Sudden death prevention in heart failure: The case of CIBIS III

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THE BETA-BLOCKER PARADOX

CIBIS III completes a fundamental scientific phase of a sequence of large clinical trials (1-7) which has established the current therapeutic principles for the management of chronic heart failure (CHF) patients (8). These comprise the use of ACE inhibitors and beta-blockers. However, while ACE inhibitors, by antagonizing the synthesis of angiotensin II, found their natural pathway from hypertension into CHF, beta-blockers followed a controversial trail. They appeared effective in the BEHAT (9) trial after myocardial infarction (MI) even in patients with depressed left ventricular (LV) function. Nonetheless, the general view of CHF as an almost exclusively cardio-circulatory mechanical disease/remodelling led to the use of inotropic interventions, with non-infrequent negative consequences on mortality (10). Furthermore, this view prevented the conception of using anti-adrenergic interventions in CHF which consequently remained a strong contraindication to the use of beta-blockers for many years. Beginning with CIBIS II, a number of trials have proven that beta-blocker therapy improves survival in CHF, with a specific action on arrhythmic sudden cardiac death (SCD) in patients with optimum background therapy, including the use of ACE inhibitors. This did not happen by chance, as a strong experimental ground had already existed and has further grown during the last few years (11); very soon after its first manifestation, ischemic heart disease triggers a profound remodelling of the autonomic nervous system, resulting in receptor changes and sprouting of neural fibers (12, 13). In line with this background stands the huge amount of clinical evidence documenting the anti-fibrillatory action of anti-adrenergic interventions. In contrast to the rapid activation of the autonomic nervous system, the renin-angiotensin system (RAS) acts primarily by promoting the progressive myocardial architectural changes, leading to inefficient LV function and pump failure (14). The same process indirectly contributes to the genesis of an arrhythmogenic substrate for SCD to occur (15, 16). However, despite the bulk of evidence documenting the striking efficacy of ACE inhibitors and, more so, of beta-blockers in CHF, both drugs are underused. Recent surveys indicate that ACE inhibitors are given to only 60% of eligible patients (17) (Fig. 1) and the picture for beta-blockers is even worse, as the percentage of treated patients among those eligible is as low as around 30%. Additionally, beta-blocker therapy is mostly given to low risk patients and as late as 6 months after a first hospitalisation for HF (18). The immediate consequence of the mistrust in (or fear of) using adequate pharmacological therapy according to the international guidelines has been the boosted use of implantable cardioverter defibrillators (ICD) in any patient with depressed LV systolic function.
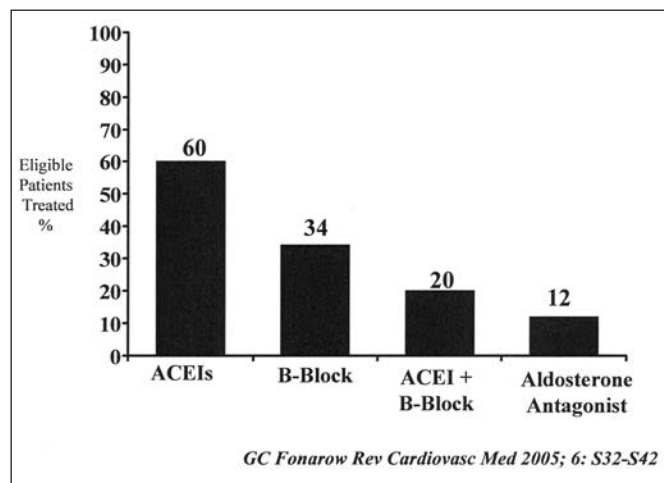
Fig. 1 - *The improvement International Survey: 1363 Physicians' practises, 15 countries, 11062 CHF patients. Percentage of eligible patients with heart failure receiving pharmacological treatment.*
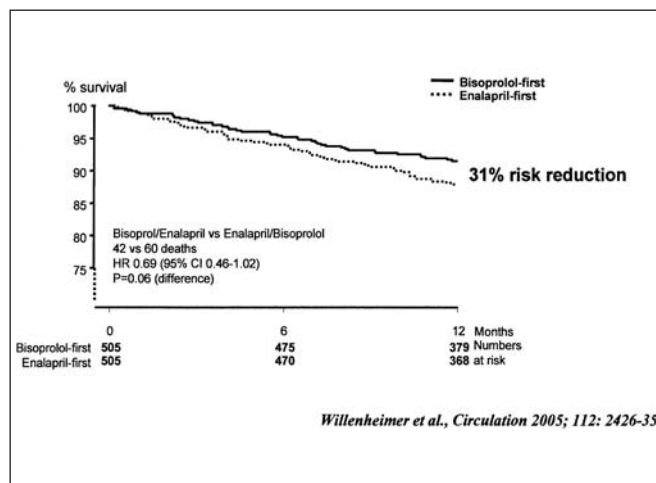

Fig. 2 - *Kaplan-Meier plot of survival at one year in the intention-to-treat sample.*

In this complex scenario, CIBIS III (19) has recently documented that beta-blocker therapy with bisoprolol can be effectively and safely initiated even prior to ACE inhibition, thus refuting the general view that this latter was a "*conditio sine qua non*" before considering anti-adrenergic interventions. Some intriguing information that emerged from CIBIS III was also a 31% all-cause mortality reduction at one year, which however did not quite reach statistical significance, possibly because of the limited sample size (Fig. 2).

Usually the drug initiated first attains a higher dose and, indeed, CIBIS III has shown that the initial use of bisoprolol, prior to starting ACE inhibition, allows up-titration to a higher dose of adrenergic inhibition. This offers a greater number of patients the benefit from beta-blockade, not only during initiation of therapy but also during combined therapy with subsequent ACE inhibition. Although the analyses in CIBIS III showed that all subgroups benefited nearly equally from a beta-blocker-first strategy, it may seem reasonable to propose that bisoprolol should be started first in patients with previous myocardial infarction, early stages of CHF or with tachycardia or ventricular

tachiarrhythmias, i.e. at high risk for SCD. Thus, if SCD prevention is what matters most in the early stage of CHF, one should consider some changes in the recommendations of the current guidelines. Combining the initial evidence from CIBIS III with the 44% SCD risk reduction observed in CIBIS II, supports the hypothesis that early introduction of bisoprolol in CHF patients, and the consequent optimal up-titration of the drug, could provide a more effective SCD prevention strategy compared to what has been seen so far. Patients can subsequently benefit from the combination therapy with beta-blockade and ACE inhibition.

THE CIBIS III: OPTIMAL PHARMACOLOGICAL STRATEGY FOR SD PREVENTION

CIBIS III randomised 1010 patients with mild or moderate, stable CHF and left ventricular ejection fraction ≤35%, without ACE inhibitor, betablocker or angiotensin-receptor-blocker therapy, to open-label monotherapy with either bisoprolol (target dose 10 mg o.d., n = 505) or enalapril (target dose 10 mg
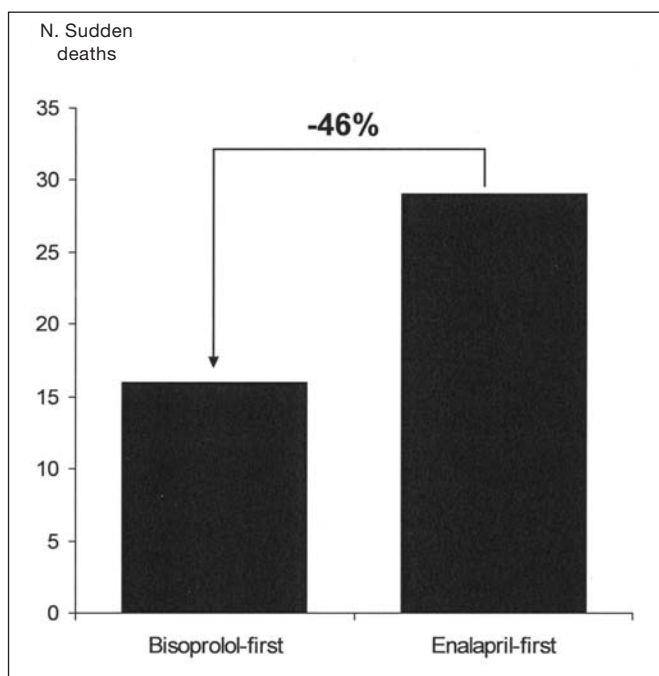
Fig. 3 - *Sudden death during the first year. At one year, in the bisoprolol-first group 16 patients had a sudden death versus 29 in the enalapril-first group: HR for sudden death, bisoprolol-first versus enalapril-first 0.54; 95% CI 0.29-1.00: P=0.049.*

b.i.d., n = 505) for six months, followed by their combination for 6-24 months. The two strategies were recently blindly compared regarding sudden death.

The masked adjudication was done by the end-point committee and 3 members of the steering committee and sudden death was defined according to the following criteria:

1) Death occurring within one hour of the occurrence of new symptoms or without symptoms.
2) Death at night during sleep (patient found dead in bed) without other cause.
3) Death in odd places (e.g. toilet room, parking lot, etc) without other cause.
4) Death within 28 days after resuscitation from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death.
5) Unwitnessed death in the absence of pre-existent progressive circulatory failure or other causes of death.

The most striking finding from this new analysis (20) was that, during the 6-month monotherapy phase, 8 of 23 deaths in the bisoprolol-first group were sudden, compared to 16 of 32 in the enalapril-first group: hazard ratio (HR) for sudden death 0.50; 95% confidence interval (CI) 0.21-1.16; P=0.107. At one year, 16 of 42 versus 29 of 60 deaths were sudden: HR 0.54; 95% CI 0.29-1.00; P=0.049. At study end, 29 of 65 versus 34 of 73 deaths were sudden: HR 0.84; 95% CI 0.51-1.38; P=0.487 (Fig. 3). There were no significant between-group differences in any other fatal events. In the bisoprolol-first group, there was an early non-significant increase in patients hospitalized for worsening of CHF, diminishing during combined therapy. This might be explained by the phenomenon of competing risks, since more patients survived in the bisoprolol-first group.

Thus, CIBIS III is now documenting that in patients with mildly or moderately symptomatic, stable CHF and 35% or less left ventricular ejection fraction starting treatment for CHF with the betablocker bisoprolol, may importantly decrease early sudden deaths, as compared to the ACE inhibitor enalapril. The benefit generated within the first 6 months extended to a significant SD reduction by one year. Further analyses are needed, though, to comprehend what happened later in the follow up that partly annuled the benefit observed in the first 12 months.

The number of patients dying from a sudden death in the enalapril-first group during the first six months of monotherapy was equal to that in the bisoprolol-first group during the entire first year. The difference in sudden deaths was accompanied by a similar reduction in all-cause mortality, although not statistically significant. Consequently, bisoprolol-first did not shift the mode of death from sudden death to death due to progressive CHF or other type of non-sudden death, either on the short or longer term.

Prior to the CIBIS III trial, a betablocker and an ACE inhibitor in monotherapy or as first CHF treatment were never directly compared with regard to the effects on sudden death (or all-cause death or hospi-

talisation) in patients with CHF. However, assessment of the effects of ACE inhibitors versus placebo (on top of a diuretic with or without digitalis) and of betablockers versus placebo (on top of an ACE inhibitor and diuretics with or without digitalis) indicates that betablockers substantially reduce sudden death, whereas there is no such evidence for ACE inhibitors. The results of the monotherapy phase in CIBIS III constitute the first data on a direct comparison between a betablocker, bisoprolol, and an ACE inhibitor, enalapril, in regard to the effect on sudden death. The results of the entire CIBIS III represent the first large-scale data comparing a strategy of beginning treatment for CHF with a betablocker followed by an ACE inhibitor with the standard regimen of an ACE inhibitor first, followed by a betablocker. The findings of CIBIS III are in agreement with those of prior trials regarding the superior effects of betablockers on sudden death and have the potential to affect clinical practice. The minor increase in risk of early worsening CHF, if any, might be a reasonable price to pay for an early reduction in sudden deaths, also in view of the fact that appropriate diuretic regimen as recommended by the international guidelines would likely prevent this from happening.

On the other hand, one may argue that the order of initiating a betablocker and an ACE inhibitor in patients with CHF does not matter, since both should be given to patients with CHF and impaired left ventricular systolic function. However, surveys show that the second agent is most often not started soon after the first drug and is frequently not given at all, and when it is prescribed it is usually given in a low dose. Even under the clinical trial conditions of CIBIS III, where investigators were forced to up-titrate both study drugs according to protocol unless they had a very good reason for not doing so, the mean dose of bisoprolol at one year was significantly higher in the bisoprolol-first group compared to the enalapril-first group. Furthermore, even if one were to give patients both treatments, the observation of an early sudden death reduction in the bisoprolol-

first group indicates the need to give CHF patients a betablocker as soon as possible.

These data do not argue against the growing use of ICD but, once more, point to the fact that management of SD risk still leaves plenty of room for implementation that can be attained by understanding and applying the appropriate concepts for adequate pharmacological regimens. Optimal beta-blocker therapy instated very early after the disease identification may prevent a number of still active individuals from dying suddenly. Once adequately instated, combined beta-blockade and ACE-inhibition do constitute a solid ground for the effective use of devices. It should indeed not be overlooked that, in MADIT II, full beta-blocker therapy significantly decreased mortality and ICD appropriate discharges (21).

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