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MEDICINE UPDATE

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Update curriculum

Obesity pharmacotherapy

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New Multicentric Trial

Fixed low dose combination therapy of

S(-)amlodipine with Atenolol (Eslo-AT)

In patients with Angina Pectoris, Hypertension or both.

48 Physicians **154 patients**

Confirm

Eslo-AT

Say YES To 'S'

S(-) Amlodipine 2.5mg & Atenolol 50mg Tablets

Add Thrust to Control

In Hypertension

- More than 78% of the patients achieved JNC-VII goal
- Significant reduction in SBP & DBP 31/19 mm Hg .
- 86.92% achieved the target heart rate of <83 beats/min.

In Hypertension with Angina

- Offers 90.69% reduction in Anginal attacks.
- 88.37% achieved the target heart rate of <83 beats/min.
- More than 74% of the patients achieved JNC 7 goal
- Significant reduction in SBP & DBP 35/19 mm Hg

Zuventus Healthcare Ltd.
A Joint Venture of Emcure
Office No. 5119, 5th Floor, D-Wing, Oberoi Garden Estates, Chandivali, Andheri (E), Mumbai 400 072.

Fixed low dose combination therapy of Atenolol with S(-)Amlodipine in patients with angina pectoris, hypertension or both: the TEN-STAR trial

Dewan Bhupesh [1], Balasubramanian Aarthi [2]
[1] Chief Medical Advisor, [2] Clinical Research Associate,
Zuventus Healthcare Ltd, Mumbai, India.

Correspondence:
Dr. Bhupesh Dewan
Zuventus Healthcare Ltd.
5119 'D' Wing, Oberoi Garden Estate, Chandivilli, Mumbai- 400 072
Tel: +91 (0) 22-30610000 / 28472823/24. Fax: +91 (0) 22-28472828/29
E-mail: bhupesh.dewan@zuventus.com; medico@zuventus.com

ABSTRACT

Introduction: The use of low dose combination antihypertensive agents is a good contemporary strategy for the treatment of patients with hypertension, a multifactorial disease.

Aim: To assess the clinical efficacy and safety of the fixed low dose combination of S(-)Amlodipine and Atenolol (**ESLO-AT**) in patients with hypertension, angina pectoris, or both.

Materials & Methods: 48 practicing physicians throughout India collaborated in the recruitment of 154 hypertensive patients, over a period of nine months. These patients were administered fixed low dose combination of 2.5mg S(-)Amlodipine and 50mg Atenolol (**ESLO-AT**). They were observed for changes in their blood pressure & heart rate over a period of 4 weeks.

Results: Significant decrease in systolic blood pressure, diastolic blood pressure and heart rate by a mean of 32 mmHg (± 2.09 CI 95%), 18 mmHg (± 1.41 CI 95%) and 15 beats/min (± 1.56 CI 95%) respectively were observed after treatment with the fixed low dose combination of S(-)Amlodipine and atenolol (**ESLO-AT**) for 4 weeks. The JNC VII recommended target blood pressure goal of ≤ 140/90 mmHg was achieved in 77.27% of the patients while 87.33% of them achieved the target heart rate goal of < 83 beats/min at the end of 4 weeks. The combination also reduced incidences of anginal attacks in patients with concomitant angina. The therapy was found to be well tolerated by the study population.

Conclusion: These findings provide further evidence of the role of fixed low dose combination therapy with S(-)Amlodipine and atenolol (**ESLO-AT**) in the management of hypertension.

Key words: *Hypertension, S(-)Amlodipine, Atenolol, low dose combination, blood pressure, angina*

INTRODUCTION

Hypertension is a major risk factor for both cardiovascular (CV) and cerebrovascular morbidity & mortality, contributing to approximately 50% of all CV events.[1] The relationship between blood pressure and CV risk is continuous – for every 20 mmHg increase in systolic blood pressure (SBP) or 10 mmHg increase in diastolic blood pressure (DBP), the risk of cardiovascular disease doubles.[1] The seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure has published guidelines for the management of hypertension, which recommend a target blood pressure of <140/90 mmHg for all patients with hypertension. These JNC VII guidelines also recommend the use of a combination of antihypertensive agents like calcium channel blockers and beta-adrenergic receptor blockers for the management of these patients.[2]

Antihypertensive agents including beta-blockers, calcium channel inhibitors, diuretics and ACE inhibitors are widely used and are associated with a 35-40% reduction in stroke, a 20-25% reduction in myocardial infarction, a > 50% reduction in heart

failure and reductions in CVD-related death rates.[1] Thus, these agents help in establishing the ultimate goal of hypertension management, that is, to reduce CV morbidity and mortality by preventing end-organ damage.[1]

Calcium channel blockers (CCBs) are used extensively in practice and data from several clinical studies show that they effectively and safely lower BP and reduce long term CV risk in a wide range of patient population.[1] Amlodipine, one of the most prescribed drugs of the long-acting CCBs,[3] has demonstrated antihypertensive and antianginal activity in many studies.[4] S(-)Amlodipine, the therapeutically active enantiomer, has demonstrated smoother and non-fluctuating reduction in blood pressure, enhanced safety and predictability of response at half the dose of the racemate.[5,6]

Unlike verapamil and diltiazem with potentially adverse electrophysiologic interactions with beta blockade, S(-) Amlodipine may display a complementary interaction with beta blockers that may maximize anti- anginal action and clinical safety.[4] While both compounds are helpful in inactivating calcium channels, beta blockers, like atenolol, do so more effectively in the heart, leading to bradycardia, and CCBs do so in the resistance vessels, leading to reduced afterload. Both these modalities of action lead to a considerable fall of blood pressure, which is counteracted in the case of beta blockers by an increase of stroke volume, and in case of CCBs by a reflexogenic increase of both heart rate and stroke volume.[7] The combined treatment of CCB and beta blocker might also have beneficial effects on the cardiac autonomic nervous activity necessary for the treatment of poorly controlled hypertensive patients.[3]

Clinical studies have used amlodipine in a dose of 2.5-10mg once daily in combination with atenolol 50-100mg once daily. Since S(-)Amlodipine, at a dose of 2.5mg, has comparable clinical efficacy to 5mg of racemic amlodipine, a combination of 2.5mg S(-)Amlodipine and 50mg Atenolol would be rational in the management of mild to moderate hypretension and angina pectoris.[8] The fixed low dose combination of S(-)Amlodipide with atenolol has been previously studied in a total of 598 Indian patients and found to be safe and effective in the management of hypertension and angina.[8,9]

The present clinical study is a post marketing surveillance carried out to reaffirm the efficacy and safety of the fixed low dose combination of S(-)Amlodipine (2.5 mg) with Atenolol (50mg) (**ESLO-AT**) in the treatment of hypertension.

MATERIALS & METHODS

This was a four week, multicentric, open clinical trial where physicians throughout India were invited to participate. 50 physicians spread across India recruited patients from October 2008 to June 2009. The criteria for qualification were diagnosis of hypertension according to JNC VII guidelines or stable angina pectoris (aged ≥ 18yrs). The patients were administered a low dose combination of S(-)Amlodipine 2.5mg and Atenolol 50mg (**ESLO-AT**) once daily and were followed up for four weeks. The patients were evaluated at baseline and after 2 and 4 weeks of therapy for sitting blood pressure, heart rate, symptom resolution (angina attacks, dyspnoea & palpitation) and adverse events. All the materials used in this study, including the drugs and case report forms, were provided by Zuventus Healthcare Ltd. The changes in blood pressure and heart rate were analyzed by taking into account the change from baseline to the end of the study. Similarly, the trends in symptom resolution and ECG findings were also analyzed taking into account the decrease (or improvement) from baseline to the end of therapy. These data were analyzed descriptively and statistically using the paired Student's T test. The statistical software used was Analyze It Version 2 and a p value of less than 0.05 was considered as statistically significant.

RESULTS

Study Population

Data corresponding to a total of 179 patients was obtained from 48 different practitioners, of which 154 patients with valid entry data were included for efficacy and safety analysis.

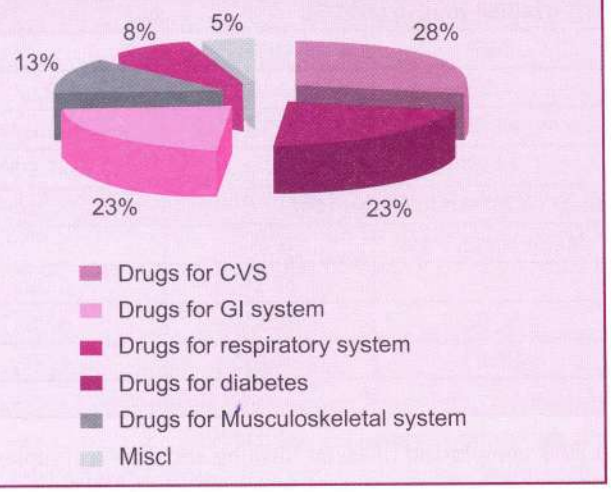
Demographic profile

The demographic data of the patients included for analysis are provided in (Table 1). Of the study population, 72.08% patients were diagnosed as having hypertension while the remaining 27.92% were diagnosed as having angina pectoris with hypertension. In addition, 18.18% of the patients also reported to have other illness including diabetes (32.14%), musculoskeletal disorders (14.28%) and respiratory disorders (14.28%).

Table 1. Demographic profile of study population

		Sample Size (N)	
Age (years)	Adults	112	52.71 + 6.581 yrs
	Geriatrics	33	69.33 + 3.86 yrs
Sex	Males	104	67.53%
	Females	50	32.47%
Severity	Stage I	20	12.98%
	Stage II	134	87.02%
Duration of Hypertension	All patients	154	3.76 yrs
	Patients with Angina	43	3.15 yrs
Baseline ECG findings	ST depression	10	6.49%
	ST elevation	5	3.25%
	T depression	2	1.29%
	Left ventricular Hypertrophy	23	14.94%
	Ischemia	17	11.04%

Figure 1. Concomitant medications used



Concomitant Medications

Of the 154 patients evaluable, 74.67% of the patients (115/154) were administered only **ESLO-AT** therapy. The remaining 25.33% of the patients (39/154) received other concomitant medication seen in (Fig.1).

Efficacy

Overall trend in blood pressure & heart rate control

ESLO-AT was associated with significant reduction in blood pressure (systolic and diastolic) as well as heart rate (Table 2). This combination therapy significantly reduced the systolic and diastolic blood pressure by a mean of 20.49 ± 13.06 mmHg & 12.11 ± 8.59 mmHg after 2 weeks and by a mean of 32.03 ± 13.24 mmHg & 18.92 ± 8.95 mmHg after 4 weeks respectively. Similarly, heart rate was decreased by a mean of 9.35 ± 6.53 beats/min after 2 weeks and 15.53 ± 9.76 beats/min ($p<0.001$) after 4 weeks.

Subgroup analysis found that ESLO was equally effective in both, patients diagnosed with only hypertension & those with both hypertension and angina. In patients with only hypertension, ESLO significantly reduced the systolic and diastolic blood pressure by 30.76 ± 11.59 mmHg and 18.77 ± 8.42 mmHg respectively while the mean heart rate reduced by 15.46 ± 10.03 beats/min ($P<0.001$). Similarly, in patients with hypertension and angina, the mean reduction in blood pressure and heart rate were found to be 35.30 ± 16.47/ 19.27 ± 10.28 mmHg and 15.67 ± 9.17 beats/min respectively ($p<0.001$).

Achievement of JNC Target Blood Pressure (≤ 140/90 mm Hg)

The treatment goal for individuals with hypertension and no other compelling condition is < 140/90 mmHg according to JNC.[7] This goal was achieved by 41.56% of the population by the 2nd week where as a higher percentage of population i.e. 77.27% achieved it at the end of 4 weeks ($p<0.001$). The mean blood pressure of these patients at the end of 4 weeks was 131.23 ± 7.25/ 82.03 ± 3.68 mmHg (Table 3). Among these patients, 15.96% had Stage I hypertension while 84.03% had stage II hypertension. Among the 22.73% of the patients who did not achieve the treatment goal, the mean baseline blood pressure of 181.77 ± 15.76/ 105.34 ± 11.62 mmHg reduced to 151.03 ± 12.02/ 88.37 ± 4.86 mmHg at the end of 4 weeks of therapy ($p<0.01$). Subgroup analysis also revealed that 78.38 % of the patients with only hypertension (mean blood pressure of 130.51 ± 6.81/ 81.55 ± 3.49 mmHg) and 74.42% of the patients with hypertension and angina (mean blood pressure of 133.18 ± 8.13/ 83.34 ± 3.92 mmHg) achieved the JNC target goal at the end of 4 weeks ($p<0.001$).

Achievement of Target Heart Rate (< 83 beats/min)

According to the Framingham Heart study[2], an ideal heart rate should be <83 beats per minute since a higher heart rate is associated with a substantially higher risk of death from a cardiovascular events as compared to that associated with lower heart rate levels. Hence, achieving a target heart rate of <83 is considered as another therapy goal. Of the study population, 56.66% of the patients achieved this target by week 2 while 87.33% of them achieved it at the end of 4 weeks therapy with **ESLO-AT** ($p<0.001$). The mean heart rate of these patients at the end of 4 weeks therapy was 74.70 ± 4.58 beats/min (Table 3). Subgroup analysis also revealed that 86.92% of the patients with only hypertension (mean heart rate of 74.87 ± 4.01 beats/min) and 88.37% of the patients with hypertension and angina (mean heart rate of 74.28 ± 5.77 beats/min) achieved this target at the end of 4 weeks therapy ($p<0.001$). One patient (1/154), however, was reported to have developed bradycardia (heart rate: 58 beats/min) at the end of therapy.

Symptom resolution

Symptoms associated with hypertension, mainly dyspnoea (N=60) and palpitation (N=64), were also followed throughout the treatment. An overall significant improvement in dyspnoea

Table 2. Overall trends in blood pressure and heart rate

	Systolic Blood Pressure (SBP) (mmHg)		Diastolic Blood Pressure (DBP) (mmHg)		Heart Rate (Beats/min)	
	Mean ± SD	Mean reduction from baseline	Mean ± SD	Mean reduction from baseline	Mean ± SD	Mean reduction from baseline
Baseline	167.76 ± 16.53		102.39 ± 9.82		91.8 ± 11.15	
Week 2	147.26 ± 12.92*	20.49 ± 13.06*	90.28 ± 7.26*	12.11 ± 8.59*	82.50 ± 8.77*	9.35 ± 6.53*
Week 4	135.73 ± 11.91*	32.03 ± 13.24*	83.47 ± 4.77*	18.92 ± 8.95*	76.27 ± 6.097*	15.53 ± 9.76*

* Changes are statistically significant ($p<0.001$)

Table 3. Trends in the Achievement of Target Blood Pressure & Heart Rate				
Achievement of JNC Target BP of <140/90 mmHg (N=154)				
Pts with SBP/DBP < 140/90mm Hg	%	SBP	DBP	
Baseline	2	1.29	140	90
Week 2	64	41.56	136.27* ± 6.48	84.84* ± 4.45
Week 4	119	77.27	131.23* ± 7.25	82.03* ± 3.68
Achievement of Target Heart rate of <83 beats/min (N=150)				
Pts with Heart rate of <83 beats/min	%	Mean Heart Rate	S.D.	
Baseline	33	22	77.27	5.02
Week 2	85	56.66	76.93*	5.05
Week 4	131	87.33	74.70*	4.58
* Changes are statistically significant (p<0.001)				

and palpitation by 98.33% and 93.73% respectively was found (p<0.001). The trend in symptom resolution during the study period is seen in (Fig 2).

In case of patients diagnosed with hypertension and angina pectoris (N=43), there was a significant decrease in the anginal attacks observed in patients treated with **ESLO-AT** by 90.69% at the end of therapy (p<0.001).

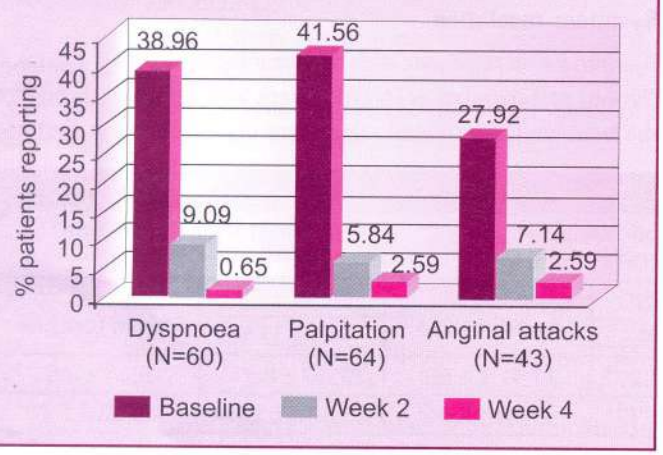
Resolution of ECG findings

A subset of the study population (46/154) revealed certain irregularities on their electrocardiogram during baseline analysis. 11.03% showed ST and/or T changes in ECG, 14.94% revealed ventricular hypertrophy while 11.04% showed presence of ischemia. Complete resolution of these findings was seen in 88.24%, 82.61% and 88.24% of these patients respectively after 4 weeks of therapy with **ESLO-AT** (p<0.05).

Safety

ESLO-AT was found to be well tolerated in this study population with 86.36% of them not reporting any adverse events including ankle oedema or facial flushing throughout the treatment period. Of the remaining patients, 7.14% complained of ankle oedema, 3.89% complained of facial flushing and 2.59% complained of other events like headache and weakness.

Figure 2. Trends in symptom resolution



DISCUSSION

The present study demonstrates the antihypertensive and anti-anginal activity of the fixed low dose combination of S(-) Amlodipine and Atenolol (**ESLO-AT**). Adequate control of blood pressure was achieved with a statistically significant reduction of the mean blood pressure in all the patients who successfully completed the month long therapy. Further, heart rate and associated symptoms were also significantly managed by this combination.

Hypertension is a multifactorial disease in which disruption of a single physiological pathway is often insufficient to control BP, necessitating administration of a combination of two drugs with different but complementary modes of action to achieve effective BP control.[1] According to the guidelines for the management of hypertension, the combined treatment of long-acting CCBs and beta blocker is recommended.[3] The combination of a beta-blocker (atenolol) with a CCB (S-amlodipine) has a dual effect: it increases antihypertensive efficacy by a synergestic effect and it reduces the side effects related to the start up of counter-regulation systems.[10] The efficacy and safety of combining atenolol with amlodipine has already been demonstrated in controlled studies.[8,9]

The reduction in blood pressure induced by **ESLO-AT**, on an average of 32/18 mmHg after one month of therapy, is similar to those observed in previous studies with the same or similar combinations.[8,9,10,11] Further, the JNC VII goal of attaining a blood pressure < 140/90 mmHg was achieved by 77.27% of the patients at the end of therapy. This reduction in blood pressure may result in subsequently decreased risks of CVD and stroke.[2] This combination was also found to be equally effective in controlling blood pressure in patients with Stage I as well as Stage II hypertension.

Similarly, the significant reduction of heart rate by an average of 15 beats/min helped 87.33% of the patients achieve a target heart rate of < 83 beats/min. This, in turn, translates into a lower

risk of death from a cardiovascular event.[2]

When dealing with the pharmacological treatment of hypertension, a crucial issue is the tolerability of drugs.[11] Low dose combination drugs, like **ESLO-AT**, produce additive hypotensive effects, but because they are comprised of submaximum doses, the side effect profile is frequently much better than that seen with similar or higher doses of monotherapy.[12] This pharmacological rational is to some extent substantiated by the results of the present study. There were no other clinical adverse experiences in patients receiving the low dose combination of **ESLO-AT** than in those reported in earlier studies.

Adverse events reported in clinical studies with combination of CCBs and beta-blockers range between 24.3 to 39.13%.[4,10,11] The incidence of adverse events reported with **ESLO-AT** in this study was 13.62%. Peripheral edema is a very common adverse event with CCBs and in case of racemic amlodipine, the incidence ranges from 20 to 30.6%.[13,14] However, it has also been proven that adverse events, especially oedema, occur less frequently with S-amlodipine, thereby contributing to more expressed, positive clinical dynamic of the state of patients receiving this drug.[15] In the present study also, oedema was found to occur in fewer patients (7.14%) receiving the combination therapy than previously reported.[11,13,14,15]

Low dose combination therapy provide varied advantages including improved efficacy as a result of their complementary actions, enhanced responder rates, fewer adverse reactions, decreased metabolic effects and increased cost effectiveness.[12] This fact has been further substantiated by the current post-marketing surveillance study of **ESLO-AT**. This combination allows normalization of blood pressure in a large number of hypertensives without compromising on the tolerability. Thus, it can be concluded that this combination is a valuable therapeutic option for the treatment of mild to moderate hypertension, angina and tachycardia.

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