ORIGINAL RESEARCH LETTER

β-blockers in exacerbations of COPD: feasibility of a randomised controlled trial

To the Editor:

Cardiac diseases are a major cause of death in patients with chronic obstructive pulmonary disease (COPD). Acute cardiac events often occur during exacerbations of COPD, and even subclinical cardiac abnormalities are linked to a worse prognosis in this setting [1, 2].

Observational studies suggest that patients on long-term β-blocker therapy have better outcomes following exacerbations of COPD, but no prospective controlled studies have been undertaken [3]. Although β-blockers have been shown to reduce morbidity and mortality in patients with heart failure and other cardiovascular diseases, patients with COPD were excluded from these trials [4]. In addition, patients with COPD exacerbations may be at greater risk of adverse effects from β-blockers, and the balance of risks and benefits needs to be established using randomised controlled trials [4, 5].

A randomised controlled trial of β-blockers in acute COPD with sufficient power to assess their impact on mortality would be a major undertaking. We performed a study to assess the feasibility of a trial of a cardioselective β-blocker in patients admitted to hospital for exacerbation of COPD.

Patients admitted with a primary diagnosis of an exacerbation of COPD to three New Zealand teaching hospitals from November 17, 2014 to August 18, 2015 were prospectively screened for eligibility. Inclusion criteria were age >40 years; >10 pack-year smoking history and airflow obstruction on spirometry (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) <70%). Exclusion criteria are listed in figure 1.

All participants gave written informed consent. Participation in the study did not influence treatment of the COPD exacerbation, which was overseen by independent physicians according to local practice. The New Zealand Health and Disability Ethics Committee approved the study (14/NTB/88).

Participants were given a test dose of 12.5 mg metoprolol tartrate within 3 days of admission (mean±SD time to administration was 41±26 h). ECG and spirometry were measured before and 2 h after the test dose. Heart rate and blood pressure were monitored for 12 h and any symptoms were assessed. Patients who tolerated the test dose were commenced on a daily dose of 23.75 mg controlled-release metoprolol succinate the following day. Blood pressure and pulse rate were measured 4 h after administration of this dose.

Patients were reviewed at hospital discharge and 2, 6 and 12 weeks following discharge. ECG, heart rate, blood pressure and spirometry were performed at each clinic visit and adverse events were recorded. The dose of metoprolol was increased stepwise (from 23.75 mg to 47.5 mg and 95 mg) at each visit to a maximum of 95 mg daily, providing that the patient was tolerating the current dose. Telephone calls to assess symptoms were made 24–48 h after each dose increase. At the end of the study, patients were either maintained on a stable dose of metoprolol or prescribed a step-down regimen according to clinical assessment and patient preference.

The study was monitored by a data and safety monitoring committee. The primary end-points for this feasibility study were the proportion of patients who could be commenced on metoprolol and complete the 12-week protocol.

572 patients with a clinical diagnosis of exacerbation of COPD were screened for inclusion. 549 patients were excluded. The most common reasons included already taking a β-blocker (n=115; 21%), discharged too quickly

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Cite this article as: Chang CL, Wong C, Beckert L. β-blockers in exacerbations of COPD: feasibility of a randomised controlled trial. *ERJ Open Res* 2017; 3: 00090-2016 [https://doi.org/10.1183/23120541.00090-2016].

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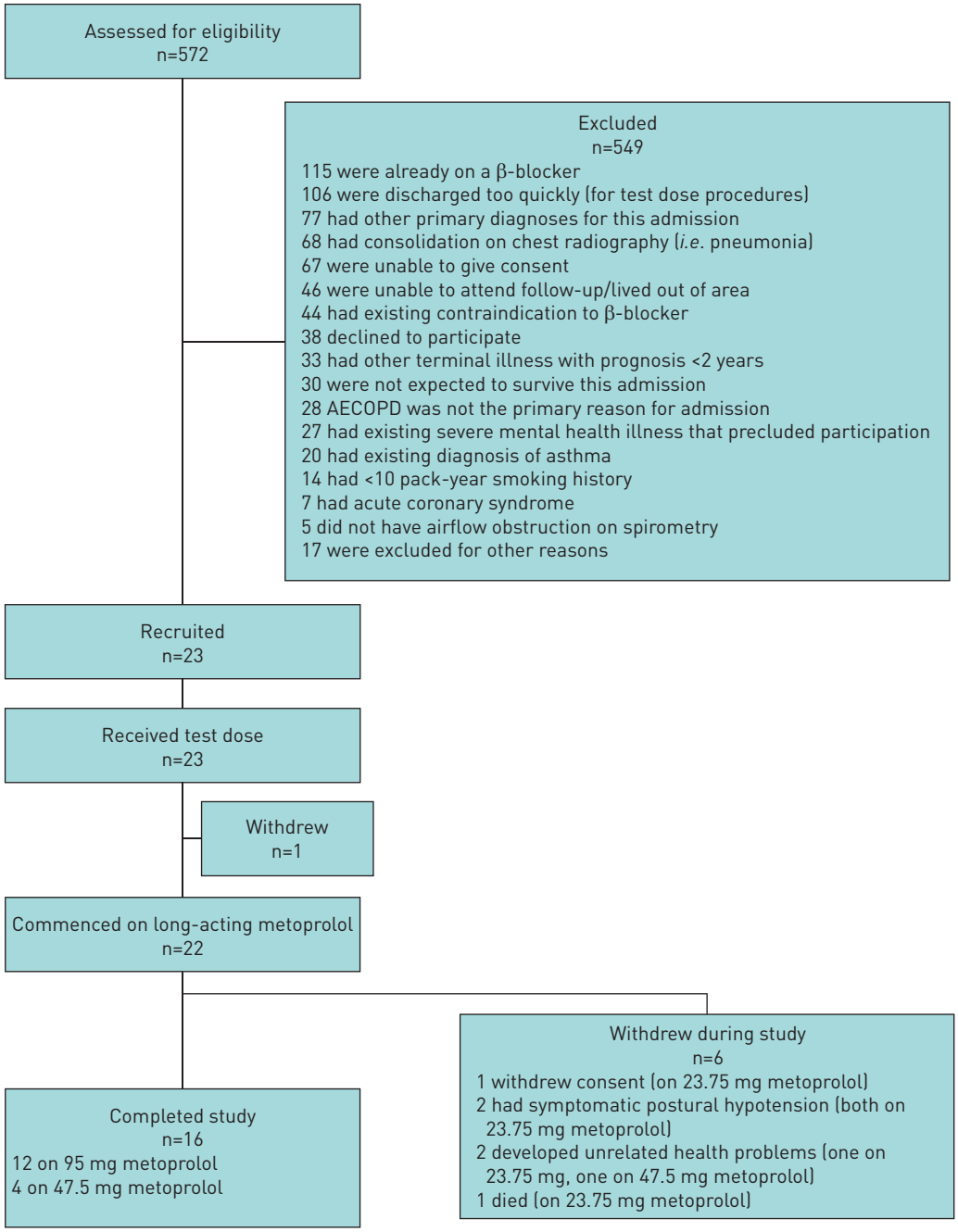

FIGURE 1 Study flow diagram. AECOPD: acute exacerbation of chronic obstructive pulmonary disease.

for the test dose (n=106; 19%), other primary diagnosis (n=77; 14%), radiological evidence of pneumonia (n=68; 12%), unable to consent (n=46; 8%) and a contraindication to β-blocker therapy (n=44; 8%) (figure 1).

23 patients (mean age 67 years, 11 females and mean smoking history 48 pack-years) received the test dose of 12.5 mg metoprolol. One patient withdrew following the test dose, but did not report adverse events related to the study drug.

22 patients were commenced on the metoprolol dose escalation protocol and 16 patients completed the study. At 12 weeks, 12 patients were taking 95 mg of metoprolol and four patients were taking 47.5 mg of metoprolol daily. The reasons for not achieving the target dose were symptomatic hypotension (n=2), bradycardia (n=1) and dyspnoea (n=1).

Of the six patients who withdrew during the study, two had developed symptomatic postural hypotension, two withdrew due to unrelated health problems, one withdrew consent after getting a second medical

opinion and one died suddenly from respiratory failure (this was deemed to be unrelated to the study drug at *post mortem*). Most participants were on low-dose metoprolol at the time of withdrawal.

A large number of adverse events were reported during the study. Despite the short study duration, eight patients were readmitted to hospital with recurrent exacerbations of COPD and two were admitted for heart failure treatment.

The mean±SD heart rate was lower at the highest dose of metoprolol (71±11 beats·min^{-1}) compared to baseline (91±16 beats·min^{-1}, p<0.01 by paired t-test). There were no significant changes in blood pressure (baseline mean systolic 128 mmHg and mean diastolic 74 mmHg; highest dose mean systolic 131 mmHg and mean diastolic 68 mmHg; p=0.36 and 0.34, respectively) or lung function (mean baseline and highest dose FEV_1 were 0.86 L and 0.86 L, respectively (p=0.77); mean baseline and highest dose FEV_1 were 33% predicted and 32% predicted, respectively (p=0.84) and the mean FEV_1/FVC ratios were 39.5% and 37%, respectively (p=0.40).

This study demonstrated the difficulties that would be encountered in a randomised controlled trial of β-blockers in COPD patients during exacerbations requiring hospitalisation. Despite screening 572 patients at three different hospitals, we could only enrol 23 participants (4.0%), indicating that recruitment is difficult in this population and setting. Recruitment was stopped after 8 months, as it was deemed that the question of feasibility could be answered based on data already collected. A review of the exclusion criteria did not reveal specific criteria that may be easily eliminated to improve recruitment (figure 1). Although the numbers recruited were small, there was a high rate of serious adverse events (48%) and withdrawals (30%) from the study. Many of these withdrawals were probably unrelated to the study drug.

We did not find any effect on lung function, the longstanding concern limiting the use of β-blockers in patients with airways disease. However, eight (36%) patients were readmitted for recurrent COPD exacerbations during the 3-month study. It is difficult to know whether the cardioselective β-blocker metoprolol influenced these exacerbations, as this rate of readmission is similar to that reported previously [6, 7]. It is possible that the use of the β-blocker prevented full lung function recovery following the acute exacerbation, although patients reported good symptomatic recovery.

To our knowledge this is the first study to prospectively enrol patients with exacerbations of COPD for a trial of β-blockers. Despite screening a large number of COPD-related admissions we were only able to recruit a small number of patients and it is clear that it would not be feasible to conduct a large randomised controlled trial of β-blockers for acute exacerbations of COPD using the current design. Although our observations are limited by the small number of subjects, the study demonstrates the difficulties in starting β-blockers during a hospital admission for COPD. Unfortunately, this is the time when patients are at the highest cardiac risk and would be most likely to benefit from the cardioprotective effects of β-blockers. The balance of risks and benefits of cardioselective β-blockers for patients with COPD have still not been determined. Future studies should consider starting these in clinically stable patients. There is observational evidence that patients established on β-blockers may have better outcomes if they experience COPD exacerbations [3].

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Received: Aug 11 2016 | Accepted after revision: Oct 16 2016

Acknowledgements: We wish to thank all the participants of this study; K. Perrin (Wellington Hospital, Wellington, New Zealand) for input into the study design; K. Sharples (University of Otago, Dunedin, New Zealand) for data safety monitoring; B. De Graaf (University of Otago, Dunedin, New Zealand) for database support using REDCap; R. Ragupathy (Waikato Hospital, Hamilton, New Zealand) for pharmacy support; the research team at each of the recruiting centres including C. Tuffery, H. Ellis and S. Hopping (Waikato Hospital), R. Ongcoy and S. Lawrence (Middlemore Hospital, Auckland, New Zealand) and L. Cousins (University of Otago, Christchurch, New Zealand); and our colleagues at Christchurch, Middlemore and Waikato Hospitals for their support of recruitment for this study.

All authors contributed to trial design. CLC, CW, LB, ES, RJH collected the data. CLC and RJH analysed the data and drafted the paper. Data analysis, interpretation and manuscript revision were supported by CW, LB, RPY and RB. All authors critically reviewed and approved the manuscript.

This study is registered at www.anzctr.org.au with identifier number ACTRN12614001095651.

Support statement: This study was supported by the Health Research Council of New Zealand (ref. 14/585). Funding information for this article has been deposited with the Open Funder Registry.

Conflict of Interest: Disclosures can be found alongside this article at openres.ersjournals.com

References

1 MacDonald MI, Shafuddin E, King PT, *et al.* Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Lancet Respir Med* 2016; 4: 138–148.
2 Chang CL, Robinson SC, Mills GD, *et al.* Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax* 2011; 66: 764–768.
3 Dransfield MT, Rowe SM, Johnson JE, *et al.* Use of β-blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; 63: 301–305.
4 Domanski MJ, Krause-Steinrauf H, Massie BM, *et al.* A comparative analysis of the results from 4 trials of β-blocker therapy for heart failure: BEST, CIBIS-II, MERIT-HF, and COPERNICUS. *J Card Fail* 2003; 9: 354–363.
5 Rutten FH, Zuithoff NP, Hak E, *et al.* β-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med* 2010; 170: 880–887.
6 Chang CL, Sullivan GD, Karalus NC, *et al.* Audit of acute admissions of chronic obstructive pulmonary disease: inpatient management and outcome. *Intern Med J* 2007; 37: 236–241.
7 Shah T, Churpek MM, Coca Perraillon M, *et al.* Understanding why patients with COPD get readmitted: a large national study to delineate the Medicare population for the readmissions penalty expansion. *Chest* 2015; 147: 1219–1226.