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Inhibition of the renin–angiotensin system for lowering coronary artery disease risk

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The renin–angiotensin system when activated exerts proliferative and pro-inflammatory actions and thereby contributes to progression of atherosclerosis, including that occurring in the coronary arteries. It thus contributes as well to coronary artery disease (CAD). Several clinical trials have examined effects of renin–angiotensin system inhibition for primary and secondary prevention of coronary heart disease. These include important trials such as HOPE, EUROPA and PEACE using angiotensin converting enzyme inhibitors, VALIANT, OPTIMAAL and TRANSCEND using angiotensin receptor blockers, and the ongoing TOPCAT study in patients with preserved ejection fraction heart failure, many of who also have coronary artery disease. Data are unavailable as yet of effects of either direct renin inhibitors or the new angiotensin receptor/neprilysin inhibitor agents. Today, inhibition of the renin–angiotensin system is standard-of-care therapy for lowering cardiovascular risk in secondary prevention in high cardiovascular risk subjects.

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Introduction

Ischemic heart disease is one of the leading causes of morbidity and mortality globally, with an age-adjusted mortality of 113 per 100 000 in the United States and over half of all cardiovascular deaths in Canada [1,2]. There has been a great deal of clinical and basic science research examining the pathophysiology, molecular and cellular biology underlying coronary artery disease (CAD). There has been evidence of activation of the renin–angiotensin system (RAS) in CAD, including genetic data and measurement of plasma renin activity in humans and results in experimental animals. Indeed, angiotensin II, the final mediator of most effects of the RAS produces pro-inflammatory, proliferative and vasoconstrictor effects on the vasculature [3] that can contribute to initiation and progression of atherosclerosis, including the atherosclerotic plaques found in CAD (Figure 1). The RAS has therefore become an essential therapeutic target for both prevention and therapy of CAD of the development of CAD. Over the last two decades, there have been a number of clinical trials examining the impact of therapies aimed both at primary and at secondary prevention of CAD. Indeed, therapies aimed at inhibiting the RAS have become part of standard-of-care therapy for secondary prevention in patients at high risk of adverse cardiovascular events [1].

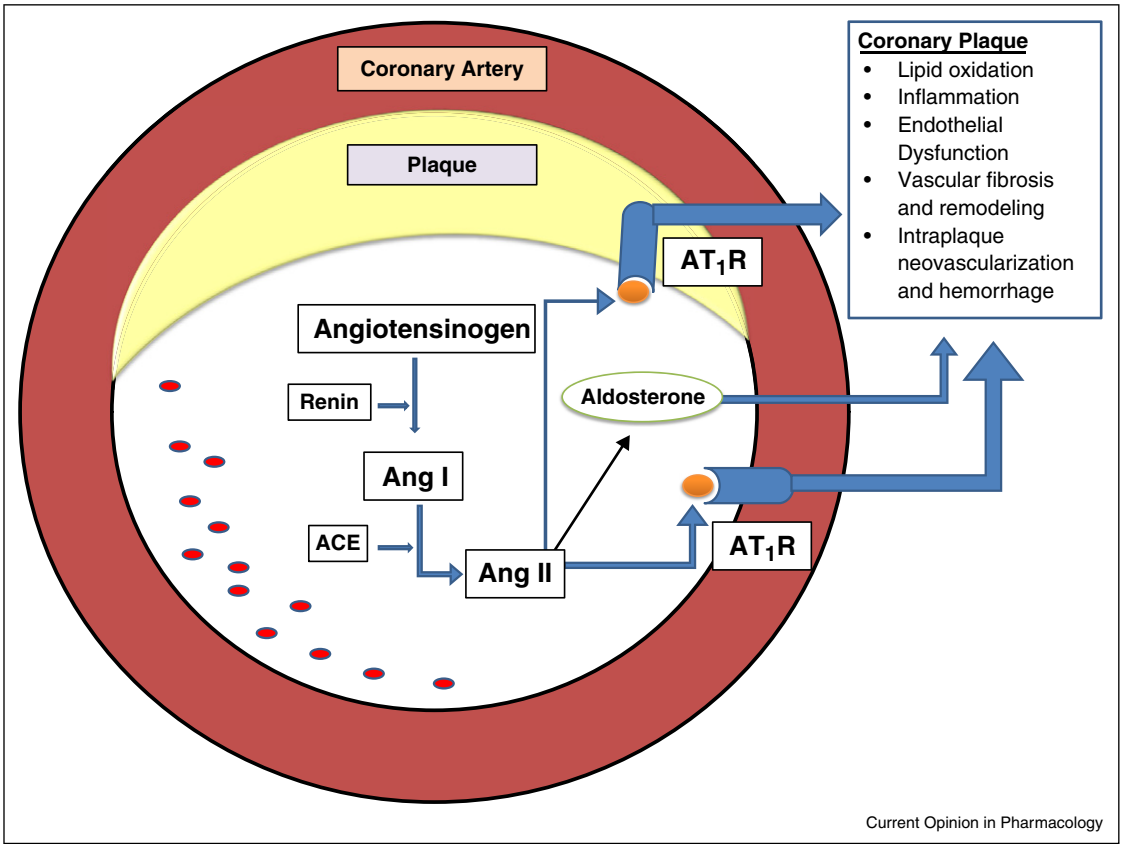
Pharmacological inhibition of the RAS in CAD

The RAS is implicated in the pathophysiology of cardiovascular disease at a number of levels. It is a complex signaling pathway and hormonal cascade that acts at the cellular level via the action of its main effector molecule angiotensin II (Ang II). Hypertension, atherosclerosis, heart failure and CAD are well-studied examples of end organ damage related to the RAS [4]. The multitude of effects of the RAS occur not only through circulating RAS peptides such as Ang II, but also through local tissue effects at the level of the vascular wall and activation of specific pathways implicated in inflammation and immunity [3,5–7].

Several medications have been developed that target specific segments of this hormonal cascade. ACE inhibitors (ACEi) inhibit the conversion of angiotensin I (Ang I) to Ang II, with the potential of reducing the vascular impact of Ang II. In the context of vascular biology, arteriolar resistance is reduced, as is the remodeling and smooth muscle cell hypertrophy in resistance vessels [8]. In several studies, endothelial function is improved [9,10], while platelet aggregation is inhibited [11]. Additionally, ACEi prevent the breakdown of bradykinin, which is a molecule that remains one of the most commonly referenced causes of the cough that appears to occur in up to 10% of patients who use ACEi. Renal dysfunction is another possible side effect related to changes in the hemodynamics of renal blood flow and the medication's effect on arteriolar resistance in renal vasculature.

Angiotensin receptor blockers (ARB) have been developed in order to target specific angiotensin receptors (AT_1 receptor) while not leading to increased concentrations of bradykinin, and thus avoiding the incident cough that occurs with ACEi. In addition to vasodilation, these medications also reduce the levels of circulating

Figure 1



The renin–angiotensin system and the pathways and mechanisms whereby it contributes to progression of atherosclerotic plaques in patients with coronary artery disease. AT_1R = angiotensin type 1 receptor.

aldosterone, which is a potent profibrotic and inflammatory molecule [12–14]. Mineralocorticoid receptor blockers like the less selective spironolactone and the more selective eplerenone block the action of aldosterone, whereas aldosterone synthase inhibitors directly inhibit the enzyme responsible for the synthesis of aldosterone. Mineralocorticoid receptor blockers have been evaluated in clinical trials of heart failure and cardiac dysfunction following myocardial infarction [12,13].

Lastly, novel medications are being evaluated in the treatment of heart failure and hypertension. Renin inhibitors such as aliskiren have been evaluated as agents for the treatment of hypertension. These medications function by reducing the formation of Ang I from angiotensinogen and thus reduce the impact of the potent vascular effects of Ang II [15]. Other innovative agents combine an ARB and a neprilysin (NEP) inhibitor (LCZ696). The NEP inhibitor portion of this molecule would prevent the degradation of specific natriuretic peptides that potentiate both vasodilation and natriuresis in selected patients [16,17].

Angiotensin converting enzyme inhibitors

There have been a number of large clinical trials examining the impact of ACEi on the continuum of cardiovascular disease. Specifically, trials have studied their impact on patients including those with hypertension, heart failure, and coronary artery disease (CAD). The use of ACEi in particular in patients with CAD has been investigated in the context of smaller studies in addition to several large clinical trials [18–23]. Their role has been established and integrated into current guidelines of a number of major cardiovascular societies [1]. Over a decade ago, the HOPE investigators [18] examined the ACEi ramipril in patients at high risk of cardiovascular disease, including patients with a history of myocardial infarction (MI) and CAD. Among patients receiving the ACEi, there was a 22% relative risk reduction in the primary endpoint of myocardial infarction, stroke, or death from cardiovascular cause (14% vs. 17.8%, RR: 0.78, $P < 0.001$). Following the Heart Outcomes Prevention Evaluation (HOPE) trial, other clinical trials further examined patients at high risk of cardiovascular disease. The EURopean trial On reduction of cardiac events with