

# An eBook on Type 2 Diabetes

## Chapter 5

# Antidiabetic Effects of Antihypertensive Drugs

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**Abbreviations:** ACEIs: Angiotensin converting enzyme inhibitors; AngI: Angiotensin I; AngII: Angiotensin II; ARBs: Angiotensin receptor blockers; AT1R: Angiotensin II type 1 receptor; AT2R: Angiotensin II type 2 receptor; DN: Diabetic nephropathy; eNOS: Endothelial nitric oxide synthase; GLUT2: Glucose transporter 2; GLUT4: Glucose transporter 4; GSH: Glutathione; MDA: Malondialdehyde; NAD(P)H: Nicotinamide adenine dinucleotide phosphate; NO: Nitric oxide; NS: Noradrenergic system; PAI-1: Plasminogen activator inhibitor-1; (P)RR: (Pro) renin receptor; RAAS: Renin angiotensin aldosterone system; ROS: Reactive oxygen species; RR: Renin receptor; SOD: Superoxide dismutase; STZ: Streptozotocin; TGF- $\beta$ : Transforming growth factor- $\beta$ ; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ .

## 1. Introduction

Hypertension and type 2 diabetes frequently occur together, and because both of these conditions predispose patients to cardiovascular and renal diseases, the diabetic hypertensive patient is at an especially elevated risk of developing adverse clinical events. This chapter discusses the most useful antihypertensive drugs with antidiabetic effects for managing these challenging patients.

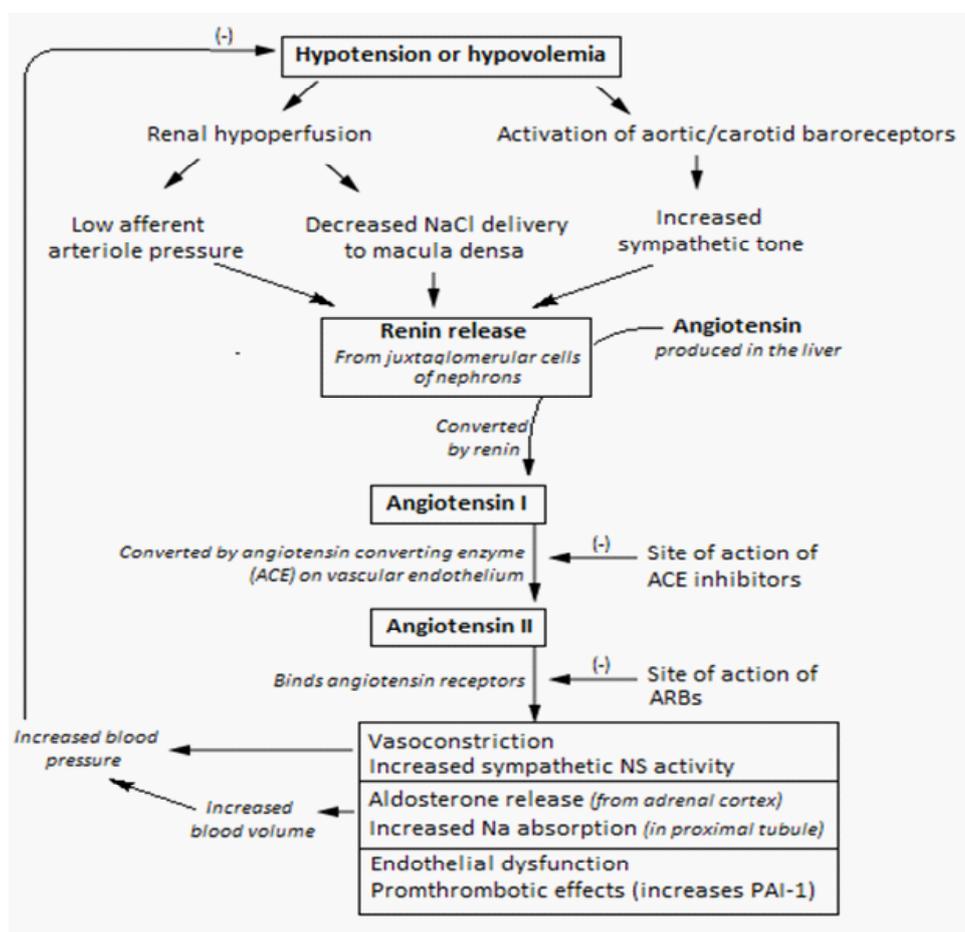
## 2. Renin Angiotensin Aldosterone System (RAAS)

Classically, RAAS is known for its role in body fluid and cardiovascular homeostasis. RAAS consists primarily of an enzymatic cascade through which angiotensinogen (Ang) is converted to angiotensin I (Ang I), which is then converted to angiotensin II (Ang II), through the action of renin and the angiotensin converting enzyme (ACE) respectively [1]. Ang II mediates its specific functions via type 1 and type 2 receptors, i.e., Angiotensin type 1 receptor (AT<sub>1</sub>R) and Angiotensin type 2 receptor (AT<sub>2</sub>R). Most of these functions are mediated by AT<sub>1</sub>R, including the potent vasoconstriction, proinflammatory, pro-oxidative, proliferative and

hypertrophic effects. Moreover, advances in cell and molecular biology have allowed the recognition of other active elements of the RAAS metabolism [1].

Over the past few years, RAAS components have been found in almost every tissue, including the heart, blood vessels, kidney, brain, pancreas, adipose tissue and skeletal muscles [2]. Furthermore, a large body of evidence indicates that RAAS activation is closely correlated to both insulin resistance and beta cell dysfunction [3].

The mechanism behind this deleterious effect appears to be related to the negative regulation, exerted by Ang II through AT<sub>1</sub>R, of several steps of the insulin signaling cascade. In addition, hyperglycemia increases the expression of RAAS components in pancreatic islets, which leads to insulin secretion modulation in beta cells, decreased adiponectin level, impaired insulin sensitivity in target tissues, inhibited glucose transporter 4 translocation and increased levels of reactive oxygen species, inflammation, and ectopic fat storage [4].



**Figure 1:** Flowchart showing the clinical effects of RAAS and the sites of action of ACEIs and ARBs [5].

The increase in the ACE2/Ang/Mas receptor axis could be associated with diminished insulin resistance by inducing the activation of insulin signaling pathways and counteracting the inhibitory effects of ACE/Ang II/AT1R. ACE2 gene therapy improves glycemic control in diabetic mice through a mechanism mediated by the Ang/Mas receptor because of its proven ability to potentiate the action of bradykinin [2,6].

There is an evidence that bradykinin itself may have an effect on enhancing insulin ac-

tion and signaling. Moreover, it is remarkable to note that, together with results from the beta cell injury studies, bradykinin stands out the key role in the pancreatic-duodenal homeobox 1 in prenatal development of the pancreas, as well as in the postnatal maintenance of the insulin production, and the glucose transporter 2(GLUT2) expression [7].

### **3. Antidiabetic Mechanisms of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists:**

Growing concern about the increasing prevalence of the metabolic syndrome and type 2 diabetes has generated substantial interest in the metabolic effects of antihypertensive drugs. Historically, most of the focus has been on disturbances in carbohydrate and lipid metabolism associated with diuretics and beta- adrenergic receptors antagonists [8,9,10].

However, the results of several large-scale clinical trials have recently begun to shift attention to the possibility that some of the newer antihypertensive agents may not only cause fewer metabolic side-effects than diuretics and beta- adrenergic receptors antagonists, but may also decrease the overall risk for type 2 diabetes. Given the morbidity and mortality associated with type 2 diabetes and hypertension, the availability of drugs that have antidiabetic as well as antihypertensive properties could be of considerable clinical value [11,12,13].

Antidiabetic effects of interrupting the RAAS in-vitro and in-vivo experiments as well as in humans have suggested a possible relationship between the RAAS and the pathogenesis of insulin resistance. For example, studies have suggested that AngII may promote impaired glucose metabolism through its effects on insulin signaling pathways, tissue blood flow, oxidative stress, sympathetic activity and adipogenesis [14,15,16].

Thus, pharmacologic interruption of RAAS with ACE inhibitors (ACEIs) or Ang II receptor blockers (ARBs) might improve glucose metabolism by interfering with AngII generation or AngII receptor activation. These observations have begun to motivate clinical trials designed to investigate whether drugs that interrupt the RAAS can ward off the development of type 2 diabetes. Indeed, given some of the evidence accumulated to date, it is possible that pharmacologic interruption of the RAAS may someday prove to be capable of improving insulin sensitivity and decreasing the risk for diabetes. Studies on animal models and in small- and large-scale clinical trials have suggested that ACEIs may have the capacity to increase insulin sensitivity and/or to decrease the risk of type 2 diabetes [14,16,17].

Although the data are not conclusive, the results of these studies have been sufficiently interesting to motivate trials to investigate the ability of ACEIs to decrease the incidence of new-onset type 2 diabetes as a primary end-point [10,18]. Studies have suggested that the antidiabetic properties of ACEIs may be largely mediated through increases in bradykinin levels, nitric oxide and the GLUT4 glucose transporter [14,19,20].

For example, metabolic studies in animals lacking bradykinin B2 receptors and in animals treated with both an ACEI and a bradykinin antagonist strongly suggest that the insulin-sensitizing effects of ACEIs involve more than just reductions in Ang II levels [14,20]. Increases in bradykinin levels stemming from converting enzyme inhibition may improve glucose metabolism by affecting insulin signaling pathways, nitric oxide production and translocation of GLUT4 [19,21].

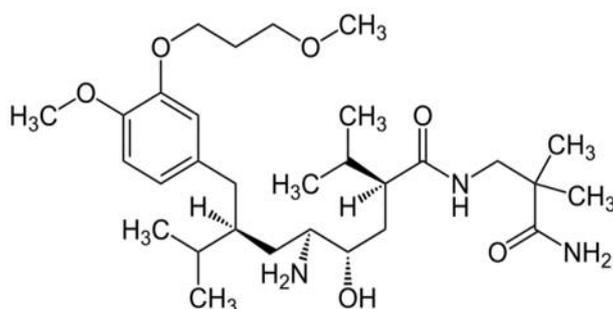
To the extent that the antidiabetic effects of ACEIs are secondary to interference with Ang II-dependent mechanisms that promote insulin resistance, one might expect ARBs to be similarly as effective as ACEIs, if not more effective; in improving insulin resistance and preventing type 2 diabetes. Paolisso et al., (1997) [22] reported that losartan-induced increases in whole-body glucose disposal were correlated with losartan-induced increases in femoral artery blood flow. However, few head-to-head comparisons have been made of the insulin-sensitizing effects of ACEIs versus ARBs and, to date, no large-scale clinical trials have compared the ability of ACEIs and ARBs to decrease the risk for diabetes [23,24,25].

Some investigators have also suggested that the inhibitory effects of AngII on insulin-signaling pathways may not be mediated by either type 1 or type 2 Ang II receptors and that another type of Ang receptor may be involved [26].

Clinical trials using ARBs have provided some indirect support for the possibility that Ang II receptor blockade per se may improve insulin sensitivity and decrease the incidence of type 2 diabetes [27].

Interventions that inhibit the activity of the RAAS like ACEIs or ARBs are renoprotective and slow progression of chronic nephropathies in animals and patients. But they have little effect on basal glucose and insulin levels, in animals without diabetes [28].

#### 4. Aliskiren



(2S,4S,5S,7S)-5-amino-N-(2-carbamoyl-2,2-dimethylethyl)-4-hydroxy-7-{{4-methoxy-3-(3-methoxypropoxy)phenyl}methyl}-8-methyl-2-(propan-2-yl) nonanamide

**Figure 2:** Chemical structure of aliskiren

Aliskiren (trade names Tekturna, US; Rasilez, UK and else where) is the first in a class of drugs called direct renin inhibitors. Its current licensed indication is essential (primary) hypertension [29].

#### **4.1. Mechanism of action**

Renin, the first enzyme in RAAS, plays a role in blood pressure control. It cleaves Ang to Ang I, which is in turn converted by ACE to AngII. AngII has both direct and indirect effects on blood pressure. It directly causes arterial smooth muscle to contract, leading to vasoconstriction and increased blood pressure. Ang II also stimulates the production of aldosterone from the adrenal cortex, which increases water and sodium reabsorption, thereby increasing plasma volume, and blood pressure. Aliskiren binds to renin and prevents the conversion of Ang to Ang I [30].

#### **4.2. Superiority of aliskiren over ACEIs**

The administration of ACEIs results in a fall in plasma AngII levels, the efficacy of ACEIs is probably limited by their inability to completely block ACE and the generation of AngII through other enzymatic pathways. However, ACEIs have other effects including interference with the breakdown of bradykinin. Long term ACEIs use is associated with a return in circulating Ang II levels following a rise in plasma renin and AngI due to the interruption of AngII feedback on renin release [31].

On the other hand, aliskiren does not affect bradykinin production and should theoretically block the actions of AngII at the AT-1R level [31].

Clinical studies indicated that aliskiren may be as effective as ACEIs and have fewer side effects. ACEIs can induce cough in susceptible individuals as a result of the increase bradykinin level. Aliskiren serves as a very good substitute for such patients [32].

Aliskiren's ideal pharmacokinetics parameters, should be considered as added advantages [33].

In a recent study (Mahfoz et al., 2016) [34] treatment with aliskiren for one month after induction of diabetic nephropathy (DN) by Streptozocin (STZ) resulted in euglycemia and normalized serum insulin concentration as compared to diabetic control rats. This effect was supported by the in-vitro study in which aliskiren resulted in dose dependent stimulation of insulin secretion from isolated rat pancreatic islets. In addition, aliskiren synergized gliclazide-induced insulin secretion in this in-vitro study. Furthermore, aliskiren normalized serum adiponectin concentration as compared to diabetic control rats, which was associated with decreased insulin resistance.

Authors assigned the observed antidiabetic effect of aliskiren to its ability to stimulate insulin secretion or decreased insulin resistance by normalizing serum adiponectin level, antioxidant or anti-inflammatory mechanisms.

Gandhi et al. (2013) [35] found that diabetic rats experienced approximately 81 % decrease in serum insulin content. However, aliskiren treatment significantly reduced blood glucose in diabetic rats. Authors explained improved insulin sensitivity effect of aliskiren by higher liver and muscle glucotransporter expression levels. In addition, Habibi et al. (2008) [36] demonstrated that renin inhibition by aliskiren attenuated insulin resistance in transgenic Ren2 rats that overexpress renin. Sun et al. (2011) [37] found an improvement in insulin resistance and lipid profile, as well as a direct antifibrotic effect in target organs in db/db mice after aliskiren treatment. Thus, a possible link between direct renin inhibition by aliskiren and insulin was suggested.

Antidiabetic effects of aliskiren treatment resulted in a renoprotective effect which was manifested by drug's ability to normalize blood urea nitrogen (BUN) and serum creatinine concentration.

Stanton et al. (2003) and Schernthaner et al. (2008) [39,40] reported that inhibition of the rate-limiting step in the RAAS (conversion of Ang to Ang I via renin) by aliskiren which leads to potent renoprotective effect is not only caused by blocking the generation of Ang II, but also by inhibiting the effects produced via activation of (Pro) renin Receptor (P) RR. Also, aliskiren can decrease the gene expression of (P) RR, and can alter the 3-dimensional configuration of renin [40].

Although renin has been considered as the enzyme responsible for the formation of AngI and has been thought to have no direct biological actions, recent studies demonstrated that it plays a pivotal role in the development of DN by binding to (P) RR in glomerular mesangial cells [40,41]. In addition to this aliskiren was reported to improve glomerular filtration in previous studies [42,43].

Mahfoz et al., (2016) [34] reported that treatment with aliskiren resulted in antioxidant effects which was manifested by significant decrease in renal malondialdehyde (MDA) level, serum Nitric oxide (NO) concentration, increase in glutathione (GSH) level and superoxide dismutase activity (SOD). This suggests that aliskiren's renoprotective effect could be explained via combating oxidative stress generated by STZ. The antioxidant effect of aliskiren is similar to the findings of earlier studies [44,45,46]. Authors suggested that increased GSH level during aliskiren treatment might be due to up-regulation of enzymatic/non enzymatic antioxidants effects or decreased reactive oxygen species (ROS) production. Aliskiren was found to decrease the NO level, which could be explained through an increase in the renal expression of nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase and endothelial nitric

oxide synthase (eNOS), thereby decreasing systemic and renal oxidative stress as proposed by Sonta et al., (2005) [47].

Beside the antioxidant potential, aliskiren reduced some inflammatory biomarkers level indicating its anti-inflammatory activity and this is consistent with its renoprotecting action. This was manifested by significant decrease in kidney tumor necrosis factor –  $\alpha$  (TNF- $\alpha$ ) and transforming growth factor –  $\beta$  (TGF- $\beta$ ) level in diabetic rats [34].

## 5. Conclusion

1. It could be concluded that some antihypertensive drugs which affect the RAAS have antidiabetic effects.
2. These drugs can synergize the effect of antidiabetic drugs. Thus the dose of antidiabetic drug may be reduced in combination therapy which may reduce the occurrence of side effects. However, further clinical studies are recommended to investigate the potential of combined therapy in diabetes mellitus.

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