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Randomized trial to optimize the dose and efficacy of beta-blocker in systolic heart failure: Japanese Chronic Heart Failure (J-CHF) Study

Discussant

**Marco Metra
Cardiology, University of Brescia**

No conflict to disclose with respect to this presentation

The value of J-CHF

- **Necessary**
 - First prospective trial to assess the effects of different doses of beta-blocker on clinical outcomes as a primary endpoint
- **Important as lower dose**
 - May be better tolerated
 - Simplify / avoid the uptitration process
- **Definitive?**

Dose response relationships with beta-blockers in heart failure (I)

Drug (trial)	End-point	Design	No. of patients	Dose dependency
Bucindolol	LVEF	Prospective, placebo control	141	Yes: LVEF
Carvedilol (MOCHA)	Submax Ex	Prospective, placebo control	345	Yes: LVEF, Mort; ? CVHosp
Metoprolol-XL (REVERT)	LV remodel.	Prospective, placebo control	149	Yes: LVESV, LVEF
Carvedilol (MUCHA)	CHF global assessment	Prospective, placebo contr	174	Yes: LVEF, outcomes

Bristow et al. Circulation 1994;89:1632; Bristow et al. Circulation 1996; 94:2807; Colucci et al. Circulation. 2007;116:49-56; Hori et al. Am Heart J 2004; 324

Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial

Masatsugu Hori, MD, PhD,^a Shigetake Sasayama, MD, PhD,^b Akira Kitabatake, MD, PhD,^c Teruhiko Toyo-oka, MD,^d Shunnosuke Handa, MD, PhD,^e Mitsuhiro Yokoyama, MD, PhD,^f Masunori Matsuzaki, MD, PhD,^g Akira Takeshita, MD, PhD,^h Hideki Origasa, PhD,ⁱ Kennichi Matsui, BA,^j and Saichi Hosoda, MD, PhD,^k on behalf of the MUCHA Investigators *Suita, Kyoto, Sapporo, Tokyo, Isehara, Kobe, Ube, Fukuoka, and Toyama, Japan*

Background The efficacy and optimum dose of β -blockers have not been established in Japanese patients with chronic heart failure (CHF). The efficacy and safety of two doses of carvedilol, a β -blocker with vasodilator and antioxidant actions, were investigated in Japanese patients with CHF.

Methods After screening and a carvedilol challenge phase, 174 patients with mild to moderate CHF were randomly assigned (double-blinded) to placebo, 2.5 mg of carvedilol twice daily, or 10 mg of carvedilol twice daily. After a 2- to 4-week uptitration phase, maintenance treatment was continued for 24 to 48 weeks. The primary end point was improvement of the global assessment of CHF by the attending physician. Secondary end points were death or hospitalization for cardiovascular disease, cardiovascular hospitalization, hospitalization for heart failure, change of left ventricular ejection fraction, and change in New York Heart Association class.

Results Carvedilol therapy achieved dose-dependent improvement of all end points (P for linear trend, range .002 to $< .001$). Both carvedilol groups showed marked risk reduction (71% to 91%) for cardiovascular and CHF hospitalization and for death or cardiovascular hospitalization (P range, .024 to $< .001$ for pairwise comparisons with placebo). No significant differences were observed for noncardiovascular hospitalization or adverse events.

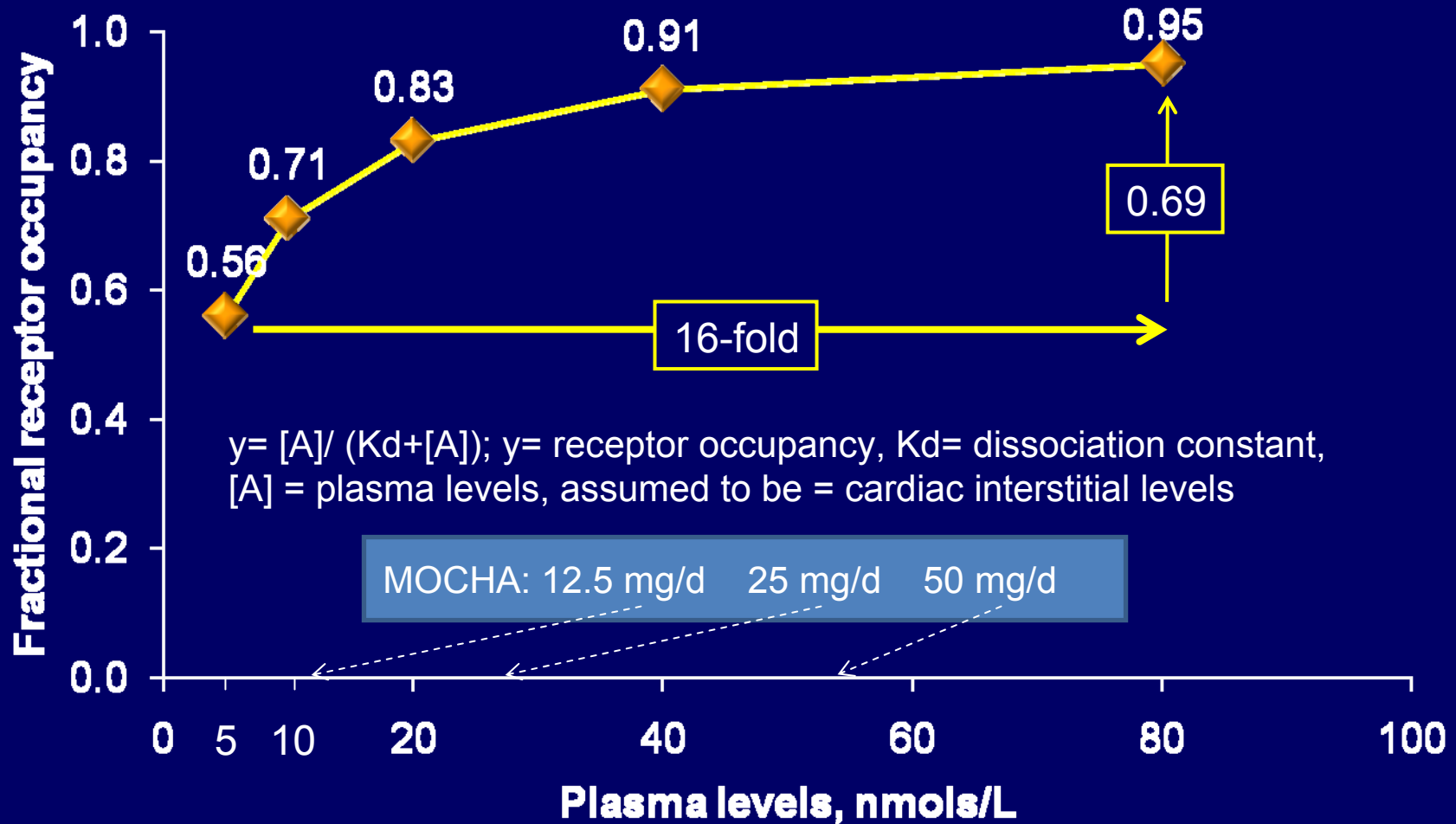
Conclusions In Japanese patients with mild or moderate CHF, carvedilol achieved dose-related improvement of CHF and left ventricular ejection fraction; cardiovascular hospitalization was markedly reduced. At 5 mg/d, carvedilol conferred an important patient benefit, less than at 20 mg/d. (*Am Heart J* 2004;147:324–30.)

Dose response relationships with beta-blockers in heart failure (II)

Drug (trial)	End-point	Design	No. of patients	Dose dependency
Metoprolol-XL (MERIT-HF)	Mortality	Retrospective placebo contr Multivariate an.	1845	No, if \approx HR
Bisoprolol (CIBIS-II)	Mortality	Retrospective placebo contr Multivariate an.	2647	Yes, low dose (<5 mg/d) vs higher doses
Carvedilol & metoprolol (COMET)	Mortality	Retrospective Multivariate an.	2599	Lower mortality with high dose
Nebivolol (SENIORS)	Mortality + CV hosp	Retrospective, Placebo contr Multivariate an.	2061	Yes, low doses (<5mg/d) vs higher doses

Wikstrand et al. J Am Coll Cardiol 2002; 40:491; Simon et al. Eur Heart J 2003;24:552; Metra et al. Eur Heart J; 2005; 26: 2259; Dobre et al. Am Heart J 2007; 154:109

Importance of the range of doses selection: different plasma levels are associated with smaller differences in receptor occupancy



Courtesy of MB Bristow, Denver, CO

Limitations of the study

- Lack of a placebo group
 - No information regarding the magnitude of drug effects
- Insufficient number of patients & events

Statistics: Number of patients needed to detect a meaningful difference*

- Clinically meaningful difference (i.e. ATLAS**): 15%
 - 80% power at a two-sided 0.05 significance level to detect a 15% lower risk with 20 vs 2.5 or 5 mg
 - vs. 2.5 mg group (event rate, 27/118, 23%)
 - **> 3000 patients** **J-CHF: 352 patients**
 - **> 1000 events** **J-CHF: 74 events**

• Statistical advice by Beth Davison Weatherly, MOMENTUM Res. Inc.
•**Packer et al. Circ 1999; 100:2312-8

Consequences of insufficient number of patients/ events

- No conclusions regarding the relationship between carvedilol dose and outcomes (primary end-point of the study)
- Inconsistencies in results
 - HR & BNP were independent predictors of outcomes / Carvedilol had dose related effects on HR & BNP / carvedilol dose was not related with outcomes
 - Previous studies

Final considerations

- To date, all outcome studies have been conducted with drug up-titration to target maximal doses
- J-CHF is the first study to assess prospectively the effects of different doses of a beta-blocker on a clinical outcome as a primary endpoint
- Results are not in agreement with previous studies
- The trial, although interesting, is underpowered to draw final conclusions
 - Results as only hypothesis generating and must not change current clinical practice based on randomized trials and guidelines