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Efficacy and Safety of the Fixed Combination of Amlodipine and Valsartan in the Treatment of Arterial Hypertension and Obesity

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ABSTRACT

Objective: This study aimed to investigate the efficacy and safety of the fixed combination of amlodipine/valsartan in patients with mild to moderate arterial hypertension (AH) and obesity during long-term treatment.
Materials and Methods: According to the protocol, 40 patients with grade I-II arterial hypertension and obesity were included in the study. All patients received a domestic combined medication Valun ("Novugen pharma," Uzbekistan) containing amlodipine 5mg and valsartan 80mg. Office blood pressure (BP) and ambulatory blood pressure monitoring (ABPM) were measured at baseline and after 12 weeks of therapy. The clinical tolerability and metabolic effects of the medication were also evaluated.
Results: The 12-week therapy with the fixed combination of amlodipine and valsartan demonstrated high antihypertensive efficacy, with a 17% reduction in mean BP and achievement of the target BP level in 100% of patients with mild to moderate AH. ABPM data showed a significant reduction in average 24-hour and daytime systolic and diastolic BP values. The combined therapy with amlodipine and valsartan also exhibited nephroprotective effects, manifested by a significant decrease in blood creatinine level, an increase in glomerular filtration rate, and a reduction in microalbuminuria levels. Amlodipine and valsartan in the combined regimen showed metabolic neutrality concerning lipid and carbohydrate metabolism and clinical safety.
Conclusion: Our study demonstrated the high antihypertensive efficacy of the fixed combination of amlodipine and valsartan, along with significant cardio- and nephroprotection, metabolic neutrality, and clinical safety, recommending this medication for the treatment of patients with mild to moderate arterial hypertension.

INTRODUCTION

One of the serious healthcare problems worldwide is the relentless increase in obesity and associated diseases. The most common cardiovascular complications of obesity include arterial hypertension (AH), ischemic heart disease (IHD), chronic heart failure, arrhythmia, pulmonary hypertension, ischemic stroke, venous stasis, deep vein thrombosis, and pulmonary embolism. AH occupies a leading position among modifiable risk factors for cardiovascular diseases and their complications in most countries. The increasing prevalence of obesity is a significant contributing factor to elevated blood pressure (BP) in individuals. Studies show that AH is less well-controlled in individuals with obesity.
According to modern clinical recommendations [1], the guidelines of the European Society of Hypertension (ESH), and the European Society of Cardiology (ESC) [2], the treatment strategy for essential AH depends on BP levels and the degree of cardiovascular risk. The main goal of treatment is the maximum reduction of the risk of cardiovascular complications (CVC) and death from them [3]. The main tasks are the normalization of BP levels to prevent complications, with a minimal occurrence of adverse drug reactions (ADR), the correction of all modifiable risk

factors (smoking, dyslipidemia, hyperglycemia, obesity), prevention, slowing the progression, and/or reducing organ damage, as well as the treatment of associated and comorbid conditions - IHD, diabetes mellitus (DM), etc.

One of the essential conditions for adequate BP control and increased patient adherence to treatment is the optimal selection of antihypertensive agents in mono- or combined pharmacotherapy. According to European recommendations for the diagnosis and treatment of AH [2], most patients, excluding those with grade 1 AH and low cardiovascular risk, are indicated for two-drug therapy using a fixed combination of an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) with a calcium antagonist (CA) or diuretic.

The Renin-Angiotensin-Aldosterone System (RAAS) plays a pivotal role both in the development of arterial hypertension (AH) and in the pathophysiological processes that ultimately lead to severe cardiovascular complications, such as stroke, myocardial infarction, vascular remodeling, nephropathy, congestive heart failure, and atherosclerotic processes. Currently, it is believed that chronic RAAS stimulation leads to the activation of growth factors and fibrosis at the tissue level, which underlies the development of pathological processes in target organs. Consequently, the blockade of the tissue component of the RAAS appears promising for achieving organ protective effects in antihypertensive therapy. The choice of a specific angiotensin II receptor antagonist (ARB) for the long-term treatment of patients with AH holds clinical significance, as these medications are prescribed lifelong.

Both ARBs and calcium antagonists (CAs) reduce blood pressure (BP) through vasodilation and exhibit natriuretic effects. However, the mechanisms underlying the antihypertensive actions of ARBs and CAs are fundamentally different. The vasodilatory effect of CAs is achieved by blocking the entry of calcium ions into the cell [4], while ARBs act through the renin-angiotensin-aldosterone system (RAAS) pathway [5]. This leads to a potentiation of the antihypertensive effects when these drug classes are used in combination for patients with AH. Such a combination is effective in high- and low-renin forms of AH, as well as in patients with obesity. The co-administration of ARBs and CAs helps neutralize the activation of counter-regulatory mechanisms, which may otherwise reduce the antihypertensive efficacy of these medications.

At present, the most realistic approach to improving antihypertensive therapy for AH lies in optimizing the use of existing fixed combinations of antihypertensive drugs. Among these combinations, the combination of RAAS blockers and long-acting calcium antagonists, specifically the fixed combination of valsartan and amlodipine, is considered a priority [5]. The pharmacokinetic profiles of this combination remain unchanged, allowing for once-daily administration. Undoubtedly, this enhances patient adherence to treatment by reducing the number of drugs taken, the frequency of administration, and also reduces the risk of adverse effects.

The EX-EFFeCTS study investigated the effectiveness of the combination of amlodipine and valsartan (Exforge) compared to amlodipine alone in patients with stage 2 arterial hypertension (AH) [6]. This multicenter, randomized, double-blind study lasted for 8 weeks and involved 646 patients with stage 2 AH (mean sitting systolic blood pressure [MSSBP] ≥160 mmHg). During the first 2 weeks, the patients were administered either amlodipine 5 mg + valsartan 160 mg or amlodipine 5 mg monotherapy. Over the following 6 weeks, the dosage was increased to either amlodipine 10 mg + valsartan 160 mg or amlodipine 10 mg monotherapy, as appropriate. If the MSSBP was still ≥130 mmHg after 4 weeks of treatment, hydrochlorothiazide was added. After 4 weeks of treatment, the reduction in MSSBP in the Exforge group was significantly greater compared to the amlodipine monotherapy group (30.1 mmHg and 23.5 mmHg, respectively; $p<0.0001$). Moreover, among patients with an initial MSSBP ≥180 mmHg, the reduction was also more pronounced in the combination therapy group compared to the monotherapy group (40.1 mmHg and 31.7 mmHg, respectively; $p=0.0018$). Differences in the effectiveness of blood pressure control also favored the combination of amlodipine + valsartan. Based on these results, the authors conclude that combining amlodipine and valsartan, which act through complementary mechanisms, is justified in the treatment of patients with stage 2 AH.

Similar findings were reported in the study conducted by Sawada T. et al. [7]. The KYOTO Heart Study, which was completed in 2009 in Japan, involved patients with uncontrolled hypertension (BP >140/90 mmHg) and a high risk of cardiovascular complications. Patients who were on any prior antihypertensive therapy, except ARBs, were included in the study and were randomized to receive either additional valsartan or intensified current therapy without ARBs. The study was prematurely terminated after 3.27 years of follow-up due to significant advantages in favor of valsartan. The reduction in the risk of fatal and non-fatal cardiovascular complications in the group receiving added valsartan was 45% ($p<0.00001$). This reduction was particularly evident in the risk of stroke (45%, $p=0.0149$) and hospitalizations due to angina (49%, $p=0.0106$). Although the study design intended to compare valsartan with all other classes of antihypertensive drugs, except ARBs, the baseline therapy was not discontinued; either valsartan was added or the doses of the initial drugs were increased, and other agents (excluding ACE inhibitors and ARBs) were added to achieve similar blood pressure control in both groups. Interestingly, 54% of patients in the valsartan group and 55% in the non-ARB therapy group were initially receiving calcium antagonists. Therefore, half of the patients in the valsartan group were receiving a combination of calcium antagonists/valsartan. The significant reduction in cardiovascular complications risk in the group receiving added valsartan demonstrates additional benefits of ARBs in improving the prognosis of patients with AH.

The study aimed to investigate the effectiveness and safety of the fixed combination of amlodipine/valsartan in patients with mild to moderate hypertension and obesity during long-term treatment.

Materials and Methods: A simple, non-randomized, prospective study included 40 patients with grade I-II hypertension and obesity, aged 35 to 65 years, of both genders, without severe concomitant diseases and cardiovascular complications (acute myocardial infarction, acute cerebrovascular disorders, heart arrhythmias). Exclusion criteria also included a history of diabetes mellitus and severe renal and hepatic insufficiency. Hypertension was diagnosed based on office blood pressure measurements (≥140/90 mmHg). Obesity was diagnosed if BMI was >30 kg/m². The majority of patients (45%) were on combination antihypertensive therapy before the study, 22.5% were on monotherapy, and 32.5% were not taking any antihypertensive medications.

All patients were prescribed the medication "Valun" (Novugen Pharma, Uzbekistan), with a fixed combination of amlodipine 5 mg/valsartan 80 mg once daily (after a one-week washout period of previous antihypertensive therapy for patients who did not achieve target blood pressure levels). Informed consent for voluntary participation in the study was obtained from all patients.

The effectiveness and safety of the treatment were evaluated over 12 weeks of therapy. The effectiveness of treatment was assessed based on the extent of blood pressure reduction, data from ambulatory blood pressure monitoring (ABPM), absence of morning blood pressure surge, achievement of target blood pressure levels, and blood pressure variability. The safety of the therapy was determined based on changes in sodium, potassium, glucose, cholesterol, triglycerides, urea, and creatinine levels, and the absence of undesirable side effects.

Table 1 presents the general characteristics of the included patients

Table 1. General characteristics of the patients included in the study.

Indicator	Group of patients receiving the fixed combination of amlodipine/valsartan (n=40)
Age (years)	46,4±7,2
Gender	Female: 23 (57,5%) Male: 17 (42,5%)
WT (sm)	Female: 143,1±11,8 Male: 111,5±10,9
Hypertension Grade, n (%)	1 ст— 19 (47,5%) 2ст — 21 (52,5%)
Office SAD (mmHg.)	155,4±9,9
Office DAD (mmHg.)	101,3±9,5
Dyslipidemia, n (%)	35 (87,5%)
Mean BMI (kg/m²)	32,5±3,6
Glucose (mmol/L)	4,6±0,8
Total Cholesterol (mmol/)	6,1±0,9
LDL (mmol/l)	3,92±1,29
HDL (mmol/l)	0,89±0,47
Triglycerides (mmol/l)	2,9±0,7
Microalbuminuria, n, (%)	13 (32,5%)
Urea (mmol/l)	6,5±2,7
Creatinine (μmol/l)	95,31±10,09
Sodium (mmol/l)	139,65±3,12
Potassium (mmol/l)	4,3±0,4
Uric acid (μmol/l)	298±66,8
eGFR (ml/min/1,73 m2)	77,18±15,97

Abbreviations: WT - waist circumference, SBP - systolic blood pressure, DBP - diastolic blood pressure, BMI - body mass index, LDL - low-density lipoprotein, HDL - high-density lipoprotein, eGFR - estimated glomerular filtration rate.

All patients underwent comprehensive clinical, instrumental, and laboratory examinations at the study inclusion and after 3 months of therapy. This included a general physical examination with anthropometric measurements, office blood pressure measurement, and ABPM. During each visit, blood pressure, heart rate, and prescribed antihypertensive and concomitant therapies were recorded, along with any changes during the study. The presence and degree of edema were also evaluated during each visit.

Office blood pressure measurements were performed at the study inclusion and after 1 and 3 months of therapy following a 10-minute rest in a seated position using an Omron M2 automatic sphygmomanometer. Between visits, patients performed self-monitoring of blood pressure twice daily (morning and evening) using an automatic sphygmomanometer, and the average value between the 2nd and 3rd measurements was recorded in a diary. ABPM was conducted at the study inclusion and after 3 months of therapy. The following parameters were analyzed: average 24-hour, daytime, and nighttime values of systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), type of diurnal blood pressure curve, and daytime and nighttime SBP and DBP variability.

At the study inclusion, all patients underwent a biochemical blood analysis, including a lipid profile, glucose, uric acid, urea, creatinine, and electrolyte levels. To assess the safety of the investigated combination drugs, the levels of creatinine, uric acid, and blood electrolytes were re-measured after 1 and 3 months of antihypertensive therapy.

Statistical analysis was performed using the licensed software package "Statistics 8.0." Mean and standard deviation was calculated for normally distributed data. A p-value < 0.05 was considered statistically significant. The results are presented as Mean ± SD.

Results of the Study: Among the examined patients (n=40, 23 females and 17 males), grade I hypertension was observed in 47.5%, and grade II hypertension in 52.5%, indicating mild to moderate hypertension overall. The study included middle-aged patients (46.4±7.2 years) with grade I-II hypertension and metabolically active obesity, confirmed by anthropometric data and the presence of metabolic disorders, particularly dyslipidemia, detected in 35 (87.5%) patients. Microalbuminuria (MAU) ranging from 30 to 100 mg/dL was observed in 13 (32.5%) patients, while severe kidney dysfunction was not detected.

After the screening examination, all patients were prescribed Valun. The initial dosage consisted of amlodipine 5 mg and valsartan 80 mg/day once daily. Throughout the observation period, 3 visits were conducted, during which office blood pressure measurements were performed: the first visit on the day of examination, and after 1 and 3 months of therapy (Table 2).

Table 2. Dynamics of office blood pressure on the background of amlodipine/valsartan fixed combination therapy.

Visit	SBP (mmHg)	DBP (mmHg)	Heart Rate (bpm)
Visit 1 (Inclusion)	155,4±9,9	101,3±9,5	80,67±5,9
Visit 2 (1 month)	128,7±11,2*	88,3±8,3*	77,58±4,3
Visit 3 (3 months)	120,5±8,7*	83,2±7,1*	81,35±4,6

Note: * - p<0.05 compared to the first visit.

During the first month of therapy with the fixed combination of amlodipine/valsartan, a significant reduction in office SBP and DBP was observed, with an average decrease of 18.5 mmHg. At the 1-month mark, blood pressure for these patients stabilized at an average of 130/90 mmHg. By the end of the observation period (3 months of therapy), there was a significant decrease in blood pressure to an average of 120.5/83.2 mmHg while on the medication. During the study, no significant changes in heart rate (HR) were observed among the patients.

Among the patients, 33 (82.5%) achieved blood pressure normalization within the first month of therapy with a dose of amlodipine 5 mg/valsartan 80 mg. Among the patients, 7 (17.5%) did not reach the target blood pressure level during the first month of therapy and required titration every 2 weeks. Upon increasing the dose of valsartan to 160 mg in these seven patients, four of them achieved the target blood pressure levels after two weeks. For the remaining three patients, a high-dose fixed combination of amlodipine 10 mg/valsartan 160 mg was used subsequently. By the end of the study, all 40 patients had achieved the target blood pressure level (as shown in Table 3).

Table 3. Number of patients who achieved the target blood pressure level during treatment.

Visits	Number of patients (n=40)
Visit 2 (1 month)	33 (82,5%)
Visit 3 (3 months)	40 (100%)

During the analysis of the 24-hour ambulatory blood pressure monitoring (ABPM) data (Table 4), a significant reduction in the average 24-hour systolic and diastolic blood pressure (SBP and DBP) was observed. On average, the SBP decreased by 16.9 mmHg, and the DBP decreased by 11.4 mmHg during the day.

Table 4: The dynamics of 24-hour ambulatory blood pressure monitoring (ABPM) during the therapy with the investigated medications.

Indicators	Group of patients receiving amlodipine/valsartan (n=40)	
	Before treatment	After treatment
Average 24-hour SBP	142,3±11,7	125,4±6,4*
Average 24-hour DBP	95,1±8,8	83,7±6,5*
Average Daytime SBP	145,2±10,3	129,3±7,6*
Average DBP	93,7±9,2	82,6±9,1*
Average Nighttime SBP	131,3±12,6	118,8±12,0*
Average DBP	83,6±11,8	75,5±10,1*
Dipper Type	12 (30%)	24 (60%)*
Non-dipper Type	23 (57,5%)	15 (37,5%)
Over-dipper Type	3 (7,5%)	1 (2,5%)
N-peaker Type	2 (5%)	0
Variability of SBP during the Day	14,5±3,7	13,6±3,2
Variability of SBP during the Night	12,6±4,2	11,7±3,5
Variability of DBPduring the Day	10,7±3,3	10,1±3,1
Variability of DBD during the Night	9,5±3,4	8,6±3,5

Note: * — p<0.05 compared to the data before treatment.

Additionally, the study found an increase in the number of patients with a normalized daily blood pressure profile (dipper) after the 3-month antihypertensive therapy. Before treatment, 30% of patients had a dipper profile, which increased to 60% after treatment. There was also a tendency towards a reduction in the variability of SBP and DBP during the daytime and nighttime. No episodes of hypotension were detected during the 24-hour blood pressure monitoring.

Alongside the antihypertensive effectiveness of the medication, its impact on metabolic processes, particularly on blood lipid and glucose levels, which are risk factors for cardiovascular diseases, is of great importance. As previously noted, 35 (87.5%) of the patients had dyslipidemia at the start of the study. Upon inclusion in the research, all patients received recommendations for weight reduction: a hypolipidemic diet with calorie restriction to 1600 kcal/day, regular physical activity for 30 minutes per day, portion size reduction, and limiting food intake in the evening. During the 3-month therapy, patients experienced an average weight reduction of 5.5±2.8 kg.

The 12-week therapy with the fixed combination of amlodipine and valsartan did not negatively impact lipid and blood glucose levels, indicating the metabolic neutrality of the administered antihypertensive therapy (Table 5).

As part of the investigation into the nephroprotective effect of the medication, laboratory data of patients were analyzed upon inclusion in the study, after 1 and 3 months of therapy. Over the observation period, the group of patients receiving the fixed combination of amlodipine/valsartan showed a tendency towards decreased creatinine levels and increased glomerular filtration rate (GFR) calculated using the CKD-EPI formula, indicating a favorable nephroprotective efficacy of the medication (Table 5).

Table 5. Dynamics of laboratory parameters during 3-month therapy with amlodipine/valsartan fixed combination (n=40).

Indicators	Before treatment	p	After treatment
Urea (mmol/l)	6,5±2,7	>0,05	7,2±1,9
Creatinine (μmol/l)	95,31±10,09	>0,05	83,17±10,15
eGFR (ml/min)	77,18±15,97	>0,05	86,23±17,43
Glucose (mmol/l)	4,6±0,83	>0,05	4,2±0,54
Sodium (mmol/l)	4,3±0,4	>0,05	4,4±0,5
Potassium (mmol/l)	139,65±3,12	>0,05	142,14±3,12
Uric acid (μmol/l)	298±66,8	>0,05	301±55,7
Total Cholesterol (mmol/l)	6,1±0,9	>0,05	5,3±0,4
LDL (mmol/l)	2,9±0,7	>0,05	2,2±0,5
HDL (mmol/l)	3,92±1,29	>0,05	3,07±1,38
Triglycerides (mmol/l)	0,89±0,47	>0,05	0,75±0,11
AI	3,75±1,13	>0,05	3,37±1,14

Note: Z - significance of differences during therapy.
Abbreviations: TC - total cholesterol, TG - triglycerides, HDL-C - high-density lipoprotein cholesterol, LDL-C - low-density lipoprotein cholesterol, AI - atherogenic index.

The safety analysis was conducted by monitoring and recording adverse reactions (adverse event reporting). During the evaluation of the safety of the fixed combination of amlodipine/valsartan, no deaths or serious adverse effects were observed throughout the study. Only 6 (15%) patients experienced mild to moderate peripheral edema of the ankles during the therapy. It is worth noting that even at high doses, the fixed combination of amlodipine and valsartan was well-tolerated, with a relatively low incidence of peripheral edema, and the incidence did not increase with the escalation of the amlodipine dose. Additionally, none of the patients discontinued the treatment due to peripheral edema. Episodes of hypotension were not observed in any of the patients during the study.

Furthermore, there were no clinically significant effects of the therapy on laboratory parameters (creatinine, total cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, potassium, sodium, and uric acid), indicating the safety of this combination therapy.

DISCUSSION

Successful control of blood pressure (BP) is a crucial aspect of treating arterial hypertension (AH). Most patients require at least two antihypertensive drugs to achieve their BP target. In this study, the antihypertensive effectiveness of the fixed combination of amlodipine and valsartan was investigated in patients with mild to moderate AH. The results demonstrated that this combination led to the achievement of target BP levels in all patients. Amlodipine and valsartan effectively reduced both peripheral and central BP, even at lower doses of the medication. In patients with obesity, not only improved BP reduction was observed but also positive effects on metabolic processes were noticed. This might be attributed to the synergistic properties of amlodipine and valsartan, as well as their ability to enhance tissue insulin sensitivity. It is noteworthy that amlodipine, like valsartan, has a beneficial effect on the kidneys, since it dilates predominantly efferent arterioles and has less effect on afferent ones [4]. Thus, intraglomerular pressure decreases, renal blood flow increases with a slight change in GFR. The increase in glomerular filtration rate in our study is most likely due to an increase in renal blood flow. As a result of improving renal hemodynamics, natriuresis and diuresis increase, aldosterone production decreases, which leads to a slowdown in the progression of nephropathy.

It is important to note that Angiotensin Receptor Blockers (ARBs), including valsartan, are well-tolerated by patients due to their high effectiveness and lower incidence of side effects. Patients' adherence to treatment is significantly improved with these drugs.

Antihypertensive therapy with ARA does not depend on the activity of the RAAS, sex and age of the patient. Valsartan does not have an "escape" phenomenon, since its action does not depend on the pathway of angiotensin II formation. This class of drugs is characterized by the highest adherence of patients to treatment due to high efficiency and fewer side effects [8].

The results of the antihypertensive efficacy of the amlodipine/valsartan combination obtained by us correspond to the data obtained earlier in clinical studies. Thus, a dose-dependent effect was demonstrated in a study by T.Philipp et al. [9] and further analysis of this study by T. Smith et al. [10], confirmed that the degree of BP reduction corresponds to the initial degree of AH. Research by D.Poldermans et al. [11] showed that in patients with BP>180/110 mm Hg. Art. the combination of amlodipine / valsartan led to a decrease in SBP by 43.0 mm Hg. This was more than the reduction achieved with the combination of lisinopril and hydrochlorothiazide in this subgroup of patients (31.2 mm Hg.).

In a multicenter, uncontrolled, two-phase study conducted by Trenkwalder et al. [12], the aim was to determine if the fixed combination of amlodipine 10 mg and valsartan 160 mg could achieve an additional reduction in mean sitting systolic blood pressure (MSSBP) in patients who inadequately responded to a 5-week therapy with the combination of ramipril 5 mg and felodipine 5 mg. The study showed positive treatment outcomes, with patients experiencing a significant additional reduction in blood pressure when switched to the fixed combination of amlodipine 10 mg and valsartan 160 mg. The treatment with this combination was well-tolerated and characterized by neutral metabolic effects.

Recently, the authors of the CPET study [13] published new data on the impact of changes in nocturnal peripheral and central systolic blood pressure on the albumin/creatinine ratio in urine. They found that the reduction in nocturnal central systolic blood pressure during treatment with valsartan/amlodipine led to a decrease in the albumin/creatinine ratio (β=0.919; p=0.020), independent of the reduction in peripheral systolic blood pressure during the night. This particular feature of the valsartan/amlodipine combination was considered a strength, as targeting the reduction of nocturnal central systolic blood pressure could become a therapeutic goal in patients with arterial hypertension.

All patients (n=40) included in the study completed the 12-week observation period, and their adherence to the therapy was high. The long-term use of the fixed combination of amlodipine and valsartan did not lead to electrolyte disturbances or other adverse effects. Notably, there was a more significant reduction in creatinine levels and an increase in glomerular filtration rate (GFR) in the patient group. Additionally, in the group of patients under investigation, 13 (32.5%) individuals experienced a reduction or complete disappearance of microalbuminuria (MAU), indicating a potential nephroprotective effect of the medication.

In conclusion, the 12-week therapy demonstrated the high antihypertensive effectiveness of the amlodipine/valsartan combination. The study also revealed a nephroprotective effect, evidenced by a significant reduction in blood creatinine levels and nearly a twofold decrease in MAU levels. The fixed combination of amlodipine/valsartan (Valun) proves to be an effective and safe treatment option for patients with mild to moderate arterial hypertension and obesity.

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