Artículo Original

Terapias antihipertensivas combinadas en pacientes con hipertensión arterial y enfermedad pulmonar obstructiva crónica.

Combined antihypertensive therapies in patients with arterial hypertension and chronic obstructive pulmonary disease

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RESUMEN

Actualmente no se disponen de estudios multicéntricos que evalúen la combinación antihipertensiva óptima para pacientes con patología comórbida.

Objetivo: evaluar la eficacia comparativa y la seguridad de las terapias antihipertensivas combinadas en pacientes con hipertensión y EPOC.

Material y métodos: Se examinaron pacientes con hipertensión arterial y EPOC a quienes se les habían recetado diferentes regímenes de tratamiento (amlodipino + perindopril o amlodipino + valsartán). La efectividad de cada tratamiento se determinó con base en un examen estándar, monitoreo diario de la PA y el ECG, indicadores de calidad de vida y la frecuencia de la depresión.

Resultados: El uso de cualquiera de las terapias combinadas para tratar la hipertensión en pacientes con EPOC contribuye a la misma mejora en la calidad de vida, la reducción de la frecuencia de la depresión y la disminución de los parámetros principales de la PA con una frecuencia comparable de efectos secundarios.

Conclusión: Las dos combinaciones evaluadas aquí, que demostraron una eficacia y tolerancia comparables, se recomiendan como el primer paso en la terapia antihipertensiva para pacientes comórbidos.

Combined antihypertensive therapies in patients with arterial hypertension and chronic obstructive pulmonary disease

ABSTRACT

There are currently no multicentre studies evaluating the optimal antihypertensive combination for patients with comorbid pathology.

Objective: To evaluate the comparative efficacy and safety of combined antihypertensive therapies in patients with hypertension and COPD.

Material and methods: Patients with arterial hypertension and COPD were examined who had been prescribed different treatment regimens (amlodipine + perindopril or amlodipine + valsartan). The effectiveness of each treatment was determined based on a standard examination, daily monitoring of BP and ECG, quality of life indicators, and the frequency of depression.

Results: The use of either of the combined therapies to treat hypertension in patients with COPD contributes to the same improvement in quality of life, reduction in the frequency of depression, and decrease in the main BP parameters with a comparable frequency of side effects.

Conclusion: The two combinations evaluated here, which demonstrated comparable efficacy and tolerance, are recommended as the first step in antihypertensive therapy for comorbid patients.

Keywords:
Hypertension.
COPD.
Therapy.
Blood pressure.

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INTRODUCTION

Cardiovascular pathology occupies a leading place in the structure of morbidity and mortality on a global scale. Its prevalence continues to grow steadily, currently reaching 30-45% among adults and more than 60% among people over 60[1,2,3]. Hypertension continues to be the main modifiable risk factor for cardiovascular complications[4,5]. Despite the active introduction of new clinical recommendations into practice and the regular review of therapeutic strategies, 30-40% of patients fail to achieve target blood pressure (BP) values[6]. According to experts, by 2025 the number of people with hypertension worldwide will increase by 15-20%, reaching almost 1.5 billion[7].

The situation is significantly aggravated when the patient has comorbidities. It has been proved that hypertension against a background of concomitant pathology is characterized by a refractory course, prognostically unfavorable indicators in daily BP monitoring (BPM), early damage to target organs, and a high probability of cardiovascular and cerebrovascular complications, requiring a careful approach to the supervision of such patients.

A common clinical situation is a combination of hypertension and chronic obstructive pulmonary disease (COPD), primarily due to the high prevalence of both diseases, common risk factors, and the pathogenic relationship[8,9,10,11,12,13]. Today, COPD is the third highest cause of mortality, although the World Health Organization made this forecast several years ago and only until 2030[14]. Every fourth patient with COPD aged 25-64 years has hypertension [6,15]. According to studies by various authors, the frequency of this comorbidity varies widely, from 6.8 to 73.3% and averaging at about 34.3%[15,16,17]. Finally, it has been shown that the combination of cardiovascular diseases and COPD leads to an increase in mortality, a deterioration in patient quality of life, and more frequent manifestations of depressive disorders[18,19].

To date, the treatment strategies for both hypertension and COPD have been proven in numerous studies; however, the nosological classifications differ. There are no clear treatment regimens for hypertension in comorbid patients. Modern clinical guidelines offer only general principles for the treatment of hypertension in patients with COPD. Hence, the question of the optimal strategy for combination antihypertensive therapy in such patients remains unresolved due to the lack of large comparative studies.

In addition, controversial issues arise due to the advisability of prescribing angiotensin-converting enzyme (ACE) inhibitors to treat hypertension in patients with COPD. According to some studies, the use of this group of drugs is unjustified due to the frequent occurrence of side effects, such as ACE-induced coughing[7,20]. However, numerous researchers emphasize that the percentage of coughing in COPD patients is no higher than in the general population. Moreover, the protective effect of ACE inhibitors on the indicator of forced expiratory volume in the first second (FEV1) in smokers has been proved[21,22,23].

Furthermore, when choosing combined antihypertensive therapies for patients with hypertension and COPD, it is not possible to rely on data from multicenter randomized trials due to their absence.

Research hypothesis: it can be assumed that both strategies of combination antihypertensive therapy have a positive effect on the clinical course of comorbid pathology and lead to an improvement in the quality of life of patients.

Hence, the aim of the study is to evaluate the comparative efficacy and safety of various modes of combined antihypertensive therapy in patients with a combination of hypertension and COPD.

MATERIALS AND METHODS

The study was conducted at the cardiology department of the SBHI RC *"Simferopol City Clinical Hospital No. 7"* and the FSOE Clinical Sanatorium *"Pogranichnik"* of the Federal Security Service of the Russian Federation in 2018-2019. The study was approved by the ethics committee of the Federal State Autonomous Educational Institution of Higher Education *"Crimean Federal University named after V.I. Vernadsky"* (minutes No. 9 of September 11, 2018).

Design: This was a prospective cohort randomized trial. The informed consent was obtained for all patients according to international conventions. The **inclusion criteria** for study were arterial hypertension stage 2 with degree 1-2, risk III (high) on the scale of stratification of the overall cardiovascular risk based on BP; the presence of risk factors, target organ damage, diabetes or clinically manifest cardiovascular diseases; COPD with spirometric class 2 according to GOLD, group B. **Exclusion criteria** were above 80 or below 40 years of age; a history of angina pectoris, myocardial infarction, cerebral stroke, severe rhythm and conduction disturbances, left ventricular aneurysm, heart defect, or chronic heart failure III-IV FC according to NYHA; grade 3 hypertension; COPD with spirometric classes 3 and 4 according to GOLD, C-D groups; and severe concomitant pathology of the internal organs.

The patients were divided into two groups, comparable in terms of sex, age, duration of the disease, baseline BP, and heart rate. Patients were randomized using a random number table generated in the program *"Statistica"*.

Patients in **Group A** (n = 44) received a combination of amlodipine and perindopril at a starting dose of 5/5 mg as antihypertensive therapy. Patients in **Group B** (n = 41) received a combination of amlodipine and valsartan at an initial dose of 5/160 mg. After 3 weeks, the need to increase the dosage of the drugs was evaluated. In addition, all patients received basic treatment for COPD, consisting of tiotropium bromide 18 μg/day and lipid-lowering therapy with rosuvastatin (based on the lipid profile).

At the beginning of the study and after 6 weeks, all patients underwent a clinical examination based on current standards, laboratory and instrumental research methods, assessment of depressive disorders on the Beck scale, and quality of life according to the SF-36 questionnaire. Daily

monitoring of blood pressure was performed on an apparatus such as ABPM - 04 "Cardiospy" company Labtech (Hungary). The range of expected values is 30-300 mm Hg.

In addition, complaints that required drug withdrawal and the incidence of coughing were also evaluated. After 6 months, the long-term results were examined (the number of hospitalizations for COPD, hypertension, the frequency of hypertensive crises, and whether the antihypertensive therapy was preserved with the prescribed regimens and dosages).

End points of the study: improvement of the clinical course of the disease, achievement of the target blood pressure level against the background of ongoing therapy, reduction in the frequency of depressive disorders, the percentage of patients receiving recommended treatment after six months, the number of hospitalizations for exacerbation of COPD and hypertensive crises.

Statistical processing of the data was carried out using the standard Statistica 10 software package. The correspondence of the signs to the normal distribution law was determined using the Shapiro-Wilk criteria. In the case of a normal distribution of a trait, quantitative data were expressed as the average value (M) and the errors of the average value (m). If the distribution was different from normal, the median (Me) and 25-75% of the quartile were calculated. Assessment of the statistical significance of differences in dependent samples with a normal distribution was performed using the student's t-test. For the distribution of a characteristic other than normal, the Wilcoxon t-test was used. When comparing the data presented in absolute frequencies, the McNemar test was used for dependent samples. In all cases, the differences were considered statistically significant at $p<0.05$.

RESULTS

In total, 85 patients with a verified diagnosis of hypertension and COPD were examined. The average age of the patients was 60.9 ± 1.06 years, and the gender ratio was 46% women and 54% men *(Table 1)*.

The dynamics of the complaints by patients based on the use of the different combined antihypertensive therapy modes were analyzed. In both groups of patients, the frequency of complaints of general weakness, noise in the head, and tinnitus statistically significantly decreased ($p<0.05$). It should be emphasized that despite the widespread view that the use of ACE inhibitors is undesirable in patients with COPD, in Group A, taking amlodipine and perindopril, no patient reported the adverse effect of ACE-induced coughing during the course of this study. In contrast, patients in Group A who were taking a bronchodilator, the frequency of complaints of coughing decreased by 12.2%.

A positive result was also obtained when studying the dynamics of office BP during treatment. Both groups experienced the same statistically significant decrease in both systolic BP (SBP) and diastolic BP (DBP) ($p<0.001$).

An analysis of the indices of the external respiratory function in the comorbid patients using the combined antihypertensive therapy modes revealed the absence of dynamics of the spirographic indices in both groups. This indicates the possibility of prescribing either of the studied combinations to comorbid patients, including ACE inhibitors, without negatively affecting the indices of the external breathing function.

TABLA 1.
Baseline characteristics of the sample.

Variable	Group A (n=41)	Group B (n=44)
Male (n, %)	22 (53.7%)	24 (54.6%)
Female (n, %)	19 (46.3%)	20 (45.4%)
Arterial hypertension degree 1 (n, %)	11 (26.8%)	12 (27.3%)
Arterial hypertension degree 2 (n, %)	30 (73.2%)	32 (72.7%)
Systolic blood pressure, mmHg, Me (25; 75% percentile)	160 (150; 165)	160 (155; 165)
Diastolic blood pressure, mmHg, Me (25; 75% percentile)	90 (90; 95.5)	90 (90; 95,5)
FEV1, %	59.20±1.21	59.50±1.28

When studying the dynamics of the main parameters of 24-hour BPM, it was possible to identify that the use of either of the antihypertensive therapy regimens in comorbid patients contributes to the same statistically significant decrease in the daily, daytime, and nightly rates of SBP, DBP, and mean blood pressure (SBP) after 6 weeks of therapy. This indicates the comparable effectiveness of antihypertensive therapy regimens in influencing average BP. *(Table 2)*

When analyzing the dynamics of as pulse BP (PsBP) – an important prognostic indicator of 24-hour BPM – it was found that both patient groups showed the same statistically significant decrease during treatment. For example, the average daily PsBP in Group A at the beginning of the treatment was 54.2 ± 1.54 mmHg and after 6 weeks it was 49.1 ± 1.29 mmHg ($p<0.001$). In Group B, it was 53.9 ± 1.34 mmHg and 47.2 ± 1.06 mmHg, respectively ($p<0.001$).

The next stage examined the dynamics of BP (StDBP) and the rate of morning rise in BP (RMR) in comorbid patients with the evaluated antihypertensive therapy regimens. It was found that the use of amlodipine + perindopril contributed to a statistically significant decrease in the variability of the average daily, and mid-day DBP. When using amlodipine + valsartan, the variability of the average daily, DBP, and mid-day SBP was decreased. The rate of morning rise during the treatment was reduced equally effectively in both groups of patients *(Table 3)*.

When analyzing the data on heart rate variability (HRV) during therapy in both groups of patients, a statistically significant increase in all time indices was revealed: SDNN, SDNNi, SDANN, RMSSD, pNN50, HRVTI *(Table 4)*.

TABLA 2.

The dynamics of 24-hour BPM in comorbid patients with different modes of antihypertensive therapy (before treatment and during therapy).

BPM indicators, mmHg	GROUP A (n=41), Me (25; 75% percentile) or M±m[a]		GROUP B (n=44), Me (25; 75% percentile) or M±m[a]	
	Before treatment	During therapy	Before treatment	During therapy
SBP per day	133 (139; 141)	123 (116; 129)***	134.5 (127; 141)	119 (115; 128.5)***
SBP day	136.9±2,13	125.2±1.70***	137.6±1.58	123.5±1.35***
SBP night	131 (123; 142)	121 (108; 125)***	131 (120; 138)	115 (124.5; 125.5)***
DBP per day	81.2±1.33	73.8±0.95***	81.1±1.25	73.4±0.99***
DBP day	83.3±1.50	75.9±1.12***	83.7±1.29	75.6±1.10***
DBP night	70.1±1.45	69.2±0.98***	76.2±1.63	69.1±1.04***
MAP per day	100.1±1.47	90.3±1.12***	98.9±1.22	89.7±1.24***
MAP day	101.7±1.62	92.7±1.29***	101.5±1.29	91.9±1.25***
MAP night	96.5±1.65	86.0±1.24***	94.3±1.70	85.3±1.44***

Note: [a] – in the case of a normal distribution, the data are indicated in the form M ± m; in the case of a distribution other than normal, in the form Me (Q1, Q3); **n** – number of people in a group; *** – p<0.001 in relation to the source data.

TABLA 3.

The dynamics of the indicators of the variability of BP and BP control in comorbid patients related to the two modes of antihypertensive therapy (before treatment and during therapy).

24-hour BPM indicators	GROUP A (n=41), Me (25; 75% percentile) or M±m[a]		GROUP B (n=44), Me (25; 75% percentile) or M±m[a]	
	Before treatment	During therapy	Before treatment	During therapy
StD SBP per day, mmHg	15.7±0.67	14.4±0.71	17.8±1.91	14.5±0.84
StD SBP day, mmHg	15.4±0.80	13.9±0.81	15.3±0.80	14.4±0.89
StD SBP night, mmHg	12 (10; 16)	11.9 (8; 16.3)	13 (10.5; 16.7)	12 (8.3; 15.5)*
StD DBP per day, mmHg	11.8±0.55	10.4±0.50*	11.0±0.58	10.3±0.63*
StD DBP day, mmHg	11.5±0.65	10.0±0.59*	11.2±0.64	9.3±0.60*
StD DBP night, mmHg	9.3±0.60	8.0±0.59*	9.7±0.85	9.8±0.89
StD MAP per day, mmHg	12.2±0.52	11.5±0.57	12.5±0.52	11.3±0.61
StD MAP day, mmHg	12.2±0.58	11.0±0.61	11.3±0.57	10.4±0.63
StD MAP night, mmHg	10.0±0.62	8.9±0.63	10.4±0.77	10.4±0.82
Rate of morning BP rise of SBP, mmHg per hour	19.2 (13.7; 28.3)	12.7 (9.8; 19.3)***	29.1 (13.5; 36)	12.5 (8.8; 27.2)***
Rate of morning BP rise of DBP, mmHg per hour	13.7 (7.5; 20.7)	9.4 (4.4; 14.9)***	15.0 (8.2; 27.3)	7.7 (7.4; 14.9)***

Note: [a] – in the case of a normal distribution, the data are indicated in the form M ± m; in the case of a distribution other than normal, in the form Me (Q1, Q3); **n** – number of people in a group; * – p<0.,05 in relation to the source data; *** – p<0.001 in relation to the source data

Thus, the use of two combined antihypertensive therapy regimens in patients with COPD improves the HRV parameters, which reflects the combined effect of the sympathetic and parasympathetic innervation and reduces the activity of the sympathetic nervous system. Furthermore, an increase in indicators shows an increase in the effect of the parasympathetic department of the autonomic nervous system on the regulation of the heart function.

In the next stage of the study, compelling data were obtained from both groups of patients, indicating an improvement in the quality of life indicators based on the SF-36 questionnaire. In addition, it was found that the use of both

TABLA 4.

The dynamics of HRV in comorbid patients with various modes of antihypertensive therapy (before treatment and during therapy).

HRV indicators	GROUP A (n=41), Me (25; 75% percentile) or M±m[a]		GROUP B (n=44), Me (25; 75% percentile) or M±m[a]	
	Before treatment	During therapy	Before treatment	During therapy
SDNN, ms	105 (80; 130)	135 (105; 170)**	110 (80; 155)	137.5 (110; 172,5)**
SDNNi, ms	38 (31; 47)	53 (45; 62)***	39.5 (30.5; 49.5)	52 (41; 61.5)**
SDANN, ms	95 (70;115)	115 (95; 150)***	102 (70; 127,5)	125 (90; 162,5)**
RMSSD, ms	32 (27, 38)	43 (32; 50)*	30 (25; 35)	37 (29.5; 46)**
pNN50, %	9 (5; 14)	14 (9; 21)**	6 (4; 10)	11.5 (8; 18)***
HRVTI, ms	430.2±26.15	604.1±29.74***	470.2±23.88	553.0±28.28*

Note: [a] – in the case of a normal distribution, the data are indicated in the form M ± m; in the case of a distribution other than normal, in the form Me (Q1, Q3]; **n** – number of people in a group; * – p<0.05 in relation to the source data; ** – p<0.01 in relation to the source data; *** – p<0.001 in relation to the source data.

TABLA 5.

The dynamics of the quality of life indicators (SF-36 questionnaire) in comorbid patients with various modes of antihypertensive therapy (before treatment and during therapy).

SF-36 Questionnaire Scales	GROUP A (n=41), Me (25; 75% percentile) or M±m[a]		GROUP B (n=44), Me (25; 75% percentile) or M±m[a]	
	Before treatment	During therapy	Before treatment	During therapy
Physical functioning	52.3±3.83	64.0±3.27***	47.4±3.50	65.0±3.15***
Physical role-based functioning	25 (0; 75)	75 (25; 100)***	25 (0; 50)	75 (25; 100)***
Pain intensity	61.3±4.46	74.5±3.52***	54.3±3.94	75.4±3.00***
General health	39.5±3.39	42.6±3.34***	36.7±3.01	42.3±2.80**
Life activity	43.3±3.73	51.8±3.38***	36.6±2.63	45.9±2.80***
Social functioning	62.5 (50; 75)	62.5 (50; 87.5)***	50 (50; 62.5)	62.5 (62.5; 75)***
Role-based functioning due to emotional state	33.3 (0; 66.7)	66.7 (33.3; 100)***	33.3 (0; 66.7)	100 (33; 100)***
Mental health	53.07±3.23	60.7±2.91**	53.2±2.65	61.3±2.77***
Physical component of health	38.4±1.36	43.1±1.24***	35.3±1.22	42.8±1.18***
Mental component of health	39.2±1.77	44.5±1.50***	38.7±1.45	44.6±1.38***

Note: [a] – in the case of a normal distribution, the data are indicated in the form M ± m; in the case of a distribution other than normal, in the form Me (Q1, Q3]; **n** – number of people in a group; ** – p<0.01 in relation to the source data

combinations of antihypertensive drugs in patients with COPD statistically significantly promoted the same recovery in both the physical and mental components of patient quality of life *(Table 5)*.

The improvement in the quality of life of comorbid patients was accompanied by an improvement in the Beck scale as well as a decrease in the manifestations of depressive disorders in the studied patients. The average score on the Beck scale in the patients of Group A before treatment was 11.6 ± 0.97, while during therapy it was 9.1 ± 0.77 (p<0.001). In the patients of Group B, it decreased from 13.0 ± 1.06 to 9.3 ± 0.78 (p<0.001).

Thus, the use of either of the combinations of antihypertensive drugs evaluated here leads not only to a decrease in the number of complaints and to an increase in the well-being of patients, but also to an improvement in the quality of life and a decrease in the manifestations of depression. Both treatment regimens are statistically equal in their effectiveness in this regard.

When studying the long-term results of therapy, the following data were obtained. In Group A, 6 months after the first visit, 87.8% of patients continued to receive the treatment at the recommended doses, allowing them to achieve the target BP level, 9.8% needed dose adjustment

and/or the addition of a third antihypertensive drug, and 2.4% canceled the treatment on their own. In Group B, 86.4% of patients continued to follow the recommendations and reached target BP levels, 9.1% needed further correction of the treatment regimen, and 4.5% received irregular therapy. The data obtained were statistically comparable.

The number of hospitalizations for the exacerbation of COPD and hypertensive crises over 6 months was also statistically the same in both groups: 7.3% of patients from Group A were treated in the pulmonology department, and 4.9% in the cardiology department. In Group B, 6.8% of patients underwent hospitalization for exacerbations of COPD, and 4.5% for hypertensive crises.

DISCUSSION

In the course of the study analyzing two combination therapy regimens, their comparable antihypertensive efficacy was established. This was confirmed by the absence of any statistically significant ($p<0.05$) features of reducing the frequency of complaints and office BP and the percentage of patients who reached the target blood pressure. In addition, the comparability of the antihypertensive effect was also confirmed by the data on the daily BP parameters, with the same statistically significant decrease in the average daily values ($p<0.001$), IAI ($p<0.001$), pulse BP ($p<0.001$), and the effect on blood pressure variability ($p<0.05$) and rate of morning BP rise $p<0.001$). In both groups, comparable positive dynamics of HRV indicators were observed ($p<0.05$), which reflects the positive effect of both combinations on the prognosis in comorbid patients.

The evaluation of the dynamics of the external respiratory function indicators demonstrated the good tolerance of both antihypertensive therapy regimens. We recorded not only the absence of the coughing side effect in comorbid patients taking ACE inhibitors but also the absence of negative dynamics of data in this category of patients. This refutes the established view that the use of ACE inhibitors is undesirable for such patients. The studies of O. Vukadinović and C.A. Goudis, D. Vukadinović, K.J. Curtis and others also demonstrated the positive effect of ACE inhibitors on the course of cardiovascular disease in patients with concomitant COPD and the absence of negative effects on the bronchopulmonary system data of comorbid patients[22,23,24].

Effective BP control was accompanied by statistically significant ($p<0.001$) positive dynamics in most indicators of the quality of life of the patients taking amlodipine + perindopril and of those taking amlodipine + valsartan. This is of great importance because in comorbid patients, there is a decrease in the quality of life and depressive disorders are common[18,19]. The long-term results also confirmed the high comparable efficacy of both antihypertensive therapy regimens. The results of the work allow us to substantiate the possibility of using any of the presented regimens for the effective treatment of hypertension in patients with concomitant COPD.

This study makes the following **contribution** to the body of knowledge. **First,** it represents the first assessment of the comparative efficacy and tolerability of a combination of an ACE inhibitor or ARBs in combination with a dihydropyridine calcium antagonist in achieving BP control in patients with a combination of arterial hypertension and COPD. **Second,** it demonstrates the comparable effectiveness of the two combined antihypertensive therapy regimens in achieving target BP as well as the positive dynamics of daily BP in this category of patients. **Third,** it proves the absence of a negative effect in both combined antihypertensive therapy regimens on the indices of respiratory function in patients with arterial hypertension and COPD. **Finally,** it demonstrates the improvement of quality of life indicators and the decrease in the severity of manifestations of depression while achieving control of BP using either of the studied combined antihypertensive therapy regimens.

The **limitations** include the relatively few participants in the study. This fact probably caused the absence of side effects from therapy with angiotensin-converting enzyme inhibitors in patients with COPD. Moreover, it should be noticed that the relevance of the results of this study is limited to patients with arterial hypertension stage 2 with degree 1-2 and COPD with spirometric class 2 according to GOLD, group B.

CONCLUSION

The use of combinations of amlodipine + perindopril or amlodipine + valsartan for the treatment of hypertension in patients with COPD contributes to a statistically equal reduction in the number of complaints, improvement in the quality of life, reduction in the frequency of depressive disorders, and decrease in the basic daily parameters of BP, variability and speed of the morning rise in BP, and pulse BP. At the same time, there is a lack of deterioration in external respiratory function and a comparable frequency of side effects. The data obtained facilitate the recommendation of either of the two regimens, which demonstrated comparable efficacy and tolerance in this study, to practicing cardiologists and general practitioners as the first step in antihypertensive therapy in patients with hypertension and COPD. For the widespread use of these antihypertensive therapy regimens in patients with a combination of hypertension and COPD in global practice, further study of this problem is necessary using large international multicenter studies.

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