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Commentary

Pharmacology of Angiotensin Receptor Blockers (ARBs) and ACE Inhibitors in Cardiovascular Disease

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DESCRIPTION

Cardiovascular Diseases (CVD) remain a leading cause of death worldwide, driven by risk factors such as hypertension, diabetes and obesity. A fundamental of CVD management, especially in hypertension and heart failure, is the modulation of the Renin-Angiotensin-Aldosterone System (RAAS), a hormonal cascade that regulates blood pressure and fluid balance. Two major classes of drugs used to target the RAAS are Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Ii Receptor Blockers (ARBs). Both classes are widely used for their efficacy in lowering blood pressure, reducing cardiovascular mortality and improving outcomes in various cardiovascular conditions. This article explores the pharmacology, mechanisms, therapeutic benefits and comparative clinical implications of ACE inhibitors and ARBs in cardiovascular disease management.

The Renin-Angiotensin-Aldosterone System (RAAS) in cardiovascular physiology

The RAAS plays a central role in maintaining blood pressure and electrolyte balance. It is activated by signals like low blood pressure, reduced sodium concentration, or sympathetic nervous system stimulation. The cascade begins with the release of renin from the kidneys, which converts angiotensinogen into angiotensin I. Angiotensin I is then converted into angiotensin II by Angiotensin-Converting Enzyme (ACE), primarily in the lungs. Angiotensin II, a potent vasoconstrictor, acts on AT1 receptors to increase blood pressure, stimulate aldosterone secretion from the adrenal cortex and trigger thirst and vasopressin release. This results in increased sodium and water retention, boosting blood pressure. In cardiovascular disease, persistent RAAS activation can lead to hypertension, endothelial dysfunction, cardiac hypertrophy and fibrosis, which contribute to heart failure and other complications.

Mechanism of action of ACE inhibitors

ACE inhibitors work by inhibiting the enzyme responsible for converting angiotensin I to angiotensin II, thereby decreasing angiotensin II levels. By lowering angiotensin II, ACE inhibitors reduce vasoconstriction, resulting in vasodilation and lower blood pressure. They also inhibit aldosterone release, leading to less sodium and water retention, further decreasing blood pressure. Additionally, ACE inhibitors reduce the breakdown of bradykinin, a vasodilator, which enhances their antihypertensive effects. Increased bradykinin levels also contribute to the beneficial effects on vascular health, although bradykinin accumulation may be associated with some side effects, like the common ACE inhibitor-induced cough.

Mechanism of action of ARBs

ARBs, such as losartan, valsartan and candesartan, selectively block the AT1 receptors, the main site where angiotensin II exerts its effects on blood pressure. By directly blocking these receptors, ARBs prevent vasoconstriction, aldosterone secretion and other downstream effects of angiotensin II. Unlike ACE inhibitors, ARBs do not affect bradykinin levels, which may explain why they tend to have fewer side effects, such as cough and angioedema, compared to ACE inhibitors.

Therapeutic benefits in Cardiovascular Disease

Hypertension: Both ACE inhibitors and ARBs are first-line treatments for hypertension. They are effective in reducing blood pressure and have been shown to decrease the incidence of stroke, myocardial infarction and cardiovascular mortality. ARBs and ACE inhibitors are particularly beneficial in patients with hypertension and coexisting conditions like diabetes and chronic kidney disease, given their renal protective effects. Several major clinical trials, such as the HOPE trial (ACE inhibitors) and the

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LIFE trial (ARBs), have demonstrated their efficacy in reducing cardiovascular events in hypertensive patients.

Heart failure: ACE inhibitors and ARBs have been shown to improve outcomes in heart failure patients by reducing preload and afterload, which reduces cardiac workload. ACE inhibitors, in particular, are recommended as first-line therapy in Heart Failure with reduced Ejection Fraction (HFrEF), as they lower mortality and hospitalization rates. When ACE inhibitors are not tolerated, such as in cases of angioedema or chronic cough, ARBs are suitable alternatives and also reduce mortality and hospitalization. Studies like the CONSENSUS and SOLVD trials have highlighted the efficacy of ACE inhibitors, while the CHARM and Val-HeFT trials have demonstrated similar benefits of ARBs in heart failure.

Post-Myocardial Infarction (MI): Following a heart attack, ACE inhibitors and ARBs can prevent adverse remodeling of the heart, reduce mortality and improve long-term outcomes. The beneficial effects are linked to reduced angiotensin II-mediated fibrosis and hypertrophy. ACE inhibitors, such as captopril and ramipril, are recommended for use after MI, particularly in patients with left ventricular dysfunction. When ACE inhibitors are not tolerated, ARBs can provide similar benefits, as shown in the VALIANT trial, which compared valsartan to captopril in post-MI patients and demonstrated comparable cardiovascular benefits.

Chronic Kidney Disease (CKD): The RAAS is implicated in the progression of CKD and both ACE inhibitors and ARBs provide renal protection, especially in patients with diabetic nephropathy. These drugs reduce proteinuria and slow the progression of kidney disease by reducing intraglomerular pressure. Studies like the RENAAL trial with losartan and the IDNT trial with irbesartan in diabetic nephropathy have shown the renoprotective benefits of ARBs. ACE inhibitors are similarly effective and are recommended as first-line therapy in diabetic patients with albuminuria.

Comparative efficacy and side effects: ACE inhibitors and ARBs are comparable in their efficacy for reducing blood pressure and cardiovascular events. However, ACE inhibitors are often preferred as first-line agents due to their more extensive clinical evidence in reducing mortality and morbidity. ARBs, on the other hand, are excellent alternatives for patients intolerant to ACE inhibitors, especially those experiencing cough or angioedema.

Emerging therapies targeting the RAAS: New approaches are being investigated to enhance RAAS blockade and address residual cardiovascular risk. One example is the dual Angiotensin Receptor-Neprilysin Inhibitor (ARNI) sacubitril/valsartan, which combines an ARB with neprilysin inhibition. Neprilysin inhibition increases levels of beneficial peptides that counteract RAAS activity, providing enhanced cardiovascular benefits, especially in heart failure.

CONCLUSION

ACE inhibitors and ARBs are foundational in the treatment of cardiovascular disease, offering significant benefits in hypertension, heart failure, post-MI and CKD. While both classes effectively reduce cardiovascular events, their pharmacologic mechanisms and side-effect profiles provide options for individualizing therapy. ACE inhibitors remain a first-line choice, but ARBs are invaluable alternatives for patients with ACE inhibitor intolerance. As research continues to refine and extend RAAS-targeting therapies, the potential for improved cardiovascular outcomes in diverse patient populations continues to expand.