Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 42, No. 11, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/j.jacc.2003.07.020

Carvedilol Alone or in Combination With Digoxin for the Management of Atrial Fibrillation in Patients With Heart Failure?

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OBJECTIVES This study examined the relative merits of digoxin, carvedilol, and their combination for the management of patients with atrial fibrillation (AF) and heart failure (HF).

BACKGROUND In patients with AF and HF, both digoxin and beta-blockers reduce the ventricular rate, and both may improve symptoms, but only beta-blockers have been shown to improve prognosis. If combined therapy is not superior to beta-blockers alone, treatment of patients with HF and AF could be simplified by stopping digoxin.

METHODS We enrolled 47 patients (29 males; mean age 68 years) with persistent AF and HF (mean left ventricular ejection fraction [LVEF] 24%) in a randomized, double-blinded, placebo-controlled study. In the first phase of the study, digoxin was compared with the combination of digoxin and carvedilol (four months). In the second phase, digoxin was withdrawn in a double-blinded manner in the carvedilol-treated arm, thus allowing a comparison between digoxin and carvedilol (six months). Investigations were undertaken at baseline and at the end of each phase.

RESULTS Compared with digoxin alone, combination therapy lowered the ventricular rate on 24-h ambulatory electrocardiographic monitoring ($p < 0.0001$) and during submaximal exercise ($p < 0.05$), whereas LVEF ($p < 0.05$) and symptom score ($p < 0.05$) improved. In phase 2, there was no significant difference between digoxin alone and carvedilol alone in any variable. The mean ventricular rate rose and LVEF fell when patients switched from combination therapy to carvedilol alone. Six-minute walk distance was not significantly influenced by any therapy.

CONCLUSIONS The combination of carvedilol and digoxin appears generally superior to either carvedilol or digoxin alone in the management of AF in patients with HF. (J Am Coll Cardiol 2003;42: 1944–51) © 2003 by the American College of Cardiology Foundation

Digoxin has been used for over two centuries for the treatment of heart failure (HF) and/or atrial fibrillation (AF) and is currently standard therapy for patients with persistent AF and HF. However, there is evidence that digoxin is inadequate for controlling the ventricular rate during exercise or when sympathetic tone is increased (1). Furthermore, digoxin does not improve survival of patients with HF and sinus rhythm, and there is little reason to suppose that there would be a prognostic benefit in patients with AF, assuming that ventricular rate control can be obtained by other means (2).

Beta-blockers have been shown to improve the prognosis of patients with HF and left ventricular (LV) systolic dysfunction, a substantial minority of whom had AF as their baseline rhythm (3–5). In patients without HF, beta-blockers improve ventricular rate control in AF when added to digoxin or when used alone (1). Among patients with AF and HF, only a few trials have specifically investigated the utility of adding a beta-blocker to digoxin (6–8). These trials suggest that beta-blockers reduce ventricular rate, improve ventricular function, and are well tolerated. However, these mechanistic studies used agents with high intrinsic sympathomimetic activity (6,8), which are now generally thought to be contraindicated in HF and were conducted before the advent of angiotensin-converting enzyme inhibitors. Furthermore, beta-blockers were added to digoxin in these studies; no comparison between beta-blockers alone versus digoxin alone, or the combination, was made.

The aim of this randomized, double-blinded study was to compare the effects of digoxin alone, carvedilol (a beta-blocker) alone and their combination in patients with HF and persistent AF.

METHODS

Patients. We recruited patients with persistent AF (>1 month) and HF who were receiving digoxin and diuretics. Heart failure was defined as appropriate symptoms of HF for more than two months and echocardiographic evidence of cardiac dysfunction (left ventricular ejection fraction [LVEF] <40% or preserved LV systolic function, together with LV hypertrophy, suggesting diastolic dysfunction in the absence of an alternative potential cause of symptoms). The following were exclusion criteria: heart rate (HR) at rest <60 beats/min, systolic blood pressure (BP) <90 mm Hg, sick sinus syndrome or complete heart block, current treatment with a beta-blocker or HR-lowering calcium channel antagonist or >200 mg amiodarone, recent major cardiovascular event or procedure, asthma or reversible

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Manuscript received April 25, 2003; revised manuscript received July 2, 2003, accepted July 7, 2003.

Abbreviations and Acronyms

AF = atrial fibrillation
BNP = brain natriuretic peptide
BP = blood pressure
ECG = electrocardiogram/electrocardiographic
HF = heart failure
HR = heart rate
LV = left ventricular
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
RPP = rate-pressure product

obstructive airways disease, serum creatinine >250 μmol/l or significant hepatic disease, uncorrected significant valvular heart disease, or any life-threatening noncardiac disease. All patients gave written, informed consent, and the protocol was approved by the local Ethics Committee.

Study design. In a randomized, controlled, double-blinded, parallel-arm study, the following treatments were assessed: digoxin alone versus the combination of digoxin and carvedilol (phase 1, duration four months) and digoxin alone versus carvedilol alone (phase 2, duration six months) (Fig. 1). Withdrawal of digoxin at the same time as initiating and uptitrating beta-blockers could increase the risk of worsening HF. Therefore, a complex study design was adopted to allow double-blinded initiation of carvedilol first, followed by double-blinded withdrawal of digoxin, once maintenance doses of carvedilol had been achieved.

Investigations were performed at baseline and after each phase. Before randomization, patients had their digoxin dose increased, if necessary, to achieve optimal resting ventricular rate control (defined as a ventricular rate of at least <90 beats/min on a 12-lead electrocardiogram [ECG]). Plasma concentrations of digoxin were monitored to avoid toxicity, except in the second phase, which would have compromised the double-blinded nature of the study. The reference levels for toxicity were 1.2 to 2.6 nmol/l. Forty-seven patients were randomized into two groups: 24 into the carvedilol treated group and 23 into the placebo group. In phase 1, both groups continued open-label digoxin; in addition, one group received double-blind carvedilol while the other received double-blind placebo. The starting dose of carvedilol was 3.125 mg b.i.d., and this was increased at two-week intervals to the target dose of 25 mg b.i.d. (uptitration period of two months) or, for patients weighing more than 85 kg, 50 mg b.i.d. In phase 2, open-label digoxin was replaced by double-blind placebo in the group already receiving double-blind carvedilol. Open-label digoxin was replaced with double-blind digoxin in the group receiving double-blind placebo in phase 1. Patients were reviewed two weeks after open-label digoxin was withdrawn or substituted to monitor for worsening HF. Repeat investigations were carried out eight weeks after open-label digoxin withdrawal or substitution (or six months after initial randomization). The randomization process involved a paired coding system during the two phases, so that no patient was left without some ventricular rate control therapy. This design allowed a double-blinded comparison between digoxin alone and carvedilol alone at the end of six-month follow-up.

Investigations. The primary prespecified outcomes for the study were: 1) LVEF by ECG-gated radionuclide ventriculography; 2) ventricular rate control by 24-h ambulatory ECG; and 3) symptoms at the end of phase 2 of the study. We also investigated exercise tolerance by 6-min corridor walk distance in all patients. In a subset of 23 patients, ventricular rate control

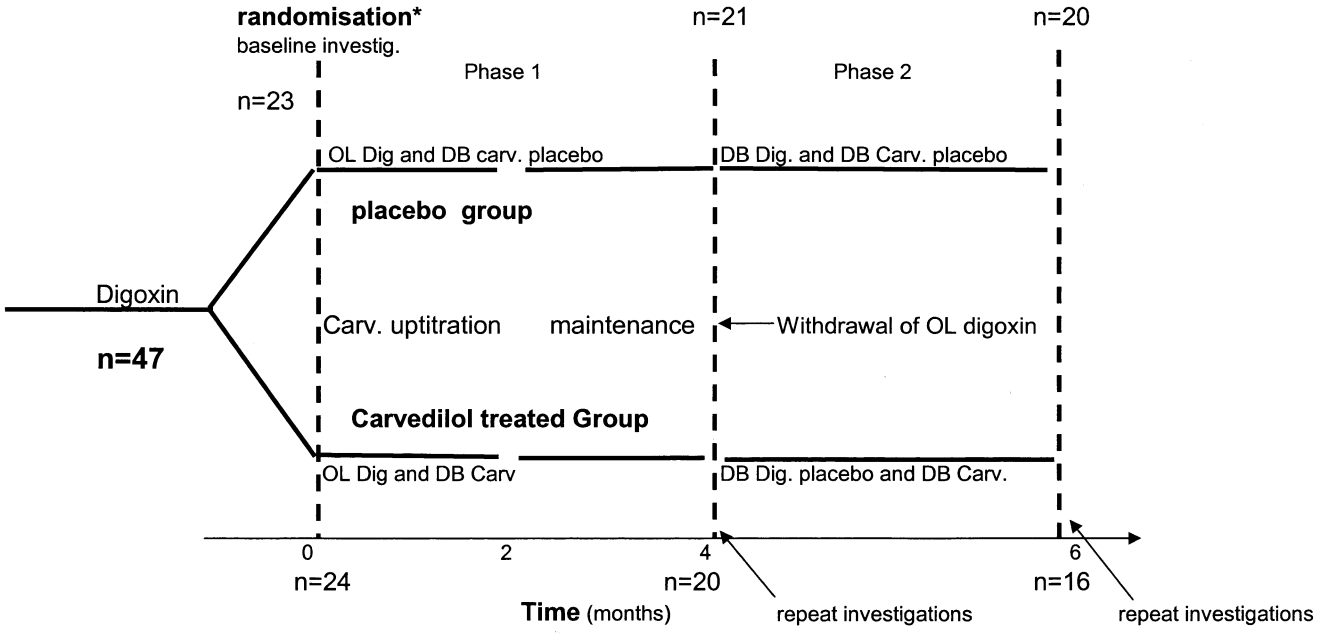

Figure 1. Study design. *Randomization at this stage determined pairing of therapies in phase 2. Carv. = carvedilol; DB = double-blind; Dig. = digoxin; OL = open-label.

during steady-state bicycle exercise test was assessed. Plasma concentrations of brain natriuretic peptide (BNP) (C-terminal, Peninsula Labs, Belmont, California) were measured.

Primary end point measurements. ASSESSMENT OF LV FUNCTION. For radionuclide ventriculography, 5 mg stannous pyrophosphate was injected intravenously into the patient 15 min before the injection of 500 MBq of technetium-99m pertechnetate. A gamma camera equipped with a general, all-purpose, parallel-hole collimator interfaced to a dedicated computer, linked to MAPS LINK medical system, was used to analyze counts. The LVEF was determined from the left anterior oblique projection using a manual method of drawing the region of interest, together with estimation of background correction. Mean LVEF was calculated in standard fashion after background correction. Calculated mean LVEF in this study was averaged from all RR intervals (both long and short) during the 10 min of recording in the left anterior oblique projection. A previous study has demonstrated that ECG-gated time-activity curves for LVEF for all beats are very similar to the averaged single-beat data (9).

VENTRICULAR RATE CONTROL. The 24-h ambulatory ECGs were obtained in all subjects during normal, unrestricted out-of-hospital activity by using a miniature tape recorder with a crystal time-generated reference track that allows correction for recording and replay speed errors to within 0.5%. For a tape to be eligible it had to have >21 h of analyzable data with AF as the basic rhythm. The ECG recordings were processed with standard precision on the MEDILOG Excel 2 system (OXFORD Instruments, Abingdon, UK).

Assessment of symptoms. We used a self-administered, quantitative questionnaire designed to measure the patient's perception of the frequency and severity of symptoms and their functional capacity. A 4-point scale (0 = absent; 3 = severe symptoms) was used for the following symptoms; chest pain/discomfort, fatigue, shortness of breath, and palpitations. For the first three symptoms, patients were asked to grade severity at rest, during walking at normal pace, and while climbing stairs. We also asked about the patient's "global" health or their sense of well-being. The responses were summed to produce a symptom score ranging from 0 (no symptoms) to 33 (worst symptoms).

Exercise tests. All patients underwent a standard 6-min corridor walk test with verbal encouragement given to the patient every 2 min. A subgroup of 11 patients in the carvedilol-treated arm and 12 patients in the placebo arm exercised on a bicycle against a resistance of 50 W at 40 rotations/min for 5 min. The remainder was either unable to exercise due to co-morbidities (n = 14), such as arthritis or hemiparesis due to stroke, or declined (n = 10). Blood pressure was recorded manually by a sphygmomanometer at rest (pre-exercise) and 3 and 5 min into exercise. The last 10 s of recorded ECG of each minute was used to determine the ventricular rate for that minute. All patients exercised in the morning between 9 AM and 12 PM.

Statistics. We used LVEF to determine the sample size. Because there are no data directly comparing digoxin to carvedilol for a change in LVEF in patients with HF, we powered the study on the expected differences in ejection fraction when comparing digoxin with the combination of carvedilol and digoxin. The mean increase in LVEF in controlled studies of carvedilol in HF patients is ~8% (10); a large percentage of the population in these trials was on maintenance digoxin therapy. Given a postulated standard deviation of 9.5% for ejection fraction, the sample size was estimated to be 44 patients (22 in each limb; beta = 0.80, alpha = 0.05).

Absolute values between groups were not compared because of expected heterogeneity in individual electrophysiologic characteristics and consequently differing responses to pharmacologic intervention. Rather, for each patient, the change from baseline for the results of investigations was determined at the end of phase 1 (four months) and phase 2 (six months). The change from baseline (i.e., before the first randomization) was then compared between groups. A paired t test for intragroup comparisons and a two-sided t test for intergroup comparisons were used for normally distributed data. The Mann-Whitney U test was used to compare differences for nonparametric data. For paired sample non-normal data, the Wilcoxon signed rank test was used. The Z test was used for the comparison of proportions, as appropriate. A value of $p < 0.05$ indicated statistical significance. To estimate the time of peak ventricular response (acrophase) and diurnal variation in the hourly mean ventricular rate for treatments, the mean hourly ventricular rate of each group was modeled by cosinor analysis (11). Group data are presented as the mean ± SD for parametric data and the median value with interquartile ranges for nonparametric data. Analysis was undertaken by SPSS statistical software, version 9.

Our statistical analysis plan did not include analysis of variance (ANOVA), as the principle analysis of interest was the comparison between monotherapies, with combination therapy being a necessary intermediate step of novel mechanistic but not novel clinical significance (as far larger subsets of patients with AF were included in landmark trials of beta-blockers in HF). However, we also explored the results of repeated measures ANOVA on the three normally distributed variables (change from baseline): 24-h ambulatory mean HR, systolic BP, and 6-min walk distance. The results for this analysis did not differ from the predefined analysis plan.

RESULTS

Tables 1 and 2 describe the demographic and clinical variables at baseline. The groups were generally well matched. Most patients were treated with angiotensin-converting enzyme inhibitors and warfarin in addition to digoxin and diuretics. Although inclusion criteria did not stipulate the presence of significant LV systolic dysfunction and allowed inclusion of patients with convincing evidence of HF with preserved LV systolic function, in fact, only three of the 47 patients recruited to this study had LVEF

Table 1. Population Characteristics at Baseline

	Carvedilol-Treated Group (n = 24)	Placebo Group (n = 23)	
Age (yrs)	68.6 ± 9.4	68.4 ± 9.8	NS
Males	14	15	NS
IHD etiology	8	11	NS
Duration of AF (weeks)	152.8 ± 204	109.2 ± 123.4	NS
Previous cardioversion attempts (n)	0.3 ± 0.6	0.7 ± 1.7	NS
Resting heart rate on ECG (beats/min)	88.5 ± 24.5	82.4 ± 19.7	NS
LVEF (%)	23.7 ± 10.4	24.7 ± 9.5	NS
LVEDD (mm)	53.3 ± 10.4	54.2 ± 9.7	NS
LA size (mm)	48.9 ± 8.3	47.9 ± 8.0	NS
NYHA class			NS
I	1	1	
II	11	16	
III	9	6	
IV	3	0	
Digoxin dose (mg)	0.25 ± 0.11	0.24 ± 0.1	NS
Digoxin plasma concentration (nmol/l)	1.55 ± 0.8	1.52 ± 0.7	NS
ACE inhibitors	17 (71%)	16 (71%)	NS
Anticoagulated	19 (79%)	19 (83%)	NS

Data are presented as the mean value ± SD or number (%) of subjects.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ECG = electrocardiogram; IHD = ischemic heart disease; LA = left atrial size; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NS = not significant; NYHA = New York Heart Association.

>40% (2 in the carvedilol-treated group and 1 in the digoxin-treated only group). All but three patients were titrated to a target dose of carvedilol (25 mg b.i.d.); two were titrated to 12.5 mg b.i.d.; and one to 6.25 mg b.i.d. No patient reverted to sinus rhythm during the trial.

Changes from baseline for 24-h mean HR, systolic BP, and 6-min walk distance were normally distributed data, whereas changes from baseline for LVEF, symptom score, and BNP were not normally distributed and analyzed as such.

Phase 1: digoxin alone versus carvedilol and digoxin in combination. Twenty of 24 patients randomized to carvedilol and 21 of 23 patients randomized to placebo completed phase 1. The mean daily dose of carvedilol achieved in the active arm was 47.6 mg. The plasma digoxin concentration did not differ significantly between groups either at baseline (Table 1) or at the end of phase 1 (1.2 ± 0.5 vs. 1.4 ± 0.5 nmol/l for digoxin alone vs. combination, respectively, $p = 0.2$). However, two patients on carvedilol developed possible symptoms of digoxin toxicity and had their digoxin dose reduced, although serum concentrations remained in the therapeutic range.

No significant change in any study variable occurred when adding placebo to digoxin. Compared with placebo, the addition of carvedilol to digoxin reduced the mean 24-h ventricular rate ($p < 0.0001$) and improved symptoms scores ($p < 0.05$) and LVEF ($p < 0.05$). New York Heart Association (NYHA) functional class also tended to improve ($p = 0.08$) with combination treatment. Changes in BNP and 6-min walk distances were not significant (Table 2).

Phase 2: digoxin alone versus carvedilol alone. In phase 2 of the study, double-blinded withdrawal of digoxin from patients on carvedilol led, by intragroup comparison, to a significant increase in the 24-h mean HR and a decline in LVEF. When the intergroup changes from baseline for these variables were compared, no significant difference between digoxin alone and carvedilol alone was noted. However, BNP values increased significantly more for carvedilol alone than for digoxin alone. There was conflicting evidence for symptomatic deterioration on withdrawal of digoxin. Symptom scores of patients who remained on therapy favored carvedilol ($p = 0.007$). However, three patients in the carvedilol-treated group developed worsening symptoms of HF, associated with a rise in HR, leading to an exit from the study on days 11, 18, and 24 days after withdrawal of digoxin. Preceding NYHA class, ventricular function, or plasma BNP did not predict deterioration. One patient developed worsening symptoms of HF when switching from open-label to double-blind digoxin. After assigning maximum symptom scores to withdrawals, a significant difference in symptoms between carvedilol alone and digoxin alone was no longer noted (Table 2).

Ventricular rate control (Figs. 2 and 3). Figures 2A to 2C, illustrates the 24-h ventricular rate profile for each phase of the study. Compared with digoxin alone, the

Table 2. Intergroup Comparisons of Treatment Effect

	Baseline Values		Phase 1 (4 Months)			Phase 2 (6 Months)		
	Pre-Carvedilol Group	Placebo Group	Combination	Digoxin	p Value*	Carvedilol	Digoxin	p Value*
24-h mean heart rate (beats/min)	81.8 ± 11.7	75.9 ± 12	65.2 ± 15‡	74.9 ± 11.2	< 0.0001	88.8 ± 18.7	75.7 ± 10.6	0.13
Systolic BP (mm Hg)	128 ± 19	132 ± 23	121 ± 24	134 ± 20	0.11	112 ± 16‡	129 ± 20	0.45
LVEF (%)	23.7 ± 10.4	24.7 ± 9.5	30.6 ± 9.6‡	26 ± 12.4§	0.048	21.6 ± 11	27.2 ± 11.7	0.15
Symptom score†	12 (7.25–17)	10 (4–17)	7 (3–12.5)‡	8 (3–15)	0.039	6 (2–17)‡	8 (5–15.5)	0.08
6-min WD (ms)	353 ± 109	354 ± 143	394 ± 82	414 ± 114	0.46	374 ± 108	403 ± 126	0.49
BNP (pg/ml)	86 (63–176.8)	122 (59–211)	153 (107–200)	120.5 (87–188)	0.11	183 (118–312)‡	79.5 (57–155)	0.03

*The p value is a test of significance for the *change from baseline* between the respective groups. †In phase 2, patients withdrawn due to worsening heart failure were assigned NYHA class IV and maximum symptom scores of 33 each. ‡Intragroup changes compared with baseline, $p < 0.05$. §One patient in this group, phase 1, had a technically inadequate radionuclide ventriculogram. Data are presented as the mean value ± SD or median value (interquartile range).

BNP = brain natriuretic peptide; BP = blood pressure; Combination = combination treatment with carvedilol and digoxin; LVEF = left ventricular ejection fraction; WD = walk distance.

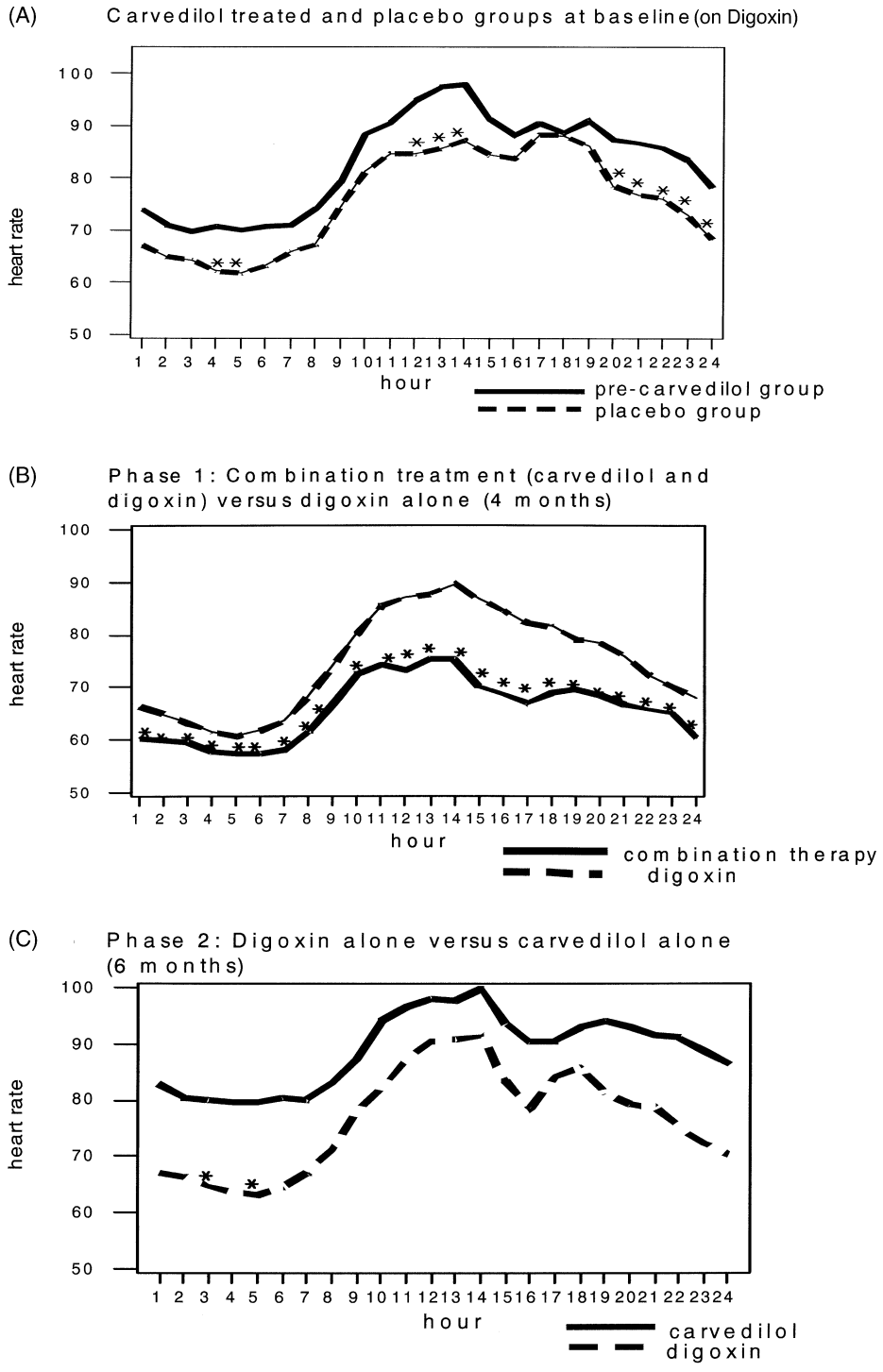

Figure 2. (A to C) Mean hourly heart rate (HR) as influenced by treatment regimen(s) during ambulatory 24-h electrocardiogram. Points with an asterisk represent significant differences in HR between groups. At baseline, by chance, the ventricular rate tended to be higher in the carvedilol-treated group throughout 24 h, but this difference was only statistically significant for a few hours. Analyses are intergroup changes from baseline values.

addition of carvedilol lowered the mean 24-h ventricular rate during both day and night (Fig. 2B). Carvedilol alone and digoxin alone were equally effective in controlling the daytime ventricular rate, but digoxin lowered the nocturnal HR to a greater extent (Fig. 2C). Carvedilol significantly reduced day-night differences in the mean hourly HR, in combination with digoxin or alone, principally by attenuating the increase in HR during waking hours (Figs. 2B and 2C). The peak ventricular rate occurred at ~15:00 h for all treatment groups. The median maximum ventricular rate was 176 beats/min on digoxin alone versus 134 beats/min on combination treatment (phase 1; $p < 0.05$). Carvedilol alone and digoxin alone appeared equally effective in reducing the median maximal ventricular rate.

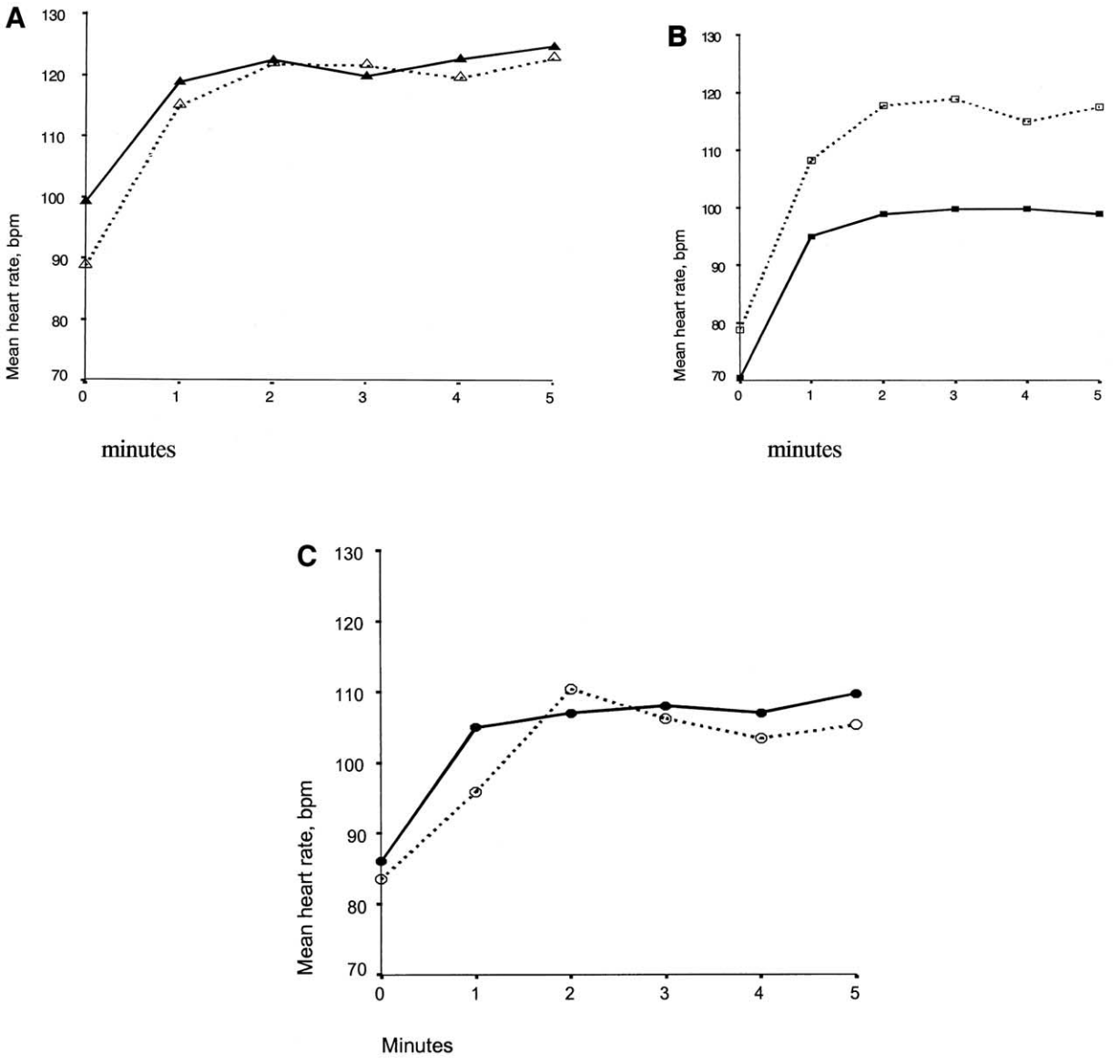

Figure 3. Ventricular rate during submaximal exercise. **(A)** Pre-carvedilol **(open triangles)** and placebo **(solid triangles)** groups at baseline. **(B)** Phase 1 (four months): combination therapy **(solid squares)** versus digoxin alone **(open squares)**. **(C)** Phase 2 (six months): digoxin alone **(open circles)** versus carvedilol alone **(solid circles)**.

Compared with digoxin, combination therapy reduced the ventricular rate at rest and throughout steady-state exercise (Fig. 3B) (peak ventricular rate 106 vs. 123 beats/min on digoxin; $p < 0.05$). Carvedilol alone and digoxin alone appeared equally effective in controlling exercise HR (Fig. 3C). The rate of rise in ventricular rate during exercise was similar for carvedilol or digoxin alone and combination treatment.

The peak rate-pressure product (RPP) was reduced on combination therapy compared with digoxin alone (15,003 ± 6,684 vs. 19,176 ± 5,463; $p < 0.007$). However, in phase 2, comparing carvedilol and digoxin monotherapies, peak RPP was not significantly different (13,583 ± 3,213 vs. 17,017 ± 3,557, $p = 0.23$). The peak ventricular rate was similar (114 ± 21 vs. 116 ± 18 beats/min, $p = 0.8$), but systolic BP (127 ± 12 vs. 157 ± 19 mm Hg, $p = 0.002$) was lower for carvedilol than digoxin.

Pauses. Compared with digoxin, combination therapy resulted in a greater mean maximum pause (2.9 ± 0.8 vs. 2.4 ± 0.6 s, $p < 0.05$). The mean maximum pause was greater for digoxin alone compared to carvedilol alone in phase 2 (2.3 ± 0.7 s vs. 1.8 ± 0.73 s for digoxin and carvedilol, respectively; $p < 0.05$). However, there was no significant difference in the numbers of pauses >3 s, either during the day (8 AM to 8 PM) or night (8 PM to 8 AM) for any treatment group.

Adverse events. In phase 1, three patients withdrew because of adverse effects subsequent to the initiation of carvedilol (one each with gastrointestinal disturbance, tiredness, and bronchospasm), and one withdrew in the placebo group (self-withdrawal). Four patients, as noted earlier, withdrew because of worsening HF during phase 2. There were three deaths during the study: two in the group

randomized to carvedilol (myocardial infarction in phase 1 and stroke in phase 2) and one in the group randomized to placebo (postoperative sepsis after transurethral resection of the prostate during phase 1).

DISCUSSION

Few studies have focused on the management of patients with both AF and HF, conditions that often co-exist (12). Our results demonstrate that, in patients with persistent AF and HF, the combination of digoxin and carvedilol, compared with digoxin alone, lowers the ventricular rate and reduces symptoms. However, few differences between carvedilol and digoxin, used as single agents, were apparent. In particular, no difference in the mean 24-h HR was observed. Withdrawal of digoxin from patients with AF treated with carvedilol appeared generally deleterious. This study, therefore, is the first to demonstrate the continued value of digoxin for the treatment of persistent AF in the setting of HF in the presence of a beta-blocker.

Ventricular rate control and LV function. A reduction in the ventricular rate during exercise and 24-h ambulatory ECG monitoring was less than that anticipated with carvedilol alone compared with digoxin alone (12). This suggests that both increased vagal tone and reduced sympathetic activation are important in controlling ventricular rate in patients with HF and AF (Figs. 2B and 3B). The sympatholytic effects of digoxin may also be complementary to those of beta-blockade (13). Digoxin was more effective at reducing the nocturnal HR, reflecting the importance of parasympathetic activation when sympathetic tone is low.

Beta-blockers consistently reduce end-diastolic volume and improve LVEF both in patients with chronic HF in sinus rhythm (10) and in those with AF (5), but the mechanisms underlying this effect are uncertain. An increase in LVEF with the addition of carvedilol could reflect a nonspecific response to a reduction in the ventricular rate. There is some evidence of HR-dependent cardiomyopathy in patients with AF and suboptimal ventricular rate control (12).

No previous study has investigated the utility of digoxin in patients with HF and persistent AF treated with beta-blockers. This is important given concerns about polypharmacy in patients with HF. For those who tolerated digoxin withdrawal, the ejection fraction declined by a median of 9%, whereas the mean 24-h ventricular rate rose by 22 beats/min to a mean of 88 beats/min. The latter was unexpected, as digoxin withdrawal has not been shown to cause such a marked increase in HR or reduction in ventricular function in patients in sinus rhythm (14). It suggests that the atrioventricular node may be less susceptible than the sinoatrial node to the effects of beta-blockers in patients with HF. Alternatively, the withdrawal of digoxin may reduce baroreflex receptor sensitivity, removing the tonic inhibition of central sympathetic drive, thereby limiting the effects of beta-blockade (13). Our findings, therefore, do not support the notion that the introduction of beta-blockers as standard treatment of HF obviates the need for digoxin in the presence of AF.

A potential criticism of this study is the accuracy of the assessment of LV function in patients with AF, due to the large variation in the RR interval. However, Bacharach et al. (9) showed that the average of single-beat values plotted against preceding RR intervals were very similar to one ECG-gated time-activity curve (as used in this study). Inagaki et al. (15) also showed that ECG-gated radionuclide ventriculography is reliable, reproducible, and sensitive to change in patients with AF.

Symptoms. There were significant improvements in symptom scores with the double-blinded addition of carvedilol to digoxin (Table 2), as demonstrated in other studies of HF, presumably reflecting the effects of therapy on underlying ventricular function (3). Most patients did not deteriorate symptomatically upon withdrawal of digoxin, despite a decline in ventricular function. This could reflect a protective effect of increased BNP levels or some other action of carvedilol, such as peripheral vasodilation. No patient with severe HF deteriorated clinically after digoxin withdrawal. All three patients who deteriorated symptomatically, necessitating withdrawal from study, were in NYHA class I or II at the end of phase 1. Longer follow-up on combination therapy might have prevented deterioration on digoxin withdrawal. However, longer follow-up on carvedilol monotherapy might have allowed declining cardiac function to be translated into a worse clinical outcome more often.

Natriuretic peptides. Plasma concentrations of BNP tended to rise when carvedilol was added to digoxin, rose further when digoxin was withdrawn, and did not predict which patients would deteriorate upon withdrawal of digoxin. Increases in natriuretic peptides have also been noted in studies of beta-blockers in patients in sinus rhythm (16) and may reflect increases in ventricular filling pressure, conversely this could be part of their therapeutic action of beta-blockers (17). These data suggest that natriuretic peptides may not be a useful aid to the management of HF with beta-blockers.

Previous studies. Synergistic effects of digoxin and beta-blockade in controlling the ventricular rate in AF have been demonstrated in previous studies, although these small studies had few patients with HF (1). It is uncertain whether all beta-blockers would exert the same benefits in patients with AF and HF, most of whom are currently treated with digoxin. A post hoc analysis of Cardiac Insufficiency BIsoprolol Study (CIBIS II) suggested that, in patients with AF, bisoprolol had no impact on survival or hospitalization for HF (18). However, retrospective analyses of the U.S. carvedilol HF trials program suggested that the benefit of carvedilol was similar in the presence or absence of AF (5), whereas a greater benefit of carvedilol on death and hospitalization was reported among patients taking digoxin, although only a minority had AF (19). Recently, the Carvedilol Or Metoprolol European Trial (COMET) has suggested that carvedilol exerts a greater effect on mortality than metoprolol, but data on patients with AF are not yet available (20).

Potential pharmacologic alternatives to beta-blockers for the control of ventricular rate in patients with AF and HF include diltiazem and amiodarone. Concerns exist about the safety of diltiazem in patients with HF (21). Deedwania et al. (22), in a post hoc subgroup analysis of the Congestive Heart Failure-Survival Trial of Anti-arrhythmic Therapy (CHF-STAT) trial, demonstrated that the ventricular rate was significantly reduced with amiodarone. Furthermore, spontaneous cardioversion occurred in 31% of those on amiodarone but only 8% of those on placebo at one year. The risk of long-term side effects with amiodarone and the known mortality benefits of beta-blockers render the latter group of agents preferable for the control of ventricular rate in patients with persistent AF and LV systolic dysfunction.

An alternative treatment strategy in this patient population is repeated cardioversion and prophylactic anti-arrhythmic therapy to maintain sinus rhythm. However, in the presence of HF and long-established AF, the failure of cardioversion, toxicity of anti-arrhythmic drugs, and early relapse are major drawbacks (12). A number of trials have investigated the utility of cardioversion versus a strategy of rate control for atrial fibrillation (23–25). None has suggested that cardioversion is superior in terms of improving symptoms, reducing stroke, or improving survival. Ventricular rate control with anticoagulation therefore seems an appropriate strategy in this population until either a subgroup is identified that would benefit from a policy of repeated cardioversion or more effective and safer methods of maintaining sinus rhythm are developed.

Conclusions. This study suggests that the combination of digoxin and carvedilol reduces symptoms, improves ventricular function, and leads to better ventricular rate control than either agent alone and therefore should be considered the standard treatment for HF patients with persistent AF.

Acknowledgments

We are grateful for the assistance of research nurses Morag Shaw and Carole Campbell at the Glasgow Royal Infirmary in the running of the study and to Elaine Clarke and Shahid Latif of the Department of Cardiology at the Glasgow Royal Infirmary for their technical assistance.

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