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**Review / *Derleme***

# Direct Inhibition of Renin

*Direk Renin İnhibisyonu*

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From the beginning of the history of renin angiotensin system (RAS) with the renal extracts in 1898 it still continues to be exciting. After angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs), direct renin inhibitors (DRI) recently entered the RAS arena. With the increasing evidence, RAS inhibition is an important treatment strategy in hypertension. Results of ongoing and future clinical trials with specific populations and focusing on protection of end-organ damage will enrich our knowledge and understanding on direct renin inhibition.

*Key words:* Renin angiotensin system; direct renin inhibitors; aliskiren; plasma renin activity.

Renal ekstraktlar ile renin anjiotensin sisteminin 1898'de ortaya konmasıyla başlayan tarihi süreci hala şaşırtıcı olmaya devam ediyor. Anjiyotensin dönüştürücü enzim inhibitörleri (ACEI) ve anjiyotensin reseptör blokerlerinden (ARB) sonra, son zamanlarda direkt renin inhibitörleri (DRI) de renin anjiyotensin alanına girdi. Giderek artan kanıtlarla, renin anjiotensin sistemi inhibisyonu hipertansiyon tadevisinde önemli bir tedavi stratejisidir. Özgün hasta grupları üzerinde ve son organ hasarını korumaya odaklanan sürmekte olan ve gelecekte yapılacak klinik calışmaların sonuçları, direkt renin inhibisyonu hakkındaki bilgi birikimimizi ve anlayışımızı zenginleştirecektir.

*Anahtar sözcükler:* Renin anjiyotensin sistemi; direkt renin inhibitörleri; aliskiren; plazma renin aktivitesi.

## BRIEF HISTORY OF THE RENIN ANGIOTENSIN SYSTEM

The history of the renin angiotensin system (RAS) began in 1898 with the studies made by Tigerstedt, a Finnish professor of physiology working at the Karolinska Institute, and his assistant Bergman. They reported the pressor effect of renal extracts and named the renal substance renin based on its origin. After the first successful experiment performed by Goldblatt et al. in 1934 inducing the experimental hypertension in the dog by the partial constriction of the renal artery using a silver clip, their technique led to the discovery of the active polypeptide. Two research groups from the University of Buenos Aires, Argentina and Eli Lilly Research Laboratories in Indianapolis working independently, simultaneously reached similar conclusions on this matter. In Buenos Aires, it was called hypertensin; in the United States, angiotonin. Then after years Eduardo Braun Menéndez from Argentina and Irving H. Page from the United States agreed to name it angiotensin. By 1956, the renin–angiotensin system was pretty well worked out.[1,2]

## DRUGS IN THE ARENA OF RAS INHIBITION

Clinical intervention in the RAS was first achieved with the introduction of Angiotensin Converting Enzyme (ACE) inhibitors, developed in the 1970s and 1980s. These inhibits are the conversion of angiotensin I into angiotensin II. Then, in the 1990s, the angiotensin II receptor blockers (ARBs), which are specific for the AT1 receptor, were introduced. Both classes of drugs are now widely used in the treatment of hypertension,

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and are also used for treating heart failure and diabetic nephropathy.[3]

Renin has long been pursued as a target for intervention in the RAS, because it catalyses the first and rate-limiting step in the cascade, and has high specificity for its substrate angiotensinogen, thereby potentially limiting the risk of side effects. However, the development of a number of first-generation peptide-like renin inhibitors was discontinued for various reasons, including low oral bioavailability and low potency. Aliskiren is the first approved member in a new class of antihypertensives, DRI.[4] The suppression of the renin angiotensin system by ACEIs and ARBs has been proven in many studies to treat hypertension and reduce cardiovascular events; however, reducing angiotensin I receptor stimulation results in the loss of the negative-feedback signal, leading to increased plasma renin activity.[5] High plasma renin activity may represent a cardiovascular risk factor.[6] Among hypertensive subjects, PRA level, is independently and directly associated with the incidence of myocardial infarction.[7] Oral administration of a renin inhibitor causes the PRA to decrease.[3] This effect may be suggested for further risk reduction.

## SOME PRECLINICAL AND CLINICAL TRIALS WITH DIRECT RENIN INHIBITOR

Aliskiren was first studied in sodium-depleted marmosets and in spontaneously hypertensive rats (SHR). Aliskiren was also shown to effectively lower blood pressure in SHRs and marmosets. Recent studies using double transgenic rats (dTGRs) with human genes for angiotensinogen and renin have corroborated early work in the marmoset and SHRs. Aliskiren decreased blood pressure in a dose-dependent manner as well as proteinuria (a marker for kidney damage) and cardiac hypertrophy. The decrease in macrophage infiltration in the heart and kidneys of the aliskiren-treated dTGRs is suggestive of a decrease in angiotensin II-mediated inflammation.[3] In dTGR, equieffective antihypertensive doses of valsartan or aliskiren attenuated end-organ damage. Thus, the results lead to the conclusion renin inhibition compares favorably to angiotensin receptor blockade in reversing organ damage in dTGR.[8]

In clinical trials Aliskiren is found to be as efficacious as the ARBs losartan and irbesartan in reducing blood pressure (BP) in patients with mild to moderate hypertension and resulted in superior BP lowering compared to the ACEI, ramipril, in patients with type 1 or 2 diabetes and mild to moderate hypertension. Moreover, a pooled analysis of seven randomized clinical trials conducted in more than 7000 patients with hypertension showed that aliskiren provided similar BP-lowering effects in the subgroup of patients 65 years of age compared with younger patients.[9] In a trial assessing the antihypertensive efficacy and safety of the combination of aliskiren and ramipril in patients with diabetes and hypertension, adding aliskiren to ramipril provided an additional mean BP pressure decrease. Aliskiren also decreased plasma renin activity (PRA) in monotheraphy group and in ramipril combination group.[10] The combination of aliskiren and valsartan at maximum recommended doses provides significantly greater reductions in blood pressure than does monotherapy with either agent in patients with hypertension, with a tolerability profile similar to that with aliskiren and valsartan alone.[11] It is reported that aliskiren provided significant additional BP reductions in combination with hidrochlorotiazide.[12] In a study designed aliskiren as add-on to amlodipine provided significant additional blood pressure lowering.[13]

## FUTURE PERSPECTIVE

Recently we have three drug classes directly inhibiting RAS to threat hypertension, consisting ACEI, ARB and DRIs. Results of ongoing and future clinical trials with specific populations and focusing on protection of end organ damage will enrich our knowledge and understanding on direct renin inhibition. Furthermore, the direct renin inhibitors' differentiating effect on PRA and newer RAS components will be investigated and will contribute our understanding.

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