

ACE inhibitors and arrhythmias

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In many descriptions of heart failure, arrhythmias are not mentioned, but every clinician is aware that arrhythmias are a common accompaniment of all degrees of heart failure. The pattern of these arrhythmias is interesting. Regular sustained arrhythmias are very unusual. Most of the arrhythmic events are isolated atrial or ventricular ectopic beats, or are brief irregular salvos of these beats constituting short runs of unsustained atrial or ventricular tachycardia.¹ Ventricular ectopic beats are detected in up to 80% of heart failure patients. Atrial fibrillation (but not atrial flutter) is a common complication of heart failure, and there is a suggestion that the threshold for ventricular fibrillation (VF) is reduced in heart failure patients.

Given that heart failure patients are compromised with respect to their cardiac output, it is surprising that a majority of the complicating arrhythmias are asymptomatic. Even modest runs of ventricular tachycardia are often unappreciated by heart failure patients, yet unquestionably they must have an important, albeit limited, haemodynamic impact.

The association of heart failure and arrhythmias has led to investigations of whether these arrhythmias are of prognostic significance. Ventricular arrhythmias, particularly those which are frequent or complex, are indeed associated with an adverse prognosis (fig 1).^{2–9} Although a direct link with sudden death has not been made, it would seem that the presence of repetitive forms of ventricular ectopic beats (that is, couplets and ventricular tachycardia) in patients with New York Heart Association [NYHA] II/III heart failure brings a prognostic disadvantage equivalent to an extra NYHA heart failure grade. These arrhythmias identified a high risk group of mild to moderate heart failure patients with a one year mortality approaching that of NYHA class IV patients not treated with angiotensin converting enzyme (ACE) inhibitors.⁵ On this analysis, the prognostic implication of such ventricular arrhythmias is substantial. These arrhythmias, as in myocardial infarction, are a marker of

risk rather than being lethal themselves.

Studies examining drug amelioration of symptoms and haemodynamics in heart failure have emphasised the awesome mortality of heart failure, but not all patients die through an inexorably progressive myocardial decline. Up to 50% of patients die suddenly.^{10,11} The identification of death as sudden in someone already ill with heart failure is difficult, but sudden death—presumptively arrhythmic—is not uncommon in heart failure.

Antiarrhythmic drugs in heart failure

Not surprisingly, the prognostic association of ventricular arrhythmias in heart failure prompted the testing of “conventional” class I (sodium channel blocking) antiarrhythmic drug treatment.¹² Although arrhythmia suppression is possible, no mortality benefits have been shown, and intolerance of the antiarrhythmic drugs proved an important limitation to the use of these drugs in heart failure. They can, and do, depress ventricular performance.¹³ Recognising this limitation, attention turned to amiodarone. This is well tolerated by heart failure patients and, arguably, is the most powerful antiarrhythmic drug currently available. The results have been mixed. In an early study,¹⁴ no benefit was seen in those patients randomised to receive amiodarone compared to their placebo treated counterparts. In the BASIS study,¹⁵ mortality benefits of amiodarone accrued to survivors of acute myocardial infarction who had ventricular arrhythmias. Cardiac failure was not a specific entry criterion, but most of these patients had some degree of cardiac decompensation. In a subsequent reanalysis of the study,¹⁶ amiodarone appeared to benefit only those with better preserved left ventricular function. No mortality benefit was seen in those with an ejection fraction of less than 40%. By contrast, a recent randomised study has reported a significantly reduced mortality (41% control *v* 33% amiodarone) when amiodarone treatment was prescribed to patients with a variety of left ventricular cardiomyopathies.¹⁷ Currently, the role of amiodarone in heart failure looks promising rather than convincing. The situation should be resolved when the results of ongoing amiodarone trials are known.

Arrhythmia mechanisms in heart failure

The pattern of arrhythmias in heart failure is different from that in many other conditions. The arrhythmias usually are short lived and

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Glossary of trials

BASIS—Basel Anti-arrhythmic Study of Infarct Survival
CONSENSUS I—Cooperative New Scandinavian Enalapril
Survival Study
Hy-C—Hydralazine Captopril trial
V-HeFT II—Vasodilator Heart Failure Trial II

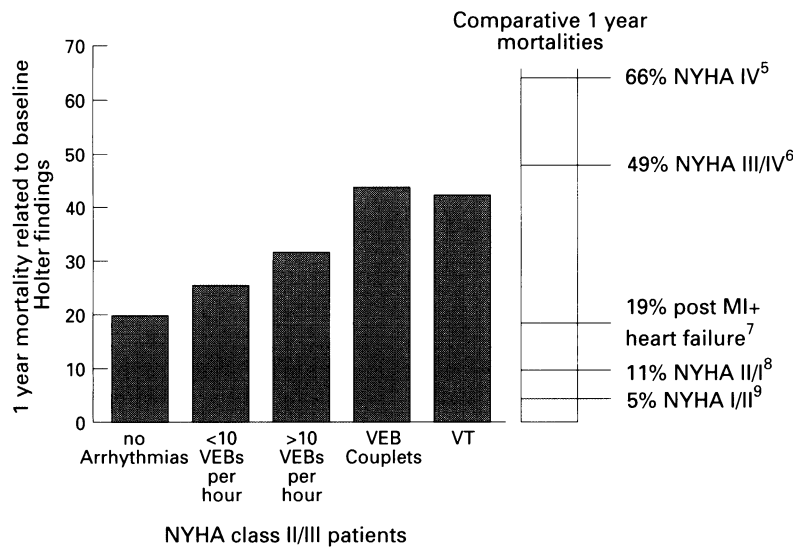


Figure 1 One year mortality related to Holter findings in subgroup of V-HeFT II patients with comparative one year mortalities in non-ACE-treated heart failure populations. Data sources are referenced. Adapted from data of Fletcher et al.⁴

tend to occur in irregular brief salvos comprising less than 10 consecutive ectopic events (atrial or ventricular). These are characteristics suggestive of triggered automaticity as a mechanism. When myocardial cells are stretched, they may be provoked to depolarise.^{18, 21} There is growing evidence that in heart failure, myocardial stretch associated with abnormal wall tension may be responsible for triggered automatic arrhythmias¹⁹ such as salvos of ventricular ectopic beats, salvos of atrial ectopic beats, and atrial fibrillation. This is an exciting new concept. It suggests that the cardiac arrhythmias which complicate heart failure are intimately linked to the basic haemodynamic problem and may even be an indicator of the severity of that problem. In animal experiments, Lucy et al²² showed a marked increase in defibrillation threshold of the dog ventricle following dilatation. Dilatation of the rabbit ventricle reduces the effective refractory period²³ which might encourage the existence of more reentry circuits. VF inducibility of the rabbit ventricle is promoted by dilatation and even more so by superadded hypokalaemia.²⁴ Ventricular hypertrophy, a common accompaniment of

heart failure modelling, is also arrhythmogenic. The defibrillation threshold of the canine heart is directly proportional to ventricular weight.²² Therapeutically, these observations open up a new antiarrhythmic approach through reduction of wall tension by vigorous "off loading". There are anecdotes of nitrate therapy reducing ventricular arrhythmias,²¹ but the strongest evidence comes from ACE inhibitor usage.^{20, 25}

ACE inhibitors, sudden death, and arrhythmias

In the CONSENSUS I study,⁵ heart failure mortality was dramatically reduced by enalapril treatment (down 31% at one year). The investigators suggested that the mortality benefit was due to an effect of stopping or slowing the progression of heart failure rather than an effect on sudden death. The sudden death rate was 11% both in enalapril treated patients and in the control population. Defining death as sudden in patients with heart failure is difficult, and it is possible that an effect of ACE inhibitor treatment on sudden presumptively arrhythmic death might have been missed. In subsequent studies, the mortality benefits of ACE inhibitor treatment have been confirmed, but until the V-HeFT II study,²⁶ there was nothing to suggest an ACE inhibitor effect on sudden death. In the V-HeFT II study, enalapril was compared to an isosorbide and hydralazine combination. Enalapril proved superior in terms not only of the mortality but also with respect to sudden death reduction (fig 2—risk reduction of 39%).^{5, 6, 8, 9, 17, 26} The effect was most pronounced in patients with lesser degrees of heart failure. This seems biologically plausible. If myocardial stretch were the mechanism of these arrhythmias, they would be expected to be more readily modified at a time before widespread fibrosis had become established. Encouraging as this evidence may appear, the findings are relative ones comparing two active treatments. Placebo, which was not tested, might have been better still.

Figure 2 Effects on sudden death observed in recent ACE inhibitor trials. Sudden death data from Doval et al¹⁷ examining amiodarone added to full antifailure therapy which included ACE inhibitors is shown for comparison.

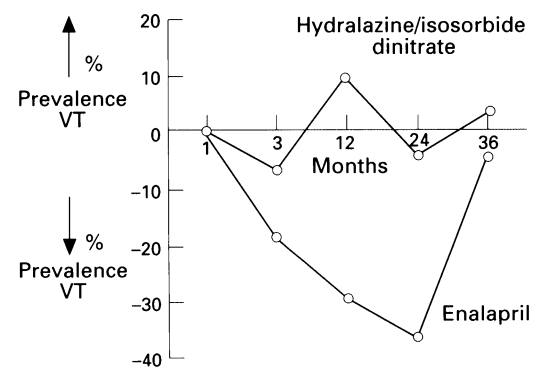
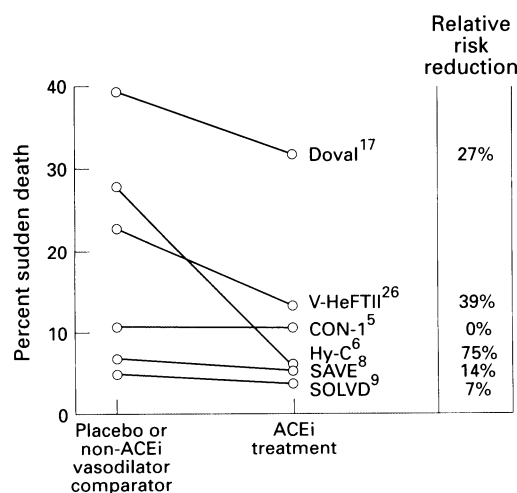


Figure 3 Treatment related changes in prevalence of Holter detected ventricular tachycardia expressed as a difference from baseline (0 months). The differences at 12 and 24 months are statistically significant. Adapted from data of Fletcher et al.³

Risks and benefits of antiarrhythmic interventions in heart failure patients

<i>Intervention</i>	<i>Benefits</i>	<i>Risks</i>
Sodium channel blocking drugs ¹¹	None for general prescription ¹¹	Common
Amiodarone ¹⁴⁻¹⁶	May be useful for individual patients Arrhythmia suppression Well tolerated Mortality effect unclear but some supportive evidence ¹⁴⁻¹⁶	LV depression ¹² Common but should be containable by careful monitoring Photosensitivity Pulmonary fibrosis Thyroid dysfunction Hepatitis Peripheral neuropathy
ACEi ^{7-9, 25-27}	Symptoms Effort capacity Prognosis Probable effect on sudden death	Few Hypotension Cough

ACEi, ACE inhibitors.

In the Hy-C study,⁶ sudden death was less in captopril treated patients than in those treated with non-ACE inhibitor vasodilators (28% *v* 7%). However, in this study there was a high level of treatment crossover.

Further support for an antiarrhythmic effect of ACE inhibitors comes from analysis of Holter recordings of heart failure patients. Both enalapril²⁵ and captopril²⁰ can reduce the frequency of ventricular ectopic beats. Despite the lack of a placebo control, the results of a Holter subgroup of V-HeFT II deserve attention.⁴ Enalapril treated patients had fewer complex ventricular arrhythmias, including ventricular tachycardia, than did their hydralazine isosorbide dinitrate treated counterparts (fig 3).⁴ While there is no proof of causality, it is noteworthy that, at one year, the enalapril associated 27% reduction of ventricular tachycardia was paralleled by a 52% reduction in sudden death.

Mechanisms of ACE inhibitor effect

There can be no doubt that ACE inhibitors profoundly affect myocardial loading conditions. However, whether or not this is the basis of ACE inhibitors' electrophysiological effects remains unclear. In an electrophysiological study comparing the ACE inhibitor captopril with a combination of hydralazine and isosorbide dinitrate, the ACE inhibitor modification of loading prolonged ventricular refractoriness, while the non-ACE inhibitor vasodilator did not.²⁷ This is consistent with experimental data suggesting that ACE inhibitors interfere with the *iK* currents and the L-type calcium current.²⁸ Further support for the clinical relevance of the ACE inhibitor's calcium channel effects comes from research in isolated guinea pig hearts, but this work also emphasised that another factor, or possibly factors, was likely to be contributory; these included loading effects, electrolyte stabilisation, and regression of left ventricular hypertrophy.²⁹ Myocardial loading changes have electrophysiological effects in themselves which may favour reentry or triggered automaticity, or both.^{18 19 30 31} ACE inhibitors also have modest β blocking properties,^{32 33} and it is possible that for some patients ACE inhibitor modification of sympathetic tone has a useful antiarrhythmic effect. ACE inhibitors also stabilise electrolyte concentrations,^{34 35} and this too may be relevant. Indeed, in one study,³⁵ ACE inhibitor mediated potas-

sium sparing effects were judged the principal antiarrhythmic action of ACE inhibitors. Angiotensin has direct electrophysiological effects,³⁶ but at present we can only speculate whether they may be relevant to heart failure arrhythmogenesis.

Conclusions

ACE inhibitors have revolutionised the management of heart failure. Yet in even the best studies there remains a high mortality for this dread condition.^{5 26} We must explore all avenues to improve the outlook for our patients. The problem of arrhythmic death looms large, and it poses a major challenge (table). Conventional antiarrhythmia agents seem ineffective. The role of amiodarone is unclear and at best would seem unlikely to be powerful. ACE inhibitors improve cardiac performance but there is now also a hint that they may offer protection against important arrhythmias which complicate heart failure. If confirmed, this would be evidence supporting an early aggressive use of ACE inhibitors in heart failure, as it would seem that only by a relatively early (prefibrosis) prescription would electrical benefits accrue.

These are exciting times for managing heart failure patients. For so long, the outlook has been bleak. ACE inhibitors have proved powerful tools; they may have more benefits than first realised.

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