## In Anemia

# Strike the Balance with the Right Hematinic

℞

# DEXORANGE®

Syrup/Capsules/Paediatric Syrup

(Ferric Ammonium Citrate)

## The Masterpiece in Hematinics


## ℞ in Anemia associated with

- Pregnancy & Lactation
- General Weakness
- Menorrhagia
- Chemotherapy induced Anemia
- Nutritional & Iron deficiency
- Lack of Appetite
- Chronic Gastrointestinal Blood Loss
- Chronic Kidney Disease

FRANCO-INDIAN PHARMACEUTICALS PVT. LTD.
20, Dr. E. Moses Road, Mumbai 400 011.

2018

# Comparative Evaluation of ACE Inhibitors for their Beneficial Effects in Patients with Ischemic Left Ventricular Systolic Dysfunction and Undergoing Coronary Artery Bypass Surgery

PS GANDHI*, RK GOYAL†, AR JAIN‡, BS MALLYA‡, MC CHAG‡, VM GUPTA‡, DS SHAH‡, BR TRIVEDI‡, NA SHASTRI‡, CB MEHTA‡, KA JAIN‡, NS BHAVASAR‡, UJ SHAH‡

## ABSTRACT

Three angiotensin-converting enzyme (ACE) inhibitors, captopril, perindopril and ramipril were compared for their effectiveness in patients having left ventricular (LV) systolic dysfunction (Left ventricular ejection fraction [LVEF] 30% as revealed by 2D echocardiography) and who underwent coronary artery bypass grafting (CABG). We enrolled 27 patients in captopril, 43 patients in perindopril and 70 patients in ramipril groups. There was about 25-36% rise in LVEF after 3 and 6 months of ACE inhibitor administration in all three groups. Perindopril treatment produced a sustained improvement in LVEF. However, the difference in terms of percent improvement in LV contractility amongst three groups was not statistically significant. After 3 and 6 months of treatment with ACE inhibitor following coronary arterial grafting, the reduction in LV diameters did not differ significantly amongst three groups. There was a significant decrease ($p < 0.05$) in LV end-diastolic diameter from baseline levels in captopril and perindopril groups after 3 months which got increased after 6 months but remained below pretreatment levels in both the groups. In ramipril group, there was not much change in this parameter from baseline levels at 3 and 6 months of treatment. After 6 months of treatment, the percent reduction in LV end-systolic diameter was also sustained in perindopril-treated patients. The percent reduction was greater in the perindopril group (3 and 6 months: 7.39 ± 5.94 and 7.73 ± 3.43, respectively) as compared to that observed in captopril group (3 and 6 months: 5.67 ± 1.05 and 2.52 ± 3.11, respectively) and ramipril group (3 and 6 months: 7.30 ± 2.75 and 4.93 ± 3.22, respectively). Mitral-valve regurgitation was greatly reduced in the captopril group at 3 as well 6 months of ACE inhibitor administration. However, the percent reduction from baseline levels was not statistically significant amongst three groups. The percent improvement in functional status was significantly greater in the ramipril treatment group (36.46 ± 3.14) after 6 months of treatment as compared to that of captopril (6.67 ± 10.64) and perindopril (4.17 ± 2.73) group. In conclusion, our data show equal beneficial effects with all three ACE inhibitors in CABG patients with LV systolic dysfunction, with marginal superiority for perindopril.

**Keywords:** ACE inhibitor, left ventricular systolic dysfunction, heart failure, coronary artery bypass surgery

About 23 million people worldwide are afflicted with heart failure (HF) and 2 million new cases of HF are diagnosed each year worldwide. As per the heart and stroke statistics update of American Heart Association (AHA), nearly 5 million people in the United States suffer from HF. A large survey namely MONItoring of trends and determinants in CArdiovascular disease (MONICA) survey found that the prevalence of left ventricular (LV) dysfunction in Britain was 2.27%. Indians and other South Asians are less likely to die from HF in comparison to Caucasians. The incidence of HF has been on the rise in past few decades. Since, myocardial infarction (MI) or severe ischemia, resulting from multiple-vessel coronary artery disease (CAD), is the main underlying cause in the LV systolic dysfunction, surgical revascularization of diseased coronary arteries by coronary artery bypass grafting (CABG) is one of the common interventions for the treatment of such patient population. However, post-surgical therapy with pharmacological measures

*Associate Professor
Dept. of Pharmacology
Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat
†Institute of Lifesciences, Ahmedabad University, Ahmedabad, Gujarat
‡The Heart Care Clinic, Ahmedabad, Gujarat
**Address for correspondence**
Dr Purvi S Gandhi
Associate Professor, Dept. of Pharmacology
Shree Dhanvantary Pharmacy College, Near Railway Station, Surat - 394 110, Gujarat
E-mail: psgandhi1975@gmail.com

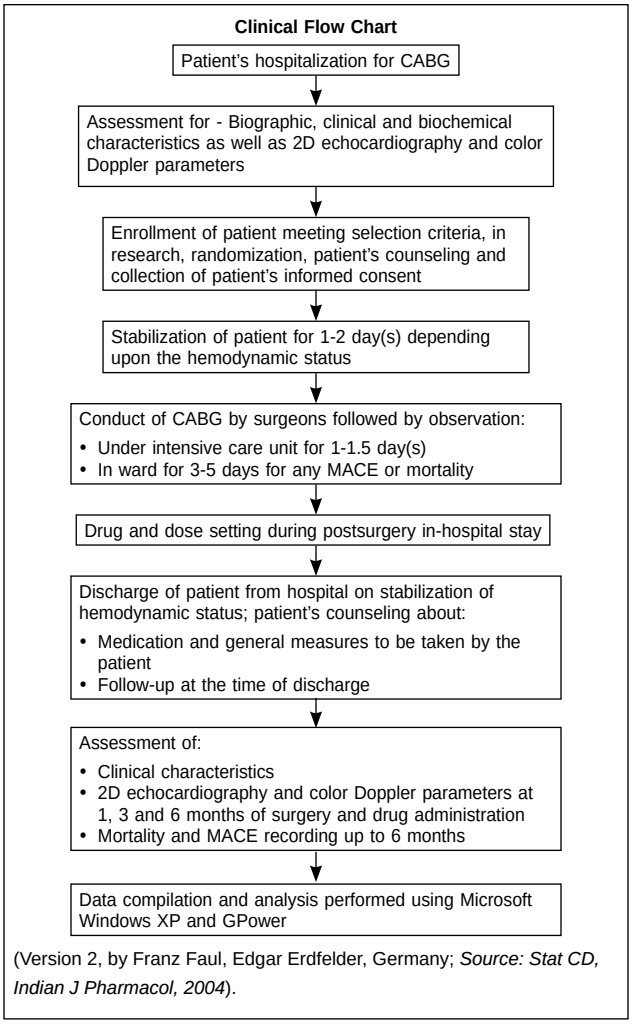
is needed to sustain the beneficial effects of the former. Involvement of neurohormonal system especially sympathetic system and renin-angiotensin-aldosterone system (RAAS) in LV remodeling through direct as well as indirect mechanism is well-documented. Several angiotensin-converting enzyme (ACE) inhibitors and antagonists of angiotensin II receptor subtype-1 ($AT_1$) have shown a significant reduction in mortality and morbidity in patients having LV systolic dysfunction. Long-term treatment with ACE inhibitors produces absolute increases in LV ejection fraction (LVEF).

Captopril has been found to reverse ventricular dilation caused by MI. Enalapril has also been reported to reverse progression of LV dilation in patients with asymptomatic systolic dysfunction. Thus, many clinical trials and researches are available showing beneficial effects of various ACE inhibitors and American College of Cardiology (ACC)/AHA practice guidelines recommend ACE inhibitors for treatment of LV systolic dysfunction, if not contraindicated. Majority of the reports on beneficial effects of ACE inhibitors in patients with LV dysfunction include placebo-controlled research and do not compare various ACE inhibitors in a single research for their beneficial effects on such patient population. In our earlier report, we found captopril and perindopril more efficient in improving LV contractility as compared to ramipril, lisinopril and losartan.

Captopril and perindopril produced a significant increase in percent LVEF as compared to other ACE inhibitors and losartan. Perindopril also decreased insulin levels significantly. There was a significant correlation between decreases in blood glucose as well as insulin levels with improvements in LVEF. However, the evidence was based on assessment of biochemical parameters to correlate the improvements in LVEF produced by these drugs, while the clinical parameters included echocardiographic evaluation. Hence, we compared various ACE inhibitors in one research for their beneficial effects on patients having ischemic LV systolic dysfunction and undergoing CABG using echocardiographic parameters.

## MATERIAL AND METHODS

The study presented here includes the research carried out at SAL Hospital and Sterling Hospital, Ahmedabad. The research was approved by the Ethics Committee of both the hospitals. Written informed consent was taken from all the patients eligible for the investigation, Moreover, all patients were explained about the procedures, the risks and benefits of the interventions.




(Version 2, by Franz Faul, Edgar Erdfelder, Germany; *Source: Stat CD, Indian J Pharmacol, 2004*).

### Study Design

It was a prospective, randomized, open-label research. The research did not include a control group since ACE inhibitors have proven absolute beneficial effects on patients with LV systolic dysfunction. Further, as per the ACC/AHA guidelines for management of HF, all the patients with LV systolic dysfunction should be treated with ACE inhibitor, if there is no contraindication. Therefore, the control group was not included and comparison amongst three ACE inhibitors was carried out.

### Patient Selection

#### Inclusion Criteria

Patients presenting with ischemic LV systolic dysfunction (defined as LVEF 30% as revealed from two-dimensional [2D] echocardiography) and undergoing CABG were included.

### Exclusion Criteria

Patients of age above 70 years, previous or recent history of second- or third-degree atrioventricular block, renal failure (serum creatinine >2.6 mg%), hepatic dysfunction (serum glutamate pyruvate transaminase [SGPT] >45 IU/L), cerebrovascular events, previous history of revascularization or valve replacement surgery were excluded from the study.

### Groups of Patients

Patients meeting the selection criteria were randomized into three groups. Randomization was done using cards indicating '1' designated to captopril, '2' designated to perindopril and '3' designated to ramipril therapy. Group I included patients receiving captopril after CABG. Group II included patients receiving perindopril treatment. In Group III, ramipril was the ACE inhibitor. Patients were evaluated at the time of enrollment a day or 2 before CABG and re-evaluated at 1, 3 and 6 months of CABG and ACE inhibitor administration. We enrolled 27 patients in Group I (captopril group), 43 patients in Group II (perindopril group) and 70 patients in ramipril group (Group III).

## TREATMENT

As per the strategy, the drug dose regimen was started with the minimum dose of the drug and allowed to attain the maximum dose. Serial dose titration was carried out depending upon the hemodynamic status of the patients. For captopril, the initial dose was 37.5 mg/day and reached up to maximum of 75 mg/day. Perindopril treatment was begun with the dose of 2 mg/day and reached maximum dose of 4 mg/day. Ramipril administration was started with 2.5 mg/day and the highest dose attained was 20 mg/day. In addition to ACE inhibitor, patients were also receiving other drugs directly affecting cardiac function such as diuretic(s), β-adrenoceptor blocker and digoxin. Other drugs used included amiodarone, isosorbide dinitrate, acetylsalicylic acid, statin, etc., depending upon the requirements. Patients were also advised of general measures about lifestyle modifications, i.e., cessation of smoking or tobacco chewing or alcoholism, regular exercise of low-medium calibre, restricted total salt intake and fluid intake (2-3 liters/day) as well as fat intake.

## BIOGRAPHIC CHARACTERISTIC ASSESSMENT

Patient's biographic characteristics, i.e., age and associated risk factors such as habit of smoking, tobacco chewing or alcoholism and family history of ischemic heart disease (IHD) were noted by questioning at the time of enrollment. Body weight was measured with the help of pedal weighing balance. Patient's height was measured in patient's standing position using vertical height-measuring column device.

### Clinical Assessment

Clinical assessment included patient's hemodynamic parameters, i.e., pulse rate, systolic and diastolic blood pressure measured in patient's seating position with elbow at the level of heart using sphygmomanometer. They were evaluated for the electrocardiogram (ECG) and CAD characteristics using coronary angiography (CAG) pattern carried out preoperatively. Functional capacity was determined as per New York Heart Association (NYHA) class for HF, assigning patients to 1 of 4 functional classes depending upon the degree of effort needed to elicit symptoms.

### 2D echocardiography and Color Doppler Assessment

2D echocardiography and color Doppler assessment was performed using CarisPlus (Esaote, USA) machine by a Cardiologist who was unaware of the treatment given. Recommendations of the American Society of Echocardiography were followed by the Cardiologist for measuring various parameters. Images were obtained from the patient lying on the left side in a supine position with the body elevated at about 30°. LVEF was assessed using standard parasternal and apical views. LV end-diastolic diameter (LVEDd) and LV end-systolic diameter (LVEDs) were measured using four-chamber and two-chamber views with apical approach at the level of papillary muscle. Severity of mitral-valve regurgitation (MR) was found out using color Doppler assessment. LVEF, LVEDd, LVEDs and MR-grade were measured a day or 2 before and 1, 3 and 6 months following CABG and ACE inhibitor administration. Mortality and MACE were noted up to 6 months of drug treatment under consideration.

### Biochemical Parameter Assessment

Blood samples from patients were collected at the time of enrollment for biochemical parameter testing, which was done in in-hospital pathology laboratory following good laboratory practices. Biochemical parameters assessed included serum glucose, serum urea, serum creatinine, SGPT, serum total cholesterol, serum triglyceride, serum high-density lipoprotein

(HDL) cholesterol, serum low-density lipoprotein (LDL) cholesterol, serum potassium ($K^+$) and serum sodium ($Na^+$).

## DATA ANALYSIS

The data were analyzed by finding mean ± standard error of mean (SEM) for numerical and ordinal data and percent of number (n) of patients for nominal data. Chi-square test was used to find difference of statistical significance in categorical measurements amongst three groups. For parametric numerical data, results were obtained by applying Student's *t*-test to find the change in characteristics from baseline levels. Analysis of variance (ANOVA) was used for numerical data to find the significant difference amongst three treatment groups. Difference amongst groups and hence treatment, was considered statistically significant if 'p' value was found to be <0.05 ($p < 0.05$). Post-hoc power analysis was done using GPower software. The power of the study (1-β) has been presented along with the respective level of significance.

## RESULTS

Baseline biographic characteristics, risk factor association and biochemical variables were similar among three groups (Tables 1-3). There was no significant difference in CAD characteristics, medication affecting cardiac function other than ACE inhibitors, hemodynamics (such as heart rate, systolic and diastolic blood pressure) and baseline 2D echocardiography characteristics amongst three groups (Tables 4-7). After 1, 3 and 6 months of ACE inhibitor administration following CABG, 2D echocardiography showed a significant ($p < 0.05$) improvement in LV contractility from baseline levels (i.e., levels at the time of enrollment) in captopril and ramipril groups. In perindopril treatment group, the increase in LVEF was found to be statistically significant after 1 and 3 months of treatment. Increase in LVEF in terms of percent change from baseline levels in individual patients did not differ significantly amongst three groups; however, the increase was greater and persistent in perindopril group (Table 7 and Fig. 1).

There was a significant decrease in LVEDd from baseline levels in captopril and perindopril groups after 3 months, which increased after 6 months, but remained below pretreatment levels in both the groups. In ramipril group, not much change in this parameter was observed from baseline levels after 3 and 6 months of treatment (Table 7 and Fig. 2). After 3 months of treatment, LVEDs was significantly decreased in captopril and perindopril groups as compared with baseline levels. However, after 6 months, there was an increase in this parameter in both the groups. In ramipril-treated patients, no significant decrease in LVEDs was observed after 3 as well as 6 months of treatment. Decrease in LVEDs in terms of percent change from baseline levels did not differ significantly amongst three groups; however, it was more persistent in perindopril group (Table 7 and Fig. 3). MR grade did not differ significantly from baseline levels within the groups as well as amongst three

**Table 1.** Baseline Biographic Characteristics of Patients

| Parameter | Group I (Captopril) (n = 27) | Group II (Perindopril) (n = 43) | Group III (Ramipril) (n = 70) |
|---|---|---|---|
| **Sex males (%)** | 27 (100%)† | 38 (88.37%) | 67 (95.71%) |
| Age (years)* | 57.14 ± 1.84 | 60.25 ± 1.34 | 56.89 ± 1.07 |
| BMI ($kg/m^2$)* | 26.36 ± 1.53 | 27.48 ± 1.13 | 25.31 ± 1.32 |
| **Lifestyle (stress)** | | | |
| Heavy | 9 (33.33%) | 3 (6.98%) | 14 (20.0%) |
| Moderate | 7 (25.92%) | 15 (34.88%) | 16 (22.86%) |
| Sedentary | 11 (40.74%) | 25 (58.14%) | 40 (57.14%) |
| **Symptoms** | | | |
| Dyspnea on exertion | 16 (59.26%) | 23 (53.49%) | 29 (41.43%) |
| Edema | 2 (7.40%) | 4 (9.30%) | 2 (2.86%) |
| Chest pain | 15 (55.55%) | 22 (51.16%) | 45 (64.29%) |

BMI = Body mass index; $kg/m^2$ = Kilogram per square meter.

*Mean ± SEM.

†Values in brackets are percent of total *n* in each group.

**Table 2.** Prevalence of Risk Factors in Patients at the Time of Enrollment

| Risk factor | Group I (Captopril) (n = 27) | Group II (Perindopril) (n = 43) | Group III (Ramipril) (n = 70) |
|---|---|---|---|
| **Habit** | | | |
| Alcoholism | 1 (3.7%)* | 0 (0%) | 4 (5.71%) |
| Smoking | 5 (18.52%) | 5 (11.63%) | 18 (25.71%) |
| Tobacco chewing | 1 (3.7%) | 6 (13.95%) | 17 (24.28%) |
| **Disease** | | | |
| DM | 10 (37.03%) | 21 (48.83%) | 36 (51.43%) |
| HT | 7 (25.92%) | 17 (39.53%) | 29 (41.43%) |
| DM + HT | 3 (11.11%) | 10 (23.26%) | 17 (24.29%) |
| **Positive family history** | | | |
| IHD | 7 (25.93%) | 8 (18.6%) | 24 (34.28%) |
| Past history of MI | 18 (66.67%) | 21 (48.84%) | 42 (60.0%) |

DM = Diabetes mellitus; HT = Hypertension; IHD = Ischemic heart disease; MI = Myocardial infarction.

*Values in brackets are percent of total *n* in each group.

**Table 3.** Biochemical Parameters at Baseline Level

| Biochemical parameter | Group I (Captopril) (n = 27) | Group II (Perindopril) (n = 43) | Group III (Ramipril) (n = 70) |
|---|---|---|---|
| RBS (mg%)* | 155.59 ± 10.82 | 149.01 ± 12.43 | 176.79 ± 7.55 |
| Serum urea (mg%)* | 29.59 ± 1.43 | 32.23 ± 1.39 | 34.34 ± 1.16 |
| Serum creatinine (mg%)* | 1.18 ± 0.08 | 1.19 ± 0.03 | 1.15 ± 0.03 |
| SGPT (IU/L)* | 28.58 ± 2.52 | 30.37 ± 1.51 | 33.4 ± 1.23 |
| Serum $K^+$ (mEq/L)* | 4.47 ± 0.07 | 4.10 ± 0.08 | 4.32 ± 0.07 |
| Serum $Na^+$ (mEq/L)* | 135.98 ± 1.47 | 135.89 ± 0.81 | 136.56 ± 0.54 |
| Serum TC (mg%)* | 112.0 ± 8.54 | 110.45 ± 4.59 | 117.65 ± 3.61 |
| Serum TG (mg%)* | 75.68 ± 6.46 | 99.53 ± 8.14 | 106.17 ± 7.49 |
| Serum LDL-C (mg%)* | 59.87 ± 6.55 | 54.56 ± 4.38 | 61.61 ± 2.96 |
| Serum HDL-C (mg%)* | 31.53 ± 1.52 | 27.96 ± 1.79 | 27.71 ± 1.22 |

HDL-C = High-density lipoprotein cholesterol; IU = International unit; $K^+$ = Potassium; LDL-C = Low-density lipoprotein cholesterol; mEq = Milliequivalence; mg = Milligram; $Na^+$ = Sodium; RBS = Random blood sugar; SGPT = Serum glutamate pyruvate transaminase; TC = Total cholesterol; TG = Triglyceride.

*Mean ± SEM.

groups after 3 and 6 months of ACE inhibitor administration. At 6 months of ACE inhibitor administration, the percent improvement in MR-grade was greatest in captopril group as compared to that produced in perindopril and ramipril groups (Table 7 and Fig. 4). The NYHA class was significantly reduced ($p < 0.05$) from baseline levels in all three groups after 3 and 6 months suggesting significant improvement in functional status in all three groups (Fig. 5). Further, in ramipril group, the percent improvement in NYHA class was statistically significant as compared to those observed in other two groups. Two patients died in ramipril treatment group during post-hospital course, one because of sudden fall in heart rate and the other because of recurrent MI. In remaining patients, no major adverse cardiovascular event (MACE) was found in all three groups during 6-month follow-up.

## DISCUSSION

Hyperactivated neurohormonal systems responsible for the cardinal effects in patients with LV dysfunction include mainly RAAS and sympathetic system. Amongst various drug therapies, inhibitors of RAAS are at the top of the recommendations. Various components of RAAS play a significant role in the development of LV remodeling; and hence in further deterioration of LV

**Table 4.** Angiographic Pattern of Stenosed Coronary Arteries as Revealed by Angiography

| | Group I (Captopril) (n = 27) | Group II (Perindopril) (n = 43) | Group III (Ramipril) (n = 70) |
|---|---|---|---|
| Single vessel disease | 0 (0%)* | 1 (2.32%) | 0 (0%) |
| Double vessel disease | 4 (14.81%) | 7 (16.28%) | 8 (11.42%) |
| Triple vessel disease | 23 (85.18%) | 35 (81.39%) | 62 (88.57%) |
| Diffusely diseased artery | 2 (7.41%) | 8 (18.60%) | 10 (14.23%) |
| **Diseased artery, lesion severity i.e., percent blockade of diameter** | | | |
| LMCA (≥50%) | 2 (7.41%) | 7 (16.28%) | 10 (14.23%) |
| LAD (100%) | 17 (62.96%) | 7 (39.53%) | 30 (42.86%) |
| LAD (70-99%) | 6 (22.22%) | 20 (46.51%) | 36 (51.43%) |
| LCx (100%) | 3 (11.11%) | 9 (20.93%) | 7 (10.0%) |
| LCx (70-99%) | 8 (29.63%) | 16 (37.21%) | 29 (41.43%) |
| RCA (100%) | 9 (33.33%) | 17 (39.53%) | 28 (40.0%) |
| RCA (70-99%) | 11 (40.74%) | 13 (30.23%) | 31 (44.29%) |

LMCA = Left main coronary artery; LAD = Left anterior descending artery; LCx = Left circumflex artery; RCA = Right coronary artery.

*Values in brackets are percent of total *n* in each group.

**Table 5.** Medication affecting Cardiac Function other than ACE Inhibitors given to patients following CABG

| Medication | Group I (Captopril) (n = 27) | Group II (Perindopril) (n = 43) | Group III (Ramipril) (n = 70) |
|---|---|---|---|
| Digoxin | 23 (85.18%)* | 29 (67.44%) | 49 (70.0%) |
| Diuretics | 25 (92.59%) | 37 (86.04%) | 62 (88.57%) |
| β-adrenoceptor blocker | 15 (55.55%) | 17 (39.53%) | 33 (47.14%) |

ACE = Angiotensin-converting enzyme; CABG = Coronary artery bypass grafting.

*Values in brackets are percent of total *n* in each group.

**Table 6.** Hemodynamic Levels in Patients at Baseline (at the Time of Enrollment) and at 1, 3 and 6 Months of Treatment

| Parameters | Group I (Captopril) (n = 27) | Group II (Perindopril) (n = 43) | Group III (Ramipril) (n = 70) |
|---|---|---|---|
| **HR (beats/min)*** | | | |
| Baseline | 79.60 ± 1.42 | 85.72 ± 2.49 | 82.71 ± 2.13 |
| 1 month | 83.0 ± 1.34 | 83.92 ± 0.84 | 83.85 ± 0.99 |
| 3 months | 81.0 ± 2.45 | 79.0 ± 1.32 | 82.4 ± 1.24 |
| 6 months | 84.0 ± 1.62 | 82.0 ± 1.12 | 86.67 ± 1.56 |
| **SBP (mmHg)*** | | | |
| Baseline | 125.4 ± 3.69 | 122.89 ± 2.82 | 123.75 ± 2.10 |
| 1 month | 119.0 ± 1.98 | 125.81 ± 2.74 | 119.84 ± 1.44 |
| 3 months | 121.0 ± 3.17 | 125.67 ± 4.11 | 127.0 ± 2.86 |
| 6 months | 126.25 ± 2.45 | 126.78 ± 3.24 | 122.0 ± 1.59 |
| **DBP (mmHg)*** | | | |
| Baseline | 76.24 ± 1.42 | 78.19 ± 1.58 | 79.75 ± 1.16 |
| 1 month | 76.18 ± 1.59 | 80.84 ± 1.08 | 78.01 ± 0.90 |
| 3 months | 83.0 ± 4.62 | 83.33 ± 0.83 | 80.8 ± 1.34 |
| 6 months | 81.34 ± 2.56 | 80.0 ± 1.27 | 83.33 ± 0.70 |

DBP = Diastolic blood pressure; HR = Heart rate; mmHg = Millimeters of mercury; SBP = Systolic blood pressure.

*Mean ± SEM.

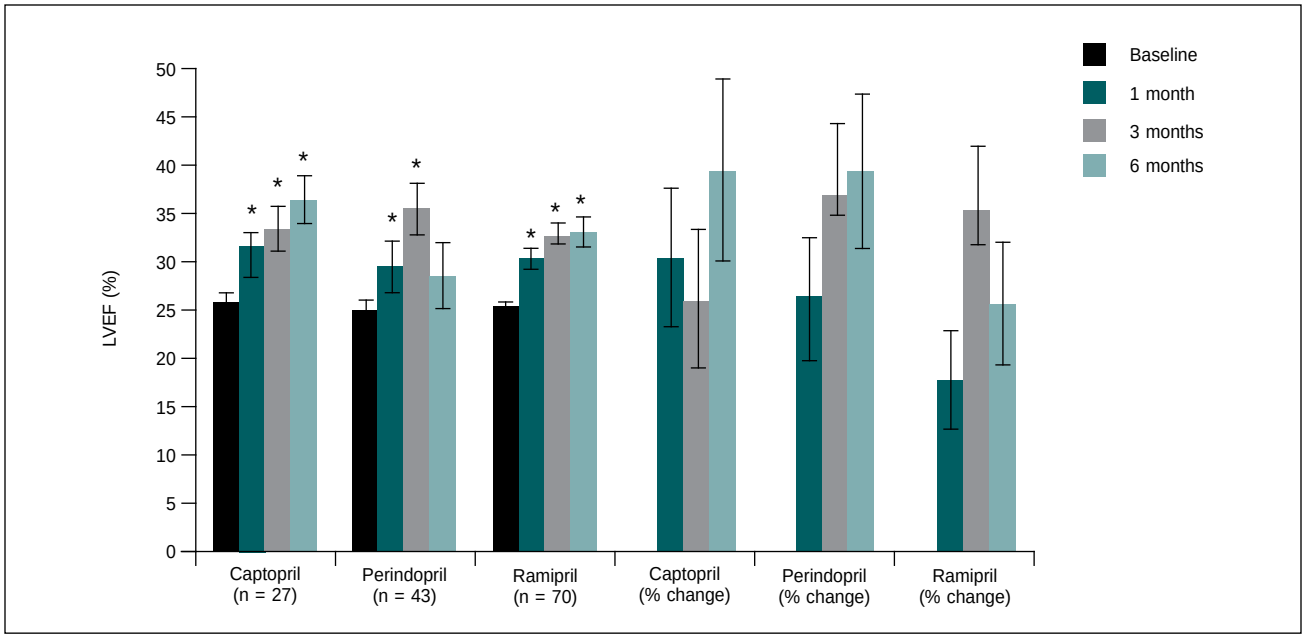



**Figure 1.** Effect of ACE inhibitors on LV contractility measured as LVEF in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from baseline ($p < 0.05$).

Power ($1-\beta$) = 0.546 at $\alpha$ = 0.4.

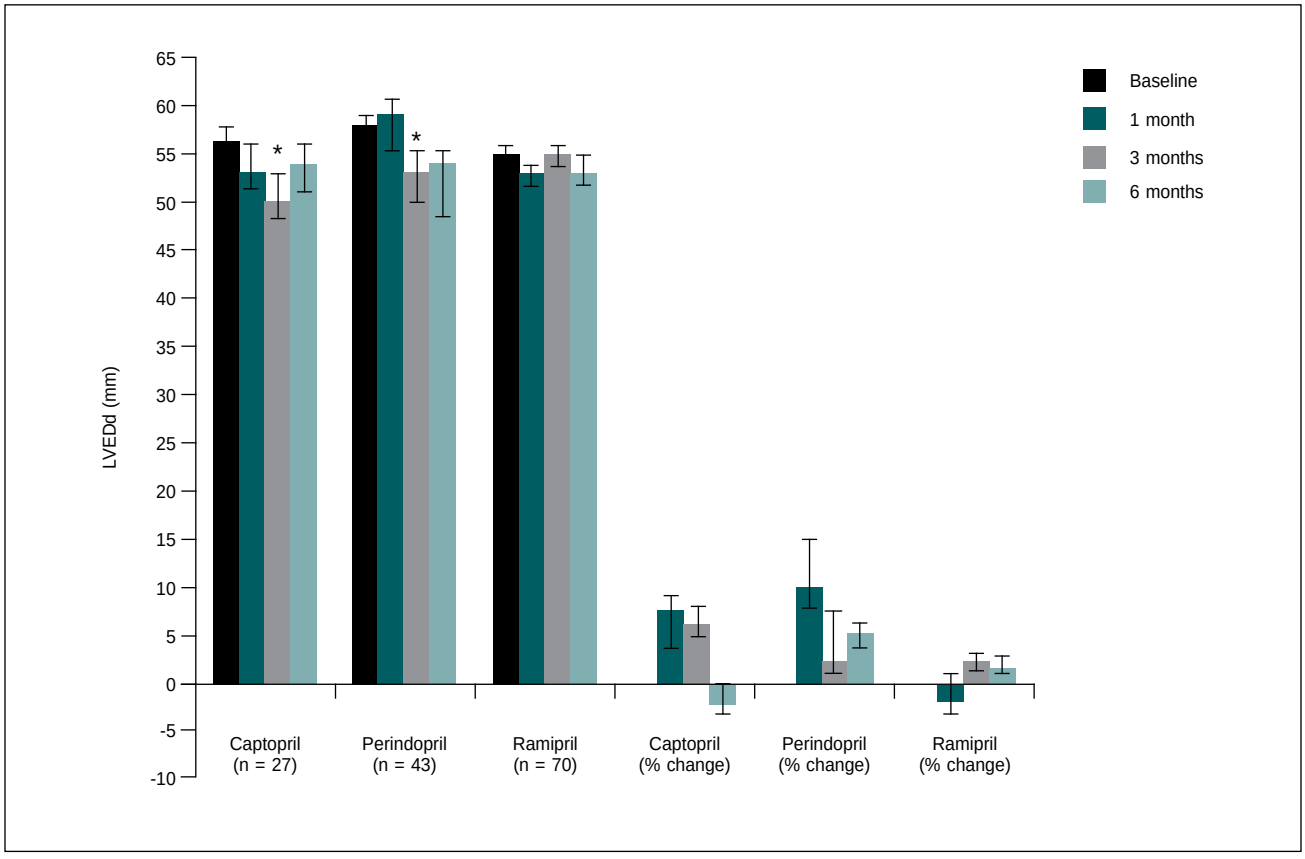



**Figure 2.** Effect of ACE inhibitors on LVEDd in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from baseline ($p < 0.05$).

**Table 7.** 2D Echocardiography and Color Doppler Characteristics and NYHA Class for HF in Patients at the Time of Enrollment (Baseline) and at 1, 3 and 6 Months of ACE Inhibitor Treatment

| Parameters | Group I (Captopril) | | Group II (Perindopril) | | Group III (Ramipril) | |
|---|---|---|---|---|---|---|
| **2D echocardiography and color Doppler** | **(n = 27)** | **% change from baseline in individual patients** | **(n = 43)** | **% change from baseline in individual patients** | **(n = 70)** | **% change from baseline in individual patients** |
| **LVEF (%)*** | | | | | | |
| Baseline | 25.89 ± 0.84 | | 24.91 ± 1.07 | | 25.21 ± 0.57 | |
| 1 month | 31.68 ± 1.95‡ | 30.38 ± 7.23 | 29.44 ± 2.65‡ | 26.12 ± 6.44 | 30.29 ± 1.14‡ | 17.74 ± 5.09 |
| 3 months | 33.25 ± 2.36‡ | 26.11 ± 7.22 | 35.43 ± 2.60‡ | 36.61 ± 7.68 | 32.59 ± 1.49‡ | 35.28 ± 6.72 |
| 6 months | 36.25 ± 2.51‡ | 39.42 ± 9.49 | 28.5 ± 3.42 | 39.2 ± 7.92 | 33.03 ± 1.58‡ | 25.61 ± 6.34 |
| **LVEDd (mm)*** | | | | | | |
| Baseline | 55.86 ± 1.60 | | 57.25 ± 1.23 | | 54.82 ± 0.90 | |
| 1 month | 52.18 ± 2.80 | 7.67 ± 3.99 | 58.56 ± 2.06 | 10.97 ± 9.49 | 52.28 ± 1.53 | -1.9 ± 2.81 |
| 3 months | 50.5 ± 2.03‡ | 6.3 ± 3.84 | 53.83 ± 2.01‡ | 3.18 ± 3.86 | 55.39 ± 1.96 | 2.99 ± 1.32 |
| 6 months | 53.98 ± 1.47 | -2.55 ± 2.07 | 54.93 ± 2.65 | 4.81 ± 1.16 | 54.14 ± 1.07 | 2.87 ± 2.05 |
| **LVEDs (mm)*** | | | | | | |
| Baseline | 44.17 ± 1.57 | | 44.37 ± 1.40 | | 43.18 ± 1.07 | |
| 1 month | 41.35 ± 2.72 | 6.37 ± 4.85 | 47.02 ± 2.32 | -2.62 ± 4.36 | 39.93 ± 1.64 | -0.7 ± 4.01 |
| 3 months | 38.28 ± 2.31‡ | 5.67 ± 1.05 | 38.18 ± 1.86‡ | 7.39 ± 5.94 | 41.83 ± 2.00 | 7.30 ± 2.75 |
| 6 months | 39.91 ± 1.28‡ | 2.52 ± 3.11 | 44.3 ± 2.87 | 7.73 ± 3.43 | 40.28 ± 1.37 | 4.93 ± 3.22 |
| **MR-grade*** | | | | | | |
| Baseline | 0.77 ± 0.11 | | 0.46 ± 0.08† | | 0.7 ± 0.08 | |
| 1 month | 0.82 ± 0.1 | -24.55 ± 38.41 | 0.49 ± 0.16 | 41.67 ± 13.14 | 0.6 ± 0.16 | -77.14 ± 58.04 |
| 3 months | 0.6 ± 0.15 | 50.0 ± 13.87 | 0.36 ± 0.12 | -2.22 ± 41.87 | 0.7 ± 0.11 | -48.75 ± 53.27 |
| 6 months | 0.5 ± 0.16 | 50.0 ± 17.41 | 0.73 ± 0.2 | -68.0 ± 53.4 | 0.68 ± 0.12 | -89.09 ± 64.3 |
| **NYHA class for HF*** | | | | | | |
| Baseline | 2.91 ± 0.18 | | 2.94 ± 0.15 | | 3.0 ± 0.15 | |
| 1 month | 2.18 ± 0.22‡ | 5.0 ± 13.41 | 1.89 ± 0.26‡ | 25.0 ± 10.8 | 2.0 ± 0.24‡ | 28.7 ± 6.07 |
| 3 months | 2.0 ± 0.17‡ | 34.72 ± 13.14 | 1.95 ± 0.14‡ | 27.45 ± 4.89 | 2.17 ± 0.15‡ | 17.86 ± 5.65 |
| 6 months | 2.67 ± 0.16 | 6.67 ± 10.64 | 2.43 ± 0.20‡ | 4.17 ± 2.73 | 2.25 ± 0.15‡ | 36.46 ± 3.14† |

2D = Two-dimensional; HF = Heart failure; LVEDd = Left ventricular end-diastolic diameter; LVEDs = Left ventricular end-systolic diameter; LVEF = Left ventricular ejection fraction; MR = Mitral-valve regurgitation; NYHA = New York Heart Association.

*Mean ± SEM.

†Significantly different as compared with other two groups ($p < 0.05$); ‡Significantly different from baseline ($p < 0.05$).

dysfunction caused by ischemia and/or infarction. Thus, suppression of these components has potential-absolute and synergistic in sustaining the beneficial effects brought about by surgical revascularization. It is recommended that all HF patients with established LV systolic dysfunction should be treated with ACE inhibitor, until there are contraindications to these agents. By inhibiting ACE, systemic and tissue as well, ACE inhibitors reduce afterload and systolic stress too.

These subsequently increase stroke volume due to facilitated stroke work. By improving renal hemodynamics and by reducing aldosterone secretion, ACE inhibitors prevent blood volume overload. Consequently, preload and diastolic wall stresses are diminished. However, different ACE inhibitors may vary in their activity and thus superiority.

Pfeffer et al (1992) found captopril treatment (at about 3.5 years of captopril administration) to be more beneficial, as compared with placebo, in

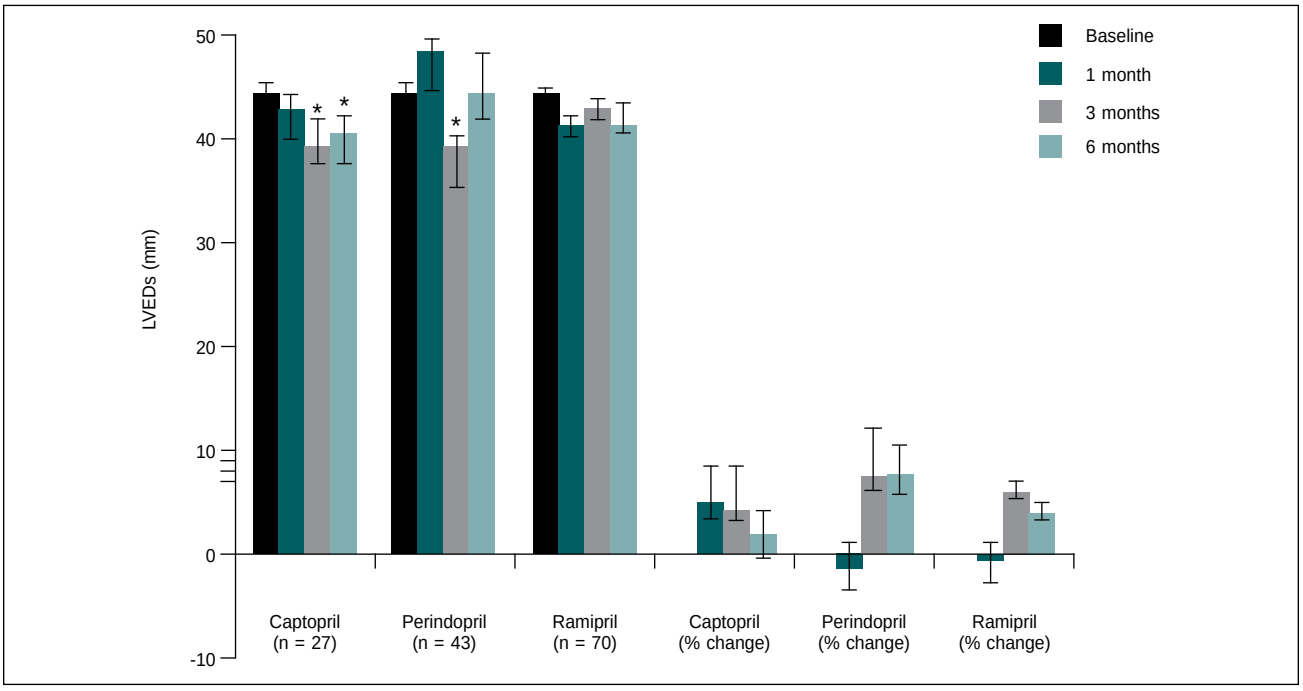



**Figure 3.** Effect of ACE inhibitors on LVEDs in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from baseline ($p < 0.05$).

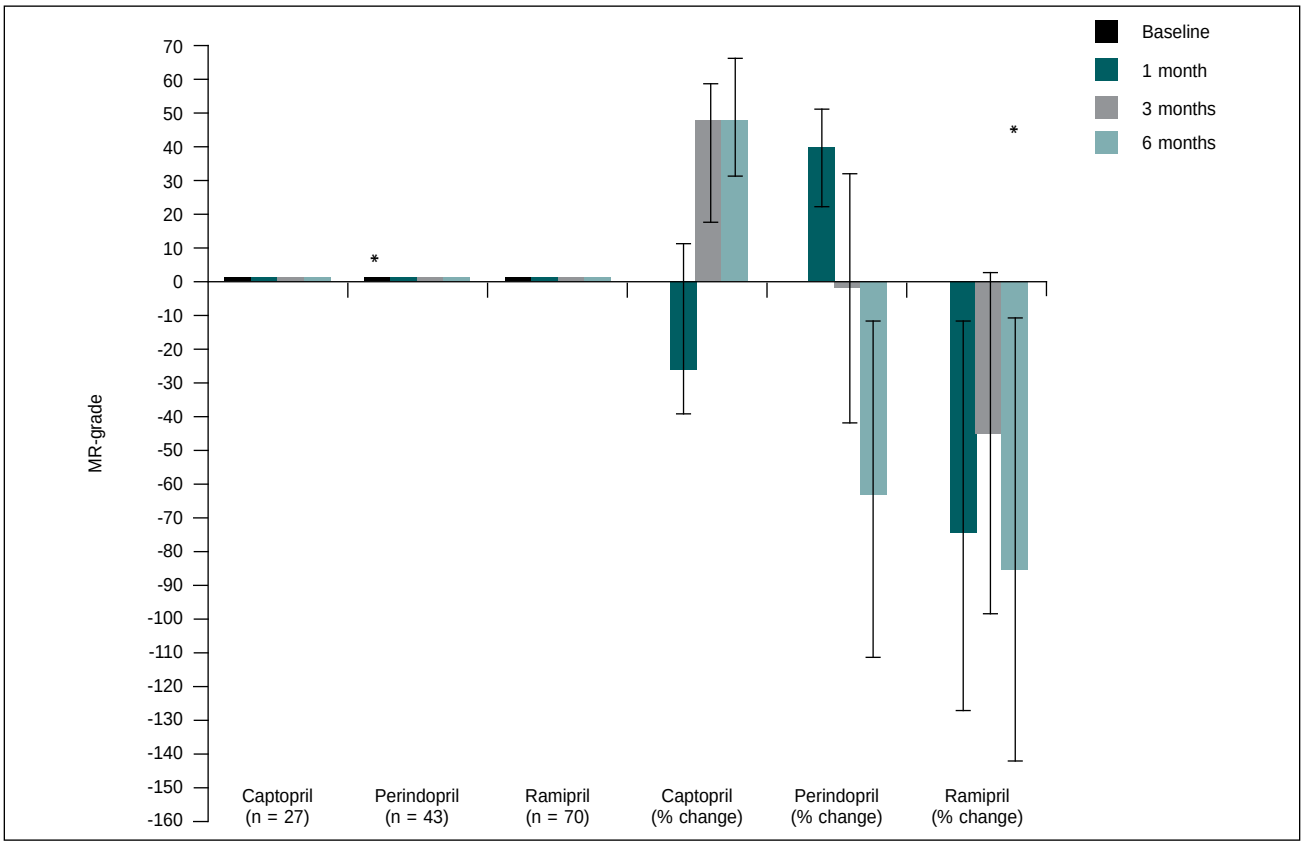



**Figure 4.** Effect of ACE inhibitors on mitral-valve regurgitation in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from other groups ($p < 0.05$).

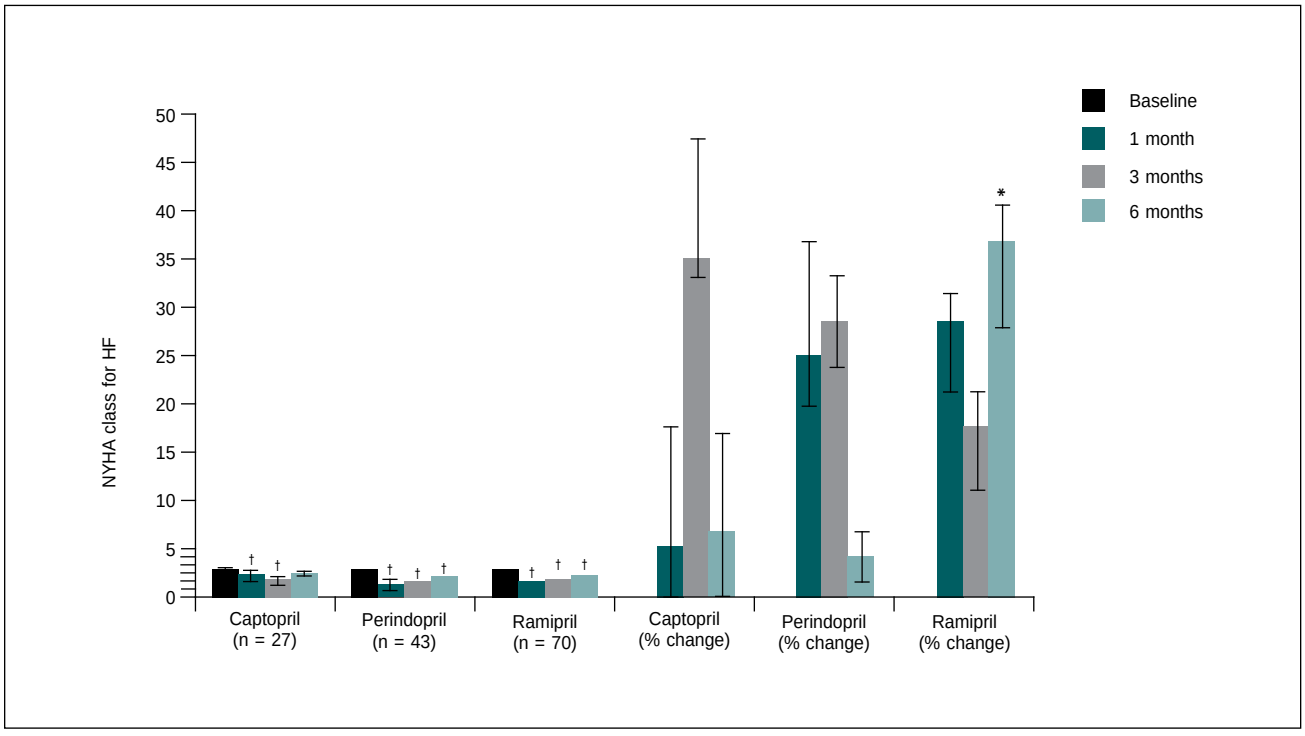



**Figure 5.** Effect of ACE inhibitors on functional status as per NYHA class for HF in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from other groups ($p < 0.05$);

†Significantly different from baseline ($p < 0.05$).

patients having LV dysfunction after an MI. They found captopril to significantly reduce mortality from cardiovascular cause with 21% risk reduction and also the incidence of major cardiovascular events, defined in terms of development of severe HF (37% reduction), congestive HF (CHF) requiring hospitalization (22% reduction) and recurrent MI (25% reduction). In EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease), perindopril was compared with placebo in patients with stable CAD. At average follow-up of 4 years, perindopril was found to produce a 20% relative risk reduction in primary endpoints viz. cardiovascular death, MI or cardiac arrest. The Heart Outcomes Prevention Evaluation (HOPE) trial reported that ramipril, when compared with placebo at 5 years of administration, significantly reduced the incidences of MI (relative risk 0.8), stroke (relative risk 0.68) or death from cardiovascular causes (relative risk 0.74). In this trial, the patient group included those having vascular diseases or diabetes *plus* another cardiovascular risk factor but low EF or HF. Thus, various large randomized placebo-controlled clinical trials have shown the absolute beneficial effects of chronic administration of ACE inhibitors on mortality and major cardiovascular events in patients having CAD with or without LV dysfunction.

Captopril, as compared with enalapril in patients with acute MI (AMI), is comparable in terms of improving LV function and survival. Ramipril and captopril are also similar for their effects on serum creatinine, serum $K^+$, cardiac events such as arrhythmias and mortality as well in patients with CHF, though ramipril significantly controls the blood pressure with longer duration of action. Three-month treatments with captopril and perindopril have been reported to produce similar effects on heart rate, systolic function and LV mass, although less number of patients in perindopril group as compared with captopril group required add-on therapy with thiazides to normalize the blood pressure. Chu-Pak et al (2002) reported no difference in mortality rates after 6 months of treatment with captopril and perindopril in patients with AMI, though perindopril treatment showed better short-term tolerance than captopril treatment did, with significantly less acute hemodynamic changes and fewer withdrawals. Pilote et al (2008) found a possible 10-15% increase in mortality with captopril and enalapril compared with ramipril among patients with CHF. However, following

adjustment for differences in used dosages, all ACE inhibitors had similar clinical efficacy administered in patients after MI. Thus, ours is probably the only research that has compared, in one subset of patient-population, the effects of captopril, perindopril and ramipril in patients with LV systolic dysfunction and who were undergoing CABG.

We found an improvement in LV contractility in all three groups treated with different ACE inhibitors. There was an increase in LVEF at 1, 3 and 6 months of ACE inhibitor administration. The beneficial effects on LV performance observed after 1 month of CABG may be mainly due to revascularization. It is possible that at 3 and 6 months, the observed improvements may be an influence of ACE inhibitor. In the presented research, the percent improvement in LVEF from baseline levels was not statistically significant among three groups, though it was slightly greater in perindopril and ramipril groups after 3 months as compared to captopril group and in captopril and perindopril groups at 6 months as compared to ramipril group. The improvement in overall cardiac function could be because of better coronary blood flow due to inhibition of sympathetic coronary vasoconstriction by ACE inhibitors and due to inhibition of endothelial as well as adventitial ACE providing better hemodynamic control by ACE inhibitors. This property of ACE inhibitors helps enhance coronary circulation and myocardial perfusion through newly placed grafts too.

In our earlier findings, we reported captopril and perindopril to be more efficient for improving LV contractility as compared to ramipril, lisinopril and losartan. Captopril and perindopril were found to produce a significant increase in percent LVEF as compared to other ACE inhibitors and losartan. There was a significant correlation between decreases in blood glucose as well as insulin levels with improvements in LVEF. In the presented work, the sustained and greater improvements observed in perindopril group could be secondary to improved glucose utilization by cardiac myocytes. Moreover, greater improvement in arterial compliance and thus reduction in afterload by perindopril might be responsible for the improvement in LV contractility. Afterload inversely affects LV contractility and has direct correlationship with peripheral vascular resistance which is a measure of arterial compliance. Various ACE inhibitors viz. captopril, lisinopril and perindopril have been shown to increase arterial compliance. However, perindopril is the ACE inhibitor that has been reported to reduce media to lumen ratio of small arteries with significantly correlated LV mass reduction. Increasing the compliance (elasticity) of even larger arteries, in addition to reduction in peripheral resistance, is also an important documented property of perindopril. Perindopril has also been reported to improve patient's hemodynamic status by improving the elasticity of resistance vessels in heart disease patients too. Furthermore, the improved compliance of conduits (by significant improvement in endothelial nitric oxide synthase expression and activity) and repair of coronary arterioles by perindopril could also be the contributing factor for greater improvement in LVEF.

Besides indirect effects, direct effects of ACE inhibitors are of significance in patients with LV systolic dysfunction. ACE inhibitors prevent ventricular dilation and thereby reduce work load of heart with further improvement in its function. In our findings, the reduction in LV systolic and diastolic diameters was observed in all three groups without any significant difference at 3 and 6 months of ACE inhibitor administration. Evidences have shown that ACE inhibitors attenuate LV remodeling. The greater beneficial effects of perindopril on both diastolic and systolic diameters as compared to captopril and ramipril group is consistent with earlier report of Masuelli et al (2002), which reported that perindopril reversed LV remodeling and improved functional status significantly in HF patients who had been switched over from enalapril treatment. The significant reduction in LVEDs by perindopril might be due to its direct effect on Tei index. Perindopril has a distinguished characteristic of suppressing cardiac aldosterone production, which is activated in failing ventricles, by suppressing cardiac ACE activity.

We found perindopril and ramipril treatments to produce negative effects on MR-grade after 3 and 6 months while captopril treatment showed favorable effects on this parameter after both 3 and 6 months of ACE inhibitor administration. Captopril is efficacious in reducing functional MR in dilated left ventricles; however, the doses used are high. MR results from a complex interaction of very small geometric and temporal changes and can occur as a result of multiple mechanisms which can not be simply overcome by inhibiting ACE.

All the ACE inhibitors used in our research (captopril, perindopril and ramipril) were found to be effective in improving functional status. There was reduction in NYHA class in all three groups from baseline levels. However, percent improvement in NYHA class at 6 months of ACE inhibitor treatment was significant

in ramipril group only. This might be because of an increase in skeletal muscle perfusion during exercise and ability of ACE inhibitors to enhance endurance performance and muscle energy metabolism. Further, various ACE inhibitors have been proved to significantly improve NYHA class for HF in patients with moderate-to-severe LV systolic dysfunction.

## CONCLUSIONS

Our findings show that all three ACE inhibitors (i.e., captopril, perindopril and ramipril) produce statistically comparable effects on heart in patients with LV systolic dysfunction undergoing CABG.

While perindopril clinically produces a marginal superiority in cardiac function, ramipril produces the greatest improvement in functional capacity.

## SUGGESTED READING


1. Kalorama. Congestive Heart Failure: Worldwide Drug and Medical Device Markets. SMi Publishing Pharmaceuticals, March 2002.
2. American Heart Association. Heart and Stroke Statistical Update, 2001.
3. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, et al. Symptomatic and asympatomatic left-ventricular systolic dysfunction in an urban population. Lancet. 1997;350:829-33.
4. Blackledge HM, Newton J, Squire IB. Prognosis for South Asian and white patients newly admitted to hospital with heart failure in the United Kingdom: historical cohort study. BMJ. 2003;327:526-31.
5. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, et al. American College of Cardiology/ American Heart Association 2004 guidelines update for coronary-artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 2004. Available from http://www.acc.org/qualityandscience/ clinical/guidelines/cabg/index.pdf. Accessed 23 July 2013.
6. Nishina T, Nishimura K, Yuasa S, Miwa S, Nomoto T, Sakakibara Y, et al. Initial effects of the left ventricular repair by placation may not last long in a rat ischemic cardiomyopathy model. Circulation. 2001;104(Suppl I): I-241-5.
7. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A Substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation. 1990;82:1724-9.
8. Dzau VJ. Tissue rennin-angiotensin system in myocardial hypertrophy and failure. Arch Int Med. 1993;153:937.
9. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med. 1991; 325:293-302.
10. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, et al; The SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. N Engl J Med. 1992;327(10):669-77.
11. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA. 1995;273:1450-6.
12. Swedberg K, Pfeffer M, Granger C, Held P, McMurray J, Ohlin G, et al. Candesatan in heart failure: assessment of reduction in mortality and morbidity (CHARM): rationale and design. J Card Fail. 1999;5:276-82.
13. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, et al; ACE-inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. Lancet. 2000;355:1575-81.
14. Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN. Effects of valsartan on morbidity and mortality in heart failure patients not receiving ACE inhibitors. J Am Coll Cardiol. 2002;40:1414-21.
15. Banerjee A, Talreja A, LeJemtel TH. Evolving rationale for angiotensin converting enzyme inhibitor therapy in chronic heart failure. Mt Sinai J Med. 2003;70:225-31.
16. Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. N Engl J Med. 1988;319(2):80-6.
17. Konstam MA, Kronenberg MW, Rousseau MF, Udelson JE, Melin J, Stewart D, et al; The SOLVD Investigators. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. Circulation. 1993;88:2277-83.
18. Hunt SA, Abraham WT, Mancini DM, Chin MH, Michl K, Feldman AM, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Available from http://circ.ahajournals.org/ cgi/content/ full/112/12/e154. Accessed 23 July 2013.
19. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G; The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342:145-53.

20. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362:782-8.
21. Goyal RK, Prajapati DV, Jain AR, Mallya BS. Effect of CABG and ACE inhibitors on cardiac function in diabetic patients. J Mol Cell Cardiol. 2001;33:A52.
22. Kossman CE; The Criteria Committee of the New York Heart Association. Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis. 6th Edition, Little Brown: Boston, Massachusetts; 1964. pp. 110-4.
23. Zimmerman BG, Sybertz EJ, Wong PC. Interaction between sympathetic and rennin-angiotensin system. J Hypertens. 1984;2:581-7.
24. Dzau VJ. Mechanism of action of angiotensin-converting enzyme (ACE) inhibitors in hypertension and heart failure: Role of plasma versus tissue ACE. Drugs. 1990;39(2):11-6.
25. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: Results of the SOLVD echocardiography substudy. Circulation. 1995;91:2573-81.
26. Dzau VJ. Renal effects of angiotensin converting enzyme inhibition in cardiac failure. Am J Kidney Dis. 1987;10: 74-80.
27. Dickstein K, Kjekshus J, The OPTIMAAL Steering Committee, for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Lancet. 2002;360:752-60.
28. McMurray JJ, Solomon S, Pieper K, Reed S, Rouleau J, Velazquez E, et al. The effect of valsartan, captopril, or both on atherosclerotic events after acute myocardial infarction an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). J Am Coll Cardiol. 2006;47(4):726-33.
29. Foy SG, Crozier IG, Turner JG, Richards AM, Framptom CM, Nicholls MG, et al. Comparison of enalapril versus captopril on left ventricular function and survival three months after acute myocardial infarction (the 'PRACTICAL' study). Am J Cardiol. 1994:73(16):1180-6.
30. De Graeff PA, Kingma JH, Viersma JH, Wesseling H, Lie KI. Acute and chronic effects of ramipril and captopril in congestive heart failure. Inter J Cardiol. 1989;23(1):59-67.
31. Agabiti-Rosei E, Ambrosioni E, Finardi G, Folino P, Gambassi G, Malini P, et al. Perindopril versus captopril: efficacy and acceptability in an Italian mutlicenter trial. Am J Med. 1992;92(4):S79-S83.
32. Chu-Pak L, Hung-Fat T, William N, Kwok-Keung C, Shu-Kin L, Kin-Kwan K, et al. Comparison of perindopril versus captopril for treatment of acute myocardial infarction. Am J Cardiol. 2002;89(2):150-4.
33. Pilote L, Abrahamowicz M, Eisenberg M, Humphries K, Behlouli H, Tu JV. Effect of different angiotensin-converting-enzyme inhibitors on mortality among elderly patients with congestive heart failure. CMAJ. 2008;178(10):1303-11.
34. Hansen ML, Gislason GH, Køber L, Schramm TK, Folke F, Buch P, et al. Different angiotensin-converting enzyme inhibitors have similar clinical efficacy after myocardial infarction. Br J Clin Pharmacol. 2008;65(2):217-23.
35. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al; American college of cardiology; American Heart Association; American Society of Echocardiography. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Circulation. 2003;108(9):1146-62.
36. Magrini F, Shimizu M, Roberts N, Fouad FM, Tarazi RC, Zanchetti A. Converting enzyme inhibition and coronary blood flow. Circulation. 1987;75(1):I168-74.
37. Perondi R, Saino A, Tio RA, Pomidossi G, Gregorini L, Alessio P, et al. ACE inhibition attenuates sympathetic coronary vasoconstriciton in patients with coronary artery disease. Circulation. 1992;85:2004-13.
38. Zhuo JL, Froomes P, Casley D, Liu JJ, Murone C, Chai SY, et al. Perindopril chronically inhibits angiotensin converting enzyme in both the endothelium and adventitia of the internal mammary artery in patients with ischemic heart disease. Circulation. 1997;96:174-82.
39. Asmar RG, Pannier B, Santoni JP, Laurent S, London GM, Levy BI, et al. Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. Circulation. 1988;78(4):941-50.
40. Chau NP, Simon A, Vilar J, Cabrera-Fischer E, Pithois-Merli I, Levenson J. Active and passive effects of anthihypertensive drugs on large artery diameter and elasticity in human essential hypertension. J Cardiovasc Pharmacol. 1992;19(1):78-85.
41. Shimamoto H, Shimamoto Y. Lisinopril improves aortic compliance and renal flow: comparison with nifedipine. Hypertension. 1995;25(3):327-34.
42. Thybo NK, Stephens N, Cooper A, Aalkjaer C, Heagerty AM, Mulvany MJ. Effect of antihypertensive treatment on small arteries of patients with previously untreated essential hypertension. Hypertension 1995;25(4 Pt 1):474-81.
43. Sihm I, Schroeder AP, Aalkjaer C, Holm M, Morn B, Mulvany M, et al. Normalization of structural cardiovascular changes during antihypertensive treatment with a regimen based on the ACE-inhibitor perindopril. Blood Press. 1995;4(4):241-8.
44. Hussar DA. New Drugs of 1999. J Am Pharm Assoc. 2000;40(2):181-221.
45. Kool MJ, Lustermans FA, Breed JG, Struyker Boudier HA, Hoeks AP, Reneman RS, et al. The influence of

perindopril and the diuretic combination amiloride + hydrochlorothiazide on the vessel wall properties of large arteries in hypertensive patients. J Hypertens. 1995;13(8):839-48.

46. Schwartzkopff B, Brehm M, Mundhenke M, Strauer BE. Repair of coronary arterioles after treatment with perindopril in hypertensive heart disease. Hypertension. 2000;36:220-5.
47. Ghiadoni L, Magagna A, Versari D, Kardasz I, Huang Y, Taddei S, et al. Different effect of antihypertensive drugs on conduit artery endothelial function. Hypertension. 2003;41:1281-6.
48. Comini L, Bachetti T, Cargnoni A, Bastianon D, Gitti GL, Ceconi C, et al. Therapeutic modulation of the nitric oxide: all ace inhibitors are not equivalent. Pharmacol Res. 2007;56(1):42-8.
49. Onodera H, Matsunaga T, Tamura Y, Maeda N, Takumi H, Sasaki S, et al. Enalapril suppresses ventricular remodeling more effectively than losartan in patients with acute myocardial infarction. Am Heart J. 2005;150(4):689.
50. Masuelli M, Brusca G, Pardo A, Pineiro D, Checkerdhemian S, Forcads P. ACE inhibitors in heart failure-switching from enalapril to Coversyl. Curr Med Res Opin. 2002;18:296-302.
51. Nearchou NS, Tsakiris AK, Lolaka MD, Zarcos I, Skoufas DP, Skoufas PD. Influence of perindopril on left ventricular global performance during the phase of inferior acute myocardial infarction: assessment by Tei index. Echocardiography. 2003;20(4):319-27.
52. Mizuno Y, Yasue H, Yoshimura M, Fuji H, Yamamoto N, Nakayama M, et al. Effect of perindopril on aldosterone production in the failing human heart. Am J Cardiol. 2002; 89(10):1197-200.
53. Seneviratne B, Moore GA, West PD. Effect of captopril on functional mitral regurgitation in dilated heart failure: a randomised double blind placebo controlled trial. Br Heart J. 1994;72(1):63-8.
54. Mancini DM, Davis L, Wexler JP, Chadwick B, LeJemtel TH. Dependence of enhanced maximal exercise performance on increased peak skeletal muscle perfusion during long-term captopril therapy in heart failure. J Am Coll Cardiol. 1987;10:845-50.
55. Willenheimer R, Rydberg E, Öberg L, Juul-Möller S, Erhardt L. ACE inhibition with ramipril improves left ventricular function at rest and post exercise in patients with stable ischaemic heart disease and preserved left ventricular systolic function. Eur Heart J. 1999;20(22):1647-56.
56. Banerjee A, Talreja A, LeJemtel TH. Evolving rationale for angiotensin converting enzyme inhibitor therapy in chronic heart failure. Mt Sinai J Med. 2003;70:225-31.
57. Bahi L, Koulmann N, Sanchez H, Momken I, Veksler V, Bigard AX, et al. Does ACE inhibition enhance endurance performance and muscle energy metabolism in rats? J Appl Physiol. 2004;96:59-64.
58. Lamas GA, Vaughan DE, Parisi AF, Pfeffer MA. Effects of left ventricular shape and captopril therapy on exercise capacity after anterior wall acute myocardial infarction. Am J Cardiol. 1989;63(17):1167-73.
59. Hutcheon SD, Gillespie ND, Crombie IK, Struthers AD, McMurdo ME. Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: a randomized double blind placebo controlled trial. Heart. 2002;88(4):373-77.
60. Barrios AV, Pena PZ, Campuzano RR, Lombera RF, Peralta Y. Utility of perindopril in mild-moderate heart failure in daily clinical practice. Rev Clin Esp. 2003;203(1):3-9.

■■■■

## Primary PCI

- Treatment strategy: Coronary artery reperfusion with percutaneous coronary intervention (PCI) or fibrinolytic therapy to all patients with an acute ST-segment elevation myocardial infarction (STEMI) who present within 12 hours of onset of symptoms.
- Primary PCI should be done within 90 minutes (door-to-balloon time) for patients who arrive at or who are transported by an emergency medical service to a PCI-capable hospital. Patients who arrive at or who are transported to a non-PCI-capable hospital should be transported urgently to a PCI-capable hospital if they can receive primary PCI within 120 minutes of first medical contact.
- For STEMI patients who present within 12 hours of symptom onset, prefer primary PCI rather than fibrinolysis as the reperfusion strategy if PCI can be delivered within 120 minutes of first medical contact by skilled practitioners.
- For patients who cannot receive timely primary PCI, fibrinolytic therapy should be given and should be administered within 30 minutes of first medical contact, and sooner if possible.
- For patients who present after 12 hours (and up to 24 hours) of symptom onset who have evidence of ongoing ischemia, prefer PCI as opposed to no reperfusion therapy.
- Do coronary angiography and possible PCI for all patients who receive fibrinolytic therapy within 3-24 hours in most of these patients.