

# Fixed-Dose Triple Combination of Antihypertensive Drugs Improves Blood Pressure Control: From Clinical Trials to Clinical Practice

Alberto Mazza · Salvatore Lenti · Laura Schiavon · Antonella Paola Sacco ·  
Fabio Dell'Avvocata · Gianluca Rigatelli · Emilio Ramazzina

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## ABSTRACT

**Introduction:** Blood pressure (BP) control is the main clinical goal in the management of hypertensive patients; however, BP in most of these patients remains uncontrolled, despite the widespread availability of antihypertensive drugs as free-combination therapy. This study compared the efficacy of a fixed-dose triple combination (FDTC) of antihypertensive drugs with that of a free combination of three antihypertensives in patients with uncontrolled hypertension.

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A. Mazza (✉)  
Hypertension Centre Certified by the Italian Society of Hypertension, S. Maria della Misericordia Hospital, AULSS 5 Polesana, Rovigo, Italy  
e-mail: alberto.mazza@aulss5.veneto.it

S. Lenti  
Hypertension Centre and Internal Medicine and Geriatrics, San Donato Hospital, USL 8, Arezzo, Italy

L. Schiavon · A. P. Sacco · E. Ramazzina  
Department of Medicine, S. Maria della Misericordia Hospital, AULSS 5 Polesana, Rovigo, Italy

F. Dell'Avvocata · G. Rigatelli  
Interventional Cardiology Unit, Division of Cardiology, S. Maria della Misericordia Hospital, AULSS 5 Polesana, Rovigo, Italy

**Methods:** Ninety-two patients (mean age  $60.8 \pm 12.1$ , 58.0% male) with uncontrolled essential hypertension (office systolic BP  $\geq 140$  or diastolic BP  $\geq 90$  mmHg) previously treated with a renin–angiotensin–aldosterone system (RAAS) inhibitor plus hydrochlorothiazide were switched to once-daily FDTC therapy with perindopril/indapamide/amlodipine (5–10/1.25–2.5/5–10 mg). Patients were age- and sex-matched with a control group of hypertensive patients receiving free-combination therapy with three drugs including a RAAS inhibitor, a diuretic, and a calcium channel blocker. Office BP and 24-h ambulatory BP monitoring (ABPM) were evaluated at baseline and after 1 and 4 months.

**Results:** Significant reductions in ambulatory 24-h, daytime, and nighttime systolic BP, and pulse pressure (PP) were found in the FDTC group relative to reductions seen with free-combination therapy, after the first month only of follow-up. Target BP values (mean 24-h ambulatory systolic/diastolic BP  $< 130/80$  mmHg) were reached by more recipients of FDTC than free-combination therapy (64.8% vs. 46.9%,  $p < 0.05$ ) at month 4 of follow-up, despite reductions in 24-h ABPM values from baseline being similar in both groups at this time point.

**Conclusion:** FDTC of perindopril/indapamide/amlodipine was effective at reducing SBP and PP in previously treated patients with uncontrolled hypertension, and well tolerated, providing support for clinicians in choosing a fixed-dose

triple combination over the free-combination of a RAAS inhibitor, a diuretic, and a calcium antagonist.

**Keywords:** Amlodipine; Antihypertensives; Hypertension; Indapamide; Perindopril; Target blood pressure; Triple fixed-dose combination

## INTRODUCTION

Despite the widespread availability of effective antihypertensive drugs, in the majority of hypertensive patients blood pressure remains uncontrolled and, in most countries, at least 50% of hypertensive patients do not achieve currently recommended blood pressure targets [1]. In this respect, clinical trials have shown that adequate blood pressure control is possible with combinations of up to four antihypertensive drugs [2–4]. American and European guidelines for the treatment of hypertension suggest [5, 6], as initial therapy, the option of a combination of two antihypertensive drugs to achieve better control and, if hypertension remains uncontrolled, the addition of a third antihypertensive drug is recommended [5].

In addition to the potential benefits of combining different drug classes owing to their possible synergistic pharmacological and physiological actions, this approach—in particular if provided at fixed doses in a single pill—also improves patient compliance to treatment [7, 8]. This strategy seems more effective than the separate administration of two or more antihypertensive agents (free-drug combination), not only in blood pressure control but also in promoting decreased cardiovascular events [9], hospitalization rates [10], and costs [11]. Although many studies have been performed comparing fixed-dose combinations with single agents [10, 12], data comparing fixed-dose and free-drug combinations are limited.

In this study, the efficacy and safety of a fixed-dose triple combination (FDTC) of antihypertensive drugs given as a single pill were compared with the use of free-drug combinations in the treatment of hypertension.

## METHODS

The aim of the study was to evaluate the efficacy and tolerability of the FDTC vs. free-combination therapy in lowering office and 24-h BP values.

### Patients

This interventional study included grade 2 (defined as SBP 160–179 mmHg and/or DBP 100–109 mmHg) hypertensive patients with uncontrolled hypertension despite previously receiving dual fixed-combination antihypertensive therapy including a renin–angiotensin–aldosterone system (RAAS) inhibitor plus a diuretic.

Exclusion criteria were a history of cardiovascular events, severe hypertension (office SBP  $\geq$  180 mmHg or DBP  $\geq$  110 mmHg), secondary hypertension, neoplastic or hepatic diseases, chronic heart or renal failure, positive history or clinical signs of ischemic heart disease, severe obesity (body weight  $>$ 150% of the ideal), disabling diseases such as dementia or inability to cooperate, pregnancy, or breast-feeding.

The study protocol was approved by local ethics committee and institutional review boards, and procedures were followed in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study. Patients could discontinue the study at any time and for any reason, and treatment was stopped if a serious adverse event occurred.

### Study Design

Consecutive patients were initially screened for inclusion criteria and patients still meeting criteria after a 4-week run-in period were enrolled in the FDTC treatment group and received perindopril/indapamide/amlodipine at doses ranging from 5/1.25/5 to 10/2.5/10 mg once daily in the morning for 4 months. An age- and sex-matched control group of hypertensive patients was screened and enrolled to receive a

free-combination of three antihypertensive agents including a RAAS blocker, a diuretic, and a calcium channel blocker. Study drug dosages in both arms were determined according to baseline arterial BP. The pressor target was defined as office-assessed SBP/DBP <140/90 mmHg, and an ambulatory blood pressure monitoring (ABPM)-assessed SBP/DBP <130/80 mmHg.

### Data Collection

Office and 24-h blood pressure values were evaluated at baseline and at month 1 and 4 of follow-up. Office blood pressure (diastolic Korotkoff phase 5) was measured in triplicate in the prone position using a mercury sphygmomanometer at 10-min intervals, taking care to avoid any terminal digit preference [6], and the average of the last two clinostatic measurements was recorded as the blood pressure. Heart rate was also taken at the same time. Pulse pressure was the difference between SBP and DBP. Arterial hypertension was defined as SBP  $\geq$  140 mmHg or DBP  $\geq$  90 mmHg. In all patients, clinic hypertension was confirmed with 24-h ABPM using an oscillometric device (TM-2430, Takeda, Japan) applied to the non-dominant arm [13].

Body mass index (BMI) was calculated as the ratio of weight (in kilograms) to squared height (in meters). Patients were classified as never or current ( $\geq$ 1 cigarette daily) smokers. Laboratory parameter monitoring included serum potassium and creatinine levels. Fasting serum creatinine (in mg/dl) was measured by Jaffé's alkaline picrate kinetic method [14] using an autoanalyzer (Hitachi Modular P, Roche diagnostic, USA).

Adherence to medication was measured indirectly through patient self-reports and pill counts.

### Statistical Analyses

Continuous variables were expressed as mean and standard deviation, and compared with analysis of variance and Bonferroni's post hoc test. The Chi-square test was used for comparisons between categorical variables. Analysis of variance for repeated measures compared changes of different blood pressure components

and serum lipids at baseline and at follow-up visits; differences between continuous variables were evaluated in the two groups with Tukey's post hoc test. All statistical analyses were performed using the SPSS package version 17.0 for Windows (SPSS, Chicago, IL, USA). The null hypothesis was always rejected for  $p < 0.05$ .

## RESULTS

Ninety-two patients (54 men and 38 women, mean age  $60.8 \pm 12.1$  years), age- and sex-matched by the case-to-case method with a control group of 92 patients, were evaluated. Consecutive patients had been screened and eligible patients enrolled between October 2015 and June 2016 in our Hypertension Centre of the Rovigo General Hospital. The general characteristics of the two treatment groups at baseline are summarized in Table 1. Mean age was  $60.8 \pm 12.1$  years in the whole study group ( $59.4 \pm 11.5$  in men and  $63.8 \pm 13.9$  in women,  $p < 0.001$ ). Mean  $\pm$  SD office BP at baseline was similar between study arms (DBP  $153.2 \pm 11.8$  vs.  $154.6 \pm 13.0$  mmHg; SBP  $95.1 \pm 5.3$  vs.  $94.0 \pm 6.7$  mmHg in the fixed vs free combination groups, respectively).

### Intervention

The antihypertensive potency of antihypertensive therapy administered was based on office BP at baseline. The distribution of dosages in the group receiving a fixed combination of perindopril/indapamide/amlodipine (in increasing order of potency) was 5/1.25/5 mg in 42.4% of patients, 5/1.25/10 mg in 2.2%, 10.2.5/5 mg in 25%, and 10/2.5/10 mg in 30.4%. The distribution of antihypertensive potency was comparable in the free-combination group.

In the free-combination group, RAAS inhibition was accomplished with angiotensin-converting enzyme inhibitors (ACEIs) in 65% of patients (of which, ramipril 40%, perindopril 30%, enalapril 25%, others 5%); whereas angiotensin II receptor blockers (ARBs) were used in 35% (of which, valsartan 35%, olmesartan 25%, telmisartan 20%, losartan 15%, others 5%); diuretics were hydrochlorothiazide 75% or indapamide 25%.

**Table 1** General characteristics of the study population at baseline

	All patients ( <i>n</i> = 184)	FDTC ( <i>n</i> = 92)	FCT ( <i>n</i> = 92)	<i>p</i> value
Age, years	60.8 ± 12.1	61.4 ± 11.8	60.1 ± 12.5	NS
Male, %	58.0	56.8	65.0	NS
Body mass index, kg/m <sup>2</sup>	28.5 ± 4.9	28.1 ± 4.7	28.9 ± 5.1	NS
Clinic BP values				
SBP, mmHg	153.7 ± 12.6	153.2 ± 11.8	154.6 ± 13.0	NS
DBP, mmHg	94.5 ± 6.0	95.1 ± 5.3	94.0 ± 6.7	NS
PP, mmHg	59.2 ± 11.2	58.1 ± 10.3	60.6 ± 12.1	NS
24-h ABPM values				
24-h SBP, mmHg	144.2 ± 9.7	144.8 ± 8.9	143.6 ± 10.8	NS
24-h DBP, mmHg	86.0 ± 6.9	85.3 ± 7.2	86.8 ± 6.5	NS
24-h PP, mmHg	58.1 ± 7.6	59.5 ± 7.2	56.8 ± 8.1	NS
Daytime SBP, mmHg	147.5 ± 9.8	147.2 ± 9.1	148.0 ± 10.9	NS
Daytime DBP, mmHg	91.7 ± 6.3	92.4 ± 5.5	90.1 ± 7.1	NS
Daytime PP, mmHg	55.8 ± 7.4	54.8 ± 7.9	57.8 ± 8.3	NS
Nighttime SBP, mmHg	129.6 ± 10.0	128.9 ± 9.3	130.5 ± 10.5	NS
Nighttime DBP, mmHg	77.0 ± 6.8	77.6 ± 7.3	76.4 ± 6.1	NS
Nighttime PP, mmHg	52.6 ± 6.3	51.3 ± 5.9	54.1 ± 7.2	NS
TC, mg/dl	198.1 ± 23.6	200.2 ± 18.3	196.8 ± 29.3	NS
LDL-C, mg/dl	123.5 ± 23.6	124.3 ± 21.2	122.8 ± 26.9	NS
HDL-C, mg/dl	52.9 ± 13.0	51.4 ± 12.7	53.3 ± 13.8	NS
Triglycerides, mg/dl	101.4 ± 40.2	99.7 ± 33.5	103.4 ± 46.8	NS
Glucose, mg/dl	99.7 ± 11.3	98.4 ± 8.3	100.8 ± 14.4	NS
Creatinine, mg/dl	1.0 ± 0.2	1.1 ± 0.1	1.0 ± 0.3	NS
Potassium, mg/dl	4.28 ± 0.27	4.17 ± 0.31	4.36 ± 0.22	NS
Diabetes, %	11.9	10.2	13.6	NS
Smokers, %	19.8	17.0	20.1	NS

Values are presented as patient numbers and percentages or means ± standard deviations

*ABPM* ambulatory blood pressure monitoring, *DBP* diastolic blood pressure, *HDL-C* high density lipoprotein, *FCT* free-combination, *FDTC* fixed-dose triple combination, *LDL-C* low density lipoprotein cholesterol, *NS* not significant, *PP* pulse pressure, *SBP* systolic blood pressure, *TC* total cholesterol

In both treatment groups, significant reductions in ABPM values were observed at month 4 of follow-up, relative to baseline (Tables 2, 3). At the first month of follow-up, significant

reductions from baseline in ambulatory 24-h, daytime, and nighttime SBP were found in the FDTC group (11.6, 16, and 11.4 mmHg, respectively) relative to reductions seen with

**Table 2** Differences for office and ambulatory values in the group treated with fixed-dose triple combination antihypertensive therapy

	Baseline (n = 92)	1st month (n = 92)	4th month (n = 89)	F	p value for trend
Office values					
SBP, mmHg	154.6 ± 13.0	139.3 ± 8.1	132.2 ± 5.1	137.0	0.0001
DBP, mmHg	94.0 ± 7.0	84.5 ± 6.7	82.9 ± 4.8	139.9	0.0001
PP, mmHg	60.6 ± 12.1	54.8 ± 7.3	50.3 ± 5.6	30.7	0.0001
HR, bpm	74.3 ± 6.9	73.3 ± 5.9	74.2 ± 4.5	1.0	0.413
ABPM values					
24-h SBP, mmHg	143.6 ± 10.8	132.0 ± 8.1	125.5 ± 5.6	82.9	0.001
24-h DBP, mmHg	86.8 ± 6.5	79.8 ± 4.6	77.9 ± 3.9	57.8	0.0001
24-h PP, mmHg	56.8 ± 8.1	52.2 ± 6.7	50.6 ± 3.4	25.2	0.001
24-h HR, bpm	72.7 ± 6.6	72.9 ± 6.3	73.2 ± 4.5	1.4	0.748
Daytime SBP, mmHg	148.0 ± 10.9	132.0 ± 8.1	128.5 ± 3.6	128.9	0.0001
Daytime DBP, mmHg	90.1 ± 7.1	83.1 ± 4.9	78.0 ± 3.9	110.1	0.0001
Daytime PP, mmHg	57.8 ± 8.3	52.2 ± 6.7	50.6 ± 3.4	33.5	0.0001
Daytime HR, bpm	75.1 ± 6.7	72.9 ± 6.3	73.2 ± 4.6	6.9	0.392
Nighttime SBP, mmHg	130.5 ± 10.5	119.1 ± 7.7	116.1 ± 4.0	78.7	0.0001
Nighttime DBP, mmHg	76.4 ± 6.1	69.3 ± 4.9	66.1 ± 3.8	94.9	0.0001
Nighttime PP, mmHg	54.1 ± 7.2	50.0 ± 5.9	50.3 ± 3.6	13.9	0.0001
Nighttime HR, bpm	67.0 ± 6.6	66.5 ± 5.4	68 ± 3.9	3.1	0.055

Values are presented as means ± standard deviations

ABPM ambulatory blood pressure monitoring, DBP diastolic blood pressure, HR heart rate, PP pulse pressure, SBP systolic blood pressure

free-combination therapy (6.9, 5.5, and 4.8 mmHg;  $p < 0.0001$ ) (Fig. 1). Reductions from baseline in ambulatory 24-h, daytime, and nighttime pulse pressures were also significantly greater with FDTC therapy (Fig. 1). However, at month 4 of follow-up, there were no significant differences in reductions from baseline between the two groups. The change from baseline in ABPM-assessed DBP was not significantly different between groups during the entire follow-up period (Fig. 1).

Both office and ABPM-assessed heart rate values were essentially unchanged.

Office SBP/DBP significantly was reduced from baseline to month 4 in both groups, but

between-group values were similar (by 22.4/11.1 mmHg at month 4 in the FDTC group and by 18.9/11.7 mmHg in the free-combination group, both  $p < 0.0001$  for trend).

At the end of the first month, target office blood pressure was reached by 70.5% of patients on FDTC and by 66.4% of those on free-combination therapy ( $p = 0.21$ ), and at the end of the fourth month by 75.6% and 71.2%, respectively ( $p < 0.34$ ). When target 24-h ABPM was evaluated, the response rate to the treatment was significantly higher in the FDTC than the free-combination therapy group, both at month 1 (45.3% vs. 32.8%,  $p < 0.05$ ) and at

**Table 3** Differences for office and ambulatory values in the group treated with a free combination of three antihypertensives

	Baseline ( <i>n</i> = 92)	1st month ( <i>n</i> = 92)	4th month ( <i>n</i> = 90)	<i>F</i>	<i>p</i> value by trend
Office values					
SBP, mmHg	153.2 ± 11.8	140.1 ± 7.3	134.3 ± 4.1	126.0	0.0001
DBP, mmHg	95.1 ± 5.3	85.4 ± 8.3	83.4 ± 5.6	132.4	0.0001
PP, mmHg	58.1 ± 10.3	56.7 ± 6.1	50.9 ± 4.8	27.2	0.0001
HR, bpm	73.4 ± 8.1	74.8 ± 7.3	75.2 ± 5.3	4.2	0.523
ABPM values					
24-h SBP, mmHg	144.8 ± 8.9	137.9 ± 7.5	127.3 ± 6.4	93.2	0.001
24-h DBP, mmHg	85.3 ± 7.2	81.8 ± 6.3	78.6 ± 4.8	78.6	0.0001
24-h PP, mmHg	59.5 ± 7.2	56.1 ± 6.7	48.7 ± 5.1	53.2	0.001
24-h HR, bpm	78.9 ± 8.2	80.1 ± 6.9	79.6 ± 5.7	3.6	0.416
Daytime SBP, mmHg	147.2 ± 9.1	141.7 ± 5.9	130.0 ± 4.8	132.4	0.0001
Daytime DBP, mmHg	92.4 ± 5.5	85.8 ± 5.7	81.2 ± 5.7	116.8	0.0001
Daytime PP, mmHg	54.8 ± 7.9	55.9 ± 7.4	48.8 ± 4.1	41.6	0.0001
Daytime HR, bpm	82.3 ± 6.8	79.4 ± 5.6	80.6 ± 6.2	11.2	0.228
Nighttime SBP, mmHg	128.9 ± 9.3	124.1 ± 8.2	118.2 ± 7.4	64.5	0.0001
Nighttime DBP, mmHg	77.6 ± 7.3	70.4 ± 6.1	69.1 ± 8.2	87.2	0.0001
Nighttime PP, mmHg	51.3 ± 5.9	53.7 ± 3.6	49.1 ± 4.3	15.4	0.0001
Nighttime HR, bpm	70.2 ± 7.8	69.7 ± 6.2	71.6 ± 5.7	8.9	0.356

Values are presented as means ± standard deviations

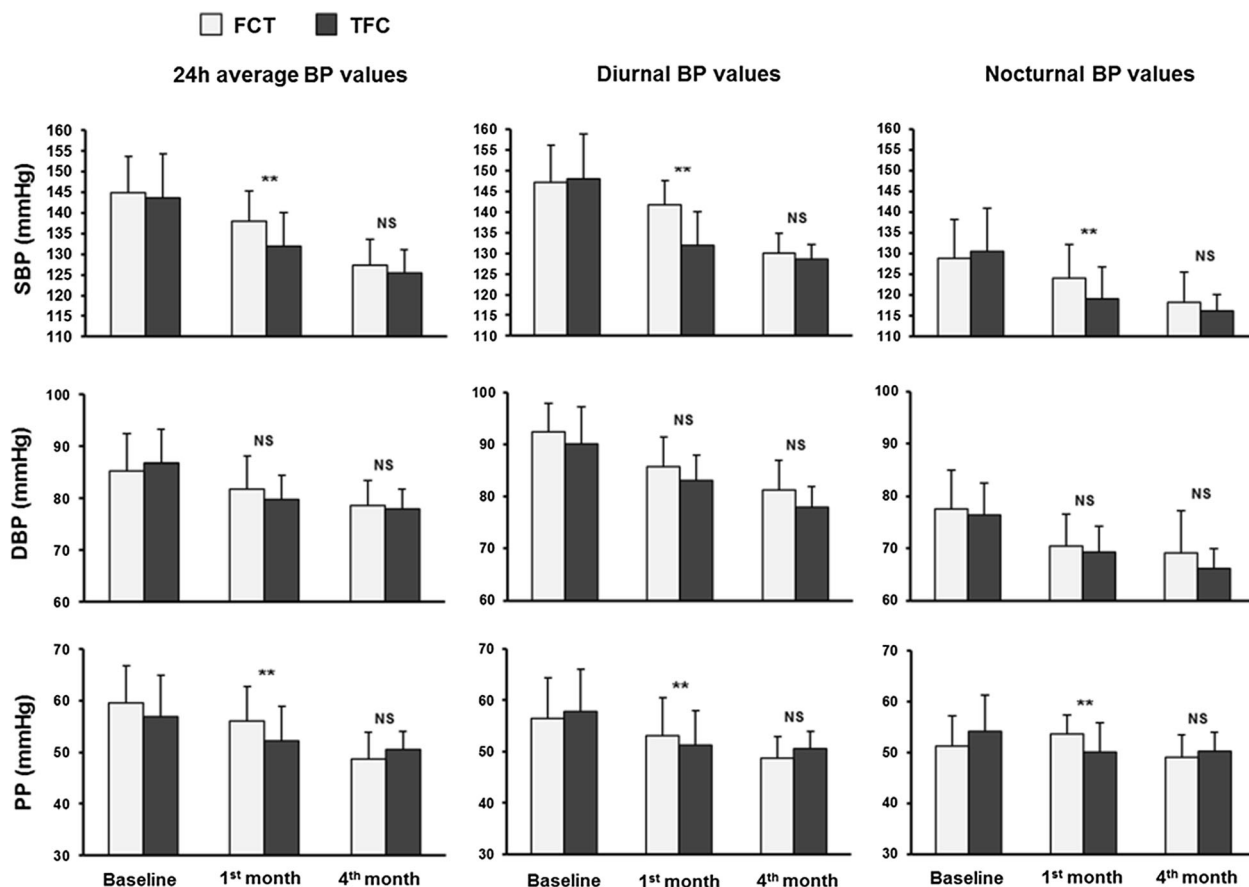
ABPM ambulatory blood pressure monitoring, DBP diastolic blood pressure, HR heart rate, PP pulse pressure, SBP systolic blood pressure

month 4 of follow-up (64.8% vs. 46.9%,  $p < 0.05$ ).

Mean changes in serum potassium values from baseline to month 4 of follow-up were greater in the FDTC group (from  $4.36 \pm 0.22$  vs.  $3.97 \pm 0.26$  [month 1] to  $3.89 \pm 0.21$  mg/dl [month 4],  $p < 0.001$ ) than in the free-combination group (from  $4.17 \pm 0.31$  vs.  $4.26 \pm 0.28$  to  $4.10 \pm 0.19$  mg/dl, non-significant difference). Three patients in the FDTC group discontinued the study (two for ankle edema and one for cough) as did two patients in the free-combination group (one for hypotension and one for dizziness).

## DISCUSSION

In our study, performed in patients with moderate hypertension who did not achieve blood pressure targets using dual fixed-combination therapy with a RAAS blocker and a diuretic, a significant improvement in blood pressure lowering and control was observed after switching to an FDTC therapy with perindopril/indapamide/amlodipine at doses ranging from 5/1.25/5 to 10/2.5/10 mg once daily. FDTC therapy was more effective than free-combination therapy in reducing blood pressure values after the first month of treatment. In addition,



**Fig. 1** Changes in 24-h ambulatory systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) with free-combination therapy (FCT) and fixed-dose triple combination (FDTC) therapy; NS not significant,

\*\* $p < 0.05$  vs. FCT; all values at 1st and 4th month are statistically significant vs. baseline ( $p < 0.05$ ). Values are presented as means

greater efficacy with FDTC therapy relative to free-combination therapy in reaching the presor target was maintained over the entire follow-up period. These effects were well tolerated.

The consistent reduction in ABPM values observed in our study has strong clinical implications, as ABPM has been shown to be a strong predictor of cardiovascular morbidity and mortality [15, 16]. Furthermore, 24-h ABPM is the most accurate means of assessing the effectiveness of antihypertensive therapy [17] and characterizes blood pressure during the night and in the early hours of the morning, when there is an increased likelihood of cardiovascular and cerebrovascular events occurring [6].

The more interesting result of our study is the effect of FDTC therapy in reducing 24-h

ABPM pulse pressure and nighttime blood pressure. The increase of pulse pressure (the pulsatile component of blood pressure) is an age-related phenomenon and the common belief is that it is an indicator of large artery stiffness [18] and an established marker of cardiovascular risk in different clinical settings [19, 20]. High pulse pressure may derive both from a rise in systolic values and from a decrease in diastolic values. In our study, the systolic component was prominent, as diastolic blood pressure remained unchanged or even increased slightly with increasing pulse pressure.

Nocturnal hypertension is a common complication of essential hypertension and well known to be associated with a worse cardiovascular risk and prognosis [21, 22]. Nocturnal

hypertension can be treated with several approaches that include lifestyle changes—such as sodium restriction and potassium supplementation—and pharmacotherapy, primarily through the use of bedtime dosing of antihypertensive agents [23]. In our study, a drop in nighttime blood pressure values was found during FDTC treatment without any evening administration of drugs, suggesting that the drugs tested in this formulation had a long half-life and an antihypertensive effect sustained during the 24 h. Efficacy of the various classes of antihypertensive agents for restoring normal dipping is not well studied. However, the RAAS blockers, the calcium antagonists, and diuretics appear to be superior to  $\alpha$ - and  $\beta$ -blockers [24, 25]. In elderly hypertensives with systolic hypertension, dihydropyridines and thiazide diuretics lowered daytime blood pressure to a greater extent than  $\beta$ -blocking drugs; perindopril had the greatest effect on nocturnal blood pressure, whereas atenolol did not show any effect [26]. However, the role of different classes of antihypertensive drugs should be assessed more in detail in clinical trials, as some drugs may accentuate nocturnal dipping, others may blunt the normal nocturnal decrease in blood pressure, and others have no effect [27].

The European hypertension guidelines recommend combining blood pressure-lowering drugs [6], particularly using fixed-drug combinations in a single pill. This suggestion may offer several advantages over free-drug combinations, e.g., better compliance and an increased adherence to the prescribed regimen [28]. This leads to an increased lowering effect and to a more rapid achievement of the target [29], which has been shown to correlate with improvement in clinical outcome and with decreased incidence of cardiovascular morbidity and mortality [30]. On the other hand, beyond the therapeutic class effects, the specific properties of perindopril, indapamide, and amlodipine suggest additional blood pressure-lowering effects relative to other antihypertensive drugs [31, 32]. The combination of perindopril plus indapamide has been shown to improve vascular endothelial function, arterial stiffness, and small artery remodelling [33],

thereby reducing pressor wave reflections during systole [34].

Furthermore—unlike other ACEIs such as enalapril in the PICXEL study [35] or ARBs—perindopril plus indapamide sustained release in the HYVET trial [36], perindopril in fixed combination with indapamide in the ADVANCE trial [34], and a combination of perindopril and amlodipine in the blood pressure-lowering arm of the ASCOT trial [37] have all shown additional and significant mortality benefits. However, long-term studies are mandatory to confirm that predicted improvements in organ protection and reduced mortality rates can be extended to the FDTC tested in our study.

A possible criticism of our results may result from the lack of a between-group difference in blood pressure-lowering effects after 4 months of treatment. This lack of effect is not surprising, as the drugs tested in the free-combination therapy group had a wide and proven efficacy in lowering blood pressure over the long term [6]. On the other hand, the greater blood pressure-lowering effect of FDTC relative to free-combination therapy observed in the short term may in part be due to the different diuretic used in the two groups. In fact, slow-release indapamide (used in our study in 75% of hypertensive patients in the FDTC therapy group) seems to have a greater antihypertensive potency than hydrochlorothiazide. As demonstrated in a recent systematic review and meta-analysis of head-to-head comparison studies, which included additional analyses [38], at commonly used doses indapamide lowers SBP more than hydrochlorothiazide, without any evidence of increased metabolic adverse effects, and with no significant effects on serum potassium. In general, thiazide diuretics lower BP via decreased peripheral arterial resistance through unknown mechanisms [5, 6], while indapamide is known to have a direct vasodilator effect from vasopressor inhibition and decreased inward flow of calcium ions in vascular smooth muscle [39]. Finally, we speculate that the better lowering effect of FDTC therapy may be due to a potentially synergistic antihypertensive effect of the included drugs in optimal combination, leading to an effect greater than the usual additive one [40].



## Study Limitations

Our study was monocentric, not blinded, and limited by its short treatment period and relatively small-sized treatment groups. Tolerability findings suggest that clinicians could adopt this new means of improving hypertension management. However, a large-scale study may be needed to determine long-term safety and clinical outcomes of triple fixed-combination over free-combination therapy.

## CONCLUSION

Our study results show the fixed-dose triple combination therapy of perindopril/indapamide/amlodipine was effective in reducing systolic and pulse pressure in patients with moderate hypertension uncontrolled by dual fixed-combination therapy. No major concern with FDTC tolerability emerged in this study. Our findings provide support for clinicians in choosing a fixed-dose triple combination over a free-combination of three antihypertensives including a RAAS inhibitor, a diuretic, and a calcium channel blocker.

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**Compliance with Ethics Guidelines.** The study protocol was approved by local ethics committee and institutional review boards, and procedures were followed in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in this study.

**Data Availability.** The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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