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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.[1] Blockade of the renin-angiotensin system by either angiotensin-converting enzyme **(ACE)** inhibition or angiotensin receptor blockade **(ARB)** has cardiovascular and reno-protective effects. However, there is still much controversy over which of the two drug classes offers more protection.[2] 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.[3] 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.[4]

Hypertension increases the risk of macrovascular and microvascular complications such as coronary artery disease, stroke, peripheral vascular disease, retinopathy, nephropathy and neuropathy.[3] Blood pressure control in diabetic patients is important since hypertension is the second commonest cause of renal failure.[5] 40% of patients with type I 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.*[1]

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.[3] 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.[3]

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 <140/90mm/Hg. 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 <130/85mm/Hg and for patients with proteinuria >1g/24h it is <125/75. The target BP in patients with renal insufficiency (serum creatinine >22µmol/l) is <130/85.[6]

ACE inhibitors (ACE-Is) 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-Is and ARBs act by reducing the stimulation of the angiotensin type 1 (AT1) receptor by its ligand angiotensin type II (AngII).[8] **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.[9]

ACE-Is block ACE thereby *decreasing the amount of AngII available* for binding to the AT1 and AT2 receptors. ACE-Is also *decrease the breakdown of bradykinin* to inactive fragments.[8] Bradykinin is a direct vasodilator and promotes release of the vasodilating substances prostacyclin and nitric oxide.[9] 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-Is.[8]

ACE-Is and ARBs both *increase plasma renin and AngI. 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

Figures 1 & 2: Schematic drawings of differential effects of ACE-Is (figure 1) and ARBs (figure 2) on the renin-angiotensin and bradykinin systems[8]

Figure 1

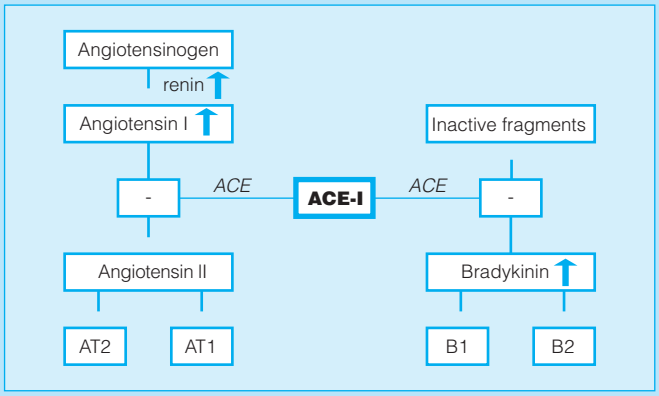
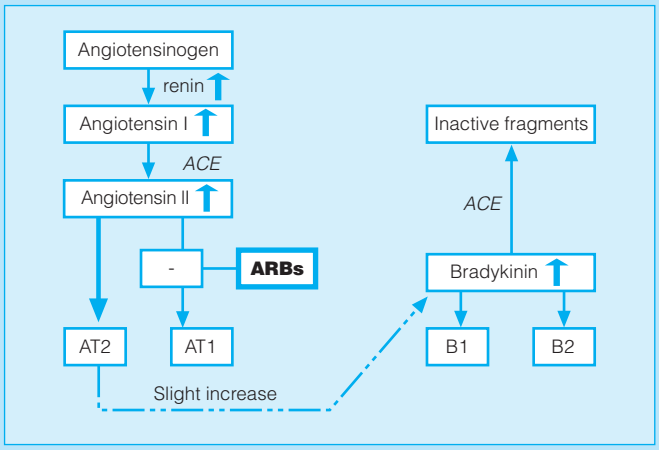


Figure 2



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

Source: *Hilgers KF, Mann JFE. ACE Inhibitors versus AT1 Receptor Antagonists in Patients with Chronic Renal Disease. J Am Soc of Nephrol 2002; 13:1100-8*

indicate that it counteracts the vasoconstrictive 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.[8] AngII inhibition results in decreased blood and intra-glomerular pressure, improved glomerular-barrier size selectivity and reduction of proteinuria.[2]

The reno-protective effect of ACE-Is and ARBs is explained by their antiproteinuric effect as demonstrated by reno-protection trails. This is consistent with the view that proteins, once leaked through the glomerular barrier, act as mediators of ongoing renal fibrosis.[2]

RENO-PROTECTIVE EFFECTS OF ACE-Is

Type 1 Diabetes

Numerous studies support the view that the use of ACE-Is reduces the risk of progression from microalbuminuria to overt albuminuria in type 1 diabetic patients.[2,10,11] **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.[2,11] 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.*[2,12] These studies support the recommendation by the American Diabetes Association that "in patients with type 1 diabetes, with any degree of albuminuria, ACE-Is delay the progression of nephropathy".[4,10]

Type 2 Diabetes

There are no well-powered studies on the effect of ACE-Is on renal disease in type 2 diabetics. Data from type 1 diabetics cannot be extrapolated to apply to type 2 diabetics. Studies have shown that ACE-Is prevent progression from microalbuminuria to overt albuminuria in type 2 diabetics, but there is insufficient data to prove whether ACE-Is can prevent loss of glomerular filtration rate (GFR) in overt nephropathy.[3,10] Some investigators have reported that these patients have abnormalities in glomerular selectivity that cannot be reversed by ACE-Is.[10]

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%.[2,9]
- In 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.*[2]
- Two large-scale 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-Is compared to other antihypertensive drugs.[8,13,14,15]
- The **PREMIER** study (Preterax in Albuminuria Regression; n=457) showed that combination therapy of perindopril and indapamide in patients with type 2 diabetes, albuminuria and hypertension showed a statistically significant higher fall in albumin excretion rate versus enalapril monotherapy (42% versus 27%. However the decrease in creatinine clearance in both groups was in keeping with that seen with most antihypertensive therapy, particularly with renin angiotensin system (RAS) inhibitors.[16]

RENO-PROTECTIVE EFFECTS OF ARBs

Type 1 Diabetes

There are no large scale trials on the long term reno-protective effects of ARBs in type 1 diabetic patients.[2]

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 **(RENAAL)** 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 reaching primary composite end point (i.e. doubling of serum creatinine, end stage renal disease (ESRD) or death)* versus placebo by 20% and 16% respectively.[2,13,17,18] The IDNT showed a decrease of 23% in the risk to reach the primary end point as compared with calcium channel blockade by amlodipine However the relative risk of reaching the primary end point in the placebo and amlodipine groups did not differ significantly.[17]

The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study showed that as compared with conventional therapy, irbesartan is better at preventing the development of clinical proteinuria and at restoring normoalbuminuria for comparable BP control in patients with incipient nephropathy.[19]

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 reno-protection over other anti-hypertensive drugs, direct comparisons between ACE-Is and ARBs in patients with renal disease are lacking.

The results of the **DETAIL** study (Diabetics Exposed to Telmisartan And enalapriL) in which enalapril was compared with telmisartan for renal end points in 250 type 2 diabetic patients with hypertension, were presented at the European Society of Cardiology Congress in 2004.[10] 82% of these patients had microalbuminuria and 18% had macroalbuminuria. After 5 years there was no significant difference in the end points between the two groups.[20,21]

Based on available data both the Joint National Committee on Prevention, Diagnosis and Management of Hypertension (JNC 7 guidelines of 2003) and the American Diabetic Association guidelines indicate that ACE-Is and ARBs can be used interchangeably.[4,7] The American Diabetes Association's current recommendations for the use of ACE-Is and ARBs in the treatment of albuminuria/nephropathy are as follows[4]:

- In hypertensive type 1 diabetics with **any degree of albuminuria**, ACE inhibitors have been shown to delay the progression of **nephropathy**
- In hypertensive type 2 diabetics with **microalbuminuria**, ACE-Is and ARBs have been shown to delay the progression to **macroalbuminuria**
- In type 2 diabetics with hypertension, **macroalbuminuria and renal insufficiency**, ARBs have been shown to delay the progression of **nephropathy**

However Strippoli *et al* disagree with this interchangeability.[7] They did a systematic review, published in the BMJ in September 2004, which evaluated the effects of ACE-Is and ARBs on renal outcomes and all cause mortality in patients with diabetic nephropathy. Of 4723 articles identified, only 43 randomized controlled trials were eligible for inclusion in the review (7545 patients in total). Of these only 3 trials compared ACE-Is with ARBs in type 2 patients with microalbuminuria. 36 trials compared ACE-Is with placebo and 4 trials compared ARBs with placebo. Based on the review they concluded that:

- ACE-Is prevent early death, but that no such evidence for ARBs exists
- Both agents prevent progression of nephropathy and promote regression to normoalbuminuria:
- ACE-Is:
  - reduce the risk of progression from microalbuminuria to macroalbuminuria by about 55%
  - increase the rate of regression from microalbuminuria to normoalbuminuria by about 3.4 times
- ARBs:
  - reduce risk of end stage renal disease and doubling of serum creatinine by 22%
  - reduce progression rate from microalbuminuria to macroalbuminuria by 51%
  - increase regression from microalbuminuria to normoalbuminuria by 42%
- The relative effects of ACE-Is and ARBs are unknown
- Thus ACE-Is should be used as first line treatment

The general consensus held, including that of Strippoli *et al*, is that there is a need for an adequately powered comparative trial of ACE-Is and ARBs, in which the reno-protective effects of both classes of medication in similar clinical settings are compared. **Table 1** summarizes some of the available trial data.

CARDIOVASCULAR PROTECTIVE EFFECTS OF ACE-Is

Type 1 Diabetes

Although the **Collaborative Study's** primary end point was doubling of serum creatinine, this study showed a 50% reduction in the secondary combined end point which included length of time to death on captopril treatment. This could therefore suggest that ACE-I treatment may be cardio-protective in overt nephropathy of type 1 diabetes.[2,11]

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

Study	*Primary Outcome*	*Secondary Outcome*	*Agents*	*Renal Protection Results*
Collaborative Study[11] (DM-1 with overt nephropathy) 409 patients	Doubling of the base-line serum creatinine concentration	Length of time to combined end points of death, dialysis and transplantation	Captopril vs. placebo	48% reduction in risk of doubling serum creatinine in the captopril group
European Microalbuminuria Captopril Study[12] (DM-1 with micro-albuminuria) 92 patients	Rate of progression to clinical proteinuria		Captopril vs. placebo	Captopril impeded progression to clinical proteinuria
micro-HOPE[2,9] (mostly DM-2 with normo- or micro-albuminuria) 3577 patients	MI, stroke, CV death	Total mortality, admission to hospital or development of overt nephropathy	Rampril vs. placebo	Ramipril decreased risk to develop overt nephropathy
UKPDS[14] (DM-2 with hypertension) 1148 patients with 758 allocated to tight BP control	Time of occurrence of 1st clinical end point related to diabetes, death related to diabetes and from all causes	MI, stroke, amputation, death from peripheral vascular disease and microvascular complications	Captopril vs. atenolol	No significant risk reduction in the progression of albuminuria or doubling of creatinine clearance of captopril over atenolol
IRMA 2[19] (DM-2 with hypertension and microalbuminuria) 590 patients	Time to the onset of diabetic nephropathy	Changes in level of albuminuria, creatinine clearance, restoration of normo-albuminuria	Irbesartan vs. placebo	Irbesartan significantly reduces rate of progression to clinical albuminuria independent of BP
IDNT[2,13,17] (DM-2 with overt nephropathy) 1715 patients	Doubling of serum creatinine, ESRD, death	CV mortality and morbidity	Irbesartan vs. amlodipine or placebo	Irbesartan decreased risk for progression to advanced diabetic nephropathy
RENAAL[2,13,18] (DM-2 with overt nephropathy) 1513 patients	Doubling serum creatinine, ESRD, death	CV mortality and morbidity	Losartan vs. conventional treatment	Losartan decreased relative risk of reaching primary end point

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 diabetics, especially those with renal disease, are at a high risk of heart failure, myocardial infarction and cardiovascular death.[8]

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.*[2,10] This study demonstrated a *significant reduction in cardiovascular mortality* with the ACE-I ramipril as compared with placebo.[9,10] The risk of the combined 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 outcomes in 1502 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 group which is *not* significantly different to the risk reduction of 20% shown in the general coronary disease population in the main EUROPA study.[22]

Other studies which compare ACE-Is with calcium channel blockers or other anti-hypertensives include the following:

- Promising results were seen with fosinopril when compared with amlodipine in the Fosinopril vs Amlodipine Cardiovascular Events Trial **(FACET).** 380 patients with type 2 diabetes and hypertension were randomly assigned to fosinopril or amlodipine. Systolic blood pressure control was better in the amlodipine 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.[10,13,23]
- In a substudy of the Appropriate Blood Pressure Control in Diabetes **(ABCD)** Trial, analysis of the secondary end point of myocardial infarction showed a lower risk for non-fatal MI in patients with diabetes taking enalapril versus nisoldipine.[10,13,15]
- In the Captopril Prevention Project **(CAPPP)** captopril was compared with a beta-blocker/diuretic combination. In a subgroup analysis of 572 patients with diabetes, blood pressure control was similar but the *captopril group had a lower risk for all-cause mortality, myocardial infarction and cardiovascular events.*[10,13,24] This substudy has however been criticized as randomization was unbalanced, 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).[10]

However, the cardio-protective effect of ACE-Is has not been found to be uniform in all studies.[10] In the UK Prospective Diabetes Study **(UKPDS)** trial 758 patients were randomly assigned captopril or atenolol. The blood pressure lowering effects of captopril or atenolol resulted in a decrease in the risk of cardiovascular and microvascular events - *no benefit of the captopril arm of the trial was found over the atenolol arm.*[9,14]

CARDIOVASCULAR PROTECTIVE EFFECTS OF ARBs

Type 1 Diabetes
Sufficient data is lacking on the cardiovascular outcomes of ARBs in type 1 diabetic renal disease.[2]

Type 2 Diabetes
- **RENAAL** and **IDNT** studies were done primarily to examine renal end points. These two studies 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 amlodipine respectively.[2,10,17,18] However, the rate of first hospitalization was significantly lower with losartan versus placebo in the RENAAL study (32% risk reduction; p=0.005).[18] Despite the large sample size of both trials, they *could not demonstrate any beneficial effect on cardiovascular events.*[2,10]
- A sub-group of 1195 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 ß-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.[25]

CARDIOVASCULAR PROTECTIVE EFFECTS OF ACE-Is vs ARBs

Direct comparative data on the cardiovascular outcomes of ACE-Is 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 RENAAL trials. However, this comparison is not a true reflection as high risk patients with dipstick-positive proteinuria were excluded from the HOPE study.[2]

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

- In the initial Evaluation of Losartan in the Elderly Study **(ELITE)** captopril was compared to losartan in elderly heart failure patients. Losartan *demonstrated 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.*[10,26,27] 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.[28]
- The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Study **(RESOLVD)** 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 Valsartan 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 other ongoing trial comparing ACE-Is and ARBs although again 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.[10,32,33] 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-Is 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-Is are the best documented treatment to delay the progression of nephropathy in type 1 diabetic patients. The inhibition of ACE, which blocks the formation of AngII, has additional effects on fibrotic and/or inflammatory processes in the kidney. Both type 1 and type 2 diabetic patients with microalbuminuria should be started early with ACE-Is as this class has shown to prevent or at least delay the occurrence of overt nephropathy.[8]

In type 2 diabetics the choice of drug is less obvious. In this population group both ACE-Is and ARBs have been shown to delay the progression of microalbuminuria to macroalbuminuria. However, only ARBs have been shown to delay the progression of renal insufficiency in type 2 diabetics 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-Is are also effective in these patients, but renal end point studies with ACE-Is in these patients have not been done to resolve this debate.[8]

There is compelling evidence that ACE-Is have a cardioprotective effect, reducing the risk of death and MI in patients with heart failure, CAD and other high-risk populations.[28] However, data is lacking to determine whether ACE-Is 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-Is in diabetics the micro-HOPE data shows better cardiovascular protection with ACE inhibition as compared to ARBs in the IDNT and RENAAL trials.

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-Is and ARBs also show conflicting results.[28]

CONCLUSION

There is a definite need for appropriately powered comparative trials of ACE-Is 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-Is or ARBs with placebo or other classes of anti-hypertensives:

- ACE-Is are reno-protective in type 1 diabetics.
- ACE-Is 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-Is 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-Is resulting in greater compliance.

Taking drug cost and the above considerations into account the use of ACE inhibitors is justified as first line treatment for all type 1 diabetics and type 2 diabetics with *early to moderate* renal disease. The use of ACE-Is in these patients will also confer cardiovascular protection associated with this drug class.

ARBs should be initiated in these patients if the patient has side effects or can't tolerate an ACE inhibitor. ARBs should also be considered in type 2 diabetics with overt nephropathy.

REFERENCES AVAILABLE ON REQUEST

Table 2: **Cardiovascular Protection Studies with ACE-I and ARBs**

Study	*Primary Outcome*	*Secondary Outcome*	*Agents*	*Cardiovascular Protection Results*
Collaborative Study[11] (DM-1 with overt nephropathy) 409 patients	Doubling of the base-line serum creatinine concentration	Length of time to combined end points of death, dialysis and transplantation	Captopril vs. placebo	50% reduction in the risk of combined secondary end points, including mortality, with captopril
micro-HOPE[2,9] (mostly DM-2 with normo- or microalbuminuria) 3577 patients	MI, Stroke, CV death	Total mortality, admission to hospital, overt nephropathy	Ramipril vs. placebo	Primary outcome lowered in ramipril group
PERSUADE (a substudy of EUROPA)[22] (DM [18% on insulin at baseline] and CAD) 1502 patients	Cardiovascular death, non-fatal MI and resuscitated cardiac arrest	Total mortality, revascularization, stroke, hospitalization for unstable angina or heart failure	Perindopril vs. placebo	19% relative risk reduction in primary outcome, but no significant reduction versus general CAD population
FACET[23] (mainly DM-2 hypertensive) 380 patients	Serum lipids and diabetes control in NIDDM patients with hypertension	Acute MI, stroke, hospitalized angina	Fosinopril vs. amlodipine	Fosinopril group had lower risk of combined secondary endpoints
ABCD[15] (Substudy: DM-2 with hypertension) 470 patients	Effect of moderate vs intense BP control on 24-hour creatinine clearance	Effect of moderate vs intense BP control on incidence of CV events (incl MI), retinopathy, neuropathy, urinary albumin excretion & LVH	Enalapril vs. nisoldipine	Significantly lower risk for non-fatal MI in enalapril versus nisoldipine group
CAPPP[13,24] (DM-2) 572 patients	Fatal and non-fatal MI, stroke or other CV deaths	Total mortality, development of ischaemic heart disease, atrial fibrillation, etc	Captopril vs. beta-blocker/diuretic combination	Captopril group had lower risk for CV events, MI and all cause mortality
UKPDS[14] (DM-2 with hypertension) 1148 patients with 758 allocated to tight BP control	Time of occurrence of 1st clinical end point related to diabetes, death related to diabetes and from all causes	MI, stroke, amputation, death from peripheral vascular disease and microvascular complications	Captopril vs. atenolol	No benefit of captopril over atenolol in secondary outcome measures
RENAAL[2,13,18] (DM-2 with overt nephropathy) 1513 patients	Doubling serum creatinine, ESRD, death	CV mortality and morbidity	Losartan vs. placebo	No benefit of losartan on CV events
IDNT [2,13,17] (DM-2 with overt nephropathy) 1715 patients	Doubling of serum creatinine, ESRD, death	CV death, MI, hospitalisation for HF	Irbesartan vs. amlodipine or placebo	No benefit on CV events
LIFE substudy[25] (most likely DM-2 with hypertension and LVH) 1195 patients	Composite CV mortality and morbidity (stroke, MI)	Total mortality, hospital admission for angina, heart failure, revascularisation	Losartan vs. atenolol	Lower incidence of primary composite end point with losartan but no significant difference in MI and stroke
RESOLVD[29] (Patients with symptomatic HF due to LV systolic dysfunction) 768 patients	Exercise performance, ventricular function, quality of life, neuro-hormones, tolerability	Optimal dose of candesartan for a larger proposed trial	Candesartan vs. enalapril	No difference between the two agents in primary outcome excluding tolerability and neuro-hormones
ELITE[5] (Patients with NYHA class II-IV HF) 722 patients	Tolerability measure of a persisting increase in serum creatinine	Composite of death and/or hospital admission for HF	Losartan vs. captopril	Losartan had 46% lowering of all cause mortality than captopril (secondary outcome)
ELITE II[27] (Patients with NYHA class II-IV HF) 3152 patients	All cause mortality	Cardiac death or resuscitated cardiac arrest	Losartan vs. captopril	No significant difference in primary and secondary outcomes
OPTIMAAL[30] (Patients with MI and HF) 5477 patients	All cause mortality	Cardiac death or resuscitated cardiac arrest	Losartan vs. captopril	No significant difference in primary and secondary outcomes
VALIANT[31] (Patients with acute MI) 14 703 patients	Death from any cause		Valsartan vs. captopril	Equivalent effect in patients at high risk for CV events after MI
ONTARGET[32,33] (Patients with high risk of CV complications) 23 400 patients	Cardiovascular death, MI, stroke, hospitalisation for CHF		Telmisartan vs. ramipril; Telmisartan vs. placebo; Telmisartan plus ramipril vs. ramipril alone	Pending

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)

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