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ACE Inhibitors and Angiotensin Receptor Antagonists and the Incidence of New-Onset Diabetes Mellitus

An Emerging Theme

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Abstract

The prevalence of type 2 diabetes mellitus continues to rise. Given the associated co-morbidities of obesity, hypertension and cardiovascular disease, the rising incidence of diabetes has important health consequences and efforts to reduce this incidence are critical. Although lifestyle modifications, including weight loss and exercise, are instrumental in the prevention of diabetes, pharmacological therapies that reduce the incidence of diabetes have the significant potential to lower risk.

The results of several large clinical trials have demonstrated that treatment with ACE inhibitors and angiotensin receptor antagonists (angiotensin receptor blockers; ARBs) may prevent or delay the onset of diabetes. These trials have demonstrated an approximately 15–30% reduction in the new onset of diabetes in those receiving ACE inhibitors and ARBs when compared with placebo or other active therapy. Although the exact mechanism underlying the effects are not entirely clear, multiple animal and human studies have demonstrated that the renin-angiotensin system plays an important role in glucose homeostasis. Although future prospective studies to clarify the role of ACE inhibitors and ARBs in preventing diabetes are ongoing, there is substantial existing evidence from completed trials that these agents may prevent the onset of diabetes.

The global burden of type 2 diabetes mellitus continues to rise as the total number of people with diabetes is expected to increase from approximately 171 million people in the year 2000 to 366 million people by the year 2030.[1] Approximately one in three individuals born in the US in the year 2000 will develop diabetes during their lifetime.[2] Although the increased prevalence of diabetes may be

partially related to changes in diagnostic criteria and improved or enhanced detection, the increasing age of the population and the epidemic of obesity are playing a crucial role in the rising burden of diabetes.

Given the significant acute and chronic health consequences associated with diabetes, any efforts to reduce the prevalence of diabetes are crucial.[3] The importance of lifestyle modification, including exercise and dietary changes, in the prevention of diabetes has been demonstrated in large clinical trials and should be aggressively emphasised.[4,5] In addition to lifestyle modification, several pharmacological therapies have been shown to reduce the incidence of new diabetes including metformin,[5] acarbose[6] and the thiazolidinedione troglitazone.[7]

The results of several large clinical trials have also demonstrated that treatment with ACE inhibitors and angiotensin receptor antagonists (angiotensin receptor blockers; ARBs) may prevent or delay the onset of diabetes. These findings have important implications given the dangerous interplay of diabetes, hypertension and heart failure. This review describes the role of ACE inhibitors and ARBs in the prevention of diabetes, and reviews evidence from recent clinical trials, potential mechanisms and future directions of research.

1. Clinical Trial Evidence

1.1 ACE Inhibitors

The most robust evidence for the beneficial effects of ACE inhibitors in the prevention of new-onset diabetes is seen in clinical trials (table I). The CAPPP (Captopril Prevention Project) trial was one of the first studies to demonstrate a reduction in the incidence of new-onset diabetes with treatment with an ACE inhibitor.[8,9] The CAPPP trial compared an antihypertensive treatment strategy based on either the ACE inhibitor captopril with conventional diuretic and/or β-adrenoceptor antagonist (β-blocker) therapy. The diagnosis of diabetes was made according to the 1985 WHO criteria, which required at least two abnormal fasting glucose values (>140 mg/dL [>7.8 mmol/L]) or, if not unequivocal, confirmation by an oral glucose tolerance test.[10] In the 10 413 nondiabetic hypertensive patients enrolled in the trial, the patients who were treated with captopril had a 14% decreased risk of developing diabetes compared with conventional therapy (relative risk [RR] 0.86; 95% CI 0.74, 0.99). Although the risk of developing diabetes was reduced in those patients assigned to captopril therapy, it was not clear whether the reduced incidence of new-onset diabetes seen in the CAPPP trial was related to the beneficial effects of an ACE inhibitor or the worsening glucose tolerance effects that have been ascribed to β-blockers[11] or diuretic therapy.[12]

ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) also demonstrated a reduction in the incidence in new-onset diabetes in patients who received ACE inhibitor therapy.[15] ALLHAT was a North American study of 33 357 men and women aged ≥55 years with hypertension and at least one additional risk factor for coronary heart disease that tested a hypertensive treatment strategy based on a diuretic (chlortalidone), an ACE inhibitor (lisinopril) or a calcium-channel antagonist (amlodipine). The diagnosis of diabetes was made according to the American Diabetes Association criteria (fasting serum glucose >126 mg/dL [>7mmol/L]).[21] Although no significant difference was noted with either strategy in the primary outcome of prevention of coronary heart disease, those assigned to the ACE inhibitor arm had an approximately 30% reduced risk of developing diabetes than those in the diuretic arm. Interestingly, a slight risk reduction in the onset of diabetes was seen in those assigned to amlodipine, considered a metabolically 'neutral' antihypertensive, when compared with chlortalidone.

Table I. Occurrence of new-onset diabetes mellitus and inhibitors of the renin-angiotensin system (RAS) in selected randomised controlled trials

Study	Treatment	No. of pts enrolled without diabetes at baseline	Duration of follow-up (y)	New-onset diabetes active therapy [no. (%)][a]	New-onset diabetes comparator therapy [no. (%)][a]	Reduced risk of developing diabetes in the RAS inhibitor treatment arm (%)
CAPPP[8,9]	Captopril vs conventional therapy (diuretic ± β-blocker)	10 413	6.1	337/5183 (6.5)	380/5230 (7.3)	↓14
HOPE[13]	Ramipril vs placebo	5 720	4.5	102/2837 (3.6)	155/2883 (5.4)	↓34
SOLVD[b][14]	Enalapril vs placebo	291	2.9	9/153 (5.9)	31/138 (22.4)	↓74
ALLHAT[15]	Amlodipine vs lisinopril vs chlorthalidone	21 294	4.9	119/1464 (8.1) lisinopril group; 154/1567 (9.8) amlodipine group	302/2606 (11.6)	↓30[c]
PEACE[16]	Trandolapril vs placebo	6 904	4.8	335/3432 (9.8)	399/3472 (11.5)	↓17
LIFE[17]	Losartan vs atenolol	7 998	4.8	241/4019 (6)	319/3979 (8)	↓25
VALUE[18]	Valsartan vs amlodipine	10 419	4.2	690/5267 (13.1)	845/5152 (16.4)	↓23
CHARM[19]	Candesartan vs placebo	5 436	3.1	163/2715 (6.0)	202/2721 (7.4)	↓22
ALPINE[20]	Candesartan ± felodipine vs hydrochlorothiazide ± β-blockers	392	1	1/196 (0.5)	8/196 (4.1)	↓87

a No. of pts with new-onset diabetes/total no. of non-diabetic patients.

b Subset of pts enrolled in the entire SOLVD study.

c Lisinopril vs chlorthalidone.

ALLHAT = Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; **ALPINE** = Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; **CAPPP** = Captopril Prevention Project; **CHARM** = Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity; **HOPE** = Heart Outcomes Prevention Evaluation; **LIFE** = Losartan Intervention For Endpoint reduction; **PEACE** = Prevention of Events with Angiotensin Converting Enzyme Inhibition; **pts** = patients; **SOLVD** = Studies of Left Ventricular Dysfunction; **VALUE** = Valsartan Antihypertensive Long-term Use Evaluation; ↓ indicates reduction.

Because of the confounding effects of diuretics and β-blockers on the development of insulin resistance and diabetes, a comparison of ACE inhibitors with placebo was necessary to establish a distinct benefit associated with ACE inhibitors from the potentially detrimental metabolic effects of diuretics and β-blockers. Such evidence was seen in the HOPE (Heart Outcomes Prevention Evaluation) study. The HOPE study compared the effects of an ACE inhibitor (ramipril) with placebo on the prevention of cardiovascular outcomes in a total of 9297 high-risk patients, including 5720 nondiabetic patients.[22] The diagnosis of diabetes was determined by self-report at follow-up visits every 6 months. In the HOPE study, ramipril was associated with a 34% risk reduction in the development of diabetes, a finding that could not be explained by ascertainment bias or concomitant medical use (e.g. β-blockers, diuretics).[13]

The recently completed PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) trial also confirmed a reduction in the new onset of diabetes in patients receiving an ACE inhibitor compared with placebo.[16] The PEACE trial compared trandolapril with placebo in the prevention of adverse cardiovascular outcomes in patients with stable coronary artery disease. The development of diabetes was reported by the participating

investigators of the trial. Although no significant difference was seen in the primary cardiovascular outcome between the two treatment strategies, individuals assigned to trandolapril had a 17% reduced risk of developing diabetes over the median follow-up of 4.8 years.

A small subanalysis of heart failure patients enrolled in the SOLVD (Studies of Left Ventricular Dysfunction) demonstrated that enalapril was associated with a dramatically reduced risk of developing diabetes when compared with placebo (hazard ratio [HR] 0.22; 95% CI 0.10, 0.46; $p < 0.0001$). The diagnosis of diabetes was defined using the American Diabetes Association criteria.[21] In this heart failure trial, the effects of enalapril were most evident in the 55 patients with impaired fasting glucose. In this small group with impaired fasting glucose, only one (3.3%) patient developed diabetes in the enalapril group versus 12 (48%) in the placebo group.[14] The risk reduction seen in SOLVD is much greater than that described in other trials with ACE inhibitors. It is intriguing to hypothesise that ACE inhibitors may be more beneficial in the insulin-resistant state of heart failure[23,24] than in those without heart failure. The small number of patients in this study warrants confirmation in larger studies in similar heart failure populations.

1.2 Angiotensin Receptor Antagonists

Data from clinical trials of ARBs have also demonstrated a reduction in new-onset diabetes associated with this class of medications. Initial clinical evidence for prevention of diabetes with an ARB was seen in the LIFE (Losartan Intervention For Endpoint reduction) trial. The LIFE trial was a randomised, placebo-controlled trial comparing the strategy of antihypertensive treatment based on either losartan or atenolol in patients aged 55–80 years with hypertension and left ventricular hypertrophy. In this trial, new-onset diabetes was defined according to 1985 WHO criteria.[10] In the LIFE trial, treatment assignment to losartan conferred a 25% reduced risk in the development of diabetes.[17] Similar to CAPPP, it was unclear whether the reduced risk of developing diabetes was related to a benefit of the ARB or related to an adverse metabolic effect of β-blocker therapy.

The VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial was designed to test the hypothesis that valsartan would reduce cardiac morbidity and mortality more than the calcium channel antagonist amlodipine in hypertensive patients at high cardiovascular risk. Although there were small differences in blood pressure between the two treatment groups, no significant difference was noted in the primary composite cardiovascular outcome between amlodipine and valsartan. Diabetes was diagnosed if the serum glucose level at the end of the trial exceeded 7.8 mmol/L (140 mg/dL). Compared with amlodipine, which is considered to be a metabolically neutral agent, assignment to valsartan was associated with a 23% reduced risk of developing diabetes.[18]

More recently, the CHARM (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity) programme reported a reduction in new-onset diabetes in patients treated with candesartan when compared with placebo. The CHARM programme assessed the effects of candesartan on cardiovascular mortality and heart failure hospitalisations.[25] It consisted of three parallel trials involving complementary patient populations with symptomatic heart failure, including a group with left ventricular ejection fraction (LVEF) ≤40% who had been previously intolerant to ACE inhibitors (CHARM-Alternative),[26] a group of patients with LVEF ≤40% currently receiving ACE inhibitors (CHARM-Added),[27] and a group of patients with symptomatic heart failure and LVEF >40% (CHARM-Preserved).[28] The development of diabetes was reported by the investigator at the end of the trial. In the overall CHARM programme,

candesartan was associated with a 22% reduction in the risk of developing diabetes.[19] The reduction in new diabetes was most marked in those individuals who were enrolled in the CHARM-Preserved trial (HR 0.60; 95% CI 0.41, 0.86; p = 0.005) and was less apparent in those enrolled in the CHARM-Alternative trial (HR 0.79; 95% CI 0.53, 1.18; p = 0.88) and in the CHARM-Added trial (HR 0.98; 95% CI 0.70, 1.35; p = 0.88) [p heterogeneity = 0.14]. Additionally, the magnitude in the reduction in new-onset diabetes appeared slightly greater in those who were not receiving concomitant ACE inhibitors (HR 0.71; 95% CI 0.53, 0.65) when compared with those who receiving ACE inhibitors during the trial (HR 0.88; 95% CI 0.65, 1.20), although the interaction did not reach statistical significance (p = 0.28).

In the smaller ALPINE (Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation) study, an antihypertensive treatment strategy of a diuretic, alone or in combination with a β-blocker, was compared with a strategy of candesartan, alone or in combination with a calcium channel antagonist (felodipine). Diabetes was diagnosed if it was reported by the investigator, a prescription of oral antidiabetic medication was made during follow-up, and two fasting plasma-glucose values of ≥7 mmol/L (≥126 mg/dL) were documented. In this trial of 392 patients, new-onset diabetes mellitus was diagnosed in eight patients in the diuretic group (4.1%) and in one patient (0.5%) in the candesartan group (p = 0.03).[20]

2. Potential Mechanisms of Action

Despite the clinical trial evidence implicating the role of the renin-angiotensin system (RAS) in glucose metabolism and the development of diabetes, the exact mechanisms by which RAS inhibition prevents diabetes is not known. It is likely that these mechanisms are multifactorial and affect both insulin secretion and insulin sensitivity (table II).[29,30]

Table II. Potential mechanisms for the reduction in new-onset diabetes mellitus from inhibitors of the renin-angiotensin system (see section 2)

Protective effect of pancreatic β-cell function through inhibition of the vasoconstrictive and potential fibrotic effects of angiotensin II in the pancreas
Improved insulin sensitivity by increasing blood flow to skeletal muscle, including local haemodynamic effects associated with activation of bradykinin/nitric oxide pathways
Inhibition of deleterious effects of angiotensin II on insulin signaling pathways
Improved glucose transport (increased expression of GLUT-4)
Facilitation of the differentiation of the adipocyte to mature adipocyte
Activation of the PPARγ system (certain ARBs)

ARBs = angiotensin receptor blockers (antagonists); **GLUT-4** = glucose tranporter-4; **PPARγ** = peroxisome proliferator-activator receptor γ.

An extensive review of the scientific evidence is beyond the scope of this review, however, we briefly discuss a few points.

The RAS may affect the angiotensin system through beneficial effects on the pancreas. Angiotensin II has been demonstrated to have significant vasoconstrictive effects on the pancreatic vasculature, which may impair blood flow to the pancreas and pancreatic β-cells.[31] In addition, activation of the RAS within the pancreas and pancreatic islets may lead to expression of enzymes and receptors that lead to a disruption of islet cell architecture, fibrosis and apoptosis.[29] Inhibition of the RAS by ACE inhibitors and ARBs appears to attenuate this fibrotic, destructive response in the islet cells.[32,33]

In addition to pancreatic β-cell preservation, ACE inhibitors and ARBs appear to influence glucose regulation by improving insulin sensitivity. Inhibition of the RAS system, through local haemodynamic effects primarily mediated by bradykinin and nitric oxide, improves blood flow to skeletal muscle, thus improving insulin sensitivity and glucose disposal.[34,35] Deleterious effects of angiotensin II on the insulin-signaling pathway through the phosphoinositol-3-kinase/protein kinase C signaling pathway in skeletal muscle and cardiovascular tissue also appear to be contributing to

insulin resistance.[36] Moreover, administration of ACE inhibitors or ARBs in animal models can increase protein expression of glucose tranporter-4 (GLUT-4) in skeletal muscle and myocardium, and thus improve glucose utilisation.[37]

Additionally, the RAS may influence insulin sensitivity by affecting adipocyte morphology and function. Angiotensin II has been shown to inhibit the differentiation of preadipocytes to mature adipocytes.[38] Such effects may favour the deposition of lipids in tissues other than a mature adipocyte such as muscle, liver and pancreas leading to insulin resistance.[39] Recent work has demonstrated that RAS blockade with ACE inhibitors or ARBs changes adipocyte morphology and leads to increased insulin sensitivity in a rat model.[40] Additionally, treatment with an ACE inhibitor (temocapril) and certain ARBs has been shown to increase adiponectin levels with improvement in insulin sensitivity.[41,42]

A final, intriguing mechanism for the reduction in new-onset diabetes relates to the ability of ARBs to activate the nuclear hormone receptor peroxisome proliferator-activator receptor gamma (PPARγ). PPARγ is a member of the nuclear receptor superfamily that is expressed in adipocytes, macrophages and muscle where it regulates and functions as a transcription factor that controls carbohydrate and lipid metabolism.[43,44] The thiazolidinediones, a group of PPARγ agonists, have been effective in the treatment of diabetes mellitus[43] and the prevention of diabetes in insulin-resistant women.[7] Recent work has demonstrated that some ARBs induce PPARγ by interacting with the PPARγ ligand-binding domain, thereby promoting PPARγ-dependent differentiation in 3T3-L1 adipocytes.[45] Activation of the PPARγ by ARBs was also observed in the absence of angiotensin II type 1 (AT_1) receptor, demonstrating that activation was independent of blocking the AT_1 receptors. The PPARγ activation appears to be contributing to the ARB-induced adiponectin stimulation described in the previous paragraph.[41] Importantly, not all ARBs share the same PPARγ-activating properties; telmisartan can activate the PPARγ at low concentrations, while irbesartan and losartan require medium and very high concentrations, respectively.[45] These findings confirm pleiotropic actions of certain ARBs that may differ based on the chemical structure of the compound, particularly the lipophilicity of the compounds, which is required to obtain intracellular concentrations to bind with PPARγ.

3. Future Issues

Despite the clinical and scientific studies demonstrating a role of the RAS in the development of diabetes, several issues remain unresolved. The clinical trials that have demonstrated a reduction in new-onset diabetes associated with ACE inhibitors and ARBs were *post hoc* analyses from a variety of different trials, and the primary endpoint of these was not the prevention of diabetes. Therefore, several definitions for the classification of diabetes have been used. The study design of the trials also varied, with some double-blind trials[13-18,20,25] and some using a prospective, open-blinded, endpoint design.[8,9] In addition, it is not clear whether the prevention of new-onset diabetes is a class effect of ACE inhibitors and ARBs, or whether there are differences between medications within the same class. The data on the differing agonist effects of ARBs on the PPARγ system[45] raise concerns that a consistent class effect cannot be assumed. Despite potential differences in mechanisms of the prevention of diabetes, the reduction in new-onset diabetes appears to be similar in magnitude between ACE inhibitors and ARBs; further work is necessary to elucidate potential differences between the two classes of drugs. Whether dual inhibition of the RAS with an ACE inhibitor and an ARB would provide greater benefit than monotherapy has not been addressed. Also, the clinical value that results from the

prevention of new-onset diabetes needs to be confirmed. Fortunately, several on-going clinical trials may provide answers to some of these questions.

The DREAM (Diabetes REduction Approaches with ramipril and rosiglitazone Medications) is a trial of approximately 5000 people with impaired fasting glucose or impaired glucose tolerance designed to prospectively test the benefits of ramipril in the prevention of diabetes compared with placebo.[46] Using a double-factorial design, the thiazolidinedione rosiglitazone will also be tested alone or in combination with ramipril. The NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) study is a multinational, randomised, placebo-controlled trial that hopes to determine whether valsartan and/or nateglinide, an insulin secretagogue, will delay or prevent the onset of diabetes in approximately 9000 patients with glucose intolerance and atherosclerosis or multiple cardiovascular risk factors.[47] The ONTARGET (ONgoing Telmisartan Alone or in combination with Ramipril Global Endpoint Trial) is a double-blind, parallel group study of approximately 22 400 patients with high cardiovascular risk.[48] The trial will consist of three arms and will evaluate the efficacy of the ARB telmisartan, the ACE inhibitor ramipril and their combination in the prevention of cardiovascular disease. The incidence of new-onset diabetes is a predefined study endpoint. Importantly, ONTARGET will provide insight into the possible differences between ACE inhibitors, ARBs and their combination in the prevention of new-onset diabetes. Those patients who cannot tolerate ACE inhibitors will be enrolled in a parallel trial, TRANSCEND (Telmisartan Randomized Assessment Study in Angiotensin Inhibitor-Intolerant Patients with Cardiovascular Disease).[48]

The clinical value of preventing new-onset diabetes also needs further support from clinical trials. As described in this review, several large antihypertensive clinical trials, such as ALLHAT[15] and VALUE,[18] have demonstrated reductions in the incidence of new-onset diabetes, but this reduction has not translated into reductions in cardiovascular disease during the time-period of the clinical trials. Largely based on results from the large trial ALLHAT,[15] the JNC-VII (Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) recommends that, because thiazide diuretics are as effective as ACE inhibitors and less expensive, they should be the preferred first choice antihypertensive drug.[49] Other investigators have argued that the duration of these clinical trials is not long enough to see the clinical value of the prevention of new-onset diabetes. This notion is supported by a recent report of 795 patients who were followed for a median of 6 years. In this group, 5.8% received a new diagnosis of diabetes. Importantly, the risk for subsequent cardiovascular disease was similar in those who developed new-onset diabetes (odds ratio [OR] 2.92; 95% CI 1.33, 6.41) to those who had previously diagnosed diabetes (OR 3.57; 95% CI 1.65, 7.73) when compared with those without diabetes.[50] Although many patients with insulin resistance will require multiple medications for blood pressure control,[51] we feel that the prevention of progression to diabetes in high-risk individuals with ACE inhibitors or ARBs should be considered when beginning antihypertensive therapy.

4. Conclusion

Multiple analyses from clinical trials have demonstrated a reduction in the development of new-onset diabetes associated with both ACE inhibitors and ARBs. The exact mechanisms of this protective effect are not entirely clear, but animal and human studies have demonstrated that the RAS plays an important role in glucose homeostasis. As we await further information from ongoing trials that are addressing unresolved issues regarding the use of ACE inhibitors and ARBs to prevent the new

onset of diabetes, the potential benefit in reducing new-onset diabetes provides another rationale for utilising inhibitors of the RAS to reduce cardiovascular risk.

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