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ANTIHYPERTENSIVE PHARMACOTHERAPY IN HYPERTENSIVE PATIENTS AT A TERTIARY CARE TEACHING HOSPITAL AND MEDICAL COLLEGE IN INDIA

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ABSTRACT

Objectives: The aim of the study was to compare the efficacy of Atenolol and Olmesartan in Stage-1 hypertension (HTN), and the adverse effect profile of Atenolol and Olmesartan in Stage-1 HTN.

Methods: A prospective, randomized, open, and parallel study was carried out in 100 patients attending the outpatient department of General Medicine Department MMIMSR, Mullana, Ambala, India with Stage -1 HTN according to joint national committee VII. The patients were randomly divided into two groups to receive Tab. Atenolol 50 mg od (Group A, n=50) and Tab. Olmesartan medoxomil 20 mg (Group B, n=50) od for a total period of 12 weeks with regular follow up every 2 weeks from the baseline. At each visit, blood pressure (BP), heart rate, and adverse effects were evaluated. Laboratory investigations were carried out at baseline and end of the study period. p<0.005 was considered statistically significant.

Results: Atenolol and Olmesartan medoxomil both significantly reduce BP and heart rate (p<0.005). Olmesartan medoxomil is more efficacious in reducing BP.

Conclusion: Olmesartan medoxomil is a better choice for Stage -1 HTN between the two drugs as it leads to a greater decrement in BP.

Keywords: Cardiovascular disease, Hypertension, Blood pressure, Systolic blood pressure, Diastolic blood pressure, Beta-blockers, Angiotensin receptor blockers, Heart rate.

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INTRODUCTION

Cardiovascular disease (CVD) is one of the most common contributors of morbidity and mortality in underdeveloped and developing countries including South Asian countries including India [1]. The emergence of the CVD epidemic during the last three to four decades has been a very concerning cause for health-care providers in recent years [2]. Among the cluster group of CVDs, hypertension (HTN) represents the most common form of cardiovascular risk factor [3]. Several previous studies have demonstrated longitudinal associations between HTN and coronary artery disease, myocardial infarction [4]. HTN is defined as blood pressure (BP) of 140/90 mmHg or more on two separate occasions measured at least 1-2 weeks apart [5]. The prevalence of HTN increases with advancing age [5]. It affects approximately onethird of the world's adult population and it is predicted to increase by 60% toward 2025 [6]. HTN is also associated with several serious conditions and accounts for 13.5% of all premature deaths, 54% of all strokes, and 47% of ischemic heart diseases [7]. The number of adults with HTN in 2025 is predicted to exponentially increase by about 60% to a total of 1.56 billion [8]. Among all the hypertensive populations in developed countries and India, the percentage of those who are adequately controlled is estimated to be 50% and 11-12.8%, respectively [9]. CVDs caused 2.3 million deaths in India in the year 1990; this is expected to double by the year 2020 [10]. HTN can be simply described as abnormal elevation in BP [11]. Primary HTN - with no obvious underlying medical causes [12] and secondary HTN - with identifiable cause [5]. According to joint national committee (INC) VII in 2003, an increase in BP was again classified into three stages of HTN [5]. The JNC 8 classification for HTN and guideline management algorithm has been recently released in 2014 [13]. Another subtype of HTN includes isolated systolic HTN defined as a wide pulse pressure HTN resulting from excessive large artery stiffness [14]. Numerous common genetic variants with small effects on BP have been identified,

for example, GUCY1A3-GUCY1B3 [15]. Several risk factors have been identified for the development of Primary or Essential HTN [16,17]. Diet: Micronutrients correlate with the prevalence of HTN and salt intake [18]. Inadequate intake of potassium, calcium, and magnesium has been implicated in the risk of HTN in various populations study but not in all trials [19,20]. Hyperlipidemia: Low high-density lipoprotein cholesterol and increased triglycerides are predictors of coronary artery heart diseases [21]. Obesity: 50% of obese patients have concomitant HTN [22] visceral obesity a strong risk factor for HTN [23-25]. The relationship between obesity and HTN is observed virtually in all societies, ages [26]. Smoking: Smoking is an independent risk factor for cardiovascular deaths and stroke in females where risk is doubled [27]. Genetics: Genes have been implicated in the causation of high BP [28,29]. Aging: It has been found that BP increases with age, especially systolic BP (SBP) [30]. Type A personality: It has been well proven that type A personality has an increased risk of atherosclerosis and coronary morbidity [31]. Newer risk factors: Fibrinogen, hyperhomocysteinemia are new emerging factors of HTN [32-35]. About 30% of populations with hyperhomocysteinemia were found to have premature atherosclerosis [36]. Secondary HTN results from an identifiable underlying cause [37,38]. In most people with high BP, increased resistance to blood flow contributes to an elevation in BP level while heart rate remains normal [39]. Most evident implicates abnormalities in the intrarenal renin-Angiotensinaldosterone system [40,41]. Korotkoff described the systolic and diastolic sounds he heard with a stethoscope [42]. Janeway abandoned the clinical use of the term: essential HTN and called the disorder: hypertensive CVD [43]. Southern Medical Journal stated that: HTN is neither a cause of nephritis or arteriosclerosis [44]. The treatment of HTN itself is a difficult [45]. In 1950 despite the advances that occurred with the availability of Reserpine, Ganglionic blocking agents, limited the effectiveness [46]. Lowering BP in patients with HTN significantly decreased cardiovascular morbidity and mortality as compared with a

placebo-controlled trial [47]. The first JNC report was issued in 1977 with updates occurring every 4-5 years [48]. In 2003, the JNC 7 report modified the previous INC 6 guidelines and recommends a thiazidetype diuretic as the preferred choice for initial monotherapy [49]. Lifestyle modifications complement to pharmacological therapy in lowering BP [50]. Diet control measures: The Diet Approach to Stop HTN trial showed a reduction in BP of 11.4/5.5 mm Hg [51]. Salt: There was a decrease of 4.8/2.5 mmhg in hypertensive patients [52,53]. Potassium: Potassium protects against vascular disease [54]. Calcium: The same inverse relationship has been shown with magnesium intake [55]. Calories and fat: Diets with fewer calories cause reductions in BP [56]. Alcohol: More than 3 drinks per day is a predictive cause for HTN [57]. Smoking: Smoking cessation decreases the risk of coronary artery [58]. Exercise: Sedentary individuals with normal BP have a 20-50% increased risk of developing HTN [59]. Various drugs are available for treatment of HTN. Clinical trials have shown that thiazides in combination with other drugs have a synergistic effect [60,61]. The veteran's affairs cooperative study class on antihypertensive agents has shown that the overall response rate in no responders was increased to 65% from 49% when combination therapy was used [62]. Betablockers: Propranolol it revolutionized the medical management [63]. Atenolol is widely used for the management of HTN [64]. Angiotensin receptor blockers: All drugs in this class are approved by Food and Drug Administration for treatment of HTN, either alone or in combination with other drugs [65]. Olmesartan is a comparatively new Angiotensin II receptor antagonist used to treat HTN.

METHODS

A prospective, randomized, open, and parallel study was carried out in 100 patients attending the outpatient department of General Medicine Department MMIMSR, Mullana, Ambala, India with Stage-1 HTN. The patients were randomly divided into two groups to receive Tab. Atenolol 50 mg od (Group A, n=50) and Tab. Olmesartan medoxomil 20 mg (Group B, n=50) od for a total period of 12 weeks with regular follow-up every 2 weeks from the baseline.

RESULTS

Results were recorded and compared from the baseline. The results of the BP of individual patients were consolidated at the end of 12 weeks after treatment for both groups.

The analysis of Fig. 1 showed the average age of the patients treated with Atenolol 50 mg Drug was 43.10 ± 7.78 years which was not significantly p>0.05 different than the average age of the patients treated under the Olmesartan 20 mg Drug, that is, 42.86 ± 9.23 . In the research study overall, 27-60 years of patients were considered and among them, 28-60 years of patients were receiving the Atenolol 50 mg Drug, and the patients in the age group of 27-60 years were receiving Olmesartan 20 mg Drug.

There were no statistical differences in context with baseline age characteristics between the two groups. The parameters were normally distributed and comparable (p-value>0.05).

The analysis of Fig. 2 showed in the research study 58.0% (58) were males and among them, 31 (62%) were receiving the Atenolol 50 mg Drug treatment, and 27 (54.0%) were receiving the Olmesartan 20 mg drug treatment. Furthermore, there were 42.0% (42) of females were involved in the study and among them, 19 (38.0%) were receiving the Atenolol 50 mg drug treatment, and 23 (26.0%) were receiving the Olmesartan 20 mg drug treatment. The p-value obtained was >0.05 which shows that there is no significant difference in gender distribution of the two study groups.

The baseline means SBP of subjects in the Atenolol 50 mg drug group was 148.60 which significantly drops down to 143.12 at week 2 assessment followed by again significant drops at each 2-week assessment and finally by the end of the 12-week assessment it significantly drops to 137.36. The baseline means SBP of subjects in the Olmesartan 20 mg drug group was 148.12 which significantly drops down to 138.28 at week 2 assessment followed by again significant drops at each 2-week assessment and finally by the end of the 12-week assessment it significantly dropped to 128.88.

It was further assessed that at baseline no significant difference was recorded among SBP levels among subjects of both drug groups but on comparative analysis at each week assessment shows that the



Fig. 1: Comparison of the mean age of Group A and Group B



Fig. 2: Gender Distribution of Subjects under Group A and Group B



Fig. 3: Comparison of Systolic Blood Pressure in Group A and Group B

subjects of Olmesartan 20 mg groups showed more decrease in SBP as compared to Atenolol 50 mg group subjects at baseline both subjects group Atenolol 50 mg and Olmesartan 20 mg had an average SBP of 148.60 and 148.12, respectively, whereas at 12th-week assessment there was significant difference recorded as values of 137.36 and 128.88, respectively.

The analysis of Fig. 4 showed that the overall reduction in SBP was more among the subjects under the drug group Olmesartan 20 mg, that is, 13.0% in the $12^{\rm th}$ week since the baseline recordings in comparison to the reduction in the same period for the subjects under the drug group Atenolol 50 mg, that is, 7.6%. Furthermore, it was analyzed that at each week's assessment the percentage drop of SBP was evident more among the Olmesartan 20 mg group subjects in comparison to Atenolol 50 mg subjects.

The baseline means diastolic BP (DBP) of subjects in the Atenolol 50 mg drug group was 94.92 which significantly drops down to 91.68 at week 2 assessment followed by a non-significant drop to 91.44 at the 4th-week assessment of subjects but after that, at each 2-week assessment there was significant drop was recorded and finally, by the end of the 12-week assessment it significantly dropped to 87.08.

The baseline mean DBP of subjects in the Olmesartan 20 mg drug group was 94.08 which significantly drops down to 88.04 at week 2 assessment and after that at each 2-week assessment there was significant drop was recorded and finally, by the end of the 12-week assessment, it significantly dropped to 81.24. It was further assessed that at baseline no significant difference was recorded among the DBP levels among the subjects of both drug groups but on comparative analysis at each week, the assessment shows that the subjects of Olmesartan 20 mg groups showed more decrease in DBP as compared to Atenolol 50 mg group subjects at baseline both subjects under group Atenolol 50 mg and Olmesartan 20 mg had average DBP of 94.92 and 94.08, respectively, whereas at 12th-week assessment there was significant difference recorded as values of 87.08 and 81.24, respectively.

The analysis of Fig. 5 showed that the overall reduction in DBP was more among the subjects under the drug group Olmesartan, that is,



Fig. 4: Comparison of Percentage Reduction in Systolic Blood Pressure of Group A and Group B



Fig. 5: Comparison of Diastolic Blood Pressure in Group A and Group B

13.6% in the 12th week since the baseline recordings in comparison to the reduction in the same period for the subjects under the drug group Atenolol, that is, 8.3%. It was analyzed at most of the week assessment the percentage drop of DBP was almost similar among both drug groups, that is, weeks 6, 10, and 12 assessment whereas the larger difference was recorded at rest 3-week assessments.

The baseline means heart rate of subjects in the Atenolol 50 mg drug group was 85.72 which significantly drops down to 83.48 at week 2 assessment followed by a significant drop at each 2-week assessment and finally by the end of the 12-week assessment it significantly dropped to 72.64.

The baseline means heart rate of subjects in Olmesartan 20 mg drug group was 86.72 which significantly drops down to 81.48 at week 6 assessment but at 8^{th} -week assessment, it was not significant drop, that is, 81.36 but after that, at each 2-week assessment there was significant drop was recorded and finally, by the end of the 12-week assessment, it significantly dropped to 78.88.

It was further assessed that at baseline no significant difference was recorded among the heart rate levels among the subjects of both drug groups as the subjects of Olmesartan 20 mg had a higher heart rate average than the subjects of Atenolol 50 mg subjects and on comparative analysis at each week assessment shows that the subjects of Olmesartan groups showed a lesser decrease in heart rate as compared to Atenolol 50 mg group subjects at baseline both subjects group Atenolol 50 mg and Olmesartan 20 mg had average heart rate of 85.72 and 86.72 respectively whereas at 12th-week assessment there was significant difference recorded as values of 72.64 and 78.88, respectively.

The analysis of Fig. 7 showed that the overall reduction in heart rate was more among the subjects under the drug group Atenolol 50 mg, that is, 15.3% in the 12^{th} week since the baseline recordings in comparison to the reduction in the same period for the subjects under the drug



Fig. 6: Comparison of Percentage Reduction in Diastolic Blood Pressure of Group A and Group B



Fig. 7: Comparison of Heart Rate in Group A and Group B

group Olmesartan 20 mg, that is, 9.0%. It was analyzed at all of the week assessment the percentage drop of heart rate was more among the Atenolol 50 mg group subjects but the opposite trend was only evident at 6th-week assessment when the subjects from the Olmesartan 20 mg showed more decrease in heart rate than the subjects from the Atenolol 50 mg group.

The subjects of the Atenolol 50 mg group their average fasting blood sugar level at baseline time was 104.1 which decreased to 92.0 at the 12th week of assessment whereas among the subject of the Olmesartan 20 mg group their average fasting blood sugar level at baseline was 105.6 but it drops down to 91.6 at the 12th-week assessment.

In the comparison of the two groups for the fasting blood sugar level, there was no significant difference was recorded at baseline and 12th week between the fasting blood sugar of subjects measured. It was concluded that among the subjects of the Atenolol 50 mg group their fasting blood sugar level decreased by -8.9% from baseline to 12th week assessment while among the subjects of the Olmesartan 20 mg group it decreased by 9.0% in a similar time frame.

Fig. 9 describes the distribution of the subjects in terms of the adverse effect of drugs and it was analyzed that the neurological symptoms in Group A, 32.0% and 26.0% subjects reported headache and dizziness, respectively, while 16.0% and 36.0% of subjects reported the same in Group B, respectively.

DISCUSSION

Regarding baseline characteristics such as age distribution, there was no statistical difference (p>0.05) between the two groups. The Mean Age for Group A patients were43.10±7.78 years and Group B patients were 42.86±9.23 years, respectively. The age group selected for our study was 18–60 years. A similar age group was taken by Jackson



Fig. 8: Comparison of percentage difference in heart rate in Group A and Group B



Fig. 9: Bar Chart Comparison of adverse drug reactions among both Drug Group Subjects under Atenolol 50 mg and Olmesartan 20 mg Drug Treatment

et al. to see the effect of antihypertensive drugs (Atenolol, Ramipril, and Amlodipine) on lowering BP in hypertensive patients of age group 18–70 years for 3 years and no statistical difference (p>0.05) between two groups regarding age distribution [66].

While comparing other baseline characteristics such as gender distribution, the p-value obtained was >0.05 which shows that there is no significant difference in gender distribution of the two study groups. In our study, there were 31 males and 19 females in Group A and under the Group B category, there were 27 males and 23 females. In a study conducted by Rasmussen *et al.*. thirteen patients, of which nine men and four women were enrolled to do a comparison between effects of Atenolol and Metoprolol on BP and heart rate at rest, during exercise and there was no statistical difference (p>0.05) between two groups in context with gender distribution [67].

The parameters of our study were normally distributed and were comparable. One of the parameters of observations was SBP. The baseline means SBP of subjects in the Atenolol drug group was 148.60 which significantly drops down to 143.12 at week 2 assessment followed by again significant drops at each 2-week assessment and finally by the end of the 12-week assessment it significantly drops to 137.36 an average reduction of 11.24 mmHg, while Freytag *et al.*. conducted a study to compare the efficacy as well as tolerability of Atenolol and Telmisartan in treatment of mild to moderate type of HTN in 489 patients for 26 weeks, they concluded that Final SBP reductions of 16.7 mmHg for the Atenolol, the difference in SBP was significant (p<0.005). When we compared the results of these studies, we found that there is a greater reduction of SBP, that is, 16.7 mmHg in Freytag *et al.*. than our study, that is, 11.24 mmHg [68].

The baseline means SBP of subjects in the Olmesartan drug group was 148.12 which significantly drops down to 138.28 at week 2 assessment followed by again significant drops at each 2-week assessment and finally by the end of the 12-week assessment it significantly dropped to 128.88, that is, an average reduction of 19.24 mmHg. A similar double-blind study was conducted by Van Miegham to compare the efficacy of Olmesartan 20 mg (n=165) and Atenolol 50 mg (n=161) for 12 weeks. They concluded that a significantly greater reduction in SBP was observed from baseline with Olmesartan (-20.7 ± 1.0) than with Atenolol (-17.2 ± 1.0). When we compared the results of these studies, we found that a reduction of 20.7 mmHg of SBP was observed in the Van Miegham study, while a reduction of 19.24 mmHg was observed in our study, and results are almost coinciding with each other [69].

The baseline means DBP of subjects in the Atenolol drug group was 94.92 which significantly drops down to 91.68 at week 2 assessment followed by a non-significant drop to 91.44 at the 4th-week assessment of subjects but after that, at each 2-week assessment there was a significant drop was recorded and finally, by the end of the 12-week assessment it significantly dropped to 87.08, thus there is a significant decrease of 7.84 mmHg (p<0.001). Alcocer *et al.* conducted an openlabel, parallel-group comparative study to analyze the clinical efficacy and safety of Atenolol 50 mg and Telmisartan 80 mg on systolic and DBP in 58 patients with mild to moderate HTN and concluded that there was a significant decrease in DBP of 10.1 mmHg versus 14.7 mmHg. When we compared the results of these studies, we found that greater reduction of DBP, that is, 10.1 mmHg in the Alcocer *et al.* study than our study, that is, 7.84 mmHg [70].

The baseline mean DBP of subjects in the Olmesartan drug group was 94.08 which significantly drops down to 88.04 at week 2 assessment and after that, at each 2-week assessment there was significant drop was recorded and finally, by the end of the 12-week assessment, it significantly drops to 81.24, thus there is the final reduction of 12.84 mmHg. Puchler *et al.* conducted a double-blind study on 328 patients with moderate to severe type HTN mean sitting DBP of 100 to 120 mmHg receiving 25 mg of hydrochlorothiazide daily randomly assigned to receive either Olmesartan (10 mg) once daily

plus HCTZ or Atenolol (50 mg) once daily plus HCTZ for 12 weeks and they concluded that mean reduction in DBP from the baseline were similar for Olmesartan group (-17.3±6.3 mmhg) and the Atenolol group (-17.2±6.4 mmHg) in patients receiving either Olmesartan (10 mg) once daily plus HCTZ or Atenolol (50 mg) once daily plus HCTZ for 12 weeks. When we compared the results of these studies, we found that there is a reduction of 17.3 mmHg of DBP in the Puchler *et al.*. study while there is a lesser reduction of DBP, that is, 12.84 mmHg in our study. The greater reduction may be due to the addition of HCTZ as an antihypertensive drug in this study [71].

The heart rates in Group A (Atenolol). The baseline means heart rate of subjects in the Atenolol drug group was 85.72 which significantly drops down to 83.48 at week 2 assessment followed by a significant drop at each 2-week assessment and finally by the end of the 12-week assessment it significantly dropped to 72.64, counting for an average reduction of 13.08 beats/min. While Pollare *et al.* conducted a study on sixty patients with primary HTN and studied the effects of Atenolol and Metoprolol and concluded that there is a significant reduction in heart rate, 9 beats/min in the supine position after medication, which was similar for Atenolol and Metoprolol. When we compared the results of these studies, we found that heart rate was decreased significantly in both of these studies but a greater reduction in heart rate was observed in our study, that is, 13.08 beats/min as compared to 9 beats/min in Pollare *et al.* study [72].

In Group B (Olmesartan), the baseline means Heart Rate of subjects in the Olmesartan drug group was 86.72 which significantly drops down to 81.48 at week 6 assessment but at 8th week assessment, it was not significant drop, that is, 81.36 but after that, at each 2-week assessment there was significant drop was recorded and finally, by the end of the 12-week assessment, it was significant drops to 78.88, that is, an average reduction of 7.8 beats/min. A fine comparative study conducted by Rasmussen et al.. on 13 patients (nine men and four women, aged 37-67 years) with mild/moderate essential HTN to do a comparison between Atenolol and Metoprolol 50, 100, and 200 mg doses given once daily on BP, and concluded that significant (p<0.001) reduction of 12 beats/min in heart rate in test situations were observed with 50 mg Atenolol [67]. While Sahana et al., studied the effect of-Atenolol 50 mg once daily versus Nebivolol 5 mg once daily (S) in patients with essential HTN and concluded that fall in heart rate was significant (p<0.0001) by 11 beats/min at the end of the 1st, 2nd, and 3rd month when compared to baseline by Atenolol 50 mg therapy. When we compared our results with these studies we concluded that although Olmesartan is reducing heart significantly by 7.8 beats/min Atenolol is found to be more significantly reducing the heart rate by 12 beats/min in Rasmussen et al.. study and 11 beats/min in Sahana et al.. studies [67,73].

Fasting blood sugar level among Group A (Atenolol) patients at baseline was 104.1 ± 14.2 mg/dl which non-significantly decreased to 92.0 ± 12.9 mg/dl, that is, it reduces by 8.9%. In Group B, (Olmesartan) subject's baseline Fasting blood sugar level was observed to be 105.6 ± 15.3 mg/dl which non significantly reduces by 9.0% to 91.6 ± 13.0 mg/dl at the end of 12 weeks of therapy. Fonseca reviewed the pathophysiology of HTN and evaluated the effects from glucose by beta-blockers, namely, Atenolol, Metoprolol, Propranolol and concluded that beta-blockers have favorable effects on glucose metabolism [74]. This study is coinciding with my study. Smith *et al.* evaluated Atenolol effects in men with type 2 diabetes mellitus during cardio respiratory exercise in both fasting and postprandial glucose and demonstrates that Atenolol decreased fasting and postprandial glucose (p<0.001). This study differs from my study, thus to confirm effects on fasting blood sugar, more studies are to be done [75].

During treatment, adverse effects were reported by the patients of both Groups. It was analyzed that the neurological symptoms headache and dizziness in Group A are 32.0% and 26.0% in subjects, respectively, while 16.0% and 36.0% in subjects in Group B, respectively. Gastrointestinal

symptoms nausea, vomiting, and diarrhea reported in Group A are 28.0% and 24.0% in subjects, respectively, while 16.0% and 8.0% in subjects reported the same in Group B, respectively.

About 26.0% of subjects in Group A reported hypotension while 28.0% reported fatigue on contrary in Group B 16.0% of subjects reported hypotension and 4.0% reported fatigue. Van Miegham conducted a double-blind study on 326 patients who are randomly assigned to receive either Olmesartan 20 mg once daily or Atenolol once daily for 12 weeks and concluded that both Olmesartan and Atenolol were well tolerated and adverse effects reported were minimal and were non-significant (p>0.001). Thus, in terms of adverse effects, my study is coinciding with this study [69].

CONCLUSION

Olmesartan is a better choice for the treatment of Stage I hypertensive patients because of a greater reduction in BP. The lesser decrement of heart rate with Olmesartan indicates its preferred use in end-organ failure clinical conditions. The fewer incidences of adverse events with Olmesartan than Atenolol indicate a better safety profile.

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AUTHOR CONTRIBUTION

The author conducted the study, collected, and processed the prescriptions and performed the analysis in detail with requisite procedures including statistical analysis, and further interpreted the data and prepared the manuscript.

CONFLICT OF INTEREST

None declared.

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Nil.

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