Dual Blockade of the Renin Angiotensin System in Diabetic and Nondiabetic Kidney Disease

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Introduction
The rationale behind combining an angiotensin-converting enzyme (ACE) inhibitor with an angiotensin II–receptor blocker (ARB) is mainly based on two major issues: ACE escape and activation of the unopposed angiotensin II type 1 receptor, it seems possible to block both the production and the action of angiotensin II, which would serve as efficient antihypertensive therapy. Exploring the beneficial effects of dual-blockade therapy is a work in rapid progress, in both diabetic and non-diabetic nephropathy. But evidence is also emerging in cardiovascular medicine, an overview of which is provided in this article.

Dual blockade of the renin angiotensin system is based on a principle of obtaining the broadest and most efficient blockade of the effects of angiotensin II, by using the combination of an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin II–receptor blocker (ARB). By combining two, different pharmacologic principles and inhibiting both the ACE and the angiotensin II type 1 receptor, it seems possible to block both the production and the action of angiotensin II, which would serve as efficient antihypertensive therapy. Exploring the beneficial effects of dual-blockade therapy is a work in rapid progress, in both diabetic and non-diabetic nephropathy. But evidence is also emerging in cardiovascular medicine, an overview of which is provided in this article.

in high doses. Alternative ways of converting angiotensin I to angiotensin II emerge by other enzymatic pathways, especially in the failing heart, the kidneys, and the large resistance vessels [1]. Chymase and cathepsin have primarily been seen as some of the major contributors to this phenomenon, but other enzymes can also contribute to the conversion of angiotensin I to angiotensin II. These enzymatic systems are possibly active in the natural human homeostasis, but an upgrade of enzymatic activity is seen in disorders in which high levels of oxidative stress are present, such as vascular proinflammatory processes and diabetes mellitus [2].

By adding an ARB to the ACE inhibitor, the effects of continuous angiotensin II production should be blocked at the receptor level. Currently, several efficient ARBs are available that block the AT1 receptor [3]. These lower blood pressure and provide cardio- and nephroprotection [4–6], as confirmed by both experimental and large trials. However, by blocking this receptor, circulating levels of angiotensin II rise and activate the other subgroups of angiotensin receptors. Currently, four subgroups of receptors are known—AT 1 to 4. The effects of subclass 3 and 4 are unknown, and, in adult human tissue, the AT2 receptors are only present at low levels. AT2 receptors are mainly in the uterus, the adrenal gland, the central nervous system, large vessels, the heart (cardiomyocytes and fibroblasts), and the kidneys. But the AT2 receptors seem to be re-expressed or upregulated in experimental cardiac hypertrophy, myocardial infarction, and wound healing [7–9]. The role of this upregulation is not totally understood, because little is known regarding the function of the AT2 receptor. Some suggest that the AT2 receptor inhibits cell proliferation and induces differentiation, apoptosis, and regeneration, much different from the effects of the AT1 receptor. The AT2 receptor has also been shown to directly reverse AT1 receptor-mediated hypertrophy, suggesting that these receptors exert opposing effects in the cardiovascular system [10••]. This has been shown in numerous experimental studies, but, recently, other experimental studies have shown that the AT2 receptor might exert exactly the opposite effect, and it has been claimed that the receptor might act more like the AT1 receptor subtype. It seems that additional blood pressure lowering can be achieved when
a specific AT2 receptor blocker is added to an AT1 receptor blocker in an experimental setting. This indicates that there might be resemblance between the actions of these two angiotensin II receptor subtypes [11]. In male Sprague-Dawley rats, the infusion of angiotensin II increased the VEGF gene and protein expression, which was attenuated with valsartan, but also with the AT2 receptor blocker PD123319 [12•]. An experimental study published this year also showed that treatment with either valsartan or PD123319 attenuated retinal VEGF expression, to the same extent [13]. These results suggest that VEGF expression, which is modulated by the AT1 receptor, may also be modulated by the AT2 receptors.

More evidence on this matter is expected to emerge within the next few years. This will clarify whether the role of an unopposed stimulation of the AT2 receptor will have a major bearing on reno- and cardioprotection and answer the question of whether combined therapy with an angiotensin II receptor blocker and an ACE inhibitor will exert an additive effect [14].

Rationale of Dual-Blockade Treatment

Dual-blockade treatment is based on the principle of obtaining the broadest and most efficient blockade of the effects of angiotensin II, by using the combination of an ACE inhibitor and an ARB.

By combining the two different pharmacologic principles and inhibiting both the ACE and the ARB, it seems possible to block both the production and the action of angiotensin II, and increase the beneficial effects of bradykinin, thereby serving as an excellent antihypertensive therapy. A recently published experimental study supports this theory [15•].

Most studies concerning dual blockade present positive results, but some negative results have been produced. Whether the theoretical considerations prove effective in humans is far from settled. In this article, we present the latest developments in clinical studies with dual-blockade therapy.

Dual Blockade in Diabetic Nephropathy

The ACE inhibitor and the ARB have both shown to be first-line treatment in hypertensive diabetic patients with renal involvement [5,6]. Treatment with either drug delays the progression of renal involvement, but end-stage renal failure is still a major complication for albuminuric patients with diabetes mellitus. This demands more effective treatment, and dual blockade might be an option in this matter. However, only a few studies have been published using the dual-blockade treatment principle to treat hypertension and nephropathy in patients with diabetes mellitus, and no large trials are currently available.

In 1999, Hebert et al. [16] were among the first to present results using dual blockade for diabetic patients in a small series of only seven patients with diabetes, hypertension, and macroalbuminuria. The study was conducted with a follow-up period of only 1 week. They found arterial blood pressure significantly lowered when adding 50 mg of losartan to concomitant ACE-inhibition treatment, but proteinuria was not significantly reduced. These modest findings were probably due to the very short follow-up period, but the study implicated that there might be an additional benefit of combining the two drug classes, without severe side effects.

The Candesartan and Lisinopril Microalbuminuria (CALM) study shortly followed. This study was performed in 197 patients previously diagnosed with type 2 diabetes mellitus, hypertension, and microalbuminuria. The patients included were treated with 20 mg lisinopril, 16 mg candesartan daily, or both drugs in combination. After 4 weeks of placebo treatment, patients were treated with lisinopril or candesartan for 12 weeks. After this period, patients continued with either monotherapy or the combination of lisinopril and candesartan for an additional 12 weeks. All three treatments significantly reduced blood pressure, with dual blockade being the most effective. The larger reduction in the urine albumin-creatinine ratio with combination treatment (50%), compared with lisinopril alone (39%) and candesartan alone (24%), was not significant [17].

Following the CALM study, a series of interesting studies with dual blockade emerged, leading to interesting results and further exploration of the benefits of the new treatment principle. The question at that time was whether the CALM results could be transferred to patient groups with more severe renal affection.

This seemed to be the case, because significant reduction in proteinuria was obtained in a small trial that included type 2 diabetic patients with nephropathy. Rossing et al. [18] conducted a study that included 18 patients with type 2 diabetes, severe proteinuria (>1g/d), and hypertension. The patients were all treated with recommended doses of long-acting ACE inhibitors among a wide variety of other antihypertensive drugs. By adding 8 mg candesartan to the ACE-inhibitor treatment, both the blood pressure and the proteinuria were significantly reduced. This was also found in a second study from the same group using the ARB irbesartan in combination with concomitant ACE-inhibitor treatment in type 1 diabetic patients with severe nephropathy and hypertension. Dual blockade again significantly reduced both blood pressure and albuminuria, compared with monotherapy [19]. Some discussion was raised regarding the influence of underdosing of the ACE inhibitor in these studies. The fact that sub-maximal doses of ACE inhibitor were used in the first studies could at least partially explain these findings. This led to further investigations with similar design, wherein, in contrast with the previous studies, the investigators added an ARB to maximal recommended doses of ACE inhibitors and still obtained blood-pressure reduction and reduction in proteinuria comparable with the reductions found in the first studies, in patients with type 1 or type 2 diabetes mellitus [20,21]. This could mean that the ACE-