Chapter

Renin Angiotensin Aldosterone System, Glucose Homeostasis, and Prevention of Type 2 Diabetes: Mechanistic Insights and Evidence from Major Clinical Trials

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Abstract

With its alarmingly rising prevalence worldwide, type 2 diabetes has become a leading cause of morbidity and mortality around the planet. Efforts to prevent progression to diabetes in individuals at risk could have a significant positive public health impact. Multiple trials examining cardiovascular outcomes of Renin-Angiotensin-Aldosterone System (RAAS) inhibitors revealed, in secondary analysis, a significantly reduced risk of new onset diabetes in participants receiving these agents. This glycemic protective effect is attributed to the known implication of RAAS in the development of insulin resistance and type 2 diabetes. The DREAM trial and the NAVIGATOR trial were two large randomized controlled studies examining, as primary outcome, the effect of Ramipril and Valsartan respectively on the incidence of diabetes in patients with prediabetes. Their results confirmed a favorable glycemic effect of RAAS inhibition agents and suggested a possible added benefit of diabetes prevention to their other several cardiovascular and blood pressure benefits.

Keywords: diabetes prevention, renin-angiotensin- aldosterone system, glucose homeostasis, ACE inhibitors, angiotensin receptor blockers, prediabetes

1. Introduction

Diabetes Mellitus (DM) is a chronic disease characterized by hyperglycemia due to impaired glucose regulation [1]. Glucose regulation is controlled by insulin, a protein hormone produced and secreted by the **β**-cells of the pancreas. Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and impaired **β**-cell function, eventually leading to decreased insulin secretion.

Prediabetes is the disease state which precedes the diagnosis of diabetes [2]. It is characterized by hyperglycemia caused by insulin resistance and **β**-cell dysfunction, as is type 2 diabetes, but before serum glucose levels reach that of diabetic diagnostic thresholds. Just as in diabetes, the diagnosis of prediabetes is made based on results of fasting plasma glucose, oral glucose tolerance test, Hemoglobin A1c, and/or random serum glucose levels [3]. Prediabetes can be defined by impaired fasting

glucose (IFG) with a fasting plasma glucose level 100–126 mg/dL (5.5–7.0 mmol/L), impaired glucose tolerance (IGT) with glucose level of 140–200 mg/dL (7.8–11.1 mmol/L) at 2 hours of the oral glucose tolerance test (OGTT), and/or HbA1c level of 5.7–6.5% (39–48 mmol/mol) [2, 3].

As the prevalence of diabetes continues to increase, it has become a severe public health problem worldwide. According to the World Health Organization (WHO) and International Diabetes Foundation (IDF), 451 million adults were diagnosed with diabetes worldwide in 2017, which was drastically increased from 108 million in 1980 [2–4]. This number is expected to increase to 693 million by the year 2045 [3]. According to the CDC, in 2015, approximately half (48.3%) of the adult population ages 65 and older had prediabetes [2].

With its many microvascular and macrovascular complications, diabetes contributes to a large portion of healthcare costs worldwide. In fact, approximately 850 billion USD of the global healthcare expenditure was spent on patients with diabetes in 2017 [2]. Research has shown that individuals with diabetes are at increased risk of cardiovascular disease (CVD), the leading cause of death worldwide [1]. The Framingham Heart study found that women with diabetes had a five times greater risk of heart failure, while men had two times greater risk, when compared to individuals of the same age and gender without diabetes [5]. Prediabetes has also been found to be independently associated with microvascular complications, macrovascular complications (including CVD) and increased risk of overall mortality [6, 7].

Aside from the increased risk of CVD in individuals with diabetes, an independent association between hypertension and insulin resistance has been established [8]. The Hong Kong Cardiovascular Risk Factor Prevalence Study found that of individuals with diabetes, 58% had elevated blood pressure, and of people with hypertension, 34% had impaired glucose tolerance. Only 42% of subjects studied with diabetes had normal blood pressure [9]. While the mechanism of this relationship is unclear, it has been hypothesized that patients with hypertension have impaired glucose tolerance due to changes in skeletal muscle tissue [10]. This common coexistence of hypertension and diabetes increases one's risk of CVD and events, and thus contributes to the increased risk of morbidity and mortality in these patients. Both hypertension and insulin resistance are components of the cardiometabolic syndrome, a group of interrelated abnormalities, which increase the risk for CVD and T2DM. Other related abnormalities include obesity, left ventricular hypertrophy, dyslipidemia, and albuminuria [10, 11].

Given the increasing prevalence of diabetes worldwide and its many complications, a significant effort has been made to explore preventive modalities. Studies have concluded that lifestyle interventions involving diet and physical activity reduce the risk of diabetes by greater than 50% [12]. However, the intense lifestyle modifications necessary to result in change are often difficult to implement. Bariatric surgery has been found to be an effective method of diabetes prevention and treatment. In a meta-analysis of 22,094 patients who had undergone bariatric surgery, diabetes was completely resolved in 76.8% of patients [13]. The Swedish Obese Subject Study, a prospective study of 4047 patients without diabetes who underwent gastric surgery, found that after 15 years, 392 of 1658 control patients developed diabetes compared to 110 of 1771 patients who underwent bariatric surgery ($p < 0.001$) [14]. Pharmacological agents such as metformin, thiazolidinediones, alpha-glucosidase inhibitors, and the glucagon-like peptide-1 agonist, liraglutide have been shown to prevent diabetes in those at risk [1, 15]. However, none of these agents have the added benefit of hypertension or CVD prevention and/or treatment. In fact, thiazolidinediones have been associated with an increased risk of congestive heart failure [12].

Pharmacological agents which act by inhibition of the Renin-Angiotensin-Aldosterone System (RAAS) including Angiotensin-converting enzyme inhibitors

Trial	Year	Study Population (No.)	Drug of interest	Comparison	Diabetes prevention (primary or secondary)	Results
DREAM	2006	IGT and/or IGF (5269)	Ramipril	Placebo	Primary	Non-significant decrease in new-onset DM (HR 0.91, 95% CI 0.80–1.03), Significantly increased regression of IFG and IGT to normoglycemia, decrease in OGTT 2 hr. glucose level.
NAVIGATOR	2008	IGT + > 50 y/o with CVD OR > 55 y/o with > 1 RF for CVD (9518)	Valsartan	Placebo	Primary	significantly reduced DM incidence by 14% (HR 0.86, 95% CI 0.80–0.92)
HOPE	2001	Multiple cardiovascular risk factors (9297)	Ramipril	Placebo	Secondary	significantly reduced risk of new-onset DM (RR 0.66, 95% CI 0.41–0.77)
CAPP	1999	Ages 25–66 with HTN (DBP > 100 mmHg) (10,985)	Captopril	diuretics and/or B-blocker	Secondary	significantly decreased risk of new-onset DM with captopril by 14% (RR 0.86; 95% CI, 0.74–0.99)
ALLHAT	2002	Hypertension + 1 or more CHD Risk factor (MI, stroke, LVH, T2DM, smoking, low HDL, other atherosclerotic CVD) (42,418)	Lisinopril	Chlorthalidone, amlodipine	Secondary	significantly decreased risk of new-onset DM among patients taking lisinopril (8.1%) vs. amlodipine (9.8%) and chlorthalidone (11.6%)
LIFE	2002	Ages 55–80, hypertension + left ventricular hypertrophy (9193)	Losartan	Atenolol	Secondary	significantly decreased risk of new-onset DM in patients taking losartan compared with atenolol (HR 0.75; 95% CI, 0.63–0.88; $p < 0.001$)
PEACE	2004	> 50 years, coronary heart disease with LVEF > 40% (8.290)	Trandolapril	Placebo	Secondary	significantly decreased incidence of new onset DM in patients taking Trandolapril (HR 0.83; 95% CI, 0.72–0.96; p=.01)
VALUE	2004	HTN and high CV risk (male, >50 years, DM, current smoker, high TC, LVH, proteinuria) (15,245)	Valsartan	Amlodipine	Secondary	significantly decreased incidence of new-onset DM in patients taking Valsartan compared with Amlodipine (HR 0.77; 95% CI 0.69–0.86; p<.0001)

Table 1.
Trials with diabetes prevention as a primary and secondary outcome of RAAS inhibition.

(ACE-I) and angiotensin receptor blockers (ARBs) have been observed to have a favorable glycemic effect, and are among candidates examined in recent diabetes prevention trials. While they are often utilized for their blood pressure-lowering effect, they have cardiovascular benefits as well. Specifically, ACE-I have been found to play a role in the reversal of left ventricular hypertrophy in patients with hypertension, and preventing left ventricular remodeling post myocardial infarction [16]. Thus, ACE-I are indicated as first line agents in patients with heart failure, left ventricular systolic dysfunction (LVEF < 40–45%) and those with acute coronary syndrome and after suffering from an acute myocardial infarction [16]. In patients with heart failure, ACE-I have been shown to reduce mortality, hospitalizations, and prevent worsening of heart failure in these individuals [16]. The benefits of ARBs are less well defined, however, the clinical trial Val-HeFT found treatment with ARB, valsartan, resulted in decreased morbidity and mortality in patients with heart failure, when compared with placebo [17]. Additionally, ARBs have been found to slow the progression of diabetic nephropathy thus preventing end stage renal disease (ESRD) in these patients. Two trials, IDNT and RENAAL conducted in 2001, revealed ARBs (Irbesartan and Losartan) to be effective in reducing proteinuria and slowing the progression of ESRD in patients with diabetic nephropathy, independent of their blood-pressure lowering effect [18, 19].

Given these benefits, RAAS inhibitors are often first line agents for treating patients with concomitant hypertension and diabetes and those at risk for CVD. Several studies to date suggest that ACE-I and ARBs have the ability to improve glycemic control by improving insulin sensitivity. **Table 1** provides a brief description of the studies and their findings. This chapter explores the possibility of utilizing RAAS inhibitors as a means of diabetes prevention and/or improved glucose tolerance and the potential mechanisms by which this could be accomplished.

2. RAAS and glucose homeostasis

The renin-angiotensin-aldosterone system (RAAS) is responsible for regulating arterial blood pressure and blood volume [20, 21]. Renin, an enzyme produced by the juxtaglomerular cells in the kidney in response to low blood pressure or decreased sodium delivery to the kidneys, converts angiotensinogen to angiotensin I. Angiotensin converting enzyme (ACE), found in the lungs and kidneys, then converts angiotensin I to angiotensin II (AG II). Angiotensin II is the predominant hormone responsible for the hemodynamic effects of RAAS, namely: sodium retention at the proximal convoluted tubules of the kidneys, arterial vasoconstriction, and release of aldosterone from the adrenal glands [22]. Angiotensin II is also responsible for the non-hemodynamic effect of RAAS related to glucose hemostasis [21, 23]. Several studies have suggested the role of RAAS in the development of insulin resistance and subsequent development of type 2 diabetes mellitus (T2DM) in humans. The pathophysiology is complex, mostly involving the skeletal muscle, adipose tissue, and pancreas [21] (**Figure 1**).

1. **RAAS and the skeletal muscle:** AG II affects glucose metabolism in the skeletal muscle through the inhibition of insulin-mediated glucose uptake and insulin signaling pathway, and a decrease in the blood supply to the skeletal muscle [21].

   Inhibition of insulin-mediated glucose uptake and insulin signaling pathway. The skeletal muscle accounts for up to 70% of insulin-mediated glucose uptake in the body, which occurs through a series of tightly regulated events in the insulin signaling pathway [23, 24]. First, insulin binds to the insulin receptor on the

surface of the skeletal muscle cell, and this activates a cascade of events that ultimately ends in translocation of the glucose transporters (GLUT-4) from intracellular vesicles to the cell membrane through which glucose is taken up by the cells [23, 24]. Therefore, inhibition at any stage in the signaling pathway will result in insulin resistance with subsequent type 2 diabetes development if left unresolved. By acting through the angiotensin II type 1 receptor (AT_1R), AG II activates NADPH oxidase, which leads to the production of reactive oxygen species that in turn inhibits insulin-mediated translocation of GLUT-4 transporters, glucose uptake, and insulin signaling pathway in the skeletal muscle [23, 24].

Decrease in the blood supply to the skeletal muscle. Studies also show that AG II contributes to insulin resistance by decreasing microvascular blood supply to the skeletal muscle [21].

2. **RAAS and the adipose tissue:** Studies have shown that local RAAS present in adipose tissue affects adipocyte differentiation through angiotensin II's action on its AT_1R receptor [21], but there are conflicting views on the exact mechanism. For example, some studies suggest that AG II inhibits adipocyte precursor differentiation, thereby decreasing the number of insulin-sensitive adipocytes leading to insulin resistance [25]. In contrast, other studies indicate that AG II stimulates adipocyte differentiation and causes an increase in adipocyte size in visceral adipose tissue leading to obesity and insulin resistance [21].

3. **RAAS and the pancreas:** Increased activity of local pancreatic RAAS is associated with impaired glucose metabolism. By acting through the AT_1R receptor, AG II decreases insulin secretion, impairs blood flow to the pancreatic islet cells, and causes inflammation and fibrosis of the pancreas, leading to impaired glucose tolerance [21].

In summary, through its different effects on the skeletal muscle, adipose tissue, and pancreas, RAAS is thought to contribute to the development of insulin resistance and development of type 2 diabetes. Therapy with RAAS inhibitors has been

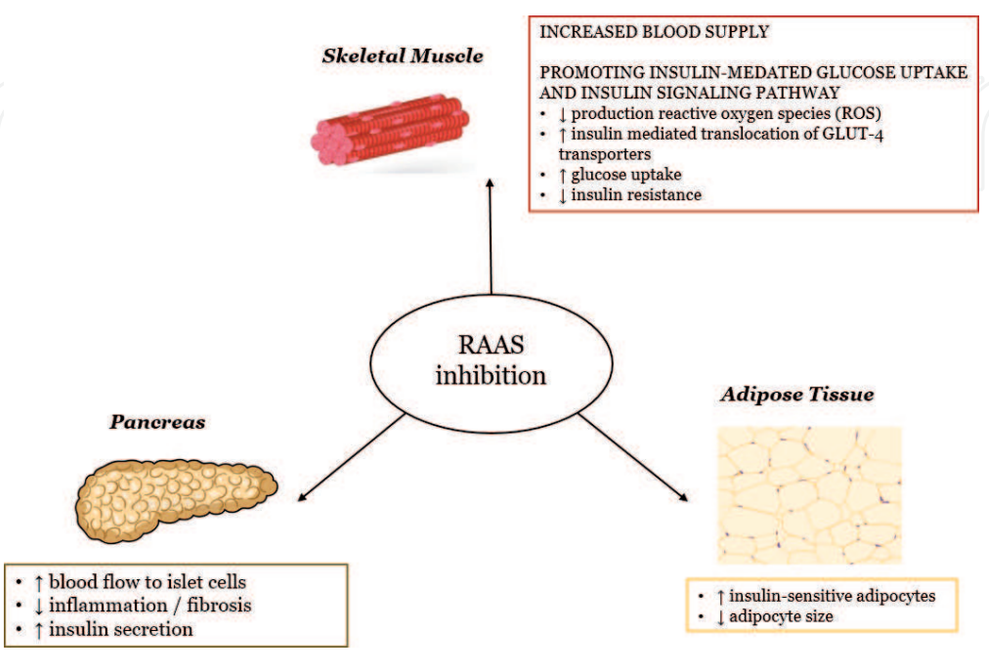

Figure 1.
Potential mechanisms implicated in favorable glycemic effect associated with RAAS inhibition.

indeed associated with favorable glycemic events. At a clinical level, several trials have examined the role of RAAS inhibition in preventing the development of type 2 diabetes in the population at risk.

3. Diabetes prevention as a secondary outcome of RAAS inhibition trials

There have been a number of trials conducted in which the primary aim was to study the effect of RAAS inhibitors on CVD and events. In addition to this primary outcome of interest, a number of these trials have found positive results with regards to their effect on diabetes prevention and improved glucose tolerance.

One of the first clinical trials to demonstrate a protective effect of RAAS inhibition on the incidence of diabetes was the Captopril Prevention Project (CAPPP) initiated in 1999. The primary aim of this trial was to compare the effect of ACE inhibition (using captopril) with conventional therapy (**β**-blockers and/or diuretics) on risk of CVD morbidity and mortality in patients with hypertension [26]. While there was no difference in prevention of cardiovascular morbidity and mortality in those treated with captopril compared with conventional therapy, authors did find that the incidence of new onset diabetes was lower in participants treated with captopril [26]. This finding supports the theory that ACE inhibition may work to prevent the development of diabetes, which may be due to captopril's ability to improve insulin sensitivity [26]. Additionally, those patients with diabetes at baseline who were treated with captopril had a lower rate of cardiovascular events and mortality when compared to those with diabetes treated with conventional therapy [26].

Another study, the Heart Outcomes Prevention Evaluation (HOPE) study, sought to explore the role of the ACE inhibitor, ramipril, on the incidence of myocardial infarction (MI), stroke, or all-cause mortality in patients with a history of vascular disease (coronary artery disease, stroke, peripheral vascular disease) or diabetes, plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or microalbuminuria), but without heart failure or any degree of left ventricular dysfunction [27]. Subjects were randomized to receive ramipril or placebo, both with the addition of 400 IU of vitamin E daily [27]. Of the primary outcomes examined, patients treated with ramipril had a significantly decreased risk of myocardial infarction, stroke, or death from cardiovascular causes (RR 0.78, 95% CI 0.70–0.86). Of the participants without a diagnosis of diabetes at study onset, there was a 34% decreased incidence of new onset diabetes in those treated with ramipril compared with placebo (RR 0.66, 95% CI 0.34–0.76) [27]. Of note, these results are consistent with the study to Evaluate Carotid Ultrasound changes in patients treated with ramipril and vitamin E (SECURE), which reported decreased fasting glucose levels in patients treated with ramipril when compared with placebo [28].

Another trial, the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), randomized participants aged 55–80 years with hypertension and electrocardiographic left ventricular hypertrophy (ECG LVH) to either losartan or atenolol [29]. The primary aim of this trial was to determine whether losartan improves LVH and thus reduces cardiovascular morbidity and mortality. Results revealed that those participants who received losartan had a decreased risk of cardiovascular events (MI and stroke), and 25% decreased risk of new onset DM when compared with atenolol (HR 0.75, 95% CI 0.63–0.88, p 0.001) [30]. It is possible that the protective effect of losartan on diabetes incidence seen in the LIFE trial could be due to the detrimental effects of atenolol, a **β**-blocker, on insulin sensitivity [10].

The presence of diabetes has been found to be associated with increased left ventricular hypertrophy, both of which are risk factors for the cardiometabolic syndrome [29]. The initial analysis of the LIFE trial found that individuals treated with losartan had an increased regression of LVH when compared to those treated with atenolol. However, patients with diabetes and LVH had less regression than those without diabetes, possibly secondary to their predisposition [29]. A secondary analysis was conducted on the participants without diabetes at baseline, which sought to determine whether in-treatment resolution or continued absence of ECG LVH is associated with decreased risk of developing diabetes [29]. This analysis revealed a 38% decreased incidence of DM in those who had resolution or continued absence of LVH (HR 0.62, 95% CI 0.50–0.78, $p < 0.001$) independent of the previously identified effects of treatment with losartan versus atenolol. This finding suggests that while DM might lead to LVH, it is possible that LVH may in fact precede the development of diabetes [29]. While the causality of this relationship is uncertain, this study proposes the idea that regression of LVH by means of RAAS inhibition might decrease the risk for DM. However, it is also possible that this observed relationship between LVH regression and decreased incidence of DM can be explained by the established association between hypertension and insulin resistance. This idea aligns with the finding that participants of the LIFE trial who developed diabetes had higher baseline systolic and diastolic blood pressures than those who did not [29].

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial, the primary aim was to compare the effectiveness of treatment with diuretic, chlorthalidone against calcium channel blocker, amlodipine and ACE-I, lisinopril in preventing coronary heart disease (CHD) or other cardiovascular events in patients with hypertension and at least one CHD risk factor [31]. As far as primary outcome of interest, chlorthalidone was found to be superior to the others in preventing the primary outcome. However, study participants on lisinopril were found to have a lower incidence of diabetes at the follow up period of four years, when compared to those placed on other antihypertensives [31].

Similarly, the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial sought to determine whether treatment with another ACE-I, trandolapril in patients with stable CAD and left ventricular ejection fraction (LVEF) > 40% would reduce cardiovascular deaths, incidence of MI or need for percutaneous coronary intervention (PCI) when compared with treatment with placebo [32]. Although a secondary end point, results from this trial revealed that the incidence of new onset DM was significantly decreased in those treated with trandolapril when compared to those in the placebo group (HR 0.83, 95%CI 0.72–0.96, $p=0.01$) [32]. Results from the PEACE trial, similar to the HOPE trial are important because they cannot be attributed to the adverse effects of the comparison drug (placebo).

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial compared coronary heart disease outcomes in patients with hypertension treated with valsartan or amlodipine [33]. While there were no differences in primary composite outcome of cardiovascular morbidity and mortality in either group, secondary analysis revealed that new-onset DM occurred significantly less in patients treated with valsartan [33]. Despite the observed decreased incidence of diabetes with valsartan use, blood pressure reduction was less in this group, compared to those treated with amlodipine, which suggests that the effect of ARBs on diabetes prevention is independent of blood pressure reduction [34].

While each of the above trials found treatment with ACE-I and ARBs to be associated with decreased incidence of new onset diabetes, it must be noted that diabetes prevention was not a defined primary outcome in any of these studies.

Thus, their results must be interpreted with caution. A few other weaknesses should be taken into consideration on review. Some of these trials, including the HOPE and PEACE trials did not perform formal glucose testing to establish glycemic status, and relied on self-report alone [32, 35, 36]. Additionally, the HOPE, CAPP, and LIFE trials all utilized **β**-blockers as comparator drugs, which allows for the possibility that the observed effect of therapy with ACE-I or ARB on diabetes prevention is due to the detrimental effects of B-blockers on development of diabetes rather than the benefits of RAAS inhibition. A large prospective cohort study (n=12,550) conducted in 2000 revealed that hypertensive patients taking **β**-blockers had a 28% increased risk of diabetes when compared to those who were not on any antihypertensive therapy [37].

4. DREAM and NAVIGATOR trials

Studies including the aforementioned trials showed a beneficial effect of RAAS inhibition with ACE-I and ARBs on diabetes prevention among patients with hypertension and other cardiovascular diseases [30, 35, 38, 39]. These trials studied diabetes prevention as a secondary outcome or post hoc analysis, thus the results should be interpreted with caution. Conversely, the DREAM and NAVIGATOR trials, conducted in 2006 and 2008, respectively, are double blind, randomized clinical trials, which were designed to determine the effect of RAAS inhibition on the incidence of diabetes as a primary outcome [40, 41]. Furthermore, in these two trials, glycemic categories were meticulously determined, defined and recorded. In both studies, DM was defined using standard criteria, fasting blood glucose (FBG) 126 mg/dl or 200 mg/dl post oral glucose load and confirmed again at a later date. In the DREAM study, even in the event that diabetes was diagnosed by an outside physician, confirmation of the diagnosis using standard plasma glucose criteria was required in addition to the prescription of an antidiabetic agent by the diagnosing physician [40].

The DREAM trial was designed to investigate the effect of ramipril, an ACE-I and rosiglitazone, a thiazolidinedione, on diabetes prevention among patients with prediabetes (IGT and/or IFG) but without cardiovascular disease. The primary outcome of this study was newly diagnosed diabetes or death, with a secondary outcome of regression to normoglycemia defined as normal fasting and 2 hour post-load glucose levels [40]. Data analysis revealed no significant difference in the development of diabetes in the ramipril group when compared to the placebo group (HR 0.91, 95% CI 0.80–1.03) [40]. However, the likelihood of regression to normoglycemia was increased among subjects within the ramipril group when compared to the placebo group (HR 1.16, 95% CI 1.07–1.27). Moreover, while the fasting plasma glucose levels did not differ between the ramipril and the placebo group at the end of the trial, the 2 hour post glucose oral load values were significantly lower among those within the ramipril group [40].

There are a number of possible explanations for the lack of reduction in DM incidence with ramipril use in the DREAM trial which was different from the results found in previous trials with ACE-I/ARBs. First, as mentioned, diagnosis of diabetes at study onset was unambiguously established in participants of the DREAM trial with an oral glucose tolerance test (OGTT), thus patients with pre-existing DM were reliably excluded from the study [40]. This was not the case for some of the other studies mentioned previously [35, 42]. Second, the demographics of the DREAM study patients differed from those of trials which showed a reduced incidence of DM with RAAS inhibitors. Compared to the participants of the DREAM trial, subjects from the other trials were older, and had established CVD, and/or

heart failure [30, 35, 36, 43, 44]. It is possible that the RAAS system is activated to a greater extent and thus ACE inhibition may have greater benefits in these individuals [45]. Third, some of the trials that revealed reduced incidence of DM among those treated with ACE-I/ARBs had compared ACE-I with other anti-hypertensives associated with dysglycemia, such as **β**-blockers, as mentioned previously. This may have led to a possible exaggeration of the effect of RAAS inhibition on diabetes prevention. Fourth, most of the previous trials that showed a beneficial effect of ACE-I And ARB on DM prevention followed the patients for longer period of time than the median 3 years that the participants of the DREAM trial were followed for [30, 32, 35, 39, 43]. Specifically, the participants of the HOPE trial were followed for 4.5 years, the PEACE trial for 4.8 years, ALLHAT study for 4.9 years, and the LIFE study for 4.8 years [30, 32, 35, 39]. In the DREAM trial, there was a late diversion of the Kaplan–Meier curves that suggested a benefit of ramipril in DM prevention after 3–5 years. Thus, it is possible that a longer and larger study may be needed to observe the effect of ramipril on DM prevention [45].

Four years after the publication of the results of the DREAM trial, the results of another trial, the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, were released [41]. This study also sought to investigate the effect of RAAS inhibition with the ARB, valsartan in addition to lifestyle modification on diabetes prevention in patients with impaired glucose tolerance and established CVD or CVD risk factors.

The NAVIGATOR trial was an improvement over the DREAM trial in several ways. First, a study-specific lifestyle-intervention program, which has previously been found to reduce risk of diabetes by up to 50%, was implemented for all patients in addition to pharmacotherapy [46, 47]. Second, there was a longer median follow up of 5 years in the NAVIGATOR trial compared with the 3 years follow up in the DREAM trial [40, 41]. Third, the NAVIGATOR trial enrolled a larger number of participants, 9306, versus 5269 participants in the DREAM trial. Another difference between these studies is that, unlike the DREAM trial, the NAVIGATOR trial enrolled patients with established CVD or CVD risk factors, who may have a greater degree of RAAS activation at baseline.

With these differences in mind, it is not surprising that while the DREAM trial found no difference between the ramipril and placebo groups with regards to diabetes prevention, the NAVIGATOR trial found that those treated with valsartan had a significantly reduced incidence of DM by 14% (HR 0.86, 95% CI 0.80–0.92, $p< 0.001$). Furthermore, patients in the valsartan arm of the study had lower mean fasting plasma glucose and 2 hours post glucose load levels. Additionally, the proportion of patients taking glucose lowering agents at the end of the study was lower in the valsartan group than in those in the placebo group.

Although significant, the 14% reduction in diabetes risk with valsartan appears smaller than the risk reduction seen in previously conducted trials involving ACE-I and ARBs [32, 35, 36, 44, 48]. One possible reason is that by the last study visit, a significantly higher proportion of subjects in the placebo arm were taking other ARBs or ACE-I (24.4% vs. 21.8%), which could have diluted the effect seen with valsartan. Another reason for this observed discrepancy could be due to a difference in the way in which glycemic status was determined at study onset and completion. Unlike the NAVIGATOR trial, a few other trials diagnosed DM by self-report rather than formal glucose testing which allows for misclassification error and possible false exaggeration of results [35].

In addition, the effect of valsartan with lifestyle modification was much smaller compared to landmark studies on diabetes prevention with lifestyle alone in which the incidence of DM was reduced by as much as 58% [46, 47, 49]. Similarly, the effect of valsartan on diabetes prevention in the NAVIGATOR trial is smaller when

compared to glucose lowering agents such as metformin, 26–31% [46, 50], acarbose 25% [51] and rosiglitazone 60% in the DREAM study [52]. It is worthy of note that the NAVIGATOR trial followed the subjects for a longer duration (5 years) compared to the trials involving these glucose lowering agents in which subjects were followed for 2.5–3.3 years.

In conclusion, the DREAM and NAVIGATOR trials showed benefit in glycemic indices but only the NAVIGATOR trial showed a reduced diabetes incidence as a primary outcome of RAAS inhibition with ACE-I and ARBs. These findings may have utility in the clinical setting, in terms of choice of antihypertensive agents to those at higher risk of DM development, in the presence or absence of CVD and its risk factors.

5. Conclusion and clinical implications

ACE-I and ARBs are currently widely used for the treatment of patients with hypertension, heart failure or asymptomatic left ventricular dysfunction, coronary artery disease, and diabetic nephropathy, with the clinical benefits of ACE-I more closely studied [53]. Based on the results from the aforementioned trials, the use of these agents may also be indicated for the prevention of diabetes and/or regression from impaired to normoglycemia. This is extremely significant in light of the emerging diabetes epidemic.

While it is not entirely clear, results from the trials explored throughout this chapter suggest that those with cardiometabolic syndrome and its risk factors including (but not limited to) hypertension, obesity, insulin resistance, and left ventricular hypertrophy may experience the greatest benefits with regards to diabetes prevention and improved glycemic control. This could be due to the fact that the RAAS system is overactive in a number of these conditions. As discussed, activation of the RAAS system and increased production of angiotensin II is thought to play a role in the development of insulin resistance and subsequent development of T2DM [21]. It is also possible that the ability of ACE-I and ARBs to prevent diabetes is in part due to their effect on blood pressure reduction and LVH regression, both of which have been shown to improve insulin sensitivity [29].

However, while results from the CAPPP trial found a decreased incidence of new onset DM in patients treated with captopril, the blood pressure of patients in this group was significantly higher throughout the study than those treated with conventional therapy with **β**-blocker and/or diuretics. This supports the hypothesis that captopril's effect on diabetes prevention might be independent of blood pressure reduction. Results from the sub-analysis of the LIFE trial suggests that the effect of RAAS inhibition with losartan on LVH regression may be partly responsible for the decreased incidence of DM. It is possible that this association is also explained in part by the relationship between blood pressure and insulin resistance [29]. In conclusion, the apparent decreased incidence of new onset diabetes seen in patients treated with ACE-I and ARBs are likely attributable to both direct and indirect effects of these agents.

Given the variety of indications for which RAAS inhibitors have been established, the additional benefit of diabetes prevention could help to alleviate polypharmacy in individuals who suffer from several of these conditions simultaneously. However, more research is needed to categorically place ACE-I and ARBs among the armamentarium of agents favoring DM prevention. Head to head studies comparing the effects of different ACE-I and ARBs would also be useful.

DOI: http://dx.doi.org/10.5772/intechopen.97737

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