

Synergistic effects of cardiac resynchronization therapy and drug up-titration in heart failure: is this enough?

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This editorial refers to ‘Optimization of heart failure medication after cardiac resynchronization therapy and the impact on long-term survival’, by C.T. Witt et al., on page 182

Drug therapy is a cornerstone in the clinical management of heart failure (HF) and there is today consistent and strong evidence that neurohormonal blockers reduce morbidity and mortality. Indeed, the three pivotal clinical trials investigating the use of beta-blockers in HF (CIBIS II, COPERNICUS, and MERIT-HF) showed an approximate 34% relative reduction in mortality.^{1–3} ACE inhibitors (ACE-i) were also shown to improve clinical outcomes in several landmark trials, including CONSENSUS, SOLVD, and SAVE.^{4–6} More recently, randomized trials have reported that angiotensin receptor antagonists (ARBs) provide incremental benefit over background therapy with ACE-i in HF^{7,8} and improve hard endpoints when used as a substitute for ACE-i in intolerant patients.⁹ In spite of the documented benefits of these drugs, there are still relevant clinical unmet needs in the management of HF, even when optimal doses are used.

Implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) have revolutionized the clinical management of patients with HF, leading to impressive benefits on mortality and hospitalizations when used in conjunction with optimized drug therapy.^{10,11} Of note, patients treated with implantable devices for cardiac rhythm management (CRM) are known to receive HF medications more often and at higher doses than those not treated with devices.^{12–14}

In this issue of the Journal, Witt et al.¹⁵ report the long-term follow-up of a large population of HF patients and show that device therapy with CRT-D or CRT-P improves the use of ACE-i/ARBs and increases the proportion of patients receiving target doses of beta-blockers. Of note, follow-up data are extended to 4 years and show that adherence to target doses remains high over the long term, with a major impact on prognosis. These results extend and strengthen findings from earlier studies.

In the IMPROVE HF,¹² patients who were treated with CRM devices received ACE-i or ARB therapy more often (and more frequently at target doses) than did those not treated with devices. Moreover, a favourable response to CRT has been reported to be associated with higher use of beta-blockers and ACE-i/ARBs, leading to a dose-dependent reduction in mortality.¹³ These results are consistent with those observed by the MADIT-CRT investigators:¹⁴ in general, the greater the efficacy of CRT, the greater the likelihood that patients remain on ACE-i/ARBs and reduced treatment with diuretics, that is time-dependently associated with an increased risk of HF events or death.

The reasons why CRT-D and CRT-P are independently associated with prescription, adherence and persistence of drug therapy at or above target doses are presently unclear. However, by restoring both mechanical and electrical synchronicity, CRT leads to an improvement in HF symptoms and blood pressure levels,¹⁶ most likely resulting in higher tolerability to neurohormonal blockade.

Notably, Witt et al.¹⁵ report that only a small fraction of patients received recommended target doses of ACE-i/ARBs and beta-blockers. Indeed, although CRT allowed sufficient room for therapy up-titration, only one-fifth to one-third of patients were on target doses at 6 months. This is consistent with the findings from the IMPROVE HF,¹² showing that only ~20% of eligible patients treated with ICD, CRT-D, or CRT-P received beta-blockers and one-third received ACE-i/ARBs at or above recommended target doses.

The impressive reduction of hard endpoints obtained with ACE-i, ARBs, and beta-blockers has been documented in randomized controlled trials, a setting of tight clinical control in which target dose therapy is pursued based on patients’ tolerance to up-titration. Achievement of target doses of HF drugs in major trials ranges from 58.6% for carvedilol in the COPERNICUS,¹⁷ to 64% for metoprolol in the MERIT-HF,¹⁸ and 84% for valsartan in the Val-HeFT.¹⁹ Of note, as far as ARBs are concerned, clinical trials allowed therapeutic drug doses considerably higher than those traditionally used in

clinical practice. Indeed, in the Val-HeFT,¹⁹ the target daily dose of valsartan was 320 mg, and in the CHARM studies^{8,9,20,21} candesartan was used at the target dose of 32 mg/day.

While international guidelines²² recommend to make every effort to achieve target doses shown to be effective in clinical trials, data from real-life clinical practice indicate a less-than optimal use of HF drugs that have a major impact on prognosis. Indeed, when compared with trial patients, non-trial patients have far more comorbidities that limit tolerability of high doses of ACE-i and beta-blockers. Moreover, patients' response to therapy (and not tolerance to up-titration) still drives the administration of HF drugs in many clinical settings. Needless to say, failure to up-titrate neurohormonal blockers to recommended doses provides less-than optimal modulation of neurohormonal systems, exposing patients to a greater risk of disease progression and mortality. Also, this behaviour affects morbidity and is particularly relevant in patients implanted with ICDs. Indeed, sub-optimal renin-angiotensin system and adrenergic blockade increase the risk of appropriate ICD interventions.^{23–25}

CRT and drug up-titration in HF patients are a clear-cut example of effective therapy integration with synergistic effects. However, it should be emphasized that, even in the setting of state-of-the-art non-pharmacological treatment, target doses of ACE-i/ARBs and beta-blockers are achieved in the real world at rates far lower than reported in the pivotal trials and recommended by the guidelines. There is still room to improve.

Conflict of interest: none declared.

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