Evaluation of Efficacy and Tolerability of Perindopril 8 mg in Bangladeshi Hypertensive Patients: Results from an Open-label, Observational, Multi-center Study (CONTROL)

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Abstract:

Background: *The CONTROL (COversyl in Newly diagnosed stage-II & unconTROlled hypertensive patients triaL) was performed with an objective to evaluate the blood pressure (BP) lowering efficacy and tolerability of Perindopril 8mg in newly diagnosed stage II patients and uncontrolled hypertensive patients among Bangladeshi population.*

Methods: *This was an open-label, observational, multi-center study conducted in consultation centers for out-patients located in different cities of Bangladesh. Adults, aged above 18 years with newly diagnosed stage-II hypertension or uncontrolled hypertension, were recruited. Patients were treated with Perindopril 4mg daily for first 1 week, afterwards uptitrated to Perindopril 8 mg daily and continued treatment for 12 weeks. Patients were followed-up at week-1, week-4, week-8 and week-12.*

Results: *In total, 245 patients were enrolled. Among them, 88 were newly diagnosed stage-II (Group-I) and 157 were uncontrolled (Group-II) hypertensive patients. Male and female distribution was 57% and 43% respectively. Mean age of patients was 54.5 ±11.7 years.*

After 12 weeks treatment, there was a significant reduction in BP from baseline ($p<0.001$) in overall population as well as in Group I and in Group II. In overall population, the mean BP reduction was -31/-15 mmHg (from 163.7/96.8 mmHg to 132.4/81.7 mmHg. In Group I, the reduction was -33/-16 mmHg (from 166.5/98.2 mmHg to 133.4/82.0 mmHg) and in Group II, -30/-14 mmHg (from 159.3/95.6 mmHg to 129.1/81.6 mmHg).

10 patients (4.1%) had to discontinue the treatment due to adverse effects. Dry cough (2%) and hypotension (1.2%) were the main cause of discontinuation. Perindopril 8mg was well tolerated as indicated by the high proportion of physicians (81%) reporting 'good' to 'excellent' tolerability at week 12.

Conclusion: *This study suggests that Perindopril 8mg is effective and safe in the treatment of hypertension in Bangladeshi patients.*

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Introduction:

Hypertension is currently one of the major health problems affecting approximately one billion individuals worldwide.[1] The number of adults with hypertension in 2025 is predicted to increase by about 60% to a total of 1.56 billion.[2] Hypertension predisposes the population to life-threatening cardiovascular, cerebrovascular and renal diseases.[3-6] High prevalence of hypertension and high incidence of related diseases in most societies

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make it the single most important cause of morbidity and mortality worldwide.[7,8]

Until recently, hypertension was associated with wealth, as suggested by its higher prevalence in developed countries.[2] However, differences between developed and developing countries are decreasing. A systematic review of studies performed between 1980 and 2003 suggested that the prevalence of hypertension had remained stable or decreased in developed countries and had increased in developing countries.[9-12] So evidence suggests the urgency to improve blood pressure (BP) control in our country.

Improving the rates of BP control at individual level requires lifestyle modification and effective antihypertensive therapy. The aim of antihypertensive treatment is to reduce BP to evidence-based targets in order to achieve maximum possible reduction in the long term total risk of cardiovascular morbidity and mortality. Most of the hypertension management guidelines have recommended to use ACE inhibitors in hypertensive patients for reducing the risk of cardiovascular morbidity and mortality.[1,13,14]

Perindopril, a long-acting ACE inhibitor, is widely studied in different types of hypertensive patients and established as an effective and well tolerated antihypertensive agent.[15-20] However, none of these studies included Bangladeshi patients. This study was conducted to evaluate the efficacy and tolerability of Perindopril (marketed under the brand name Coversyl®), uptitrated to the maximal recommended dose for the control of BP in hypertensive patients seen in consultation centers for out-patients in Bangladesh.

Methods:

Study Design: This was an open-label, multi-centered, practice-based, observational clinical study. The study was conducted among out-patients. The patients were recruited and followed-up by selected investigators. Study treatment period was 12 weeks for each patient after being enrolled. The objective of this study was to assess the effects of Perindopril 8 mg, administered once daily, on systolic blood pressure (SBP) and diastolic blood pressure (DBP) of newly diagnosed stage II hypertensive patients and uncontrolled hypertensive patients. Another objective was to assess the clinical efficacy and tolerability of Perindopril 8mg in these patients as rated by their physicians.

Patients: Men or women e"18 years old were eligible if they were newly diagnosed with stage II hypertension (BP e" 160/100 mmHg taking no antihypertensive medication) or had uncontrolled hypertension (BP e" 140/90 mmHg or e" 130/80 for diabetics even after taking a single antihypertensive medication). Patients were excluded in case of pregnant or lactating female, known to have allergy to study medication, hypertension with a known secondary cause, a clinically unstable condition, severe gastro-intestinal, renal or hepatic disease which may interfere with absorption, metabolism or excretion of drugs. Patients were recruited during the time May to August 2008 and all patients had given consent prior to enrolment in the study.

Study Procedure: For each patient, at visit 1 (week 0), after sitting for 3 minutes, 3 BP readings, separated by 1 minute intervals were taken and averaged for a mean baseline sitting SBP and DBP. Other variables collected at this visit were age, gender, weight, associated diseases and concomitant treatment. BP measurement was obtained with the mercury sphygmomanometer at rest from the same arm by same investigator. DBP was measured according to phase V (absence of Korotkoff vascular sounds). This process was repeated and occurrence of adverse events was investigated in each follow-up visit (week 1, week 4, week 8 and week 12). Case Report Form was filled-up immediately after each visit.

The following treatment strategy was followed by the physicians:

a. Newly diagnosed patients with stage-II hypertension: Patients were started with Perindopril 4 mg and then uptitrated to Perindopril 8 mg after 1 week.

b. Patients with uncontrolled hypertension with current medication:

- Uncontrolled on ACEis, ARBs, CCBs and Diuretics: Patients were switched to Perindopril 4 mg and then uptitrated to Perindopril 8 mg after 1 week.
- Uncontrolled on Perindopril 4 mg: Patients were uptitrated to Perindopril 8 mg

- Uncontrolled on ß-blocker: If the patient had no ischemic heart disease, ß-blocker was withdrawn by decreasing the dose. Then Perindopril 4 mg was started and uptitrated to Perindopril 8 mg after 1 week. If the patient had ischemic heart disease, Perindopril 4 mg was added on top of ß-blocker and then uptitrated to Perindopril 8 mg after 1 week.

(ACEis = angiotensin-converting enzyme inhibitors; ARBs = angiotensin-receptor blockers; CCBs = calcium channel blockers)

Tolerability Assessments: Each investigator rated Perindopril 8 mg therapy as excellent, good, satisfactory or poor depending on the occurrence of adverse events.

Data Analysis: Analysis was done on the Intent-To-Treat (ITT) population. ITT Patients were all patients who had received at least one dose of Perindopril 8 mg, for whom baseline and at least one post baseline sitting SBP and DBP measurements were recorded and had a completed safety case report form. All statistical tests were two-tailed and all analyses were considered statistically significant if $p<0.05$. Baseline demographics and clinical characteristics were compared between 'newly diagnosed stage II hypertensive patients' and 'uncontrolled hypertensive patients' using *Student t test* and the $\div^2$ test for continuous and categorical variables respectively. *Paired t test* was performed to test the mean BP changes from baseline to postbaseline measurements. Subgroup analysis was performed by age, gender, presence of diabetes and patients treated with previous antihypertensives.

Results:

A total of 245 patients were enrolled in this study. Among them 88 were newly diagnosed as stage II hypertensive patients (Group I) and 157 were patients of uncontrolled hypertension (Group II). All patients met the criteria of ITT patients. 10 patients did not complete the study due to adverse effects.

Baseline Characteristics

Mean age of patients was 54.5 years (±11.7) and mean weight was 66.4 kgs (± 9.2). Male and female distribution was 57% and 43% respectively. About a quarter (23.3%) of the respondents were e"65 years old. The baseline mean sitting SBP and DBP was 163.7 (± 11.5) mmHg and 96.8 (± 7.8) mmHg respectively. Mean heart rate was 81 (± 9) beats per minute.

Table I

Baseline patient demographics and clinical characteristics

Characteristics	Patients prescribed Perindopril (n = 245)
Male (%)	140 (57.1 %)
Female (%)	105 (42.9 %)
Age in years (mean ± SD)	54.5 ± 11.7
≥65 yrs (%)	57 (23.3%)
Weight in kgs (mean ± SD)	66.4 ± 9.2
Blood pressure in mmHg	
SBP (mmHg, mean ± SD)	163.7 ± 11.5
DBP (mmHg, mean ± SD)	96.8 ± 7.8
Heart rate (bpm, mean ± SD)	81 ± 9
Associated disease (%)*	151 (61.6%)
Ischemic heart disease	66 (43.7)
Diabetes mellitus	64 (42.4)
Dyslipidemia	57 (37.7)
Chronic kidney disease	6 (4.0)
Heart failure	4 (2.6)
Cardiac arrhythmia	1 (0.7)
Other diseases	24 (15.9)

**multiple response*SBP = systolic blood pressure; DBP = diastolic blood pressure; bpm = beats per min.

Almost 62% of the respondents had one or more diseases associated with hypertension (Table I). Ischemic heart disease, diabetes mellitus and dyslipidemia were most prevalent. Few patients had chronic kidney disease, heart failure or cardiac arrhythmia. Around 16% patients had other diseases like benign hypertrophy of prostate, gout, bronchial asthma, rheumatoid arthritis, osteoarthritis and chronic obstructive pulmonary disease.

Reductions in Blood Pressure

In the overall population, the mean BP was reduced significantly ($p<0.001$) from 163.7/96.8 mmHg at baseline to 132.4/81.7 mmHg by week 12. The overall BP reduction at week12 was -31.3/-15.1 mmHg. All SBP and DBP reductions at week 1, week 4, week 8 and week 12 were statistically significant ($p<0.001$, Figure 1).

After the first follow-up at week 1, all the patients were up-titrated to Perindopril 8mg. This resulted in a clinically significant total reduction in both SBP and DBP at week 12.

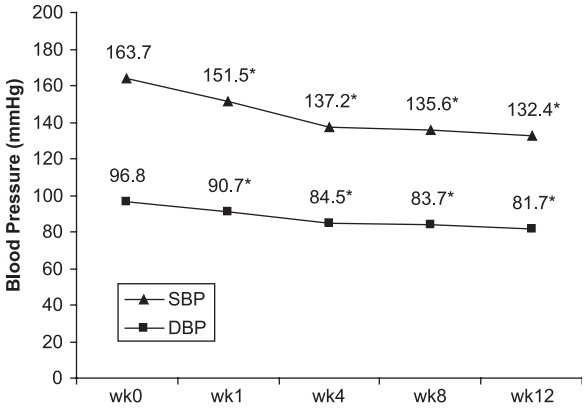

Fig.-1: *Changes in mean systolic and diastolic blood pressure after 12 weeks therapy with Perindopril 8 mg (*p<0.001 vs baseline)*

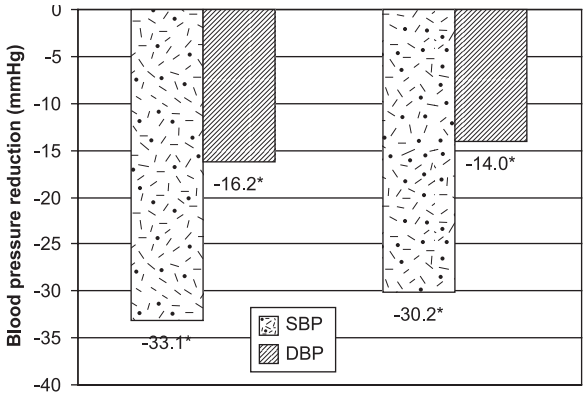

Fig.-2: *Mean BP reductions in Group 1 and Group 2 from baseline after 12 weeks therapy with Perindopril 8mg (*p<0.001 vs baseline)*

The mean reductions from baseline in SBP and DBP at week 12 for Group I and Group II are shown in figure 2. In Group I, the reduction was -33.1/-16.2 mmHg (from 166.5/98.2 mmHg to 133.4/82.0 mmHg) and in Group II, -30.2/-14.0 mmHg (from 159.3/95.6 mmHg to 129.1/81.6 mmHg). The BP reduction from baseline was statistically significant in both groups (p<0.001).

Sub-group Analysis

Age and Gender

Sub-populations according to age and gender showed statistically significant reductions (p<0.001) in mean BP at week 12 from baseline (Table II).

Patients on other antihypertensives

Patients of Group II were non-responsive to their previous antihypertensives. Treatment with Perindopril 8mg for 12 weeks had produced significant reduction from baseline in SBP and DBP in these patients (Figure 3).

Baseline SBP values

Sub-populations according to baseline SBP values showed statistically significant (p<0.001) reductions in mean sitting BP from baseline at week 12 (Table III).

Table II

Effect of Perindopril 8mg on blood pressure of sub-populations

Demographic subgroups	N	BP (mmHg) Baseline	Week 12	BP reduction from baseline
Age				
<65 yrs	188	161.8±17.3/96.8±7.7	131.7±10.3/81.5±4.7	-30.1/15.3
≥65 yrs	57	170.9±15.0/96.6±9.1	138.2±10.1/82.6±5.6	-32.7/14.0
Gender				
Male	140	164.4±15.0/96.6±6.9	133.5±10.5/82.1±4.9	-30.9/14.5
Female	105	162.9±19.8/96.9±9.4	132.6±11.0/81.2±5.0	-30.3/15.7

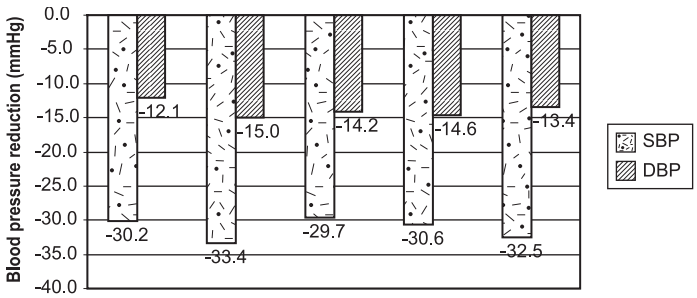

Fig.-3: *Mean BP reductions at week 12 with Perindopril 8mg in patients non-responsive to previous antihypertensives (*p<0.001 vs baseline).*

Table-III

*Mean change in blood pressure from baseline after 12 weeks therapy with Perindopril 8mg (*p<0.001 vs baseline)*

Sub-groups by SBP (mmHg)	Mean SBP before treatment (wk0)	Mean SBP after treatment (wk12)	Mean difference (SBP)	p value	Mean DBP before treatment (wk0)	Mean DBP after treatment (wk12)	Mean difference (DBP)	p value
140-159(n=79)	146.0	124.8	21.2	<0.001	94.0	79.5	14.5	<0.001
160-179(n=120)	165.0	134.5	30.5	<0.001	98.3	82.5	15.8	<0.001
≥180(n=46)	181.4	139.8	41.6	<0.001	99.7	83.1	16.6	<0.001

Tolerability Assessment

Overall 12.6% (31) of the total patients had experienced adverse effects. The most commonly reported adverse effect was 'dry cough' reported by 4.9% of patients at 1st follow-up visit. It was declined to 2.1% at the study end as cough was not caused by Perindopril in some patients and cough was disappeared with time. Hypotension was reported by 1.6% of patients. Other problems (2%) experienced were headache and palpitation.

Out of 245 patients, 10 patients (4.1%) had to discontinue due to adverse effects. Dry cough (2%) and hypotension (1.2%) were the main cause of discontinuation.

Evaluation of the physicians regarding tolerability of Perindopril 8mg in treating Group I and Group II patients showed that the drug was tolerated excellently by almost 36% of the respondents. Tolerability was good in case of 45% of the respondents, satisfactory for 18% and poor for 1% of the respondents (Figure 4).

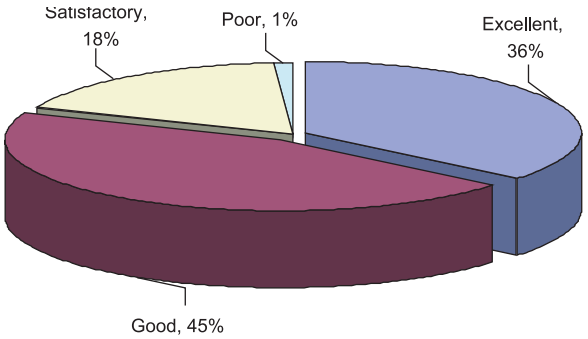

Fig.-4: *Evaluation of the physicians regarding tolerability of Perindopril 8mg.*

Discussion:

This open-label, multi-center, practice-based, observational clinical trial was undertaken to assess the effectiveness and tolerability of Perindopril 8mg in real-life practice settings with hypertensive patients both newly diagnosed and those having uncontrolled hypertension with their existing therapy. This study also evaluated physicians' rating of tolerability of Perindopril 8mg in these patients.

This study has successfully confirmed the antihypertensive effectiveness and tolerability of Perindopril 8mg in hypertensive patients in Bangladesh. Perindopril 8mg was effective in both male and female patients and in patients younger and older than age 65 years.

Titration approach adopted in the study gave clinically significant results also shown in other studies.[15-20] Chazova I, Mychka V, Kirilova M, et. al.[15] studied the dose-dependent efficacy of Perindopril in patients with arterial hypertension in Russia. The study included 2,200 patients. Average age was 56.2 ± 0.2 years, and 42.6% were men and 57.4% women. In the study patients, the incidence of metabolic syndrome was 44.3%, family history of cardiovascular diseases was 18.3%, and diabetes mellitus was 13.2%. Most (83.2%) patients were previously treated, but had uncontrolled blood pressure. Among the study population, 538 patients were treated with Perindopril 4mg for the first 2 weeks, afterwards uptitrated to perindopril 8mg and continued treatment for 16 weeks. After dose uptitration to perindopril 8mg, mean reduction in SBP/DBP reached -29.4/-13.3 mmHg. In our study, the mean BP reduction was -31.3/-15.1 mmHg. The study differs from our study in some context like baseline BP was slightly higher in our study (163.7/

96.8 versus 159.8/94.9 mmHg) and treatment duration of our study was less (12 weeks versus 16 weeks).

Tsoukas G, Anand S, Yang K, et. al. also studied the dose-dependent antihypertensive efficacy of Perindopril in Canadian hypertensive patients. A total of 8,298 hypertensive patients entered the study: 56% with newly diagnosed hypertension and 44% with uncontrolled hypertension. Treatment consisted of perindopril 4mg/day, uptitrated to 8mg/day as required for BP control at visit 2 (2 to 4 weeks after) and followed up for 12 weeks. Among the study population, there were 666 patients having severe hypertension with baseline BP of 178.1/97.6. These patients were uptitrated to Perindopril 8mg. In these patients, the BP reduction was -36.2/-15.3 mmHg. The reduction is slightly higher than our findings. This is due to the fact that the baseline BP was higher compared to our study.

Our study also established that Perindopril 8mg is well tolerated by the Bangladeshi hypertensive patients. Discontinuation rate was low (4.1%) caused by dry cough and hypotension. High proportion of physicians (81%) reported 'good' to 'excellent' tolerability with Perindopril 8mg in their patients. The similar findings also revealed in other studies of Perindopril done in different countries. 15-20

Conclusion:

The strength of this study is that it included patients from daily practice of physicians which could represent the hypertensive population of our country. Limitations are small sample size (compared to community-based studies done abroad), lack of control group and non-randomization.

Our findings suggest that, for the hypertensive population in Bangladesh, Perindopril 8mg is an effective, safe and well tolerated antihypertensive. Also uptitration to full dose would be more effective in patients being treated unsuccessfully with other antihypertensives.

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