What is the Role of Direct Renin Inhibitors in the Treatment of the Hypertensive Diabetic Patient?

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ABSTRACT

The renin-angiotensin system (RAS) is the most important mechanism leading to cardiovascular and renal damage in diabetic patients. Studies conducted until now have unequivocally demonstrated that antihypertensive treatment with RAS blockers (angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers) improve the prognosis of patients with diabetes, by reducing rates of cardiovascular events and preventing or delaying the progression of diabetic nephropathy. However, despite the benefits of such treatment, cardio-renal events are still very frequent in diabetics. Several strategies for reducing this cardiovascular and renal risk have been

proposed, but among them, a more complete blockade of the RAS seems the most attractive. Direct renin inhibitors are RAS blockers with some particularities, such as their ability to reduce plasma renin activity or the possibility to modulate tissue and intracellular RAS, which could represent a theoretical advantage when treating diabetic patients. In experimental and clinical studies conducted until now, aliskiren is able to reduce blood pressure in diabetics, alone or in combination with ACE inhibitors or angiotensin-receptor blockers. Moreover, aliskiren reduces markers of cardiac and renal disease, such as left ventricular hypertrophy or post-infarction ventricular remodeling, as well as proteinuria in diabetics already treated with other RAS blockers. The translation of these promising results to the clinical arena is currently being investigated in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE), where more than 8600 diabetic patients with chronic kidney disease and at high-risk of cardio-renal events are treated with aliskiren or placebo added to the current treatment consisting of another RAS blocker. If positive, aliskiren will be the treatment of choice in the prevention of cardio-renal disease in diabetics.

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IMPORTANCE OF THE RENIN-ANGIOTENSIN SYSTEM IN THE DEVELOPMENT OF VASCULAR AND RENAL DAMAGE IN DIABETES

The enzymatic cascade known as the renin-angiotensin system (RAS) is the most important mechanism contributing to the physiological regulation of the cardiovascular system. Originally developed for the defense against excess loss of fluid during extreme situations, it has gained growing interest in recent years as one of the major components in the onset and progression of atheromatosis and its clinical consequences, the cardiovascular events.^{1,2}

The active enzyme renin is considered as the initiator element of the RAS. It promotes the hydrolysis of angiotensinogen and its importance is paramount in the process of RAS activation. Angiotensin II is the main effector of RAS, through its union to the angiotensin receptor type 1 (AT₁) receptor. At the vascular level, the consequences are the increased tone of vascular smooth muscle cells with consequent vasoconstriction and blood pressure elevation. It also acts on central and renal receptors generally promoting fluid retention, which in turn also elevates blood pressure. Angiotensin II is also a mediator of inflammatory, proliferative, oxidative, proaggregant, and procoagulant actions, all crucial in the development of endothelial dysfunction, vascular proliferation, the formation and composition of the extracellular matrix, and in the processes leading to plaque formation, development, vulnerability, and rupture, and therefore, the likelihood of suffering cardiovascular events.¹

There is clear evidence that the RAS is overactive in patients with risk factors for developing cardiovascular diseases as well as in those who have suffered or will suffer the consequences of it. Although the main parameters of the RAS measurable in serum are not increased, a hyperactivity of the paracrine RAS develops in situ in the majority of cells and tissues involved in vascular physiology and pathophysiology.³ In recent years, the presence of elements of the RAS inside the cells, especially renin, has also been reported. This intracellular RAS appears to play an important role in the perpetuation of organ damage in patients at cardiovascular risk.⁴ In this sense, diabetes is no exception and the studies carried out in both experimental animals and humans demonstrate that the RAS is responsible for the development and progression of vascular injury.

THE CURRENT EVIDENCE REGARDING TREATMENT WITH RAS INHIBITORS IN DIABETES

The main evidence concerning the importance of RAS in the pathogenesis of renal and vascular damage in diabetes comes from clinical trials on pharmacological interruption of the system. In general, data were obtained from studies conducted in diabetic patients alone, or from diabetic patients included in studies carried out in general hypertensive cohorts (Table 1).^{5–18} In this study three types of studies are reviewed. Firstly, those comparing RAS blockade against placebo; secondly, a direct comparison between RAS inhibition and other antihypertensive treatments; and thirdly, those studies specifically focused on diabetic nephropathy.^{19–26}

Studies Versus Placebo or Control Group

Three studies have been reported until now. Two of them recruited diabetic patients exclusively,

Table 1. Studies comparing RAS blockade versus other treatments in patients with diabetes.

Acronym ^{ref}	RAS blockade	Comparator	Primary endpoint	Other benefits
STENO-2 ^{5,6}	ACEi (ARB if intolerant)	Control	Combined CV events reduced	Total mortality CV mortality
ADVANCE ⁷	Perindopril	Control	Combined macro and microvascular events reduced	Total mortality CV mortality
HOPE ^{8,9}	Ramipril	Placebo	Combined CV events reduced	Total mortality CV mortality
UKPDS ^{10,11}	Captopril	Atenolol	No differences in combined CV events	
ABCD-H ¹²	Enalapril	Nisoldipine	Myocardial infarction reduced*	
FACET ¹³	Fosinopril	Amlodipine	Combined CV events reduced	
CAPPP ^{14,15}	Captopril	Diuretics and/or beta-blockers	Combined CV events	Total mortality
STOP-2 ¹⁶	ACE inhibitors	Calcium channel blockers; diuretics and/or beta-blockers	No differences in combined CV events	
LIFE ^{17,18}	Losartan	Atenolol	Combined CV events reduced	Total mortality CV mortality

*Trial halted after differences in myocardial infarction observed (four in enalapril, 24 in nisoldipine).

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blockers; CV=cardiovascular; RAS=renin-angiotensin system.

while the third was carried out in patients at high risk for cardiovascular events, in which a significant portion had diabetes.

The effect of a multifactorial intervention on mortality in type 2 diabetes (STENO-2) study^{5,6} consisted of a multifactorial intervention therapy (intensive therapy), which included an angiotensin-converting enzyme (ACE) inhibitor, versus the usual care in 160 patients with type 2 diabetes. Patients assigned to intensive therapy had reduced diabetes-related complications, including cardiovascular events and development of nephropathy, retinopathy, and autonomic neuropathy. A few years later, a longer follow-up of this cohort also brought evidence of a reduction in overall mortality of about 50%. As mentioned, the STENO-2 study included a multifactorial therapeutic approach, and it is difficult to attribute the benefits

observed to a single particular intervention, although treatment with ACE inhibitors was possibly an important contributing factor.

A second study, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial included more than 11,000 type 2 diabetic patients in a factorial design that included an intensive metabolic control by the addition of gliclazide sustained release, and an intensive blood pressure control adding the fixed combination of an ACE inhibitor (perindopril) and a diuretic (indapamide) to the usual therapy.⁷ Blood pressure (BP) values at the end of the study were 136/73 mmHg in the active treatment group and 140/73 mmHg in the placebo group. This more pronounced BP drop was accompanied by a reduction in the primary endpoint of macro and microvascular events of 9%,

and most importantly, reductions in both overall and cardiovascular mortality by 14% and 18%, respectively. Other secondary endpoints, such as the number of coronary events and the development of new onset nephropathy were also significantly reduced in patients receiving active treatment with perindopril.

Additional evidence comes from the Heart Outcomes Prevention Evaluation (HOPE) study.⁸ This trial evaluated the benefit of treatment with an ACE inhibitor, ramipril in the prevention of cardiovascular events in high-risk patients, defined as having documented coronary or cerebrovascular disease, peripheral arteriopathy, or diabetes with at least an additional cardiovascular risk factor. A third of the patients (3577) were diabetic and were subjected to a specific analysis.⁹ In such patients (as in the overall cohort), treatment with ramipril was associated with a better prognosis with significant reductions in the combined endpoint composed of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. A reduction in overall mortality and the development of nephropathy was also observed.

Studies Versus Other Antihypertensive Drugs

As in studies against placebo, the results obtained by comparing two antihypertensive strategies come from studies carried out exclusively in diabetic patients or by specific analyses of diabetic patients included in large hypertension trials. The United Kingdom Prospective Diabetes Study (UKPDS)¹⁰ compared captopril versus atenolol in patients with type 2 diabetes. There was no difference between the two strategies at the end of the study. An extended follow-up period upheld the neutrality of the comparison between the two treatments.¹¹

By contrast, the two studies carried out in USA did show significant differences in favor of using

treatment with ACE inhibitors. The Appropriate Blood Pressure Control in Diabetes Study (ABCD)¹² compared diabetic hypertensive patients randomized to receive the ACE inhibitor, enalapril, or the calcium antagonist, nisoldipine. The study was prematurely halted by observing a difference in the incidence of myocardial infarctions (24 in the nisoldipine-treated group compared to only four in the enalapril-treated group). Moreover, the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET)¹³ trial showed similar results, whereby the rate of cardiovascular events in diabetic patients was 19% in those treated with amlodipine, compared to 7% in those receiving fosinopril.

Again, more evidence comes from studies conducted in hypertensive patients (Captopril Prevention Project [CAPPP],^{14,15} Swedish Trial in Old Patients with Hypertension-2 study [STOP-2],¹⁶ and Losartan Intervention for Endpoint Reduction trial [LIFE]^{17,18}), by extracting data from the diabetic subgroup. The CAPPP trial¹⁴ compared treatment with captopril against conventional treatment with diuretics or beta blockers in a cohort of hypertensive patients. In the subgroup of diabetic patients (572 patients, 5%), captopril treatment significantly reduced the combined endpoint of cardiovascular death, myocardial infarction, and nonfatal stroke by 41%.¹⁵ In similar circumstances, the STOP-2 trial¹⁶ compared treatment with ACE inhibitors, calcium antagonists, or conventional diuretics and/or beta blockers, in hypertensive patients older than 60 years. No significant differences in the overall cohort or the subgroup of diabetics were observed.

The LIFE trial was the only study conducted with an angiotensin-receptor blocker (ARB),¹⁷ which compared losartan versus atenolol in hypertensive patients over 55 years with left ventricular hypertrophy. In the overall cohort of patients losartan reduced the combined primary

endpoint, mainly due to a reduction in stroke rates. In the diabetic subgroup, these benefits were even more obvious and affected not only the combined endpoint, but the rate of death was also prevented by losartan in comparison to atenolol.¹⁸

A unique, but important trial has compared the two major classes of RAS blockers (ACE inhibitors and ARB) in diabetic patients. The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET)²⁷ study compared treatment with ramipril or telmisartan in a cohort of patients at high cardiovascular risk, of which one-third were diabetic. Although a specific analysis in the cohort of diabetics has not been reported, the presence of such disease did not influence the main results, revealing a non-inferiority of telmisartan, compared to ramipril.

NEED FOR STRICT BP CONTROL

Some studies showing a better outcome when diabetic patients are treated with ACE inhibitors or ARB could be related to better BP control. This has been the case in both the UKPDS¹⁰ and the ADVANCE⁷ trials. In this view, a meta-analysis of several studies suggested that diabetic patients benefitted most from strict BP control.²⁸ This does not necessarily mean that BP should be reduced to very low values. In this sense, the results from the ONTARGET trial²⁷ in the arm receiving the combination of ramipril and telmisartan, and especially the more recent results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study²⁹ have both questioned the need for a lower BP target in diabetics. Specifically, the ACCORD study failed to demonstrate a significant clinical benefit of reducing BP below 120/80 mmHg, compared to the classical values of 140/90 mmHg in a large cohort of patients with type 2 diabetes.

The BP control in diabetic patients with extreme frequency requires the use of combination therapy. In this sense, both adding a thiazide diuretic or a calcium channel blocker to the RAS blocker are suitable options. Combination of a RAS blocker and thiazide diuretic has been successful in several outcome trials, such as the aforementioned ADVANCE⁷ or LIFE^{17,18} studies. However, two recent trials have suggested that the combination of a calcium channel blocker added to the RAS blocker could be the best option. Thus, in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study,³⁰ patients treated with amlodipine, the vast majority in combination with the ACE inhibitor perindopril, had a better prognosis with reductions in all cardiovascular variables compared with patients receiving the beta-blocker, atenolol, the vast majority combined with a thiazide diuretic. A specific analysis of diabetic patients subsequently performed showed that this benefit was maintained in this subgroup.³¹ More recently, the renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH) study³² compared the combination of the ACE inhibitor, benazepril, with the calcium channel blocker, amlodipine, against the same ACE inhibitor with the diuretic hydrochlorothiazide in high-risk hypertensive patients, also showing a better cardiovascular and renal outcome³³ in patients treated with the ACE inhibitor-calcium channel blocker combination. The analysis of the diabetic subgroup also showed benefits of such combination.³⁴

Studies of Prevention/Regression of Renal Disease

The highest level of evidence concerning the benefits of RAS blockade in diabetic patients undoubtedly lies in preventing the onset and

progression of diabetic nephropathy. Early clinical trials were focused on patients with nephropathy secondary to type 1 diabetes. Thus, Lewis et al.¹⁹ showed that treatment with captopril slowed the progression of the diabetic nephropathy in patients with proteinuria or mild renal insufficiency. A few years later, another study examined the effect of RAS blockade in patients without nephropathy or in early stages (microalbuminuria).²⁰ The Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes (EUCLID) study showed that lisinopril was able to prevent the progression of microalbuminuria to proteinuria, although there was no effect in preventing the onset of microalbuminuria in normoalbuminuric type 1 diabetics.

More recently, studies have focused on patients with type 2 diabetes and have examined both the prevention and progression of renal disease in different evolutionary stages, from microalbuminuria to end-stage renal failure. Two different studies have reported the prevention of the appearance of microalbuminuria by using treatment with either the ACE inhibitor, trandolapril,²⁹ or the ARB, olmesartan.²² These data were also indirectly confirmed in the aforementioned ADVANCE study,⁷ in which the addition of a combination that included perindopril reduced the appearance of new cases of microalbuminuria by 20%.

In patients with microalbuminuria, treatment with RAS blockers is able both to reduce the level of protein excretion and the appearance of overt nephropathy, ie, proteinuria or renal failure. Thus, the Irbesartan Micro Albuminuria in type 2 diabetic subjects (IRMA-2) study with irbesartan showed a reduction in the onset of overt diabetic nephropathy.²³ The effect was dose dependent, and the administration of 300 mg had a greater protective effect than 150 mg. A similar study with another ARB,

valsartan, compared with the calcium channel blocker, amlodipine, also showed a greater reduction in microalbuminuria levels in those treated with the former.²⁴

Finally, in patients with advanced renal disease (proteinuria and/or mild renal failure), two other studies with the ARBs irbesartan²⁵ or losartan²⁶ have demonstrated their ability to slow the progression of the disease by reducing the combined endpoint of doubling the levels of serum creatinine, end-stage renal disease, or death.

RESIDUAL RISK MANAGEMENT IN DIABETIC PATIENTS TREATED WITH RAS INHIBITORS

As a result of abovementioned evidence, the current situation is that a vast majority of diabetic patients are currently treated with a RAS blocker. Such treatment will reduce the urinary excretion of albumin and, to a lesser extent, the progression of renal disease, as well as a reduction in the incidence of cardiovascular disease is expected. However, the high probability of developing cardio-renal events in diabetic patients means that, even assuming such reduction, the incidence will still be high. It seems logical to investigate the possible effects of new treatment strategies in order to achieve a greater reduction of this residual risk. In this regard, both a strict control of blood pressure values and the simultaneous management of other risk factors play an important role in the protection of the diabetic patient. However, even taking this into account, some preliminary evidence also suggests the usefulness of a more complete or a better blockade of the RAS.

Two possibilities could be theoretically anticipated in order to obtain a better RAS blockade. Firstly, using drugs promoting a blockade of the RAS in the initial phase of the

cascade, with the theoretical advantages that this entails. Some experimental evidence of direct renin inhibitors (DRI) might support this option. Secondly, a more complete RAS blockade by the simultaneous use of two RAS inhibitors, combining ACE inhibitors and ARB, or combining one of these two classes with a DRI.

A Possible Differential Role of DRI in Diabetes

Aliskiren is the first and unique DRI available approved for oral treatment of hypertension. Some particularities in its mechanism of action could be of interest in diabetic patients (Table 2). Diabetes is characterized by hyperactivation of the RAS especially at the intracellular and interstitial levels. In this regard, although both ACE inhibitors and ARB are able to act at the tissue level, it has been reported that only aliskiren could be effective in blocking the intracellular RAS.⁴

Another theoretical advantage of aliskiren is that, as compared with ACE inhibitors or ARB, it does not promote an increase in plasma renin activity (PRA).³⁵ Although the clinical significance of this feature is still unknown, elevated PRA has been associated with a worse cardiovascular prognosis in large clinical trials.^{36,37} Finally, diabetes is also characterized by an increase in pro-renin, which is able to be converted in active renin when joining

its specific receptor. Treatment with aliskiren impairs this conversion in active renin and chronic treatment has also been associated with a down-regulation of the renin receptor. All these actions could theoretically be beneficial when treating patients with diabetes.³⁸

Some clinical evidence preliminarily supports these advantages. Thus, unlike other antihypertensive drug classes, the BP reduction during treatment with aliskiren seems not to be impaired in diabetics with respect to non-diabetics, as reported in a pooled analysis of 10 randomized trials.³⁹ Whether this could be translated into better organ protection in diabetic patients is currently under investigation.

Simultaneous Dual RAS Blockade

The simultaneous use of an ACE inhibitor and an ARB-2 in diabetic patients has been evaluated regarding antihypertensive and antiproteinuric effects, as well as cardiovascular protection. A meta-analysis published some time ago⁴⁰ showed that the simultaneous administration of ACE inhibitors and ARB had no important additive effects, with reductions of approximately 4 mmHg compared to monotherapies, less than observed with other types of antihypertensive combinations. Data in patients with diabetes were too scarce to draw any conclusion. With respect to the antiproteinuric effect itself, combination therapy with ACE inhibitors and ARB clearly promotes a more pronounced decrease in urinary excretion of albumin than either one or the other drug class.⁴¹ However, this benefit has not been translated into greater cardiovascular or renal protection. Thus, in the only outcome study, which included more than 30% of diabetics, the combination of telmisartan and ramipril did not result in a greater benefit either in the cardiovascular or the renal outcomes, but it was associated with

Table 2. Particularities of the mechanism of action of aliskiren which could have some impact in diabetic patients.

Inhibition of the RAS cascade at the beginning
Reduction in PRA levels during chronic treatment
Inhibition of pro-renin activation at the receptor level
Inhibition of the intracellular RAS

RAS=renin angiotensin system; PRA=plasma renin activity

a higher rate of treatment-related adverse events and dropouts.^{19,42}

The role of a different dual RAS blockade based on a combination of a DRI and either an ACE inhibitor or an ARB has also been evaluated in terms of antihypertensive efficacy, cardiac biomarkers, and antiproteinuric effects (Table 3). Moreover, other elements of cardiac protection have appeared when the subgroup of diabetic patients has been examined, and a large study of cardiovascular and renal protection is currently ongoing.

Firstly, the antihypertensive efficacy of aliskiren in combination with other RAS blockers has been evaluated in two studies using ramipril and valsartan, respectively.^{43,44} In the former, 837 hypertensive diabetics were randomized to ramipril (5 to 10 mg), aliskiren (150 to 300 mg), and their combination. The latter showed a superior antihypertensive effect in comparison to the monotherapies, with average decreases of 4.6/2.1 compared to ramipril. The second study included 1797 hypertensive patients randomized to receive aliskiren 300 mg, valsartan 320 mg, or their combination. Again the combination was superior to the monotherapies. Although no specific analysis was performed in the subgroup of diabetics, a group of trials specifically looking at diabetics is currently ongoing (TARGET HIGHER program).

Secondly, two studies assessing the effect of aliskiren on markers of cardiac damage have

specifically analyzed the subgroup of diabetic patients included in the overall cohort study. The former evaluated the effect of aliskiren 300 mg, losartan 100 mg, or their combination for 9 months on left ventricular mass, determined by magnetic resonance imaging in patients with left ventricular hypertrophy.⁴⁵ Final results showed no differences among the three treatment groups in the reduction of ventricular mass (5.4%, 4.7%, and 6.4%, respectively). However, the heterogeneity analyses revealed an influence of the diabetes status, with greater reductions in left ventricular mass in diabetics receiving the combination of aliskiren and losartan.⁴⁵ A similar finding was seen in a more recent study, which evaluated the effect of aliskiren when added to standard therapy including an ACE inhibitor or an ARB on ventricular remodeling after a myocardial infarction.⁴⁶ Without differences between aliskiren and placebo in the overall cohort studied, the subgroup analyses also revealed a significant effect of aliskiren in reducing ventricular remodeling in diabetics.⁴⁶

Thirdly, the main level of evidence that suggests a potential role of aliskiren in patients with diabetes comes from studies that have focused on reducing proteinuria. Among them the most important is the Aliskiren In The Evaluation Of Proteinuria In Diabetes (AVOID) study.⁴⁷ in which nearly 600 patients with diabetic nephropathy were randomized to receive aliskiren or placebo added to background therapy with losartan. At the end of the study, the group that received aliskiren showed a significantly greater reduction (20%) in urinary albumin excretion. Another study combining aliskiren and irbesartan yielded the same results.⁴⁸

Of particular interest is the evaluation of renal adverse effects in the AVOID study. Previous studies with ACE inhibitors and ARB used in combination showed that despite a greater

Table 3. Effects of aliskiren on cardio-renal markers in diabetic patients.

Reduction in proteinuria combined to losartan vs. losartan alone in diabetic nephropathy
Reduction of post-MI LV remodeling compared to placebo
Reduction of LV mass combined to losartan vs. losartan alone in LVH patients
MI=myocardial infarction; LV=left ventricular; LVH=left ventricular hypertrophy

effect on proteinuria, this treatment was often accompanied by an increased rate of renal adverse events, including an accelerated loss of renal function and hyperkalemia. Indeed, in the ONTARGET trial,²⁷ more cases of acute renal failure and need of temporary dialysis was observed in patients simultaneously receiving telmisartan and ramipril. By contrast, data from the AVOID trial⁴⁷ did not show the same profile of adverse effects with the use of aliskiren. Thus, the decline in glomerular filtration rate was similar in the group treated with both aliskiren and losartan compared to those receiving losartan alone. Moreover, overall rates of hyperkalemia were similar (5% in the aliskiren group and 5.7% in the placebo group). In a subsequent analysis of the subgroup with more impaired renal function at baseline (stage 3: glomerular filtration rate 30-60 mL/min/1.73 m²), the rate of patients developing significant renal dysfunction (creatinine above 2 mg/dL) was higher in the placebo group than in the aliskiren treated group⁴⁹ (Figure 1).

Figure 1. Proportion of patients with stage 3 chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m²) who develop renal dysfunction (serum creatinine >2 mg/dL) after treatment with losartan or with the combination of aliskiren and losartan. The AVOID study.⁴⁹ **P*=0.032 vs. placebo + losartan group.

CONCLUSION

These results are clearly encouraging and suggest that treatment with aliskiren in combination with other RAS inhibitors may result not only in a reduction in proteinuria, with the beneficial effect that it supposedly entails, but also the theoretical possibility of a long-term renal protection. This hypothesis has resulted in the design of a large outcome study in diabetics with renal disease. Thus, the Aliskiren Trial in Type 2 Diabetics Using Cardio-Renal Endpoints (ALTITUDE) is currently examining the effect of aliskiren added to standard treatment, which should include an ACE inhibitor or an ARB, on both cardiovascular and renal outcomes in more than 8600 diabetic patients with nephropathy (either proteinuria or reduced GFR along with microalbuminuria or previous history of cardiovascular events).⁵⁰ The study is currently underway and final results are expected in 2013. A possible positive outcome will probably modify the current approach for RAS blockade in diabetic patients and will position DRI as the drug of choice, alone or combined with other RAS blockers.

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