ACE inhibitors in heart failure: effect on mode of death

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The treatment of heart failure with ACE inhibitors, especially following acute myocardial infarction, is now well established. Several excellent studies have convincingly demonstrated increased survival and reduced morbidity necessitating fewer hospital admissions.

In the Acute Infarction Ramipril Efficacy (AIRE) study 5 mg b.d. of the ACE inhibitor ramipril were given to patients with some clinical evidence of heart failure, even if transient, 3–10 days after myocardial infarction. After an average treatment period of 15 months, all-cause mortality as the primary end-point was shown to be markedly reduced (27% risk reduction, 95% CI: 11%–40%, P=0.002)\(^1\). Pre-defined secondary and tertiary endpoints were the time to the first validated outcome, i.e. death or myocardial re-infarction, severe resistant heart failure or stroke, and the mode of death. In this issue Cleland et al.\(^2\) report the results of the secondary and tertiary endpoints of the AIRE study. According to these results, ramipril reduced the risk of 'sudden death' by 30% (95% CI: 8%–47%; P=0.011), whereas the risk of death from 'circulatory failure' was reduced insignificantly (P=0.237) by 18%. These results appear to be in disagreement with results of previous studies on ACE inhibitors in patients with heart failure.

Garg and Yusuf\(^3\) performed a comprehensive meta-analysis for all completed, published or unpublished randomized, placebo-controlled trials of ACE inhibitors that were at least 8 weeks in duration and had determined total mortality by intention to treat. Such a meta-analysis including several large trials is supposed to have a greater power than a single trial. As expected the meta-analysis revealed a significant reduction in total mortality (odds ratio [OR] 0.77; 95% CI: 0.67–0.88; P<0.001) and in the combined endpoint of mortality and hospitalization for congestive heart failure (OR 0.65; 95% CI: 0.57–0.74; P<0.001). Similar benefits were observed with different ACE inhibitors. The greatest benefit was seen in patients with the lowest ejection fractions. The reduction in mortality was primarily due to fewer deaths from progressive heart failure (OR 0.82; 95% CI: 0.60–1.11) a trend but no significant therapeutic effect could be demonstrated.

This apparent discrepancy in the reduction in sudden death between the AIRE study and most other studies in patients with impaired left ventricular function after myocardial infarction is most likely not drug related. Similar benefits for mortality and for mortality or hospitalization were observed with several different ACE inhibitors\(^6\), which may differ in their pharmacokinetics but not in their pharmacodynamics.

The only study demonstrating a reduction in sudden death in patients with heart failure was the V-HeFT-II study\(^4\). In contrast to all other trials in which ACE inhibitors were compared with placebo, in the V-HeFT-II study the control group received hydralazine/ISDN. Probably due to a reflex mechanism these vasodilators increase sympatho-neuronal activity as shown by plasma catecholamine determinations. In patients receiving ACE inhibitors, even a decrease in plasma catecholamines has been observed; the ACE inhibitors not only reduce afterload by peripheral vasodilation but in contrast to hydralazine and nitrates additionally reduce sympathetic activity by inhibiting presynaptic noradrenaline release induced by activation of angiotensin II receptor \(^5\).

In the study of Cleland et al.\(^2\) 'objective definitions' were used to assess the mode of death. A satisfactory concordance of 82% between independent assessments by two clinicians could be achieved. The question arises, however, whether 'objective definitions' for 'sudden cardiac death' in contrast to 'circulatory failure' really allow a clear separation of these two lethal complications? In patients with heart failure, impaired left ventricular function is the most important risk factor for life-threatening ventricular tachyarrhythmias, and conversely, severe ventricular tachyarrhythmias may further impair left ventricular function. The majority of patients with heart failure ultimately die from ventricular fibrillation with or without preceding deterioration of left ventricular function. Due to the suddenness of death, preceding deterioration of left ventricular function may well escape even careful clinical observation. The question remains, therefore,
whether a differentiation between circulatory failure and sudden death can be achieved with accuracy, especially if the patient dies out of hospital? Is it really justified to classify 93% out-of-hospital deaths as sudden?

Cleland et al.[3] correctly do not equate sudden death with arrhythmic death. In other studies of ACE inhibitors in heart failure and in Garg’s meta-analysis, however, sudden death was presumed to be arrhythmic[3]. The distinction between circulatory failure or progressive heart failure and sudden or arrhythmic death aims to give insight into the mechanisms by which ACE inhibitors reduce mortality in patients with heart failure. It is established[3] that ACE inhibitors reduce total mortality and hospitalization for congestive heart failure mainly by retarding the progression of heart failure. A direct antiarrhythmic effect of ACE inhibitors has neither been documented in clinical observations nor in animal experiments. This view is shared by Cleland et al.[2], who conclude that ‘retarding the progression of heart failure appears to be a major factor contributing to the reduction in mortality both by reducing circulatory failure and by reducing sudden death’. Reduction in sudden death, as observed in the AIRE study, can be attributed to several mechanisms such as (1) reduction in acute circulatory failure, (2) reduction in secondary arrhythmic death causally related to less impaired left ventricular function and (3) reduction in the use of positive inotropic, potentially proarrhythmic drugs due to less severe heart failure. Alternatively, one would have to assume a reduction in primary arrhythmic death, which, however, has not convincingly been observed in any placebo-controlled trial.

Thus, it might well be that the reduction in sudden death suggested by Cleland et al.[3] still reflects the same beneficial effect of ACE inhibitors on left ventricular function as seen in other studies; the difference in the mode of death might be due to the definitions used and the assessment performed. In fact, retarding the progression of heart failure seems to be much more desirable and rewarding than fighting sudden death, which among all causes of death seems to be one of the more acceptable. At his 80th anniversary a former Olympic silver medallist of the 400 m sprint and later Professor at the University of Heidelberg expressed one last wish, to die suddenly in the mountains which he loved so much. I can imagine that at his age I shall have the same wish and I hope that medical progress will not be able to prevent it.

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References

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Epidemiology of dilated cardiomyopathy: a still undetermined entity

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Epidemiological information on heart failure is obtained from various sources and the results can be difficult to compare because of differences in ascertainment and classification of the syndrome. According to the available data, the prevalence seems to range from 3 to 20 individuals/1000, rising to 30–100 individuals/1000 for those aged over 65 years. The incidence in the general population ranges from 1 to 5