Evaluation of Efficacy and Tolerability of Losartan and Ramipril Combination in the Management of Hypertensive Patients with Associated Diabetes Mellitus in India (LORD Trial)

Shashank R Joshi, ME Yeolekar, KK Tripathi, J Giri, AK Maity, M Chopda, S Gujarathi, S Maroli, A Maity for the LORD Trial Group+

Abstract
Aim: The study was conducted to evaluate efficacy and tolerability of fixed dose combination (FDC) of Losartan and Ramipril in the management of mild to moderate hypertensive Native Asian Indian patients with associated diabetes mellitus. The secondary objective was to evaluate the efficacy of the combination in reducing microalbuminuria.

Material and Methods: The study was an open, non-comparative, multicentric clinical trial conducted in seven Indian centres in 315 eligible patients. All the patients were treated with Losartan 50 mg + Ramipril 2.5 mg or Losartan 50 mg + Ramipril 5 mg once a day in 12 weeks and consisted of a total of eight visits.

Results: The mean age of patients was 52.93 years (range 45 - 60 years). Of the total patients, 62.86% were males and 37.14% were females. The mean prestudy systolic blood pressure was 160.56 ± 14.44 which was significantly reduced to 126.85 ± 9.78 at the end of 12 weeks (P < 0.001). Similarly the mean diastolic blood pressure was 98.91 ± 8.33 at baseline (stage 1) which was significantly reduced to 79.82 ± 5.42 at the end of 12 weeks (P < 0.001). A mean fall of 33.72 mmHg in systolic blood pressure and the mean fall of 19.10 mmHg was observed in systolic and diastolic blood pressure respectively at the end of the treatment which was statistically highly significant (P < 0.001). The JNC-VII goal of blood pressure < 130/80 was achieved in 79.05% patients after the treatment which losartan and ramipril combination only. Microalbuminuria (urinary albumin excretion > 30 but < 300 mg/day) was seen in 83/250 (33.2%) patients and 135 (54%) patients had clinical proteinuria (albuminuria) at baseline. At the end of the therapy 20.8% patients achieved normoalbuminuria. Good to excellent efficacy response was reported in 98.09% patients and 98.41% patients reported good to excellent tolerability to the treatment.

Conclusion: The fixed dose combination of Losartan and Ramipril showed good to excellent efficacy response in 98.10% patients and achieved a target blood pressure of 130/80 mmHg in 79.05% patients in 12 weeks. The combination reduced the urinary albumin excretion in majority of the patients with microalbuminuria and proteinuria (the major marker of nephropathy).

INTRODUCTION
The optimal or dual RAAS inhibition to salvage renal function is an emerging concept. LORD study was conducted to evaluate efficacy and tolerability of Losartan + Ramipril in the management of hypertensive (mild to moderate) patients with associated diabetes mellitus. The secondary objective was to evaluate the efficacy of the combination in reducing microalbuminuria.

Patients and Methods
The study presented in this report was an open non-
comparative, Phase IV (controlled) clinical trial conducted during the period of January 2003 to August 2003. The study was conducted at seven centres all over India in total of 325 patients. All the investigators were provided with the study material (CRFs and study drugs in visit-wise packing for each patient) and the product details (product literature, pack insert, relevant references on international trials). A written informed consent was obtained from all the patients before starting the treatment. The trial was conducted as per the Declaration of Helsinki and a prior ethics committee approval was obtained.

All the patients were treated with fixed dose combination (FDC) Losartan 50mg + Ramipril 2.5mg or Losartan 50mg + Ramipril 5 mg once a day depending upon the baseline blood pressure and overall response of the patients in terms of efficacy and tolerability. The duration of treatment was 12 weeks and consisted of a total of eight visits including the baseline visit. Follow-up visits were scheduled on day 7, day 14, day 28, day 42, day 56, day 70 and day 84. A variation of + 2 days was allowed.

Following were the inclusion and exclusion criteria for selection of the patients.

**Inclusion Criteria**

* Patients of either sex between 18 - 60 years of age
* Patients with confirmed diagnosis of essential hypertension with diabetes mellitus

**Exclusion Criteria**

* Patients with hypersensitivity to Losartan or Ramipril
* Pregnant / lactating woman or woman of child-bearing potential not following adequate contraceptive measures
* Evidence of severe cardiac, renal and hepatic insufficiency
* Patient unwilling or unable to comply with the study procedures
* Patient likely to be non-compliant (alcohol, smoking or drug abusers)
* Any condition, that in the opinion of the investigator does not justify patient’s inclusion in the study

Patients with mild to moderate hypertension and associated diabetes mellitus. All the eligible patients were explained about the nature of the study and about the drug. A patient information sheet was given to them in a language understood by them and a written informed consent was obtained from all the patients.

**Assessments**

At the initial visit a complete demographic data was collected that included age, height, weight, smoking and alcohol habits etc. A complete patient medical history including the history of hypertension, previous antihypertensive medication, history of diabetes was recorded. Associated risk factors, other associated illness and medications including the current antidiabetic treatment was recorded. General examination that included heart rate, body temperature and respiration rate were recorded. Clinical examination included recording of the systolic/diastolic supine blood pressure. Two or more determinations in each position were obtained using an appropriately sized cuff. Depending upon the baseline systolic and diastolic blood pressure, the dosage was decided by the investigators. At subsequent follow up visits which were scheduled on day 7, 14, 21, 28, 56, 70 and 84, a complete general examination and clinical examination (as mentioned above) was performed.

**Laboratory Investigations**

The pre- and post-study laboratory investigations included S.bilirubin, SGPT, SGOT, for assessment of liver function, BUN, s.creatinine, for assessment of kidney function, lipid profile viz. cholesterol, triglycerides, blood sugar, serum electrolytes, urine analysis, and if required ECG. urine for microalbuminuria was assessed by both ratio, spot test and even 24 hour in a select few center. Microalbuminuria for measurement of 24 hours urine albumin excretion was performed both pre- and post study to check the kidney function and to study the effect of combination treatment on of diabetic patients (kidney function).

**Efficacy and Safety**

At the end of the treatment global efficacy was assessed by investigators based on the control achieved in blood pressure after a 4-week treatment. Global efficacy was judged on a three-point scale by the investigator as follows: Excellent (SBP ≤ 130 mmHg and DBP ≤ 80 mmHg); Good (≥ 10 mmHg drop in diastolic blood pressure) and Unsatisfactory (no significant change from baseline).

Adverse events whether considered treatment related or otherwise were monitored throughout the study period and were graded as mild (awareness of signs and symptoms but easily tolerated), moderate (discomfort sufficient to reduce or affect normal daily activity) and severe (causes inability to work / requires hospitalization/ results in permanent disability or is life-threatening) Adverse events were recorded in the appropriate sections provided in the case record forms. A separate section was provided in the case record form to record the serious adverse event in observed during the treatment period. The investigators were instructed to immediately report such serious adverse event to the company or the study monitor. Overall global assessment of tolerability was graded as on a three-point scale by the patient as follows: excellent, good or unsatisfactory respectively.

**Statistical Analysis**

**Data Management**

The data was computerized with single entry and 100% manual checking for errors. Also range checks have been performed for extreme values. All queries which could be resolved from entries elsewhere have been resolved in-house. Other queries have been clarified from the investigators.

**Analysis**

The main evaluation of interest was the statistical analysis of all randomized patients where there are no major protocol
was statistically analyzed by applying the appropriate statistical tests.

The demographic characteristics of patients are given in Table 1. The mean age of patients was 52.93 years (range 45-60 years). Of the total patients, 62.86% were males and 37.14% were females. The mean weight of patients was 62.85 ± 11.33 Kg whereas the mean height of patients was 163.33 ± 8.53. The mean duration of diabetes mellitus was < 1 to > 10 years. Most of the patients (65.71%) had a history of diabetes for <1 to 5 years. Other risk factors included obesity (32.06%), smoking and alcohol (22.86%).

**History of Previous Antihypertensive Medications**

The eligible patients were asked to stop the previous (ongoing) antihypertensive medications one week before initiating the study drugs. The previous antihypertensive medications included calcium channel blockers 110 (34.93%), beta blockers 50 (15.87%), ACE inhibitors 6 (1.90%), diuretics 10 (3.17%), angiotensin receptor antagonists 6 (1.90%), ACE inhibitors + other class 7 (2.22%), beta blockers + other class 13 (4.13%) and other class 59 (18.73%).

A total of 93.65% were on monotherapy and were unable to achieve the target blood pressure. Remaining 6.34% patients were switched over to the study drug Losartan and Ramipril for achieving a better control.

**Profile of Antidiabetic Medication**

The enrolled patients were associated with diabetes mellitus and were on antihyperglycemic medications. A total of 68.89% patients were on sulfonylureas, 1.59% patients were on biguanides, 4 (1.27%) patients were on Insulin. Other antidiabetic medications included combination therapy with insulin or sulfonylureas orthiazolidinediones etc.

Depending upon the severity of hypertension, the eligible patients were dispensed with either losartan 50 + ramipril 2.5mg or losartan 50 + ramipril 5mg to be taken once daily till the next follow-up visit. A total of 165 patients (52.38%) were given losartan 50 + ramipril 2.5mg and 150 patients (47.62%) were given losartan 50mg + ramipril 5mg.

**Clinical Investigations**

There was no significant change in the pulse rate and respiratory rate over the treatment period as compared to baseline (p>0.05). The mean systolic blood pressure at baseline was 160.56 ± 14.44 which was reduced to 150.61 ± 16.28 on day 7 and further to 141.29 ± 14.15 on day 28 and to 134.67 ± 11.82 on day 56. (Fig. 1) A mean fall of 9.96 mmHg was observed after a week’s treatment with Losartan + Ramipril combination which was statistically highly significant (p<0.001, by t test). At the end of the treatment period i.e. at week 12, the mean systolic blood pressure was 126.85 ± 9.78 that was well below goal set by the JNC VII for diabetic hypertensives. Similarly the mean diastolic blood pressure was 98.91 ± 8.33 at baseline (stage I) which was significantly reduced to 92.34 ± 9.31 after a week’s treatment with Losartan + Ramipril combination. A further gradual fall in diastolic blood pressure was achieved over the treatment period. After 12 weeks the mean diastolic blood pressure was 70.82 ± 5.42. Both systolic and diastolic mean blood pressure after 12-

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### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>[n=315]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [yrs]</td>
<td>52.93 ± 6.85</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>* Male</td>
<td>198 (62.86%)</td>
</tr>
<tr>
<td>* Female</td>
<td>117 (37.14%)</td>
</tr>
<tr>
<td>Weight [Kg]</td>
<td>62.85 ± 11.33</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>163.33 ± 8.53</td>
</tr>
<tr>
<td>Severity of hypertension</td>
<td></td>
</tr>
<tr>
<td>* Pre-HT and NYHA Stage I ≤ 140-159/ ≤ 90-99</td>
<td>173 (54.92%)</td>
</tr>
<tr>
<td>* NYHA Stage II</td>
<td>142 (45.08%)</td>
</tr>
<tr>
<td>* 160-179/100-109</td>
<td></td>
</tr>
<tr>
<td>Blood Sugar level [mg %]</td>
<td></td>
</tr>
<tr>
<td>* Fasting</td>
<td>141.87 ± 50.35</td>
</tr>
<tr>
<td>* Post prandial</td>
<td>197.21 ± 63.29</td>
</tr>
<tr>
<td>Mean duration of Diabetes Mellitus</td>
<td></td>
</tr>
<tr>
<td>* ≤ 1 year</td>
<td>109 (34.61%)</td>
</tr>
<tr>
<td>* &gt;1 - 5 years</td>
<td>98 (31.11%)</td>
</tr>
<tr>
<td>* 6 - 10 years</td>
<td>82 (26.03%)</td>
</tr>
<tr>
<td>* &gt; 10 years</td>
<td>26 (8.25%)</td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
</tr>
<tr>
<td>* Obesity</td>
<td>101 (32.06%)</td>
</tr>
<tr>
<td>* Smoking/Alcohol</td>
<td>72 (22.86%)</td>
</tr>
<tr>
<td>Associated medical history</td>
<td></td>
</tr>
<tr>
<td>* Retinopathy</td>
<td>1 (0.32%)</td>
</tr>
<tr>
<td>* Nephropathy</td>
<td>1 (0.32%)</td>
</tr>
<tr>
<td>* Others</td>
<td>116 (36.83%)</td>
</tr>
</tbody>
</table>
week treatment was below the target blood pressure as per JNC VII guidelines for diabetic hypertensives.

Overall the combination treatment achieved a mean fall of 33.72 mmHg in systolic blood pressure which was significantly greater than that reported for the individual drugs. Similarly a mean fall in diastolic blood pressure at the end of 12 week treatment was 19.10 mmHg which was significantly higher than those reported with individual drugs. (Fig. 2)

A total of 144 patients had stage I hypertension, 158 patients had stage II hypertension and 13 patients had prehypertension at baseline. None of the patients was normotensive, although 10 patients had normal systolic but high diastolic blood pressure at baseline and five patients had normal diastolic but high systolic blood pressure at baseline. At the end of the treatment, as seen from Fig. 3, 249 (79.05%) patients became normotensives, 61 (19.36%) patients reached the prehypertension category and only five (1.59%) patients remained in the stage I hypertension category. Treatment with Losartan and Ramipril combination thus achieved a target goal of SBP/DBP 130/80 in a total of 249 (79.05%) patients after 12 weeks.

**Laboratory Investigations**

The laboratory parameters viz. s bilirubin, SGPT, SGOT (liver function), BUN, s.creatinine (kidney function), s.triglycerides (lipid profile) s.electrolytes viz. potassium (K+), chloride (Cl-), sodium (Na+) remained unchanged post-treatment.

However, there was a significant fall in serum cholesterol and random blood sugar from baseline. The mean baseline serum cholesterol was 204.49 ± 38.52 which was significantly reduced to 195.80 ± 38.37 mg% after treatment (p<0.005 by student’s ‘t’ test). Similarly there was a significant reduction in random blood sugar which was which significantly reduced to 136.50 ± 39.81 after 12 weeks as compare to 153.68 ± 50.85 at baseline.

**Microalbuminuria**

Microalbuminuria is the presence of an abnormally elevated urinary albumin in the absence of clinical proteinuria i.e. albumin/Creatinine ration ≥ 2.5 mg/mmol (men) or 3.5 mg/mmol (women) and <30 mg/mmol, in either 24 h or timed overnight collection of urine.

Microalbuminuria for measurement of 24 hours urine albumin excretion was performed both pre- and post study to check the kidney function and to study the effect of combination treatment on of diabetic patients (kidney function).
However since the laboratory investigations were optional the data on microalbuminuria was obtained only in 250/315 patients. As seen from Fig. 4, only 32 patients (12.8%) patients had normal albuminuria (i.e. urinary albumin excretion < 30 mg/day). Whereas, 83/250 (33.2%) patients had microalbuminuria (urinary albumin excretion > 30 but < 300 mg/day) at baseline and 135 (54%) patients had clinical proteinuria (albuminuria) at baseline. After 12 week treatment, there was a reduction in number of patients having proteinuria/microalbuminuria. A total of 84 (33.60%) patients had normoalbuminuria as compared to 32 (12.8%) at baseline. 83 patients had microalbuminuria and 83 vs 135 patients had proteinuria. The study drug was effective in reducing the high urine albumin excretion in 23.8% patients whereas, 20.8% patients with higher than normal urine albumin excretion achieved normoalbuminuria.

Adverse Drug Reactions

The most commonly reported adverse drug reaction reported by patients was dry cough, which was reported in 13 (4.13%) patients of which only three patients had moderate severity and 10 patients had mild severity of this event. Other less frequently reported events were chest pain (0.32%), headache (0.32%), vertigo (0.32%), abdominal pain (0.32%), giddiness (0.32%) and hypoglycemia (0.63%) all of which were mild in nature. All the reported events were however resolved after few days. None of the adverse event was severe enough to require hospitalization or discontinuation of the therapy (Table 2).

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of patients (%)</th>
<th>Severity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry cough</td>
<td>13 (4.13)</td>
<td>Mild</td>
<td>Resolved</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (0.32)</td>
<td>Mild</td>
<td>Resolved</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.32)</td>
<td>Mild</td>
<td>Resolved</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (0.32)</td>
<td>Mild</td>
<td>Persisted</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2 (0.63)</td>
<td>Mild</td>
<td>Resolved</td>
</tr>
<tr>
<td>Pain in abdomen</td>
<td>1 (0.32)</td>
<td>Moderate</td>
<td>Resolved</td>
</tr>
<tr>
<td>Giddiness</td>
<td>1 (0.32)</td>
<td>Mild</td>
<td>Resolved</td>
</tr>
<tr>
<td>Total</td>
<td>20 (6.35)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Global Assessment

Efficacy and Tolerability

The efficacy of the treatment was assessed by investigators at the end of the 12-week treatment period based on overall reduction in SBP/DBP and overall response/improvement in patient’s condition. Good to excellent response was reported in 98.09% patients. Only six patients (1.90%) had unsatisfactory efficacy response.

Global tolerability to the treatment was assessed at the end of 12-week treatment period by patients. 98.41% patients reported good to excellent tolerability to the treatment. Only 1.59% patients reported unsatisfactory tolerability, which may be due to the adverse event experienced by those patients.

Overall Assessment of combination

At the end of the study the investigators were asked if they would continue using this combination. The investigators decided to continue the treatment in 299/315 (94.92%) patients whereas in 16.

DISCUSSION

The prevalence of diabetes is increasing worldwide, and is predicted to double within the next 20 years. Hypertension in diabetes is an important cardiovascular risk factor in diabetes mellitus, with major implications for morbidity, mortality and the healthcare costs. In India with a population of billion and a wide rural urban divide, the rate of rise of non communicable diseases is ultra rapid. The rate of rise of Indian patients with hypertension, diabetes, coronary artery disease and dyslipidaemia beats all predictions by public health workers.1

It has been postulated that in diabetes, there is a role for the RAAS in mediating many of the functional effects such as changes in intraglomerular haemodynamics as well as structural changes in diabetic kidney. Treatment with agents that interrupt the RAAS such as ACE inhibitors and ARBs have been shown to confer renoprotection in experimental and human diabetic nephropathy.2

There is an accumulative evidence that pharmacologic therapy that interrupts RAAS may offer special benefits in reducing CVD and renal disease in diabetic patients with hypertension.3

ARBs and ACE inhibitors provide comparable reductions in blood pressure and proteinuria. Some experts also propose that these two in combination has an additive effect against hypertension and proteinuria.4

In patients with microalbuminuria or clinical nephropathy, both ACE inhibitors and ARB are considered first line therapy for the prevention of and progression of nephropathy.5

Several studies have proved the efficacy and clinical benefits of the combination therapy with ARB and ACE inhibitor.

Hamroff and colleagues6 found in an open study in 43 patients with congestive heart failure, that the addition of losartan to the treatment regimen of patients who were already on ACE inhibitors did provide an additional 15-mmHg decrease in systolic blood pressure, with no noticeable impact on serum potassium or creatinine values. The decrease was well tolerated, even in patients who had symptomatic hypotension during up-titration of the ACE inhibitor.

In another study, McKeilvie and colleagues7 compared the effect of candesartan alone versus combination therapy with enalapril versus enalapril alone. Combination therapy was superior to single-agent therapy in preventing left ventricular dilatation and suppression of aldosterone. Additionally there was trend towards an improved ejection fraction (EF) with combination therapy.

In the pilot phase of the International Randomized Evaluation of Strategies for Left Ventricular Dysfunction
A superior effect on BP and a tendency towards a more pronounced drop in urinary albumin excretion of dual blockade of the RAS compared with single blockade has been reported in type II patients with microalbuminuria.90

LORD trial was conducted in a total of 315 diabetic hypertensive patients. Most of the patients 207/315 (65.71%) had a history of diabetes for <1-5 years and rest had a history for more than 6-10 years. The diabetes was controlled using antidiabetic monotherapy or combination therapy. All the eligible patients after a washout period of 8 to 10 days were switched over to the treatment with combination of losartan 50mg and ramipril 2.5/5mg for 12 weeks.

Majority of the patients (52.38%) had stage I hypertension (blood pressure <140-159/90-99 mmHg) and were treated with losartan 50mg + ramipril 2.5 mg. Whereas patients with stage II hypertension (blood pressure >160/>100 mm Hg) were treated with losartan 50 mg + ramipril 5mg. The mean fall of 33.72mm Hg was achieved in systolic blood pressure and 19.10mm Hg was achieved in diastolic pressure at the end of the treatment.

Overall, 250 patients were evaluated for Microalbuminuria of which, 12.8% patients had normoalbuminuria, 33.20% had microalbuminuria and 54% had clinical proteinuria. The striking results in terms of significant reduction in urine albumin excretion were obtained. Significant reduction in urine albumin excretion was seen in 23.8% patients. Overall, 20.8% patients who had microalbuminuria or proteinuria at baseline achieved normoalbuminuria at the end of therapy.

The combination was not only effective in lowering blood pressure to the target level but was also very safe as evident from the results of tolerability assessment. It is also evident from Investigators’ decision to continue the treatment in 299/315 (94.92%) of the patients.

CONCLUSION

In hypertensive diabetic patients, intensive pharmacological treatment to achieve the blood pressure of less than 130/80mm Hg may even be more important in reducing cardiovascular risks than is the control of blood glucose.

LORD trial has proved that an angiotensin II receptor blocker- Losartan and an ACE inhibitor - Ramipril in combination provide comparable reduction in blood pressure as well as in proteinuria a major marker in development of diabetic nephropathy.

The combination showed good to excellent efficacy response in 98.10% patients and achieved a target blood pressure of 130/80 mm Hg in 79.05% patients in 12 weeks. The combination reduced the urinary albumin excretion in majority of the patients with microalbuminuria and proteinuria (the major marker of nephropathy). The combination thus promises to have a potential to occupy an important role in management of patients with diabetes and hypertension.

LORD Study Group Investigators

Shashank R Joshi, Honorary Endocrine and Metabolic Physician, Asian Health Care and Lilavati Hospital, Honorary Assistant Professor, Department of Medicine, Grant Medical College and Sir JJ Group of Hospitals, Mumbai; ME Yeolekar, Dean, Chief - Medical ICU, Professor and Head, Department of Internal Medicine, LTM Medical College and General Hospital, Sion, Mumbai; KK Tripathi, Professor of Medicine and Nephrologist, Department of Medicine, Instt. of Med. Sciences, Banaras, Hindu University, Varanasi; J Giri, KG Hospital and Post Graduate Medical Institute, Coimbatore; AK Maiti, Ex-Director, Professor and Head, Department of Cardiology, IPGMER and SKKM Hospital, Calcutta, M Chopda, Interventional Cardiologist, Chopda Medicare and Research Centre Pvt. Ltd., Cardiac Care, ICCU and Diagnostic Centre and Hospital, Nasik, S Gujarathi, Physician & Cardiologist, Apollo Nursing Home, Indore, S Maroli, Associate Professor, Department of Pharmacology, Incharge of Nuclear Medicine Unit, LTM Medical College and General Hospital, Sion, Mumbai.

LORD Study Group co-investigators

Nitin Butala, Madhura Patwardhan, Shilpa S Joshi, Naval G Daver, PS Shah, Neha Gupta, Asian Health Care Mumbai; VR Ambavane, RA Patil, Resident LTM Medical College and General Hospital, Sion, Mumbai, E Philip, D Ramamoorthy, Resident, KG Hospital and Post Graduate Medical Institute, Mumbai; AK KG Chopda, Ex-Director, Chief Medical ICU, Professor and Head, Department of Pharmacology, Grant Medical College and Sir JJ Group of Hospitals, Mumbai; M Abhyankar, R Joshi, Medical Monitors, Unichem Laboratories Limited, Mumbai; Dilip Pawar, Chief Medical Monitor, Unichem Laboratories Limited, Mumbai.

The LORD study was funded by an unrestricted research grant from Unichem Laboratories. Unichem Laboratories manufacturers LORAM™ which is a fixed dose combination of Losartan and Ramipril and therefore has commercial interest in the said trial. Unichem monitors on the study were Dr. Dilip Pawar and Ms. Meghana Abhankar.
REFERENCES


API Announcement

Oration:
Suggestions are invited from members of the Association of Physicians of India for the following assignments so as to reach Dr. Sandhya Kamath, Hon. General Secretary, not later than 20th March, 2004.

Hoechst Senior Lectureship - 2005
There are no prescribed nomination/application forms for the above oration but, persons are selected from the recommendations received from members of the Association. The recommendations for the above assignments must be accompanied with reasons for recommending a particular person showing the value of his/her research and 8 copies each of three of his/her publications. All papers in connection with the suggestions such as the bio-data, list of publications etc., should be submitted in 8 sets by the proposer. The recipient of the above oration should deliver a lecture pertaining to his/her work at the Annual Conference of API in January - 2005.

The completed application form of the above assignment should reach to Dr. Sandhya Kamath, Hon. General Secretary of API, Laud Mansion, 3rd Floor, 21 MK Road, Opp. Charni Road, East, Mumbai 400 004, not later than 20th March, 2004.

Those who have already been confirmed an Oration/Lectureship/Award are not eligible to apply for the same category.

The members of the Governing Body of API and the members of the Faculty Council of ICP are not eligible to receive any Oration/Lectureship/Award.