Underuse of beta blockers in patients with heart failure

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Key words

ACE inhibitors, angiotensin receptor blockers, guidance, heart failure, Nepal

doi: 10.5837/bjc.2013.005

Br J Cardiol 2013;**20**:11–13

Angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and beta blockers improve outcomes in patients with chronic heart failure secondary to left ventricular systolic dysfunction.

As outlined in the recent European Society of Cardiology (ESC) guidelines for the treatment of heart failure,[1] the pivotal trials with beta blockers were conducted in patients with continuing symptoms and a persistently low ejection fraction (EF), despite treatment with an ACE inhibitor and, in most cases, a diuretic. Despite this, "there is consensus that these treatments are complementary and that a beta blocker and an ACE inhibitor should both be started as soon as possible after diagnosis of heart failure with reduced ejection fraction (HF-REF)".[1] This is, in part, because ACE inhibitors have a modest effect on left ventricular remodelling, whereas beta blockers often lead to a substantial improvement in EF. Furthermore, beta blockers are anti-ischaemic, are probably more effective in reducing the risk of sudden cardiac death, and lead to a striking and early reduction in overall mortality.

Surprisingly, for whatever reasons, these drugs are not always prescribed. The EuroHeart Failure Study showed that heart failure drugs, particularly beta blockers, were underused, and when they were prescribed, this was in inappropriately low doses.[2] It has also been shown, within UK primary care practice, that even when commenced beta blockers are commonly used at low dose and over half of patients have stopped taking them by three years.[3]

The study from Chitwan, Nepal, reported overleaf shows that this problem is not unique to Europe. The retrospective analysis suggests that only 22–32% of heart failure patients were prescribed beta blockers. Why? It may be a throwback to the past, where beta blockers were deemed to be contraindicated in patients with left ventricular dysfunction, the author suggests.

This view may still prevail among some prescribers in the UK. But, in an era where the National Institute for Health and Clinical Excellence (NICE)[4] recommends that ACE inhibitors (or ARBs licensed for heart failure, if ACE inhibitors are not tolerated) and beta blockers are first-line drug treatment for heart failure due to left ventricular systolic dysfunction, it is crucial that we move forward to ensure that our patients receive optimal care and dispel this myth. The Quality Standards from NICE published in 2011[5] form a basis from which heart failure services can be developed to ensure that all potential patients receive best possible treatments (including education) and have access to the multi-disciplinary heart failure team ●

Our letter from Nepal overleaf shows underuse of beta blockers is a widespread problem

Conflict of interest

PK has received speaker fees and/or advisory board reimbursement from A Menarini, Boehringer Ingelheim, Novartis, Pfizer, Servier and Vifor. HP: none declared.

References

1. McMurray JJV, Adamopoulos S, Anker S *et al*. ESC guidelines for the diagnosis and treatment of chronic and acute heart failure 2012. *Eur Heart J* 2012;**33**:1787–847. http://dx.doi.org/10.1093/eurheartj/ehs104

2. Komajdaa M, Follath F, Swedberg K *et al*.; The Study Group of Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure Survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. *Eur Heart J* 2006;**27**:2725–36. http://dx.doi.org/10.1016/S0195-668X(02)00700-5

3. Kalra PR, Morley C, Barnes S *et al*. Discontinuation of beta-blockers in cardiovascular disease: UK primary care cohort study. *Int J Cardiol* 2012; e-publication. http://dx.doi.org/10.1016/j.ijcard.2012.06.116

4. National Institute for Health and Clinical Excellence. Chronic Heart Failure. Management of chronic heart failure in primary and secondary care. London: NICE, 2010.

5. National Institute for Health and Clinical Excellence. Heart failure quality standard. London: NICE, 2011. Available from: http://guidance.nice.org.uk/QS9

EDITORIAL

Time to reconsider current practice

Letter from Nepal

Specific classes of medications such as angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, angiotensin receptor blockers and beta blockers are known to decrease the risk of hospitalisation and death in heart failure (HF) patients because these agents have been shown to attenuate the remodelling and systemic effects of adrenergic and neurohormonal activation.[1] Of these medications, certain beta blockers (bisoprolol, carvedilol and metoprolol succinate) seem to have the most pronounced effect on decreasing mortality as demonstrated by several randomised-controlled trials.[2-5] Carvedilol, bisoprolol and metoprolol succinate have been shown to improve mortality outcomes in patients with mild-to-moderate HF, especially in those patients already receiving an ACE inhibitor.

As the cardiac adrenergic drive initially supports the performance of the failing heart, long-term activation of the sympathetic nervous system exerts deleterious effects, and such effects can be antagonised by the use of beta blockers. Moreover, long-term treatment with beta blockers in patients with HF decreases the circulating levels of vasoconstrictors such as norepinephrine, renin, endothelin, and pro-inflammatory cytokines,[2,6] and may up-regulate myocardial $beta_1$-receptor density,[7] which, in turn, may help restore the inotropic and chronotropic responsiveness of the myocardium.

Table 1 gives a brief summary of major landmark trials of beta blockers used in HF and their major outcomes.[2,3,5,8,9] Most of these trials included patients in New York Heart Association (NYHA) class II and III, with the exception of COPERNICUS (Carvedilol Prospective Randomised Cumulative Survival),[2] which had class IV patients. These randomised trials demonstrated that among patients with HF and reduced systolic function, beta blockers confer a 10% to 40% reduction in mortality and hospitalisation within one year.

Because of the favourable effects of beta blockers on survival and disease progression, current guidelines for management of HF recommend initiation of treatment with a beta blocker as soon as left ventricular (LV) dysfunction is diagnosed,[1] however, the use of beta blockers in patients with HF in our setting was not studied much. In a retrospective analysis of a total of 255 patients admitted with HF in College of Medical Sciences, Bharatpur, we found that only 32% of patients were receiving beta blockers, whereas 64% of patients were receiving an ACE inhibitor, angiotensin receptor blocker in 16%, and 48% of patients received spironolactone. Similarly, in another study conducted in Shahid Gangalal National Heart Centre, Kathmandu, among 1,771 patients who were admitted to the medical intensive care unit (ICU) with a diagnosis of HF, we found that only 22% of patients had received beta-blocking agents.[10] Despite current guidelines suggesting the use of a beta-blocking agent in patients with HF, only 22–32% of patients in our setting were receiving this class of drug. This relatively low percentage of HF patients treated with beta blockers may be explained by the fact that the translation of results of trials on this class of drugs into practice is more difficult since beta blockers have long been contraindicated in HF patients. Since there is clear evidence of the effectiveness of beta blockers in HF, it is recommended that physicians treating patients with HF should try to initiate beta blockers while the patient is in hospital under their care and should not withhold beta blockers based on fear of side effects – 'start low, go slow' is the rule

Conflict of interest

None declared.

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Table 1. Summary of landmark beta blocker heart failure trials

Trial	US Carvedilol HF study	MERIT-HF	CIBIS-II	COPERNICUS	CAPRICORN
Drug	Carvedilol	Metoprolol CR/XL	Bisoprolol	Carvedilol	Carvedilol
Functional class	Mostly NYHA II–III	Mostly NYHA II–III	Mostly NYHA III	NYHA IV	Post-MI HF
LV ejection fraction	23%	28%	27%	20%	33%
Mean/median follow-up	6.5 months	12 months	16 months	10.4 months	12 months
Total mortality	3.2 *vs.* 7.8 RRR=65%	7.2 *vs.* 11 RRR=34%	12 *vs.* 17 RRR=34%	11.2 *vs.* 16.7 RRR=35%	12 *vs.* 15 RRR=23%

Key: CAPRICORN = carvedilol post-infarct survival control in LV dysfunction; CIBIS-II = cardiac insufficiency bisoprolol study II; COPERNICUS = carvedilol prospective randomised cumulative survival; CR/XL = controlled-release formulation; HF = heart failure; LV = left ventricle; MERIT-HF = metoprolol CR/XL randomised intervention trial in congestive heart failure; MI = myocardial infarction; NYHA = New York Heart Association; RRR = relative risk reduction

References

1. Hunt SA. 2009 focused update incorporated into the ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2005 Guidelines for the Evaluation and Management of Heart Failure). *Circulation* 2009;**119**:e391–e479. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.192065

2. Packer M, Coats AJ, Fowler MB *et al*. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**:1651–8. http://dx.doi.org/10.1056/NEJM200105313442201

3. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–07. http://dx.doi.org/10.1016/S0140-6736(99)04440-2

4. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure. A Bayesian meta-analysis. *Ann Intern Med* 2001;**134**:550–60.

5. Packer M, Bristow MR, Cohn JN *et al*. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;**334**:1349–55. http://dx.doi.org/10.1056/NEJM199605233342101

6. Ohtsuka T, Hamada M, Hiasa G *et al*. Effect of beta blockers on circulating levels of inflammatory and anti-inflammatory cytokines in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2001;**37**:412–17. http://dx.doi.org/10.1016/S0735-1097(00)01121-9

7. Gilbert EM, Abraham WT, Olsen S *et al*. Comparative hemodynamic, left ventricular functional and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. *Circulation* 1996;**94**:2817–25. http://dx.doi.org/10.1161/01.CIR.94.11.2817

8. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–90. http://dx.doi.org/10.1016/S0140-6736(00)04560-8

9. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13. http://dx.doi.org/10.1016/S0140-6736(98)11181-9

10. Regmi S, Maskey A, Dubey L. Profile of heart failure study in patients admitted in MICU. *Nepalese Heart Journal* 2009;**6**:35–8.

Course review

BJC Learning angina programme

www.bjcardio.co.uk/learning

Editors: Mulcahy D, Purcell H
Publisher: Medinews Cardiology Limited, London, 2012
ISBN: 978-0-9573701-0-4

Coronary heart disease is responsible for one sixth of UK deaths. Improvements in making an earlier diagnosis and more effective management have aided a reduction in mortality over the last two decades. Such improvements would not have been possible without well thought-out and carefully constructed guidance and teaching programmes. With the spread of internet technology, online medical education has seen an exponential growth in popularity. The *British Journal of Cardiology* (BJC) has recently launched its e-learning site BJC Learning and its first e-learning programme on angina (www.bjcardio.co.uk/learning).

The angina e-learning programme is a series of interactive evidence-based learning modules designed to cover all aspects of the condition, from epidemiology, prevention and pathophysiology, through to the most up-to-date diagnostic and management options.

Each module requires approximately one to two hours to complete and one CPD point is given for each hour of learning. The modules are clear and concisely written, making them easy to read. They assume minimal prior knowledge and can therefore be useful towards a wide range of audiences. For example, the diagnosis of angina module includes a wonderful summary of the differential diagnosis of chest pain, detailing pertinent history and examination features used in the diagnostic process. Reading through the paragraphs really reminds us of receiving a well thought-out teaching session from a cardiology consultant. The same module also contains a dedicated section for GPs covering a step-wise approach to patients with chest pain in the clinic.

The wide range of specialist authors is reflected in the comprehensive manner through which different aspects of coronary heart disease are approached, providing not only well-referenced factual information, but also insight into how and why cardiology guidelines evolved.

One of the most striking features we noticed is the resourcefulness of the modules' illustrations and multimedia. Appreciation for this is especially obvious on the topic of advanced cardiac imaging where no amount of text can replace watching dye running through stenosed arteries, or an impaired ventricle contracting on cardiac magnetic resonance imaging.

Each learning module comes with a certificate upon completion – to obtain it you must pass a test, which comprises of a series of multiple choice questions. Although a few questions seem slightly arbitrary in terms of requiring the reader to recall specific statistics, the tests overall are suitably tailored to the contents of each module, and do well in terms of reinforcing the key learning points. A two-attempt limit on each test also ensured that we remained focused at all times.

An e-learning module series should be assessed on the quality of its contents and how effectively it teaches this information to users. We found the BJC angina modules not only achieved these criteria but were also a joy to read. They are also available free of charge with an accompanying course textbook. To those who wish to learn more about coronary heart disease, we highly recommend using the BJC as a user-friendly one-stop resource for your learning needs.

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