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Commentary

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial

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Abstract

Previous trials (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure [MERIT-HF], Cardiac Insufficiency Bisoprolol Study [CIBIS] II) have demonstrated a mortality benefit of β-adrenergic blockade in patients with mild to moderate heart failure. The recent Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial has extended these results to a more advanced patient population. This trial did not, however, include patients who could not reach compensation, patients with far advanced heart failure symptoms, or a significant number of black patients. Future studies of β-blockade may focus on these patients or patients with asymptomatic left ventricular dysfunction.

Keywords: β-adrenergic blocking agents, heart failure, mortality, race

Introduction

Heart failure medical therapy has undergone drastic evolution in the past 15 years. The shift in our understanding of how to optimally treat this clinical syndrome has been only slightly less dramatic than the shift in conceptual thought effected by the Polish astronomer Nicolas Copernicus (1473–1543), after whom the COPERNICUS trial is named. Copernicus proposed, based on his observations, the concept of a heliocentric solar system, as opposed to the previously accepted Ptolemiac theory of the earth as a fixed mass in the universe. The theory of giving a beta-blocker, a negatively inotropic and chronotropic agent, to a heart failure patient was perhaps as counter-intuitive and revolutionary as was Copernicus' heliocentric solar system, inasmuch as when first proposed it did not fit the accepted paradigm of the day. Only through years of small mechanistic studies and, ultimately, through large clinical trials has the old 'hemodynamic' paradigm of heart failure treatment fallen. Current theory now proposes that multiple compensatory neurohormonal, cytokine and mechanical stretch signals activate intracellular pathways that lead to progressive myocardial dysfunction, pathologic hypertrophy and remodeling, and cell loss [1]. Inhibition of neurohormonal activation by angiotensin converting enzyme (ACE) inhibitors [2,3] or beta-blocking agents [4–8] has shown an attenuation or reversal in the pathological remodeling process [9,10], a shift in phenotype back towards normal [11], and even a reduction in cell death [12]. Furthermore, clinical trials with β-blockers conducted in mild to moderate heart failure populations have shown a consistent mortality benefit, with large reductions in cardiovascular death, reductions in hospitalization, and improvement in quality of life [4–6].

ACE = angiotensin converting enzyme; BEST = β-Blocker Evaluation of Survival Trial; CIBIS = Cardiac Insufficiency Bisoprolol Study; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; FIRST = Flolan International Randomized Survival Trial; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; NYHA = New York Heart Association; SOLVD = Studoies of Left Ventricular Dysfunction.

Basic design of the COPERNICUS trial

It was unclear prior to the COPERNICUS trial [7] whether patients with advanced heart failure would derive a benefit from beta-blockade, as these are the patients who are most dependent on adrenergic support. The COPERNICUS trial was a double-blind, placebo-controlled, multicenter study of the effect of carvedilol, a nonselective beta-blocker with alpha$_1$ blocking properties and anti-oxidant effects on mortality in patients with more advanced heart failure. To be randomized in this trial, a patient had to have heart failure symptoms of heart failure at rest or on minimal exertion for at least 2 months. While New York Heart Association (NYHA) class was not assessed in this trial, these criteria fit the NYHA class III or IV criteria. Patients also had to have an ejection fraction of 0.25 or less, and had to be on ACE inhibitors and diuretics for at least 2 months. Importantly, patients with more than minimal evidence of fluid retention (pulmonary or peripheral edema) were excluded, as were patients in the intensive care unit, and patients who had recently received class IV diuretics or inotropes within 4 days.

Results of the COPERNICUS trial

As the COPERNICUS trial has only been presented orally, the results presented here are preliminary. The COPERNICUS trial recruited 2289 patients from 152 sites who were randomized to carvedilol ($n = 1156$) or placebo ($n = 1133$) and were followed for a mean of 316 days [7]. In the United States, 482 patients were randomized at 117 sites, and only 121 patients in the COPERNICUS trial were black. The study was stopped early for a highly significant mortality benefit. Carvedilol reduced mortality by 35% (95% confidence interval, 19–48% reduction) and the annual placebo mortality in this study was 18.5%, suggesting an advanced heart failure population. Subgroup analysis showed a consistent benefit across all strata, and permanent treatment withdrawal was lower in the carvedilol group than in the placebo group, suggesting good tolerability of carvedilol.

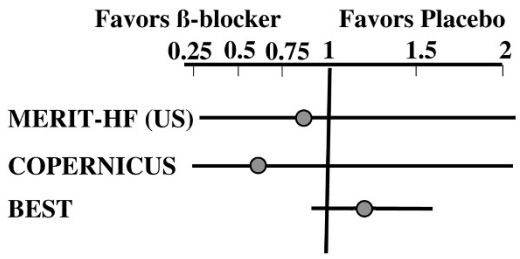
Commentary

The COPERNICUS study confirms the findings of earlier trials [4–6] that had demonstrated a benefit of β-blocking agents in patients with mild to moderate heart failure and extends the spectrum of eligible patients for this therapy to a more advanced population. One previous trial, the β-Blocker Evaluation of Survival Trial (BEST) [8], had examined a population of advanced heart failure and failed to demonstrate a benefit in the population as a whole. In this previous study, however, nonblack patients had a significant benefit while black patients did not, and patients with NYHA class IV heart failure did not demonstrate a benefit. The failure of BEST to demonstrate a benefit in advanced heart failure as compared with COPERNICUS may be related to both the population studied (BEST had many more blacks and had no requirement for euvolemia) and the drug used (bucindolol versus carvedilol).

With regard to the population studied, most of the patients recruited into the COPERNICUS trial as well as the other positive β-blocker trials were white European patients [4–7]. This population thus appears to respond well to β-blockers, while a more heterogeneous population in the United States may have responded less well. In BEST, 627 black patients followed for almost 2 years were recruited [13,14]. As BEST stratified by race (black versus nonblack), there was good balance between the placebo and bucindolol groups at baseline within the black population. After 208 deaths (94/305 placebo deaths and 114/322 bucindolol deaths), there was no clear benefit of bucindolol in this group of patients. The COPERNICUS trial only recruited 121 black patients, among which 7 of 63 black placebo patients died and 4 of 58 black carvedilol patients died (hazard ratio, 0.60; 95% confidence interval, 0.18–2.05) [7]). While it is encouraging that the mortality goes in the correct direction with carvedilol, the certainty of this finding is low because the confidence intervals are very wide. An analysis of black patients in all the large β-blocker trials does not, in fact, show a clear benefit of this therapy in the black population (Fig. 1).

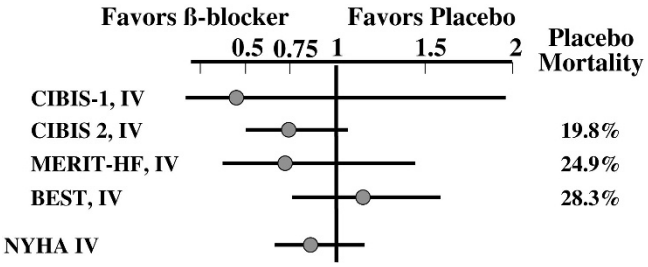
While the COPERNICUS trial shows a mortality benefit in an advanced heart failure population, it is important to examine what patients were actually enrolled in this study. The COPERNICUS trial represents a euvolemic set of patients with a low ejection fraction, and symptoms that would conventionally be classified as NYHA class III or IV. The low cutoff for ejection fraction in the COPERNICUS trial almost certainly increased the mortality compared with other trials that used a higher ejection fraction enrollment criterion, in view of the powerful negative effect of left ventricular ejection fraction on mortality [15]. While the MERIT-HF study randomized a less advanced population of patients with mild to moderate heart failure, a *post hoc* analysis of patients within that study who were NYHA class III (90%) or class IV (10%) and had a left ventricular ejection fraction ≤ 0.25, inclusion criteria similar to the COPERNICUS trial, increases the annual placebo mortality in MERIT-HF from 11.0 to 19.1% (Wikstrand J, personal communication, 2000) [16]. Although MERIT-HF was not designed to recruit patients with advanced heart failure, the elimination of NYHA class II patients and patients with an ejection fraction > 0.25 results in a population with a higher placebo mortality than COPERNICUS (19.1% versus 18.5%). The elevation in placebo mortality is thus not necessarily due to clinical severity of heart failure, but rather is partly the function of a low ejection fraction cutoff. The 26% mortality at 6 months in the ACE-inhibitor arm of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial [17] and the 37% mortality at 6 months in the ACE-inhibitor alone arm of the The Flolan International Randomized Survival Trial (FIRST) trial [18] clearly demonstrate that there are NYHA class IV patients who have much more advanced heart

Figure 1



Relative risks of death in blacks from all causes according to trial. Horizontal lines, 95% confidence intervals.

Figure 2



Relative risks of death in NYHA class IV patients from all causes according to trial. Horizontal lines, 95% confidence intervals.

failure than those recruited in the COPERNICUS trial. COPERNICUS does not address the benefits of β-blocker therapy in these populations.

While the COPERNICUS patients have advanced heart failure, they were also selected for the ability to achieve compensation. The patients who can achieve compensation are most probably those who have contractile reserve, while those without contractile reserve are more clinically ill. Patients with contractile reserve have the best hemodynamic response to β-blocker therapy, while those without contractile reserve have little or no improvement in ejection fraction [19,20]. This is important because a worsening of ejection fraction may relate to a neutral or even an adverse mortality benefit with β-blockade [21]. The mean systolic blood pressure of 123 mmHg in the COPERNICUS trial, which is higher than that seen in other trials of class IV heart failure [17,18], also suggests the presence of contractile reserve. The investigators, by specifying that only euvolemic patients are allowed in the COPERNICUS trial, may thus have selected out the most sick (class IV) patients who would not benefit from β-blocker therapy.

As the COPERNICUS trial did not assess NYHA functional class during the study, it is also clear that COPERNICUS provides no direct information relative to the question of whether β-blockers can be used in class IV heart failure. A meta-analysis of mortality in NYHA class IV heart failure subgroups from CIBIS II, MERIT-HF, and BEST are presented in Figure 2. While it is clear that the answer for class IV is still unclear, the hazard ratios in class IV of less than 1.0 in many of these trials suggest that some (but not necessarily all) class IV patients will benefit. Because the annual placebo mortality in MERIT-HF class IV patients was 25% and that in BEST was 28%, it is clear that COPERNICUS was not comprised of subjects comparable with class IV heart failure. Much of the benefit of COPERNICUS may accordingly have been in patients who would be conventionally assessed as NYHA class III (symptoms on mild exertion) as opposed to those who were class IV (symptoms at rest or with any activity).

Another reason for the difference between BEST and the COPERNICUS trial may relate to the sympatholytic effect of bucindolol [22]. Bucindolol reduced systemic norepinephrine in BEST [13,22], which is presumably the result of its potent β_2-receptor blocking activity [8,13,22,23]. Although carvedilol also blocks β_2 receptors at target final doses, the baroreceptor unloading and/or presynaptic effects on norepinephrine release of full α_1-blockade prevents carvedilol from reducing systemic norepinephrine levels and probably mitigates the effects of carvedilol on lowering cardiac adrenergic drive [23]. One other agent that lowers systemic (as well as cardiac) adrenergic drive has been recently evaluated in a heart failure clinical trial, and this agent, moxonidine, increased mortality [24]. It could thus be that excessive loss of β-adrenergic drive at the levels of both neurotransmitter release and receptor blockade becomes a liability in certain heart failure populations who are critically dependent on adrenergic support. This may be especially important in the black population in BEST who tended to have the largest reduction in plasma norepinephrine with bucindolol therapy [13] and who had the worst ventricular function at baseline (ie are most dependent on adrenergic support) [13].

Based on the results of the COPERNICUS study and other recently conducted β-blocker heart failure trials, it is important to consider where the database is robust enough to ethically preclude further placebo-controlled trials, and in what populations further controlled trials need to carried out. The role of either second or third generation β-blocking agents in far advanced heart failure (class IV or subjects moving between class IIIb and IV) is, in our view, still unclear, and further placebo-controlled trials are justified. Based on the BEST data, the role of β-blocking agents in blacks with advanced heart failure is also unresolved. There is also virtually no data in the setting of class I–II heart failure, which is a population analogous to that studied in the SOLVD Prevention Trial [25]. Although the soon to be reported CAPRICORN trial will provide information on a postmyocardial infarction left ventricular dysfunction population, this is a decidedly different patient

population from that investigated in the SOLVD Prevention trial. Established asymptomatic left ventricular dysfunction with no or mild symptoms is therefore another population where placebo-controlled trials are justified and needed.

Conclusions

The COPERNICUS study is a very important clinical trial that has added significant support to the β-blocker hypothesis and reassures us of the safety and benefit of these drugs in a subset of patients with more advanced heart failure. It would, however, be inappropriate to overextend the findings of the COPERNICUS trial to advanced heart failure patients who lack potential for reversal and are not in a compensated state.

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