Adherence to treatment guidelines in the pharmacological management of chronic heart failure in an Australian population

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Abstract

Background To document the pharmacotherapy of chronic heart failure (CHF) and to evaluate the adherence to treatment guidelines in Australian population. Methods The pharmacological management of 677 patients (female 46.7%, 75.5 ± 11.6 years) with CHF was retrospectively analyzed. Results The use of angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) and β-blockers were 58.2 % and 34.7 %, respectively. Major reasons for non-use of ACE inhibitors/ARBs were hyperkalemia and elevated serum creatinine level. For patients who did not receive β-blockers, asthma and chronic obstructive pulmonary disease were the main contraindications. Treatment at or above target dosages for ACE inhibitors/ARBs and β-blockers was low for each medication (40.3% and 28.9%, respectively). Conclusions Evidenced-based medical therapies for heart failure were under used in a rural patient population. Further studies are required to develop processes to improve the optimal use of heart failure medications.

Keywords: heart failure; ACE inhibitors; angiotensin receptor; β-blockers; prognosis

1 Introduction

Chronic heart failure (CHF) has emerged as a major public health problem in Australia. Improved survival after myocardial infarction combined with an aging population, means a heart failure epidemic may appear within the next two decades.[1–3] Despite considerable advances in treatment to increase long-term survival, CHF is still associated with a high mortality rate.[4]

Pharmacotherapy is an important component of CHF management which not only improves symptoms but also reduces cardiac remodeling and neuro-endocrine activation to prevent worsening of symptoms and reduces mortality.[5] Accumulated evidence shows that ACE inhibitors/Angiotensin II receptor blockers (ARBs) and β-blockers could reduce the high mortality in patients with CHF.[6,7] Furthermore, better implementation of pharmacotherapy was associated with better prognosis in patients with CHF.[8–9]

In prior studies of Australian population, ACE inhibitors/ARBs and β-blockers were underutilized in some medical centres, especially in rural regions where the prevalence of heart failure is higher than capital city and metropolitan areas.[10–12] However, a recent study in Western Australia showed ACE inhibitors/ARBs and β-blockers use was more evidenced based.[13]

Little is known about current heart failure management regimes in other rural regions of Australia, which may differ from those reported a decade ago. The aim of the present study was to investigate the status of pharmacotherapy, especially the use of ACE inhibitors/ARBs and β-blockers, in CHF patients in a regional medical centre, and to compare with the present CHF management guidelines.

2 Methods

This study is a retrospective analysis of medication use for in-patient management of CHF in Wagga Wagga Base Hospital, a major regional hospital in rural New South Wales. From Jan 2003 to Dec 2007, medical records of 667 consecutive in-patients with heart failure were selected and reviewed by the investigators. Entry criteria for the study required a diagnosis of CHF according to the 2006 Australian guidelines, i.e., on the basis of the presence of typical
clinical features and appropriate investigation. This study received approval from the Ethics Committees for Human Research of the Charles Sturt University and the Greater Southern Area Health Service.

Baseline clinical data, prescription patterns and use of medical resources were recorded in all patients. When multiple etiological factors for heart failure were present, the one judged by the cardiologists to be predominant was identified as the primary cause. Electrocardiography, serum creatinine level and serum potassium level were measured in hospital for all patients.

All prescribed medications and dosing schedules were recorded. Dosing adequacy of ACE inhibitors/ARBs and β-blockers was gauged against recommendations from guidelines for CHF treatment of Australia (2006). Target doses achieved of ACE inhibitors/ARBs and β-blockers were recorded according to the ESC guidelines (2008). For patients not prescribed ACE inhibitors/ARBs, contraindications including chronic renal failure (serum creatinine > 220 µmol/L), hyperkalemia (serum potassium > 5.0 mmol/L), bilateral renal artery stenosis, severe aortic stenosis and angioedema were noted. For patients not prescribed β-blockers, contraindications included asthma, second or third degree heart block, sick sinus syndrome (in the absence of a permanent pacemaker) and sinus bradycardia (< 50/min).

### 2.1 Statistical analysis

Data are summarized as mean ± SD. The characteristics of patients’ medication use were summarized with descriptive statistics. A $P$ value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS 13.0 (SPSS Inc, USA).

### 3 Results

The clinical and demographic characteristics of the studied population are presented in Table 1. Over 50% of patients were class 3–4 by NYHA classification of heart failure. Ischaemic heart disease was the most common cause of heart failure, affecting 55.5% of patients, although hypertension was documented in 62.5% of patients. Common co-morbidities were hypertension, myocardial infarction (MI), arrhythmia, hypercholesterolemia, chronic obstructive pulmonary disease (COPD) and arthritis. In patients with arrhythmia (31.8%), the most common type was atrial fibrillation. Left ventricular ejection fraction (EF) was assessed by echocardiography in 242 (36%) patients. Among these, preserved systolic function, defined as a left ventricular EF of 45% or greater, was identified in 50.4%.

### Table 1. Clinical characteristics of patients with heart failure ($n = 677$). Values are mean ± SD or $n$ (%).

| Variables                  | Data            |
|----------------------------|-----------------|
| Age (years)                | 75.5 ± 11.6     |
| Female                     | 316 (46.7)      |
| Duration in hospital (days)| 5.7 ± 8.3       |
| Number of past hospitalisations | 7.5 ± 8.1    |
| NYHA class III-IV          | 347 (51.3)      |
| Etiology                   |                 |
| Ischaemic                  | 376 (55.5)      |
| Non-ischaemic              | 301 (44.5)      |
| Co-morbidities             |                 |
| Hypertension               | 423 (62.5)      |
| Angina                     | 97 (14.3)       |
| MI                         | 249 (36.8)      |
| CABG                       | 132 (19.5)      |
| Cardiomyopathy             | 64 (9.5)        |
| Valvular                   | 75 (11.1)       |
| Arrhythmia                 | 215 (31.8)      |
| Pacemaker                  | 81 (12)         |
| Diabetes                   | 193 (28.5)      |
| Hypercholesterolemia       | 145 (21.4)      |
| Stroke                     | 78 (11.5)       |
| Depression                 | 62 (9.2)        |
| COPD                       | 199 (29.4)      |
| Arthritis                  | 133 (19.6)      |
| Systolic BP < 100 mmHg     | 39 (5.8)        |
| Heart rate ≥ 100/min       | 203 (30.0)      |
| ECG assessment             |                 |
| Atrial fibrillation/flutter| 156 (23.0)      |
| Sinus tachycardia          | 67 (9.9)        |
| Ventricular tachycardia    | 4 (0.6)         |
| LV function assessment     | 242 (35.7)      |
| EF ≥ 45%                   | 122 (50.4)      |
| EF < 45%                   | 120 (49.6)      |
| Serum potassium > 5.0 mmol/L | 141 (20.8)    |
| Serum creatinine > 220 µmol/L | 79 (11.7) |
| Serum potassium > 5.0 mmol/L and creatinine > 220 µmol/L | 38 (5.6) |

NYHA: New York Heart Association; MI: myocardial infarction; CABG, coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; BP: blood pressure; ECG: electrocardiography; LV: left ventricle; EF: ejection fraction.

As shown in Table 2, ACE inhibitors or ARBs were used in 394 (58.2%) patients, with ACE inhibitors in 296 (43.7%) and ARBs in 121 (17.9%). Twenty-three patients simultaneously
Table 2. Cardiovascular medication use in patients with chronic heart failure.

| Agents                        | n (%)  |
|-------------------------------|--------|
| ACE inhibitors or ARBs        | 394 (58.2) |
| ACE inhibitors                | 296 (43.7) |
| ARBs                          | 121 (17.9) |
| ACE inhibitors + ARBs         | 23 (3.3) |
| β-blockers                    | 235 (34.7) |
| ACE inhibitors + β-blockers   | 130 (19.2) |
| Diuretics                     | 488 (72.0) |
| Digoxin                       | 126 (18.6) |
| Spironolactone                | 78 (11.5) |
| CCBs                          | 74 (10.9) |
| DHPs                          | 46 (6.8) |
| Non-DHPs                      | 28 (4.1) |
| Statins                       | 148 (21.9) |
| Aspirin                       | 257 (38.0) |
| Clopidogrel                   | 35 (5.2) |
| Warfarin                      | 141 (20.8) |
| Amidarone                     | 34 (5.0) |
| Sotalol                       | 10 (1.5) |
| Nitrates                      | 94 (13.9) |

ACE: angiotensin converting enzyme; ARBs: angiotensin receptor blockers; CCB: calcium channel blocker; DHPs: dihydropyridines.

Table 3. Non-usage and possible reasons of ACE inhibitors and β-blockers.

| Agents non-used | n     | Possible reasons                  | n (%) |
|-----------------|-------|-----------------------------------|-------|
| ACE inhibitors/ARBs | 283   | Serum potassium > 5.0 mmol/L     | 141   |
|                 |       | Serum creatinine > 220 µmol/L    | 79    |
|                 |       | Systolic BP < 80 mmHg            | 0     |
|                 |       | Unknown                           | 101   |
| β-blockers      | 442   | Asthma                            | 44    |
|                 |       | Complete atrioventricular block   | 1     |
|                 |       | Systolic BP < 80 mmHg            | 0     |
|                 |       | HR < 50 /min                      | 5     |
|                 |       | COPD                              | 155   |
|                 |       | Unknown                           | 237   |

Table 4. Target doses achieved of ACE inhibitors/ARBs and β-blockers.

| Agents          | Target doses achieved n(%) |
|-----------------|---------------------------|
| ACE inhibitors / ARBs | 159 (40.3)  |
| β-blockers      | 68 (28.9)  |

Received ACE inhibitors and ARBs. β-blockers were used in 235 (34.7%) patients in this group. Other common cardiovascular drugs include diuretics (72%), digoxin (18.6%), spironolactone (11.5%), aspirin (38.0%), warfarin (20.8%), statins (21.9%), and nitrates (13.9%).

As shown in Table 3, among patients not receiving ACE inhibitors (n = 283), contraindications were documented in 64.3% (n = 182), including 141 (49.8%) with repeated reading serum potassium > 5.0 mmol/L, 79 (27.9%) with repeated reading serum creatinine > 220 µmol/L (38 cases had both serum potassium > 5.0 mmol/L and serum creatinine > 220 µmol/L). In another 101 patients, no definite contraindications were identified. Among patients not receiving β-blockers, contraindications were documented in 50 patients, including 44 (9.9%) with asthma, five cases with heart rate < 50 beats/minutes at admission, and one case with complete heart block. Other possible reasons for not receiving β-blockers may be concomitant COPD, which was present in 155 patients (Table3).

Target-dosages of ACE inhibitors/ARBs were achieved in 159 patients, which accounted for 40.3% of patients who received ACE inhibitors/ARBs. Target-dosages of β-blockers were achieved in 68 patients, which accounted for 28.9% of patients who received β-blockers (Table 4).

4 Discussion

In this study, we have shown that ACE inhibitors/ARBs and β-blockers were underused in patients with heart failure in a rural Australian hospital, compared with published guidelines. Main reasons of non-use of these drugs were elevated serum potassium and creatinine level for ACE inhibitors/ARBs, and asthma for β-blockers. The proportion of patients who achieved target-dosage of ACE inhibitors/ ARBs and β-blockers was also low.

In the analysis of Cardiac Awareness Survey and Evaluation (CASE) study[2,10], which was conducted in Australia in 1998, the prescribing rate of ACE inhibitors and β-blockers were 51.4% and 12.6% respectively in rural towns. The ACE inhibitors usage in our study was lower than that in the CASE study; however, the use of β-blockers, and ACE inhibitors along with β-blockers was higher than that of the CASE study. The higher use of β-blockers and ACE inhibitors combined with β-blockers compared to the CASE study may reflect increased evidenced based therapy over the study period.

The major reason relating to low usage of ACE inhibitors in our study is perceived contraindications. We noted that 26% of the patients had hyperkalemia or serum creatinine levels of 220 µmol/L or higher, thus restricting the use of...
ACE inhibitors or ARBs if these were true and repeated findings. However, 35.6% of the patients who did not receive ACE inhibitors/ARBs had no identifiable contraindications. One possible explanation is that some physicians may have concerns over polypharmacy and the risk of side effects in elderly heart failure patients (average 75.5 years in our cohort). In patients > 65 years, β-blockers, ACE inhibitors and ARBs have similar mortality benefit to that observed in younger patients.[15] Therefore, these agents should be prescribed to all elderly patients in the absence of contraindications. Another potential barrier for underuse is at the patient level, as age, disease severity, comorbidities and concomitant drug intake may impact on the prescriptions of heart failure medications.[16]

For β-blockers, the most common reasons for under-prescribing may be concerns about the possible side effects, co-morbidities, polypharmacy, or contraindications such as asthma. However, in our patients who did not receive β-blockers, few had a genuine contraindication. These results are in line with the recent Euroheart survey.[17] Co-morbidities and other therapies had a significant impact on the use of β-blockers, which were more often prescribed to patients with ischaemic heart disease and less often to patients with COPD. In this study, 35% of the patients who did not receive β-blockers had COPD, which is not considered as a compelling contraindication for β-blockers. Severity of heart failure symptoms may also affect the use of β-blockers. In patients with volume overload or recent treatment with positive inotropic agents, therapy with β-blockers may be delayed, although these patients may tolerate therapy well during initiation and upward dose titration.[18]

In our study, 23 patients received ACE inhibitors additional to ARBs. This may be due to severe heart failure and patients remaining symptomatic despite optimal treatment with an ACE inhibitor and β-blockers, as indicated in ESC guideline 2008.[15] However, addition of ARBs in patients already receiving treatment of ACE inhibitors and β-blockers may be associated with a worse outcome and more side effects.[19,20] Therefore, in most conditions, ARBs should only be used as an alternative for patients unable to tolerate ACE inhibitors.

Target dosages were achieved in 40.3% of patients on ACE inhibitors/ARBs and in 28.9% on β-blockers, which were consistent with results of a recent study,[21] but lower than the recommended high target doses.[14] Large-scale trials showed that target doses of ACE inhibitors/ARBs and β-blockers provide the optimal improvement in left ventricular function and reduction in mortality and hospitalizations.

In summary, in this retrospective study, ACE inhibitors/ARBs and β-blockers were underprescribed in patients with CHF. Target doses achieved for both drug groups were also lower than the international standards. Contraindications to ACE inhibitors/ARBs and β-blockers were the major reasons for non-use of these medications, but in many cases the reasons for non-use were unidentifiable. Further studies are required to develop protocols or clinical pathways to improve the use of heart failure medications in particular ACE inhibitors and β-blockers.

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References

1. McLean AS, Eslick GD, Coats AJ. The epidemiology of heart failure in Australia. *Int J Cardiol* 2007; 118(3): 370–374.
2. Krum H, Tonkin AM, Currie R, et al. Chronic heart failure in Australian general practice: the Cardiac Awareness Survey and Evaluation (CASE) study. *Med J Aust* 2001; 174(9): 439–444.
3. He SW, Wang LX. Impact of anaemia on the outcomes of chronic heart failure: a meta-analysis and systemic review. *Congest Heart Fail* 2009; 15(3): 123–130.
4. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: Survival trends in 12,220 index admissions in Leicestershire 1993–2001. *Heart* 2003(6); 89: 615–620.
5. Krum H, Jelinek MV, Stewart S, et al. Guidelines for the prevention, detection and management of people with chronic heart failure in Australia 2006. *Med J Aust* 2006; 185(10): 549–556.
6. Hunt SA, Abraham WT, Chin MH, et al. 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. *Circulation* 2005; 112(12): e154–235.
7. Granger CB, McMurray JJ, Yusuf S, et al. 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(9386): 772–776.
8. Störk S, Hense HW, Zentgraf C, et al. Pharmacotherapy according to treatment guidelines is associated with lower mortality in a community-based sample of patients with chronic heart failure: A prospective cohort study. *Eur J Heart Fail* 2008; 10(12): 1236–1245.
9. Komajda M, Lapuerta P, Hermans N, et al. Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. *Eur Heart J* 2005; 26(16): 1653–1659.
10. Clark RA, Eckert KA, Stewart S, et al. Rural and urban differentials in primary care management of chronic heart
failure: new data from the CASE study. *Med J Aust* 2007; 186(9): 441–445.

11 Granmyr J, Ball P, Curran S, *et al*. Evidence-based management of CAD in a rural community. *Aust J Rural Health* 2007; 15(4): 241–246.

12 Wang L, Curran S, Ball P, *et al*. Pharmacotherapy for atrial fibrillation in elderly hospitalized patients with comorbid congestive heart failure in Australia: a retrospective study. *Curr Ther Res* 2008; 69(6): 514–524.

13 Tang TH, Hung J, Finn J. The effect of evidence-based medication use on long-term survival in patients hospitalised for heart failure in Western Australia. *Med J Aust* 2010; 192(6): 306–310.

14 Dickstein K, Cohen-Solal A, Filippatos G, *et al*. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; 29(19): 2388–2442.

15 Arif SA, Mergenhagen KA, Del Carpio RO, *et al*. Treatment of systolic heart failure in the elderly: an evidence-based review. *Ann Pharmacother* 2010; 44(10): 1604–1614.

16 Koschack J, Jung HH, Scherer M, *et al*. Prescriptions of recommended heart failure medication can be correlated with patient and physician characteristics. *Int J Clin Pract* 2009; 63(2): 226–232.

17 Komajda M, Follath F, Swedberg K, *et al*. 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* 2003; 24(5): 464–474.

18 Krum H. Consider β-blockers with heart failure. *BMJ* 2009; 338: b1728.

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(23): 1667–1675.

20 Pfeffer MA, McMurray JJ, Velazquez EJ, *et al*. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; 349(20): 1893–1906.

21 Fonarow GC, Albert NM, Curtis AB, *et al*. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation* 2010; 122(6): 585–596.