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COMPARATIVE ANALYSIS OF AMLODIPINE AND LERCANIDIPINE: MECHANISMS, LIMITATIONS, AND PROSPECTS OF COMBINED ANTIHYPERTENSIVE THERAPY

Background. *Arterial hypertension remains a leading factor in cardiovascular mortality. Fixed-dose combinations provide long-term blood pressure control and increase adherence to therapy. Amlodipine is the pharmacokinetic standard for fixed-dose combinations due to its long half-life and stable exposure, whereas lercanidipine – a third-generation drug with better tolerability – remains underrepresented in combination regimens.*

Aim of the study. *To compare the pharmacokinetic, pharmacodynamic, and clinical characteristics of amlodipine and lercanidipine, and to substantiate the role of lercanidipine in combination antihypertensive therapy within rationally designed fixed-dose combinations.*

Materials and methods. *A structured literature review (according to international standards for the preparation of systematic reviews) was conducted in the scientific literature databases PubMed, Scopus, Web of Science, and Cochrane Library for the years 2020–2025. 50 sources were selected after screening 847 records. The design encompassed three stages: comparison of drug profiles, analysis of microcirculatory mechanisms, and the development of a physiologically based pharmacokinetic protocol.*

Results. *Amlodipine (half-life of 30–50 hours) is minimally affected by food and metabolism by the cytochrome P450 3A4 isoenzyme, and has a powerful evidence base from large-scale clinical trials. Lercanidipine provides a 24-hour effect due to a membrane depot and is characterized by a lower incidence of peripheral edema (9 percent versus 19 percent). Dependence on the cytochrome P450 3A4 isoenzyme and a pronounced effect of food intake limit its use in fixed-dose combinations. The combination with renin-angiotensin-aldosterone system blockers neutralizes the residual risk of edema through postcapillary vasodilation and provides a synergistic blood pressure reduction without unwanted pharmacokinetic interactions.*

Conclusions. *Amlodipine remains the standard for combination therapy. Physiologically based pharmacokinetic modeling and optimized dosage forms are capable of overcoming the pharmacokinetic limitations of lercanidipine and expanding its role in fixed-dose combinations.*

Key words: *hypertension, amlodipine, lercanidipine, calcium channel blockers, fixed-dose combinations.*

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ПОРІВНЯЛЬНИЙ АНАЛІЗ АМЛОДИПІНУ І ЛЕРКАНІДИПІНУ: МЕХАНІЗМИ, ОБМЕЖЕННЯ ТА ПЕРСПЕКТИВИ КОМБІНОВАНОЇ АНТИГІПЕРТЕНЗИВНОЇ ТЕРАПІЇ

Актуальність. *Артеріальна гіпертензія залишається провідним фактором серцево-судинної смертності. Фіксовані дозові комбінації забезпечують тривалий контроль тиску та підвищують прихильність до терапії. Амлодипін є фармакокінетичним еталоном для фіксованих дозових комбінацій завдяки тривалому періоду напіввиведення та стабільній експозиції, тоді як лерканідипін – препарат третього покоління з кращою переносимістю – залишається недостатньо представленим у комбінованих схемах.*

Мета дослідження *– порівняти фармакокінетичні, фармакодинамічні та клінічні характеристики амлодипіну і лерканідипіну та обґрунтувати роль лерканідипіну в комбінованій антигіпертензивній терапії у складі раціонально розроблених фіксованих дозових комбінацій.*

Матеріал і методи. *Структурований огляд літератури (згідно з міжнародними стандартами підготовки систематичних оглядів) у базах наукової літератури за 2020–2025 рр. Відібрано 50 джерел після скринінгу 847 записів. Дизайн охоплював три етапи: порівняння профілів препаратів, аналіз мікроциркуляторних механізмів і розроблення фізіологічно обґрунтованого фармакокінетичного протоколу.*

Результати дослідження. *Амлодипін (період напіввиведення 30–50 год) має мінімальний вплив їжі та метаболізму ізоферменту цитохрому P450 3A4, а також потужну доказову базу масштабних клінічних досліджень. Лерканідипін забезпечує цілодобовий ефект завдяки мембранному депо та характеризується нижчою частотою периферичних набряків (9% проти 19%). Залежність від ізоферменту цитохрому P450 3A4 і виражений вплив прийому їжі обмежують його застосування у фіксованих дозових комбінаціях. Комбінація з блокаторами ренін-ангіотензин-альдостеронової системи нівелює залишковий ризик набряків через посткапілярну вазодилатацію та забезпечує синергетичне зниження тиску без небажаних фармакокінетичних взаємодій.*

Висновок. *Амлодипін залишається стандартом комбінованої терапії. Фізіологічно обґрунтоване фармакокінетичне моделювання та оптимізовані лікарські форми здатні подолати фармакокінетичні обмеження лерканідипіну й розширити його роль у фіксованих дозових комбінаціях.*

Ключові слова: *артеріальна гіпертензія, амлодипін, лерканідипін, блокатори кальцієвих каналів, фіксовані дозові комбінації.*

Introduction. Relevance. Arterial hypertension remains a principal determinant of cardiovascular mortality (Kuneinen et al., 2024). Therapeutic efficacy increasingly depends on pharmacologically rational fixed-dose combinations (FDCs) that ensure sustained blood pressure control and optimized tolerability, making component selection a central challenge in cardiovascular pharmacology (Elgendy et al., 2025; Sagar et al., 2024). Current clinical guidelines (Ministry of Health of Ukraine, ESH, German Society of Cardiology) position calcium channel blockers, notably amlodipine, as foundational agents in both monotherapy and combination regimens (Dubrov et al.,

2024; Mancia et al., 2023; Kintscher et al., 2025). Notably, the pharmacological approaches and clinical evidence base synthesized in this review integrate data from both Western clinical registries – including the guidelines of the European Society of Cardiology and German Society of Cardiology – and Eastern clinical frameworks, particularly established Chinese and Asian hypertension management guidelines (Yang et al., 2025; Liang et al., 2021), which collectively reinforce the clinical relevance of calcium channel blocker-based fixed-dose combinations across ethnically and geographically diverse patient populations. Amlodipine's prolonged elimination half-life and stable systemic exposure ensure high reproducibility of clinical response, establishing it as the pharmacokinetic standard in most contemporary FDCs (Park et al., 2024). Conversely, lercanidipine – despite superior tolerability – exhibits limited application in FDCs due to shorter half-life, CYP3A4-dependent metabolism, and susceptibility to food and drug interactions, increasing exposure variability and impeding standardization of combination therapy (Zhou et al., 2014). The efficacy of fixed antihypertensive combinations is determined by pharmacokinetic synchronization, particularly concordance in elimination half-life and exposure stability (Oh et al., 2019). This study tests the hypothesis that pharmacokinetic alignment critically differentiates the roles of amlodipine and lercanidipine in modern antihypertensive pharmacotherapy through systematic comparative analysis.

Existing comparative research on lercanidipine versus amlodipine remains methodologically limited in scope. The largest head-to-head outcome study – a propensity-score–matched analysis of 47,640 patients – confirmed comparable MACE incidence between lercanidipine and amlodipine (2.8% vs. 4.1%, P = 0.11), yet did not address pharmacokinetic compatibility, CYP3A4 interaction risk, or FDC design rationale (Jeon et al., 2025). A comprehensive nephroprotective review explicitly identified the absence of studies in hypertensive patients with CKD as a gap, yet did not translate lercanidipine's pharmacokinetic constraints into combination therapy frameworks (Hajdys et al., 2023). Similarly, systematic reviews and meta-analyses encompassing over 9,500 patients reported blood pressure outcomes but provided no pharmacokinetically synchronized rationale for lercanidipine-based FDC development (Manolis et al., 2025). The novelty of this work lies in the systematic integration of pharmacokinetic, pharmacodynamic, and microvascular data to construct a rational evidence-based framework for lercanidipine-containing FDCs – an approach not previously synthesized in the literature. Practically, this analysis provides clinicians with a comparative decision tool for agent selection in combination therapy and proposes a translational research roadmap to overcome current limitations of lercanidipine in fixed-dose regimens.

Objective of the study. To compare the pharmacokinetic, pharmacodynamic, and clinical characteristics of amlodipine and lercanidipine in order to substantiate the use of lercanidipine in combination antihypertensive therapy with other agents and to develop practical clinical strategies.

Materials and methods. This study was designed as a structured narrative review with an evidence-based translational component. A systematic literature analysis, conducted in accordance with the PRISMA 2020 guidelines, served as the primary methodological framework for comparative evaluation of the pharmacokinetic, pharmacodynamic, and clinical characteristics of Amlodipine and Lercanidipine in the context of fixed-dose combinations. The general experimental plan involved three progressive stages: 1) systematic data extraction of PK/PD profiles; 2) evaluation of microvascular mechanisms underlying adverse events; and 3) the development of a translational PBPK-informed roadmap. The underlying hypothesis is that targeted pharmacokinetic alignment and combination with non-CYP3A4-interacting RAAS blockers will overcome lercanidipine's limitations, optimizing FDC efficacy and tolerability. The literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library for the period 2020–2025 (last search date: December 15, 2025), using predefined keywords including «amlodipine», «lercanidipine», «calcium channel blockers», «fixed-dose combination», «pharmacokinetics», «pharmacodynamics», «hypertension», and «drug interactions». Beyond systematic evidence synthesis, the study incorporates a translational research perspective: a physiologically based pharmacokinetic (PBPK)-informed roadmap and a fixed-dose combination design proposal are presented as expert interpretations derived from the analyzed literature, rather than original experimental findings. Documents from EMA, FDA, ESC guidelines (2024), and Ukraine's Ministry of Health were analyzed alongside randomized controlled trials, cohort studies, systematic reviews, meta-analyses, and pharmacokinetic studies of dihydropyridine calcium channel blockers. All pharmacokinetic data points analyzed in this review are derived from certified clinical trials, and the PBPK modeling parameters are validated through algorithms consistent with FDA/EMA regulatory standards. Publications lacking systematic methodology, irrelevant animal studies, duplicates, and high-bias articles were excluded. Two independent reviewers screened 847 records, including 42 publications and 8 documents (50 total sources). Study quality was assessed using Cochrane Risk of Bias 2.0 and Newcastle–Ottawa

Scale. The applied pharmacokinetic parameters (T½, AUC, Cmax, bioavailability) were evaluated in comparison to standard indirect methods of antihypertensive effect assessment (office blood pressure measurement, 24-hour ambulatory monitoring, pulse wave velocity), to contextualise the pharmacokinetic data within established clinical endpoints used in both European and Asian hypertension management guidelines. Data on pharmacokinetics (T½, Tmax, Cmax, AUC, bioavailability, Vd), pharmacodynamics (blood pressure, heart rate, vascular selectivity), efficacy, safety, and CYP3A4 interactions were extracted. Due to heterogeneity, qualitative synthesis without meta-analysis was performed.

Results of the study and their discussion. Comparison of PK/PD – why this matters for combination. Pharmacokinetics. Amlodipine**,** with a long half-life (30–50 h), provides a stable 24-hour effect regardless of the dosing regimen, which makes it optimal for fixed combinations (Wang et al., 2023). Lercanidipine**,** despite a short plasma T½ (8–10 h), acts for 24 hours due to a membrane depot in the vascular wall; however, its pharmacokinetics are sensitive to CYP3A4 and food, which leads to exposure variability (Grassi et al., 2017). Which, in turn, is also worth noting – amlodipine combines predictability and an evidence base for universal combinations, whereas lercanidipine requires an individual approach (Wang et al., 2023; Hajdys et al., 2023). The data obtained during the analysis are presented in Table 1.

Pharmacodynamics. The efficacy and safety of **amlodipine** have been demonstrated in landmark trials (ASCOT-BPLA, ALLHAT, VALUE), which has made it a cornerstone for FDCs (Dahlöf et al., 2005; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002; Sever 2004). A massive evidence base provides an «evidence pull»: new combinations with amlodipine are approved without large-scale trials.

Lercanidipine has a limited evidence base compared with amlodipine due to the absence of large multicenter studies. However, as a highly lipophilic third-generation dihydropyridine (LogP >6), it provides stable 24-hour calcium channel blockade with high precapillary selectivity and minimal impact on cardiac function (Grassi et al., 2017). The key effect of lercanidipine is selective dilation of resistance arterioles, which reduces systemic vascular resistance and arterial blood pressure (Grassi et al., 2017; Michel et al., 2020; Largeau et al., 2021). However, precapillary vasodilation with unchanged tone of postcapillary venules creates a transmicrovascular imbalance: hydrostatic pressure in the capillary bed (Pc) increases, which according to Starling's law enhances transmural filtration into the interstitium: $Jv = Kf [(Pc – Pi) – \sigma(\pi c – \pi i)]$ (Grassi et al., 2017; Michel et al., 2020; Largeau et al., 2021). Additionally, DHP-CCBs suppress the myogenic response and the venoarteriolar reflex – compensatory mechanisms that limit the rise in Pc during orthostatic loading (Grassi et al., 2017; Michel et al., 2020; Largeau et al., 2021). This leads to «vasodilatory» edema, resistant to diuretics, since it is not associated with sodium retention (Grassi et al., 2017; Michel et al., 2020; Largeau et al., 2021). Due to its high lipophilicity and gradual release from the membrane depot, lercanidipine causes peripheral edema less frequently (9%) compared with amlodipine (19%), while the rate of discontinuation due to edema is 2.1% vs 8.5%, respectively (Leonetti et al., 2002). Although lercanidipine's known clinical advantage is a significantly lower incidence of peripheral edema compared to amlodipine, the absolute risk remains a barrier to adherence. Therefore, the strict rationale for combining it with RAAS blockers is twofold: it completely neutralizes this residual transmicrovascular fluid leak via postcapillary venodilation, and achieves synergistic blood pressure control without introducing competitive CYP3A4 drug interactions (fig. 1). This rationale is grounded in complementary hemodynamic actions: while Lercanidipine selectively dilates

Table 1

Comparative evidence base and clinical implications of amlodipine vs. lercanidipine for fixed-dose combinations (FDCs)

Parameter	Amlodipine	Lercanidipine	Sources
Evidence base	+++	+	Yang, J., et al. 2025; Hanauer Schaab, E., et al. 2020
CV outcome data	+++	±	Bulsara, K. G., et al. 2024; Grassi, G., et al. 2017
Plasma t½	↑↑ (30–50 h)	↓ (8–10 h)	Wang, J. G., et al. 2023; Grassi, G., et al. 2017
PK stability	+++	+	Bulsara, K. G., et al. 2024; Hanauer Schaab, E., et al. 2020
CYP3A4 sensitivity	±	+++	Hajdys, J., et al. 2023; Courlet, P., et al. 2021
Food effect	−	+++	Bulsara, K. G., et al. 2024; Álvarez, C., et al. 2012
PK/PD predictability	+++	+	Bulsara, K. G., et al. 2024; Hanauer Schaab, E., et al. 2020
Peripheral edema	+++	+	Liang, L., et al. 2022; Liang, H., et al. 2021
FDC suitability	+++	±	Dat, T. V., et al. 2024; Scholze, J., et al. 2011

Note: +++ = high / well established; = moderate / limited; ± = inconsistent or indirect; − = absent or clinically negligible; ↑↑ = prolonged; ↓ = short; PK – pharmacokinetics; PD – pharmacodynamics; FDC – fixed-dose combination; CV – cardiovascular

precapillary arterioles, RAAS blockers – via angiotensin II suppression – counteract postcapillary venular constriction, thereby restoring microvascular fluid balance. This pharmacodynamic synergy is not merely additive but mechanistically targeted, representing a principal advantage of this combination over lercanidipine monotherapy or its pairing with agents lacking postcapillary effects (e.g., beta-blockers, diuretics).

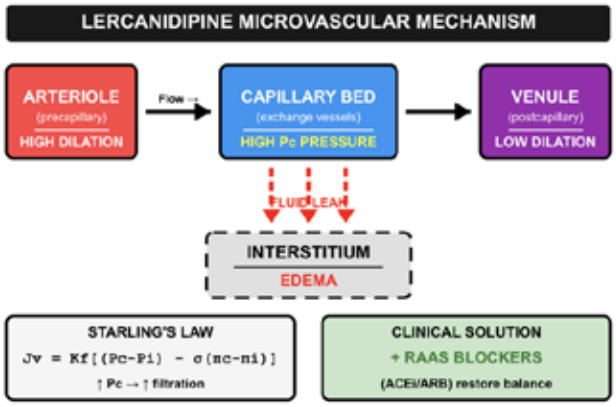

Fig. 1. Pharmacodynamic prerequisites for combination therapy: microvascular mechanisms of lercanidipine

The pharmacokinetic rationale for the use of lercanidipine in fixed combinations with RAAS blockers, according to the model we propose, is based on the characteristics of its metabolism. The drug has low bioavailability (10%) due to intensive first-pass metabolism with predominant availability of the active S-enantiomer (Hajdys et al., 2023; Wang et al., 2023). Changes in CYP3A4 activity significantly affect exposure (risk of hypotension or reduced efficacy). A pronounced food effect (increased bioavailability) leads to variability in Cmax; therefore, administration in the fasting state (≥15 min before breakfast) is recommended (Hajdys et al., 2023; Wang et al., 2023). Combination with RAAS blockers without interaction with CYP3A4 should minimize risks and ensure a predictable profile (table 2).

Clinical implementation: design of FDC regimens and accompanying strategies. Optimization of the lercanidipine + RAAS blocker combination, according to our model, requires: (1) avoidance of CYP3A4 interactions; (2) monitoring of creatinine and potassium for 1–2 weeks in chronic kidney disease and diabetic nephropathy; (3) administration of lercanidipine in the fasting state (15 min before breakfast) to ensure 24-hour action; (4) contraception in women (RAAS blockers are teratogenic). The FDC is based on microvascular balance: precapillary vasodilation is compensated by the postcapillary effect of the RAAS blocker.

Research roadmap for FDCs with lercanidipine. The obtained results are presented in fig. 2. Step 1. PBPK modeling with a population PK approach allows control of drug concentrations. Baseline bioavailability is defined as $F = F_a \times F_g \times F_h$, where F_a is absorption, F_g is intestinal metabolism via CYP3A4, and F_h is hepatic metabolism: $F_h \approx \frac{Q_h}{(Q_h + fu_b \times CLint,hep)}$ (Kato et al., 2003; Varma et al., 2010). A dual-circuit PBPK architecture accounts for CLint,gut and CLint,hep, scaled via IVIVE, with adjustments for free fraction and hepatic blood flow (Sugiyama et al., 2023; Yamazaki et al., 2022). The model integrates interactions with other drugs and food, predicting efficacy across different patient populations.

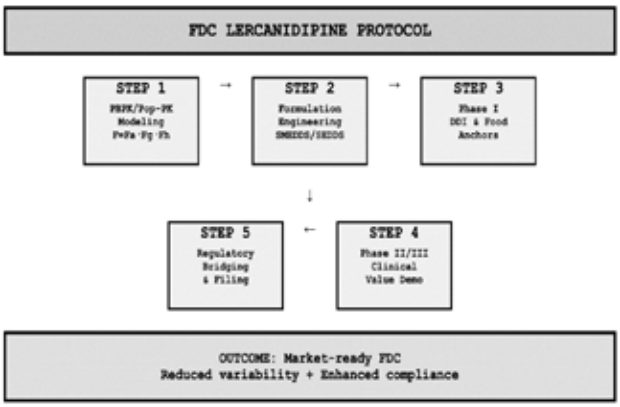

Fig. 2. FDC Lercanidipine Protocol

Table 2

Pharmacokinetic Compatibility of RAAS Blockers with Lercanidipine

RAAS-blocker	CYP3A4 interaction	PK compatibility: lercanidipine	Clinical rationale	Sources
Perindopril	–	+++	Prodrug; no CYP3A4 involvement; synchronized 24-h effect	Hassan, D., et al. 2025; Devissaguet, J. P., et al. (1990)
Enalapril	–	+++	Esterase activation; no effect on lercanidipine metabolism	Laizure, S. C., et al. 2013; Hussain, M., et al. 2024
Valsartan	–	+++	CYP2C9 metabolism; pharmacokinetically neutral	Liu, Y., et al. 2022; Yuan, L. J., et al. 2022, Patel P, et al 2025

Note: +++ = high PK compatibility; – = no clinically relevant CYP3A4 interaction

The mechanism of the food effect is explained by three factors: increased solubility due to bile salts, delayed gastric emptying, and saturation of intestinal enzymes (Wang et al., 2025). Separate submodels are used for the R- and S-enantiomers (Wang et al., 2025; Tistaert et al., 2019); the S-form has ~20% higher AUC and Cmax. The model includes absorption, permeation, precipitation, and drug–drug interactions for the intestine and liver. For inhibitors, CYP3A4 inactivation is considered; for inducers, activation via the pregnane X receptor is accounted for. Calibration should accordingly be performed using a 15-fold increase in AUC with ketoconazole, ≈3-fold with cyclosporine, food/fasting ≈3:1, S/R ≈1.2. The population model should use two compartments with covariates (BMI, sex, age, liver function) and a Bayesian approach. The effectiveness of the proposed steps ensures a comprehensive approach to FDC development. The main parameters and target metrics are presented in table 3.

Step 1 involves ensuring the construction of dose «window» tables for fasted/fed and DDI scenarios, justifying the replacement of part of DDI studies with PBPK simulations (FDA/EMA), and defining formulation targets. **Step 2** is focused on formulation engineering to minimize food effects and control Cmax via lipid systems (SMEDDS/SEDDS) and controlled release. Lipid systems improve solubilization, reduce differences between fasted/fed states, and limit Cmax peaks; optimization is performed by composition, particle size, and stability. Controlled release is implemented using polymer matrices. Validation is performed via Level A IVIVC and intestinal fluid simulation, optimization – by DoE. Analytical control – chiral LC-MS/MS for R- and S-enantiomers. **Step 3 (Phase I):** Replicative crossover studies with DDI and food «anchors» validate PBPK and Pop-PK models. Key endpoints are AUC_{0-t}, $AUC_{0-\infty}$, and Cmax with separate analysis of R- and S-enantiomers. RSABE is applied for highly variable parameters. Analytical control must be performed using chiral LC-MS/MS with ISR; safety must be monitored using edema panels. **Step 4 (Phases II–III):** assessment of FDC efficacy. **Phase II** compares lercanidipine + ARB (valsartan) versus amlodipine + ARB. The primary endpoint is mean 24-hour systolic blood pressure based on ambulatory blood pressure monitoring; secondary endpoints include edema incidence, changes in central hemodynamics, and time to dose change due to adverse effects. Grouping should be performed by sex, age, BMI; analysis – MMRM. **Phase III** should include elderly subjects, individuals with CKD, polypharmacy, and diverse ethnic groups. The objective is non-inferiority of the FDC in reducing 24-hour SBP and superiority with respect to edema. Morning fasted dosing, adherence via SMS, smart blisters, and electronic diaries. Step 5: Regulatory bridging and dossier. Data from Physiologically Based Pharmacokinetic (modeling), bioequivalence, and labeling are integrated into the FDA/EMA dossier. The PBPK package includes development and validation of models describing bioavailability, enantioselectivity, drug–drug interactions, and food effects. The statistical plan governs logarithmic models and scaled bioequivalence conditions. Human-factors studies optimize labeling.

Experimental base for modeling. A multi-level program for setup and validation of pharmacokinetic models in accordance with regulatory requirements is proposed. **A. In vitro and ex vivo parameters.** Solubility in FaSSIF/FeSSIF, lipolysis, and permeation (PAMPA, Caco-2) are evaluated. Chiral LC-MS/MS provides assessment of S- and R-enantiomers. Metabolism in microsomes and hepatocytes determines Vmax, Km, and CYP3A4 inhibition parameters (Ki, k_inact, K_I). Protein binding (fu_b) and tissue distribution are evaluated. **B. Population PK diagnostics.** GOF, pcVPC in fasted/fed states and with DDI, NPDE, and shrinkage assessment are applied; validation of enantioselective models for S/R predictions is performed. **C. Covariates and clinical risks.** Scenarios for different ages, hepatic

Table 3

Key parameters and target metrics of the development steps

Step	Focus	Key Targets	Outcome
1	Formulation goals	$d_c$ff, R(t), fed/fasted, Cmax	Defined QTPP
2	Formulation optimization	50–80 nm; biphasic release (20–30% fast / 12–24 h); fed/fasted AUC ≤1.5; Cmax ≤1.3; stability ±10–15%	Stable PK, minimal food effect
3 (Ph I)	DDI & BE strategy	AUCR: keto ≈15, rifampicin <0.2–0.3; CV ≥30%	DDI confirmation, RSABE justification
4 (Ph II)	Proof of concept	8–12 weeks; SBP non-inferiority	BP control + edema reduction
4 (Ph III)	Confirmatory	24–52 weeks; δSBP ≈3 mmHg	Benefit/risk & market value
5	Registration	PBPK-supported	Integrated dossier, reduced in-vivo burden

Note: QTPP – quality target product profile; Cmax – peak concentration; DDI – drug–drug interaction; RSABE – reference-scaled bioequivalence; SBP/δSBP – systolic BP / non-inferiority margin

impairment (Child–Pugh A/B), and polypharmacy (≥5 drugs) are modeled taking into account CYP3A4 and P-glycoprotein. The influence of BMI, sex, and protein binding on hepatic extraction is analyzed. The program forms a database for PBPK and population pharmacokinetic model parameterization and assessment of drug interaction risks.

Practical recommendations. The five-stage program combines pharmacological, clinical, and regulatory requirements. Optimal regimen – fasting intake in the morning. Strong CYP3A4 inhibitors and grapefruit should be avoided or dose reduced by ~50%; with inducers – individual adjustment or drug replacement. Formulation ensures stable bioavailability (SMEDDS/SEDDS <80 nm or controlled release) with fed/fasted ratio ≤1.5. Clinical program: DDI studies in phase I, in phases II–III – non-inferiority for systolic pressure and superiority for edema. Regulatory dossier includes PBPK qualification, scaled bioequivalence, and human-factors studies.

Conclusions

1. Amlodipine, due to its unique pharmacokinetic properties, kinetic buffering, and robust evidence base, has become a universal platform for combination therapy and the standard for fixed-dose combinations.

2. Lercanidipine, despite better tolerability and lower incidence of edema, predominantly remains a monotherapy drug due to shorter T½, CYP3A4 dependence, pronounced food-effect, and limited evidence base.

3. The proposed research roadmap (PBPK/pop-PK modeling, innovative formulations, and targeted clinical trials) opens prospects for overcoming these limitations and expanding lercanidipine use in fixed-dose combinations. The comparison confirms: the decisive factor for success is not only efficacy or tolerability, but the drug's ability to integrate into pharmacokinetically synchronized and evidence-based strategies.

BIBLIOGRAPHY

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002. Vol. 288. № 23. P. 2981–2997. DOI: https://doi.org/10.1001/jama.288.23.2981

Álvarez C., Gómez E., Simón M., Govantes C., Guerra P., Frías J., García-Arieta A. Differences in lercanidipine systemic exposure when administered according to labelling: in fasting state and 15 minutes before food intake. *European journal of clinical pharmacology.* 2012. Vol. 68. № 7. P. 1043–1047. DOI: https://doi.org/10.1007/s00228-012-1215-8

Bulsara K. G., Patel P., Cassagnol M. Amlodipine. StatPearls [Internet]. Treasure Island (FL) : StatPearls Publishing, 2025 Jan. Updated 2024 Apr 21. URL: https://www.ncbi.nlm.nih.gov/books/NBK519508/

Courlet P., Guidi M., Alves Saldanha S., Cavassini M., Stoeckle M., Buclin T., Marzolini C., Decosterd L.A., Csajka C. Population pharmacokinetic modelling to quantify the magnitude of drug-drug interactions between amlodipine and antiretroviral drugs. *European journal of clinical pharmacology*. 2021. Vol. 77. № 7. P. 979–987. DOI: https://doi.org/10.1007/s00228-020-03060-2

Dahlöf B., Sever P. S., Poulter N. R., Wedel H., Beevers D. G., Caulfield M., Collins R., Kjeldsen S. E., Kristinsson A., McInnes G. T., Mehlsen J., Nieminen M., O'Brien E., Ostergren J., ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet (London, England). 2005. Vol. 366. № 9489. P. 895–906. DOI: https://doi.org/10.1016/S0140-6736(05)67185-1

Dat T. V., Tu V. L., Thu L. N. A., Quang N. N. A., Binh V., Nga N. T. Q., Loc D. H., Nguyen T. T. H., Tam D. N. H., Huynh H. H., Trung T. D., Do U., Phat N. T., Hung D. T., Nguyen Q. H., Yen N. T. H., Minh L. H. N. Effectiveness of perindopril/amlodipine fixed-dose combination in the treatment of hypertension: a systematic review. *Frontiers in pharmacology*. 2024. Vol. 14. 1156655. DOI: https://doi.org/10.3389/fphar.2023.1156655

Devissaguet J. P., Ammoury N., Devissaguet M., Perret L. Pharmacokinetics of perindopril and its metabolites in healthy volunteers. *Fundamental & clinical pharmacology.* 1990. Vol. 4. № 2. P. 175–189. DOI: https://doi.org/10.1111/j.1472-8206.1990.tb00486.x

Elgendy M. S., Taha H. I., Amin A. M., Khlidj Y., Ezz M. R., Elgamasy M. A., Almezaine A., Faheem M. A., Rajab I., Abuelazm M. The efficacy and safety of low-dose triple combination for hypertension treatment: a systematic review and meta-analysis of randomized controlled trials. *Naunyn-Schmiedeberg's archives of pharmacology.* 2025. Vol. 398. № 7. P. 7721–7736. DOI: https://doi.org/10.1007/s00210-025-03790-z

Grassi G., Robles N. R., Seravalle G., Fici F. Lercanidipine in the Management of Hypertension: An Update. *Journal of pharmacology & pharmacotherapeutics.* 2017. Vol. 8. № 4. P. 155–165. DOI: https://doi.org/10.4103/jpp.JPP_34_17

Hajdys J., Fularski P., Leszto K., Majchrowicz G., Stabrawa M., Młynarska E., Rysz J., Franczyk B. New Insights into the Nephroprotective Potential of Lercanidipine. *International journal of molecular sciences.* 2023. Vol. 24. № 18. 14048. DOI: https://doi.org/10.3390/ijms241814048

Hanauer Schaab E., Lanchote V. L., Balthazar Nardotto G. H., Marques Pereira M. P., Dantas M., Paiva C. E., Barbosa Coelho E. Effect of Lercanidipine on the Pharmacokinetics-Pharmacodynamics of Carvedilol Enantiomers in Patients With Chronic Kidney Disease. *Journal of clinical pharmacology*. 2020. Vol. 60. № 1. P. 75–85. DOI: https://doi.org/10.1002/jcph.1485

Hassan D., Peeters L. E. J., Rietdijk W. J. R., van Domburg B., Bahmany S., Sassen S. D. T., Hesselink D. A., Schinkel A. F. L., Manintveld O. C., Galema T. W., van der Net J. B., Lafeber M., Tumkaya T., Koch B. C. P., Versmissen J. Differences in antihyperten-

sive drug blood levels in patients with hypertension (DECISION): a prospective study comparing pharmacokinetics and pharmacodynamics of perindopril in younger and older patients. *Blood pressure*. 2025. Vol. 34. № 1. 2580368. DOI: https://doi.org/10.1080/08037051.2025.2580368

Hussain M., Basheer S., Khalil A., Haider Q. U. A., Saeed H., Faizan M. Pharmacogenetic study of CES1 gene and enalapril efficacy. *Journal of applied genetics*. 2024. Vol. 65. № 3. P. 463–471. DOI: https://doi.org/10.1007/s13353-024-00831-w

Jeon J., Ryoo S., Oh S., Hong S. J., Yu C. W., Kim Y. H., et al. Comparative effectiveness of lercanidipine and amlodipine on major adverse cardiovascular events in hypertensive patients. *Am J Hypertens*. 2024. 38(2). 139-147. DOI: https://doi.org/10.1093/ajh/hpae147

Kato M., Chiba K., Hisaka A., Ishigami M., Kayama M., Mizuno N., Nagata Y., Takakuwa S., Tsukamoto Y., Ueda K., Kusuhara H., Ito K., Sugiyama Y. The intestinal first-pass metabolism of substrates of CYP3A4 and P-glycoprotein-quantitative analysis based on information from the literature. *Drug metabolism and pharmacokinetics.* 2003. Vol. 18. № 6. P. 365–372. DOI: https://doi.org/10.2133/dmpk.18.365

Kintscher U., Berrisch-Rahmel S., Genth-Zotz S., Halbach M., Mahfoud F., Weil J. ESC Pocket Guidelines: Elevated Blood Pressure and Hypertension, Version 2024. Deutsche Gesellschaft für Kardiologie – Herz-und Kreislaufforschung e.V. Börm Bruckmeier Verlag GmbH, 2025. URL: https://leitlinien.dgk.org/2025/pocket-leitlinie-erhoehter-blutdruck-und-hypertonie-version-2024/

Kuneinen S. M., Kautiainen H., Ekblad M. O., Korhonen P. E. Multifactorial prevention program for cardiovascular disease in primary care: hypertension status and effect on mortality. *Journal of human hypertension*. 2024. Vol. 38. № 4. P. 322–328. DOI: https://doi.org/10.1038/s41371-024-00900-x

Laizure S. C., Herring V., Hu Z., Witbrodt K., Parker R. B. The role of human carboxylesterases in drug metabolism: have we overlooked their importance? *Pharmacotherapy.* 2013. Vol. 33. № 2. P. 210–222. DOI: https://doi.org/10.1002/phar.1194

Largeau B., Cracowski J.-L., Lengellé C., Sautenet B., Jonville-Béra A.-P. Drug-induced peripheral oedema: An aetiology-based review. *British Journal of Clinical Pharmacology.* 2021. Vol. 87. P. 3043–3055. DOI: https://doi.org/10.1111/bcp.14752

Leonetti G., Magnani B., Pessina A. C., Rappelli A., Trimarco B., Zanchetti A., COHORT Study Group. Tolerability of long-term treatment with lercanidipine versus amlodipine and lacidipine in elderly hypertensives. *American journal of hypertension*. 2002. Vol. 15. № 11. P. 932–940. DOI: https://doi.org/10.1016/s0895-7061(02)03000-5

Liang H., Zhang X., Ma Z., Sun Y., Shu C., Zhu Y., Zhang Y., Hu S., Fu X., Liu L. Association of CYP3A5 Gene Polymorphisms and Amlodipine-Induced Peripheral Edema in Chinese Han Patients with Essential Hypertension. *Pharmacogenomics and personalized medicine*. 2021. Vol. 14. P. 189–197. DOI: https://doi.org/10.2147/PGPM.S291277

Liang L., Kung J. Y., Mitchelmore B., Cave A., Banh H. L. Comparative peripheral edema for dihydropyridines calcium channel blockers treatment: A systematic review and network meta-analysis. *Journal of clinical hypertension (Greenwich, Conn.).* 2022. Vol. 24. № 5. P. 536–554. DOI: https://doi.org/10.1111/jch.14436

Liu Y., Kong X., Jiang Y., Zhao M., Gao P., Cong X., Cao Y., Ma L. Association of AGTR1 A1166C and CYP2C9-3 Gene Polymorphisms with the Antihypertensive Effect of Valsartan. *International journal of hypertension*. 2022. 7677252. DOI: https://doi.org/10.1155/2022/7677252

Mancia G., Kreutz R., Brunström M., Burnier M., Grassi G., Januszewicz A., Muiesan M. L., Tsioufis K., Agabiti-Rosei E., Algharably E. A. E., Azizi M., Benetos A., Borghi C., Hitij J. B., Cifkova R., Coca A., Cornelissen V., Cruickshank J. K., Cunha P. G., Danser A. H. J., Kjeldsen S. E. et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *Journal of hypertension*. 2023. Vol. 41. № 12. P. 1874–2071. DOI: https://doi.org/10.1097/HJH.0000000000003480

Manolis A. J., Kallistratos M. S., Camafort M., Coca A. Efficacy and safety of lercanidipine combination in hypertensive patients. *J Hypertens Cardiol*. 2025;3(4):38–49. DOI: 10.14302/issn.2329-9487.jhc-25-5778

Michel C. C., Woodcock T. E., Curry F. E. Understanding and extending the Starling principle. *Acta anaesthesiologica Scandinavica*. 2020. Vol. 64. № 8. P. 1032–1037. DOI: https://doi.org/10.1111/aas.13603

Oh M., Shin J. G., Ahn S., Kim B. H., Kim J. Y., Shin H. J., Shin H. J., Ghim J. L. Pharmacokinetic comparison of a fixed-dose combination versus concomitant administration of amlodipine, olmesartan, and rosuvastatin in healthy adult subjects. *Drug design, development and therapy*. 2019. Vol. 13. P. 991–997. DOI: https://doi.org/10.2147/DDDT.S202730

Park J. W., Chung H., Kim J. M., Kim N. Y., Hong S. H., Kim K. A., Park J. Y. Pharmacokinetics of a Fixed-Dose Combination Product of Amlodipine, Losartan, Ezetimibe, and Rosuvastatin and Its Comparison with Co-administration of Four Individual Components in Healthy Participants. *Drugs in R&D.* 2024. Vol. 24. № 2. P. 179–186. DOI: https://doi.org/10.1007/s40268-024-00460-y

Patel P., Launico M. V. Angiotensin II Receptor Blockers (ARB). StatPearls [Internet]. Treasure Island (FL) : StatPearls Publishing, 2025 Jan. Updated 2025 May 5. URL: https://www.ncbi.nlm.nih.gov/books/NBK537027/

Sagar S., Patel P. Angiotensin Receptor Blockers and HCTZ Combination Drugs. StatPearls [Internet]. Treasure Island (FL) : StatPearls Publishing, 2025 Jan. Updated 2024 Aug 16. URL: https://www.ncbi.nlm.nih.gov/books/NBK606100/

Scholze J., Bramlage P., Trenkwalder P., Kreutz R. Efficacy and safety of a fixed-dose combination of lercanidipine and enalapril in daily practice. A comparison of office, self-measured and ambulatory blood pressure. *Expert opinion on pharmacotherapy.* 2011. Vol. 12. № 18. P. 2771–2779. DOI: https://doi.org/10.1517/14656566.2011.626770

Sever P. The VALUE trial: a commentary. Journal of the renin-angiotensin-aldosterone system : JRAAS. 2004. Vol. 5. № 3. P. 99–101. DOI: https://doi.org/10.3317/jraas.2004.033

Sugiyama Y., Aoki Y. A 20-Year Research Overview: Quantitative Prediction of Hepatic Clearance Using the In Vitro-In Vivo Extrapolation Approach Based on Physiologically Based Pharmacokinetic Modeling and Extended Clearance Concept. *Drug metabolism and disposition: the biological fate of chemicals.* 2023. Vol. 51. № 9. P. 1067–1076. DOI: https://doi.org/10.1124/dmd.123.001344

Tistaert C., Heimbach T., Xia B., Parrott N., Samant T. S., Kesisoglou F. Food Effect Projections via Physiologically Based Pharmacokinetic Modeling: Predictive Case Studies. *Journal of pharmaceutical sciences*. 2019. Vol. 108. № 1. P. 592–602. DOI: https://doi.org/10.1016/j.xphs.2018.05.024

Varma M. V., Obach R. S., Rotter C., Miller H. R., Chang G., Steyn S. J., El-Kattan A., Troutman M. D. Physicochemical space for optimum oral bioavailability: contribution of human intestinal absorption and first-pass elimination. *Journal of medicinal chemistry*. 2010. Vol. 53. № 3. P. 1098–1108. DOI: https://doi.org/10.1021/jm901371v

Wang J. G., Palmer B. F., Vogel Anderson K., Sever P. Amlodipine in the current management of hypertension. *Journal of Clinical Hypertension*. 2023. Vol. 25. P. 801–807. DOI: https://doi.org/10.1111/jch.14709

Wang Z., Xu W., Liu D., Li X., Liu S., Wu X., Wang H. Impact of Food Physical Properties on Oral Drug Absorption: A Comprehensive Review. *Drug design, development and therapy.* 2025. Vol. 19. P. 267–280. DOI: https://doi.org/10.2147/DDDT.S497515

Yang J., Chen S., Chai D., Peng F., Sun N., Lin J. Amlodipine-Based Therapy and Its Effect on Time in Target Range and Long-Term Blood Pressure Variability Across Age Groups in Chinese Patients With Primary Hypertension: A Retrospective Study. *Journal of clinical hypertension (Greenwich, Conn.).* 2025. Vol. 27. № 9. e70151. DOI: https://doi.org/10.1111/jch.70151

Yamazaki S., Evers R., De Zwart L. Physiologically-based pharmacokinetic modeling to evaluate in vitro-to-in vivo extrapolation for intestinal P-glycoprotein inhibition. *CPT: pharmacometrics & systems pharmacology.* 2022. Vol. 11. № 1. P. 55–67. DOI: https://doi.org/10.1002/psp4.12733

Yuan L. J., Qian J. C., Li X. Y., Cui J., Cai J. P., Hu G. X. Enzymatic activity on valsartan of 38 CYP2C9 variants from the Chinese population. *Chemico-biological interactions.* 2022. Vol. 353. 109799. DOI: https://doi.org/10.1016/j.cbi.2022.109799

Zhou Y. T., Yu L. S., Zeng S., Huang Y. W., Xu H. M., Zhou Q. Pharmacokinetic drug-drug interactions between 1,4-dihydropyridine calcium channel blockers and statins: factors determining interaction strength and relevant clinical risk management. *Therapeutics and clinical risk management*. 2014. Vol. 10. P. 17–26. DOI: https://doi.org/10.2147/TCRM.S55512

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REFERENCES

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (2002). Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*, 288(23), 2981–2997. https://doi.org/10.1001/jama.288.23.2981

Álvarez, C., Gómez, E., Simón, M., Govantes, C., Guerra, P., Frías, J., & García-Arieta, A. (2012). Differences in lercanidipine systemic exposure when administered according to labelling: in fasting state and 15 minutes before food intake. *European journal of clinical pharmacology*, 68(7), 1043–1047. https://doi.org/10.1007/s00228-012-1215-8

Bulsara, K. G., Patel, P., & Cassagnol, M. (2025). Amlodipine. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK519508/

Courlet, P., Guidi, M., Alves Saldanha, S., Cavassini, M., Stoeckle, M., Buclin, T., Marzolini, C., Decosterd, L. A., & Csajka, C. (2021). Population pharmacokinetic modelling to quantify the magnitude of drug-drug interactions between amlodipine and antiretroviral drugs. *European journal of clinical pharmacology,* 77(7), 979–987. https://doi.org/10.1007/s00228-020-03060-2

Dahlöf, B., Sever, P. S., Poulter, N. R., Wedel, H., Beevers, D. G., Caulfield, M., Collins, R., Kjeldsen, S. E., Kristinsson, A., McInnes, G. T., Mehlsen, J., Nieminen, M., O'Brien, E., Ostergren, J., & ASCOT Investigators (2005). Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet (London, England), 366(9489), 895–906. https://doi.org/10.1016/S0140-6736(05)67185-1

Dat, T. V., Tu, V. L., Thu, L. N. A., Quang, N. N. A., Binh, V., Nga, N. T. Q., Loc, D. H., Nguyen, T. T. H., Tam, D. N. H., Huynh, H. H., Trung, T. D., Do, U., Phat, N. T., Hung, D. T., Nguyen, Q. H., Yen, N. T. H., & Minh, L. H. N. (2024). Effectiveness of perindopril/amlodipine fixed-dose combination in the treatment of hypertension: a systematic review. *Frontiers in pharmacology*, 14, 1156655. https://doi.org/10.3389/fphar.2023.1156655

Devissaguet, J. P., Ammoury, N., Devissaguet, M., & Perret, L. (1990). Pharmacokinetics of perindopril and its metabolites in healthy volunteers. *Fundamental & clinical pharmacology*, 4(2), 175–189. https://doi.org/10.1111/j.1472-8206.1990.tb00486.x

Dubrov, S. O., Kovalenko, V. M., Vakaliuk, I. P., Zhurba, S. V., Koval, S. M., Katerenchuk, I. P., Kovalenko, O. Ye., Kushnirenko, S. V., Mischenko, L. A., Mischenko, V. M., Sokolova, L. K., & Gulenko, O. I. (2024). Unified clinical protocol of primary and specialized medical care «Hypertensive disease (arterial hypertension)» (Approved by Order of the Ministry of Health of Ukraine No. 1581 dated September 12, 2024). https://www.dec.gov.ua/wp-content/uploads/2024/09/ykpmd_1581_12092024_dod.pdf

Elgendy, M. S., Taha, H. I., Amin, A. M., Khlidj, Y., Ezz, M. R., Elgamasy, M. A., Almezaine, A., Faheem, M. A., Rajab, I., & Abuelazm, M. (2025). The efficacy and safety of low-dose triple combination for hypertension treatment: a systematic review and meta-analysis of randomized controlled trials. *Naunyn-Schmiedeberg's archives of pharmacology,* 398(7), 7721–7736. https://doi.org/10.1007/s00210-025-03790-z

Grassi, G., Robles, N. R., Seravalle, G., & Fici, F. (2017). Lercanidipine in the Management of Hypertension: An Update. *Journal of pharmacology & pharmacotherapeutics,* 8(4), 155–165. https://doi.org/10.4103/jpp.JPP_34_17

Hajdys, J., Fularski, P., Leszto, K., Majchrowicz, G., Stabrawa, M., Młynarska, E., Rysz, J., & Franczyk, B. (2023). New Insights into the Nephroprotective Potential of Lercanidipine. *International journal of molecular sciences,* 24(18), 14048. https://doi.org/10.3390/ijms241814048

Hanauer Schaab, E., Lanchote, V. L., Balthazar Nardotto, G. H., Marques Pereira, M. P., Dantas, M., Paiva, C. E., & Barbosa Coelho, E. (2020). Effect of Lercanidipine on the Pharmacokinetics-Pharmacodynamics of Carvedilol Enantiomers in Patients with Chronic Kidney Disease. *Journal of clinical pharmacology,* 60(1), 75–85. https://doi.org/10.1002/jcph.1485

Hassan, D., Peeters, L. E. J., Rietdijk, W. J. R., van Domburg, B., Bahmany, S., Sassen, S. D. T., Hesselink, D. A., Schinkel, A. F. L., Manintveld, O. C., Galema, T. W., van der Net, J. B., Lafeber, M., Tumkaya, T., Koch, B. C. P., & Versmissen, J. (2025). Differences in antihypertensive drug blood levels in patients with hypertension (DECISION): a prospective study comparing pharmacokinetics and pharmacodynamics of perindopril in younger and older patients. *Blood pressure,* 34(1), 2580368. https://doi.org/10.1080/08037051.2025.2580368

Hussain, M., Basheer, S., Khalil, A., Haider, Q. U. A., Saeed, H., & Faizan, M. (2024). Pharmacogenetic study of CES1 gene and enalapril efficacy. *Journal of applied genetics*, 65(3), 463–471. https://doi.org/10.1007/s13353-024-00831-w

Jeon, J., Ryoo, S., Oh, S., Hong, S. J., Yu, C. W., Kim, Y. H., Kim, E. J., & Joo, H. J. (2025). Comparative effectiveness of lercanidipine and amlodipine on major adverse cardiovascular events in hypertensive patients. *Am J Hypertens*, 38(2), 139–147. https://doi.org/10.1093/ajh/hpae147

Kato, M., Chiba, K., Hisaka, A., Ishigami, M., Kayama, M., Mizuno, N., Nagata, Y., Takakuwa, S., Tsukamoto, Y., Ueda, K., Kusuhara, H., Ito, K., & Sugiyama, Y. (2003). The intestinal first-pass metabolism of substrates of CYP3A4 and P-glycoprotein-quantitative analysis based on information from the literature. *Drug metabolism and pharmacokinetics*, 18(6), 365–372. https://doi.org/10.2133/dmpk.18.365

Kintscher, U., Berrisch-Rahmel, S., Genth-Zotz, S., Halbach, M., Mahfoud, F., & Weil, J. (2025). ESC Pocket Guidelines: Elevated Blood Pressure and Hypertension, Version 2024. Deutsche Gesellschaft für Kardiologie – Herz-und Kreislaufforschung e.V. Börm Bruckmeier Verlag GmbH. https://leitlinien.dgk.org/2025/pocket-leitlinie-erhoehter-blutdruck-und-hypertonie-version-2024/

Kuneinen, S. M., Kautiainen, H., Ekblad, M. O., & Korhonen, P. E. (2024). Multifactorial prevention program for cardiovascular disease in primary care: hypertension status and effect on mortality. *Journal of human hypertension*, 38(4), 322–328. https://doi.org/10.1038/s41371-024-00900-x

Laizure, S. C., Herring, V., Hu, Z., Witbrodt, K., & Parker, R. B. (2013). The role of human carboxylesterases in drug metabolism: have we overlooked their importance? *Pharmacotherapy*, 33(2), 210–222. https://doi.org/10.1002/phar.1194

Largeau, B., Cracowski, J.-L., Lengellé, C., Sautenet, B., & Jonville-Béra, A.-P. (2021). Drug-induced peripheral oedema: An aetiology-based review. *British Journal of Clinical Pharmacology*, 87, 3043–3055. https://doi.org/10.1111/bcp.14752

Leonetti, G., Magnani, B., Pessina, A. C., Rappelli, A., Trimarco, B., Zanchetti, A., & COHORT Study Group (2002). Tolerability of long-term treatment with lercanidipine versus amlodipine and lacidipine in elderly hypertensives. *American journal of hypertension*, 15(11), 932–940. https://doi.org/10.1016/s0895-7061(02)03000-5

Liang, H., Zhang, X., Ma, Z., Sun, Y., Shu, C., Zhu, Y., Zhang, Y., Hu, S., Fu, X., & Liu, L. (2021). Association of CYP3A5 Gene Polymorphisms and Amlodipine-Induced Peripheral Edema in Chinese Han Patients with Essential Hypertension. *Pharmacogenomics and personalized medicine*, 14, 189–197. https://doi.org/10.2147/PGPM.S291277

Liang, L., Kung, J. Y., Mitchelmore, B., Cave, A., & Banh, H. L. (2022). Comparative peripheral edema for dihydropyridines calcium channel blockers treatment: A systematic review and network meta-analysis. *Journal of clinical hypertension (Greenwich, Conn.),* 24(5), 536–554. https://doi.org/10.1111/jch.14436

Liu, Y., Kong, X., Jiang, Y., Zhao, M., Gao, P., Cong, X., Cao, Y., & Ma, L. (2022). Association of AGTR1 A1166C and CYP2C9-3 Gene Polymorphisms with the Antihypertensive Effect of Valsartan. *International journal of hypertension,* 2022, 7677252. https://doi.org/10.1155/2022/7677252

Mancia, G., Kreutz, R., Brunström, M., Burnier, M., Grassi, G., Januszewicz, A., Muiesan, M. L., Tsioufis, K., Agabiti-Rosei, E., Algharably, E. A. E., Azizi, M., Benetos, A., Borghi, C., Hitij, J. B., Cifkova, R., Coca, A., Cornelissen, V., Cruickshank, J. K., Cunha, P. G., Danser, A. H. J., … Kjeldsen, S. E. (2023). 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *Journal of hypertension*, 41(12), 1874–2071. https://doi.org/10.1097/HJH.0000000000003480

Manolis, A. J., Kallistratos, M. S., Camafort, M., & Coca, A. (2025). Efficacy and safety of lercanidipine combination in hypertensive patients. *J Hypertens Cardiol*, 3(4), 38–49. https://doi.org/10.14302/issn.2329-9487.jhc-25-5778

Michel, C. C., Woodcock, T. E., & Curry, F. E. (2020). Understanding and extending the Starling principle. *Acta anaesthesiologica Scandinavica*, 64(8), 1032–1037. https://doi.org/10.1111/aas.13603

Oh, M., Shin, J. G., Ahn, S., Kim, B. H., Kim, J. Y., Shin, H. J., Shin, H. J., & Ghim, J. L. (2019). Pharmacokinetic comparison of a fixed-dose combination versus concomitant administration of amlodipine, olmesartan, and rosuvastatin in healthy adult subjects. *Drug design, development and therapy*, 13, 991–997. https://doi.org/10.2147/DDDT.S202730

Park, J. W., Chung, H., Kim, J. M., Kim, N. Y., Hong, S. H., Kim, K. A., & Park, J. Y. (2024). Pharmacokinetics of a Fixed-Dose Combination Product of Amlodipine, Losartan, Ezetimibe, and Rosuvastatin and Its Comparison with Co-administration of Four Individual Components in Healthy Participants. *Drugs in R&D,* 24(2), 179–186. https://doi.org/10.1007/s40268-024-00460-y

Patel, P., & Launico, M. V. (2025). Angiotensin II receptor blockers (ARB). In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK537027/

Sagar, S., & Patel, P. (2025). Angiotensin receptor blockers and HCTZ combination drugs. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK606100/

Scholze, J., Bramlage, P., Trenkwalder, P., & Kreutz, R. (2011). Efficacy and safety of a fixed-dose combination of lercanidipine and enalapril in daily practice. A comparison of office, self-measured and ambulatory blood pressure. *Expert opinion on pharmacotherapy,* 12(18), 2771–2779. https://doi.org/10.1517/14656566.2011.626770

Sever, P. (2004). The VALUE trial: a commentary. *Journal of the renin-angiotensin-aldosterone system: JRAAS,* 5(3), 99–101. https://doi.org/10.3317/jraas.2004.033

Sugiyama, Y., & Aoki, Y. (2023). A 20-Year Research Overview: Quantitative Prediction of Hepatic Clearance Using the In Vitro-In Vivo Extrapolation Approach Based on Physiologically Based Pharmacokinetic Modeling and Extended Clearance Concept. *Drug metabolism and disposition: the biological fate of chemicals,* 51(9), 1067–1076. https://doi.org/10.1124/dmd.123.001344

Tistaert, C., Heimbach, T., Xia, B., Parrott, N., Samant, T. S., & Kesisoglou, F. (2019). Food Effect Projections via Physiologically Based Pharmacokinetic Modeling: Predictive Case Studies. *Journal of pharmaceutical sciences*, 108(1), 592–602. https://doi.org/10.1016/j.xphs.2018.05.024

Varma, M. V., Obach, R. S., Rotter, C., Miller, H. R., Chang, G., Steyn, S. J., El-Kattan, A., & Troutman, M. D. (2010). Physicochemical space for optimum oral bioavailability: contribution of human intestinal absorption and first-pass elimination. *Journal of medicinal chemistry,* 53(3), 1098–1108. https://doi.org/10.1021/jm901371v

Wang, J. G., Palmer, B. F., Vogel Anderson, K., & Sever, P. (2023). Amlodipine in the current management of hypertension. *J Clin Hypertens*, 25, 801–807. https://doi.org/10.1111/jch.14709

Wang, Z., Xu, W., Liu, D., Li, X., Liu, S., Wu, X., & Wang, H. (2025). Impact of Food Physical Properties on Oral Drug Absorption: A Comprehensive Review. *Drug design, development and therapy*, 19, 267–280. https://doi.org/10.2147/DDDT.S497515

Yang, J., Chen, S., Chai, D., Peng, F., Sun, N., & Lin, J. (2025). Amlodipine-Based Therapy and Its Effect on Time in Target Range and Long-Term Blood Pressure Variability Across Age Groups in Chinese Patients with Primary Hypertension: A Retrospective Study. *Journal of clinical hypertension (Greenwich, Conn.)*, 27(9), e70151. https://doi.org/10.1111/jch.70151

Yamazaki, S., Evers, R., & De Zwart, L. (2022). Physiologically-based pharmacokinetic modeling to evaluate in vitro-to-in vivo extrapolation for intestinal P-glycoprotein inhibition. *CPT: pharmacometrics & systems pharmacology*, 11(1), 55–67. https://doi.org/10.1002/psp4.12733

Yuan, L. J., Qian, J. C., Li, X. Y., Cui, J., Cai, J. P., & Hu, G. X. (2022). Enzymatic activity on valsartan of 38 CYP2C9 variants from the Chinese population. *Chemico-biological interactions*, 353, 109799. https://doi.org/10.1016/j.cbi.2022.109799

Zhou, Y. T., Yu, L. S., Zeng, S., Huang, Y. W., Xu, H. M., & Zhou, Q. (2014). Pharmacokinetic drug-drug interactions between 1,4-dihydropyridine calcium channel blockers and statins: factors determining interaction strength and relevant clinical risk management. *Therapeutics and clinical risk management*, 10, 17–26. https://doi.org/10.2147/TCRM.S55512

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