ACE-INHIBITORS VERSUS ANGIOTENSIN RECEPTOR BLOCKERS IN RENAL AND CARDIOVASCULAR PROTECTION IN DIABETIC PATIENTS

EDITORIAL

Hypertension presents a major risk factor for cardiovascular morbidity and mortality in patients with diabetes. Blockade of the renin-angiotensin system by either angiotensin-converting enzyme (ACE) inhibition or angiotensin receptor blocker (ARB) has cardiovascular and reno-protective effects. However, there is still much controversy over which of the two drug classes offers more protection. This article takes a closer look at the cardiovascular and reno-protective effects of both classes in the diabetic population.

INTRODUCTION

Hypertension is a common co-morbid condition in diabetic patients. Approximately 20-60% of diabetic patients become hypertensive depending on age, obesity and ethnicity. Hypertension in type 1 diabetic patients is usually caused by underlying diabetic nephropathy, and as such may only present at the time that the patient develops micro-albuminuria. In type 2 diabetic patients, hypertension is already present in about one third of patients at the time of diagnosis of diabetes.

Hypertension increases the risk of macrovascular and microvascular complications such as coronary artery disease, stroke, peripheral vascular disease, retinopathy, nephropathy and neuropathy. Blood pressure control in diabetic patients is important since hypertension is the second commonest cause of renal failure. 40% of patients with type 1 diabetes and 35% of type 2 diabetic patients develop diabetic nephropathy. Therefore control of hypertension in patients with diabetic nephropathy would improve mortality and decrease progression to end-stage renal disease.

HYPERTENSION AS A RISK FACTOR FOR COMPLICATIONS OF DIABETES

There is a twofold increase in the risk of coronary events in men and fourfold increase in women with diabetes. This increased risk could be attributed to the frequency of associated cardiovascular risk factors such as dyslipidaemia, hypertension and clotting abnormalities. It has been noted in observational studies that patients with diabetes and hypertension have double the risk of cardiovascular disease as compared to non-diabetic patients with hypertension. Diabetic patients with hypertension also have an increased risk of diabetic-specific complications such as retinopathy and nephropathy. In the UK Prospective Diabetes Study (UKPDS), it was shown that a 10mmHg decrease in mean systolic blood pressure resulted in risk reduction of 12% for any diabetic complication. 15% for deaths related to diabetes, 11% for myocardial infarction and 13% for microvascular complications.

GENERAL BLOOD PRESSURE MANAGEMENT

According to the Southern African Hypertension Guideline Update of 2003, the general target blood pressure (BP) for anti-hypertensive management is <140/90mmHg. However, stricter control of blood pressure is required for patients with co-existing risk factors, end organ damage and co-morbid conditions such as diabetes mellitus. The goal of BP-lowering treatment for diabetic patients is <130/85mmHg and for patients with proteinuria >1g/24h it is <125/75. The target BP in patients with renal insufficiency (serum creatinine >29mmol/l) is <130/85. 7

ACE inhibitors (ACE-I) and ARBs are the two classes of anti-hypertensives most widely used in diabetic patients as they have been shown to slow the deterioration of renal function and decrease proteinuria. 7

DIFFERENTIAL EFFECTS OF ACE INHIBITION vs ANGIOTENSIN RECEPTOR BLOCKADE

ACE-I and ARBs act by reducing the stimulation of the angiotensin type 1 (AT1) receptor by its ligand angiotensin type 1 (AngII). See figures 1 & 2. AngII is a powerful vasoconstrictor and promotes growth of vascular smooth muscle and plaque rupture, possibly by stimulating release of endothelin, inhibiting fibrinolysis, and promoting thrombosis.

ACE-I block ACE thereby decreasing the amount of AngII available for binding to the AT1 and AT2 receptors. ACE-I also decrease the breakdown of bradykinin to inactive fragments. Bradykinin is a direct vasodilator and promotes release of the vasodilating substances prostacyclin and nitric oxide. Hence, AT1 and AT2 receptors are activated less whereas the B1 and B2 receptors for bradykinin are activated more. The kinins have therefore shown a significant contribution to the blood pressure lowering effect of ACE-I.

ACE-I and ARBs both increase plasma renin and AngII. ARBs also increase AngII resulting in activation of the AT2 receptor while AT1 receptor is blocked. The physiologic function of AT2 is still a matter of research but most studies indicate that it counteracts the vasocostricitive and proliferative effects of AT1 e.g. by promoting apoptosis and decreasing fibrosis. However, stimulation of AT2 may contribute to the pro-inflammatory actions of AngII in the kidney. AngII inhibition results in decreased blood and intra-glomerular pressure, improved glomerular-barrier size selectivity and reduction of proteinuria.

The reno-protective effect of ACE-I and ARBs is explained by their antiproteinuric effect as demonstrated by reno-protective trials. This is consistent with the view that proteins, once leaked through the glomerular barrier, act as mediators of ongoing renal fibrosis.

RENO-PROTECTIVE EFFECTS OF ACE-I

Type 1 Diabetes

Numerous studies support the view that the use of ACE-I reduces the risk of progression from microalbuminuria to overt albuminuria in type 1 diabetic patients. 10,11 The Collaborative Study, a study of 409 type 1 diabetics with overt nephropathy showed a 48% reduction in risk of doubling serum creatinine in the captopril versus placebo group. 11 The results of the European Microalbuminuria Captopril Study in type 1 diabetic patients with microalbuminuria but no hypertension showed a decrease of approximately 75% in the risk to develop overt nephropathy with ACE inhibition. 12,13 These studies support the recommendation by the American Diabetes Association that “patients with type 1 diabetes, with any degree of albuminuria, ACE-I delay the progression of nephropathy.” 12,13

Figure 1 & 2: Schematic drawings of differential effects of ACE-Ias (figure 1) and ARBs (figure 2) on the renin-angiotensin and bradykinin systems

Legend to Figures 1 & 2:

AT1 - angiotensin type 1 receptor
AT2 - angiotensin type 2 receptor
B1 - bradykinin type 1 receptor
B2 - bradykinin type 2 receptor

Type 2 Diabetes

There are no well-powered studies on the effect of ACE-Is on renal disease in type 2 diabetes. Data from type 1 diabetes cannot be extrapolated to apply to type 2 diabetes. Studies have shown that ACE-Is prevent progression from microalbuminuria to overt albuminuria in type 2 diabetes, but there is insufficient data to prove whether ACE-Is can prevent loss of glomerular filtration rate (GFR) in overt nephropathy. To date, some investigators have reported that these patients have abnormalities in glomerular selectivity that cannot be reversed by ACE-Is.

The following is an overview of some of the studies available:

- A sub-study of the Heart Outcomes Prevention Evaluation (HOPE) trial, the micro-HOPE, consisting of 3577 patients with diabetes (mainly type 2), showed that the ACE-I ramipril, as compared with placebo, reduced the risk to develop overt nephropathy in patients who were either normo- or microalbuminuric by 24%. 2-5
- A randomized controlled trial of normoalbuminuric patients with type 2 diabetes, ACE inhibition with enalapril resulted in a 12.5% reduction in the risk to develop microalbuminuria. 7
- Two randomized studies, the UK Prospective Diabetes Study Group (UKPDS) and the Appropriate Blood Pressure Control in non-insulin-dependent Diabetes (ABCD) as well as a smaller study by Ravid et al (n=74) did not show a significant risk reduction in diabetic nephropathy of ACE-I compared to other antihypertensive therapies.

RENO-PROTECTIVE EFFECTS OF ARBs

Type 1 Diabetes

There were no large scale trials on the long term renoprotective effects of ARBs in type 1 diabetic patients.

Type 2 Diabetes

Both the Irbesartan in Diabetic Nephropathy Trial (IDNT) and the Reduction of Endpoints in Type 2 Diabetes Mellitus with Angiotensin II Antagonist Losartan (REDUCE-IT) trial compared ARBs with conventional treatment in patients with type 2 diabetes and overt nephropathy. The two trials each included more than 1500 patients (IDNT n=1715; RENAAL n=1513) and showed that ARB treatment decreased the relative risk of primary composite endpoint: doubling of serum creatinine, end stage renal disease (ESRD) or death) versus placebo by 20% and 16% respectively. 8-11 The IDNT showed a decrease of 23% in the risk to reach the primary end point as compared with calcium channel blocker amlopidine However the relative risk of reaching the primary end point in the placebo and amlopidine groups did not differ significantly. 11 The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study showed a significant reduction in diabetic therapy, irbesartan is beneficial preventing the development of clinical proteinuria and at restoring normoalbuminuria for comparable BP control in patients with incipient nephropathy. 12

RENO-PROTECTIVE EFFECTS OF ACE-Is vs ARBs

Although some of the above-mentioned trials indicate that blocking the RAS offers a greater advantage for renoprotection over other anti-hypertensive drugs, direct comparisons between ACE-Is and ARBs in patients with renal disease are lacking.

Table 1: Summary of some of the Renal Protection Studies with ACE-Is and ARBs

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome</th>
<th>Secondary Outcome</th>
<th>Agents</th>
<th>Renal Protection Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborative Study 1</td>
<td>Doubling of the baseline serum creatinine concentration</td>
<td>Length of time to combined end points of death, dialysis and transplantation</td>
<td>Captopril vs. placebo</td>
<td>48% reduction in risk of doubling serum creatinine in the captopril group</td>
</tr>
<tr>
<td>European Microalbuminuria Captopril Study 2</td>
<td>Rate of progression to clinical proteinuria</td>
<td></td>
<td>Captopril vs. placebo</td>
<td>Captopril impeded progression to clinical proteinuria</td>
</tr>
<tr>
<td>micro-HOPE</td>
<td>MI, stroke, CV death</td>
<td>Total mortality, admission to hospital or development of overt nephropathy</td>
<td>Ramipril vs. placebo</td>
<td>Ramipril decreased risk to develop overt nephropathy</td>
</tr>
<tr>
<td>UKPDS</td>
<td>Time of occurrence of 1st clinical end point related to diabetes, related death, related to diabetes and from all causes</td>
<td>MI, stroke, amputation, death from peripheral vascular disease and microvascular complications</td>
<td>Captopril vs. atenolol</td>
<td>No significant risk reduction in the progression of albuminuria or doubling of creatinine clearance of captopril over atenolol</td>
</tr>
<tr>
<td>IRMA-2</td>
<td>Time to the onset of diabetic nephropathy</td>
<td>Changes in level of albuminuria, creatinine clearance, restoration of normoalbuminuria</td>
<td>Irbesartan vs. placebo</td>
<td>Irbesartan significantly reduces rate of progression to clinical albuminuria independent of BP</td>
</tr>
<tr>
<td>IDNT</td>
<td>Doubling of serum creatinine, ESRD, death</td>
<td>CV mortality and morbidity</td>
<td>Irbesartan vs. amlopidine or placebo</td>
<td>Irbesartan decreased risk for progression to advanced diabetic nephropathy</td>
</tr>
<tr>
<td>RENAAAL</td>
<td>Doubling serum creatinine, ESRD, death</td>
<td>CV mortality and morbidity</td>
<td>Losartan vs. placebo</td>
<td>Losartan decreased risk of death or cardiovascular disease end point</td>
</tr>
</tbody>
</table>

Legend to Table 1: Myocardial Infarction (MI), Cardiovascular (CV), End Stage Renal Disease (ESRD), Diabetes Mellitus type 1 (DM-1), Diabetes Mellitus type 2 (DM-2)
Type 2 Diabetes

Type 2 diabetes, especially those with renal disease, are at a high risk of heart failure, myocardial infarction and cardiovascular death.12,13 Findings from the micro-HOPE study support the use of ACE inhibition to prevent cardiovascular complications in patients with type 2 diabetes irrespective of renal disease.1,12 This study demonstrated a significant reduction in cardiovascular mortality with the ACE-I ramipril as compared with placebo.12,15 The risk of heart failure as a primary end point of myocardial infarction, stroke and cardiovascular death was reduced by 25%.10

The PERSUADE study, a substudy of EUROPA, investigated the effect of perindopril on reducing cardiovascular death, non-fatal MI and other cardiovascular endpoints in 1,562 diabetic patients with stable coronary artery disease but no heart failure.18% of patients were on insulin at baseline. There was a 19% relative risk reduction of cardiovascular outcomes in this subgroup which is not significantly different to the risk reduction of 20% shown in the general coronary disease population in the main EUROPA study.18

Other studies which compare ACE-I’s with calcium channel blockers or other anti-hypertensives include the following.

• Promising results were seen with fosinopril when compared with amiloride in the Fosinopril vs Amlodipine Cardiovascular Events Trial (FACET). Patients with type 2 diabetes and hypertension were randomly assigned to fosinopril or amiloride. Systolic blood pressure control was better in the amiloride group while diastolic blood pressure control was similar in both groups. However, the fosinopril group had a significantly lower risk of the combined outcome of acute myocardial infarction, stroke or hospitalized angina.10,13,14
• In a substudy of the Appropriate Blood Pressure Control in Diabetics (ABCD) Trial, the risk of cardiac end point patients with diabetes taking enalapril versus nisoldipine.10
• In the CAPPP prevention project, captopril was compared with a beta-blocker/diuretic combination. In a small subgroup analysis of 572 patients with diabetes, blood pressure control was similar but the captopril group had a lower risk of heart failure.10,14,15 This substudy has however been criticized as randomization was unequal and the diastolic BP goal was only 90mmHg and the analysis was done post hoc.13

A meta-analysis of the above 3 studies indicated a significant risk reduction in cardiovascular events, myocardial infarction and all-cause mortality (relative risk 0.49, CI 0.36-0.67).11 Therefore, the cardioprotective effect of ACE-I’s has not been found to be uniform in all studies.12 In the UK Prospective Diabetes Study (UKPDS) trial 758 patients with microalbuminuria were randomized to captopril or atenolol. The blood pressure lowering effect of captopril or atenolol was decreased in the risk of cardiovascular and microvascular events - no benefit of the captopril arm of the trial was found over the atenolol arm.11,14,15

CVD CARdiovascular PROTECTIVE EFFECTS OF ARBs

Type 2 Diabetes

Substantial data lacking on the cardiovascular outcomes of ARBs in type 2 diabetic renal disease.2

Type 2 Diabetes

• RENAAL and IDNT studies were done primarily to examine renal end points. The RENAAL study had a secondary composite outcome of cardiovascular mortality and morbidity. Neither study demonstrated significant differences in cardiovascular morbidity or mortality with either losartan or irbesartan when compared with placebo or amiodipine respectively.2,9,17,18 However, the rate of first hospitalization was significantly lower with losartan versus placebo in the RENAAL study (32%, CI 0.005).13 Despite the sample size of both trials, they could not demonstrate any beneficial effect on cardiovascular events.15,17,18
• A sub-group of 1,195 patients with diabetes, hypertension and signs of left ventricular hypertrophy (LVH) were evaluated in the Losartan Intervention for Endpoint Reduction in Hypertension study (LIFE). The B-blocker atenolol was compared with the ARB losartan. Losartan was more effective than atenolol in decreasing the combined risk of cardiovascular morbidity and mortality in these patients.2

CVD CArdiovascular PROTECTIVE EFFECTS OF ACE-I’s vs ARBs

Direct comparative data on the cardiovascular outcomes of ACE-I’s versus ARBs in diabetic patients is lacking. The micro-HOPE data from patients with diabetes and renal impairment shows better cardiovascular protection with ACE inhibition as compared to ARBs in the IDNT and RENAAAL trials. However, this comparison is not reflective of high risk patients with diabetic-proximate proteinuria were excluded from the HOPE study.2

There have been several trials that directly compared the effects of ACE-I’s and ARBs on cardiac events and outcomes but the results are not specified for diabetic subgroups. Some of the available studies are as follows:

• In the initial Evaluation of Losartan in the Elderly Study (ELITE) captopril was compared with losartan in elderly heart failure patients. Captopril was justified as a significant reduction in all cause mortality, which was a secondary end point of the trial, as compared to captopril. However, ELITE II, which was a more appropriately powered study, found no statistically significant difference in all-cause mortality.10,19,27 One debate raised on this study is whether the dose of losartan (50mg/day) was adequate as compared to the dose of captopril (150mg/day) used in the ELITE trials.28
• The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Study (REVEAL) compared candesartan with enalapril in congestive heart failure patients. The two agents were found to be comparable in terms of left ventricular remodeling. There was no difference in NYHA functional class. However, in the candesartan and combined groups there were a greater number of

events.10,29

• The Optimal Trial in Myocardial Infarction with Angiotensin II Losartan Study (OPTIMAAL) also compared losartan with captopril in patients after an acute myocardial infarction. The result was a non-significant difference between the two agents in reducing the primary end point of all-cause mortality.10,30
• The VALIANT in Acute Myocardial Infarction Trial (VALIANT) also compared valsartan with captopril in patients after an acute myocardial infarction. The result was valsartan is as effective as captopril in patients who are at a high risk for cardiovascular events following a myocardial infarction.10,31

There is at least one ongoing trial comparing ACE-I’s and ARBs although it does not apply specifically to diabetic patients:

• The ONTARGET trial is long-term multinational outcome study with the primary objectives of determining if the combination of the telmisartan and ramipril is more effective than ramipril alone, if telmisartan is at least as effective as ramipril, and if telmisartan is superior to placebo (TRANSCEND) in providing cardiovascular protection for high-risk patients.12 However, the results of this trial are still awaited and analysis in the diabetic sub-group will need to be done.

See Table 2 for current data on cardiovascular protection of ACE-I’s and ARBs. (See next page.)

It is of importance to note that ARBs are consistently better tolerated with a lower side effect profile.10

SUMMARY

In view of the trials discussed in this article, ACE-I’s are the best documented treatment to delay the progression of nephropathy in type 1 diabetic patients.35,36 ACE-I inhibition of ACE, which blocks the formation of AngII, has additional effects on fibrinolytic and/or inflammatory processes in the kidney. Both type 1 and type 2 diabetic patients with microalbuminuria were started early with ACE-I as there was shown to prevent or at least delay the occurrence of overt nephropathy.36

In type 2 diabetes the choice of drug is less obvious. In this population group both ACE-I’s and ARBs have been shown to delay the progression of microalbuminuria to macroalbuminuria. However, only ARBs have been shown to show the delay of progression of renal insufficiency in type 2 diabetes with overt nephropathy, resulting in the ADA recommendations that ARBs should be first line treatment for this group. There is circumstantial evidence that indicates that ACE-I’s are also effective in these patients, but renal end point studies with ACE-I’s in these patients have not been done to resolve this.4,37

There is compelling evidence that ACE-I’s have a cardioprotective effect, reducing the risk of death and MI in patients with heart failure, CAD and other high-risk populations.38 However, data is lacking to determine whether ACE-I’s have added cardioprotective effects in diabetic patients.

There is conflicting data as to whether ARBs have a beneficial effect on cardiovascular events in diabetic patients. When ARBs are compared with ACE-I’s in diabetics the micro-HOPE data shows better cardiovascular protection with ACE inhibition as compared to ARBs in the IDNT and RENAAAL trials.4,36

In general ARBs have been shown to reduce hospitalization due to heart failure when compared to placebo, but data on the reduction in death and MI is conflicting. Head-to-head cardioprotective comparisons with ACE-I’s and ARBs also show conflicting results.

CONCLUSION

There is a definite need for appropriately powered comparative trials of ACE-I’s and ARBs to enhance and clarify existing data on their reno- and cardioprotective function in diabetics.

Until such data is available the following conclusions can be made based on available evidence from studies comparing ACE-I’s or ARBs with placebo or other classes of anti-hypertensives:

• ACE-I’s are reno-protective in type 1 diabetics.
• ACE-I’s and ARBs both prevent progression from microalbuminuria to overt albuminuria in type 2 diabetics.
• ARBs decrease the risk of progression to renal insufficiency in diabetes type 2 patients with overt nephropathy.
• ACE-I’s are cardioprotective, reducing the risk of death and MI in high-risk populations.
• ARBs reduce hospitalization due to heart failure, but data on the reduction in death and MI is conflicting.
• ARBs have been shown to have fewer side effects than ACE-I’s resulting in greater compliance.

Taking drug cost and the above considerations into account the use of ACE-I’s should be considered in diabetics with early to moderate nephropathy.35 Type 1 diabetics with overt nephropathy. ARBs should also be considered in type 2 diabetes with overt nephropathy.36

REFERENCES AVAILABLE ON REQUEST
### Table 2: Cardiovascular Protection Studies with ACE-I and ARBs

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome</th>
<th>Secondary Outcome</th>
<th>Agents</th>
<th>Cardiovascular Protection Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborative Study(^1)</td>
<td>Doubling of the base-line serum creatinine concentration</td>
<td>Length of time to combined end points of death, dialysis and transplantation</td>
<td>Captopril vs. placebo</td>
<td>50% reduction in the risk of combined secondary end points, including mortality, with captopril</td>
</tr>
<tr>
<td>micro-HOPE(^2) (mostly DM-2)</td>
<td>MI, Stroke, CV death</td>
<td>Total mortality, admission to hospital, over-pneophropy</td>
<td>Ramipril vs. placebo</td>
<td>Primary outcome lowered in ramipril group</td>
</tr>
<tr>
<td>PERSUADE</td>
<td>Cardiovascular death, non-fatal MI and resuscitated cardiac arrest</td>
<td>Total mortality, revascularization, stroke, hospitalization for unstable anoga or heart failure</td>
<td>Perindopril vs. placebo</td>
<td>19% relative risk reduction in primary outcome, but no significan- t reduction versus general CAP population</td>
</tr>
<tr>
<td>FACET(^3) (mainly DM-2 hypertensive)</td>
<td>Serum lipids and diabetes control in NIDDM patients with hypertension</td>
<td>Acute MI, stroke, hospitalized angina</td>
<td>Fosinopril vs. amiodipine</td>
<td>Fosinopril group had lower risk of combined secondary endpoints</td>
</tr>
<tr>
<td>ABCD(^4) (Substudy: DM-2 with overt nephropathy)</td>
<td>Effect of moderate vs intense BP control on 24-hour creatinine clearance</td>
<td>Effect of moderate vs intense BP control on incidence of CV events</td>
<td>Enalapril vs. nisoldipine</td>
<td>Significantly lower risk for non-fatal MI in enalapril versus nisoldipine group</td>
</tr>
<tr>
<td>CAPP(^5) (DM-2)</td>
<td>Fatal and non-fatal MI, stroke or other CV deaths</td>
<td>Total mortality, development of ischaemic heart disease, atrial fibrillation, etc.</td>
<td>Captopril vs. beta-blocker/duretic combination</td>
<td>Captopril group had lower risk for CV events, MI and all cause mortality and LVH</td>
</tr>
<tr>
<td>UKPS(^6) (most likely DM-2 with hypertension)</td>
<td>Time of occurrence of 1st clinical end point related to diabetes death related to diabetes and from all causes</td>
<td>MI, stroke, amputation, death from peripheral vascular dis-ease and microvascular complications</td>
<td>Captopril vs. atenolol</td>
<td>No benefit of captopril over atenolol in secondary outcome measures</td>
</tr>
<tr>
<td>RENAAL(^7) (DM-2 with overt nephropathy)</td>
<td>Doubling serum creatinine, ESRD, death</td>
<td>CV mortality and morbidity</td>
<td>Losartan vs. placebo</td>
<td>No benefit of losartan on CV events</td>
</tr>
<tr>
<td>IDNT(^8) (DM-2 with overt nephropathy)</td>
<td>Doubling of serum creatinine, ESRD, death</td>
<td>CV death, MI, hospitalisation for HF</td>
<td>Irbesartan vs. amiodipine or placebo</td>
<td>No benefit on CV events</td>
</tr>
<tr>
<td>LIFE substudy(^9) (most likely DM-2 with hypertension and LVH)</td>
<td>Composite CV mortality and morbidity (stroke, MI)</td>
<td>Total mortality, hospital admission for angina, heart failure, revascularisation</td>
<td>Losartan vs. atenolol</td>
<td>Lower incidence of primary composite end point with losartan but no significant difference in MI and stroke</td>
</tr>
<tr>
<td>RESOLVD(^10) (Patients with symptomatic HF due to LV systolic dysfunction)</td>
<td>Exercise performance, venticular function, quality of life, neuro-hormones, tolerability</td>
<td>Optimal dose of candesartan for a larger proposed trial</td>
<td>Candesartan vs. enalapril</td>
<td>No difference between the two agents in primary outcome excluding tolerability and neuro-hormones</td>
</tr>
<tr>
<td>ELITE(^11) (Patients with NYHA class II-IV HF)</td>
<td>Tolerability measure of a persisting increase in serum creatinine</td>
<td>Composite of death and/or hospital admission for HF(^12)</td>
<td>Losartan vs. captopril</td>
<td>Losartan had 46% lowering of all cause mortality than captopril (secondary outcome)</td>
</tr>
<tr>
<td>ELITE II(^13) (Patients with NYHA class II-IV HF)</td>
<td>All cause mortality</td>
<td>Cardiac death or resuscitated cardiac arrest</td>
<td>Losartan vs. captopril</td>
<td>No significant difference in primary and secondary outcomes</td>
</tr>
<tr>
<td>OPTIMAL(^14) (Patients with MI and HF)</td>
<td>All cause mortality</td>
<td>Cardiac death or resuscitated cardiac arrest</td>
<td>Losartan vs. captopril</td>
<td>No significant difference in primary and secondary outcomes</td>
</tr>
<tr>
<td>VALIANT(^15) (Patients with acute MI)</td>
<td>Death from any cause</td>
<td>Cardiac death or resuscitated cardiac arrest</td>
<td>Valsartan vs. captopril</td>
<td>Equivalent effect in patients at high risk for CV events after MI</td>
</tr>
<tr>
<td>ONTARGET(^16) (Patients with high risk of CV complications)</td>
<td>Cardiovascular death, MI, stroke, hospitalisation for CHF</td>
<td>Telmisartan vs. ramipril; Telmisartan vs. placebo</td>
<td>Telmisartan plus ramipril vs. ramipril alone</td>
<td>Pending</td>
</tr>
</tbody>
</table>

**Legend to Table 2:** Cardiovascular (CV), Myocardial Infarction (MI), End Stage Renal Disease (ESRD), blood pressure (BP), Non Insulin Dependent Diabetes Mellitus (NIDDM), Heart Failure (HF), Left Ventricular (LV), Left Ventricular Hypertrophy (LVH), New York Heart Association (NYHA), Diabetes Mellitus type 1 (DM-1), Diabetes Mellitus type 2 (DM-2)