Advantages of Renin-Angiotensin System Blockade in the Treatment of Cardiovascular Diseases

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The renin angiotensin system (RAS) plays a key role in the regulation of cardiovascular function, with angiotensin II being involved in homeodynamic and non-hemodynamic mechanism in the pathophysiology of cardiovascular disease. A number of studies demonstrated that pharmacological modulation of the RAS, either with angiotensin converting (ACE) inhibitor or an angiotensin II receptor blocker (ARB), provides cardiovascular and renal protection. Blockade of the RAS, either with ACE inhibitors or ARBs, decreases cardiovascular morbidity and mortality in high risk patients. ACE inhibitors as well as ARBs are drugs of choice in congestive heart failure, as well as in diabetic nephropathy. Especially, the combined RAS blockade with ACE inhibitors and ARBs was more effective than monotherapy in diabetic or non-diabetic nephropathy with proteinuria. However, this combined RAS blockade was not equally dominant in treatment of hypertension and was not recommended for widespread antihypertensive use. Key words: renin angiotensin system ACE inhibitors, angiotensin II receptor blocker.

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1. RAS AND CARDIOVASCULAR DISEASES

The RAS plays a major role in control of blood pressure. The key physiological role of the RAS is to maintain blood pressure in situations where renal blood flow or blood volume is reduced. Therefore, in healthy, well hydrated individuals, this system is relatively inactive. In some patients with essential hypertension, elevated renin levels were found and so called hyperreninemic form of hypertension was diagnosed. This meant that the RAS was directly responsible for the increased values of blood pressure. Within the RAS, angiotensin II has the key role in development of the chain of pathophysiological conditions. Furthermore, it is also established that angiotensin II plays a role of paramount importance in the chain of events, that leads to the clinical picture of both hypertension and heart failure that ultimately determines the prognosis of individuals with a blood pressure elevation or an impaired heart (1, 2). Angiotensin II causes a release of catecholamine from the adrenal gland, oxidative stress, endothelial dysfunction, growth in vascular smooth muscles, increase of fibroblasts, inflammation, vasoconstriction, thrombosis and vascular remodeling. It also releases metalloproteinase that can cause a rupture of atherosclerotic plaque (3). It has long been recognized that the blockade of the RAS would be desirable from a therapeutic point of view in conditions such as hypertension, congestive heart failure and diabetic nephropathy. Angiotensin II, the major effector peptide of the RAS, has several detrimental actions, as mentioned above (1). In addition to its role in regulating blood pressure, RAS is involved in altering the process of structural adaptation of the heart. By means of that it contributes to the development of left ventricular hypertrophy (LVH), heart failure and renal disease in patients with hypertension. As a result, blockade of the RAS with ACE inhibitors or ARBs is a key element of strategies to reduce cardiovascular risk. Several possibilities aiming at the suppression of these deleterious activities have been explored (1, 4).

Drugs that interfere with angiotensin II formation reduce arterial pressure and can reverse remodeling effects of angiotensin II (5). This is why RAS blockade provides a rational approach to the treatment of hypertension, renal diseases, heart failure and of cardiovascular diseases in general. Through of blockade of the RAS we can stop the pathophysiological and cardiovascular continua. Three groups of drugs that can block the RAS are presently available: ACE inhibitors, ARBs and renin inhibitors. The two most established classes of RAS blockers, ACE inhibitors and ARBs, are effective antihypertensive agents and are widely used to treat hypertensive target organ damage.
2. ACE INHIBITORS AND RAS BLOCKADE

ACE inhibitors are recommended as the first line therapy in the management of hypertension as well as the therapy for conditions such as heart failure, left ventricular dysfunction, myocardial infarction, diabetes mellitus, or recurrent stroke. ACE inhibitors are drugs of choice in the treatment of hypertension and LVH. They protect the blood vessels indirectly by the antihypertensive effect, and directly inhibit carotid atherogenesis and thrombogenesis. Accordingly, ACE inhibitors have antithrombotic, anti-ischemic and anti-atherosclerotic effects. The HOPE study emphasized their role in cardiovascular protection in high risk patients (6). In this study, 9297 patients aged ≥55 years with a history of coronary artery disease, stroke, peripheral vascular disease or diabetes plus at least one additional cardiovascular risk factor were treated with ramipril or placebo for 4 years. Ramipril treatment was associated with a 22% reduction in risk of combined myocardial infarction, stroke and cardiovascular mortality (relative risk, 0.78; 95% confidence interval (CI), 0.70–0.86; \( P < 0.001 \)), an effect that, to some extent, was independent of blood pressure lowering. The benefits of ACE inhibitors have also been evaluated and confirmed in specific subgroups of patients, including patients with previous stroke or transient ischemic attack in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and elderly patients in the Second Australian National Blood Pressure Study (7, 8). Given at the start of myocardial infarction, they may act to prevent post-infarction remodeling and decrease the incidence of left ventricular failure. So, they have been shown to be effective in the treatment of hypertension and congestive heart failure, and to exhibit protective effects on arteries, the heart and the kidneys.

In addition, these drugs have a favorable hemodynamic and metabolic profile and protect the vascular tree. The ACE inhibitors have the effect of increasing availability of bradykinin, which serves both as a vasodilator and growth inhibitor. In turn, bradykinin appears to stimulate nitric oxide and prostaglandin \( E_2 \), providing yet further vasodilator actions. This has been one of the essential differences between ACE inhibitors and ARBs because the beneficial effects of kinins such as nitric oxide (NO) and PGJ_{2} release may be diminished during ARB therapy (1, 2).

As summarized by the Blood Pressure Trialists’ in trials up to 2005, ACE inhibitors based therapy was better than placebo against stroke, coronary heart disease, heart failure, major cardiovascular events, cardiovascular death, and total mortality (5). When compared against diuretic/beta blocker based therapy, ACE inhibitor based therapy provided equal protection against stroke, coronary heart disease, and chronic heart failure. When compared against calcium channel blockers based therapy, ACE inhibitor therapy was 19% better for chronic heart failure risk (5).

2.1. ARBs, hypertension and RAS blockade

ARBs have proven to be efficacious and superior to placebo in large controlled trials. The hypotensive effect of the available compounds lasts 24 hours, and therefore they can be used as once daily drugs. In comparative studies, ARBs were equipotent to ACE inhibitors, hydrochlorothiazide, beta blockers, and calcium antagonists (9). In trials with hard end points such as end-stage renal failure in diabetic nephropathy and stroke in left ventricular hypertrophy, they were better than comparators (10). Furthermore, systemic review of 50 studies comparing ACE inhibitors with ARBs revealed similar blood pressure control and outcomes yet with less cough during ARB therapy (11). The angioedema associated with ACE inhibitors does not occur with ARBs, although ARBs should be prescribed cautiously in patients with a history of ACEI-induced angioedema.

It was believed that effective blockade of the RAS could not be achieved with ACE inhibitors. Treatment with ACE inhibitors leads to reactive renin stimulation due to interruption of angiotensin II induced feedback control of renin release. This increase in plasma renin activity may ultimately lead to increased angiotensin II generation by ACE-independent synthetic pathways (chymase) (12). This is why it was supposed that RAS blockade would be more efficacious and complete in combination with an ARB. The widespread use of this combination has now been questioned by the results of ONTARGET, in which the combination of full doses of telmisartan and ramipril reduced the initial blood pressure values slightly more than the reduction seen with the administration of one or the other drug alone, without, however, any further reduction in cardiovascular or renal endpoints (except proteinuria), and indeed with a greater number of renal side effects and a more frequent discontinuation of the initial treatment (13). In the group that received the combination of ramipril and telmisartan there was a significant increase of hyperkalemia, hypotension and renal dysfunction. Clearly, however the ACE inhibitor/ARB combination did not offer that advantage in the management of hypertension. On the basis of ONTARGET study, the use of the ACE inhibitor/ARB combination cannot be recommended in the treatment of hypertension.

2.2. Left ventricular hypertrophy

The presence of LVH in patients with hypertension is an independent risk factor for development of heart failure, acute myocardial infarction, stroke and sudden cardiac death. There is an evident relationship between LVH and the RAS. Out of the leading five hypertensive drugs, calcium channel blockers, ACE inhibitors, and ARBs reduce left ventricular mass to a greater extent than do \( \beta \) blockers (including vasodilator \( \beta \) blockers) and diuretics. In a prospective trial (Losartan Intervention For Endpoint reduction in hypertension [LIFE] study) with hypertensive patients who had left ventricular hypertrophy at baseline the investigators consistently reported that reduction of left ventricular hypertrophy was greater with the ARB losartan than with the \( \beta \) blocker atenolol, and this effect was maintained at similar blood pressure levels throughout the whole follow-up of 5 years (14). In the LIFE study, both protection against sudden death and the incidence of new diabetes were related to the regression of LVH. The drugs which block the RAS cause to the most sig-
nificant reduction in LVH, with ARBs and ACE inhibitors being stronger than other antihypertensive drugs. Decreasing LVH leads to reduction in cardiovascular risk (15).

### 2.3. Congestive heart failure

Congestive heart failure is one of the sequelae of long standing hypertension. There is good evidence that increased levels of angiotensin II and aldosterone with vasoconstriction and sodium retention have adverse effects in congestive heart failure. Therefore, blocking the RAS, whether at the level of angiotensin II production (with ACE inhibitors) or at the angiotensin II receptor site would be beneficial. ACE inhibitors have changed our understanding and treatment of congestive heart failure. Several studies have shown that patients with congestive heart failure due to systolic dysfunction, either symptomatic or asymptomatic, with an ejection fraction less than 35%, who received an ACE inhibitor showed a statistically significant reduction in mortality compared with patients who did not receive an ACE inhibitor. It seems that ARBs are as effective as ACE inhibitors and produce less side effects than ACE inhibitors in patients with congestive heart failure. Adding the ARB to the ACE inhibitor gave better results in more severe heart failure with the mean ejection fraction about 25% (ValHeft and CHARM trial) (16, 17).

In the VALIANT study, combining the ACE inhibitor, captopril, with the ARB, valsartan, increased the rate of adverse events without reducing the primary outcomes, although in post hoc analysis a reduction in the risk of hospitalization for heart failure was documented (18).

#### 2.4. Atrial fibrillation

The RAS plays an important role in occurrence and recurrence of atrial fibrillation. Guidelines suggested angiotensin receptor antagonists and ACE inhibitors as preferred drugs in hypertensive patients at risk of developing atrial fibrillation. Hypertension is the most important risk factor for atrial fibrillation. Treatment with ARBs reduced the frequency of atrial fibrillation in patients without atrial fibrillation at baseline by 21%. In another large scale prospective study with hypertensive patients at high cardiovascular risk new atrial fibrillation onset was less frequent in those on ARBs than in those on calcium antagonists (19). However, in two trials, treatment with ACE inhibitors seemed not to reduce the rate of new atrial fibrillation onset in hypertensive patients (20, 21). Nevertheless, in patients with congestive heart failure, both ACE inhibitors and ARBs were effective in the reduction of the development of atrial fibrillation. Two specific trials have been completed quite recently CAPRAF and GISSI-AF and their results are not supportive of protective effects from angiotensin receptor antagonists against recurrence of atrial fibrillation (22, 23).

The results of a meta-analysis demonstrate that the RAS plays a role in atrial structural and electrophysiological remodeling. Angiotensin II activates pathways leading to atrial fibrosis, and can affect outward potassium current involved in the pathogenesis of atrial fibrillation. The most consistent evidence that ACE inhibitors and ARBs prevent atrial fibrillation is in studies on the prevention of atrial fibrillation in patients with heart failure and on the prevention of atrial fibrillation post-cardioversion and during medical therapy for paroxysmal atrial fibrillation (24). In another meta-analysis including almost 12 000 patients with systolic heart failure, and therefore at high risk of atrial fibrillation, beta-blockers were found to significantly reduce (by about 27%) the incidence of atrial fibrillation. A history of atrial fibrillation and systolic heart failure may be a specific indication for using b-blockers (25, 26).

#### 2.5. Cerebrovascular diseases

The best prevention from stroke is successful blood pressure control. Studies show ARBs and, to a certain degree, ACE inhibitors to be efficacious in stroke prevention beyond blood pressure control. How can this result be explained? (4). In animal studies, treatment with ARBs improved neurological outcome of focal cerebral ischemia and protected brain tissue against ischemic injury. The use of ARBs can not only prevent ischemic effects of angiotensin II, which take place through AT1 receptors, but also may stimulate AT2 receptors, leading to improvement of the brain ischemia. In the brain region adjacent to the infarct area, AT1 receptor density remained unaltered but AT2 receptors were upregulated in neurons, and selective blockade of central AT2 receptors abolished the neuroprotective effect of ARBs (27). In hypertensive patients with left ventricular hypertrophy but without previous stroke, the LIFE study showed a 25% reduction in strokes with ARB based regimen than the β blocker based regimen (14). In the Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) trial, the ARB eprosartan was associated with a reduced risk of recurrent stroke compared with the calcium channel blocker nitrendipine, despite a similar reduction in blood pressure (28). Treatment with ARBs reduces the risk of both primary and secondary stroke beyond the effects of blood pressure lowering. Data clearly show that the protection from stroke is greater with ARB treatment than with ACE inhibitors (29). Recently, an extensive meta-analysis showed that ARBs seem to offer superior protection against Alzheimer’s disease and dementia compared with other antihypertensive and cardiovascular drugs (30).

#### 2.6. Kidney diseases and diabetic nephropathy

The RAS plays an important role in the pathogenesis of kidney diseases and diabetic nephropathy. RAS blockade with ACE inhibitors and ARBs may stop further progression of renal disease. With the introduction of ACE inhibitors in the treatment of diabetic nephropathy, the number of patients treated with dialysis has been reduced to the half. Studies show ACE inhibitors and ARBs to have the strongest anti-proteinuric effect associated with renoprotective and vasculoprotective effect, when compared with other antihypertensive drugs. In patients with diabetes and diabetic nephropathy, ACE inhibitors and ARBs significantly reduce progression of the renal disease. Reduction of existing proteinuria has been documented both in diabetic and in non-diabetic patients. In addition to being renoprotective, ACE inhibitors and ARBs have also been shown to reduce cardiovascular events in diabetic
patients. Post-hoc analysis of these trials (Reduction of Events with Angiotensin Converting Enzyme Inhibition [RENAAL] and Irbesartan Diabetic Nephropathy Trial [IDNT]) showed a reduction of cardiovascular morbidity and mortality (31, 32). In diabetic patients with atherosclerotic disease, the HOPE and sub-study investigations documented that ramipril lowered cardiovascular death by 37% and total mortality by 24% (33). In VALUE and LIFE studies, there were fewer new cases of diabetes in the ARB cohort. An important finding with ACE inhibitors and ARBs, especially when compared with beta blockers or diuretics, is the decreased development of new diabetes.

In type 1 diabetic nephropathy, ACE inhibitors have been shown to reduce proteinuria and protect against progressive glomerular sclerosis and loss of renal function. In type 2 diabetic nephropathy, trials with ARBs have shown similar renal protection.

3. CONCLUSION

The RAS plays a key role in development of hypertension, heart failure and nephropathy associated with proteinuria. RAS blockade with ACE inhibitors and ARBs may stop further progression of heart failure, as well as progression of renal failure, diabetic and non-diabetic nephropathy with or without proteinuria. Blockade of the RAS using the above drugs may provide not only cardiac, renal and vascular protection reducing the risk of development of new diabetic cases, but also an excellent antihypertensive effect. Owing to RAS blockade, cardiovascular morbidity and mortality decreased significantly, particularly in cardiac failure and diabetic nephropathy with proteinuria. Combined RAS blockade with an ACE-inhibitor and ARBs is justified only for renal proteinuria, both in diabetic and non-diabetic patients. The combination of ACE inhibitors and ARBs is not recommended for treatment of hypertension. In congestive heart failure, ACE inhibitors and ARBs may be combined when symptoms persist despite diuretic, beta blocker and when RAS remains activated despite ACE inhibition.

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