

Reza Tabrizchi

Division of Basic Medical Sciences,
Faculty of Medicine, Memorial
University of Newfoundland,
St John's, NL, Canada

Guidelines for choosing drugs in chronic heart failure

In a recent article, Komajda and colleagues (2005) presented data gathered from the Medical Management of Chronic Heart Failure in Europe and its Related Costs (MAHLER) survey in support of the view that adherence to guidelines in treating patients with chronic heart failure is a strong predictor of fewer cardiovascular hospitalizations in clinical practice.

Five types of drugs were considered as the agents of choice in the treatment of chronic heart failure: angiotensin-converting enzyme (ACE) inhibitors, β -adrenoceptor antagonists (blockers), potassium sparing diuretic (spironolactone), cardiac glycosides, and diuretics other than the potassium-sparing class. The total number of patients included in the trial were 1421, of whom 1333 (93.8%) completed the study. Baseline medications in these patients were ACE inhibitors (69%), angiotensin type 1 receptor antagonists (17.6%), β -adrenoceptor antagonists (53%), diuretics (79%), cardiac glycosides (41%), and spironolactone (28%). Adherence was considered perfect if the first three (T3) drugs (ACE inhibitor, β -adrenoceptor antagonist, and spironolactone) were used, and this was compared with a situation when either the latter three were not used concomitantly or a condition in which all five (T5) were used as part of the regime to treat chronic heart failure. The overall guideline adherence indicators for T3 and T5 were 60% and 63%, respectively, with class adherence for ACE inhibitors (85.4%), diuretics (83%), β -adrenoceptor antagonists (58%), cardiac glycosides (52%), and spironolactone (36%) (Komajda et al 2005). Of particular interest, are two issues that are worth addressing based on the findings from the Komajda et al report.

First, the data presented supports the view that β -adrenoceptor antagonists are underutilized in the treatment of patients with chronic heart failure. This is somewhat surprising as there is substantive evidence to indicate that this class of drugs should form an integral part of a strategy in treating patients with this condition. A previous survey on the quality of care among patients with heart failure in Europe had also revealed an underutilization of β -adrenoceptor antagonists in these patients (The Study Group of Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology 2003). The evidence from this report seems to indicate that the rate of prescription for β -adrenoceptor antagonists was 36.9%, with metoprolol being the most widely used (40.3%) agent among the β -adrenoceptor antagonists. There is clear evidence from a number of clinical trials that indicate the benefits of β -adrenoceptor antagonists in patients with left systolic dysfunction (Packer et al 1996, 2001; CIBIS-II Investigation and Committee 1999; MERIT-HF Study Group 1999). As well, post-hoc analysis of the data from Metoprolol Randomized Intervention Trial in Congestive Heart Failure on many levels, ie, frequency of hospitalization, quality of life, and functional class, indicate the clear beneficial effects of this class of drugs in treating patients with chronic heart failure (Hjalmarson et al 2000; Goldstein et al 2001; Ghali et al 2002; Gottlib et al 2002; Wikstrand et al 2002). The use of this class of drugs reduces hospitalization due to worsening heart failure, increases life expectancy, and reduces all-cause hospitalization (Tabrizchi 2003). Thus, perhaps a greater effort should be made to encourage the appropriate use of this class of drugs in patients with chronic heart failure.

Second, the trend was that the group of patients taking the three drugs, ie, ACE inhibitor, β -adrenoceptor antagonist, and spironolactone (T3), were more likely to experience hospitalization due to cardiovascular problems when compared with those taking the five drugs (T5). This off-hand observation, if real, clearly needs closer examination. Perhaps not surprisingly, a relatively simple hypothesis to explain this observation would be on the basis of the pharmacological actions of the three agents employed. The simple explanation would be an unwanted elevation of serum potassium levels resulting in higher incidence of cardiovascular problems. It is interesting that following the publication of the Randomized Aldactone Evaluation Study (RALES; The RALES Investigators 1996) there was an increase in the use of spironolactone. The concomitant use of spironolactone and ACE inhibitors in patients with heart failure was stable in the period of early 1994 until early 1999 (~34 per 1000 patients) (Juurlink et al 2004). However, subsequent to the publication of RALES, the rate of prescription increased significantly ($p < 0.001$) by a factor of approximately fivefold (149 per 1000) by late 2001. Of interest was the rate of hospital admission associated with hyperkalemia, which was 2.4 per 1000 in early 1994 and 4.0 per 1000 in early 1999, and that rate increased further after the publication of RALES to 11.0 per 1000 ($p < 0.001$) by late 2001 (Juurlink et al 2004). The use of ACE inhibitor and spironolactone together has the potential to create a greater risk of the serum potassium becoming elevated in patients with heart failure as does the use of a β -adrenoceptor antagonist (Swenson 1986; Hamad et al 2001; Tamirisa et al 2004).

Therefore, it should not be a surprise that the combination of the three would provide a clinical situation that could predispose the patient to a greater risk of manifesting an elevated level of serum potassium. Moreover, one reason that the five drug combination may not produce the same outcome is because of the fact that drugs such as thiazides and loop diuretics cause some degree of serum potassium depletion by the virtue of their pharmacological effects in the nephron. This action may prevent the rise in serum potassium to levels that precipitate the cardiovascular problems exhibited by the patients on the T3 drugs.

This hypothesis, of course, can easily be tested by examining electrolyte records of patients on these drugs admitted for cardiovascular problems. However, more importantly, the medical community must be made aware

of the risk associated with this form of drug interaction and implement appropriate guidelines to prevent its occurrence in this patient population.

References

- CIBIS-II Investigation and Committee. 1999. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*, 353:9–13.
- Ghali JK, Piña IL, Gottlieb SS, et al. 2002. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in metoprolol extended-release randomized intervention trial in heart failure (MERIT-HF). *Circulation*, 105:1585–91.
- Goldstein S, Fagerberg B, Hjalmarson Å, et al. 2001. Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. *J Am Coll Cardiol*, 38: 932–8.
- Gottlieb SS, Fisher ML, Kjekshus J, et al. 2002. Tolerability of beta-blocker initiation and titration in the metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *Circulation*, 105:1182–8.
- Hamad A, Salameh M, Zihlif M, et al. 2001. Life-threatening hyperkalemia after intravenous labetalol injection for hypertensive emergency in a hemodialysis patient. *Am J Nephrol*, 21:241–4.
- Hjalmarson Å, Goldstein S, Fagerberg B, et al. 2000. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure. *JAMA*, 283:1295–302.
- Juurlink DN, Mamdani MM, Lee DS, et al. 2004. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*, 351:543–51.
- Komajda M, Lapuerta P, Hermans N, et al. 2005. Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. *Eur Heart J*, April 12 [Epub ahead of print].
- MERIT-HF Study Group. 1999. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). *Lancet*, 353:2001–7.
- Packer M, Bristow MR, Cohn JN, et al. 1996. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*, 334:1349–55.
- Packer M, Coats AJS, Fowler MB, et al. 2001. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*, 344:1651–8.
- Swenson ER. 1986. Severe hyperkalemia as a complication of timolol, a topically applied beta-adrenergic antagonist. *Arch Intern Med*, 146:1220–1.
- Tabrizchi R. 2003. Should β -blockers form the cornerstone for the treatment of congestive heart failure? *Expert Rev Cardiovasc Ther*, 1:157–60.
- Tamirisa KP, Aaronson KD, Koelling TM. 2004. Spironolactone-induced renal insufficiency and hyperkalemia in patients with heart failure. *Am Heart J*, 148:971–8.
- The RALES Investigators. 1996. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol*, 78:902–7.
- The Study Group of Diagnosis of the Working Group on Heart Failure the European Society of Cardiology. 2003. The EuroHeart Failure Survey programme – a survey on the quality of care among patients with heart failure in Europe. *Eur Heart J*, 24:464–74.
- Wikstrand J, Hjalmarson Å, Waagstein F, et al. 2002. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol*, 40:491–8.