicity and Pharmacogenomic Assessment Method

Ethnicity may contribute to variation in study findings because allele frequencies, linkage patterns, environmental exposures, dietary sodium intake, and antihypertensive prescribing patterns differ across populations (Eastwood et al., 2024; Hur et al., 2026; Zhang et al., 2019; Iniesta et al., 2019). Findings from European cohorts may not be directly transferable to Asian, African, or admixed populations. This issue is particularly important for CYP2D6, CYP2C9, ACE, AGTR1, ABCB1, and other genes with population-dependent variant frequencies.

Ethnicity should not, however, be used as a substitute for genotype. Broad ethnic classifications contain substantial within-group genetic diversity and may also reflect socioeconomic, clinical, and healthcare-system differences. Future studies should report self-identified ethnicity, genetic ancestry where available, specific variants tested, phenotype assignment procedures, and the representation of minority populations.

Differences in pharmacogenomic assessment methods also affect comparability. Some studies used targeted single-gene testing, while others applied multigene panels, electronic prescribing databases, or clinical decision-support systems. Targeted testing may provide detailed information on a specific drug–gene pair but miss interactions involving other medications. Multigene panels provide broader coverage but differ in the genes, alleles, copy-number variants, and phenotype-translation algorithms included (Picard et al., 2026; Chen et al., 2021; Rodrigues et al., 2026; Smith et al., 2020).

Studies based only on theoretical interaction databases may identify potential drug–gene interactions without confirming medication exposure, adherence, drug concentration, or clinical outcomes. Likewise, genotype-based phenotype assignment may be inaccurate when concomitant enzyme inhibitors or inducers cause phenoconversion. Prospective studies should therefore combine genotyping with a complete medication history, inhibitor and inducer assessment, dialysis timing, drug concentrations where feasible, and standardized clinical outcome measurement.

Sample size also affects the stability of pharmacogenomic findings. Small studies may contain few poor or ultrarapid metabolizers and may therefore produce imprecise effect estimates. Rare variants cannot be evaluated reliably without larger multicenter cohorts. Conversely, large registry studies may have sufficient statistical power but lack detailed genotype, administration-time, adherence, and dialysis-prescription data. The contrasting strengths and weaknesses of small mechanistic studies and large observational studies help explain why findings are not always consistent.

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

Clinical Implications

The findings support a structured, individualized medication review rather than routine application of genotype testing or automatic withholding of antihypertensive medication before every dialysis session (Collins et al., 2019). Medication assessment should consider the specific antihypertensive drug, dose, indication, administration time, dialyzability, residual kidney function, ultrafiltration target, prior intradialytic blood pressure pattern, potential enzyme inhibitors, and available pharmacogenomic information.

CYP2D6 information may be most clinically relevant when a patient receiving metoprolol experiences otherwise unexplained bradycardia, recurrent hypotension, or intolerance, particularly when a CYP2D6 inhibitor is also prescribed. CYP2C9 information may be relevant when losartan appears ineffective despite adequate adherence, although sodium and volume excess, dose, and competing clinical factors must first be evaluated.

Pharmacogenomic testing should not replace medication reconciliation, assessment of drug necessity, and evaluation of dialysis-related causes. Its greatest value may occur when integrated with clinical pharmacy services and multidisciplinary decision-making. Clinical pharmacists can identify potentially inappropriate medications, distinguish pharmacokinetic from pharmacodynamic interactions, recognize phenoconversion, evaluate dose timing, and determine whether a reported drug–gene pair is clinically actionable (Bellanca et al., 2023; Sugarman et al., 2016; Hahn & Roll, 2021; Marques-Garcia & Martinez-Bravo, 2026; Porrogi, 2026).

Strength and Limitations of the Evidence

The principal strength of this review is the integration of three areas that are often examined separately: antihypertensive polypharmacy, pharmacogenomic variation, and intradialytic complications. The review also distinguishes direct evidence from maintenance hemodialysis populations from contextual evidence derived from non-dialysis or mixed CKD populations.

Nevertheless, several limitations affect the strength of the conclusions. First, narrative reviews, clinical reviews, and systematic reviews predominated, creating a risk that the same primary studies were represented in multiple publications. Second, only a small number of prospective pharmacogenomic studies were available, and even fewer directly evaluated intradialytic outcomes. Third, the included populations differed in dialysis status, age, ethnicity, CKD severity, comorbidity burden, medication exposure, and sample size.

Fourth, polypharmacy and intradialytic hypotension were not defined consistently. Fifth, individual drugs within the same antihypertensive class differed in metabolism and dialyzability, but some studies reported only class-level exposure. Sixth, information on medication timing, adherence, enzyme inhibitors, ultrafiltration rate, residual kidney function, and dialysis prescription was frequently incomplete. Seventh, pharmacogenomic assessment methods varied from single-variant testing to multigene panels and theoretical interaction databases. Finally, many reported associations were indirect and did not establish that pharmacogenomic variation caused intradialytic complications.

The evidence supports a plausible contribution of pharmacogenomic variation to interindividual differences in antihypertensive effectiveness and safety. However, the current literature does not justify attributing intradialytic hypotension, intradialytic hypertension, or other dialysis complications solely to CYP2D6, CYP2C9, or another genetic pathway. Larger prospective studies should simultaneously evaluate genotype, phenotype, medication concentrations, administration timing, drug dialyzability, dialysis parameters, and standardized intradialytic outcomes before pharmacogenomic-guided antihypertensive management can be routinely recommended in maintenance hemodialysis populations.

ISSN 2776-1150 (Print), ISSN 2776-1169 (online)

CONCLUSION

Antihypertensive polypharmacy is a highly common condition among patients with chronic kidney disease (CKD) undergoing hemodialysis and reflects the complexity of managing hypertension and cardiovascular comorbidities in this population. The literature synthesis shows that the use of combinations of several antihypertensive classes not only increases medication burden but also raises the risk of variations in therapeutic response and the occurrence of intradialytic complications. These findings indicate that blood pressure control in hemodialysis patients cannot be separated from a comprehensive evaluation of the number, types, and rationality of the medications used. The scientific evidence compiled in this review confirms the significant role of pharmacogenomic interactions, particularly drug–gene and drug–drug–gene interactions involving drug-metabolizing genes such as CYP2D6 and CYP2C9, in determining the effectiveness and safety of antihypertensive therapy. These genetic variations, when interacting with reduced kidney function and the use of multiple medications, contribute to the occurrence of intradialytic hypotension, intradialytic hypertension, bradycardia, electrolyte disturbances, and other clinical complaints that affect hemodynamic stability and patients' quality of life. This indicates that intradialytic complications are not solely influenced by drug class or timing of administration, but rather by a combination of genetic, pharmacokinetic, and pharmacodynamic factors. The implications of these findings emphasize the need for a more individualized and measurable approach to antihypertensive management in hemodialysis patients. The integration of pharmacogenomic information with polypharmacy evaluation, dose adjustment based on kidney function, and deprescribing of non-essential medications has the potential to improve treatment safety and reduce the risk of intradialytic complications. The involvement of clinical pharmacists and multidisciplinary collaboration are important elements in implementing this strategy.

SUGGESTION

At the same time, prospective primary studies are still needed to specifically evaluate the impact of pharmacogenomic implementation on intradialytic outcomes, in order to support the development of more applicable clinical recommendations for the hemodialysis population.

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