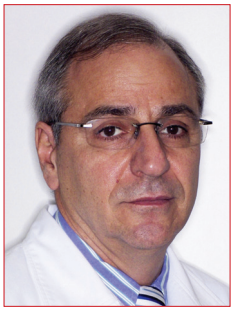
> "Rates of adherence to medication regimens are alarming, with over 50% of patients, on average, abandoning the treatment prescribed. Addressing the issue of medication adherence should be a priority. Given the inverse relationship between complexity of regimens and adherence, a different approach to improve adherence may be to address regimen complexity. Fixed-dose combination drugs have been proposed as a means to ease the burden of taking multiple medications and to improve adherence."

# The complementary and synergistic role of combining β-blockers and ivabradine in patients with chronic heart failure:

## a focus on carvedilol/ivabradine fixed-dose combination

by E. A. Bocchi, *Brazil*



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***Polypharmacy is a reality in current heart failure (HF) treatment practices, and optimal therapy in HF patients is difficult to achieve. In real life, adherence to such treatments is very low. Fixed-dose–combination drugs (FDCs) have been proposed as a means to decrease the burden of taking multiple medications and to improve adherence. The use of FDCs may significantly increase adherence rates. Combinations of heart-rate–modifying drugs have potential for formulation as FDCs. Heart rate is significantly related to prognosis in HF, and an elevated resting heart rate in HF patients can identify those who might benefit from treatment with heart-rate–reducing drugs. Ivabradine and β-blockers can reduce heart rate, improving HF outcome, whereas published data suggest that amiodarone, digoxin, and verapamil may not be safe or that their safety is controversial in HF patients. Although the concept of FDCs has not been tested in randomized double-blind prospective trials in HF, the coadministration of ivabradine plus β-blocker has high potential to benefit HF patients. Results from SHIFT (Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine Trial) and other studies on the effects of ivabradine support the combination of β-blockers and ivabradine to improve outcomes in HF patients. Combination pills may be an effective tool to help address medication adherence issues in outpatient treatment of HF. Carivalan (carvedilol/ivabradine), an FDC comprised of ivabradine plus β-blocker, is expected to increase adherence and reduce costs while preventing major HF events.***

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### The fixed-dose combination concept for heart failure

Polypharmacy is a reality in current heart failure (HF) treatment practices. The drug armamentarium for chronic HF with reduced ejection fraction (HFrEF) has rapidly evolved and expanded over the past 2 decades to include a number of effective therapies.[1,2] The realization of optimal therapy in HF patients is difficult to achieve. In actuality, adherence to these treatments is very low.[3,4] Rates of adherence to medication regimens are alarming,[5] with over 50% of patients, on average, abandoning the treatment prescribed. Addressing the issue of medication adherence should be a priority. Given the inverse relationship between complexity of regimens and adherence, a different approach to improve adherence may be to address regimen complexity. Fixed-dose combination drugs (FDCs) have been proposed as a means to ease the burden of taking multiple medications and to improve adherence. Such treatments may significantly increase adherence rates. Meta-analysis results have shown a 20% relative reduction in the rate of nonadherence for FDCs

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compared with that of component drugs taken separately.[5] Choosing the right combination of drugs in the FDC is a real challenge. The combination of medications that affect heart rate (HR) have potential as FDC formulations.

## Heart rate as a prognostic factor

A 1987 report of the Framingham Study showed that HR over 30 years of follow-up was associated with all-cause, cardiovascular, and coronary mortality rates.[6] To date, 38 studies have been published on the association between elevated HR and mortality.[7,8] Over a median follow-up period of 14.7 years, patients with a resting HR at or above 83 beats per minute (bpm) at baseline had a significantly higher risk for total mortality and cardiovascular mortality than the reference group, after adjustment for multiple clinical variables.[9]

In patients with stable coronary artery disease and left-ventricular dysfunction, the HR of 70 bpm or greater was associated with increased risk for cardiovascular death (34%), admission to hospital for HF (53%), admission to hospital for myocardial infarction (46%), and coronary revascularization (38%).[10] For every increase of 5 bpm, there were increases in cardiovascular death (8%), admission to hospital for HF (16%), admission to hospital for myocardial infarction (7%), and coronary revascularization (8%).

HR was significantly related to prognosis in HF.[11,12] Also, in a failing myocardium model, peak isometric twitch tension occurred at lower frequencies of stimulation of the myocardium, suggesting that HR reduction could improve contractility.[13]

## Heart rate as a target for pharmacological treatment of chronic heart failure in sinus rhythm

Elevated resting HR in HF identifies a subgroup of patients who could benefit from treatment with HR-reducing drugs. β-blockers, ivabradine, digoxin, amiodarone, and verapamil have been prescribed to reduce HR.

### ◆ *Digoxin*

Recently, the use of digoxin in HF has declined, partially because of concerns about safety after the publication of observational studies reporting increased mortality with digoxin.[14] In a systematic review and meta-analysis about safety and efficacy of digoxin, this drug was associated with a neutral effect on mortality in randomized trials and a small but significant reduction in rate of all-cause hospital admission.[14]

However, a number of retrospective studies of consecutive patients and clinical trial databases and prospective cohort studies have questioned the efficacy and safety of digoxin therapy in HF.[15] It should be noted that the outpatients enrolled in the DIG (Digitalis Investigation Group) trial differ markedly from an unselected contemporary HF population in terms of demographics (ie, age, sex, and ethnicity) and background therapy. Thus, an appropriately designed and powered randomized, double-blind, placebo-controlled trial should be conducted to establish the broader clinical utility of digoxin in stable ambulatory patients with HF.

### ◆ *Amiodarone*

In the era predating β-blocker/ivabradine use, the GESICA trial *(Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina),* with predominance of nonischemic cardiomyopathy, was the first investigation to demonstrate that reduction in HR may be associated with improvement in outcomes in patients with HF. For patients with a HR at or above 90 bpm, amiodarone therapy reduced mortality to 38.4% compared with 62.4% in control patients. Both sudden death and progressive HF death (relative risk, 0.60; 95% confidence interval, 0.30 to 1.03; $P<0.06$) were reduced, and functional capacity was improved. In patients with a HR below 90 bpm, amiodarone did not alter survival.[16] Also, in CHF-STAT (Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy), with predominance of ischemic etiology, left ventricular ejection fraction (LVEF) increased more in the amiodarone patients than in the placebo group at each evaluation time point.[17] However, this difference was not associated with greater clinical improvement, lesser diuretic requirements, or fewer hospitalizations for HF. Amiodarone was associated with a high incidence of side effects. Furthermore, it was recently reported that use of amiodarone may be associated with increased mortality in HF patients.[18] Subgroup analyses of primary prevention implantable cardioverter defibrillator (ICD) trials, as well as large studies evaluating amiodarone for atrial fibrillation, have also suggested an increased risk of death with amiodarone. A systematic review and meta-analysis of randomized controlled trials also reported a possible increase in all-cause mortality associated with the use of amiodarone compared with standard medical therapy.[19]

### Selected abbreviations and acronyms

| | |
|---|---|
| ACE | angiotensin-converting enzyme |
| bpm | beats per minute |
| CARVIVA-HF | Effect of CARVedilol, IVAbradine or their combination on exercise capacity in patients with Heart Failure |
| CHF-STAT | Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy |
| CIBIS-ELD | Cardiac Insufficiency BIsoprolol Study in ELDerly |
| DIG | Digitalis Investigation Group |
| GESICA | *Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina* |
| HF | heart failure |
| HFrEF | heart failure with reduced ejection fraction |
| HR | heart rate |
| SHIFT | Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine Trial |

◆ *β-blockers*

Beneficial effects of β-blocker agents in HFrEF seem to be due in part to drug-mediated HR reduction. In an analysis of 35 trials, a close relation was reported between all-cause annualized mortality rate and HR, and a strong correlation was shown between change in HR and change in LVEF. It was suggested that a major contributor to the clinical benefits of β-blocker therapy in systolic HF could be the HR-lowering effect of these agents. Also, the magnitude of HR reduction may be more important.[20] Furthermore, a meta-analysis including 23 β-blocker trials showed that the magnitude of HR reduction is statistically significantly associated with the survival benefit of β-blockers in HF, whereas the dose of β-blocker is not.[21]

◆ *Verapamil*

The nondihydropyridine calcium-channel blockers (verapamil and diltiazem) have a negative chronotropic effect that may slow the sinus rate, and an additional negative dromotropic effect at the atrioventricular node level. However, on the basis of its negative inotropic effects, verapamil is contraindicated in HFrEF.[22]

◆ *Ivabradine*

Apparently, the beneficial effects of ivabradine are associated mainly with HR reduction. Ivabradine reduced cardiovascular death, hospital admission for worsening HF, and deaths due to HF. Fewer serious adverse events occurred in the ivabradine group than in the placebo group.[23]

## Combination of heart-rate–reducing drugs in heart failure treatment

In the DIG trial, digoxin was tested concomitant with baseline medications that included diuretics, angiotensin-converting enzyme (ACE) inhibitors, nitrates, and vasodilators, without drugs that affect HR.[24] In the GESICA trial, amiodarone was tested in HF on top of concomitant baseline use of digoxin in 75.2% to 77.6% of patients (values correspond to patients with HR below 90 bpm and those with HR at or above 90bpm, respectively). In other studies, β-blocker was tested on top of digoxin (51%-99% of patients, depending on the study), diuretic (90%-99%), ACE inhibitor/angiotensin II receptor blocker (89%-97%), direct-acting vasodilator/nitrates (32%-58%), spironolactone (20%), amiodarone (14%-18%), calcium antagonists (2%), aspirin (46%), and lipid-lowering agents (25%-27%).[25-27] In the SHIFT trial (Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine Trial), ivabradine was tested on top of concomitant treatment with baseline drugs that reduce HR (β-blocker, about 90% of patients; cardiac glycosides, 22%).

## Rationale for the combination of heart-rate–reducing drugs in heart failure: β-blockers and ivabradine

Ivabradine and β-blockers can reduce HR, improving HF outcome, whereas published data suggest that amiodarone, digoxin, and verapamil may not be safe in HF patients. Although β-blockers improve prognosis, they are often underused in clinical practice and are seldom prescribed at the doses proven to reduce events. In the SHIFT trial, at baseline, around 90% of patients were receiving β-blocker.[23] However, only 26% of patients received target doses of β-blocker. The mean daily dosage of β-blockers in the study were as follows: carvedilol, about 17.8 mg; bisoprolol, about 3.4 mg; metoprolol succinate, about 60 mg; metoprolol tartrate, 47.4 mg; and nebivolol, about 3 mg. The reasons for failure to reach target dose were hypotension (about 45%), fatigue (32%), dyspnea (14%), dizziness (about 13%), bradycardia (6%), and other (roughly 10%). These data are consistent with doses used in clinical practice reported in international registries or in other randomized studies. For example, in the CIBIS-ELD study (Cardiac Insufficiency Bisoprolol Study in Elderly) reported by Dungen et al, dosing achieved by forced titration was very similar to that observed in SHIFT, with at least 50% of the target dose achieved in 55% of the patients.[28] The European survey in 3226 patients with chronic HF showed that 87% of patients with HF were treated with a β-blocker, but the target doses of carvedilol, bisoprolol, and metoprolol, as defined by the European Society of Cardiology (ESC) guidelines, were only reached in 37%, 21%, and 21% of patients, respectively.[29] Recent analysis showed that in well-managed HFrEF patients, high HR was frequent even after aggressive β-blocker titration and often despite being on at least 50% of guideline-recommended β-blocker dose.[30]

Baseline data of the SHIFT trial indicated that a substantial proportion of patients in clinical practice who cannot tolerate the target doses of β-blockers would benefit from the addition of ivabradine on top of optimized treatment for HF.[23] These findings support the rationale for the prescription of β-blocker combined with ivabradine.

The rationale for combining β-blockers and ivabradine is related to the different mechanisms for HR reduction and different hemodynamic profiles, suggesting that their actions at heart level are synergic and not limited to sinus node rate, cardiac output, and an increase in cardiac dimensions. In patients with advanced HF, acute administration of ivabradine reduced HR while increasing stroke volume and thus maintained cardiac output.[31] This acute effect is different from that observed with β-blockers that have a direct negative and lusitropic effect, and it has been shown that when administered acutely, β-blockers reduce stroke volume.[32] This might explain why the initial uptitration of β-blockers is often difficult. Long-term therapy with ivabradine in patients treated with β-blockers reversed LV remodeling, as showed by a SHIFT echo substudy.[33] One potential explanation for the beneficial effect of ivabradine in combination with β-blocker on cardiac dimensions is the reduction in afterload.[34] It was observed that after 8 months of treatment, ivabradine induced a significant reduction in effective arterial elastance and improved total arteri-

al elastance. Contractility remained unchanged and ventricular-arterial coupling was improved, resulting in a higher stroke volume in ivabradine-treated patients.

## Results of the combination of β-blocker and ivabradine on outcome in heart failure patients: SHIFT trial and small studies

The CARVIVA-HF trial (Effect of CARVedilol, IVAbradine or their combination on exercise capacity in patients with Heart Failure) was a randomized, open, blinded end point study to assess the effect of HR reduction from carvedilol, ivabradine, and their combination on exercise capacity in HF patients receiving maximal doses of ACE inhibitor.[35] HR was reduced in all three groups, but to a greater extent in the group receiving the combination. The distance walked on the 6-minute walk test and the exercise time on the myocardial oxygen consumption ($MVO_2$) test significantly improved in the ivabradine and combination groups, as did peak oxygen consumption ($VO_2$). No changes in these parameters were found with carvedilol. The patients receiving ivabradine or the combination had a better quality of life.[35]

In another prospective, open-label, nonrandomized, single-center study performed in 69 patients with chronic HFrEF, adding ivabradine to carvedilol treatment was associated with lower resting HR at 5 months; apart from HR reduction, the combination was associated with improvements in 6-minute walk test results and ejection fraction (all $P<0.05$).[36] Furthermore, patients receiving ivabradine and carvedilol had better exercise capacity than those on carvedilol alone. In addition, adding ivabradine to carvedilol in patients with chronic HF improved the uptitration of β-blocker.[36] The higher doses of carvedilol achieved in the combination group could be explained by the different and complimentary hemodynamic effects of β-blockers and ivabradine, as ivabradine administration has been shown to significantly increase stroke volume in patients with severe chronic HF.[31] The increase in stroke volume caused by ivabradine is clinically relevant because β-blockers reduce stroke volume during initiation, the first months of treatment, and during uptitration. This effect of β-blockade could be compensated for by prescribing ivabradine with lower initial doses of β-blockers. Ivabradine also reduces left ventricular end-diastolic pressure, unlike β-blockers, with this effect still present when ivabradine is coadministered with a β-blocker, resulting in increased stroke volume and maintenance of cardiac output.[34]

A comparative, randomized study compared two treatment strategies in patients with HFrEF, with patients receiving either β-blockers alone or ivabradine plus β-blockers starting 24 hours after hospital admission. The study concluded that early coadministration of ivabradine and β-blockers was feasible and safe and produced a significant decrease in HR observed at 28 days and 4 months after hospital discharge. It also seemed to improve systolic function and other functional and clinical parameters of HF patients in the short term.[37] Furthermore, a recent systematic review and meta-analysis reported that the rate of combined end point comprising readmission for HF and cardiovascular death was lower in the group receiving ivabradine plus β-blocker than in the group receiving β-blocker alone.[38]

Subanalysis of the SHIFT trial reported that patients treated with carvedilol in combination with ivabradine had 20% significantly lower rates for the primary composite end point of cardiovascular death or hospitalization for worsening HF, a 27% significantly lower rate of HF hospitalization, and a 20% lower rate of cardiovascular hospitalization than those prescribed carvedilol with placebo.[39] The dosage of carvedilol had no detectable effect and there were no unexpected safety issues. The dosage was relatively stable during the study, and 88% of patients continued on the same dosage for the duration of coprescription (89% of the group on carvedilol in combination with ivabradine and 86% of the group on carvedilol in combination with placebo). Carvedilol was the most frequently used β-blocker in patients with systolic HF in the SHIFT study. It was also the most widely prescribed β-blocker in a European registry including nearly 9000 patients with systolic HF, in which 57% of patients were receiving carvedilol.[40]

## Conclusion

β-Blockers reduce mortality in HF patients. However, they are often underused in clinical practice and are seldom prescribed at the doses proven to reduce events. Although the concept of FDCs has not been tested in randomized, double-blind prospective trials in HF, the coadministration of ivabradine and β-blocker may have high potential to benefit HF patients. The effects of ivabradine reported in the SHIFT trial and other studies support the combination of β-blockers and ivabradine to improve the outcome in HF patients. Furthermore, it would be less expensive and easier to administer as a single FDC pill, providing incremental improvement in adherence. No problems have been detected regarding the bioavailability, pharmacokinetics, or interaction between ivabradine and β-blockers. In general, patients' acceptance and adherence to treatment with the FDC are better than with administration of the component drugs given separately.[41] Although titration to target doses is preferable, many patients are unable to tolerate maximally recommended doses even in the clinical trials, and most patients in real life are on lower doses. It is important to recognize that doses of these therapies that are lower than maximal have been shown to confer substantial benefit in HF patients.[42] Combined multidrug formulations (ie, FDCs) may therefore provide a simple, convenient, and effective treatment strategy to combat the increasing burden of HF. Combination pills may represent an effective tool to help address drug nonadherence in the outpatient treatment of HF. Carivalan, an FDC combining ivabradine and the β-blocker carvedilol, is expected to increase adherence and reduce costs while preventing major HF events. ■

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*Keywords: β-blocker; exercise capacity; fixed-dose combination drug; heart rate; ivabradine*