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Comment on "Clinical trials update from the European Society of Cardiology meeting 2005: CIBIS-III, by JGF Cleland and others".

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Comment on "Clinical trials update from the European Society of Cardiology meeting 2005: CIBIS-III, by JGF Cleland and others.

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We read with interest the summary of and comment on the Cardiac Insufficiency BIsoprolol Study (CIBIS) III presentation at the 2005 European Society of Cardiology meeting in September (1). We would like to correct one factual error and express some different points of view from those put forward by Cleland et al in their article.

Firstly, CIBIS III did not show a greater propensity for hospitalisation with worsening heart failure in the bisoprolol-first group. There was, however, a non-significant increased rate of worsening heart failure occurring *either* as a primary cause for hospitalisation *or* as an event during hospitalisation for another cause (2). We have not as yet analysed if there actually was an increased hospitalisation rate due to worsening of heart failure.

Secondly, the rules for the futility analysis were not changed during the study. In the paper presenting and discussing the rationale and design of CIBIS III (3), we state that non-inferiority for bisoprolol-first versus enalapril-first is considered proven if the entire 95% confidence interval for bisoprolol-first versus enalapril-first is below *relative risk* (RR) 1.125. This is also clearly depicted in Figure 2 of that paper (3). In the setting of CIBIS III, RR 1.125 corresponds to *hazard ratio* (HR) 1.17. Both correspond to an *absolute risk* increase of 5%. However, there is a misspelling in the text (3), indicating that the HR should be less than 1.125. This number actually refers to the RR. The correct HR should be 1.17. This misspelling might have caused some confusion.

Thirdly, Cleland et al claim that the study design is not compatible with current guidelines or clinical practice. A clinical trial does not have to be. On the contrary, a clinical trial is usually intended to challenge and, if possible, to advance current clinical practice as well as guidelines. Furthermore, Cleland et al claim that a common practice is to start both an ACEI

and a beta-blocker simultaneously. This is not evidence-based practice. There are no guideline recommendations to start both an ACEI and a beta-blocker simultaneously. Quite the opposite, the European guidelines (4) recommend to start with an ACEI and to add a beta-blocker on top of the target dose of the ACEI.

As regards the time interval between initiating the two agents, we have no knowledge about the optimum time interval between starting an ACEI and initiating a beta-blocker, or the opposite, in patients with chronic heart failure. In CIBIS III, the monotherapy phase was six months. Thus, a patient started on bisoprolol received enalapril approximately 3.5 months after reaching the target dose of bisoprolol, which was up-titrated during 2.5 months. Patients who were started on enalapril received the first dose of bisoprolol around five months after reaching the target dose of enalapril, which was up-titrated during one month. However, CIBIS III was not designed to assess the optimum time interval between starting the respective drugs and does not allow for any conclusions in this regard. When designing CIBIS III, on the one hand, we wanted a long period of monotherapy to increase the chance of finding any differences between the two strategies, should these exist. On the other hand, the duration of the monotherapy phase had to be ethically justifiable. We agree with Cleland et al that most physicians would probably *aim* to start their patients on the second drug earlier than in CIBIS III. Nevertheless, many CHF patients never receive a beta-blocking drug, whereas many others remain on an ACEI for extended periods of time (5-7). Furthermore, those who do receive combined therapy usually receive a sub-optimal dose of the beta-blocker (5-7). Consequently, there is no definitive answer to the question of the optimum time interval between starting these agents.

Fourthly, Cleland et al claim that CIBIS III was essentially a study comparing two monotherapies. We do not agree. Surveys have shown that, in clinical practice the first initiated therapy, usually an ACEI, is given at a substantially higher dose than the second therapy, usually a beta-blocker (5,7). One reason for doing CIBIS III was to test if this would also hold true if therapy were started with a beta-blocker. Indeed, irrespective of if it was bisoprolol or enalapril, the first initiated drug was significantly more often prescribed at 50% or more of the target dose, as compared with the second drug (2). This finding may be important to future morbidity and survival and indicates that CIBIS III, indeed, was a comparison between treatment initiation strategies rather than monotherapies.

Fifthly, Cleland et al suggest that there should have been a third, combined arm in CIBIS III. However, the aim of CIBIS III was to compare the two treatment initiation strategies head to head. A three-armed trial would have been a different trial, certainly one well worth doing.

Lastly, we would like to point out that reference 12 in the paper by Cleland et al refers to the tolerability results of CARMEN, not the efficacy results, which were published in (8).

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