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# ARTERIAL HYPERTENSION: A MODERN VIEW OF THE PROBLEM (LITERATURE REVIEW)

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**Abstract.** Arterial hypertension is the most common chronic disease worldwide and the major risk factor for disability and premature mortality. It contributes significantly to the economic and social burden and can severely impair health-related quality of life. The aim of this review is to comprehensively evaluate and synthesise the current literature on the risk factors, contemporary theories of pathogenesis, diagnostic approaches and treatment strategies for arterial hypertension. This article also aims to identify and highlight the main clinical areas, prevention and management strategies for arterial hypertension. The review analyses recent studies on the functional and structural alterations of the cardiovascular system associated with arterial hypertension. The risk factors contributing to the development of arterial hypertension are examined in detail, emphasising the role of hereditary predisposition, age, gender, personality traits, lifestyle habits and co-morbidities. On the basis of the available scientific evidence, we propose that haemodynamic disturbances, inflammatory processes, gut microbiota, immune status, hormonal dysregulation and structural changes in blood vessels play a pivotal role in its pathophysiology. Accordingly, therapeutic management should include dietary modification, regular physical activity, healthy lifestyle, regulation of mineral balance, increased consumption of fermented dairy products and pharmacological interventions.

**Keywords**: cardiovascular system, arterial hypertension, risk factors, clinical presentation, diagnosis, pharmacotherapy.

## Артериялық гипертензия: мәселенің заманауи көрінісі (шолу)

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**Аңдатпа.** Артериялық гипертензия Дүние жүзінде ең таралған созылмалы ауру және мүгедектік пен мезгілсіз өлімнің негізгі қауіп факторы болып табылады. Ол экономикалық және әлеуметтік жағдайға айтарлықтай үлес қосады және денсаулыққа байланысты өмір сапасын айтарлықтай нашарлатуы мүмкін. Бұл шолудың мақсаты – артериялық гипертензияның қауіп факторлары, патогенезінің заманауи теориялары, диагностикалық тәсілдер және емдеу стратегиялары бойынша қазіргі әдебиеттерді кешенді түрде бағалау және синтездеу. Бұл мақала, сонымен қатар, артериялық гипертензияның негізгі клиникалық бағыттарын, алдын алу және басқару стратегияларын анықтауға және көрсетуге бағытталған. Шолуда артериялық гипертензиямен байланысты жүрек-қантамыр жүйесінің функционалдық және құрылымдық өзгерістері туралы соңғы зерттеулер талданады. Артериялық гипертензияның дамуына ықпал ететін қауіп факторлары тұқым қуалайтын бейімділіктің, жастың, жыныстың, тұлғаның ерекшеліктерінің, өмір салты әдеттерінің және қосалқы аурулардың рөліне баса назар аудара отырып, егжей-тегжейлі зерттеледі. Қолда бар ғылыми дәлелдерге сүйене отырып, біз оның патофизиологиясында гемодинамикалық

бұзылулар, қабыну процестері, ішек микробиотасы, иммундық статус, гормоналды реттелудің бұзылуы және қан тамырларының құрылымдық өзгерістері шешуші рөл атқаратынын ұсынамыз. Сондықтан терапиялық басқару диетаны өзгертуді, тұрақты физикалық белсенділікті, салауатты өмір салтын, минералды балансты реттеуді, ашытылған сүт өнімдерін тұтынуды арттыруды және фармакологиялық араласуды қамтуы керек.

**Түйін сөздер:** жүрек-қантамыр жүйесі, артериялық гипертензия, қауіп факторлары, клиникалық көрінісі, диагностикасы, фармакотерапия.

## Артериальная гипертония: современный взгляд на проблему (обзор)

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**АННОТАЦИЯ.** Артериальная гипертензия является наиболее распространенным хроническим заболеванием во всем мире и основным фактором риска инвалидности и преждевременной смертности. Она вносит значительный вклад в экономическое и социальное бремя и может серьезно ухудшить качество жизни, связанное со здоровьем. Целью данного обзора является всесторонняя оценка и синтез современной литературы по факторам риска, современным теориям патогенеза, диагностическим подходам и стратегиям лечения артериальной гипертензии. Данная статья также направлена на выявление и выделение основных клинических областей, стратегий профилактики и лечения артериальной гипертензии. В обзоре анализируются недавние исследования функциональных и структурных изменений сердечно-сосудистой системы, связанных с артериальной гипертензией. Факторы риска, способствующие развитию артериальной гипертензии, подробно рассматриваются с акцентом на роль наследственной предрасположенности, возраста, пола, черт личности, образа жизни и сопутствующих заболеваний. На основе имеющихся научных данных мы предполагаем, что гемодинамические нарушения, воспалительные процессы, микробиота кишечника, иммунный статус, гормональная дисрегуляция и структурные изменения кровеносных сосудов играют ключевую роль в ее патофизиологии. Соответственно, терапевтическое лечение должно включать изменение диеты, регулярную физическую активность, здоровый образ жизни, регулирование минерального баланса, увеличение потребления кисломолочных продуктов и фармакологические вмешательства.

**Ключевые слова:** сердечно-сосудистая система, артериальная гипертония, факторы риска, клиническая картина, диагностика, фармакотерапия.

### Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide. Identifying individuals at high risk of developing CVD and effectively reducing the morbidity and mortality associated with these diseases is a critical public health concern [1].

Arterial hypertension (AH) is the most common chronic disease worldwide and a major risk factor for disability and premature death, accounting for over 9 million deaths annually. Recent epidemiological studies have revealed a 10% prevalence of sustained hypertension among individuals diagnosed with AH, indicating that these patients are at increased cardiovascular risk. In addition, these studies have identified specific subgroups of patients with an even higher risk of morbidity and mortality, requiring the implementation of active pharmacological therapy [2].

The development of AH is influenced by a variety of factors, and the underlying causes and mechanisms of its progression are complex and multifactorial. AH is a common condition, and its prevalence increases with age. Approximately 65% of people aged 60 years and over are affected, and more than 70% of those aged 85 years and over are affected. CVD remains the leading cause of death in people aged 65 years and older.

Uncontrolled arterial hypertension is often the underlying cause of cardiovascular complications. It is estimated that up to 50% of people in the general population are unaware of their hypertensive status, and only half of those who are aware of their condition have adequate blood pressure control.

**The aim of this review** is therefore to comprehensively evaluate and summarise the existing literature on the risk factors, aetiology, pathogenesis, diagnostic approaches and therapeutic strategies for the management of AH.

**Cardiovascular Disease Risk Assessment**

Certain diseases have been found to be more prevalent among individuals of shorter stature, including AH, coronary heart disease, heart failure, and ischemic stroke. In contrast, taller individuals exhibit a higher prevalence of atrial fibrillation and venous thromboembolism. This has led to ongoing debate regarding the optimal implementation of height as a stratification parameter in CVD risk assessment, with the aim of further reducing CVD incidence and mortality rates [1].

Studies involving family and twin cohorts have demonstrated the genetic underpinnings of AH, with genetic factors accounting for approximately 40% of the increase in blood pressure in humans. About 50% of patients with primary AH exhibit a hereditary predisposition, attributed to mutations in genes such as those encoding angiotensinogen, angiotensin II receptors, angiotensin-converting enzyme, renin, aldosterone synthetase, and the β-subunits of amiloride-sensitive sodium channels in renal epithelium, among others. Consequently, AH remains a leading cause of death due to cardiac complications [3].

Despite extensive research on socially significant diseases, the role of magnesium deficiency as a risk factor in AH has yet to be fully elucidated. Magnesium acts as a natural antagonist to calcium, enhancing the production of local vasodilators (prostacyclin and nitric oxide) and modulating the vascular response to various vasoactive substances, including endothelin-1, angiotensin II, and catecholamines. Magnesium also stimulates aldosterone production and exacerbates the vascular inflammatory response, while decreasing the expression and activity of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, and catalase, as well as the levels of key antioxidants, including vitamins C and E and selenium. Furthermore, magnesium plays a regulatory role in the effects of catecholamines under both acute and chronic stress conditions.

Given that arterial hypertension is currently the most prevalent cardiovascular disease in the general population, it serves as a significant risk factor for the development of atrial fibrillation. Therefore, it is recommended to regularly monitor the heart rate and perform long-term ECG monitoring to detect atrial fibrillation in at-risk individuals.

AH, along with diabetes and obesity, are recognised risk factors for the severity of COVID-19 infection. Blood serum apelin levels were found to be lower in patients with AH and obesity compared to controls. In addition, low levels of apelin and nitric oxide in individuals with arterial hypertension, obesity, diabetes or COVID-19 infection may exacerbate the progression of these conditions[4].

Renal microcirculation plays a critical role in the pathogenesis of AH. Chronic hypertension places sustained pressure on large arteries, leading to their stiffening. This results in an increase in central blood pressure, which directly contributes to further impairment of renal microcirculation.

**Modern Theories of Pathogenesis**

AH is a complex, interconnected, and progressive cardiovascular syndrome with multifactorial etiology. Intestinal microbiota, through the production, modification, and degradation

of various bioactive metabolites by microbes, plays a significant role in maintaining blood pressure homeostasis and in the pathogenesis of AH. Comparable mechanisms have been identified in animal models, and to a lesser extent, in human studies. Interventions involving probiotics, prebiotics, antibiotics, and fecal microbiota transplantation have shown promising results in modulating blood pressure regulation and hypertension pathogenesis.

Numerous studies have demonstrated that hypertensive damage to organs and target tissues is not solely associated with hemodynamic disturbances. Inflammation also plays a pivotal role in the pathophysiology of arterial hypertension, exacerbating the disease process. Cells of the innate immune system, including monocytes/macrophages and dendritic cells, contribute to hypertension through their effects on renal and vascular function. Skin-resident monocytes/macrophages, regulatory T cells, cytotoxic T cells, and myeloid-derived suppressor cells have all been implicated in the regulation of blood pressure. Sodium intake has been shown to stimulate the activity of various subpopulations of monocytes/macrophages, dendritic cells, and T cells, thereby influencing hypertension development [5].

Both innate and adaptive immune responses are crucial in the pathogenesis of AH and hypertensive organ damage. Recent experimental data strongly support the involvement of the complement system in the development of AH.

In a study of male and ovariectomised female rats treated for 2 weeks with an angiotensin II (ANG II) solution, increases in blood pressure were observed in both male and female rats. However, in uninjured females (without ovariectomy) a decrease in blood pressure was observed. In addition, ANG II treatment increased endoplasmic reticulum (ER) stress biomarkers in the subfornical organ of both male and female brains. Notably, the increase in these biomarkers was less pronounced in uninjured females compared to oophorectomised females. The authors concluded that estrogen has a protective effect against ANG II-induced ER stress in the brain, which may provide a protective mechanism for women against hypertension-induced neurological complications.

**Clinical Features**

Research has demonstrated that changes in sex hormones play a crucial role in the pathophysiology of hypertension in postmenopausal women. Estrogens impact the vascular system by promoting vasodilation, inhibiting vascular remodeling processes, and modulating the renin-angiotensin-aldosterone system as well as the sympathetic nervous system. This provides a protective effect against arterial stiffness in women of reproductive age, an effect that diminishes significantly after menopause.

Martin and colleagues investigated the effects of angiotensin-converting enzyme (ACE) inhibitory peptides derived from dietary proteins on blood pressure regulation. Their findings revealed that the peptide isoleucine-tryptophan reduces the activity of angiotensin-converting enzyme (ACE) in tissues, lowers the activity of matrix metalloproteinase-2, and improves coronary blood flow reserves. These results suggest that whey protein hydrolyzate could serve as an innovative nutritional supplement for managing blood pressure.

Gliemann explored whether hypertension is associated with changes in capillary muscle morphology and density, and how physical exercise might normalize these parameters. The study found that essential hypertension is linked to narrowing of the capillary lumen in skeletal muscle and thickening of the basement membrane. It is hypothesized that physical exercise can improve gas exchange in hypertensive individuals through structural changes in capillaries.

The relationship between high blood pressure and headaches has been well-documented in medical literature. A headache may be a symptom of hypertension, particularly when blood pressure is extremely elevated or rises rapidly. Numerous studies support the hypothesis that individuals with migraines are at an increased risk of developing hypertension. Conversely, the risk of developing migraines or other types of headaches in hypertensive patients appears to be low. The mechanisms underlying both migraine and AH may overlap, involving endothelial dysfunction, impaired autonomic cardiovascular regulation, and activation of the renin-angiotensin system [6].

Additionally, scientific databases contain evidence suggesting a connection between tinnitus and AH.

**Diagnostics**

Cardiovascular risk is closely associated with several factors, including elevated systolic and diastolic blood pressure, overweight, obesity, physical inactivity, smoking, age, family history, and gender. The primary organs affected by hypertension include the heart, brain, blood vessels, kidneys, and retina [7].

Accurate assessment and continuous monitoring of microcirculatory perfusion, perfusion dynamics, vascular structure, and oxygen saturation are essential components of managing arterial hypertension. Recent research employing non-invasive techniques has highlighted the importance of evaluating the retinal vasculature, as changes in the retinal layer provide an early indication of both functional and structural alterations in arterial hypertension. These changes can also reflect alterations in cerebral vessels [8].

Mercury exposure is considered a risk factor for hypertension and other CVD. The literature provides insights into the mechanisms by which mercury accelerates the development of hypertension, including its effect on reducing the bioavailability of nitric oxide (NO). Consequently, individuals exposed to mercury are at a higher risk of developing hypertension. According to Armignacco et al., it is suggested that the development of various forms of endocrine hypertension may be associated with specific DNA methylation patterns in the blood [9].

AH is an important cardiovascular risk factor in athletes. Factors such as exercise behaviour, use of non-steroidal anti-inflammatory drugs (NSAIDs), stimulants and poor dietary habits may contribute to the development of hypertension in athletes. Those involved in high-intensity exercise may be particularly susceptible to AH. In young athletes, confirmed AH warrants consideration of secondary causes of hypertension, while older athletes require comprehensive cardiovascular risk stratification [10].

AH exacerbates the severity of atheromatous lesions in experimental animal models, potentially worsening similar conditions in humans. However, atherosclerosis is more closely linked to disorders in lipoprotein metabolism than to other factors.

Despite significant advancements in the diagnosis and management of AH, less than half of patients with hypertension (defined as <140/90 mmHg) achieve adequate blood pressure control. Out-of-office blood pressure measurements are particularly important in identifying cases of white-coat hypertension, where blood pressure readings are elevated in a clinical setting but normal outside of it [10].

**Prevention and treatment**

Managing conditions that prevent or delay the onset of hypertension is essential. This includes maintaining a healthy diet, reducing intake of saturated fats and sodium, increasing consumption of fruits and vegetables, and achieving and sustaining an optimal body weight. A calorie-restricted diet has been shown to significantly reduce blood pressure and improve endothelial dysfunction [7].

In cases where treatment is successful, patients are often advised to further reduce their blood pressure. Key non-pharmacological strategies to combat hypertension include reducing dietary salt, limiting alcohol consumption, quitting smoking, ensuring proper nutrition, engaging in physical activity, and normalizing body weight. First-line pharmacological agents for managing AH include long-acting dihydropyridine calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and thiazide-like diuretics. For patients who do not achieve adequate control with these first-line agents, mineralocorticoid receptor blockers are considered effective. Most individuals with essential hypertension can attain optimal blood pressure control and significantly reduce the risk of CVD with a combination of first-line antihypertensive drugs and lifestyle modifications [11].

The treatment of AH begins with dietary modifications. Noteworthy attention is being given to three recently purified and identified peptides derived from marine products, whose bioactive properties—including antioxidant, antihypertensive, and antidiabetic effects—have been extensively studied [12].

Several studies have evaluated the impact of dietary supplements or food fortification with calcium on blood pressure in individuals across all age groups with normal blood pressure. Increased calcium intake led to a reduction in systolic and diastolic blood pressure by 1.37 mmHg and 1.45 mmHg, respectively. It was found that this effect was more pronounced at daily calcium doses exceeding 1000 mg. The reduction in blood pressure was particularly significant among younger individuals [13].

Other studies have examined the effects of combinations of calcium and magnesium, as well as calcium and potassium, on blood pressure. However, none of these combinations demonstrated a significant impact on blood pressure regulation.

Fermented milk has been suggested to have a blood pressure-lowering effect in humans. In a review of 15 studies involving 1,232 participants, moderate reductions in systolic blood pressure were observed, but no significant effect on diastolic blood pressure was found. The quality of the included studies varied, leading to the conclusion that fermented milk should not be used as a long-term treatment for hypertension or as a sole method for lowering high blood pressure.

Physical activity is widely recognised as a cornerstone of a healthy lifestyle. Our findings suggest that moderate intensity walking three to five times a week (20-40 minutes per session and 150 minutes per week for about three months) can lead to a reduction in blood pressure [14].

Aerobic exercise, when performed regularly, has no adverse effects and serves as a beneficial adjunctive therapy in the management of hypertension. Factors such as genetic background, the underlying etiology of hypertension, and individual differences in the pharmacodynamics and pharmacokinetics of antihypertensive medications may lead to varying blood pressure responses during physical activity.

Lifestyle modifications, including dietary changes and increased physical activity, are effective strategies for lowering blood pressure, preventing hypertension, and mitigating its associated complications. Pharmacological treatments also play a pivotal role in controlling blood pressure and preventing cardiovascular events. First-line antihypertensive drugs include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine calcium channel blockers, and thiazide diuretics.

The use of antihypertensive medications has significantly altered the natural progression of arterial hypertension. The primary complications of untreated, severe hypertension include heart failure, cerebral hemorrhage, and kidney failure.

There are numerous effective antihypertensive drugs available for achieving optimal blood pressure control. However, the question of how much to lower blood pressure remains a matter of debate. The 2013 European and German national guidelines recommend a target blood pressure of <140/90 mmHg for most patients. A recent study, the SPRINT trial, suggested that lowering blood pressure even further may benefit certain patients.

Results from a large randomized trial clearly indicated no significant difference in the prevention of myocardial infarction, stroke, or vascular mortality between patients taking antihypertensive medications in the morning versus those taking them in the evening. This suggests that patients may take their antihypertensive medications at any time of day [15].

Some studies suggest that in patients with arterial hypertension, taking one or more prescribed antihypertensive drugs before bedtime, rather than upon waking, leads to better blood pressure control (with a significant reduction in blood pressure during sleep). More importantly, this approach has been associated with a substantial reduction in severe cardiovascular complications [16].

Most clinical trial data recommend initiating antihypertensive therapy with a low dose of chlorthalidone, unless there are clear indications for an alternative medication. Additional agents (typically in this order: angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor

blockers (ARBs), calcium channel blockers, beta-blockers, alpha-blockers, aldosterone antagonists, direct vasodilators, and alpha(2)-agonists) may be added as needed to achieve effective blood pressure control.

Recent randomized clinical trials have demonstrated a significant benefit of antialdosterone medications, particularly spironolactone, as a fourth-line therapy in patients with stable hypertension [2].

Malhamé I, Dong S, and their colleagues found that prenatal administration of loop diuretics reduced systolic blood pressure (SBP) and cardiac output, while postnatal use decreased the need for additional antihypertensive medications.

Approximately two-thirds of individuals with type 2 diabetes mellitus (T2DM) also suffer from hypertension. The presence of AH exacerbates the frequency of both microvascular and macrovascular complications in these patients. The combination of hypertension and T2DM increases the risk of CVD fourfold compared to the general population. A target blood pressure of <140/90 mm Hg is effective for most patients; however, individual patient characteristics should always be taken into account. All classes of antihypertensive drugs are suitable for treating AH in patients with T2DM. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are excellent first-line options for treating primary or early hypertension in patients with T2DM and albuminuria. Most of these patients experience stable AH, making it necessary to prescribe a combination of two or more drugs. Thiazide and thiazide-like diuretics may be effective alone or in combination with ACE inhibitors or ARBs. Calcium channel blockers are ideal second- or third-line agents, and mineralocorticoid receptor antagonists should be added as third-line therapy.

A systematic review and meta-analysis have shown that thiazide and thiazide-like diuretics remain effective in lowering blood pressure in patients with chronic kidney disease [17].

Several studies have investigated the effect of finerenone on 24-hour ambulatory blood pressure in patients with chronic kidney disease and type 2 diabetes. Finerenone, a selective non-steroidal mineralocorticoid receptor antagonist with a short half-life, was found to reduce both diurnal and nocturnal blood pressure. Notably, these blood pressure reductions were sustained over 24 hours, even with once-daily morning dosing, regardless of the drug's half-life [18].

An interactive web-based hypertension self-monitoring system was evaluated in a study. Participants were asked to take daily blood pressure and heart rate measurements using a mobile phone, while receiving eight-week reports on their health status, symptoms, lifestyle, medications, and any side effects. The system also included reminders and motivational messages. After 8 weeks and 12 months, the proportion of participants who achieved a target blood pressure of <140/90 mm Hg increased. As a result, compared to conventional treatment, a higher proportion of participants attained controlled blood pressure (<140/90 mm Hg) [19].

A discrepancy between blood pressure readings in the legs and arms may indicate peripheral arterial disease (PAD), often signified by lower blood pressure in the legs compared to the arms. Arterial blockages in the legs can lead to symptoms such as rest pain and critical limb ischemia, a condition where there is an abrupt loss of blood flow to the limb due to a thrombus or fat blockage. This can require revascularization (restoration of blood flow through the opening of blocked arteries) or, in severe cases, amputation. Managing arterial hypertension in individuals with PAD requires careful consideration, as antihypertensive medications may lower blood pressure but also potentially impair blood flow in already blocked arteries, thereby reducing oxygen supply and influencing disease progression. This necessitates a delicate balance in treatment to minimize the risk of cardiovascular events, such as heart attack or stroke, and prevent mortality.

Diuretics have been shown to significantly reduce the overall incidence of cardiovascular diseases and heart failure compared to calcium channel blockers. On the other hand, calcium channel blockers have been found to reduce the incidence of stroke when compared to angiotensin-converting enzyme (ACE) inhibitors. Moreover, in comparison to angiotensin receptor blockers (ARBs), calcium channel blockers were associated with a reduction in the frequency of myocardial

infarction, although they led to an increased incidence of heart failure compared to both ACE inhibitors and ARBs [20].

Some studies have explored the gradual reduction in the dose of antihypertensive drugs prior to their discontinuation. These studies suggest that it is generally safe to withhold antihypertensive medications in elderly patients for "high blood pressure" or as part of primary prevention for cardiovascular diseases. However, it is crucial that older individuals do not discontinue their medications without consulting a healthcare professional first [21].

Acupuncture, an integral component of traditional Chinese medicine, involves the insertion of thin needles into specific points on the body. It is often used to lower blood pressure and alleviate hypertension-related symptoms. A systematic review of medical databases demonstrated that acupuncture led to short-term reductions in blood pressure (ranging from 1 to 24 hours). However, there is currently insufficient evidence to support the long-term effectiveness of acupuncture in the management of hypertension.

**Conclusions**

A retrospective review of the scientific literature from international databases regarding the current issues of AH revealed that factors such as hereditary predisposition, age, gender, personal characteristics, unhealthy habits, and comorbid conditions continue to play significant roles in the development of AH.The pathogenesis of AH is associated with hemodynamic disturbances, inflammatory processes, intestinal microbiota imbalances, immune system dysfunction, hormonal dysregulation, and structural changes in blood vessels. Effective management of AH includes dietary modifications, physical activity, the maintenance of a healthy lifestyle, mineral regulation within the body, and the inclusion of fermented dairy products. Pharmacologically, first-line antihypertensive agents, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, dihydropyridine calcium channel blockers, and thiazide or thiazide-like diuretics, remain the cornerstone of treatment. While the efficacy of acupuncture in the management of hypertension is evident, further research is necessary to confirm its long-term effectiveness.

**Conflict of interest.**

The authors declare no conflicts of interest.

This material has not been previously submitted for publication in any other journals and is not currently under consideration by any other publishers

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