



ASSESSMENT OF THE EFFICACY AND TOLERABILITY OF A FIXED DOSE COMBINATION OF NEBIVOLOL AND AMLODIPINE ESSENTIAL HYPERTENSION

Anita Dharmavarapu^{*1}, Sushma Attuluri², Nuha Rasheed³, Phani Kumar Nimmala⁴, Himanshu Rai⁵ and Sahithi K.⁶

¹Testing Technician, Department of Metrology, Northern Automotive Systems Ltd, Gilwern, Abergavenny NP7 0EB, UK.

²Assistant Professor, Department of Pharmacology, Nizam Institute of Pharmacy, Deshmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.

³Assistant Professor, Department of Pharmaceutics, Nizam Institute of Pharmacy, Deshmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.

⁴Senior Scientist, ADL Department, PCI Pharma, U.K.

⁵Krupanidhi College of Pharmacy, Carmelaram Road, Off Sarjapur Road, Chikka Bellandur, Carmelaram Post, Varthur Hobli, Bengaluru, Karnataka 560035, India.

⁶BDS, Malla Reddy Institute Of Dental Sciences, Suraram X Roads, Jeedimetla, Quthbullapur, Hyderabad, Telangana 500055, India.

***Corresponding Author: Anita Dharmavarapu**

Testing Technician, Department of Metrology, Northern Automotive Systems Ltd, Gilwern, Abergavenny NP7 0EB, UK.

Mail ID: anita.gracefull@gmail.com, mohdsaleempharma@gmail.com

Article Received on 14/06/2017

Article Revised on 05/07/2017

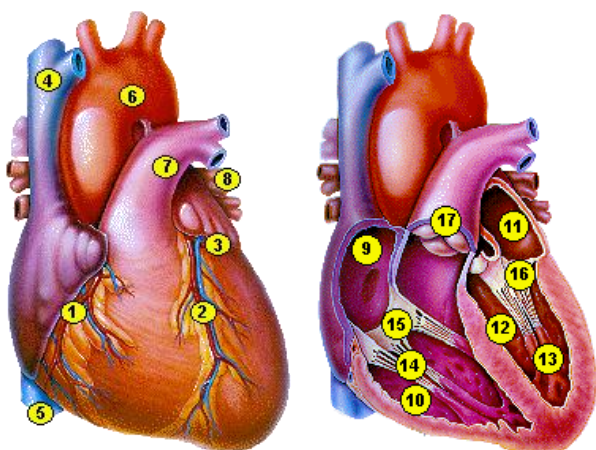
Article Accepted on 26/07/2017

ABSTRACT

Aim: From the literature review we found that no comparison study has been done between the combination of Nebivolol/Amlodipine with Atenolol/Amlodipine in Indian patient. So current study is being designed to compare the two combination therapy in treatment of essential hypertension. **Objective:** The primary objective was to demonstrate that Nebivolol–Amlodipine combination therapy is superior to Atenolol–Amlodipine combination therapy with respect to mean fall in systolic blood pressure (SBP) and diastolic blood pressure (DBP). The secondary objective was to compare the response rate and to evaluate the tolerability of study medications between 2 treatment groups. **Results:** Our study has shown that once daily treatment with Nebivolol /Amlodipine offers superior antihypertensive efficacy over Atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

KEYWORDS: Atenolol, Renin Angiotensin System, Blood Pressure, Renin-Angiotensin-Aldosterone system, efficacy.

INTRODUCTION



- | | |
|-----------------------------|-----------------------|
| 1. Right Coronary | 9. Right Atrium |
| 2. Left Anterior Descending | 10. Right Ventricle |
| 3. Left Circumflex | 11. Left Atrium |
| 4. Superior Vena Cava | 12. Left Ventricle |
| 5. Inferior Vena Cava | 13. Papillary Muscles |
| 6. Aorta | 14. Chordae Tendineae |
| 7. Pulmonary Artery | 15. Tricuspid Valve |
| 8. Pulmonary Vein | 16. Mitral Valve |
| | 17. Pulmonary Valve |

Fig: 1^[1] Heart Anatomy.

Regulating blood pressure The Renin Angiotensin-Aldosterone System

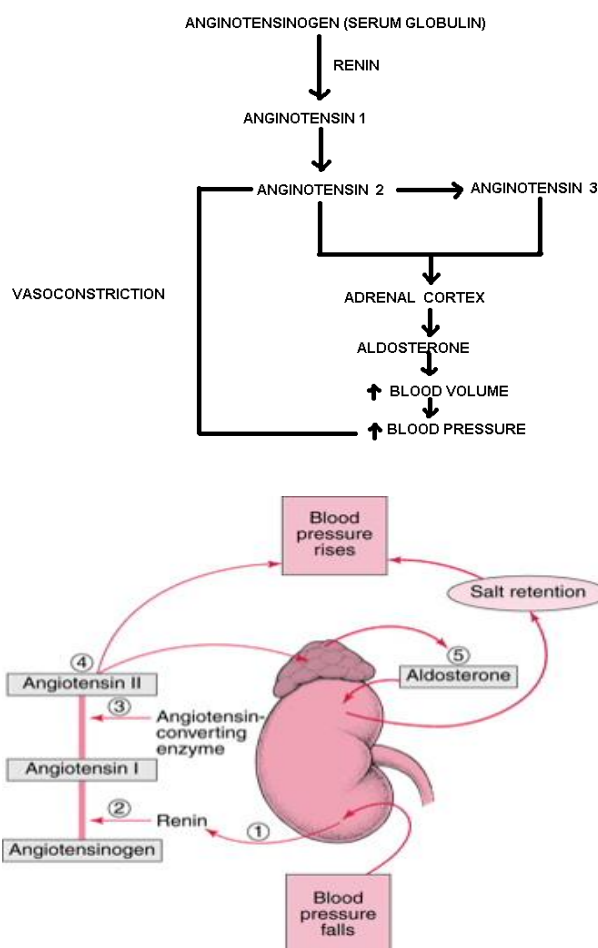


Fig 2: The Renin Angiotensin-Aldosterone System.

The renin-angiotensin-aldosterone system is a series of reactions designed to help regulate blood pressure.

1. When blood pressure falls (for systolic, to 100 mm Hg or lower), the kidneys release the enzyme rennin into the bloodstream.
2. Renin splits angiotensinogen, a large protein that circulates in the bloodstream, into pieces. One piece is angiotensin I.
3. Angiotensin I, which is relatively inactive, is split into pieces by Angiotensin-converting enzyme (ACE). One piece is angiotensin II, a hormone, which is very active.
4. Angiotensin II causes the muscular walls of small arteries (arterioles) to constrict, increasing blood pressure. Angiotensin II also triggers the release of the hormone aldosterone from the adrenal glands and antidiuretic hormone from the pituitary gland.

Aldosterone causes the kidneys to retain salt (sodium) and excrete potassium. The sodium causes water to be retained, thus increasing blood volume and blood pressure.

AIM AND OBJECTIVE

- 1) From the literature review we found that no comparison study has been done between the combinations of Nebivolol/Amlodipine with Atenolol/Amlodipine in Indian patient.
- 2) So current study is being designed to compare the two combination therapy in treatment of essential hypertension.
- 3) The primary objective was to demonstrate that Nebivolol-Amlodipine combination therapy is superior to Atenolol-Amlodipine combination therapy with respect to mean fall in systolic blood pressure (SBP) and diastolic blood pressure (DBP).
- 4) The secondary objective was to compare the response rate and to evaluate the tolerability of study medications between 2 treatment groups.

MATERIAL AND METHODS

Study

Study Design: This randomized, comparative, multicentre, 12 week, outpatient study evaluated antihypertensive efficacy of Nebivolol/Amlodipine combination in comparison with Atenolol /Amlodipine alone.

Study Medication: Patients were selected into two groups.

- 1) Fixed Dose Combination of Nebivolol (5mg) plus Amlodipine (2.5mg).
- 2) Fixed Dose Combination of Atenolol (25mg) plus Amlodipine (2.5 mg).

The study drugs were administered orally once daily in morning.

Subjects

Patient selection

Willing to sign informed consent and ready for regular follow-up we enrolled in the study.

Inclusion Criteria

Patients (either untreated or pre-treated with anti hypertensive agents) of either sex, aged 18 years and above, diagnosed of essential hypertension as per JNC 7 criteria.

Exclusion Criteria

- 1) Patients with DBP >109 mmHg were excluded from the study.
- 2) Patients with secondary hypertension, known history of hypersensitivity to study medication, patients with severe hypertension, significant medical illness, patients with electrolyte imbalance, abnormal hepatic, and renal functions were excluded from the trial.
- 3) Pregnant and lactating women or females of childbearing potential not practicing contraception were excluded from the study.

Ethics Committee

- 1) The study was approved by independent ethics committee of each centre.
- 2) All patients were provided an oral explanation about the nature of the study and about study drugs by the investigator at each centre.
- 3) An information sheet was provided in a language understood by the patient, and written informed consent was obtained from each participant before any study related procedure.
- 4) The execution and monitoring of the study was done in accordance with the requirements of good clinical practice.

Efficacy Evaluation

- 1) Efficacy of the therapy in treated patients was evaluated by BP measurement at each study visit throughout study period.
- 2) Blood pressure was measured by auscultator method.
- 3) Measurements were performed after 10 minutes rest in duplicate separated by 2 minutes and then average was taken.
- 4) If the first 2 readings of DBP differed by more than 5 mmHg, additional reading was obtained and average of 2 closest reading was taken.
- 5) The study investigator at each site performed all the BP measurements throughout the study period.
- 6) The same method was followed at all study sites for BP measurement.
- 7) Patients were termed as responder if their BP was controlled (SBP, 140 mmHg and DBP < 90 mmHg).

Safety Evaluation

- 1) All enrolled patients were evaluable for tolerability assessment.
- 2) Safety evaluation was based on adverse events (AEs) reported during the study.
- 3) AEs were categorized by the investigator based on their intensity as mild, moderate, or severe and the relationship to the study drug as none, probably not, possible, probable or definite.
- 4) At every visit during the entire study period, the reported AEs, clinical state of patients and details of concomitant medications, if any were captured.
- 5) Blood samples were obtained at baseline and at the end of 3 months therapy or at last follow-up visit for early termination/withdrawal cases to perform hematology and biochemistry tests including complete blood count urine routine, electrocardiogram, serum electrolytes (Na⁺, Cl⁺, K⁺), fasting blood glucose.

Statistical analysis

- 1) The primary objective was to show that Nebivolol / Amlodipine combination therapy is superior to Atenolol/Amlodipine combination therapy with respect to mean fall in SBP and DBP at the end of therapy from baseline. The sample size calculation

required approximately 192 patients to be randomized and 174 evaluable patients (87 patients per treatment group) to complete the study to detect a treatment difference of at least 5 mmHg in the primary comparison with a power of 80% at 5% level of significance (2 sided).

- 2) Descriptive statistics, including mean, SD, frequency counts and percentage for categorical variables were used to compare treatment groups at baseline with respect to demographic characteristics. The treatment groups were compared for homogeneity at baseline using tests like Student's t test, Mann-Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables.
- 3) The 2 treatment groups were similar with respect to demographic characteristics. For data analysis, the whole population was divided into 2 subgroups, escalated patients and non escalated patients. None escalated patients included patients who received the baseline therapy up to 1 month and remained controlled on the same therapy to the end of study. While escalated patients include patients continued on the baseline therapy up to 1 month but escalated to respective step-up therapies due to poor or no response to the baseline therapies. Both the treatment groups were compared after 1 month and the end of the study using Student's t test, Mann – Whitney U test as appropriate. All statistical tests were resided and the level of significance were set at 0.05. Statistical analysis was performed using statistical software MINITAB 14.

RESULTS**Patient distribution**

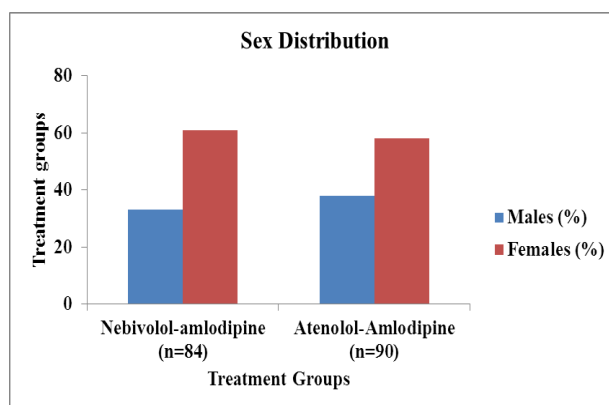
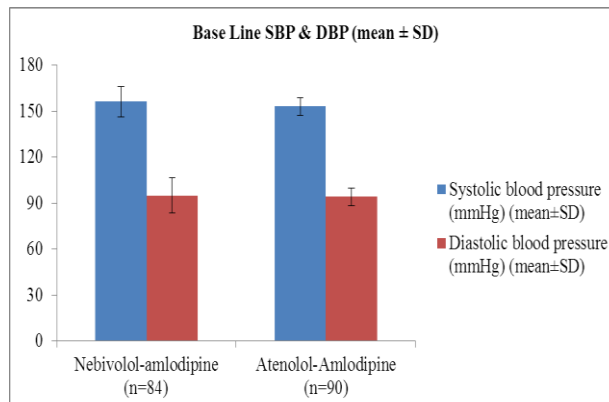
- 1) A total of 190 eligible patients (Nebivolol/Amlodipine combination therapy: 94; Atenolol/Amlodipine: 96) satisfying inclusion/exclusion criteria were enrolled on the study.
- 2) Nine patients from combination group and six patients from mono therapy group were lost to follow-up
- 3) 1 patient from combination group was withdrawn due to adverse event.
- 4) A total of 174 patients completed the study (Ne/Am combination therapy: 84; At/Am combination therapy: 90). The 2 treatment groups were similar with respect to demography and baseline disease characteristics (Table 1).

Table 1: Baseline characteristics of patients.

Parameters	Nebivolol-amlodipine (n=84)	Atenolol-Amlodipine (n=90)	P value
Males (%)	33 (35.11)	38 (39.58)	0.524
Females (%)	61 (64.89)	58 (60.42)	-
Mean age (years) (range)	53.3 ±12.0 (25-80)	55.2±11.9(28-80)	0.274
Mean weight (kg) ±SD	61.1 ±10.8	59.8±10.7	0.395
Mean height (cm) ±SD	158.1 ±10.3	156.9±10.2	0.422
Heart rate (breaths/min) ±SD	79.62 ±7.54	79.46±6.86	0.880
Respiration rate (breaths/min) (mean± SD)	15.50± 2.96	15.49±2.53	0.979
Stage I essential hypertension	53	62	0.248
Stage II essential hypertension	41	34	-
Systolic blood pressure (mmHg) (mean±SD)	156.17 ±9.82	153.1±11.6	0.051
Diastolic blood pressure (mmHg) (mean±SD)	95.06± 5.79	94.07±5.54	0.230

Efficacy after 4 weeks of therapy

At the end of 4 weeks of therapy, 62 patients from Ne/Am combination group and 50 patients from At/Am combination group responded to the therapy (SBP < 140 mmHg and DBP < 90 mmHg) ($P = 0.012$) (Table 2). Mean fall in SBP (-30.0 ± 10.4 vs. -25.08 ± 9.05 ; $P = 0.008$) and DBP (-18.10 ± 7.45 vs. -14.78 ± 7.48 ; $P = 0.021$) was significantly superior in Ne/Am combination therapy as compared with At/Am combination therapy at the end of 4 weeks. Mean SBP and mean DBP was significantly lower in Ne/Am combination group as compared with At/Am combination therapy group at the end of 4 weeks of therapy ($P < 0.05$) (Table 2). Responders from both the treatment groups remained controlled till the end of therapy (day 90). Figure shows fall in mean SBP and DBP for responders on starting therapies.

**Fig 3: Sex distribution.****Fig 4: Base line sbp and dbp.****Table 2: Changes in baseline BP measurements for responders at the end of 4 weeks of therapy.**

Efficacy parameters	Nebivolol-amlodipine(n=62)	Atenolol-Amlodipine (n=50)	P value
Mean SBP (mmHg)(at baseline) (mean ±SD)	154.77±9.29	152.68±8.37	0.213
Mean SBP(mmHg)P (at 4 weeks) (mean ±SD)	124.74±6.76	127.60±7.97	0.046
Mean DBP (mmHg) (at baseline) (mean ±SD)	95.35±5.90	94.64±5.02	0.490
Mean DBP (mmHg) (at 4 weeks) (mean ±SD)	77.26±5.59	79.86±5.66	0.017
Mean fall in SBP (mmHg) (mean±SD)	-30.0±10.4	-25.08±9.05	0.008
Mean fall in DBP (mmHg) (mean ±SD)	-18.10±7.45	-14.78±7.48	0.021

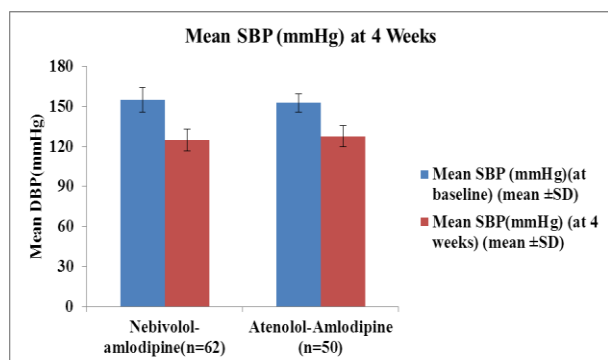


Fig 5: Mean SBP at 4 weeks.

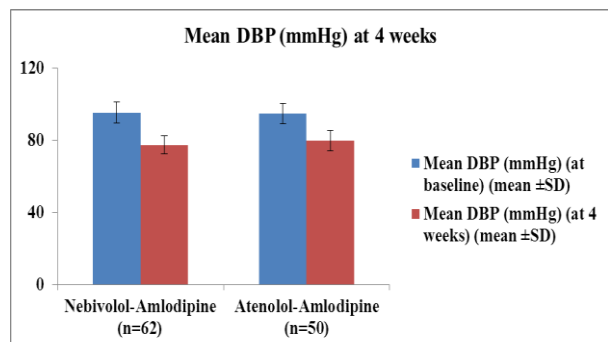


Fig 6: mean DBP at 4 weeks.

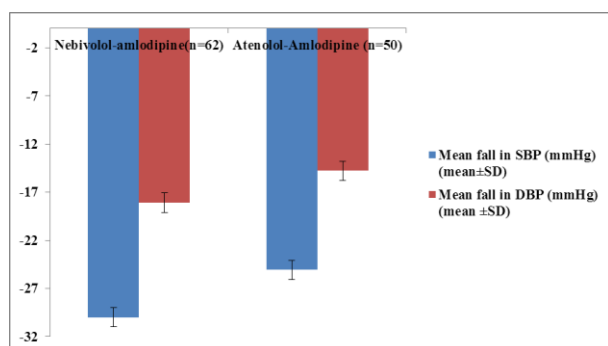


Fig 7: Mean fall in SBP and DBP at 4 weeks.

Efficacy after 12 weeks of therapy

- 1) Sixty-two non responders (Ne/Am combination therapy:22; At/Am combination therapy:40) were escalated to respective step-up therapies to receive Nebivolol 5 mg/ Amlodipine 2.5 mg and Atenolol 50 mg/ Amlodipine 2.5 mg for further 8 weeks. At the end of therapy, total 23 patients (Ne/Am combination therapy: 12; At/Am combination therapy group: 11) responded to the step-up therapies (SBP < 140 mmHg and DBP < 90 mmHg). Step-up therapy of Ne/Am combination group showed significantly better response rate as compared with step-up therapy of Atenolol/Amlodipine (P = 0.035) (Table 3).
- 2) Both the step-up therapies were comparable with respect to mean fall in SBP and mean fall in DBP (P > 0.05) at the end of therapy. However, at the end of 12 weeks, mean SBP (127.82 ± 8.90 vs. 138.0 ± 14.4; P = 0.001) and mean DBP (81.73 ± 8.78 vs. 87.35 ± 5.50; P = 0.011) were significantly lower in Ne/Am combination group as compared with those in At/Am combination therapy group (Table 3). Nonresponders at the end of treatment period (10: Ne/Am combination group and 29: At/Am combination therapy group) were then treated appropriately at the discretion of the investigator.
- 3) At the end of therapy, significantly more number of combination treated patients achieved normalization of BP (SBP < 120 mmHg and DBP < 80 mmHg) as compared with At/Am combination therapy (33 vs. 19) (P = 0.009). In both the treatment groups, the fall in BP was maximum at the end of 4 weeks of therapy, and subsequently the fall was maintained till the end of therapy, that is, day 90 (Figure 2).

Table 3: Changes in baseline BP measurements for nonresponders at the end of therapy.

Efficacy parameters	Nebivolol-amlodipine (n=22)	Atenolol-Amlodipine (n=40)	P value
Mean SBP (mmHg) (at 4 weeks)	136.1 ±10.3	142.9 ±10.3	0.016
Mean SBP (mmHg) (at 12 weeks)	127.82 ±8.90	138.0 ±14.4	0.001
Mean DBP (mmHg) (at 4 weeks)	88.36 ±4.60	89.05 ±6.84	0.640
Mean DBP (mmHg) (at 12 weeks)	81.73 ±8.78	87.35 ±5.50	0.011
Mean fall in SBP (mmHg)	-10.1 ±10.4	-4.6 ±6.1	0.109
Mean fall in DBP (mmHg)	-6.64 ±8.74	-2.70 ±6.80	0.076
Responders	12	11	0.035
Nonresponders	10	29	-

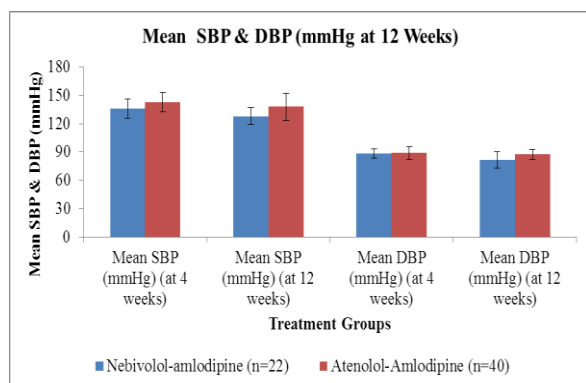


Fig 8: Mean SBP& DBP.

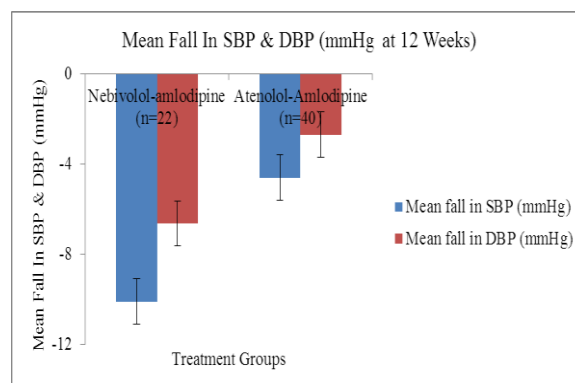


Fig 9: Mean fall in SBP & DBP at 12 weeks.

Table 4: Mean changes in serum electrolytes and blood sugar from baseline to end of study for all patients.

Laboratory parameters	Visit	Nebivolol-amlodipine (n=84)	Atenolol-Amlodipine (n=90)	P value
Sodium (mEq/L)	Baseline	137.46 ±5.03	137.17 ±4.63	0.619
	End	137.46 ±5.40	137.66 ±5.40	
	P value	1.0	0.441	
Potassium (mEq/L)	Baseline	3.99± 0.68	4.03± 0.72	0.600
	End	4.14 ±0.56	4.26 ±0.54	
	P value	0.129	0.025	
Random blood glucose (mg/dL)	Baseline	113.93 ±47.54	102.24 ±23.59	0.245
	End	103.66 ±48.99	105.03 ±29.51	
	P value	0.328	0.480	

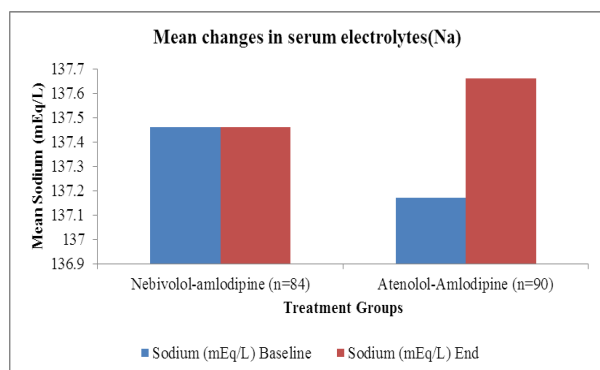


Fig 10: Mean changes in Serum Electrolytes (Na).

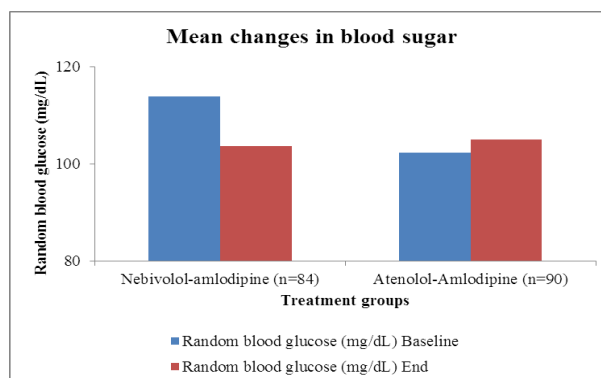


Fig 12: Mean changes in Blood Sugar.

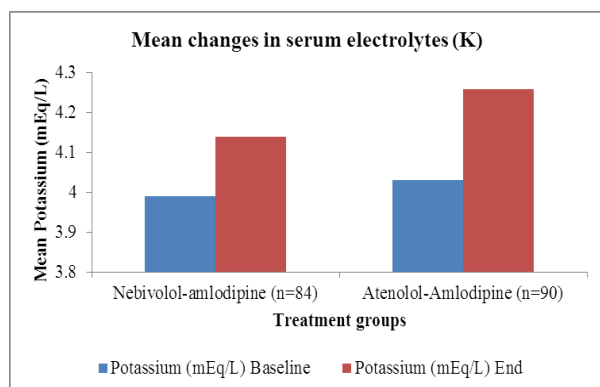


Fig 11: Mean change in Serum Electrolytes (K).

Tolerability assessment

- 1) A total of 4 patients reported adverse events, 3 from combination therapy and 1 from monotherapy.
- 2) Edema, gastritis, and abdominal pain were reported in patients treated with combination therapy and giddiness was reported in patients treated with monotherapy.
- 3) All reported adverse events were of mild-to - moderate in severity. None of the patients reported serious adverse event.
- 4) The laboratory evaluations were done at baseline and at the end of therapy.
- 5) Mean change s from baseline for various laboratory parameters were evaluated at the end of 3 months for all patients.
- 6) There was non-significant reduction in heart rate at the end of therapy with either treatment.

- 7) No significant changes from baseline were observed in haematology or biochemistry parameters (Table 4).
- 8) Changes in blood glucose levels and lipid profile (high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol) were clinically unremarkable across the therapy groups.

Safety Assessment

Side effects found with Atenolol-Amlodipine combinations

- 1) Tiredness - in up to 26 percent of people
- 2) Low (hypotension) - up to 25 percent
- 3) Slow heart rate (bradycardia) - up to 18 percent
- 4) Dizziness - up to 13 percent
- 5) Cold hands or feet -- up to 12 percent
- 6) Depression - up to 12 percent (*see Atenolol and Depression*)
- 7) Shortness of breath -- up to 6 percent
- 8) Fatigue - up to 6 percent.

Other common side effects of Atenolol (occurring in 2 to 4 percent of people) include but are not limited to:

- 1) Leg pain
- 2) A decrease in blood pressure when going from a lying-down or sitting position to standing
- 3) A spinning sensation (vertigo)
- 4) Lightheadedness
- 5) Diarrhea
- 6) Nausea

Side effects found with Nebivolol-Amlodipine combination

- 1) Headache -- in up to 9 percent of people
- 2) Fatigue -- up to 5 percent
- 3) Dizziness -- up to 4 percent
- 4) Diarrhea -- up to 3 percent
- 5) Nausea -- up to 3 percent
- 6) Insomnia -- up to 1 percent.

DISCUSSION

- 1) The primary goal of treating hypertension is to reduce their blood pressure to target level, which eventually leads to a reduction in the long-term total risk of cardiovascular morbidity and mortality.
- 2) In this regard, although some considerations are necessary before generalizing the results, the present study clearly demonstrated that combination therapy with a β -blocker and a calcium channel blocker is an effective method to achieve the target blood pressure without major safety issues.
- 3) This randomized, comparative, multicentre, 12 week, outpatient study evaluated antihypertensive efficacy of Nebivolol/Amlodipine combination in comparison with Atenolol/Amlodipine alone.
- 4) The results of this study showed that, combination therapy with Nebivolol/Amlodipine is superior to Atenolol/Amlodipine combination therapy with respect to mean fall in SBP, DBP, response rate, and normalization of BP.s

- 5) After 4 weeks of therapy with Atenolol 25 mg, our study reported a fall of -20.6/-10.34 in SBP/DBP which is comparable to that reported in literature (-17.6/-12.5). In our study, for responders after 4 weeks of therapy, low-dose combination of Nebivolol 5 mg/Amlodipine 2.5 mg was found to be superior to low-dose Atenolol 25 mg/Amlodipine 2.5mg combination therapy with respect to mean fall in SBP (P = 0.008), mean fall in DBP (P = 0.021) and response rate (P = 0.012).
- 6) One reason for combining a calcium antagonist with a β -adrenoceptor antagonist in the treatment of mild to-moderate hypertension is that the latter should improve the patient tolerability of the former by preventing any initial reflex tachycardia which may, in it, because of some adverse effects.
- 7) Preliminary studies in stroke-prone spontaneously hypertensive rats have shown that significant synergism exists between Atenolol and Amlodipine in lowering and stabilizing blood pressure.
- 8) The results of our study confirmed that the combination therapy with Nebivolol /amlodipine is superior to Atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

CONCLUSION

In conclusion, our study has shown that once daily treatment with Nebivolol /Amlodipine offers superior antihypertensive efficacy over Atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

BIBLIOGRAPHY

1. <http://www.webhealthcentre.com/centers/hyper.asp> Retrived on 12/5/2012.
2. <http://www.health.am/cardio/more/anatomy-of-the-heart.html> retrived on 25/6/2012.
3. http://www.biologyabout.com/od/humananatomybiology/ss/heart_anatomy.htm Retrived on 25/6/2012.
4. Lima.M, Mendez V, Perez W. Gross anatomy of heart in the western grey kangaroo. Int. J. Morphol. Dec 2009; 27(4): 1099-104.
5. Calder AL, Co EE, Sage MD. Coronary arterial abnormalities in pulmonary atresia with intact ventricular septum. Am J Cardiol, 1987; 59: 436-42.
6. Burrows PE, Freedom RM, Benson LN, Moes CA, Wilson G, Koike K, Williams WG. Coronary angiography of pulmonary atresia, hypoplastic right ventricle, and ventriculocoronary communications. Am J Roentgenol, 1990; 154: 789-95.
7. Pasquini L, Sanders SP, Parness IA, Wernovsky G, Mayer JE Jr, Van der Velde ME, et al. Coronary echocardiography in 406 patients with d-loop transposition of the great arteries. J Am Coll Cardiol, 1994; 24: 763-8.
8. Hanley FL, Sade RM, Blackstone EH, Kirklin JW, Freedom RM, Nanda NC. Outcomes in neonatal pulmonary atresia with intact ventricular septum. A

- multiinstitutional study. *J Thorac Cardiovasc Surg*, 1993; 105: 406–27.
9. Jatene AD, Fontes VF, Paulista PP, Souza LC, Neger F, Galantier M, Sousa JE. Anatomic correction of transposition of the great vessels. *J Thorac Cardiovasc Surg*, 1976; 72: 364–70.
 10. Gittenberger-de Groot AC, Sauer U, Oppenheimer-Decker A, Quaegebeur J. Coronary arterial anatomy in transposition of the great arteries: a morphologic study. *Pediatr Cardiol*, 1983; 4(Suppl 1): 15–24.
 11. Vrancken Peeters MP, Gittenberger-de Groot AC, Mentink MM, Hungerford JE, Little CD, Poelmann RE. The development of the coronary vessels and their differentiation into arteries and veins in the embryonic quail heart. *Dev Dyn*, 1997; 208: 338–48.
 12. McKay R, Anderson RH, Smith A. The coronary arteries in hearts with discordant atrioventricular connections. *J Thorac Cardiovasc Surg*, 1996; 111: 988–97.
 13. www.pfizerindia.com/health_hy.html retrived on 12/5/2012.
 14. www.wrongdiagnosis.com/h/hypertension/symptoms.html.
 15. www.diethealthclub.com/health-issues-and-diet/hypertension.html.
 16. www.webmd.com/hypertension-high-blood-pressure/tc/high-blood-pressure-hypertension-symptoms.html.
 17. <http://www.mco.edu/org/whl/bloodpre.html>. Accessed April 1, 2003.
 18. <http://www.americanheart.org/presenter.jhtml?identifier=576>. Accessed April 1, 2003.
 19. <http://www.nhlbi.nih.gov/about/nhbpep/index.htm>. Accessed March 5, 2003.
 20. Promising. Y, Nelson MR, McNeil JJ, Peeters A et al. "PBS/RPBS cost implications of trends and guideline recommendations in the pharmacological management of hypertension in Australia, 1994-1998". *Med J Aust*, Jun 4 2001; 174(11): 565–8.
 21. Chobanian A et al. "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report". *JAMA*, 2003; 289: 2560–72.