Introduction
The renin and the renin-angiotensin-aldosterone system (RAAS) have an undeniable relevance in the pathogenesis of the cardiovascular disease (CV), and during the last years it has advanced considerably as regards to the knowledge of the vascular atherosclerosis disease due to the development of drugs that block the RAAS in some way. Though we have evidences of the existence of renin since more than 100 years, the scientific interest for this molecule started in 1934, when Goldblatt published...
his first paper about renal ischemia in rats and its relation with the blood hypertension (BHT). The first direct renin inhibitors (DRI) for clinical investigation have been developed approximately 50 years ago, though it has been during the last five years when evidences have been collected thanks to a high number of clinical trials, until the approval of the aliskiren by the Food and Drug Administration (FDA) in March 2007 and the European Medicines Agency (EMEA) in August 2007, as the first oral DRI for the treatment of the BHT.

Since aliskiren constitutes the first drug of the first new class of antihypertensive introduced in more than one decade, the development and the pharmacology of this molecule count with wide and detailed revisions in the scientific literature. It seems considerable to think that the renin is a very appropriate objective when blocking the RAAS, taking into account that it corresponds with the first step in the system regulation. The first trials to achieve an inhibition of the renin were based on the use of antibodies against the renin, peptide analogues of the precursors of the renin and peptides based on the molecular structure of the statins. The development of the molecular disposition and the determination of the crystallographic structure of the active site of the renin have contributed essentially in the identification of the renin inhibitors. The distinctive drug of this new class of non-peptide drugs is the aliskiren, an oral active hypertensive, with a high affinity for the renin, which confers a high selectivity for this enzyme.

There is no doubt that the RAAS constitutes a fundamental therapeutic objective when achieving a reduction of the morbimortality associated to the progression of the atherosclerosis disease and, therefore, of the CV and renal disease, for being one of the main pathogenic agents that cause the development of organic damage and a risk increase of CV events onset. There is an increasing number of evidences that endorse the antihypertensive efficacy of aliskiren, both in monotherapy and in pharmacological combination which offer results of good tolerability and a good safety profile. We have revised in this article the characteristics that distinguish aliskiren as antihypertensive, evaluating the potential advantages of the RAAS blocking by means of this new pharmacology class and determining the prevention capacity as regards to the development of organic damages through the results of the most recent clinical trials, though there are important ongoing studies about morbidity and mortality. It is expected that the results shall be useful to reply to a great number of questions.

**Need of new antihypertensive therapies**

The RAAS is one of the most important pharmacology objectives when treating the hypertensive patient. The angiotensin-converting enzyme inhibitors (ACEIs) and the angiotensin II receptor antagonists (ARA II) have a moderate effective antihypertensive effect that achieves the prevention of complications arisen from the CV disease evolution associated to the insufficient control of the CV risk factors, with a scarce number of side effects associated to its use. Likewise, the antagonists of the aldosterone are a coadjuvant therapy with high effectiveness at situations of wild BHT of different causes. However, the morbidity and mortality associated to the CV disease are still very high, therefore the approach on the need of another class of drugs that add some clinical benefit by means of a different approach of RAAS inhibition is very justified.

A great number of basic investigation studies suggest that the drugs that inhibit the RAAS should provide a cytoprotector benefit in the target organ tissues, achieving a higher organic protection compared to the rest of the antihypertensive drugs, with similar reductions of blood pressure (BP). However, the studies about clinical results in relation to the possible independent added benefits of the BP with ACEI or ARA II have offered contradictory results on some occasions, in part because these drugs do not achieve a complete inhibition of the RAAS. The DRI might provide a higher organ protection through a more complete inhibition.

**Comparison of aliskiren with the rest of the RAAS inhibitor drugs**

The inhibition of the angiotensin II (Ang II) and the cessation of the production of cytokines that stimulate the cellular growth, free radicals, mediators of inflammation and tissue fibrosis that dependent on the Ang II, are some of the mechanisms that contribute to the clinical benefit determined by the renin-angiotensin-aldosterone blocker system (RAAS) in the CV and renal therapeutic. However, the heterogeneous methods of RAAS suppression present relevant differences at a biochemical level. The DRI favors the increase of the circulating and intrarenal renin level when interrupting the renin-angiotensin II
negative feedback as the ACEI and the ARA II. However, the catalytic activity of the renin molecules inhibits completely during day with the use of the DRIs, inducing a very low plasma level of Ang I and II. On the contrary, the enzymatic activity of the renin that is generated by a kidney that has received ACEI or ARA II is kept active, resulting in a high circulating level of Ang I and a lower level of Ang II. These differences in the release of renin might counteract the pharmacological inhibition of SAAR at the end of the ACEI or ARA II dose interval. Considering its high renin affinity, its inhibitory strength, its slow dissociation from the binding site to the active site of the renin and its pharmacological half-life, aliskiren should inhibit each of the renin molecules released to blood flow or the kidney. In this way, the DRIs might offer an additional protection compared to the rest of the RAAS inhibitors when interfering with the high renin and pro-renin catalytic activity, once these molecules have bound to the receptor.19

The discovery of the pro-renin receptor and the recent advances in the knowledge of its functions are changing the concept and understanding of the RAAS at present. The observation that the pro-renin molecule is activated from the biological point of view when binding to its receptor has a special interest considering the recent data that relate this molecule with the microvascular pathology development in the diabetic patient.20 However, a great amount of information about this matter has been unknown during some time. One of the questions that should be solved is if aliskiren inhibits the renin and pro-renin enzymatic activity once they get bound to the receptor of the latter. If the DRIs get to inhibit these recently discovered actions of the renin and the pro-renin, they can have a therapeutic advantage on the ACEI and the ARA II. Another relevant question is if the DRIs alter the activation of the intracellular routes, not mediated by the Ang II, induced by binding to the pro-renin receptor, as there are no clear data on this regard up to date. Another difference with the rest of the drugs that achieve the RAAS blocking is that aliskiren induces a stronger vasodilatation response in healthy subjects who have received a diet low in sodium compared to the ACEI.21 The clinical implications arisen of these data might be relevant regarding to the capacity of organ protection under circumstances in which the generation of intrarenal Ang II has activation routes depending or not of the converting enzyme, as in patients with diabetic nephropathy or in patients with a high salt intake, in which it is expected a higher benefit in the inhibition of the renin in the renal tissue.22

**Update of the clinical evidences provided by aliskiren**

The treatment with ACEI and ARA II is accompanied by benefits in morbimortality in patients throughout the CB continuum.23 However, there is an extensive discussion whether the RAAS inhibition offers a higher CV protection compared to other antihypertensive therapies for most of the patients.24 Among the reasons put forward to explain the possible causes for which there is no consensus among the results of the published clinical trials, it can be observed the insufficient reduction of BP among the groups and the use of inadequate doses, entailing an incomplete system inhibition.

Since its introduction in the 90s, the ARA II have arisen a great clinical expectation given the promising results on the protection of the target organs that set out higher than those offered by the ACEI, as they eliminated the release effect of the Ang II, which was observed as positive when promoting the receptors activity that increase the release of nitric acid, therefore other protector mechanisms of the blood vessel start. However, there is an increase in the CV mortality in the population that has to set out the possibility of finding improvements in the therapeutic. Aliskiren provides a new opportunity to prove if a higher inhibition of RAAS shall be translated into a higher organic protection regardless of the effect on the BP compared to the ACEI and the ARA II.

A main question that should be solved is to observe if in case of a determined reduction of BP, similar for all the pharmacological classes, there would be a higher organ protection with aliskiren, or which would be the response when adding DRI to the patient who already takes one of the other drugs. Oparil et al. have published recently a double-blind study that included 1,797 patients with level 1 and 2 BHT who have been randomized to receive aliskiren, valsartan, a combination of both or placebo during 8 weeks.25 The combination of aliskiren and valsartan in the maximum recommended doses (300 and 320 mg/day, respectively) offered a higher reduction of the BP values, both in the clinics and in the outpatient 24 hours monitoring, compared to each drug in single therapy.
In the dose in which it has been commercialized, in other words, 150 and 300 mg, aliskiren has proved an adequate tolerability with a profile of adverse effects similar to placebo, very close as the one we know about the ARA II. It does not cause cough as it does not inhibit the metabolism of bradicinines. It has a remarkable affinity characteristic for the renin at a renal level, therefore it also seems logical to think in promising renal protection effects. In this sense, both the ACEI and the ARA II have proved to be superior to the rest of the antihypertensive drugs that do not block the RAAS when improving the renal prognosis. The superiority of the ACEI is endorsed, both in diabetic and non diabetic patients, by its capacity of slowing down the chronic renal disease progression, while the ARA II have proved to prevent, return and delay the nephropathy in hypertensive patients with T2D.

Though it seems clear that the ACEI and the ARA II achieve a slowing down of the proteinuric nephropathy, it does not seem so evident that they might prevent the development of the advanced renal disease, though they delay the replacing renal treatment starting approximately 6-8 months. The most recent data on the usefulness of the combination of both RAAS inhibitors in patients at high risk have suggested that it does not offer a CV benefit superior than any other of them in monotherapies. Therefore, the therapeutic strategy based on aliskiren should reply to the matter about if it could be superior regarding to the prevention and regression of the organic lesion, in delaying the onset of CV events and, mainly, in improving the mortality associated to the CV disease. There are preclinical data related to the organic protection associated to the treatment with aliskiren that should be confirmed in the ongoing clinical trials at present.

As other endocrine systems, the RAAS has a capacity of controlled auto-regulation through a system of inhibition by negative feedback. The stimulation of the AT1 receptor by the Ang II suppresses the renin release. When blocking the action of the Ang II on its receptor, the ARA II interferes in the feedback circuit and stimulates the production of renin. When valsartan is indicated in monotherapy, the plasma renin activity (PRA) is increased, while if it is combined with aliskiren, the PRA is reduced (table 1). If the activation PRA compensatory action really limits the effectiveness of the suppressor drugs of the AT1 drugs, it can be understood that the concomitant administration with a DRI shall achieve a more complete suppression of the system and a better organ protection related to the ARA II in monotherapy.

When assessing concrete data about the organic protection in patients at high risk treated with aliskiren, it has to be taken into account a program of clinical studies ongoing at present whose objective is the evaluation of aliskiren all through the CV continuum. The first data that are being published are from two studies in patients at high risk of CV. The AVOID (Aliskiren in Evaluation of Proteinuria in Diabetes) is a 24 week multicenter, randomized, double-blind study which included 599 hypertensive patients with T2D and proteinuria and who received losartan during 12-14 previous weeks in optimum doses to achieve the BP objective and diabetes values. Aliskiren was added after these 12 weeks (150 mg) or placebo, and 12 weeks later the dose of aliskiren was increased up to 300 mg during 12 more weeks. The objective of this study was to determine if the concomitant treatment reduces effectively the albumin urinary excretion, compared to a treatment with losartan in doses that

Table 1. Differences in biochemical action on the RAAS elements

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ACEI: angiotensin-converting enzyme inhibitors; ARA II: angiotensin II receptor antagonists; CR: concentration of plasmatic renin; ND: no sufficient data available; PRA: plasmatic renin activity.
had already demonstrated to be renal protectors. The results of the study evidenced that adding aliskiren to the usual therapy achieved a reduction of the proteinuria in an addition of 20% (p ≤0.0009) compared to placebo in this type of patients with controlled BP. Moreover, 24.7% of the patients to whom aliskiren was added reached an equal or higher than 50% reduction in the proteinuria as from the basal level, compared to the 12.5% of the patients who received placebo (p= 0.0002). The tolerability of aliskiren taking was similar to placebo. The authors conclude that adding aliskiren to this population of patients at high risk offered a protection of the renal function.

In the target organ lesion, the data corresponding to the study ALLAY (Aliskiren in Left Ventricular Assessment of Hypertrophy) have proved a similar reduction in the antihypertensive standard therapy in hypertensive patients with overweight and left ventricular hypertrophy diagnosis (LVH). In the study ALOFT (Aliskiren Observation of Heart Failure Treatment), 302 patients have been randomized with class II-IV heart failure of the New York Heart Administration (NYHA) with BHT history and a plasmatic concentration of BNP (brain natriuretic peptide) higher than 100 pg/mL and who received stable treatment with ACEI and beta-blockers, to take in comparison to those who received placebo, in which there was an increase of 762 ± 6.123 pg/mL (p= 0.0106) in the group that received added aliskiren relative to the final value of NT-proBNP as retic peptide) higher than 100 pg/mL and who received stable treatment with ACEI and beta-blockers. The authors conclude that adding aliskiren to this population of patients at high risk offered a protection of the renal function.

Conclusions
We can conclude that the DRIs, which representative is aliskiren, are consolidated as a new pharmacological class with an action mechanisms exerted through a new form of RAAS suppression, and what we know at present about the RAAS inhibition causes an increase of the plasmatic renin activity. Therefore, it is necessary to know more data in relation to the response of the renin-pro-renin bond with its receptor and the possible vascular damage, as well as the potential improvement of the actions mediated by such binding and the inhibition by aliskiren. Both in monotherapy and in combination, the high effectiveness and tolerability of aliskiren has been demonstrated. Finally, there are data about the organ protection in patients at high cardiovascular risk.

Practical considerations

- Aliskiren is the first drug that is a direct inhibitor of the renin administered by oral route.
- Unlike the ACEI or the ARA II, that do not achieve a complete inhibition of the renin-angiotensin-aldosterone system, the direct inhibitors of the renin seem to provide a higher organ protection through a more complete inhibition.
- Aliskiren is effective both in monotherapy and in combination with other drugs. Additionally, data are appearing about the benefits of this drug regarding to organ protection in patients with high cardiovascular risk.

Declaration of potential conflict of interests
J.A. García-Donnaire and L.M. Ruilope Urioste state that there are no conflicts of interests as regards to the content of this article.

References