

Blocking the renin-angiotensin-aldosterone system to prevent diabetes mellitus

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Abstract

Type 2 diabetes mellitus (DM) is increasing around the world, and the public health impact of DM, driven largely by cardiovascular disease complications, underpins the importance of continued efforts toward primary prevention of DM. Only a few interventions have been shown to prevent DM, with none of them yet proven to improve cardiovascular risk commensurately. Accumulating evidence suggest that drugs that block the renin-angiotensin-aldosterone system (RAAS), many of which have proven cardiovascular disease (CVD) benefit, also have favourable effects on parameters of glucose metabolism and incident diabetes. Here we review the evidence accumulated to date from animal studies, clinical mechanistic studies and clinical trials regarding the effect of RAAS inhibition and incident DM.

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Key words: angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), diabetes, prevention, renin-angiotensin-aldosterone system.

Introduction

Type 2 diabetes mellitus (DM) is a worldwide epidemic with a prevalence that is expected to double by the year 2025, affecting over 5% of the adult population.¹ Cardiovascular consequences of DM, especially coronary heart disease (CHD),^{2,4} make the prevention of diabetes and its vascular complications of paramount public health relevance.

Few strategies successfully prevent the development of DM,⁵ and no studies yet have demonstrated that prevention

of DM leads to a commensurate reduction in CHD risk. Recent clinical trials reveal that therapeutic lifestyle modification and some pharmacological interventions can postpone the onset of DM. The Finnish Diabetes Prevention Study and the Diabetes Prevention Program (DPP) both demonstrated that aggressive lifestyle modification with weight loss, physical activity, and nutrition counselling can reduce the progression to DM among patients with baseline impairment in glucose metabolism, including those with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).^{6,7}

In addition to lifestyle modification, several drug therapies have been demonstrated to prevent or delay the onset of DM among high-risk patients. Acarbose and metformin were each associated with a 30% risk reduction in the development of diabetes within the Study To Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) and DPP, respectively.^{7,8} Long-term follow-up data of the STOP-NIDDM trial suggest a reduction of cardiovascular risk among patients treated with acarbose, implying that preventing the onset of DM does lower cardiovascular risk.⁹ However, the small number of cardiovascular events in that study, challenges the validity of the observations, and criticisms of the study execution, end point definition and data reporting have been debated.¹⁰⁻¹² No long-term data from the DPP are presently available. Moreover, the risk of developing DM after discontinuing either medical regimen remains unknown.

These findings have aroused interest in the potential for other drugs that may slow the progression to overt DM in susceptible individuals. The thiazolidinediones (TZDs) improve whole body insulin sensitivity, a major factor for the development of DM, and thus hold promise for its prevention. In one small, double-blinded study of Hispanic women with a history of gestational DM, the TZD troglitazone reduced the incidence of DM by more than 50% relative to placebo.¹³ This protective benefit persisted for up to eight months after discontinuing the medication. More recently, a large-scale randomised clinical trial demonstrated a statistically significant 60% reduction in incident diabetes associated with three years of rosiglitazone treatment versus placebo among a cohort of subjects with IGT or IFG at study entry.¹⁴ However, this study was not designed or powered to assess the effects of the intervention on micro- or macrovascular disease complications. Factorial data from the Effect of Ramipril on the Incidence of Diabetes (DREAM) trial regarding comparison of the effect of the angiotensin-converting enzyme inhibitor (ACE-I) ramipril against placebo on incident DM are discussed below.

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More recently, evidence indicates that blockade of the renin-angiotensin-aldosterone system (RAAS) with an ACE-I or angiotensin-II type 1 receptor blocker (ARB) may prevent DM. The present discussion reviews the evidence accumulated to date from animal studies, clinical mechanistic studies and clinical trials regarding the effect of RAAS inhibition and incident DM.

Background

The first ACE-I was isolated from Brazilian pit viper venom in the early 1970s.¹⁵ Soon thereafter, captopril was approved for clinical use to treat hypertension.^{16,17} Studies using ACE-Is have subsequently demonstrated improved outcomes in patients with heart failure, hypertension, myocardial infarction, diabetic nephropathy and in long-term cardiovascular risk prevention.¹⁸ Evidence has recently indicated that ACE inhibition may also have a role in preventing the development of DM.

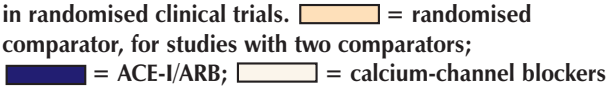


Animal studies



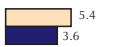

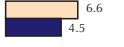




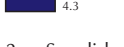
Several animal studies have shown improved glucose tolerance and enhanced insulin-mediated glucose disposal associated with ACE inhibition during both acute¹⁹⁻²³ and chronic administration.^{22,24-27} The enhancement in glucose disposal with ACE inhibition generally correlates with the degree of underlying insulin resistance and appears to modulate intracellular insulin signalling.^{28,29} Hydralazine and losartan failed to improve glucose-mediated disposal in euglycaemic insulin clamp studies in insulin-resistant rats, suggesting that the improvement in insulin sensitivity observed with ACE-Is is independent of haemodynamic effects.²³ In the aggregate, the animal studies reviewed demonstrate a consistent trend for improved glucose disposal with ACE inhibition over a variety of experimental protocols.

Human studies

Case reports of hypoglycaemia following administration of captopril or enalapril were published nearly 20 years ago.³⁰⁻³³ Extending these observations, multiple case-control studies have found an association between ACE-I use and incidence of severe hypoglycaemia in patients with DM.³⁴⁻³⁶ Chronic administration of ACE-Is has also been associated with improved insulin sensitivity in human studies. Four months of treatment with captopril improved insulin sensitivity relative to hydrochlorothiazide (HCTZ), an effect deemed to be independent of the adverse effect of HCTZ on glucose metabolism.³⁷ In another blinded study in 436 patients, enalapril was associated with a reduction in fasting blood glucose relative to HCTZ and atenolol.³⁸ Similarly, other studies with captopril,^{39,40} cilazapril,⁴¹ delapril,⁴² enalapril,⁴³⁻⁴⁵ lisinopril⁴⁶ and trandolapril⁴⁷ have all demonstrated improved glucose metabolism and/or insulin sensitivity during long-term drug therapy. These results are not ubiquitous, however, as other clinical studies have reported negative results in non-diabetic patients with essential hypertension,⁴⁸ as well as hypertensive patients with type 2 diabetes⁴⁹⁻⁵¹ or type 1 diabetes.^{52,53}

These studies have been mostly small in size, and they vary widely in patient selection, design, methodology and end points. The effect of the drug on blood glucose was

Figure 1. Summary of the reported effect of angiotensin-converting enzyme inhibitors (ACE-Is) (A) and angiotensin receptor blockers (ARBs) (B) on incident diabetes observed in randomised clinical trials.  = randomised comparator, for studies with two comparators;  = ACE-I/ARB;  = calcium-channel blockers

Trial	Comparators	Eligibility size	Sample	Duration	Incident diabetes (%)
A. ACE-I trials					
CAPPP ⁵⁴	Captopril vs. beta-blocker and/or thiazide	Hypertensive	10,413	6.1 years	 7.3 6.5
STOP HTN-2 ⁵⁸	Beta blockers or thiazides vs. calcium channel blockers vs. ACE-I	Elderly, hypertensive	6,641	6.3 years	 10.0 9.9 9.6
HOPE ⁵⁹	Ramipril vs. placebo	High-risk patients	5,720	5.0 years	 5.4 3.6
ALLHAT ⁶⁴	Chlorthalidone vs. amlodipine vs. lisinopril	Hypertensive, age 55+, 1+ CV risk factor	14,816	4.9 years	 11.6 9.8 8.1
ANBP 2 ⁶²	HCTZ vs. enalapril	Hypertensive, ages 55-84	5,626	4.1 years	 6.6 4.5
PEACE ⁶³	Trandolapril vs. placebo	CAD and preserved EF	8,290	4.8 years	 11.5 9.8
DREAM ⁶⁵	Ramipril vs. placebo	IGT/IFG	5,269	3 years	 19.5 18.1
B. ARB trials					
LIFE ⁶⁶	Losartan vs. atenolol	HTN and LVH	7,998	4.8 years	 8 6
CHARM ⁶⁷	Candesartan vs. placebo	CHF	5,439	3.1 years	 7.4 6
SCOPE ⁶⁸	Candesartan vs. placebo	Ages 70-89 and HTN	4,342	3.7 years	 5.3 4.3

Key: CAPPP = Captopril Prevention Project; STOP HTN-2 = Swedish Trial in Old Patients with Hypertension-2; HCTZ = hydrochlorothiazide; HOPE = Heart Outcomes Prevention Evaluation trial; ALLHAT = Antihypertensive and Lipid-Lowering treatment to Prevent Heart Attack Trial; CV = cardiovascular; ANBP 2 = Australian National Blood Pressure 2 trial; PEACE = Prevention of Events with Angiotensin-Converting Enzyme Inhibition trial; CAD = coronary artery disease; EF = ejection fraction; DREAM = Effect of Ramipril on the Incidence of Diabetes trial; IGT = impaired glucose tolerance; IFG = impaired fasting glucose; LIFE = Losartan Intervention For Endpoint reduction trial; HTN = hypertension; LVH = left ventricular hypertrophy; CHARM = Effects of Candesartan in Patients with Heart Failure (CHARM) trial; CHF = congestive heart failure; SCOPE = Study on COgnition and Prognosis in the Elderly trial

often small and rarely corrected for the confounding influence of weight change and physical activity parameters, each of which may influence insulin sensitivity. The evidence from these studies does not support the conclusion that ACE-I use is associated with major changes in insulin sensitivity *in vivo* for either non-diabetic or diabetic patients with hypertension. The evidence deriving from studies of patients with impaired glucose tolerance is more convincing, however.

Large-scale clinical trials: ACE-Is

Observations from published randomised clinical trials on the effect of ACE-Is on incident diabetes are summarised in figure 1A. The Captopril Prevention Project (CAPPP) randomised nearly 11,000 hypertensive patients to treatment with captopril or conventional antihypertensive therapy

