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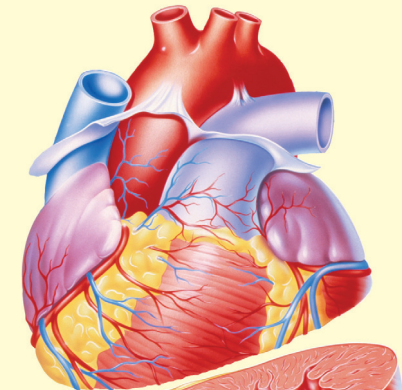
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# A clinical guide

**New insights into  
early drug treatment of  
chronic heart failure**

### Sudden cardiac death



**Progressive  
heart failure  
death**



**Ronnie Willenheimer, Henry Krum**

# Critical issues for initiating treatment of chronic heart failure

Significant advances have been made in the management of chronic heart failure (CHF) over the last decade. As a result of widespread use of agents to inhibit the activation of neurohormonal systems, the life expectancy of patients has been substantially increased and the quality of life significantly improved.

However, it is estimated that about 15–20% of patients die during the early months of treatment.<sup>1</sup> Many of these patients who die suddenly are already receiving standard therapy including an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker.

Therefore, clinicians face a therapeutic dilemma: what treatment strategy is most likely to prevent early mortality in patients with chronic heart failure?

Current guidelines recommend that treatment is initiated with an agent which blocks the renin angiotensin system. Only when such an agent is titrated to the maximum tolerated dose should another agent – usually a beta blocker – be added.

Yet, this universal recommendation is not based on clinical evidence. Until recently, no study has compared the effectiveness of different strategies for initiating treatment. However, this question has now been addressed in the unique Cardiac Insufficiency Bisoprolol Study (CIBIS) III Trial.

In this clinical guide, two internationally recognised authorities on heart failure – Professor Ronnie Willenheimer and Professor Henry Krum – evaluate the mechanistic arguments for reconsidering strategies for the effective early management of patients with CHF. They also discuss the evidence from clinical trials including CIBIS III. Finally, they provide practical advice for the clinician and discuss individual case studies which may make a more patient-tailored approach to initial therapy possible.

## Reference

1. Levy D, Kenchaiah S, Larson MG *et al.* Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;**347**:1397-402.

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- Introduction
- The evidence supporting the use of ACE inhibitors in CHF
- The evidence supporting the use of beta blockers in CHF
- The rationale for performing CIBIS III
- The results of CIBIS III
- Possible interpretations and clinical implications of the CIBIS III results (including case studies)
- Summary/the future

**Chapter 2**

**Effect on sudden death**

Beta blockers have been well demonstrated to have a major effect on sudden death reduction. This has been observed in most major beta blocker studies where the magnitude of reduction in death via a sudden death modality is as great, if not greater, than other modes of death such as progressive pump failure. These observations are of considerable relevance given the natural history of the heart failure disease process. In the MERIT-HF study the mode of death was explored according to NYHA Class. It was clearly demonstrated there was an increase in sudden death in the early stages of heart failure, ie. NYHA II with a progressive diminution of sudden death as a percentage of all deaths as NYHA Class (ie. severity of disease) increases. These observations suggest that a drug with anti-arrhythmic properties such as a beta blocker may be particularly beneficial in the early stages of heart failure progression and therefore may be the preferred first-line agent as the first neurohormonal antagonist therapy in this setting. In contrast, ACE inhibitors, whilst possessing modest anti-arrhythmic properties, have not been demonstrated to provide a major benefit on mortality via this mechanism (sudden death). The only study in which a sudden death benefit was demonstrated with ACE inhibitors was the V-HeFT-II study and this was in comparison to hydralazine/nitrates which may have pro-arrhythmic properties of their own by stimulating neurohormonal systems.

**Effect of beta blockers on mode of death**

| Study         | Mode of Death | Placebo (%) | Beta blocker (%) |
|---------------|---------------|-------------|------------------|
| US Carvedilol | Sudden death  | ~4.5        | ~2.5             |
|               | Pump failure  | ~3.5        | ~1.5             |
| CIBIS III     | Sudden death  | ~6.5        | ~4.5             |
|               | Pump failure  | ~4.5        | ~2.5             |
| MERIT-HF      | Sudden death  | ~7.5        | ~5.5             |
|               | Pump failure  | ~4.5        | ~2.5             |

**Effects on mortality and hospitalisations**

There have been no studies where beta blockers have been given as monotherapy looking at major clinical outcomes in patients with heart failure. However, in the major beta blocker trials a small percentage of patients were not able to tolerate or, for whatever reason, did not receive ACE inhibitors or ARBs as background therapy. Krum *et al.* recently meta-analysed the effect of beta blockers on clinical outcomes according to use of background ACE inhibitors and ARBs.

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