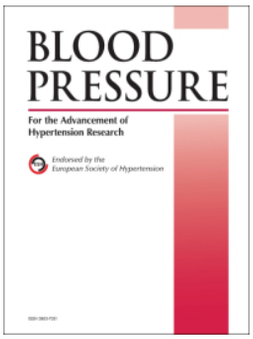

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REVIEW ARTICLE

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What is resistant arterial hypertension?

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ABSTRACT

Purpose: The current review is to describe the definition and prevalence of resistant arterial hypertension (RAH), the difference between refractory hypertension, patient characteristics and major risk factors for RAH, how RAH is diagnosed, prognosis and outcomes for patients.

Materials and Methods: According to the WHO, approximately 1.28 billion adults aged 30–79 worldwide have arterial hypertension, and over 80% of them do not have blood pressure (BP) under control. RAH is defined as above-goal elevated BP despite the concurrent use of 3 or more classes of antihypertensive drugs, commonly including a long-acting calcium channel blocker, an inhibitor of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a thiazide diuretic administered at maximum or maximally tolerated doses and at appropriate dosing frequency. RAH occurs in nearly 1 of 6 hypertensive patients. It often remains unrecognised mainly because patients are not prescribed $\geq$3 drugs at maximal doses despite uncontrolled BP.

Conclusion: RAH distinctly increases the risk of developing coronary artery disease, heart failure, stroke and chronic kidney disease and confers higher rates of major adverse cardiovascular events as well as increased all-cause mortality. Timely diagnosis and treatment of RAH may mitigate the associated risks and improve short and long-term prognosis.

PLAIN LANGUAGE SUMMARY

- Resistant arterial hypertension is a serious condition that leads to severe cardiovascular complications, such as heart attack, stroke and death.
- It is defined as above-goal elevated blood pressure despite the concurrent use of 3 or more classes of antihypertensive medications administered at maximum or maximally tolerated doses and at appropriate dosing frequency.
- Non-adherence to antihypertensive medications must be excluded before resistant arterial hypertension is diagnosed.
- Blood pressure should be measured appropriately. A person should sit in a comfortable chair with back supported, both feet flat on the ground, and legs uncrossed for at least 5 min before blood pressure measurement. A cuff length is supposed to be at least 80% and a width of at least 40% of the arm circumference. Placing the cuff directly on the skin of the upper arm at the level of the heart. Obtaining 3 readings 1 min apart. Discarding the first reading and taking the mean of the second and third readings
- Resistant arterial hypertension should be distinguished from refractory hypertension, when blood pressure remains uncontrolled on maximal or near-maximal therapy of 5 or more antihypertensive agents of different classes.

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Resistant arterial hypertension; hypertension; blood pressure; antihypertensive treatment; risk factors; cardiovascular disease

Definition of resistant arterial hypertension

Resistant arterial hypertension (RAH) is a high risk condition, leading to impaired cardiovascular disease (CVD) outcomes and increased all-cause mortality [1]. It is defined as above-goal elevated blood pressure (BP) despite the concurrent use of 3 or more classes of antihypertensive drug, commonly including a long-acting calcium channel blocker, an inhibitor of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [ARB]), and a thiazide diuretic. All agents should be administered at maximum or maximally tolerated doses and at appropriate dosing frequency. BP should be measured appropriately and the BP threshold for

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diagnosis and treatment goals should be in line with current clinical practice guidelines [2]. Patients with the white-coat effect should not be included in the definition of RAH as well as those non-adhering to the diagnosis of RAH [3]. Controlled resistant hypertension is said to be present when BP is controlled on ≥4 antihypertensive medications at maximal or maximally tolerated doses [1]. Apparent treatment resistant hypertension (aTRAH) is a term used when medication dose, adherence, or out-of-office BP is not documented or accounted for, and pseudo resistance cannot be excluded in a patient on ≥3 antihypertensive agents [1].

Errors in BP measurement and techniques

Errors in BP measurement can account for the misdiagnosis of RAH. BP results are typically dependent on the patient preparation, environmental conditions, cuff size and measurement techniques, requiring an average of at least two readings obtained on at least two separate occasions [2,4]. Out-of-office BP and self-monitored BP require proper technique for accurate BP results [2,5,6]. A study comparing standard triage BP measurements by clinic staff with an automated device obtaining up to 6 BP measurements 1 min apart, while the patient was unsupervised and seated in a quiet room, showed inaccurately increased BP measurement in 33% of patients referred as RAH [7]. Inappropriately elevated cuff pressure may occur in patients with severe arterial disease and stiff, calcified arteries, a condition called pseudohypertension [8].

Proper BP measurement technique includes [4,9]:

- Preparing the individual by emptying a full urinary bladder and then sitting with legs uncrossed and back, arm and feet supported in a quiet room, ideally 5 min before the first BP measurement is obtained;
- Choosing a BP cuff with a cuff length of at least 80% and a width of at least 40% of the arm circumference;
- Placing the cuff directly on the skin of the upper arm at the level of the heart on the supported arm;
- Obtaining three readings 1 min apart. Discarding the first reading and taking the mean of the second and third reading

White-coat effect

The 'white-coat effect' is defined as an inappropriate BP response to a clinic visit, but there is no agreement as to exactly how it should be defined. The most widely used definition is the BP difference between the average clinic and daytime ambulatory measurements [4]. In contrast to previous observations Mancia et al. recently showed that the risk of CVD complications in patients with white-coat hypertension without organ damage is higher compared with the risk in hypertensive patients with controlled BP [10]. To rule out true RAH, an out-of-office BP monitoring is generally required. The white-coat effect has been attributed to an alerting reflex triggered by the healthcare provider or the clinic environment that activates the sympathetic nervous system [11]. A clinically significant white-coat effect may be present in 28% up to 39% of individuals with aTRAH identified by office BP measurement [12]. De la Sierra et al. found that among >8200 patients with apparent RAH included in the *Spanish Ambulatory Blood Pressure Monitoring Registry*, 62.5% were classified as having true RAH, while the remaining 37.5% were identified as having white coat hypertension [13].

Medication non-adherence

Non-adherence to antihypertensive medications must also be excluded before RAH is diagnosed. Medication non-adherence is very common in patients with more severe hypertension [14,15]. Approximately 50–80% of hypertensive patients demonstrate suboptimal adherence to antihypertensive medications [16,17]. This relatively high proportion of non-adhering patients that may mimic RAH is related, at least in part, to the large pill burden, dosing complexity, expense, high frequency of adverse reactions with multidrug antihypertensive regimens, poor patient–clinician relationship and clinician inertia with reduced insistence on adherence despite patients being consistently non-adherent [16]. Several systematic reviews and meta-analyses have assessed the impact of interventions, including modification of antihypertensive therapy, on adherence to antihypertensive medications [18,19]. Thus, in patients with hypertension, fixed-dose combination regimens reduced the risk of medication non-compliance by 24% compared to free-drug combination regimens [20]. In the recently published meta-analysis (15 RCI and 7415 participants) showed that the behavioural self-monitoring interventions combined with tailored advice compared to usual care or minimal intervention resulted in higher and significant changes in both SBP and diastolic blood pressure (DBP) (SBP: −2.92 mmHg, 95% CI −3.94 to −1.90, $n = 3102$ vs −0.72 mmHg, 95% CI −1.67 to 0.23, $n = 4199$, $\chi^2 = 9.65$, $p = .002$; DBP: −2.05 mmHg, 95% CI −3.10 to −1.01, $n = 968$ vs 1.54 mmHg, 95% CI −0.53 to 3.61, $n = 400$, $\chi^2 = 9.19$, $p = .002$) [21].

RAH vs refractory hypertension

Refractory hypertension is a condition when BP remains uncontrolled on maximal or near-maximal therapy of five or more antihypertensive agents of different classes, including a long-acting thiazide-like diuretic (such as chlorthalidone) and mineralocorticoid antagonists [1]. RAH can ususally brought under control by adjusting treatment. In contrast, refractory hypertension most often cannot be controlled despite skillful attempts to use synergistic antihypertensive drugs.

Prevalence of resistant arterial hypertension worldwide and by demographics

Among the treated adults with hypertension, RAH occurs in approximately in 12–15% of population-based and 15–18% of clinic-based reports [22–26] mostly in those with a long history of hypertension and chronic kidney disease (CKD) [24,27]. In population- and clinic-based studies, some RAH cases may remain unrecognised because patients are not prescribed $\geq$3 drugs at maximal doses despite uncontrolled BP. In contrast, clinical trials usually include forced titration schemes that unmask RAH by reducing the prevalence of suboptimal treatment [28]. Demographic correlates of RAH include black race, older age and male sex [29]. RAH is characterised by variable clustering of distinct demographics, comorbidities, physiological aberrations and metabolic abnormalities. However, these factors are not mutually exclusive because, in fact, they can be substantially interdependent (e.g. non-dipping or reverse dipping BP and sympathetic nervous system overactivity, visceral obesity and excess aldosterone secretion) [1].

Interestingly, the number of articles on RAH on PubMed per year increased substantially after the advent of renal denervation in 2009. However, it may have reached a peak in 2015 and seems to plateau or even decline since then (Figure 1).

Patient's characteristics of RAH

Lifestyle risk factors

Obesity

Findings from the NHANES (*National Health and Nutrition Examination Survey*) of 13,375 hypertensive adults demonstrated that body mass index (BMI) $\geq$30 kg/m^2 approximately doubles the risk for aTRH [28]. In 14,461 patients with RAH in the *Spanish Ambulatory Blood Pressure Monitoring Registry*, a BMI $\geq$30 kg/m^2 was also an independent risk factor for RAH (odds ratio, 1.62; 95% CI 1.32–1.99) [30]. Among 3367 hypertensives with chronic kidney disease (CKD), increasing levels of obesity were independently associated with higher risks of aTRH, ranging from an odds ratio of 1.52 (BMI $\geq$ 30 kg/m^2) to 2.26 (BMI $\geq$ 40 kg/m^2) [24]. In the study with over >470,000 patients from the Kaiser Permanente Southern California health system, obesity (BMI $\geq$ 30 kg/m^2) was also found to be an independent risk factor for RAH (odds ratio, 1.62; 95% CI 1.42–1.51) [29]. The *Dietary Approaches to Stop Hypertension* (DASH) recommended eating pattern consistently reduces BP by 6.7/3.5 mmHg as documented in a recent meta-analysis [31,32]. However, in the REGARDS cohort, a low DASH diet questionnaire score was not independently associated with aTRH [33].

Dietary sodium

Higher dietary sodium intake is independently associated with increases in arterial BP [34–37]. However, relatively large interindividual and racial variations in 'salt sensitivity' of BP exist. This leads to excess volume retention, vascular dysfunction, arterial stiffness, sympathetic activation, impaired renin–angiotensin axis suppression, mineralocorticoid receptor activation and immune cell modulation [38–40]. Several studies demonstrated a significant reduction in BP among patients with RAH following a low sodium diet [41,42].

Physical inactivity

Both reduced physical activity and lower physical fitness are independent risk factors for hypertension. [33,43–47]. Self-reported inactivity was not predictive of RAH among patients in the REGARDS cohort [48]. Conversely, a thrice-weekly treadmill walking exercise program for 8–12 weeks significantly lowered daytime ambulatory BP ($6 \pm 12/3 \pm 7$ mmHg; $p = 0.03$) among 50 treated patients with RAH [48].

Alcohol intake

Alcohol intake has been linked to increases in BP and the risk for developing hypertension [49–51]. The dose–response association may differ between men (linear) and women (J shaped) [51] and is modified by metabolic genes [50]. Drinking alcohol >30–50 g/day was an independent risk factor for hypertension [52].

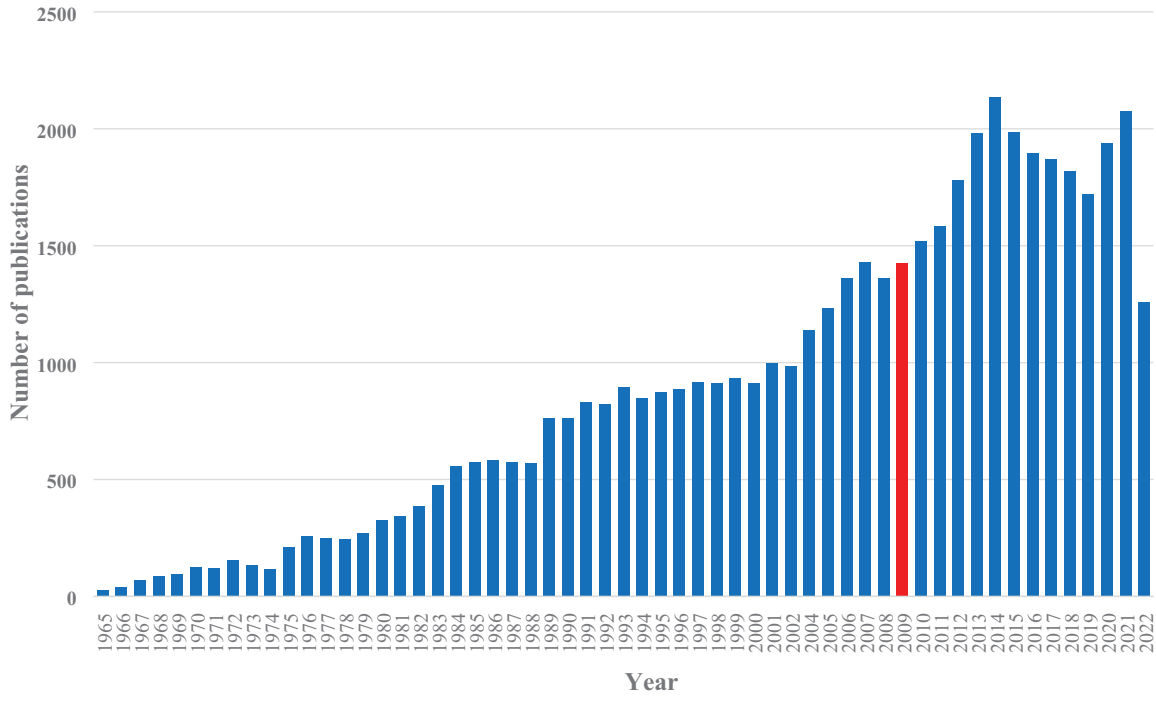

Figure 1. Number of yearly articles on resistant arterial hypertension (RAH) on PubMed increased substantially after the advent of renal denervation in 2009.

Anxiety and depression

Globally, up to 33.7% of the population are suffering from anxiety disorder during lifetime [53]. In the systematic review and meta-analysis of eight prospective studies [54], baseline anxiety increased risk of incident hypertension, the pooled adjusted HR was 1.55 (95% CI 1.24–1.94), with strong heterogeneity detected (PQ $<$ 0.001; $I^2 = 84.6\%$). Recent studies showed a positive association between comorbid anxiety and RAH [55]. In particular, patients with RAH scored higher points in Beck Depression Inventory ($\geq$5 points) and the Hamilton Anxiety Scale ($\geq$3 points)compared with healthy controls and non-resistant hypertensive patients [56]. Depression can negatively affect the course of hypertension, interfere with adherence to medications [3].

Natural disasters, catastrophes, war

Mental and physical stress, insomnia, excess salt intake due to consumption of stored food, and infection (pneumonia) is a leading cause of hypertension during natural disasters, catastrophes and war [57]. Hypertension-related diseases develop immediately after a disaster, and their risk continues until the living environment stabilised and lifestyle habits are improved [57]. Large individual differences in the elevation of BP and duration of elevated BP exist. Thus, SBP 5–25 mmHg average increase has been reported increase for 2–4 weeks after an earthquake [58]. Survey of Health, Ageing and Retirement in Europe (SHARE) demonstrated that exposure to war during childhood is associated with increased lifetime risk of CVD, diabetes, high cholesterol and hypertension [59].

Patient comorbidities

Multiple comorbidities have been associated with RAH. Such as obesity [60–62], left ventricular hypertrophy [63], albuminuria [64,65], diabetes mellitus [29,60,64,66], CKD [29,60,67], higher Framingham 10-year risk score [60], and obstructive sleep apnoea (OSA) [68]. A very high proportion (60 – 84%) of individuals with RAH have sleep apnoea [69–71]. Other sleep abnormalities are also manifest in RAH (relative to those with controlled hypertension or normotensives), including shorter sleep duration, reduced sleep efficiency and less rapid eye movement sleep [72].

Physiological derangements

Physiological aberrations in RAH include vascular disease/dysfunction as evidenced by high rates of peripheral [60] and carotid artery atherosclerosis [63], impaired endothelial function [65,73], reduced arterial compliance and raised systemic vascular resistance [61], all of which appear to be more pronounced in RAH compared with non-RAH. The normal nocturnal decline in BP is also attenuated in a high proportion (43 – 65%) of individuals with RAH [12,74,75].

Metabolic derangements

RAH has also been associated with metabolic derangements, including hyperuricaemia [22] aldosterone excess [76] and suppressed circulating renin levels [77]. In general, RAH is characterised by exquisite salt sensitivity of BP. Reducing dietary sodium intake to levels significantly below the level of usual intake in Western societies (e.g. 50 mmol/day) promptly and impressively lowers BP in many individuals with RAH [41].

Genetic variants

Heritability of RAH was shown in some family-based studies indicating that 50–60% of BP variability can be attributed to genetic factors [78–80]. Common genetic variants influencing BP have been identified at >300 independent loci, but require scores based on hundreds of thousands of individuals for their detection as their individual contribution is minute [81]. The majority of genetic studies of RAH had significant limitations such as non-adequate sample sizes

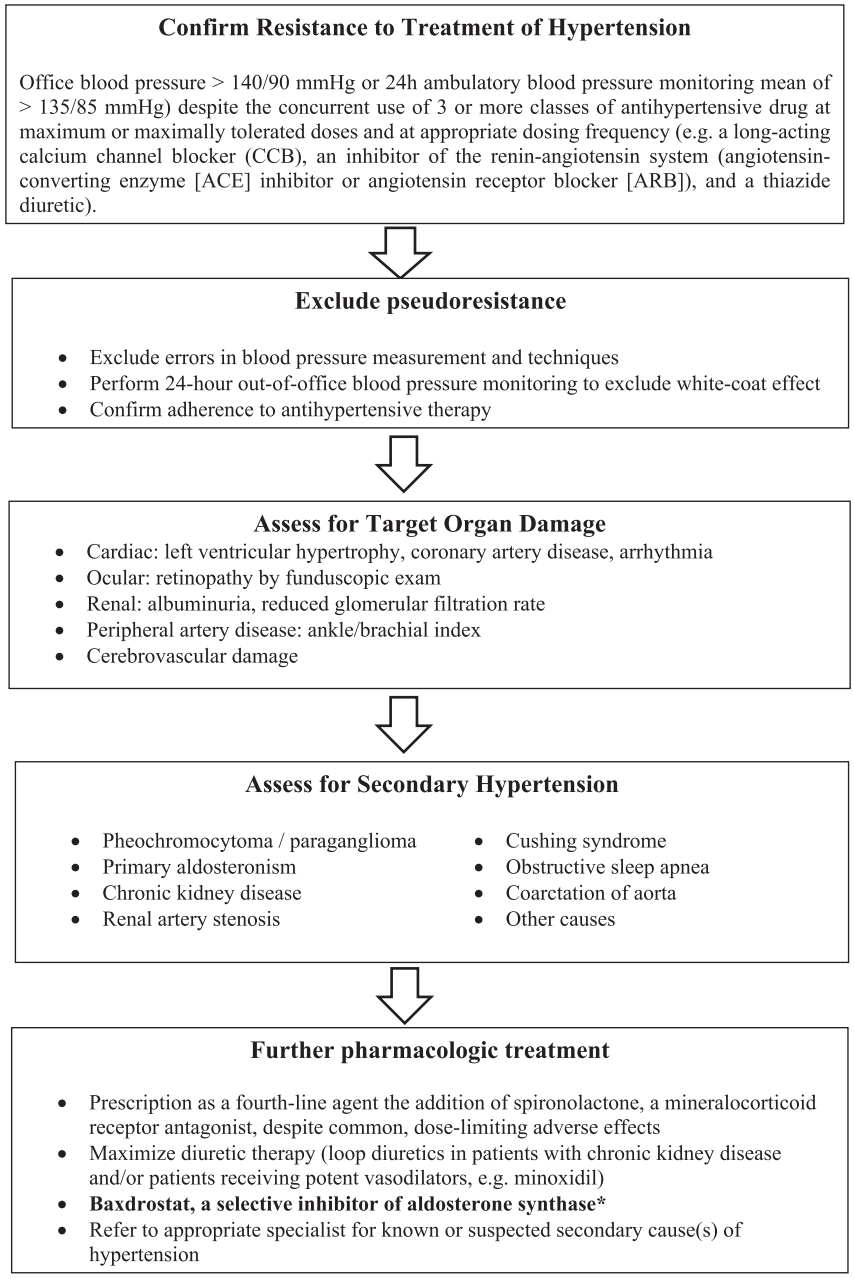

Figure 2. Diagnosis of resistant arterial hypertension (modified from [3]). *Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension. Dose-dependent changes in systolic BP of −20.3, −17.5, −12.1 mmHg were observed in the 2-, 1-, 0.5-mg Baxdrostat in patients with treatment-resistant hypertension [95].

and multiple testing across the many candidate gene studies [82–86].

Prognosis and outcomes of resistant arterial hypertension

In a retrospective study of >200,000 patients with new onset hypertension, those with RAH were 47% more likely to suffer the combined outcomes of death, myocardial infarction, heart failure, stroke, or CKD over the median 3.8 years of follow-up [87]. In a study with over 400,000 participants, patients with RAH had a 32% increased risk of developing end-stage renal disease, a 24% increased risk of an ischaemic heart event, a 46% increased risk of heart failure, a 14% increased risk of stroke and a 6% increased risk of death compared with patients without RAH [88]. Prospective studies using ambulatory BP monitoring showed an almost 2-fold increased risk of CVD events in patients with true RAH compared with those with hypertension responsive to treatment [12,69,89–91].

RAH is associated with worse outcomes among patients with some comorbid conditions. Thus, in patients with coronary artery disease, RAH is associated with higher rates of major adverse cardiovascular events (MACE; i.e. CV death, myocardial infarction and stroke) [28,92,93]. In patients with CKD, RAH is associated with higher risk of myocardial infarction, stroke, peripheral arterial disease, heart failure and all-cause mortality compared with those without RAH [24]. Conversely, RAH is not associated with increased adverse clinical events in patients with heart failure with reduced ejection fraction and may lower the risk for heart failure-related rehospitalization [94].

Further pharmacologic treatment

According to the recent guidelines, a prescription as a fourth-line agent the addition of spironolactone, a mineralocorticoid receptor antagonist, despite common, dose-limiting adverse effects is recommended [3]. Diuretic therapy may be maximised, e.g. loop diuretics in patients with chronic kidney disease and/or patients receiving potent vasodilators (e.g. minoxidil) (Figure 2).

Recently published Phase 2 Clinical Trial of Baxdrostat for Treatment-Resistant Hypertension showed a dose-dependent changes in systolic BP of −20.3, −17.5, −12.1 mmHg were observed in the 2-, 1-, 0.5-mg Baxdrostat in patients with treatment-resistant hypertension [95]. **Baxdrostat**, a selective inhibitor of aldosterone synthase, a likely cause of treatment resistance acts by suppressing hormone synthesis rather than by blocking the mineralocorticoid receptor. Preclinical and phase 1 studies have shown that baxdrostat has high selectivity (selectivity ratio, 100:1) for aldosterone synthase as compared with the enzyme required for cortisol synthesis, 11β-hydroxylase, which shares 93% sequence similarity with aldosterone synthase [96].

Patients should be referred to appropriate specialists for known or suspected secondary cause(s) of hypertension (Figure 2).

Conclusion

RAH is a serious disorder where patients had a substantially increased risk of developing end-stage renal disease, major adverse cardiovascular events and stroke, heart failure and all-cause mortality compared with patients without RAH. Timely diagnosis of RAH will allow prompt preventive and therapeutic interventions to mitigate RAH-associated outcomes.

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