

What is the exact mechanism behind the use of angiotensin-converting enzyme (ACE) inhibitors in patients with ischemic heart disease (IHD)?

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Ischemic heart disease is a condition primarily caused by the formation of atherosclerotic plaques in the coronary vasculature, leading to imbalance of oxygen supply and demand, and initially manifests as chronic stable angina. Per Hurst's *The Heart*, angina usually occurs in patients with coronary artery disease (CAD) affecting ≥ 1 of the large epicardial arteries.¹ The goals of therapy are to alter the underlying process of atherosclerosis and provide symptomatic relief using medications such as nitrates, beta blockers, calcium channel blockers, and ranolazine. Angiotensin-converting enzyme inhibitors are recommended for patients with CAD and diabetes mellitus and/or left ventricular systolic dysfunction. The basis for this recommendation was likely derived from the results of a meta-analysis conducted by Shekelle et al, in which the investigators determined estimates of mortality for different subgroups of patients from 12 randomized clinical trials of ACE inhibitors and beta blockers.² The ACE inhibitors have consistently demonstrated significant reductions in both morbidity and mortality, with benefits observed in patients with all severities of symptomatic heart failure as well as patients with asymptomatic left ventricular dysfunction.

The mechanism of action of ACE inhibitors in heart failure/IHD is unclear, although several have been proposed.³ One hypothesis is that ACE inhibitors may modulate myocyte responses to the intracardiac renin-angiotensin system. It is thought that there may be enhanced activity of ACE within the myocardium, and an increase in ACE binding sites has been observed in patients with advanced heart failure. Another proposed mechanism is through reduction of sympathetic nervous activity, which is known to be increased in patients with heart failure. A third mechanism is an increase in kinins (e.g., bradykinin) associated with ACE inhibitor use. Bradykinins have been shown to cause vasodilation with the release of endothelial nitric oxide. Angiotensin-converting enzyme inhibitors may also normalize nitric oxide synthase expression and inhibit the release of endothelin, a vasoconstrictor. In addition to these, other effects attributed to ACE inhibitors that may lead to improvements in patients with IHD are possible alterations/reduction of proinflammatory cytokine levels, alteration of hypercoagulable states through reduction of fibrinogen and von Willebrand factor and improvement of fibrinolytic factors.

A search of the literature revealed numerous articles discussing the aforementioned possible mechanisms. Examples of these include reviews by Rosenson,⁴ Dai and Kloner,⁵ Probstfield and O'Brien,⁶ and Hammoud et al.⁷

In summary, it appears that there are strong data to support the use of ACE inhibitors in patients with IHD, but there is no clear consensus regarding the mechanism(s) of action. Likely, the benefits of ACE inhibitors are related to not 1 but several possible mechanisms.

References:

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