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Research Letter

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# Efficacy and safety of once-daily carvedilol in patients with atrial fibrillation: A randomized, double-blind, placebo-controlled trial

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Heart rate (HR) control is a mainstay of atrial fibrillation (AF) management. Guidelines recommend first-line β-blockers for HR control in paroxysmal, persistent, or permanent AF.[1] Carvedilol, a nonselective β-blocker, has a documented HR-lowering effect; in a dose-escalation study of Japanese patients with chronic AF (AF Carvedilol study), each dose of carvedilol (5, 10, or 20 mg once daily) significantly reduced HR from baseline (HR ≥80 beats/min) during 6 weeks of treatment.[2] Although off-label carvedilol indications include AF,[3] there are currently no phase 3 clinical trial data to support carvedilol use for HR control in patients with AF. We report results from a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with persistent or permanent AF treated with once-daily carvedilol (Dilatrend SR capsule, Chong Kun Dang Pharmaceutical, Seoul, Republic of Korea) 8, 16, or 32 mg for 6 weeks (ClinicalTrials.gov identifier NCT03950843). Eligible patients who received carvedilol during the 6-week treatment period entered a 4-week open-label extension period.

Overall, 154 subjects were enrolled (safety analysis set). Subjects in the full analysis set received carvedilol (n = 93) or placebo (n = 42): the mean age was 66.4 ± 9.6 years; mostly were male (72.6%), with a mean resting HR of 98.3 ± 14.7 beats/min and a $CHA_2DS_2$-VASc score of 2.43 ± 1.64; and the majority (80.7%) had a modified European Heart Rhythm Association score of 2a. Most subjects had persistent AF (77.0%), and the mean AF duration was 60.7 ± 73.8 months. There were no significant between-group differences in baseline characteristics. Change in 24-hour mean HR from baseline

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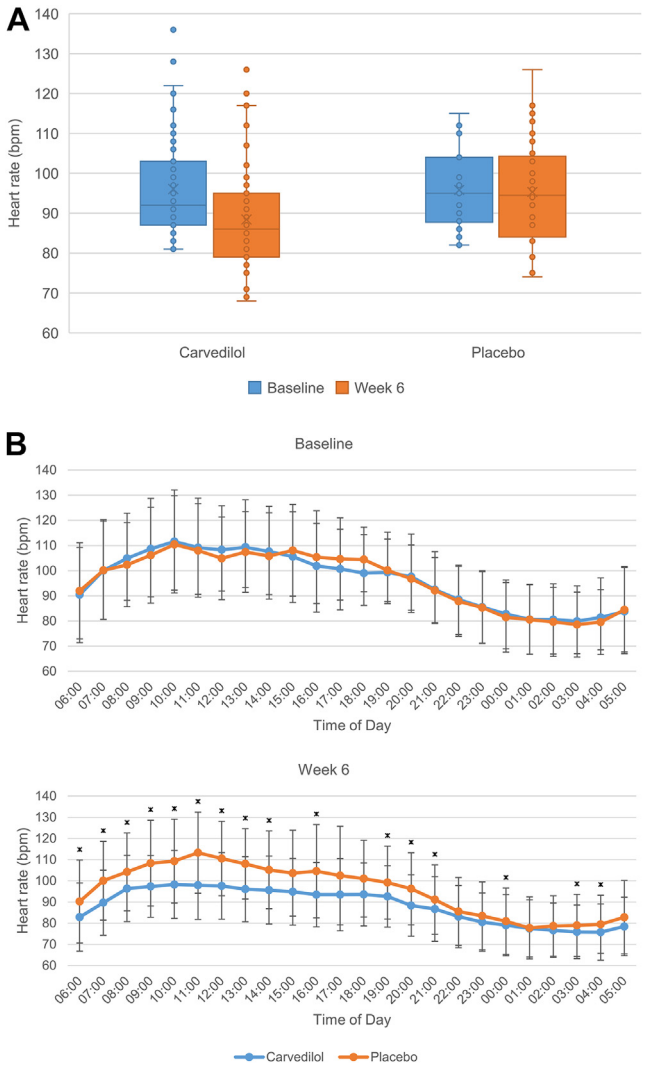


**Figure 1**
(**A**) Change in 24-hour mean heart rate from baseline to week 6 and (**B**) hourly mean heart rate over 24 hours at baseline (*upper panel*) and week 6 (*lower panel*). *Statistically significant between-group differences.

to week 6 (primary end point) was reduced significantly by carvedilol vs placebo ($P < 0.0001$) (Figure 1A); changes were maintained in the 4-week extension period. Post hoc subgroup analysis showed that changes in 24-hour mean HR from baseline to week 6 with carvedilol were dose dependent: respective mean changes for carvedilol 8 mg (n = 14), 16 mg (n = 26), and 32 mg (n = 53) were −5.07 ± 5.97, −9.69 ± 6.34, and −7.58 ± 8.00 ($P = .0072$, $P < .0001$, and $P < .0001$, respectively). More subjects achieved HR < 80 beats/min at week 6 (secondary end point) in carvedilol vs placebo groups (30.1% vs 14.3%; $P = .0499$), with a risk difference of 15.82 (95% confidence interval 1.72–29.93). Carvedilol was associated with a significant improvement in modified European Heart Rhythm Association scores from baseline to week 6 ($P < 0.0001$; secondary end point).

Hourly mean HR at baseline was similar between the 2 groups (Figure 1B, upper panel), but at week 6, carvedilol produced significant changes from baseline in hourly mean HR at each hourly time point. In contrast, no significant changes from baseline in hourly mean HR were found in the placebo group. At week 6, modest but significant decreases in hourly mean HR were generally observed with carvedilol compared with placebo during the daytime, but there were fewer significant between-group differences at nighttime (exploratory end points) (Figure 1B, lower panel).

In the safety analysis set, 60 treatment-emergent adverse events (TEAEs) were reported in 43 subjects (27.9%) during the 6-week trial: 43 adverse events in 31 subjects (29.8%) in the carvedilol group and 17 in 12 subjects (24.0%) in the placebo group. Most TEAEs were mild (41 cases) or moderate (18 cases) in severity. The most common TEAEs were dizziness in 9 subjects (5.8%) and dyspnea in 7 subjects (4.6%).

This is the first pivotal phase 3 clinical trial to show the efficacy of once-daily carvedilol for HR control in patients with AF. Compared with placebo, carvedilol significantly decreased 24-hour mean HR from baseline to week 6 and this effect was maintained during the 4-week extension period. Changes were dose dependent with higher carvedilol doses (16 and 32 mg) effecting larger changes than the 8 mg dose. Similar results were reported in the Japanese AF Carvedilol study of patients with persistent or permanent AF, which demonstrated that once-daily carvedilol significantly reduced HR from baseline during 6 weeks of treatment.[2]

In conclusion, carvedilol for 6 weeks was effective in reducing HR in patients with AF and maintained efficacy during the extension period. Carvedilol was well tolerated, and the safety profile was consistent with previous reports.

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