

RAS Blockade for Every Diabetic Patient: Pro and Con

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The first part of this manuscript offers an overview of clinical data supporting the use of renin-angiotensin system (RAS) inhibitors in every patient with type 1 or type 2 diabetes, based on the known role of the RAS in blood pressure regulation and organ protection. In the second part, a possible, relevant role of drugs other than RAS-active compounds in treating hypertension and preventing cardiovascular disease in type 2 diabetic patients is underlined, paying particular attention to calcium-channel blockers, either alone or, better, in combination with ACE inhibitors.

PRO ARGUMENT—The guidelines of the European Society of Hypertension and the European Society of Cardiology recognize that the first monotherapy to be given to a diabetic patient with elevated blood pressure is an RAS suppressor, either an ACE inhibitor or an angiotensin receptor blocker (ARB) when micro- or macroalbuminuria are present (1). They also recognize that in order to lower blood pressure, all effective and well tolerated drugs can be used. Having admitted the possibility of non-RAS suppression therapies as first line, the guidelines continue by saying that the great majority of diabetic patients will sooner or later present hypertension and that most of them will require combination therapy. In this case, they specify that a blocker of the RAS should be a regular component of the combination and the one preferred when monotherapy is sufficient. In summary, an RAS

blocker should be used when an elevation of blood pressure, even within the high normal range, is detected.

The recent reappraisal of European Society of Hypertension Guidelines (2) confirms that initiation of therapy in the high normal range is reserved for diabetic patients with some degree of target organ damage (TOD), in particular microalbuminuria.

Are the guidelines wrong? Probably not, because RAS suppression has three different aspects:

- 1) Capacity to control blood pressure alone or in combination
- 2) Capacity to prevent and/or regress TOD
- 3) Capacity to protect patients with high global cardiovascular risk

I will briefly analyze these three aspects that have led the European Society of Hypertension and the European Society of Cardiology to consider that every diabetic patient deserves to be treated with an ACE inhibitor or an ARB.

Capacity to control blood pressure alone or in combination

RAS suppressors have been shown to be good antihypertensive drugs with a capacity to lower blood pressure similar to that of other monotherapies. Particularly in combination with a diuretic and/or a calcium channel blocker, they have shown very positive and early results specifically in the form of fixed combinations as shown by the data of the ACCOMPLISH

(Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension) study (3). Other combinations with a β -blocker or an α -blocker are much less frequently used (except when specific combinations for β -blockers are present). So from the point of view of capacity to attain the elected blood pressure goal, there is no reason to consider any other type of therapy as preferential.

Capacity to prevent and regress TOD

The cardiorenal continuum described by Dzau et al. (4) can be subdivided in clinical practice into three stages: the first is that in which we only detect cardiovascular risk factors (in the case of diabetes) in the absence of what characterizes the second and third stages; second is asymptomatic TOD (the most commonly detected in clinical practice are albuminuria, a diminished estimated glomerular filtration rate, and the presence of electrocardiogram alterations compatible with left ventricular hypertrophy [LVH]); and the third is symptomatic TOD or overt cardiovascular disease.

The finding of TOD represents an advanced stage in the cardiorenal continuum predicting that the time to initiation of symptomatic TOD or overt disease is nearer than compared with the previous stage.

In diabetic patients, renal protection includes prevention of new onset microalbuminuria, which has been shown to be dependent on the combination of blood pressure control and RAS suppression by the BENEDICT (Bergamo Nephrologic Diabetes Complications Trial) and the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) studies (5,6). The latter study also proved that these two objectives ensure a decrease or even a normalization of albuminuria and a decrease in the progression of advanced diabetic nephropathy (6,7). However, more strict blood pressure control (attaining values <120 mmHg for systolic blood pressure together with RAS suppression and of course other medications) could be partly deleterious for renal function as shown by the ACCORD (Action to

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The pro argument is made by L.M.R., and the con argument is made by A.S.

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Control Cardiovascular Risk in Diabetes) study (8).

Diminution of albuminuria with RAS suppressors has been shown to protect the cardiovascular system from future events as shown by the LIFE (Losartan Intervention For Endpoint reduction in hypertension) and RENAAL (Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan) studies (9,10)

With respect to LVH, this cardiac alteration can be prevented with trandolapril, as shown in the BENEDICT and TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Patients with Cardiovascular Disease) studies (5,11), and the use of RAS suppressors together with that of calcium channel blockers has been shown to be the best to regress/reduce LVH even to normal ranges (12).

In summary, available data indicate that RAS suppressors are particularly suitable to prevent or regress TOD.

Capacity to protect patients with a high global cardiovascular risk

Diabetic patients are considered to have a level of risk similar to that observed in nondiabetic patients in situations of secondary prevention (13), in which the administration of RAS suppressor is mandatory in order to prevent cardiovascular events and death. This has been shown by the meta-analysis of HOPE (Heart Outcomes Prevention Evaluation), EUROPA (European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease), and PEACE (Prevention of Events with Angiotensin-Converting Enzyme Inhibition) studies (14). The need for an ACE inhibitor or an ARB in diabetic patients cannot only be based on the presence of TOD, in particular albuminuria, but should also include the potential capacity of these drugs to diminish atherothrombotic events. This statement puts an end to the sterile discussion that RAS suppression does not protect renal function in the absence of albuminuria (longer follow-ups are needed to provide further proof) because cardiovascular protection makes the use of these drugs mandatory, independent of renal outcome.

In summary, diabetic patients deserve to be treated either with an ACE inhibitor or an ARB immediately when they are diagnosed, provided blood pressure is in the range of high-normal or above. In cases where symptomatic TOD is present,

treatment with an ACE inhibitor or ARB is recommended even if blood pressure is within normal range.

CON ARGUMENT—RAS-active compounds have revolutionized the therapeutic approach to the treatment of hypertension, becoming one of the most innovative classes of drugs discovered over the past 5 decades. However, despite their proven efficacy in slowing the progression of renal damage during the course of both type 1 and type 2 diabetes through their powerful antiproteinuric effect (15–17), some concerns can be raised regarding the compelling indication to their use in every patient with type 1 or type 2 diabetes. These concerns can be summarized in three main points: 1) the real nephroprotective effect in type 2 diabetic patients with normal albumin excretion rate is still under debate; 2) trial evidence of superiority in reducing cardiovascular risk when compared with other antihypertensive drugs—such as diuretics or calcium channel blockers—is lacking; and 3) although RAS blockers are credited with cardioprotective mechanisms other than blood pressure lowering (reduction in angiotensin II-mediated vasoconstriction, thrombosis, salt/water retention, oxidative stress and inflammation, and promotion of vascular remodeling and restructuring [18]) it is uncertain that these ancillary mechanisms add significantly to the reduction of cardiovascular risk in patients with diabetes.

RAS-active compounds and nephroprotection in type 2 diabetes

The only randomized clinical trial documenting efficacy of an ACE inhibitor in the primary prevention of diabetic nephropathy (or, better, its early marker microalbuminuria) in type 2 diabetes is BENEDICT, a placebo-controlled study in which ramipril significantly reduced the incidence of microalbuminuria over a 5-year follow-up (5). So far, this result has not been convincingly replicated using an ARB, as shown by the recent DIRECT (Diabetic Retinopathy Candesartan Trial) study (19). Here, three large cohorts of normoalbuminuric patients with type 1 or type 2 diabetes and different degrees of retinal involvement were randomized to receive candesartan or placebo. Although the primary outcome was progression of retinopathy, incidence of microalbuminuria was also analyzed, and the ARB did not perform better than placebo over a period of 5 years.

RAS-active compounds and reduction of cardiovascular risk

Regarding this second point, it is relevant to recall that one of the most complete meta-analyses so far performed of primary and secondary prevention trials indicates that reduction of blood pressure, in particular systolic pressure, per se can account for the main cardiovascular outcomes (20). Aggregate information from the numerous clinical trials published over the last few years is consistent with the conclusion that the four main classes of drugs—diuretics, RAS-active compounds, calcium channel blockers, and β -blockers—have a substantially identical antihypertensive efficacy. For example, a meta-analysis of 354 randomized trials including more than 40,000 individuals on active treatment and 16,000 on placebo, concluded that a standard dose of any of these drugs induces equivalent response, reducing systolic values by 9.1 mmHg and diastolic values by 5.5 mmHg (21); similarly, no difference in the antihypertensive effect is detected among different drugs in type 2 diabetic individuals, even in head-to-head comparison (22). Thus, in most patients, a standard dose of a RAS-active compound is likely to exert an antihypertensive effect comparable to that of any other antihypertensive agent. In addition, several large, long-term studies carried out over the last 10 years have shown that the different classes of antihypertensive drugs are equally effective in the prevention of mortality or cardiovascular events in type 2 diabetes. The INVEST (International Verapamil-Trandolapril Study) study, including more than 22,500 hypertensive patients with coronary impairment, compared a nondihydropyridinic calcium channel blocker and a β -blocker, with the opportunity to add an ACE inhibitor or a diuretic in order to reach the target. The two treatments achieved similar systolic and diastolic blood pressure plateaus, but there was no difference in the primary end point (all-cause death, nonfatal myocardial infarction, and nonfatal stroke) either in nondiabetic or diabetic patients (23). The IDNT (Irbesartan versus Amlodipine Diabetic Nephropathy Trial) (24), with more than 1,700 patients with hypertension and nephropathy, while documenting a remarkable nephroprotective effect of the ARB, was unable to show superiority of irbesartan in terms of incidence of major cardiovascular events, cardiovascular and total mortality. In the latter study, cardiovascular risk

reduction was not the primary outcome. However, other studies with a cardiovascular primary end point have failed to attain superior cardiovascular protection with RAS-active compounds (25). In TRANSCEND, performed in a large cohort of patients intolerant to ACE inhibitors with cardiovascular disease or diabetes with end-organ damage, telmisartan had no significant effect on the primary outcome (the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure) at the end of a 5-year follow up, despite significantly lower blood pressure values achieved in the treatment group (26).

The cardiovascular effects of a dual blockage of RAS require mention. In the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study, the combined use of telmisartan and ramipril was associated with more adverse events in patients with established atherosclerotic vascular disease or with diabetes and end-organ damage (27). In a separate prespecified analysis aimed to test the superiority of this treatment in preventing proteinuria, an adverse effect of combination therapy on typical renal outcomes and on decline of glomerular filtration rate was evident (28). It is well known that the American Heart Association guidelines do not currently recommend the combined use of ACE inhibitors and ARBs.

Another element to consider when starting an antihypertensive therapy should be the ethnicity of the patients. Information from both ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) and LIFE studies (29,30) clearly establish the primacy of diuretic-based over RAS compounds-based therapy in the management of black hypertensive patients without renal disease or heart failure, confirming the lesser benefit of RAS inhibitors in preventing cardiovascular outcomes in this ethnic group. These trials have provided further refinement that guides the use of RAS inhibitors for control of hypertension.

Recently, this nonsuperiority of RAS-active compounds in protecting the heart has been extended to prediabetic states. In the NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) study in patients with impaired glucose tolerance and established cardiovascular disease or risk factors, valsartan but not nateglinide reduced the incidence of type 2 diabetes but failed to affect the cardiovascular event rate

(composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina) when compared with placebo (31). Similarly, in DREAM (Diabetes REDuction Assessment With ramipril and rosiglitazone Medication) ramipril did not reduce the incidence of the primary end point (death or diabetes onset) in >5,200 patients with impaired fasting glucose or impaired glucose tolerance (32).

Evidence accrued from meta-analyses, however rigorous, may miss important details. For example, one might ask whether the various antihypertensive agents differ in cardioprotection *vis* cerebrovascular protection. Here, the comprehensive evaluation carried out by the Blood Pressure Lowering Treatment Trialists' Collaboration, may offer helpful clues. In over 33,000 diabetic patients and 125,000 nondiabetic individuals allocated to different antihypertensive drug classes as well as more versus less aggressive therapeutic schemes, the following results were obtained. First, the different drugs are always better than placebo, and the intensive rather than conventional antihypertensive treatment makes the real difference in terms of prognosis. Second, no difference between ACE inhibitors and other classes was detected for major cardiovascular events (33). However, ACE inhibitors and, even more, ARBs were slightly better in reducing risk of coronary artery disease, whereas calcium channel blockers provided significant advantages in terms of cerebrovascular protection. Several years ago, Verdecchia et al. (34) performed a similar meta-analysis of 28 placebo-controlled trials, (180,000 patients) to test whether different drug classes differed for heart or brain protection. The results confirmed a better efficacy of ACE inhibitors in preventing myocardial infarction and superiority of calcium channel blockers in preventing stroke, irrespective of the attained blood pressure values. More recently, these observations have been supported by a huge meta-analysis including almost half a million patients in three categories: no personal history of cardiovascular disease, history of cardiovascular disease, and personal history of stroke. All drug classes showed the same efficacy in reducing cardiovascular disease for any given level of blood pressure reduction; the only compounds showing a small additive effect were, as expected, β -blockers in the 3

months immediately following an acute myocardial infarction, and calcium channel blockers in the prevention of stroke. Neither the pretreatment of blood pressure nor the preexistence of cardiovascular disease seemed to play any role. The higher the blood pressure, the better the drug effect with the effect of age being marginal (35).

Obviously, such clues as are derived from the compilation of heterogeneous material cannot constitute indications; nevertheless, they may help the therapeutic choice in the individual patient with a specific phenotype (e.g., with a strong family history of stroke).

The real role of the "ancillary mechanisms"

It is relevant to try to point out the real weight of ancillary mechanisms, for example the anti-inflammatory effects exerted by RAS-active drugs, in preventing macrovascular complications in type 2 diabetes. Several observations performed in cell and animal models have documented relevant anti-inflammatory and antiproliferative properties of RAS-active compounds (36) that have the potential to improve myocardial function and performance (37) and vascular dispensability by reducing arterial stiffness (38). In theory, all these mechanisms should translate into cardiovascular benefit in the patient with diabetes; however, clinical trial evidence for a material role of the so-called "pleiotropic effects" is, at present, scanty, given that in the presence of comparable blood pressure levels, RAS-active drugs do not seem to offer any supplementary cardiovascular protection.

One might object that it is very difficult to reach an adequate blood pressure control in type 2 diabetic patients using just one compound: combination therapy is often required from the very beginning. From this perspective, a RAS-active drug should definitely be used, especially for its nephroprotective effect. This is definitely true, but the clinical complexity of diabetes should favor specific associations. For example, several clinical trials have shown that calcium channel/RAS blockade combinations provide greater blood pressure reductions and improve renal function and metabolic outcomes in patients with diabetic and nondiabetic kidney disease early and to a greater extent than diuretic-based combinations (39), presumably also by increasing arterial compliance, arterial dispensability, and flow-mediated vasodilation.

In conclusion, improvement in blood pressure control in patients with type 2 diabetes and hypertension is associated with a definite, clinically relevant reduction in risk of micro- and macrovascular disease. RAS-active compounds clearly provide better nephroprotection than other antihypertensive agents, but they may be equal in terms of cardioprotection. Irrespective of the drug class, an optimal blood pressure control often requires the use of several compounds, if the benefits are to be sustained.

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