

# Angiotensin II receptor antagonists: the development of the pathophysiological and clinical research

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Neurohormonal activation is one of the hallmarks of chronic heart failure and inhibition of the neurohormonal systems, in particular the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), have become important targets in heart failure. Indeed, the favorable effect of angiotensin-converting enzyme (ACE) inhibitors in heart failure has largely been attributed to the blockade of angiotensin II production, the target hormone of the RAAS, with favorable effects on the clinical course, including prolonged survival<sup>1-4</sup>. Angiotensin II also contributes to the generalized (and mostly deleterious) activation of other neurohormonal systems both within the heart and throughout the body by promoting the release of agents such as norepinephrine, endothelin and aldosterone. The importance of aldosterone in heart failure has been overlooked in recent years because ACE-inhibitor-related reductions in angiotensin were thought to eliminate aldosterone production. Such suppression of circulating aldosterone, however, is transient, as exemplified by the term *escape* used to describe the phenomenon<sup>5</sup>. Indeed, the blockade of aldosterone receptors by spironolactone, in addition to standard therapy comprehensive of ACE-inhibitors, substantially reduces the risk of both morbidity and death among patients with severe heart failure<sup>6</sup>.

In addition, many of the benefits of the blockade of the RAAS in the field of heart failure appear to be related to the ability of the drugs to inhibit further cardiac remodeling<sup>7</sup>. What is not clear is the mechanism by which ACE-inhibitors lead to favorable changes in cardiac structure and function. Other than to block the production of an-

giotensin II through the converting-enzyme pathway, ACE-inhibitors also block the breakdown of bradykinin that reduces vasomotor tone by enhancing the release of vasodilator substances from the vascular endothelium, such as nitric oxide. It has also been shown to have antigrowth properties, which, at least in some animal experiments, account for the favorable effects of ACE-inhibitors on cardiac remodeling<sup>7,8</sup>.

In addition to ACE-inhibitors and aldosterone-receptor blockers, there are now alternative pharmacological approaches to blocking the RAAS.

## Development of a novel mechanism for interrupting the renin-angiotensin-aldosterone system

Selective blockade of the angiotensin II AT<sub>1</sub> receptor represents a novel mechanism for interrupting the RAAS without altering the potential benefits of AT<sub>2</sub> receptor stimulation<sup>9-11</sup>.

Selective blockade of the angiotensin AT<sub>1</sub> receptor has several possible advantages over inhibition of ACE. Urata et al.<sup>12-14</sup> have shown that there are a number of ACE-independent pathways for angiotensin II formation in human tissues and cardiovascular diseases, so that the conversion of angiotensin I to angiotensin II may involve a chymase-dependent pathway in addition to ACE. Moreover, activation of angiotensin II-forming chymase has been observed in various disease models such as cardiomyopathy, chronic mitral regurgitation as well as in the failing human heart<sup>11</sup>. This so-called *escape* from suppression of the RAAS during ACE-

inhibition is so often encountered in circumstances of increased activity, but its clinical relevance is largely unknown<sup>15</sup>. Very recently, Roig et al.<sup>16</sup> have found that 50% of patients had increased angiotensin II levels, despite high-dose ACE-inhibitors, and that their prognosis was worse compared to patients in whom angiotensin II remained suppressed.

Another potential advantage of selective blockade of the angiotensin AT<sub>1</sub> receptor is the enhanced stimulation of the angiotensin AT<sub>2</sub> receptor. Evidence suggests that stimulation of the AT<sub>2</sub> receptor may have beneficial effects on the vasculature, although the consequences of activation of these receptors are only beginning to be understood. Several studies have shown that stimulation of angiotensin AT<sub>2</sub> receptors inhibits cell proliferation and that angiotensin II-induced cardiomyocyte hypertrophy is increased by selective blockade of the AT<sub>2</sub> receptor<sup>17-19</sup>. Interestingly, it has recently been suggested that angiotensin II receptor blockers, in addition to blockade of the angiotensin II AT<sub>1</sub> receptor, might stimulate bradykinin through the unprotected AT<sub>2</sub> receptor<sup>20</sup>. Although these findings will need further confirmation, ACE-inhibitors decrease stimulation of the AT<sub>2</sub> receptor, while angiotensin II receptor blockers increase stimulation of this receptor because of the increase in circulating levels of angiotensin II that interact with other unblocked angiotensin II receptors.

Taken together, these findings suggest that the vascular protective effects observed with AT<sub>1</sub> receptor antagonists may be at least partially caused by an unopposed antigrowth effect of AT<sub>2</sub> receptor stimulation. In contrast, such a response would not be obtained with ACE-inhibitors, since these drugs equally antagonize AT<sub>1</sub> and AT<sub>2</sub> receptors by inhibiting the generation of angiotensin II<sup>11</sup>.

Furthermore, the blockade of the angiotensin AT<sub>1</sub> receptor prevents some of the difficulties associated with ACE-inhibitor treatment<sup>21</sup>, that have a number of side effects including dry cough, angioedema, and urticaria. There is some evidence suggesting that the side effects associated with ACE-inhibitors are not produced by inhibition of angiotensin II synthesis but rather inhibition of kininase 2, which leads to a reduction in bradykinin metabolism.

Selective blockade of AT<sub>1</sub> receptors, therefore, not only represents an alternative mechanism for interrupting the RAAS but potentially offers several therapeutic advantages compared with ACE-inhibition, and the difference in mode of action theoretically favors add-on therapy and raises the intriguing possibility that combination therapy with both classes of drugs could offer benefits beyond those seen with either of the agents alone<sup>7</sup>.

This hypothesis was confirmed in a recent double-blind study in a small group of patients with heart failure, in which clinical conditions improved when an AT<sub>1</sub> receptor blocker was added to maximal ACE-inhibition<sup>22</sup>. The combination of candesartan and enalapril pre-

vented an increase in left ventricular volume that occurred with either of the drugs alone and appeared to have favorable effects on the neurohormonal profile of these patients, despite a trend toward an increased number of events in patients treated with candesartan<sup>23</sup>.

However, the recently published ELITE (Evaluation of Losartan in the Elderly) II study has not demonstrated a significant difference in terms of all-cause mortality in patients with heart failure treated with losartan in comparison with an ACE-inhibitor, despite a better tolerability profile of the AT<sub>1</sub> receptor blocker<sup>24</sup>. In the near future other data from ongoing clinical studies will be available. One of these, the Val-HeFT (Valsartan Heart Failure Trial), is evaluating the effect of AT<sub>1</sub> receptor blockade used as add-on therapy in patients already receiving ACE-inhibitors<sup>25</sup>. Another one, the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity), is investigating the role of AT<sub>1</sub> blockade in patients with left ventricular systolic dysfunction and intolerant to ACE-inhibition, or in addition to ACE-inhibitors; furthermore, the third arm of this study is studying the effects of candesartan in heart failure patients with diastolic dysfunction (left ventricular ejection fraction > 0.40)<sup>25</sup>.

The results of these large trials are being extensively awaited and will provide important information about the exact place of AT<sub>1</sub> receptor blockers in patients with heart failure. Until such time, however, ACE-inhibitors remain the cornerstone of the treatment in heart failure, despite their limitations, since their value in these patients is beyond doubt<sup>15</sup>.

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