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**TITLE:**

# Commencement of cardioselective beta-blockers during hospitalisation for acute exacerbations of chronic obstructive pulmonary disease

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**ABSTRACT:**

Background: In patients with chronic obstructive pulmonary disease (COPD) and comorbid cardiovascular disease emerging evidence suggests a benefit in commencing cardioselective beta-blockers.

Aim: Our objective was to determine the safety of beta-blocker commencement during hospitalisation for acute exacerbation of COPD.

Methods: A retrospective cohort study of 1,071 patients hospitalised for acute exacerbation of COPD was conducted across two tertiary hospitals over a 12-month period. We identified 36 patients in whom beta-blocker therapy was commenced during admission. Primary outcome of the study was to assess cardiovascular and respiratory adverse events related to the commencement of beta-blocker therapy.

Results: The most common indications for beta-blockers were atrial fibrillation (53%) and acute coronary syndrome (36%). Metoprolol was the most commonly prescribed beta-blocker (75%). No patients suffered clinically significant decline of respiratory function following the commencement of a beta-blocker, including worsening respiratory symptoms, oxygen, bronchodilator or ventilation requirements. These results were demonstrable in patients with reversible airways disease and advanced COPD. Only one patient (2.8%) experienced symptomatic hypotension after 48 hours of therapy.

Conclusion: The commencement of cardio-selective beta-blockers during acute exacerbations of COPD appears to be well-tolerated



**KEYWORDS:**

1. Beta-blocker

2. Chronic obstructive pulmonary disease
3. Cardiovascular disease
4. Acute exacerbation of COPD
5. Safety

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**TITLE:**

# Commencement of cardioselective beta-blockers during hospitalisation for acute exacerbations of chronic obstructive pulmonary disease

## Introduction

Chronic obstructive pulmonary disease (COPD) is a disabling chronic lung condition that encompasses a spectrum of disease, characterised by poorly reversible and progressive airflow limitation (1). The World Health Organisation estimates over 65 million people worldwide are affected by moderate to severe COPD, accounting for over 5% of global deaths (2). Only a proportion of COPD-related mortality is directly related to respiratory disease while death from cardiovascular complications is frequent among those with mild to moderate COPD (3-5).

The cardiac-related morbidity and mortality has been partly attributed to the chronic inflammatory state associated with long-term COPD (6-8). Acute exacerbations of COPD are particularly important periods of increased cardiac stress with observational evidence demonstrating increased risk of acute myocardial infarction (AMI) during and following these admissions (9-12) Additionally, pharmacotherapy used to treat COPD may increase the risk of cardiovascular events in those with pre-existing cardiovascular disease (13). A high proportion of morbidity and mortality up to one-year following acute exacerbations of COPD (AE-COPD) can be attributed to cardiovascular disease (9, 10, 14).

Interest in the cardiovascular complications of COPD patients has increased over recent years. Beta-blockers are of specific interest as they have long been considered contraindicated in COPD due to concerns of adverse respiratory effects, particularly in those with reversible airways disease (15). However, beta-blockers are now not only considered relatively safe in stable outpatients with regards to long-term respiratory function and symptoms, but there is growing evidence of their potential benefits on exacerbation frequency and mortality outcomes (16-20). Despite this, recent studies have demonstrated continuing under-prescription in suitable COPD patients with clear indications for beta-blocker therapy (21, 22).

The safety of introducing beta-blockers during periods of acute respiratory illness, such as an acute exacerbation of COPD, remains unresolved (8, 23). To examine this, we performed a retrospective cohort study to assess the safety of beta-blocker initiation in patients admitted to hospital with an acute exacerbation of COPD. Specifically, we were interested in determining the rates of cardiovascular and respiratory adverse effects associated with beta-blocker therapy.

**Methods**

A retrospective cohort study was conducted across two metropolitan tertiary hospitals, the Royal Melbourne Hospital and the Austin Hospital, Melbourne Australia. Data collection occurred using medical records for those admitted to hospital between 1st July 2013 and 30th June 2014. This study received ethics approval from the Melbourne Health Human Research Ethics Committee.

*Study Criteria*

Patients were included if admitted to hospital for AE-COPD. Patients were identified using International Classification of Diseases, Tenth Edition (ICD-10) coding system, including primary diagnosis of acute exacerbation of COPD- unspecified (J44.9), or primary diagnosis of pneumonia (J10-16) and/or primary diagnosis of acute respiratory failure (J96) with secondary diagnosis of acute exacerbation of COPD. These ICD-10 codes were selected to capture all patients admitted to hospital for AE-COPD.

Patients were excluded if they did not have a primary diagnosis as listed above, or if beta-blocker therapy was not administered during admission, administered for less than 24 hours, or if it was documented as a regular medication prior to admission.

*Definitions*

Patients were classified as having a newly initiated beta-blocker if they received the first dose during admission and received at least 24 hours of beta-blocker therapy.

COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry requirements for diagnosis of a post-bronchodilator forced expiratory volume in one second (FEV-1) to Forced Vital Capacity (FVC) ratio <0.70 (1). Severity of obstructive lung disease was defined according to the GOLD staging categories: Stage I, FEV-1 ≥80% predicted; Stage II, FEV-1 50-79% predicted; Stage III, FEV-1 30-49% predicted; Stage IV, FEV-1 <30% predicted. Significant bronchodilator reversibility was defined as an improvement in FEV-1 of >200ml and at least 12% with bronchodilator. Acute hypoxaemic and hypercapnic respiratory failure were defined according to arterial blood gas results (partial pressure of oxygen <60mmHg and partial pressure of carbon dioxide >50mmHg with pH <7.35, respectively).

*Patient Demographics*

Patient demographics including age, gender, length-of-stay, smoking status and treating specialty team were recorded. Spirometric data were recorded for patients if testing was performed within

one year either side of the date of admission. If more than one set of respiratory function tests existed within this two-year period, then the results closest to the admission date were used for this study.

*Outcomes*

The primary outcome of the study was to assess cardiovascular and respiratory adverse events related to the commencement of beta-blocker therapy**. Bradycardia and symptomatic hypotension were recorded as cardiovascular adverse effects. Increased oxygen requirement was defined as a persistent increase in fraction of inspired oxygen for more than 12 hours following the introduction of beta-blocker therapy. Reduction in oxygen saturation, as determined by pulse oximetry, was defined as persistent oxygen desaturation of more than 5% from baseline for greater than twelve hours following introduction of beta-blocker therapy. Increased ventilatory demand was defined as the introduction of or upgrade to non-invasive ventilation, including continuous positive airway pressure or bilevel positive airway pressure, or invasive mechanical ventilation following the introduction of beta-blocker therapy. Increased bronchodilator requirement was defined as a >25% increase in 24-hour cumulative bronchodilator dose compared to cumulative dose in the 24 hours prior to introduction of beta-blocker therapy.**

**Results**

From the original cohort of 1,071 patients admitted to hospital for an acute exacerbation of COPD, we identified 36 patients with COPD in whom beta-blocker therapy was commenced during an admission with AE-COPD. Mean age was 77.1 years (± 8.7) at admission and 52.7% were female. All patients had previously had a spirometry-confirmed diagnosis of COPD, with mean Forced Expiratory Ratio (FER) of 48.2% (± 13.1%). The majority of patients (61%) were admitted under a respiratory specialist unit with a median length of stay of 7.5 days (interquartile range 5 - 13.75). Table 1 summarises patient characteristics and on-admission medications.

***Respiratory and Cardiac Comorbidities***

In the 36 patients included in the study, the median FEV-1 as a percentage of predicted value was 47.5%. When categorized by GOLD staging, four patients (11%) had mild airflow limitation (stage I), 11 patients (31%) had moderate airflow limitation (stage II), 17 patients (47%) had severe airflow limitation (stage III), and four patients (11%) had very severe airflow limitation (stage IV)**.** Additionally, three patients (8.3%) demonstrated significant bronchodilator reversibility. One-third of patients were current smokers. At least one pre-existing cardiovascular comorbidity was present in 32 patients (89%), with the most prevalent being hypertension and hyperlipidaemia (67% and

56%, respectively). Ischaemic heart disease was present in 14 patients (39%). Of the 13 patients with chronic heart failure, six (17%) had reduced ejection fraction, four (11%) had preserved ejection fraction, and three (8%) had unknown echocardiography results. Acute respiratory failure was present in 12 patients (33%), including five hypoxic (13.9%) and seven hypercapnic (19.4%). Active cancer was present in four patients, two of whom had primary pulmonary malignancies.

***Beta-blocker therapy***

As per the exclusion criteria, no patient was receiving long-term beta-blocker therapy prior to admission was included. Table 2 details the beta-blocker agent and indication in the 36 patients with prior spirometry-confirmed COPD who were included in this study. In 15 patients (41.7%), beta-blockers were commenced within 48 hours of admission. The most common indications for beta-blocker therapy included rate control of atrial fibrillation (19/36, 53%), non-ST segment elevation myocardial infarction (NSTEMI) (12/36, 33%), and optimisation of medical management of heart failure (3/36, 8.3%).Cardioselective beta-blockers accounted for 97% of those prescribed in this study, including metoprolol (27/36, 75%), bisoprolol (5/36, 14%), nebivolol (2/36, 6%) and atenolol (1/36, 3%), while carvedilol, a non-selective beta-blocker, was prescribed in one patient (3%).

***Outcomes***

Beta-blockers were continued throughout the admission following initiation of therapy in 35 patients (97%). **Following beta-blocker commencement no patients required an increase in fraction of inspired oxygen; no patients demonstrated persistent oxygen desaturation of more than 5% from baseline for greater than twelve hours; no patients were initiated on, or upgraded to non-invasive ventilation or invasive mechanical ventilation, and no patients had increased bronchodilator requirements (See Table 3).**

One patient had their beta-blocker ceased due to symptomatic hypotension. This was a 77-year-old female (Patient 31 in Table 2) who was commenced on metoprolol (25mg twice daily) following NSTEMI on presentation for AE-COPD. Hypotension was observed 36 hours following initiation and the beta-blocker was co-administered with amlodipine, ramipril and sublingual glyceryl trinitrate. Metoprolol and amlodipine were ceased two days after initiation of the beta-blocker, in order to improve the hypotension. No other commonly recognised adverse effects of beta-blockers were reported during admission in the 36 patients, including bradycardia, central nervous system effects (nightmares, insomnia, hallucinations), or worsening of peripheral vascular disease.

**Discussion**

Our study provides evidence that cardioselective beta-blockers can be safely initiated and are well tolerated in patients during AE-COPD hospitalisations**.** All patients had experienced exacerbation severe enough to warrant hospital admission, and a majority of the cohort had severe or very severe COPD. Despite this, no patients experienced respiratory complications of beta-blocker therapy, despite beta-blocker therapy being commenced within 48 hours of admission in 41.7% of the cohort. No patients experienced a deterioration in clinically-important respiratory outcomes, and beta-blockers were continued until discharge in all but one patient.

No patients in this study required an increase in bronchodilator dosing following the initiation of beta-blockers, despite the theoretical pharmacological interaction between beta-agonist bronchodilators and beta-blockers (13, 24, 25). This supports previous studies demonstrating that cardioselective beta-blockers may not affect bronchodilator responsiveness in patients with stable COPD (26-28). Whilst pre- and post-beta-blocker spirometric data were not able to be used to accurately determine the presence of any beta-blocker induced bronchoconstriction in this cohort, we believe that increased bronchodilator requirements represent a suitable surrogate clinical marker. This apparent safety and lack of requirement for an increase in bronchodilator is particularly reassuring given the known potential for increased cardiac toxicity as a consequence of increased beta agonist use, notably including tachycardia and myocardial infarction (29).

One patient had beta-blocker therapy ceased following an adverse cardiovascular effect. This individual (Patient 31, Table 2) experienced symptomatic hypotension following initiation of beta-blocker therapy, in the setting of being treated with multiple anti-hypertensive agents. This adverse effect may have been avoided with appropriate patient selection, a lower initiating dosing of metoprolol, or a reduction in some of the other anti-hypertensive agents the patient was receiving. Beta-blockers are known to cause bradycardia and hypotension, particularly in elderly patients, and in combination with other antihypertensive agents (30).

No patients developed worsening hypoxaemia, required an increase in supplemental oxygen therapy, or were escalated higher levels of ventilation following the commencement of beta-blockers.

Our findings add to the limited evidence for beta-blocker use during an admission for AE-COPD. A retrospective study by Kargin and colleagues examined beta-blocker commencement in COPD patients with respiratory failure in the intensive care unit (ICU) (31). Over 85% of included patients were admitted for AE-COPD and the authors concluded that beta-blockers were not associated with increased length of ICU stay, duration of ventilation or mortality compared with other heart rate-lowering drug use. Although only one of our patients was admitted to ICU, our study provides

reassurance beta-blockers can be considered for suitable COPD patients with an indication for beta-blocker therapy in a ward-based (non-ICU) inpatient setting.

In our study, three patients demonstrated significant bronchodilator reversibility on respiratory function tests performed within two years of the date of admission. These three patients all received cardioselective beta-blockers during the acute exacerbation of COPD without experiencing any adverse respiratory outcomes. Whilst no formal respiratory function tests were performed to confirm this result, we believe a lack of clinical deterioration during the AE-COPD is particularly pertinent given the growing understanding of the asthma-COPD overlap syndrome(32, 33). This also contrasts prior small studies reporting acute deterioration in respiratory function following the initiation of a beta-blocker (26, 28, 34). This is may be due to these studies assessing the effects of non-selective beta-blockers. Importantly, 41.6% of patients in our cohort had beta-blockers initiated within 48 hours of admission without significant consequences. This strengthens our suggestion that these medications may be safe to introduce during AE-COPD, as theoretically the first 48 hours following admission are the most vulnerable from a respiratory perspective. The vast majority of beta-blockers used in our cohort were cardioselective (97%). These have previously been shown to have minimal acute effects on respiratory function (35). Additionally, over half of the patients in the study had severe to very severe airflow limitation, suggesting that beta-blockers may be safely introduced during AE-COPD even in patients with advanced lung disease.

The safety of beta-blockers in patients with stable COPD has been established (16) with associated mortality benefits suggested in retrospective studies in patients with comorbid cardiovascular disease (30, 36, 37). In addition, some studies indicate a reduced rate of AE-COPD in this cohort receiving beta-blocker therapy (18, 38, 39). Despite this, under-prescribing of beta-blocker therapy in COPD patients with comorbid cardiac disease is common and has been independently demonstrated in a number of cohorts (21, 22, 40). The reasons for this are not known and are likely multifactorial, but include prescriber caution (41, 42), reflecting previous concerns that beta-blockers were harmful in COPD patients.

The burden of cardiac morbidity across all severities of COPD is significant and often underdiagnosed (25, 43-45).Over a third of patients in this study had a history of ischaemic heart disease and/or heart failure. International guidelines recommend the use of beta-blocker in patients with heart failure with reduced ejection fraction and in those with a history of prior AMI (46, 47). Contemporary reviews have emphasized the relationship between COPD and cardiovascular disease, and the importance of optimal management in patients with these comorbid diseases (23, 25, 48). Cardiac comorbidity is highly prevalent in the COPD population and our study suggests that an

admission for AE-COPD may provide an opportunity to safely optimise its medical management (4, 11, 49).

As well as serving as a good window of opportunity for commencement of beta-blockers in COPD with mortality-reducing cardiac indications, there is potential for significant short-term benefit. Experimental research indicates that both stable COPD and acute exacerbations of COPD are associated with systemic and airway inflammation (6, 7). It is also well-established that systemic inflammation leads to endothelial dysfunction, atherosclerotic plaque instability, platelet activation and altered cardiac electrophysiology; increasing the risk of coronary artery disease, acute coronary syndrome and cardiac arrhythmias (49-52). AE-COPD is also a period of increased known risk factors for arrhythmogenesis, including hypercapnia, oxidative stress and systemic inflammation (53-55). Furthermore, cardiac biomarkers are commonly elevated during AE-COPD and are associated with increased mortality both in-hospital and following discharge (56-58), demonstrating the implications of cardiac stress in AECOPD. Increased mortality following AE-COPD is observed beyond 60 days, with most of these deaths being cardiac in nature (5). The impact of beta-blocker prescription on such complications during the post-AECOPD period is not known and is an area for future prospective studies.

Cardiac comorbidity is frequently underappreciated in patients with COPD and represents a significant area for improvement in clinical management (23). The introduction of beta-blockers to manage and potentially prevent these recognised complications of AE-COPD may become common practice. Of note, experimental animal models have suggested that chronic beta-blocker use may provide additional benefits in pulmonary physiology and COPD pathophysiology, including increasing pulmonary $\beta_2$-adrenoreceptor density, attenuating inflammatory cell infiltration and cytokine levels, and decreasing mucous hypersecretion (59-61); proposing a therapeutic role for beta-blockers in COPD independent of comorbid cardiovascular disease states. Further research must be focused on transforming these experimental results into clinical outcomes.

**Limitations**

A number of limitations were identified in this study. As is inherent in a retrospective study design such as our own, it is difficult to ensure all patients have the clinical tests and observations performed that allow for an objective, quantitative comparator. Hence we have had to rely on the accurate recording of clinical signs and outcomes occurring during admission. We have chosen these objective and categorical outcomes to represent clinical surrogate markers in place of spirometry and arterial blood gas results. Biases are inherent in all retrospective studies, including the inability to account for all underlying confounders. Selection bias may also be present as those patients who

were significantly unwell during the admission, and potentially more likely to have adverse events, were less likely to have received a beta-blocker due to the unknown safety of these medications during an AE-COPD. Some adverse effects are likely to be underestimated in our study, including erectile dysfunction and central nervous system effects, due to lack of reporting and under-recording of adverse effects of this nature during an acute admission.

**Conclusion**

Our study demonstrates that the commencement of beta-blocker therapy during an acute exacerbation of COPD may be safe with regards to respiratory outcomes. Appropriate patient selection will minimise potential adverse effects, and given the high incidence of cardiac morbidity and mortality during these periods of acute respiratory distress, beta-blockers may confer benefits. These observations require confirmation in prospective studies.

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**Table 1: Summary of patient characteristics and on-admission medications**

| **Demographics** | | | **Respiratory Function** | |
|---|---|---|---|---|
| Mean Age (SD) | 77.1 years (+/- 8.7) | | Mean FEV-1 (% predicted; SD) | 51.9% (+/- 18.4%) |
| Female | 19/36 (52.7%) | | Mean FER (SD) | 48.2% (+/-13.1%) |
| Mean LOS (SD) | 11.2 days (+/- 8.9) | | BD Reversibility | 3/36 (8.3%) |
| Median LOS | 7.5 days | | **Cardiovascular Medications** | |
| Treating Team | | | ACE-inhibitor/ARB | 15/36 (41.7%) |
| *Respiratory* | 22/36 (61.1%) | | Antiplatelet | 20/36 (55.6%) |
| *General Medicine* | 14/36 (38.9%) | | Anticoagulant | 15/36 (41.7%) |
| Current/Former Smokers | 12/24 | | Statin | 27/36 (75%) |
| Acute Respiratory Failure | 12/36 (33.3%) | | Loop diuretic | 14/36 (38.9%) |
| *Hypoxic* | 5/36 (13.9%) | | Aldosterone antagonist | 3/36 (8.3%) |
| *Hypercapnic* | 7/36 (27.8%) | | **Respiratory Medications** | |
| **Comorbidities** | | | Short-acting beta-agonist | 35/36 (97.2%) |
| Hypertension | 24/36 (66.7%) | | Short-acting antimuscarinic | 12/36 (33.3%) |
| Hyperlipidaemia | 20/36 (55.6%) | | Long-acting beta-agonist | 31/36 (86.1%) |
| Diabetes Mellitus | 11/36 (30.6%) | | Long-acting antimuscarinic | 30/36 (83.3%) |
| Ischaemic Heart Disease | 14/36 (38.9%) | | Inhaled corticosteroid | 32/36 (88.9%) |
| Heart Failure | 13/36 (36.1%) | | | |
| PVD | 10/36 (27.8%) | | | |
| Pre-existing AF | 11/36 (30.6%) | | | |
| Cerebrovascular Disease | 3/36 (8.3%) | | | |
| Current Malignancy | 4/36 (11.1%) | | | |

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BD, bronchodilator reversibility; FER, forced expiratory ratio; FEV-1, forced expiratory volume in one second; LOS, length of stay; PVD, peripheral vascular disease; SD, standard deviation

**Table 2: Detailed description of the demographics and admission for all patients with spirometry-confirmed COPD included in the study**

| Patient | Age (years) | Gender | Indication | Beta-blocker and initial dose | Day of admission initiated/LOS | FEV-1 | FVC | FER | Bronchodilator Reversibility | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 59 | M | AF | Metoprolol 25mg BD | 2/6 | 0.77 (25%) | 3.67 (95%) | 21 (27%) | No | - |
| 2 | 91 | M | NSTEMI | Metoprolol 12.5mg BD | 4/21 | 0.48 (33%) | 1.50 (66%) | 32 (46%) | No | - |
| 3 | 91 | M | AF | Metoprolol 25mg BD | 1/24 | 0.95 (43%) | 2.03 (66%) | 65 (47%) | No | - |
| 4 | 87 | M | AF | Bisoprolol 1.25mg daily | 1/5 | 1.06 (53%) | 2.17 (74%) | 49 (70%) | No | - |
| 5 | 71 | M | AF | Metoprolol 12.5mg BD | 1/2 | 1.60 (80%) | 3.18 (120%) | 50 (66%) | No | - |
| 6 | 54 | F | NSTEMI | Metoprolol 12.5mg BD | 4/11 | 0.56 (24%) | 1.91 (65%) | 37 (51%) | No | - |
| 7 | 71 | M | AF | Metoprolol 12.5mg BD | 1/8 | 0.94 (34%) | 1.48 (41%) | 64 (83%) | No | - |
| 8 | 81 | M | NSTEMI | Nebivolol 1.25mg daily | 5/7 | 2.01 (75%) | 3.19 (88%) | 63 (85%) | No | - |
| 9 | 93 | F | NSTEMI | Metoprolol 25mg BD | 2/10 | 0.98 (45%) | 2.09 (65%) | 47 (68%) | No | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 81 | F | AF | Metoprolol 12.5mg BD | 6/11 | 0.86 (49%) | 1.96 (82%) | 44 (59%) | No | - |
| 11 | 77 | F | STEMI | Metoprolol 25mg BD | 4/16 | 0.99 (47%) | 2.04 (73%) | 49 (65%) | No | - |
| 12 | 83 | F | NSTEMI | Metoprolol 12.5mg BD | 3/5 | 0.70 (49%) | 1.57 (78%) | 45 (61%) | No | - |
| 13 | 76 | F | AF | Metoprolol 25mg BD | 2/5 | 0.89 (42%) | 1.99 (74%) | 44 (75%) | No | - |
| 14 | 83 | F | SVT | Metoprolol 25mg BD | 2/5 | 0.69 (41%) | 1.71 (76%) | 40 (55%) | Yes | - |
| 15 | 89 | F | AF | Metoprolol 12.5mg BD | 4/19 | 1.00 (59%) | 1.64 (71%) | 61 (84%) | No | - |
| 16 | 76 | F | NSTEMI | Metoprolol 25mg BD | 14/37 | 0.97 (46%) | 1.69 (60%) | 52 (69%) | No | - |
| 17 | 74 | M | HF Optimisation | Carvedilol 3.125mg BD | 7/8 | 2.4 (78%) | 3.7 (90%) | 65 (88%) | No | - |
| 18 | 84 | M | AF | Bisoprolol 2.5mg daily | 10/20 | 1.8 (50%) | 3.97 (81%) | 45 (63%) | No | - |
| 19 | 71 | F | AF | Metoprolol 25mg BD | 1/2 | 1.3 (62%) | 2.0 (78%) | 66 (85%) | No | - |
| 20 | 70 | M | NSTEMI | Bisoprolol 2.5mg daily | 2/24 | 0.44 (23%) | 1.72 (73%) | 26 | No | Intubated for T2-RF refractory to NIV. NSTEMI while intubated in ICU, and commenced on beta-blocker. |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Extubated two days later without issue |
| 21 | 74 | M | AF | Metoprolol 25mg BD | 20/34 | 1.2 (40%) | 2.8 (75%) | 43 (41%) | No | - |
| 22 | 83 | M | AF | Bisoprolol 2.5mg daily | 4/8 | 0.89 (55%) | 2.63 | 34 (47%) | No | - |
| 23 | 84 | M | HF Optimisation | Metoprolol 25mg BD | 2/6 | 1.3 (93%) | 2.4 (116%) | 54 (77%) | No | - |
| 24 | 80 | F | AF | Metoprolol 25mg BD | 3/7 | 0.72 (44%) | 1.93 (87%) | 37 (50%) | No | - |
| 25 | 72 | F | HF Optimisation | Metoprolol 12.5mg BD | 6/8 | 1.46 (98%) | 2.14 (116%) | 68 | No | - |
| 26 | 67 | F | AF | Bisoprolol 2.5mg daily | 3/7 | 0.9 (39%) | 2.4 (87%) | 38 (50%) | Yes | - |
| 27 | 78 | F | AF | Metoprolol 12.5mg BD | 8/28 | 0.8 (48%) | 2.1 (99%) | 38 (40%) | No | - |
| 28 | 66 | F | AF | Metoprolol 12.5mg BD | 2/5 | 1.46 (47%) | 3.75 (89%) | 39 (53%) | No | - |
| 29 | 79 | M | NSTEMI | Metoprolol 12.5mg BD | 1/5 | 1.22 (82%) | 2.00 (99%) | 61 (82%) | No | - |
| 30 | 66 | M | NSTEMI | Nebivolol 1.25mg daily | 3/3 | 1.95 (71%) | 3.05 (85%) | 63 (80%) | No | - |
| 31 | 77 | F | NSTEMI | Metoprolol 25mg BD | 1/13 | 0.93 (46%) | 2.39 | 39 (53%) | No | Beta-blocker ceased after two days |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | secondary to symptomatic hypotension |
| 32 | 76 | F | NSTEMI | Metoprolol 25mg BD | 3/6 | 1.05 (47%) | 2.20 (78%) | 47 (74%) | No | - |
| 33 | 77 | M | AF | Metoprolol 25mg BD | 4/6 | 1.05 (56%) | 1.47 (60%) | 63 (82%) | No | - |
| 34 | 84 | M | AF | Atenolol 25mg daily | 2/5 | 1.49 (63%) | 2.54 (74%) | 57 (80%) | Yes | - |
| 35 | 69 | F | AF | Metoprolol 25mg BD | 3/5 | 0.83 (28%) | 3.82 (98%) | 22 (29%) | No | - |
| 36 | 75 | F | NSTEMI | Metoprolol 25mg BD | 5/10 | 1.42 (56%) | 2.46 (69%) | 58 (79%) | No | - |

AF, atrial fibrillation; BD, twice-daily; FEV-1, forced expiratory volume in one-second; FER, forced expiratory ratio; FVC, forced vital capacity; HF, heart failure; ICU, intensive care unit; LOS, length-of-stay; NIV, non-invasive ventilation; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; SVT, supraventricular tachycardia; T2RF, type-2 respiratory failure

**Table 3: Summary of beta-blocker therapy and adverse outcomes**

| **Beta-blocker Indication** | |
|---|---|
| AF | 19/36 (52.7%) |
| NSTEMI | 12/36 (33%) |
| HF Optimisation | 3/36 (8.3%) |
| SVT (other than AF) | 1/36 (2.8%) |
| STEMI | 1/36 (2.8%) |
| **Beta-blocker Prescribed** | |
| Metoprolol | 27/36 (75%) |
| Bisoprolol | 5/36 (13.9%) |
| Nebivolol | 2/36 (5.6%) |
| Carvedilol | 1/36 (2.8%) |
| Atenolol | 1/36 (2.8%) |
| **Adverse effects following beta-blocker commencement** | |
| Increased oxygen requirement | 0/36 (0%) |
| Reduction in oxygen saturation | 0/36 (0%) |
| Increased ventilatory demand | 0/36 (0%) |
| Increased bronchodilator requirement | 0/36 (0%) |
| Hypotension | 1/36 (2.8%) |
| Bradycardia | 0/36 (0%) |
| AF, atrial fibrillation; HF, heart failure; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; SVT, supraventricular tachycardia | |