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Foreword

ACE inhibitors: current understanding and future directions

The aim of this supplement is to consolidate our present knowledge in both the basic and clinical aspects of angiotensin converting enzyme (ACE) inhibition in hypertension and heart failure and to highlight new areas of research that may have implications for future clinical practice. The role of ACE inhibitors for the treatment of cardiovascular disease has expanded since the development of the first orally effective agents in the late 1970s.

For the basic scientist the development of ACE inhibitors has been a useful means of examining the role of the renin-angiotensin system (RAS) in physiological preparations and animal models of disease. ACE inhibitors have stimulated interest in the molecular biology of the RAS in the vascular and other systems. The recent discovery of polymorphisms in both the ACE and angiotensinogen genes may prove to be of considerable clinical importance.

Observational studies in cardiovascular disease are useful in generating hypotheses but give only partial insight into the importance of pathophysiological systems in the generation of disease. ACE inhibitors are the means by which the importance of the RAS in health, hypertension, and heart failure and in many other diseases has been elucidated. We now look forward to the development of new tools for the dissection of the RAS system still further (renin inhibitors and angiotensin II receptor antagonists).

For the practising clinician ACE inhibitors are an essential tool for the treatment of hypertension and heart failure. The impact on the management of heart failure has been large because ACE inhibitors not only improve symptoms but also delay progression and death. Evidence that the natural history could be altered has in turn stimulated greater efforts to earlier and more accurate diagnosis.

For the epidemiologist and health economist ACE inhibitors have provided a major stimulus to defining properly the problem at the community level. This has lead to the startling realisation that, even with the cost conscious health care delivery system in the United Kingdom and the fact that probably less than half of patients with heart failure currently undergo the minimum adequate diagnostic procedures,[1] the management of heart failure still consumes almost 2% of the entire resources of the National Health Service. Heart failure is becoming more common as treatment improves survival after myocardial infarction, as the population ages, and as diagnostic criteria for heart failure become stricter. In the next 50 years heart failure is likely to be the single most important condition that medical hospital services have to deal with. ACE inhibitors have the potential to improve the quality and duration of life in heart failure and may reduce health costs.[2]

When ACE inhibitors were first developed many believed that they would be of little more than novelty value, with perhaps a small role for the treatment or diagnosis of renovascular hypertension. That indication is now questioned, but ACE inhibitors are an excellent choice for the treatment of most patients with hypertension. A series of landmark studies starting in 1987 with CONSENSUS and culminating (so far) in the AIRE study have shown that ACE inhibitors should be used not only in all grades of heart failure associated with left ventricular dilatation and systolic dysfunction but also in patients with substantial left ventricular dysfunction after infarction. The ISIS-4 and GISSI-3 studies now suggest that there is a case for treating all patients after myocardial infarction with an ACE inhibitor, at least for the first six weeks.

However, many issues are still to be resolved. What is the optimal dose of an ACE inhibitor? Can the mortality benefits observed in heart failure be transferred to hypertension? Data from the SOLVD and SAVE studies indicate that ACE inhibitors can reduce the risks of recurrent infarction in those with established left ventricular dysfunction with or without heart failure: this reduction in reinfarction is especially prominent in patients who also have angina.[3] But can these findings be extrapolated to all patients with or at risk of atherosclerotic coronary disease, or indeed with atherosclerotic complications at other sites? Mechanisms exist by which ACE inhibitors could retard the progression of atheroma, reduce the risks of plaque rupture, or ameliorate the consequences of ruptured plaque. We need to know which of these mechanisms is most important in this protective effect of ACE inhibitors. We now have the means to determine whether the protective effect is mediated through reduction in angiotensin II or increases in bradykinin/prostaglandin/nitric oxide or other effects of ACE inhibitors.

Undoubtedly, given the right conditions, innovative new classes of drugs will continue to advance our knowledge in many areas of medicine. This opportunity is particularly welcome in an area such as heart failure that despite being widespread and important has been relatively neglected until now.

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