



Perindopril/Indapamide/Amlodipine in Hypertension: A Profile of Its Use

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Abstract

The single-pill combination (SPC) of perindopril (PER)/indapamide (IND)/amlodipine (AML) is a valuable and convenient treatment option for patients with hypertension controlled with two-drug SPC of PER/IND + AML given as two separate pills at the same dose level. PER [an angiotensin-converting enzyme (ACE) inhibitor], IND (a thiazide-like diuretic) and AML (a calcium channel blocker) are well established antihypertensive agents, which have been available for a long time as monotherapies and dual SPCs and have complementary mechanisms of action. Once-daily PER/IND/AML provided effective BP control, with good tolerability, in patients with uncontrolled hypertension in clinical trials and in large observational prospective studies. The efficacy and tolerability of PER/IND/AML was similar to that of PER/IND + AML in a randomized clinical trial. The therapeutic effect of PER/IND/AML was associated with improved health-related quality of life. Thus, switching from the two-pill PER/IND + AML regimen to single-pill PER/IND/AML reduces pill burden and simplifies drug administration, which may improve adherence to treatment, leading to better BP control and clinical outcomes.

Plain Language Summary

Approximately one-quarter of patients with hypertension require three antihypertensive agents to achieve BP control. However, complex treatment regimens and high pill burden reduce treatment adherence, which in turn leads to poor BP control. Perindopril (PER), indapamide (IND), amlodipine (AML) belong to the core drug classes for the treatment of hypertension. These drugs have been available for a long time as monotherapies and two-drug single-pill combinations. Once-daily PER/IND/AML provides very good BP control in patients with uncontrolled hypertension and is generally well tolerated. The single-pill PER/IND/AML has similar efficacy and tolerability to PER/IND + AML given as two separate pills. Therefore, switching from PER/IND + AML to PER/IND/AML reduces pill burden and simplifies the treatment regimen, which may improve adherence to treatment, leading to better BP control and clinical outcomes. Thus, PER/IND/AML is a valuable and convenient treatment option for patients with hypertension controlled with PER/IND + AML at the same dose level.

Digital Features for this Adis Drug Q&A can be found at <https://doi.org/10.6084/m9.figshare.17020076>.

1 What is the Rationale for Using PER/IND/AML in Hypertension?

Uncontrolled hypertension increases the risk of all-cause mortality and cardiovascular diseases [1]. In $\approx 25\%$ of patients, three antihypertensive agents are required to

Adis Evaluation of PER/IND/AML in Hypertension

Currently, the only triple component SPC that includes an ACE inhibitor (perindopril) and a thiazide-like diuretic (indapamide).

Provides effective BP control, with good tolerability; improves health-related quality of life.

Similar efficacy and tolerability to PER/IND + AML given as two pills.

Reduces pill burden, which may improve adherence to treatment, leading to better clinical outcomes.

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Table 1 Prescribing summary of perindopril/indapamide/amlodipine (Triplixam®) in hypertension in the EU [14]**What is the approved indication of PER/IND/AML?**

Substitution therapy for the treatment of essential hypertension in pts already controlled with PER/IND SPC + AML. PER/IND/AML is not suitable as initial therapy

How is PER/IND/AML available?

As film-coated tablets in four strengths (mg): 2.5/0.625/5 | 5/1.25/5 | 5/1.25/10 | 10/2.5/5 | 10/2.5/10

What is the recommended dosage of PER/IND/AML?

One tablet daily (preferably in the morning, before a meal) at the same dose level as previous PER/IND SPC + AML; if dose change is required, titration should be done with individual components

How should PER/IND/AML be used in special populations?

Pts with kidney function impairment	Moderate (CL_{CR} 30–60 mL/min): 10/2.5/5 and 10/2.5/10 doses contraindicated; starting treatment with the adequate dosage of the free combination is recommended; monitor serum potassium and creatinine levels Severe ($CL_{CR} < 30$ mL/min): use is contraindicated
Pts with hepatic impairment	Severe: use is contraindicated Mild to moderate: use with caution
Elderly pts	Treat according to kidney function, as PER elimination is decreased in the elderly
Paediatric pts	Efficacy and safety not established
Women who are pregnant	Not recommended during first trimester; contraindicated during second and third trimesters
Women who are breastfeeding	Use is contraindicated

What are the potential clinically relevant interactions for PER/IND/AML?

Concomitant use contraindicated	Aliskiren [in pts with diabetes mellitus or impaired kidney function ($GFR < 60$ mL/min/1.73 m ²)], sacubitril/valsartan, extracorporeal treatments (e.g. dialysis or hemofiltration)
Concomitant use not recommended	Lithium, other ACEI, other ARB, aliskiren, estramustine, potassium-sparing drugs, co-trimoxazole, dantrolene, grapefruit
Use concomitantly with special care	Allopurinol, anaesthetic agents, antidiabetic agents (insulin; oral), antihypertensives, atorvastatin, baclofen, calcium, cardiac glycosides, ciclosporin, corticosteroids, CYP3A4 inducers/inhibitors, digoxin, diuretics (nonpotassium-sparing, potassium-sparing), gold, imipramine-like antidepressants, immunosuppressive agents, iodinated contrast media, intravenous amphotericin B, mTOR inhibitors, neuroleptics, NSAIDs, procainamide, racecadotril, simvastatin, stimulant laxatives, sympathomimetics, tetracosactide, Torsades de pointes-inducing drugs, vasodilators, warfarin

In which other patient populations is the use of PER/IND/AML contraindicated?

Pts hypersensitive to the active substances, sulfonamides, dihydropyridine derivatives, any other ACEI or any of the excipients
Pts with: untreated decompensated heart failure, hereditary/idiopathic angioedema, hepatic encephalopathy, hypokalaemia, severe hypotension, shock (including cardiogenic shock), obstruction of the left ventricle outflow tract, hemodynamically unstable heart failure after acute myocardial infarction, or unilateral (if single functioning kidney) or significant bilateral renal artery stenosis

Consult local prescribing information for further details

ACEI angiotensin-converting enzyme inhibitors, AML amlodipine, ARB angiotensin receptor blockers, CL_{CR} creatinine clearance, SPC fixed-dose combination, GFR glomerular filtration rate, IND indapamide, mTOR mechanistic target of rapamycin, PER perindopril, pts patients

achieve BP control [2]. However, complex treatment regimens and increased pill burden decrease adherence to treatment, which in turn leads to poor BP control [3]. Thus single-pill combinations (SPCs) of three drugs play a crucial role in the management of hypertension [4–7].

Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), diuretics and calcium channel blockers (CCB) form the core of drug treatment for hypertension, according to the current treatment guidelines [4–7]. Perindopril (PER), indapamide (IND) and amlodipine (AML) fulfil the criteria for the choice of core antihypertensive drugs [4–6]. These drugs have complementary pharmacological actions and good pharmacokinetic compatibility (Sect. 2). When combined, they can produce a synergistic increase in antihypertensive efficacy, while also potentially counteracting each other's known class effects.

PER, IND and AML as monotherapies and as two-drug SPCs (PER/IND, PER/AML, IND/AML) have long been

available, and are routinely prescribed by healthcare practitioners for the treatment of hypertension. The safety and efficacy of these products have been demonstrated in large clinical programs; in addition to reducing BP, they have proven beneficial effects on mortality, morbidity and target organ protection (Sect. 2).

In large observational studies, PER, IND and AML triple therapy administered as two separate pills (PER/IND + CCB or PER/AML + IND) effectively reduced BP in patients with hypertension uncontrolled on one or two drugs, including those with type 2 diabetes mellitus (T2DM), obesity and/or metabolic syndrome [8–11]. A substudy of the ADVANCE trial supports a combination of CCB and PER/IND for reducing the risk of mortality (Sect. 2.4) [12]. These data lend further compelling rationale for a SPC of PER/IND/AML. This article provides a narrative review of PER/IND/AML in the treatment of hypertension, with representative prescribing information summarized in Table 1.

2 How Do the Drugs in the Fixed-Dose Combination Work?

The pharmacokinetic properties of PER, IND and AML are well established [13]. The pharmacokinetics of individual components after administration of the triple-component SPC were similar to those after administration of individually marketed products, PER/IND and AML, for several dose strengths. There was no clinically relevant pharmacokinetic interaction between the three drugs when administered as a SPC [13].

2.1 Perindopril

PER is a prodrug that is hydrolysed *in vivo* to the active metabolite perindoprilat, which inhibits angiotensin-converting enzyme (ACE) at both plasma and tissue levels [14–16]. ACE converts angiotensin I to angiotensin II, a vasoconstrictor. PER-induced decrease in plasma angiotensin II results in increased plasma renin activity, decreased aldosterone secretion, increased bradykinin (a vasodilator) availability and reduced total peripheral resistance. Thus, PER reduces BP mainly by suppression of the renin-angiotensin-aldosterone system (RAAS), with bradykinin also contributing to this action. At tissue level, perindoprilat predominantly acts on vascular wall and the kidney, with no salt and water retention or reflex tachycardia during chronic treatment. PER is effective in all grades of hypertension. Following a single oral dose, BP reduction is maximal at 4–6 h postdose and the efficacy is maintained through 24 h. In responders, BP is normalized typically after 1 month's treatment, and is maintained without tachyphylaxis [14–16]. PER has a positive effect on ischemia, atherosclerosis, inflammation, thrombosis, platelet aggregation, endothelial function, cardiovascular structure and function, and albuminuria [16]. PER improved cardiovascular and mortality outcomes in patients with stable coronary artery disease (CAD) without heart failure (EUROPA) and in elderly post-myocardial infarction (MI) patients with preserved left ventricular ejection fraction (PREAMI) [16].

2.2 Indapamide

IND is a thiazide-like diuretic that inhibits sodium and chloride reabsorption in the cortical dilution segment in the kidney, resulting in increased excretion of these ions in the urine [14, 17–19]. Thus, the antihypertensive effect of IND results from increased urine output; it also lowers systolic BP (SBP) by acting as a vasorelaxant. IND has a 24–34 h duration of action. It is superior to hydrochlorothiazide (HCTZ) in reducing SBP and to enalapril in reducing left ventricular

mass index (LVMI) in hypertensive patients and in reducing microalbuminuria in hypertensive patients with diabetes mellitus [14, 17–19]. BP reduction with IND reduced the risk of fatal and nonfatal stroke by 29% in patients with a history of stroke or transient ischemic attack (PATS) [20].

2.3 Amlodipine

AML is a dihydropyridine CCB that inhibits the transmembrane influx of calcium into cardiac muscle and vascular smooth muscle [14, 21]. The antihypertensive effect of AML is due to peripheral vasodilation and subsequent reduction in systemic vascular resistance. AML has a half-life of 30–45 h, which allows for once-daily administration [14, 21].

There was no significant difference between AML, chlorthalidone and lisinopril in reducing fatal coronary heart disease (CHD) or nonfatal MI and all-cause mortality in patients aged ≥ 55 years with hypertension and at least one other CHD risk factor (ALLHAT) [22]. AML reduced adverse cardiovascular events in patients with CAD and normal BP (CAMELOT) [23]. It did not slow progression of early coronary atherosclerosis in patients with CAD, but reduced hospitalizations for unstable angina and revascularization (PREVENT) [24]. Of note, valsartan did not differ from AML in reducing cardiac morbidity and mortality in hypertensive patients with high cardiovascular risk (VALUE) [25].

2.4 Dual Combinations

PER/IND effectively reduced BP in several placebo-controlled and active comparator (losartan, atenolol, irbesartan) trials in patients with hypertension, including elderly patients and those with kidney function impairment [26]. PER/IND was associated with numerically better BP response and BP control rates (as defined in Sect. 3) than losartan, and was more effective than atenolol in elderly patients [26]. PER \pm IND reduced the risk of fatal and nonfatal stroke in very elderly patients (HYVET) [27] and in hypertensive or non-hypertensive patients with a history of stroke or transient ischemic attack (PROGRESS) [28]. PER/IND reduced the risk of major macrovascular or microvascular events by 9% and the risk of death from cardiovascular disease by 18% versus placebo in patients with T2DM (ADVANCE) [29]; the risk of death decreased further in patients on a CCB at baseline versus no CCB at baseline (ADVANCE-CCB) [12].

PER/AML SPC was more effective than individual components (PATH), and a PER/AML strategy was associated with greater BP reduction than a valsartan/AML strategy in patients with mild to moderate hypertension [30]. In hypertensive patients with ≥ 3 other cardiovascular risk factors, AML \pm PER was associated with reduced incidence of

major cardiovascular events, all-cause mortality and new-onset diabetes, compared with atenolol ± bendroflumethiazide (ASCOT-BPLA) [31]. The two strategies did not differ significantly for the primary endpoint of non-fatal MI plus fatal CHD; it must be noted that the study became underpowered for this endpoint due to early termination because of higher mortality and worse secondary outcomes with atenolol ± bendroflumethiazide versus AML ± PER [31]. The addition of PER to a CCB reduced the composite of cardiovascular mortality, nonfatal MI and resuscitated cardiac arrest by 35% in patients with stable CAD in EUROPA (post hoc analysis) [32].

3 What is the Efficacy of PER/IND/AML in Clinical Studies?

The efficacy of once-daily PER/IND/AML was assessed in several randomized [33–36] and prospective [37–45] clinical studies. BP control rate was typically defined as the proportion of patients achieving SBP and diastolic BP (DBP) target values of < 140 and < 90 mmHg, respectively. Where reported, BP response rate was defined as BP control, and/or ≥ 20 mmHg decrease in SBP, and/or ≥ 10 mmHg decrease in DBP [35, 36].

3.1 Compared with PER/IND or PER/AML

Triple-component SPC PER/IND/AML was superior to dual-component SPC PER/IND in a randomized, double-blind trial in patients with uncontrolled hypertension on current treatment (Table 2) [36]. PER/IND/AML was significantly more effective than PER/IND in reducing office supine SBP (primary endpoint) and DBP from baseline at month 1 (Table 2); the between-group difference in supine SBP/DBP was – 3.1/– 2.8 mmHg. The effect was confirmed by office standing BP measurements. The between-group difference (– 5.3/– 3.7 mmHg) became even more prominent when the white-coat effect was excluded. The triple SPC was associated with significantly higher BP control (Table 2) and BP response (72% vs 53%; $p \leq 0.001$) rates versus dual SPC at month 1. Progressive improvements in BP control rates were seen in both groups, reaching 82% at study end (month 4). Fewer patients who started on PER/IND/AML required uptitrations than those who started on PER/IND. Uptitrations were associated with further significant ($p < 0.001$ vs month-1 values) BP reduction in both groups at month 4 [36].

In this study, ambulatory BP, home BP and central ambulatory BP measurements in subgroups of patients confirmed the superiority of PER/IND/AML over PER/IND [36, 46]. The ambulatory BP findings are summarized in Table 3 [46]. The mean change from baseline in global home SBP/DBP

at month 1 was – 10.3/– 6.0 mmHg with PER/IND/AML versus – 5.0/– 3.2 mmHg with PER/IND (between-group difference – 4.9/– 3.1 mmHg; $p < 0.001$ for both SBP and DBP) [36]. Similar results were seen for day- and night-time ambulatory and home BP. Consistent with office BP, ambulatory and home BP measurements also demonstrated the uptitration efficacy of PER/IND/AML [36]. For central ambulatory BP, significant ($p \leq 0.05$) between-group differences in favour of PER/IND/AML was seen at 1 month for SBP (– 4.5, – 5.0 and – 4.1 mmHg for 24-h, daytime and night-time, respectively) and DBP (– 2.7 and – 3.4 mmHg for 24-h and daytime) [46]. Significant ($p \leq 0.05$) between-group differences in favour of PER/IND/AML were also seen for central pulse pressure and other derived parameters [46].

In an open-label trial (PRECIOUS), PER/IND/AML 4/1.25/5 mg was effective in patients with uncontrolled hypertension and PER/AML 4/5 mg was effective in those with newly diagnosed or uncontrolled hypertension [44]. After 4 months of treatment, BP control was achieved in 83.0% and 77.7% of patients in the triple and dual SPC arms. Two-thirds of the patients required no or just one uptitration of the treatment [44].

3.2 Compared with PER/IND + AML

Triple therapy with PER/IND/AML as a single pill showed greater antihypertensive efficacy than PER/IND + AML given as two separate pills in a 12-week pilot study in patients ($n = 12$) with hypertension and no comorbidities [47]. In a subsequent randomized, open-label trial, PER/IND/AML was as effective as the equivalent dose of PER/IND + AML in patients with uncontrolled hypertension on maximal dose monotherapy or dual therapy (Table 2) [35]. At week 12, there was no significant between-group difference for office supine SBP/DBP (primary endpoint) and BP control rate, with both groups showing clinically meaningful improvements for these endpoints (Table 2). Similar results were seen for BP response rate (89.2% vs 87.1%). Most of these improvements were seen by the first post-baseline visit at week 4 and were maintained through week 12 [35].

3.3 Compared with PER + IND + AML

Triple-component SPC PER/IND/AML provided better antihypertensive efficacy, with other beneficial outcomes, compared with free combination of the same agents in patients with uncontrolled hypertension, including those with comorbid T2DM and obesity [33, 34, 45].

In a 12-week randomized trial, PER/IND/AML plus atorvastatin was associated with generally greater antihypertensive efficacy (Table 2) and cardiovascular risk reduction than the equivalent dosage of the same regimen

Table 2 Efficacy of once-daily perindopril/indapamide/amlodipine in reducing office blood pressure

Study	Target population	Treatment (mg)	No. of pts	FU (mo)	SBP ^a (mmHg)	DBP ^a (mmHg)	BP control ^b (% pts)
Randomized clinical studies							
Mourad et al. [36]	SBP/DBP \geq 150/90 mmHg on \leq 2 AH; no DM or kidney impairment	P/I/A (5/1.25/5)	225	1	-19.2 [†]	-13.2 ^{†††}	32 ^{††}
		P/I (5/1.25)	224	1	-17.3	-10.1	25
Nedogoda et al. [35]	SBP \geq 140 to $<$ 160/DBP \geq 90 to $<$ 100 mmHg on single or dual AH	P/I/A (5/1.25/5)	75	3	-21.5	-15.3	81.1
		P/I (5/1.25) + A (5)	73	3	-20.0	-14.8	80.0
Marazzi et al [34]	On P + I or A; LDL-C $<$ 130 mg/dL; no DM, kidney or liver impairment	P/I/A (10/2.5/5-10) ^c	83	3	-19.5 ^{††}	-9.5	89 [†]
		P + I + A (10/2.5/5-10) ^c	79	3	-14.4	-8.3	80
Non-randomized clinical studies							
Mazza et al. [42]	Grade II HT uncontrolled on RAAS + diuretic	P/I/A (5/1.25/5 to 10/2.5/10)	92	4	-22.4 ^{***}	-11.1 ^{***}	64.8 ^{d†}
		RAAS-I + diuretic + CCB	92	4	-18.9 ^{***}	-11.7 ^{***}	46.9 ^d
Thacker et al. [43]	SBP/DBP \geq 140/90 mmHg on dual therapy	P/I/A (4/1.25/5) \rightarrow + P (4)	218	6	-28.5 ^{***}	-13.8 ^{***}	96
Netchessova et al. [39]	Grade I–III HT	NA	796	5	-36.2 ^{***}	-17.1 ^{***}	$>$ 85
Larina et al. [38]	Grade II–III HT on P + I + A	P/I/A (5/1.25/4 \rightarrow 10/2.5/8)	92	3	-17 [*]	-7 [*]	NA
Popescu and Balan [40]	Grade II HT	P/I/A (5/1.25/5)	46	3	-26 ^{**}	-11 ^{**}	NA
Popescu and Balan [37]	Grade III HT	P/I/A (10/2.5/10)	28	3	-44 ^{**}	-28 ^{**}	85.7
Prospective observational studies							
PETRA [49]	Grade I–III HT, high CV risk factors and accompanying disorders	P/I/A ^e	11,209	3	-24.8 ^{***}	-11.4 ^{***}	72.8
TRIO ^f [50]	SBP $>$ 140–179 mmHg	P/I/A ^e	992	3	-35.3 ^{**}	NA	87.8 [†]
		Control	260	3	-29.4	NA	81.8
CONTROL-3 [52]	Grade I–III HT	P/I/A ^e	2285	4	-32.6 ^{**}	-14.5 ^{**}	82
TRICOLOR [51]	NA	P/I/A	1247	4	-34.8 ^{***}	-15.2 ^{***}	93.3

A amlodipine, AH antihypertensives, CCB calcium channel blocker, CV cardiovascular, DBP diastolic BP, DM diabetes mellitus, FU follow-up, I indapamide, LDL-C low-density lipoprotein cholesterol, NA not available, P perindopril, pts patients, RAAS-I renin-angiotensin-aldosterone system inhibitor, SBP systolic BP

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ vs baseline, [†] $p \leq 0.05$, ^{††} $p \leq 0.01$, ^{†††} $p < 0.001$ vs comparator

^aMean change from baseline

^bSBP/DBP $<$ 140/ $<$ 90 mmHg, unless indicated otherwise

^cPlus atorvastatin 20 mg

^dProportion of patients achieving target ambulatory SBP/DBP $<$ 130/80 mmHg

^eUptitrated as required following local clinical practice

^fP/I/A: dual + single components allowed, although triple fixed-dose combination was used in 96.3% pts. Control: any treatment other than P, I and A. Complementary antihypertensives allowed in both groups

in free combination in patients with uncontrolled hypertension and no diabetes mellitus, liver or kidney failure ($n = 305$) [34].

In a subsequent 6-month, randomized, open-label trial, PER/IND/AML was associated with greater BP control (80% vs 58% at 3 months; 85% vs 53% at 6 months; $p < 0.05$ for both) and a better ambulatory BP profile in general (Table 3) than the equivalent-dose free combination in obese

patients with moderate to severe hypertension uncontrolled on dual therapy ($n = 75$) [33]. The SPC was significantly ($p \leq 0.05$) better than the free combination in terms of 24-h hypertensive time index, 24-h BP variability and the degree of night-time BP reduction. The SPC was also associated with more frequent use of lower dose levels and lesser use of maximal doses for BP control, compared with the free combination [33].

Table 3 Efficacy of once-daily perindopril/indapamide/amlodipine in reducing 24-h ambulatory blood pressure

Study	Target population	Treatment (mg)	No. of pts	FU (mo)	SBP ^a (mmHg)	DBP ^a (mmHg)
Randomized studies						
Topouchian et al. [46]	SBP/DBP \geq 150/90 mmHg on \leq 2 AH; no DM or kidney impairment	P/I/A (5/1.25/5)	101	1	- 8.5** [†]	- 5.4** [†]
		P/I (5/1.25)	109	1	- 4.1**	- 3.4**
Koval et al. [33]	Obese pts with moderate-to-severe HT	P/I/A (4/1.25/5 to 8/2.5/10)	39	6	- 22.9*	- 15.9** [†]
		P (4-8) + I (1.25-2.5) + A (5-10)	36	6	- 15.0**	- 6.8
Non-randomized study						
Mazza et al. [42]	Grade II HT uncontrolled on RAAS-I + diuretic	P/I/A 5/1.25/5 to 10/2.5/10	92	4	- 18.1*	- 8.9*
		RAAS-I + diuretic + CCB	92	4	- 17.5*	- 6.7*
Prospective observational study						
PETRA [49]	Grade I-III HT, high cardiovascular risk factors and accompanying disorders	P/I/A	76	3	- 20.9**	- 7.5**

A amlodipine, AH antihypertensives, BL baseline, CCB calcium channel blockers, DBP diastolic blood pressure, FU follow-up, HT hypertension, I indapamide, P perindopril, pts patients, RAAS-I renin-angiotensin-aldosterone system inhibitor, SBP systolic blood pressure

* $p \leq 0.05$, ** $p \leq 0.001$ versus BL, [†] $p \leq 0.05$, ^{††} $p \leq 0.001$ versus comparator

^aMean change from BL

These findings were supported by a prospective clinical study in obese patients with hypertension and T2DM ($n = 87$) [45]. A group of patients received PER/IND/AML 4/1.25/5 mg and a matching control group received an equivalent free combination for 6 months; both groups received T2DM and hyperlipidaemia treatments and implemented dietary changes for weight loss. The baseline characteristics were well balanced between the groups. The BP control rate (target SBP/DBP 130/80 mmHg) was higher with the SPC than with the free-combination at 3 months (95.65% vs 80.49%; $p = 0.03$) but it did not differ significantly between the groups at 6 months (97.83% vs 92.68%), indicating BP control was achieved early with the SPC. The SPC was also associated with a lower likelihood of visiting a physician for hypertension-mediated target organ damage (relative risk 1.27; 95% CI 1.01-1.61; $p = 0.045$) and a lower risk for clinical worsening of hypertension, T2DM and obesity (relative risk 1.37; 95% CI 1.02-1.84; $p = 0.03$) [45].

3.4 Compared with a RAAS Inhibitor, a Diuretic and a CCB

PER/IND/AML was more effective than a free triple combination of a RAAS inhibitor, a diuretic and a CCB in a prospective clinical study in patients with hypertension uncontrolled on a dual SPC of RAAS inhibitor/diuretic [42]. Patients were switched to PER/IND/AML, and an age- and sex-matched control group received the free triple combination, for 4 months. Office BP (Table 2) and ambulatory BP (Table 3) decreased significantly versus baseline in both treatment groups. However, significantly more SPC than

free combination recipients achieved target ambulatory BP (Table 2). The SPC was also more effective than the free combination in reducing ambulatory SBP and pulse pressure at month 1. Furthermore, BP variability was significantly lower with the SPC than with the free combination [42]. At 14 months, 77.1% and 72.4% of patients in the SPC and free combination arms achieved target office BP [48].

3.5 Noncomparative Data

In prospective noncomparative studies, PER/IND/AML effectively reduced BP in patients with grade I-III uncontrolled hypertension, including those with comorbid T2DM, metabolic disorders or a high cardiovascular risk (Table 2) [37-40, 43]. The efficacy of PER/IND/AML was confirmed by central BP measurements in one study; the mean change from baseline in central SBP/DBP at 5 months was - 24.7/- 11.8 mmHg ($p \leq 0.001$ for both SBP and DBP), with 86.7% and 90% of patients achieving target central SBP and DBP, respectively [39]. Where reported, PER/IND/AML significantly ($p \leq 0.05$) reduced maximum BP, BP variability, morning BP elevations and hypertensive time index [38]. Triple-component SPCs, including PER/IND/AML, were also effective in patients with resistant hypertension [41].

4 What is the Effectiveness of PER/IND/AML in Clinical Practice?

PER/IND/AML was effective in controlling BP in patients with uncontrolled hypertension in large observational prospective studies conducted in Hungary (PETRA [49]),

Russia (TRIO [50], TRICOLOR [51]) and Greece (CONTROL-3 [52]). In these studies, PER/IND/AML significantly reduced office BP, with 73–93% of patients achieving BP control (Table 2). Office BP findings were supported by ambulatory BP monitoring in PETRA (Table 3) [49] and self-monitored BP in TRIO [50]. In CONTROL-3, the proportion of patients with normal or high normal BP increased from 3% at baseline to 82% at 4 months; the proportion of patients with grade I or II hypertension reduced from 70 to 0.4% during the same period [52]. In PETRA, the ambulatory hypertensive time index decreased significantly from 60.17 to 32.67% [49].

In PETRA, PER/IND/AML effectively reduced office and ambulatory BP in patients with all grades of hypertension and the magnitude of reduction appeared to increase with increasing disease severity at baseline (Fig. 1). Similar results were seen in TRIO [50] and CONTROL-3 [52]. PER/IND/AML was effective in clinically relevant hypertensive subgroups, including those with comorbid diabetes mellitus or impaired glucose tolerance ($n = 232$), overweight or obesity ($n = 817$) or chronic kidney disease ($n = 176$) [50]. In these patients, the mean change from baseline in office SBP/DBP at 3 months on PER/IND/AML was $-35.1/-16.0$ mmHg, $-35.2/-15.6$ mmHg and $-37.7/-17.1$ mmHg, respectively, and the corresponding BP control rates were 82.3%, 87% and 82.7% [50]. At baseline in CONTROL-3, 50.1% of 2285 patients were at high or very high risk for cardiovascular diseases; these patients showed a relatively greater degree of SBP reduction with PER/IND/AML [52].

In PETRA, 45.1%, 33.5% and 21.4% of patients were being treated with 5/1.25/5 mg, 10/2.5/5 mg and 10/2.5/10 mg strengths of PER/IND/AML, respectively, at the final visit (i.e. month 3), suggesting the lowest dose was adequate in nearly half of the target population [49]. In clinical practice, switching to PER/IND/AML was associated with a significant ($p \leq 0.001$) reduction in the number of antihypertensive tablets taken per day (3.3 vs 1.2) [53].

5 What are the Other Benefits of PER/IND/AML?

Patients with left ventricular hypertrophy at baseline who did not achieve a reduction in LVMI during antihypertensive therapy are at an increased risk for cardiovascular events [4, 48]. PER/IND/AML reduced LVMI in patients with hypertension [37, 40, 48]. In a randomized trial (Sect. 3.4), PER/IND/AML provided greater LVMI reduction ($-8.3\% \pm 4.9\%$ vs $-2.0 \pm 2.1\%$; $p < 0.0001$) and left ventricular hypertrophy regression (43.5% vs 30.4% of patients; $p < 0.05$) from baseline at 14 months than a triple free combination of a

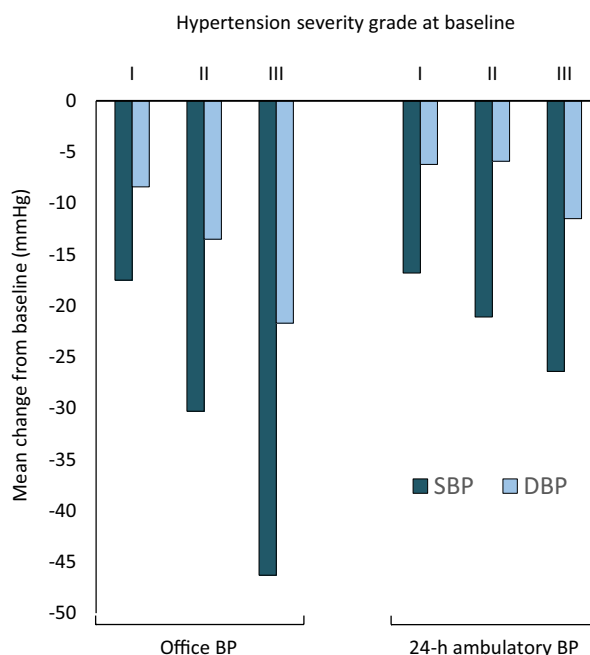


Fig. 1 Efficacy of perindopril/indapamide/amlodipine against different grades of hypertension in a 3-month prospective observational study (PETRA) [49]. *DBP* diastolic blood pressure, *SBP* systolic blood pressure

RAAS inhibitor, a diuretic and a CCB [48]. PER/IND/AML also improved vascular stiffness parameters, which may lead to increased microcirculation and decreased cardiovascular complications [39, 54].

In PETRA, PER/IND/AML treatment was associated with significant ($p < 0.0001$) improvements in metabolic parameters, including total cholesterol (-8.6%), low-density lipoprotein cholesterol (-11.4%), triglyceride (-12.1%), fasting glucose (-6.6%), glycosylated hemoglobin (-6.5%) and serum urate (-6.1%) levels [49]. The SPC also improved glomerular filtration rate [49, 50] and reduced microalbuminuria [55] in hypertensive patients, suggesting it may provide nephroprotection in this population.

5.1 Health-Related Quality of Life

The therapeutic effect of PER/IND/AML was associated with improvements in health-related quality of life (HR-QOL) in hypertensive patients, as assessed by the 36-Item Short Form Survey [50] or the World Health Organization Quality-of-Life Scale (WHOQOL-BREF) [43]. In TRIO, the mean mood score increased significantly in the PER/IND/AML group versus baseline and control ($p < 0.001$ for both), with no significant changes in other variables in both groups [50]. In another study, the BP-lowering effect of the

SPC significantly ($p < 0.05$) improved depression, with a slight improvement in anxiety level, as assessed by the Hospital Anxiety and Depression Scale [38]. In small clinical trials, after 3 months' PER/IND/AML treatment, investigators rated each patient's general condition or well being as 'excellent' or 'improved' in $\approx 89\%$ of patients (the other rating categories were 'appropriate' or 'worse') [37, 40].

5.2 Adherence to Treatment

The use of triple-component SPC PER/IND/AML was associated with high adherence to treatment in the clinical practice setting [52, 56]. In CONTROL-3, patient-reported treatment adherence was assessed using the Hill-Bone high BP adherence scale, which assesses three behavioural domains (medication-taking, reduced sodium intake and appointment-keeping), with the total score ranging from 14 (high adherence) to 56 (low adherence) [52]. After 1 and 4 months' PER/IND/AML treatment, total scores were 19.1 and 18.7, respectively. A higher treatment adherence was associated with a greater SBP reduction [52].

In clinical studies, compliance to PER/IND/AML treatment was high (87–98.5% of patients) [33–36] and was significantly ($p < 0.05$) higher than that seen with the free combination of PER + IND + AML (94% vs 85% [34]; 87% vs 61% [33]). Where reported, Morisky Medication Adherence scale scores significantly ($p < 0.05$) increased over 3 months' treatment with the SPC [38, 41].

6 What is the Tolerability of PER/IND/AML?

PER/IND/AML was generally well tolerated in patients with hypertension, with no unexpected safety concerns [14, 34–36, 42–44]. The nature and types of adverse reactions with the combination were generally similar to those with the individual components [14]. The common ($\geq 1/100$ to $< 1/10$ patients) adverse reactions to PER and AML given separately are: dizziness, headache, paraesthesia, somnolence, dysgeusia, visual impairment, diplopia, tinnitus, vertigo, palpitations, flushing, hypotension and associated effects, cough, dyspnoea, gastrointestinal disorders (abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting, change of bowel habit), pruritus, rash, muscle spasms, ankle swelling, asthenia, oedema and fatigue. Apart from potential hypokalaemia, the only common adverse reaction to IND was maculopapular rash. None of the adverse reactions with PER, IND or AML were 'very common' ($\geq 1/10$ patients), with the exception of oedema related to AML [14]. The safety and tolerability profile of PER/IND/AML was generally similar to that of PER/IND [36], PER/IND + AML [35], PER + IND + AML [34] or

a free combination of a RAAS inhibitor, a diuretic and a CCB [42].

In clinical studies, adverse events (AEs) with PER/IND/AML were of mild to moderate severity and the majority were not treatment-related [34–36, 42–44]. The most common treatment-emergent AEs with PER/IND/AML in a representative randomized clinical trial are shown in Fig. 2 [36]. The incidence of treatment-emergent AEs with PER/IND/AML 5/1.25/5 mg, 5/1.25/10 mg, 10/2.5/5 mg and 10/2.5/10 mg was 9.2%, 15.0%, 14.8% and 12.9%, respectively, suggesting the SPC remained tolerable regardless of the dosage [36]. Of note, PER/IND/AML was associated with low incidences of peripheral oedema and cough (expected with AML and PER, respectively) with no evidence for a dose effect for cough [36]. Where reported, these AEs could be managed by temporary dose reduction [34]. AEs leading to discontinuation of PER/IND/AML included oedema, cough, asthenia and dizziness, erectile dysfunction and hypertension [35, 36, 42]. Reduced creatinine clearance [35] and increased serum potassium levels [42] have been reported with PER/IND/AML.

PER/IND/AML was also well tolerated in the clinical practice setting, with no new safety signals [49–52]. The incidence of AEs in clinical practice is lower than typically seen in clinical trials. In PETRA, the largest observational study ($n = 11,209$), the overall incidence of AEs was $\approx 0.5\%$ (65 AEs in 55 patients) [49]. Three of these were serious

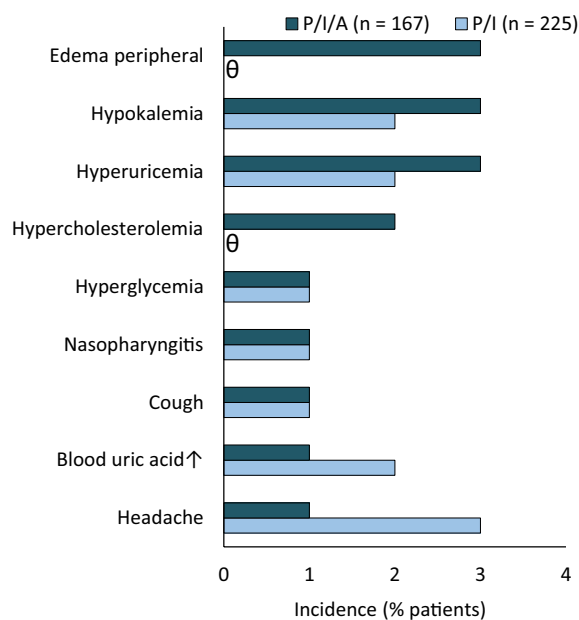


Fig. 2 Treatment-emergent adverse events reported in $\geq 1\%$ of patients in any treatment group in a randomized, double-blind trial in patients with hypertension [36]. θ incidence 0%, \uparrow increased, P perindopril 5 mg, I indapamide 1.25 mg, A amlodipine 10 mg

AEs, none of which were treatment-related. AEs presumed to be related to study treatment by treating physicians occurred in 51 patients: the most common of these were leg oedema (0.07% of patients), unproductive cough (0.04%), tachycardia (0.03%), dizziness (0.03%) and hypotension (0.02%) [49].

7 What is the Current Clinical Position of PER/IND/AML?

PER/IND/AML as a single pill is a valuable and convenient treatment option for essential hypertension. In Europe, it is indicated for patients who have already achieved BP control with the SPC of PER/IND + AML given as two separate pills at the same dose level. The triple SPC offers flexible dosing and may improve compliance in some patients. The antihypertensive efficacy of PER/IND/AML is similar to that of PER/IND + AML in patients with hypertension uncontrolled with one or two drugs. PER/IND/AML reduced BP, leading to a large proportion of patients achieving their target BP levels, in clinical trials and large prospective observational studies in a wide range of patient populations. The therapeutic effect of the SPC is associated with improved HR-QOL.

Ambulatory and home BP measurements have stronger prognostic evidence than office BP measurements because they can identify patients with white coat, masked, morning and night-time hypertension, as well as those with BP variability [4, 57]. Furthermore, central BP is considered a better predictor of cardiovascular events than brachial BP [58]. PER/IND/AML reduces ambulatory, home and ambulatory central BP in patients with hypertension, providing additional support to its efficacy. High BP variability increases the risk of target organ damage and cardiovascular events [57]. PER/IND/AML, with its 24-h duration of action, preserves the physiologic circadian BP pattern by reducing BP variability.

PER/IND/AML is generally well tolerated in patients with hypertension, with tolerability and safety profiles consistent with those expected from the individual components. Cough, a well-known class effect of ACE inhibitors, is less frequent with PER than with other drugs in this class, and it can be mitigated by the addition of a CCB, such as AML [59]. PER reduces AML-induced oedema [60] and it can correct kaliuresis induced by diuretics, such as IND [61]. Consistent with these counterbalancing actions, PER/IND/AML is associated with low incidences of cough and oedema, and these AEs are easily manageable.

The latest European [4, 5] and international [6, 7] treatment guidelines recommend triple therapy with ACEI or ARB + CCB + diuretic for hypertension uncontrolled on single or dual therapy with these agents. This guidance

applies to patients with uncomplicated hypertension, as well as to those with comorbid CAD or chronic kidney disease [4]. Currently, three triple-component SPCs (PER/IND/AML, olmesartan/AML/HCTZ and valsartan/AML/HCTZ) are available in Europe, two of which include ARB (olmesartan and valsartan). ACEI are favoured over ARB in patients with certain comorbidities, such as acute or chronic coronary syndromes, diabetes mellitus or heart failure with reduced ejection fraction [62–65], and thiazide-like diuretics (such as IND and chlorthalidone) are preferred over HCTZ [5, 6, 66]. Thus, PER/IND/AML not only fulfils the guidelines' criteria for triple therapy, but is currently the only triple-component SPC that includes an ACEI (PER) and a thiazide-like diuretic (IND).

Hypertensive patients with comorbid diabetes mellitus and/or metabolic syndrome are at increased risk of cardiovascular diseases; the recommended office SBP/DBP target in these patients is 120–130/< 80 mmHg [4]. PER/IND/AML provides rapid BP control in this population, while also reducing the risk of target organ damage and clinical worsening of their diseases. The SPC has a favourable effect on metabolic parameters. In evidence-based medicine studies, combinations of PER, IND and AML reduced cardiovascular and mortality risks [67]. Taken together, these data indicate that PER/IND/AML is a rational choice that conforms to 2018 ESC/ESH guidelines in patients with diabetes mellitus and/or metabolic syndrome [67].

Poor adherence to treatment is the most important cause of poor BP control and correlates with a higher risk of cardiovascular events [4]. Consequently, treatment guidelines place a strong emphasis on improving adherence by simplifying treatment regimens through the use of single-pill strategy in most patients [4–6]. The use of PER/IND/AML improves adherence in the clinical practice setting. Thus, in patients receiving PER/IND + AML as two pills, switching to single-pill PER/IND/AML simplifies drug administration and may improve adherence, leading to better BP control and clinical outcomes. PER/IND/AML is available in multiple dose strengths, allowing convenient and flexible dosing.

Data on the effect of PER/IND/AML on mortality and morbidity in the long term are still lacking. Data from head-to-head comparisons of PER/IND/AML with other triple-component SPC would also be of interest.

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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