1. Introduction

Hypertension affects approximately 972 million people worldwide and it is second only to diabetes as the leading independent cause of end-stage renal disease (ESRD) (1). Elevations in blood pressure are a strong independent risk factor for chronic kidney disease (CKD) progression, and the presence of albuminuria and proteinuria entails increased cardiovascular morbidity and mortality (2, 3).

About 80% of CKD patients are hypertensive and kidney function and blood pressure are clearly related to both physiologic and pathologic conditions constituting a “vicious cycle” (4). In this pathologic scenario, there is a renin–angiotensin system (RAS) hyperactivity associated to progression of renal damage. Current guidelines indicate as the first choice of antihypertensive intervention, the pharmacologic blockade of the RAS. Nonetheless, both response to treatment and renal protection have considerable inter-individual variability. The main aims of this review are to describe the genetic characteristics of RAS components and to identify the possible pharmacogenetic implications for RAS-blocker drugs in the hypertension–CKD scenario. To date, RAS polymorphisms have not been consistently associated to antihypertensive response and studies focusing on CKD are scarce. Nonetheless, pharmacogenetic studies for the RAS-blocker drugs could still be further explored, especially with new generation tools and focusing not only on the antihypertensive response, but also on renal protection as well.

Keywords: pharmacogenetics, renin–angiotensin system, chronic kidney disease, hypertension, angiotensin-converting enzyme inhibitor

2. RAS components and their genetic characteristics

RAS was discovered more than one century ago, but its significance in the pathogenesis of hypertension and renal disorders has gained wide acceptance only during the past several decades, largely through the development of specific pharmacological agents designed to block the system (10 – 13).
Classical RAS components and their genetic characteristics are presented below.

2.1. Renin
Renin, a protease mainly produced by the juxtaglomerular cells of the kidney, is encoded by the \textit{REN} gene located on chromosome 1q32. Renin occurs in organs other than the kidney, e.g., in the brain, where it is implicated in the regulation of numerous activities. The enzyme which catalyzes the first step in the activation pathway of angiotensinogen to angiotensin I (Fig. 1) and its gene mutation have been associated with hyperreninemia, hyperuricemic nephropathy, and renal tubular dysgenesis (OMIM 179820) (14 – 16).

2.2. Angiotensinogen, angiotensin I, and angiotensin II
Angiotensinogen, a precursor of angiotensin and encoded by the \textit{AGT} gene located on chromosome 1q42 – q43, is mainly produced by the liver and found in the a2-globulin fraction of plasma. In the RAS, angiotensinogen is cleaved by renin (Fig. 1) and \textit{AGT} mutations were related to renal tubular dysgenesis, susceptibility to essential hypertension, and preeclampsia (OMIM 106150) (17 – 19). A meta-analysis performed by our group analyzing data involving 26,818 subjects from 46

![Diagram of the Renin–angiotensin system and bradykinin pathways](image)

**Fig. 1.** Renin–angiotensin system and bradykinin pathways. Angiotensinogen is a precursor of angiotensin produced by the liver. Renin, an enzyme produced by the juxtaglomerular cells of the kidney, catalyzes the first step in the activation pathway of angiotensinogen to angiotensin I. ACE (angiotensin I-converting enzyme), mainly produced by the lungs and kidney, plays a pivotal role by hydrolyzing angiotensin I into angiotensin II. This product interacts with angiotensin II receptors, leading to potent vasoconstriction, release of aldosterone by the adrenal cortex, ADH (antidiuretic hormone) secretion by the pituitary gland, renal sodium and fluid retention, sympathetic overdrive, and thirst. There are two distinct subtypes of cell surface receptors, angiotensin II receptors types 1 and 2 (AT1 and AT2). AT1 seems to mediate the major cardiovascular effects of angiotensin II. In pathologic conditions, RAS is hyperactive, leading to hypertension and kidney lesions in a “vicious cycle”. In the bradykinin system, kininogens are multifunctional proteins synthesized in the liver that circulate in the plasma and other body fluids. The tissue kallikrein is synthesized in the cells as a precursor and converted into an active form by the cleavage of an amino terminal peptide. The enzymatic action of kallikreins on kininogens generates bradykinin that interacts with bradykinin receptors and elicits numerous responses, including vasodilatation, edema, smooth muscle spasm, and stimulation of pain fibers. The kininases, such as ACE, are present in the plasma, endothelial cells, and in the tissues to regulate the physiological functions of the kinins in the body.
studies regarding the most-studied AGT variants identified significant associations of the T174M and G-217A polymorphisms with hypertension risk (20).

2.3. Angiotensin I-converting enzyme (ACE) and angiotensin I-converting enzyme-2 (ACE2)

ACE or kininase II is a dipeptidyl carboxypeptidase encoded by the ACE gene, located on chromosome 17q23.3, whereas the ACE2 gene is located on chromosome Xp22 and it may counteract some of the effects of ACE (21). ACE is mainly produced by the lungs and plays a pivotal role in the RAS by hydrolyzing angiotensin I into angiotensin II. This product is a potent vasopressor and it acts on the adrenal cortex causing the release of aldosterone (Fig. 1). In addition, ACE is also able to inactivate bradykinin—a potent vasodilator (15, 22, 23). ACE genetic variants have been associated with renal tubular dysgenesis, microvascular complications of diabetes, progression of a severe acute respiratory syndrome, and the susceptibility to myocardial infarction and Alzheimer’s disease (OMIM 106180); however, several association studies showed controversial results and the current interpretation is that genetic variants of the gene regulate the ACE serum concentration, but there is no clear correlation of this quantitative trait with increased cardiovascular risk (24 – 30).

2.4. Angiotensin receptors 1 and 2

Two pharmacologically distinct subtypes of cell surface receptors, angiotensin receptors types 1 and 2 (AT1 and AT2), interact with angiotensin II. AGTR1 and AGTR2 genes are located on chromosomes 3q21 – q25 and Xq21 – 23, respectively. AT1 seems to mediate the major cardiovascular effects of angiotensin II, leading to effects such as vasoconstriction, increased arterial blood pressure, increased myocardial contractility, and sodium and water retention (Fig. 1) (12, 15, 23, 31 – 33). Some AGTR1 variants were associated with susceptibility to essential hypertension and renal tubular dysgenesis (OMIM 106165) (14, 34, 35).

2.5. Bradykinin receptor B2

Bradykinin receptor B2 (BRB2), encoded by the BDKRB2 gene, located on chromosome 14q32.1 – q32.2, mediates bradykinin vasodilatation in the kinin system. Kininogens are multifunctional proteins synthesized in the liver and they circulate in the plasma and other body fluids. Tissue kallikrein is synthesized as a precursor and converted into its active form by the cleavage of an amino terminal peptide. The enzymatic action of kallikreins on kininogens generates bradykinin, a 9-amino acid kinin that interacts with bradykinin receptors and elicits numerous responses, including vasodilatation, edema, smooth muscle spasm, and stimulation of pain fibers. The kininases, kinin-inactivating enzymes (such as kininase I, kininase II, or angiotensin-converting enzyme), are present in the plasma, endothelial cells, and in different tissues to regulate the physiological functions of the kinins in the body (Fig. 1) (36, 37). The BDKRB2 9 pb insertion/deletion (I/D) polymorphism has been found to affect the transcription of the gene in a cis-acting manner and has been associated with several cardiovascular related phenotypes (OMIM 113503) (38, 39).

2.6. Aldosterone synthase

Aldosterone synthase, encoded by the CYP11B2 gene, located on chromosome 8q21 – q22, is a steroid 11/18-β-hydroxylase that functions in mitochondria in the zona glomerulosa of the adrenal cortex to synthesize the mineralocorticoid aldosterone (40). Some studies described the importance of common polymorphisms in adrenal synthetic genes in altering corticosteroid biosynthesis. CYP11B2 variants were associated with corticosterone methylxoydase types I and II deficiency (congenital hypoaldosteronism) and increased the aldosterone-to-renin ratio (OMIM 124080) (40 – 42).

2.7. Local RASs

Recently, several local RASs have been discovered in organs such as the heart, brain, pancreas, kidney, and adipose tissue, and novel actions of angiotensin II have emerged among which is its ability to act as immunomodulator, profibrotic molecule, and inhibitor of insulin signaling (43, 44). However, the exact role and influence of the local RAS on specific organ diseases or studied phenotypes is not completely understood (45).

Although circulatory derived angiotensin II is generated by the actions of renin and ACE, tissue angiotensin II synthesis may use alternative enzymes, such as cathepsins and chymase, depending on the stimulus. The most important of these alternative pathways in the cardiovascular system is thought to be chymase-dependent (46). The site of the tissue angiotensin II generation, whether extracellular or intracellular, further determines angiotensin II-forming pathways. On the basis of the site of angiotensin II synthesis, the tissue RAS has been further categorized into the extracellular (autocrine/paracrine) and intracellular (intracrine) (47, 48). An enzyme inhibition study showed an involvement of renin and chymase, but not ACE, in intracellular angiotensin II synthesis, following exposure to high glucose (49). Some studies also demonstrated a significant contribution of chymase in cardiac angiotensin II generation (47, 50, 51).

This new information adds to the already known complexity of the system and opens the possibility that discordant responses between the systemic and local
systems may impair our ability to identify and measure relevant phenotypes derived from the action of RAS components.

3. Pathophysiological relationship between hypertension and CKD

RAS hyperactivity has been described as the most important event contributing to glomerular hypertension (52, 53). Increases in blood pressure are physiologically prevented from affecting the renal microvasculature by the proportionate vasoconstriction of the preglomerular vasculature, such that the pressure load transmitted from the systemic circulation to the glomerular capillary is blunted, and glomerular hydrostatic pressure remains relatively constant in the face of changing blood pressure. Failure of the auto-control response results in elevated glomerular hydrostatic pressure, hyperfiltration, and proteinuria (54 – 56). Current guidelines have suggested that pharmacological intervention should reduce 1) blood pressure and 2) the transmission of pressure to renal microvasculature. Guidelines suggest RAS blockers [e.g., ACE inhibitors or angiotensin II-receptor blockers (ARB)] as the first choice for treating hypertension and for interrupting progression of renal damage in CKD patients (7, 57 – 60).

4. RAS drugs

RAS is an important therapeutic target and drugs that block this system have been extensively developed, such as ACE inhibitors and ARB. This blocking has been postulated as the first choice for treatment of hypertension in CKD patients (7). However, some studies indicated that, even under appropriate ACE inhibitors or ARB use, the renal end point was reached during follow-up by approximately one third of all patients (4, 6, 61, 62).

Several ACE inhibitor trials for CKD patients were conducted and showed a slower decline in renal function with the use of this class of antihypertensive medication. Lewis et al. identified a doubling of serum creatinine concentrations in 25 patients in the captopril group, as compared with 43 patients in the placebo group ($P = 0.007$) and concluded that this drug protected against deterioration in renal function in insulin-dependent diabetic nephropathy and it was significantly more effective than blood-pressure control alone (63). Ruggenenti et al., in patients with chronic nephropathy and high risk of rapid progression to ESRD, reported that ramipril reversed the tendency of the glomerular filtration rate (GFR) to decline with time (64). Moreover, a treatment period of sufficient duration (> 36 months) eliminated the need for dialysis in most individuals (64).

In another trial, Ruggenenti et al. assessed whether ACE inhibitors prevent microalbuminuria in subjects with hypertension, type 2 diabetes mellitus (DM), and normal urinary albumin excretion (UAE) (65). The study enrolled 1,204 subjects (who were randomly assigned to receive at least three years of treatment with trandolapril) and concluded that the trandolapril or combination of trandolapril and verapamil reduced the incidence of microalbuminuria (65, 66).

Similarly, some ARB trials for CKD patients were developed and positive results of renal function preservation with the use of the drug have been observed. Viberti et al. proposed that the use of valsartan decreases UAE regardless of blood pressure reduction in 332 type 2 diabetic patients with microalbuminuria (67). The UAE at 24 weeks was 56% (95% CI, 49.6% to 63.0%) of baseline with valsartan and 92% (95% CI, 81.7% to 103.7%) of baseline with amloidipine, a highly significant between-group effect ($P < 0.001$). Valsartan decreased UAE similarly in both the hypertensive and normotensive subgroups and more patients reversed to normoalbuminuria with valsartan (29.9% vs. 14.5%; $P = 0.001$) (67). Parving et al. evaluated the renoprotective effect of irbesartan in 590 hypertensive patients with type 2 diabetes and microalbuminuria. They concluded that irbesartan was renoprotective regardless of its blood-pressure-lowering effect (68). Other studies reported similar findings (6, 61, 69).

Levels of angiotensin II have been shown to rise under treatment with ACE inhibitors or with ARBs, because of a compensatory increase in non-ACE–dependent angiotensin II production. In addition, there may still appear an “aldosterone escape or aldosterone breakthrough”, i.e., an increase in aldosterone concentrations in the presence of RAS blocking. In recent years, some studies have shown that aldosterone plays a role in the development and progression of diabetic nephropathy, regardless of angiotensin II and blood pressure levels (70, 71). “Aldosterone escape” occurs in as many as half of all patients on chronic ACE inhibitor or under ARB treatment and this long-term inter-individual variability should be focused on the following pharmacogenetic studies. For this reason, the combined use of RAS-blocker drugs, higher dosages, and/or direct renin inhibition has been proposed (4, 46, 72, 73).

Aliskiren, the first direct renin inhibitor to receive approval for hypertension treatment, reduces the production of all downstream products derived from angiotensinogen. In addition, a clinical study reported that aliskiren reduces plasma and urinary excretion of aldosterone and thus may provide additional renoprotective effects (74). This drug has been shown to be an effective antihypertensive agent and some studies have
also evaluated aliskiren as a potential renoprotective agent in CKD using proteinuria as a surrogate marker of CKD progression (8, 75 – 78). Parving et al. enrolled 599 patients with nephropathy in a randomized and double-blind study. The patients were randomly assigned to receive 6 months of treatment with aliskiren or placebo, in addition to losartan. They observed that the treatment with 300 mg of aliskiren daily, as compared with placebo, reduced the mean urinary albumin-to-creatinine ratio by 20% (P < 0.001); there was only a small difference in blood pressure and the total numbers of adverse and serious adverse events were similar in the groups. Thus, they concluded that aliskiren may have renoprotective effects that are independent of its blood-pressure–lowering effect in patients with hypertension, type 2 diabetes, and nephropathy (75). However, long-term studies are needed to demonstrate the efficacy and safety of aliskiren in specific clinical settings. Thus, the ALTITUDE trial (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints), which included 8606 patients with type 2 diabetes, proteinuria, and a high cardiovascular risk, compared the effects of aliskiren or placebo added to the current treatment consisting of another RAS blocker. ALTITUDE was designed to determine the potential cardio-renal benefit and safety of aliskiren in combination with ACE inhibitors or ARB in high risk patients with type 2 diabetes. However, Novartis announced that following the seventh interim review of data from the ALTITUDE study, a decision to terminate the trial has been taken on the recommendation of the independent Data Monitoring Committee (DMC) overseeing the trial. The DMC concluded that patients were unlikely to benefit from the treatment added on top of standard anti-hypertensives and identified higher adverse events in patients receiving aliskiren in addition to the standard care in the trial, such as an increased incidence after 18 – 24 months of a non-fatal stroke, renal complications, hyperkalemia, and hypotension in this high-risk study population (Novartis, 2011, available at www.novartis.com).

The most recent analysis of the ONTARGET (79) and TRANSCEND (80) studies have documented that the initial treatment-induced reduction in albuminuria is highly predictive of reduction of fatal and non-fatal renal and cardiovascular events. However, results from ONTARGET showing a lack of an additional outcome benefit over monotherapy, with a concomitant increased risk of hyperkalemia, renal impairment, and hypotension, discourage the use of ACE inhibitors / ARBs combination in patients at high risk of cardiovascular events. When added to an ACE inhibitor or an ARB in patients with chronic heart failure, aliskiren reduced the brain natriuretic peptide, a change also predictive of an improved outcome in this condition (81, 82). In this current scenario, a pharmacogenetic evaluation might potentially indicate which patients have increased risk for cardiovascular events and, in contrast, which patients would benefit from aliskiren addition to their treatment regimen.

5. Pharmacogenetic implications

In this section, we describe the available evidence supporting the association of genetic variants of the RAS and pharmacogenetic responses of important vascular and renoprotection phenotypes. Table 1 shows a summary.

Age, male gender, blood pressure, dyslipidemia, obesity, smoking, and a history of cardiovascular disease have been described as predictors of microalbuminuria and renal progression, but there is still great interindividual variability among pharmacological responses and renoprotection, suggesting the possible role of genetic components. In this regard, our group observed that ACE and AGT functional genetic variants modulate the risk of microalbuminuria conferred by increased blood pressure levels in the general population, but pharmacological treatment was not evaluated (83, 84).

5.1. ACE gene

ACE 287 pb I/D polymorphism has been associated with higher circulating plasma ACE concentrations (85 – 87), thus a pharmacogenetic effect on RAS intervention is plausible. Regarding the relationship between RAS-blocker response and genetic variants, the ACE I/D gene polymorphism is the most studied.

A prospective, randomized, clinical study aimed to compare the effects of a lisinopril treatment or placebo on the UAE rate in 530 patients with type 1 DM for 2 years. It was conducted and the effect of the ACE I/D variant was studied. They concluded that the ACE inhibitor compared with placebo reduced albuminuria by 51.3%, 14.8%, or 7.7% in patients carrying II, ID, or DD genotypes, respectively (88). Another three studies using patients with type 1 DM and treated with ACE inhibitors showed an association of the I allele with the best outcomes for renal phenotypes (89 – 91). For type 2 DM, the data are controversial, but So et al. observed that over a median period of 44.6 months, ACE inhibitor therapy decreased mortality, ESRD, or progression to estimated GFR < 15 mL/min per 1.73 m2 more effectively in II plus ID than in DD carriers (92).

For the ARB treatment, a double blind, multicenter, prospective, randomized, placebo-controlled clinical trial designed to evaluate the renal effects of losartan in 1,513 type 2 diabetic patients has also studied the role of ACE gene variants. The authors identified that patients carry-
Table 1. Findings of pharmacogenetic studies involving main RAS genes

<table>
<thead>
<tr>
<th>Gene and polymorphism</th>
<th>Drug</th>
<th>Finding</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>ACE I/D</em></td>
<td>lisinopril</td>
<td>Patients carrying II genotype had higher albuminuria reduction.</td>
<td>88</td>
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<tr>
<td><em>ACE I/D</em></td>
<td>captopril, enalapril, lisinopril</td>
<td>I carriers had best outcomes for renal phenotypes.</td>
<td>89 – 91</td>
</tr>
<tr>
<td><em>ACE I/D</em></td>
<td>ACEi</td>
<td>Therapy decreased mortality, ESRD, or progression more effectively in II plus ID than in DD carriers.</td>
<td>92</td>
</tr>
<tr>
<td><em>ACE I/D</em></td>
<td>losartan</td>
<td>D allele indicated an unfavorable renal prognosis.</td>
<td>93</td>
</tr>
<tr>
<td><em>ACE I/D</em></td>
<td>ARB</td>
<td>DD genotype demonstrated diminished renoprotection.</td>
<td>94</td>
</tr>
<tr>
<td><em>ACE I/D</em></td>
<td>enalaprilat</td>
<td>II genotype carriers had greater and longer lasting effect on blood pressure.</td>
<td>96</td>
</tr>
<tr>
<td><em>ACE G12269A, C17888T, G20037A</em></td>
<td>ramipril</td>
<td>Individuals with 12269AA genotype responded to ramipril significantly faster.</td>
<td>98</td>
</tr>
<tr>
<td><em>ACE I/D</em></td>
<td>irbesartan</td>
<td>Patients with ACE II genotype showed a greater reduction in diastolic blood pressure.</td>
<td>97</td>
</tr>
<tr>
<td><em>ACE I/D</em></td>
<td>benazepril, fosinopril, imidapril, lisinopril</td>
<td>No association*.</td>
<td>99 – 101</td>
</tr>
<tr>
<td><em>ACE I/D</em></td>
<td>losartan, telmisartan, valsartan</td>
<td>No association.</td>
<td>102 – 104</td>
</tr>
<tr>
<td><em>AGT M235T</em></td>
<td>ACEi</td>
<td>The risk of myocardial infarction was increased in patients with MT or TT genotype compared to MM.</td>
<td>107</td>
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<tr>
<td><em>AGT rs7079 (C/A)</em></td>
<td>benazepril</td>
<td>AA genotype was significantly associated to higher blood pressure.</td>
<td>108</td>
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<tr>
<td><em>AGT M235T</em></td>
<td>benazepril, captopril, fosinopril, imidapril</td>
<td>No association.</td>
<td>99, 109, 110</td>
</tr>
<tr>
<td><em>AGT M235T</em></td>
<td>losartan, telmisartan, valsartan</td>
<td>No association.</td>
<td>102 – 104</td>
</tr>
<tr>
<td><em>AGTR1</em> haplotypes</td>
<td>benazepril</td>
<td><em>AGTR1</em> haplotypes were associated with blood pressure reduction.</td>
<td>108</td>
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<tr>
<td><em>AGTR1</em> rs275651, rs5182</td>
<td>perindopril</td>
<td>Determinants of treatment benefit and blood pressure response.</td>
<td>114</td>
</tr>
<tr>
<td><em>AGTR1 A1166C</em></td>
<td>benazepril, fosinopril, imidapril, trandolapril</td>
<td>No association.</td>
<td>99, 115, 116</td>
</tr>
<tr>
<td><em>AGTR1 A1166C</em></td>
<td>losartan, telmisartan, valsartan</td>
<td>No association.</td>
<td>102 – 104</td>
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<tr>
<td><em>REN rs2887284</em></td>
<td>ACEi</td>
<td>Polymorphism was associated to response of renin and angiotensin II levels.</td>
<td>118</td>
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<td><em>REN C5312T</em></td>
<td>valsartan</td>
<td>Responder rates were different between the genotypes: 72.8% in CC vs. 58.0% in CT/TT.</td>
<td>102</td>
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<td><em>REN C5312T</em></td>
<td>losartan</td>
<td>Nocturnal blood pressure reductions were greater in 5312T allele carriers.</td>
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<tr>
<td><em>ACE2</em> rs2106809</td>
<td>captopril</td>
<td>Reduced antihypertensive response. Diastolic blood pressure was lower in ACE2 T allele carriers than in CC genotype.</td>
<td>119</td>
</tr>
<tr>
<td><em>AGTR2</em> haplotypes</td>
<td>benazepril</td>
<td>No association.</td>
<td>108</td>
</tr>
<tr>
<td><em>AGTR2</em> C3123A</td>
<td>valsartan</td>
<td>No association.</td>
<td>102</td>
</tr>
<tr>
<td><em>BDKRBB2 –58T/C</em></td>
<td>ACEi</td>
<td>Frequencies of the TT genotype and T allele were significantly higher in the patients with a cough than in patients without a cough.</td>
<td>120</td>
</tr>
<tr>
<td><em>CYP11B2 –344C/T</em></td>
<td>fosinopril</td>
<td>No association.</td>
<td>121</td>
</tr>
</tbody>
</table>

ACEi: angiotensin-converting enzyme inhibitors (specific drug was not available). ARB: angiotensin II-receptor blockers (specific drug was not available). *No association: no significant evidence reported about polymorphism–drug treatment interaction.

Patients carrying the D allele of the *ACE* gene have an unfavorable renal prognosis, which can be mitigated and even improved by losartan (93). Another study also observed that patients carrying the DD genotype demonstrate a diminished response to ARBs in terms of renoprotection and that *ACE* gene polymorphism needs to be taken into ac-
count when using ARBs as a means of renoprotective therapy (94).

A meta-analysis of randomized clinical trials of RAS inhibitor therapy in diabetics and non-diabetics was performed on progression to ESRD as the primary outcome variable in DD, ID, or II genotypes considered separately. In summary, the experimental treatment compared with placebo decreased the risk of progression to ESRD by 36%. In patients with the DD and ID genotype, RAS inhibition compared with placebo decreased the risk of ESRD by 68% and 23%, respectively, and the odds ratio (OR) was statistically significant in both groups. Of note, within each subgroup, patients with diabetic and non-diabetic proteinuric nephropathy showed a similar response to RAS inhibition, with a non-significant trend to increased risk reduction in those with non-diabetic nephropathy within the DD subgroup (95).

Regarding hypertension and blood pressure, Ueda et al. investigated the possible effects of contrasting betic nephropathy within the DD subgroup (95). A trend to increased risk reduction in those with non-diabetic proteinuria showed a similar response to RAS inhibition, with a non-significant trend to increased risk reduction in those with non-diabetic nephropathy within the DD subgroup (95).

5.3. AGTR1 gene

Several studies have linked AGTR1 variants, especially the A1166C polymorphism, with blood pressure phenotypes, hypertension, and heart diseases (111–113). However, only one study reported that haplotypes for the AGTR1 polymorphism could be associated with blood pressure reduction in response to benazepril (108). A recent study identified two AGTR1 polymorphisms (rs275651 and rs5182) associated with response to perindopril treatment (114). Some studies did not find the same influence for ACE inhibitors (99, 115, 116) or ARBs (102–104).

5.4. REN, ACE2, AGTR2, BDKRB2, CYP11B2, and NR3C2 genes

Recent studies indicated that changes in blood pressure were significantly different between genotypes of REN C5312T in valsartan or losartan monotherapy (102, 117). Another study reported, in a total of 400 newly diagnosed hypertensives, that rs2887284 in intron 9 of REN is associated with the response of renin and angiotensin II levels to the ACE inhibitor treatment (118). Two case-controls and a clinical trial of 3408 untreated hypertensive patients, described that the ACE2 rs2106809 confers a reduced antihypertensive response to captopril (119). Two studies evaluated the association of the AGTR2 polymorphisms (C3123A and haplotype analysis) with valsartan and benazepril, respectively, but no significant difference was found (102, 108). A study concluded that a genetic variant of the BDKRB2 −58T/C could be involved in an ACE inhibitors–related cough (120). Regarding the CYP11B2 gene, a study reported that patients carrying the −344CC genotype presented a greater blood pressure reduction with hydrochlorothiazide than those carrying CT and TT genotypes (121). However, a study was performed and indicated no pharmacogenetic asso-
association between the ACE inhibitor and CYP11B2 genotype (99). Polymorphisms in the NR3C2 gene, which encodes a receptor for cortisol and aldosterone, could also affect CKD and a hypertension treatment with ACE inhibitor and ARB drugs, since aldosterone is one of the final mediators of the RAS. For these six genes, there were no sufficient studies in detail; thus, further studies are needed regarding pharmacogenetic interventions.

6. Perspectives and conclusions

Antihypertensive and CKD pharmacogenetic studies present both positive and negative results, but the main problems are methodological limitations, mainly reduced statistical power due to the reduced number of patients, and the lack of a clear definition of what the correct phenotype to be measured would be. Two previous well-documented reviews were published on this (122, 123). Farahani et al. explored potential biases which may be contributing to discordant results in gene–drug interaction studies. They concluded that most studies contain biases driven from patient selection, combining different alleles, combining different therapeutics, and combining rather different end points (122). On the other hand, Konoshita et al. used different conditions for a study selection and found 11 studies with a number of patients > 200. They concluded that the conventional genetic variants of the RAS (ACE I/D, AGT M235T, and AGTR1 A1166C) were not associated with antihypertensive response, at least by one individual polymorphism, but significant associations have been reported for other gene variants (123).

Today, two important points may assist us in obtaining the right information from these markers. First, advances in technology allow performing association studies with a large number of patients examining several polymorphisms. Of particular importance, most previous studies analyzed only one or few markers. These are clearly insufficient when one considers a complex trait such as renal protection or blood pressure and a regulation/treatment via RAS. Second, several large-scale clinical trials have now been developed and pharmacogenetic studies should be part of the design and analytical strategy of these studies. For example, The PERGENE (Perindopril Genetic Association) study is one of the first pharmacogenetic analyses within a randomized clinical trial demonstrating new genetic determinants of clinical treatment benefits of ACE inhibitors (30, 114). They were able to demonstrate a relative resistance to ACE inhibitors in patients with unfavorable alleles of the AGTR1 and BDKRB2 genes and one out of four patients with coronary artery disease experienced a markedly diminished benefit of treatment with perindopril (114, 124). In this scenario, one could potentially suggest that the results of the ALTITUDE trial could be significantly different if pharmacogenetic information were to be considered in the randomization and enrollment phase (82).

In conclusion, the use of RAS-blocker drugs is the antihypertensive treatment of choice in CKD patients, and in this scenario, pharmacogenetic interventions could result in a personalized treatment leading to more effective and efficient use of these medications. However, for antihypertensive–CKD pharmacogenetic treatment to be translated into clinical practice, some points must be discussed: cost-effectiveness, number of genetic markers necessary to have high accuracy in prediction, physician’s awareness of inter-individual variability in drug response, RAS drugs monotherapy or combined, presence of additional medications (polypharmacy), other diseases, and specific-population ethnicity (125, 126). In addition, it would be interesting to understand the mechanisms of how each genetic polymorphism alters responsiveness of CKD patients to RAS-blocker drugs since few of these connections are clear in this pharmacogenetic context.

To date, RAS polymorphisms have not been consistently associated to pharmacogenetics of antihypertensive drugs and studies on interindividual variation of CKD protection are scarce. Pharmacogenetic studies for the RAS-blocker drugs could still be further explored. There is no clear consensus on the role of these markers, since few studies have no limitations and several negative results were also obtained with limitations, mainly statistical power and number of patients. Furthermore, even the main genes studied (ACE, AGT, and AGTR1) plus some promising genes not studied in detail (REN, ACE2, AGTR2, BDKRB2, CYP11B2, and NR3C2) should be explored, but with pharmacogenetic study designs that minimize the limitations and thus allows for more solid conclusions.

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References


Renin–Angiotensin System Pharmacogenetics

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