European Heart Journal – Cardiovascular Pharmacotherapy (2015) **1**, 189–190
doi:10.1093/ehjcvp/pvv022

EDITORIAL

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

Massimo Volpe[1,2]* and Pietro Francia[1]

[1]Cardiology, Department of Clinical and Molecular Medicine, St Andrea Hospital, Sapienza University, Rome, Italy; and [2]I.R.C.C.S. Neuromed, Pozzilli (IS), Italy

Online publish-ahead-of-print 29 April 2015

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

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal – Cardiovascular Pharmacotherapy* or of the European Society of Cardiology.

* Corresponding author. Tel: +39 0633775654, Fax: +39 0633775061, Email: massimo.volpe@uniroma1.it

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 guidelines[22] 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, suboptimal 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.

References

1. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
2. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**: 2001–2007.
3. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;**106**:2194–2199.
4. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;**316**:1429–1435.
5. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;**325**: 293–302.
6. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;**327**:669–677.
7. Krum H, Carson P, Farsang C, Maggioni AP, Glazer RD, Aknay N, Chiang YT, Cohn JN. Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT. *Eur J Heart Fail* 2004;**6**:937–945.
8. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;**362**:767–771.
9. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–776.
10. Leyva F, Nisam S, Auricchio A. 20 years of cardiac resynchronization therapy. *J Am Coll Cardiol* 2014;**64**:1047–1058.
11. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, Sudden Cardiac Death in Heart Failure Trial I. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.
12. Heywood JT, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Gheorghiade M, Inge PJ, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN. Comparison of medical therapy dosing in outpatients cared for in cardiology practices with heart failure and reduced ejection fraction with and without device therapy: report from IMPROVE HF. *Circ Heart Fail* 2010;**3**:596–605.
13. Schmidt S, Hurlimann D, Starck CT, Hindricks G, Luscher TF, Ruschitzka F, Steffel J. Treatment with higher dosages of heart failure medication is associated with improved outcome following cardiac resynchronization therapy. *Eur Heart J* 2014; **35**:1051–1060.
14. Penn J, Goldenberg I, McNitt S, Polonsky B, Ruwald MH, Zareba W, Moss AJ, Alexis JD. Changes in drug utilization and outcome with cardiac resynchronization therapy: a MADIT-CRT Substudy. *J Card Fail* 2015; doi:10.1016/j.cardfail.2015.03.006.
15. Witt CT, Kronborg MB, Nohr EA, Mortensen PT, Gerdes C, Nielsen JC. Optimization of heart failure medication after cardiac resynchronization therapy and the impact on long-term survival. *Eur Heart–Cardiovascular Pharmacotherapy* 2015;**1**: 182–188.
16. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of Medical Therapy Pacing, Defibrillation in Heart Failure Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
17. Krum H, Roecker EB, Mohacsi P, Rouleau JL, Tendera M, Coats AJ, Katus HA, Fowler MB, Packer M, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. *JAMA* 2003;**289**:712–718.
18. Wikstrand J, Wedel H, Ghali J, Deedwania P, Fagerberg B, Goldstein S, Gottlieb S, Hjalmarson A, Kjekshus J, Waagstein F. How should subgroup analyses affect clinical practice? Insights from the Metoprolol Succinate Controlled-Release/Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Card Electrophysiol Rev* 2003;**7**:264–275.
19. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–1675.
20. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003; **362**:759–766.
21. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;**362**:777–781.
22. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–1847.
23. Francia P, Balla C, Uccellini A, Ricotta A, Modestino A, Frattari A, Salvati A, Volpe M. Low-dose angiotensin receptor blockers as an alternative to ACE-inhibitors increase the risk of appropriate ICD interventions in heart failure. *Int J Cardiol* 2010; **145**:522–524.
24. Francia P, Palano F, Tocci G, Adduci C, Ricotta A, Semprini L, Caprinozzi M, Balla C, Volpe M. Angiotensin receptor antagonists to prevent sudden death in heart failure: does the dose matter? *ISRN Cardiol* 2014;**2014**:652421.
25. Saxon LA, Bristow MR, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, Feldman AM, Galle E, Ecklund F. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. *Circulation* 2006;**114**:2766–2772.