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Hospitalisations for Acute Exacerbation of COPD

Patterns of Disease, Risk Prediction and Treatment Implications

Catherina Li-Lin Chang

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Medicine
Waikato Clinical School
The University of Auckland
January 2011
For my Dad, who believed I could do anything.
The most exciting phrase to hear in science, the one that heralds new discoveries, is not "Eureka!" but rather "hmm.... that's funny..."

- Isaac Asimov

Preamble

This thesis is comprised of the author’s body of investigations into practical management issues relating to COPD exacerbations. The majority of the research questions stem from personal queries in the authors’ clinical practice when managing patients and when the literature was unable to provide adequate answers. Work done answering one question often uncovered further gaps in medical knowledge, so for each question answered, many new ones became apparent.

The retrospective study in Chapter Two provides a point of reference for the hospital patient population that the author works with in New Zealand and demonstrates that the New Zealand health care system is able to deliver treatment to internationally acceptable standards and achieve similar outcomes. It also documents important health disparities between Māori and non- Māori patients, which is an important finding for New Zealand and deserves further exploration. In addition, this study became the forerunner for a cohort study designed to prospectively examine two intriguing findings that had been observed
retrospectively – namely that the CURB65 score and cardiac biomarkers may predict increased mortality in patients with acute exacerbations of COPD.

This prospective cohort study provided data for the bulk of this thesis. Chapters Three and Four describe the correlations of elevated CURB65 score and biomarkers of cardiac dysfunction (NT-proBNP and Troponin T) with increased mortality in patients hospitalised for exacerbation of COPD. Together, these simple risk prediction tools may aid clinicians in making management decisions and help facilitate discussions between patients and their families. These findings also provide insights into the pathophysiology of COPD exacerbations, which may open up an exciting avenue of research into the potential use of cardio-protective agents (such as β-blockers) in the treatment of acute exacerbations of COPD.

Chapter Five is a randomised controlled trial that addresses the therapeutic dilemma of using β-blocker therapy in patients with COPD. A substantial body of evidence now supports the use of cardio-selective β-blockers in patients with stable COPD, however the effect of β-blockers on the airway during an exacerbation of COPD is not well studied. This study examines the interaction between β₁-selective, non-selective β-blockers and β₂-agonists in COPD patients after acute broncho-constriction and demonstrated that selective β₁-blockers do not appear to significantly affect response to bronchodilator therapy at low to moderate doses but they do at higher doses. Putting these findings together, we speculate that the group of patients that may benefit from cardio-protective therapy can be identified using elevated cardiac biomarkers and these patients can be safely treated with low
to moderate doses of cardio-selective β-blockers during an acute exacerbation
without fear of reducing the effectiveness of airways treatment.

The research described in this thesis was carried out in conjunction with the author’s
training in respiratory and sleep medicine. The chapters reflect transition from a
trainee working within the framework of established treatment protocols, to a
physician and researcher looking for new treatment avenues in patients with
complex multi-system disease. I believe that this work has meaningfully furthered
our knowledge of the understanding of acute COPD exacerbations and highlights
possible new approaches to treatment.
Co-authors’ Contributions and Acknowledgements

I was the major contributor to all aspects of the research presented in this thesis including study design, ethics applications, patient recruitment, data acquisition, statistical analysis, data interpretation, writing of manuscripts for peer-reviewed journals and the writing of this thesis.

There are a number of colleagues to whom I am deeply indebted for their tremendous contributions to the work that comprises this thesis. The co-authors for each chapter are listed in full and their contributions all satisfy the ICMJE criteria for authorship.

The work presented in this thesis was under the supervision of Dr Bob Hancox and Dr Graham Mills, both of whom gave invaluable insights into research planning, study design and data interpretation. I was the lucky beneficiary of Bob Hancox’ statistics advice and manuscript word count-reduction weekend workshops, all supported by intravenous infusions of tea and biscuits. Thank you both for inspiring and encouraging me when I started making baby-steps down the research pathway. Thank you for trusting me with the research fund. Thank you for your patience, understanding and quiet encouragements when I was going through patches where the road to completion seemed to stretch so far that I doubted ever getting there. I have benefited tremendously from your expert guidance and sound judgement. What you have taught me about research, life and everything will stand me in good stead in the years to come.
Thank you to Dr Noel Karalus and Dr John McLachlan, the two Heads of Department of Respiratory Medicine during the time when the research was conducted at Waikato Hospital. Without their active support and facilitation these projects would not have been possible. Thank you to all the clinical staff who have been my most loyal recruitment team.

Special thanks should also go to Glenda Sullivan, Clinical Nurse Specialist, patient recruiter and data collector extraordinaire. I do not know how I would have survived an entire year of consecutive admissions recruitment without you.

I would also like to thank Manisha Cooray, my research assistant for making sense of even what I sometimes cannot understand. I would like to thank Chris Tuffery, Nancy Carey and Sheryl Hayett for all their practical research advice, various form templates and a constant stream of chocolates. Steve Holmes designed the database that we used. Mark Chatsfield provided invaluable statistical advice.

I express my sincerest gratitude to all the research patients who voluntarily gave up their time to participate in the studies.

The work presented in this thesis was funded by the Waikato Respiratory Research Fund and the Waikato Medical Research Foundation.

Finally, I would like to thank Scott, my husband, my sounding board, my editor, my partner and my pillar of strength. Thank you for living through the ups and downs of
my research over the years. Thank you for listening patiently when I could not stop
talking about some finer points of data interpretation. Thank you for weathering the
storm that is this MD with grace and understanding. I truly cannot have done this
without you.

This thesis is dedicated to the memory of my father, James Chang. Dad, I am sorry
that you did not live to see its completion. Thank you for instilling in me a love for
knowledge. I still remember vividly the day you told me that you were proud of me
for asking a question that you did not know the answer of and that we can learn
together. This is for you.
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### Abbreviations

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<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>APACHE</td>
<td>Acute Physiology and Chronic Health Evaluation</td>
</tr>
<tr>
<td>ATS</td>
<td>American thoracic society</td>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<tr>
<td>BMI</td>
<td>body-mass index</td>
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<tr>
<td>BNP</td>
<td>Brain or B-type natriuretic peptide</td>
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<tr>
<td>BTS</td>
<td>British thoracic society</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
<td>CRB65</td>
<td>confusion, respiratory rate $\geq$ 30/min, low systolic (&lt;90mmHg) or diastolic (&lt;60mmHg) blood pressure and age $&gt; 65$ years</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CURB65</td>
<td>confusion, elevated serum urea &gt; 7mmol/L, respiratory rate $\geq$ 30/min, low systolic (&lt;90mmHg) or diastolic (&lt;60mmHg) blood pressure and age $&gt; 65$ years</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>FEV$_1$</td>
<td>forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FiO$_2$</td>
<td>fraction of inspired oxygen</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global initiative for chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>ICD</td>
<td>International classification of diseases</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
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<tr>
<td>ISWT</td>
<td>incremental shuttle walking test</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>MMRC</td>
<td>modified medical research council</td>
</tr>
<tr>
<td>NICE</td>
<td>National institute for health and clinical excellence</td>
</tr>
<tr>
<td>NIV</td>
<td>non-invasive ventilation</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-brain natriuretic peptide</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>partial pressure of carbon dioxide in arterial blood</td>
</tr>
<tr>
<td>PaO₂</td>
<td>partial pressure of oxygen in arterial blood</td>
</tr>
<tr>
<td>PD₂₀</td>
<td>cumulative dose causing 20% fall in FEV₁</td>
</tr>
<tr>
<td>pH</td>
<td>the negative logarithm (base 10) of the molar concentration of dissolved hydrogen ions</td>
</tr>
<tr>
<td>PEFR</td>
<td>peak expiratory flow rate</td>
</tr>
<tr>
<td>PSI</td>
<td>pneumonia severity index</td>
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<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
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<tr>
<td>RR</td>
<td>relative risk</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>V̇O₂</td>
<td>rate of oxygen uptake per minute</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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Publications


Chapter One

Literature Review
“In opening the chest, it is not unusual to find that the lungs do not collapse, but they fill up the cavity completely on each side of the heart.

When experienced, this will appear full of air... The bronchus of the trachea are often at the same time a good deal filled with mucous fluid.”

- René Laënnec, *Treatise of Diseases of the Chest*, 1821

### 1.1 COPD: Introduction

Chronic obstructive pulmonary disease (COPD) encompasses a broad spectrum of disease characterised by chronic expiratory airflow limitation that is incompletely reversible and generally progressive [1-3]. It involves a combination of small airway obstruction (chronic bronchitis and bronchiolitis) and parenchymal destruction (emphysema) to varying degrees. Diagnosis is usually made, and disease severity graded, using spirometry. The most important cause is tobacco smoking which is preventable and appears to be decreasing in Western countries but may be increasing in Asia and Eastern Europe and in specific demographics such as female Maori teens. The cost to society in terms of health effects, social cost and economics is massive and looks set to stay that way for decades [4, 5].

Chronic obstructive pulmonary disease has been acknowledged as a clinical entity for nearly 200 years. René Laënnec, inventor of the stethoscope, described the coexistence of emphysema and chronic bronchitis in 1821 [6]. Landmark meetings in 1959 and 1962
defined the components of the disease which formed the foundation of the current
definition [7, 8]. Since that time it has been the focus of volumes of research and academic
debate as well as public, political and tobacco company discussion. It is beyond the scope of
this review to cover all this research. This literature review is limited to a general overview
of COPD and studies relevant to the management of acute exacerbations in hospital,
particularly pertaining to risk prediction and the role of cardiac biomarkers.

1.1.1 Pathophysiology

Many complex interacting risk factors have been implicated in the pathogenesis of COPD,
but the most important factor is chronic inflammation resulting from inhalation of toxic
compounds. The most common of these is tobacco smoke [5]. In the small airways,
recurrent toxin exposure leads to disruption of the epithelial barrier, breakdown of
mucociliary clearance, infiltration of the airway walls by inflammatory cells and scar
formation in the airway walls. These processes combine to result in thickened airway walls,
reduced lumen calibre and bronchoconstriction, leading to longer lung expiratory time
constants and gas trapping. Beyond the terminal bronchiole, infiltration of inflammatory
cells and destruction of alveolar walls leads to emphysema. The reduction in elastic recoil
from parenchymal destruction compounds the problem of small airways obstruction leading
to further gas-trapping [9, 10].

The underlying disease process in COPD produces characteristic physiological abnormalities
that are measureable. In brief, inflammation, airways obstruction and gas trapping may
manifest as reduced FEV₁ and FEV₁/FVC ratio, while parenchymal destruction and impaired
gas exchange can be indicated by decreased gas transfer factor [2]. Gas exchange,
ventilation and perfusion abnormalities result in hypoxaemia and hypercapnia which worsen with the disease progression and exacerbations. A combination of endothelial dysfunction, pulmonary artery remodelling and inflammatory cell infiltrates leads to the development of pulmonary hypertension in moderate to severe COPD [11, 12].

Although tobacco smoking is the most important risk factor related to the development of COPD, a significant proportion of cases cannot be attributed to smoking alone [13]. Strong evidence supports the importance of genetic factors, for example alpha-1-antitrypsin deficiency, in the development of COPD with or without smoking [14-17]. Other well established risk factors include long standing asthma [18, 19], air pollution [20-22], second hand smoking [23, 24], biomass smoke exposure [25-27] and most recently occupational particulate exposure [13, 28-30]. Associations between dietary variations such as inadequate vitamin D [31] and excessive cured meat consumption [32, 33]; chronic pulmonary infections [34]; and COPD have also been observed although causal relationships have not been established.

1.1.2 Clinical Features

Common symptoms of COPD include dyspnoea, cough and sputum production. Chronic cough and sputum may precede airflow limitation by many years [35, 36]. The clinical course is insidious and the disease may go undiagnosed for years. Dyspnoea may initially be present only on exertion but with disease progression occurs with less exertion or even at rest. Some patients present simply with an increasingly sedentary lifestyle as they modify their activities to avoid exertional dyspnoea [37]. Some patients remain undiagnosed until their first exacerbations [38].
Chronic bronchitis is defined by the presence of cough and sputum (on most days for more than three months in two consecutive years) although the pattern of sputum production in many patients is more variable [39]. Wheeze and chest tightness are also commonly reported but their absence does not exclude the diagnosis.

COPD is usually progressive over time but the clinical course may vary between individuals. Fletcher and Peto in their landmark paper demonstrated that lung function in susceptible smokers declines at an accelerated rate (80-150mL/year) compared to those who had never smoked (10-15mL/year) [40]. Importantly, stopping further exposure to noxious agents such as tobacco smoke has been shown to slow disease progression and reduce all cause mortality [40-43].

Patients with advanced COPD may develop secondary pulmonary hypertension and associated cor pulmonale, which frequently presents as increased systemic salt and fluid retention [44, 45]. Haemoptysis can also occur both as a manifestation of chronic bronchitis and in association with exacerbations. It may also herald thoracic malignancy and thus warrants further investigation. Obstructive sleep apnoea can also co-exist in individuals with COPD (over-lap syndrome) and these patients have an increased risk of hospitalisation from COPD exacerbations and a reduced survival rate [46-48].

The extra-pulmonary effects of COPD are increasingly recognised and may contribute to disease severity in individual patients. It is often impossible to separate co-morbid conditions from systemic consequences of COPD. Systemic effects of COPD may be directly attributable to the disease process while co-morbidities occur in association with COPD
because of shared risk factors. Further, some COPD treatments such as systemic corticosteroids may compound the severity of any co-existing conditions.

Potential systemic consequences of COPD are numerous. Inactivity, de-conditioning and elevated energy expenditure with increased work of breathing can lead to weight loss, nutritional depletion and osteoporosis [49-52]. Muscle mass may be reduced even in patients with relatively normal total body weight and can be exacerbated by concomitant corticosteroid therapy [53]. Respiratory and peripheral muscle strength is often reduced leading to impaired functional capacity and poorer health status.

In concert with the physical effects, COPD also impacts significantly on psychosocial function. The prevalence of clinical anxiety and mood disorders in patients with COPD is higher than in the age-matched population [54-56]. Panic disorders may occur in as many as one in three patients with COPD and these patients have worse quality of life, more frequent exacerbations and hospitalisations and poorer treatment adherence [57, 58].

Increased systemic inflammation, oxidative stress and circulating levels of acute phase proteins and cytokines in patients with COPD have been the subject of much research and debate. In 2004, Gan et al performed a systematic review including 14 studies and concluded that individuals with COPD had significantly raised levels of several markers of inflammation including C-reactive protein (CRP), interleukin-6, activated leucocytes and tumour necrosis factor-α (TNFα) [59]. However whether this represented independent processes related to common risk factors (such as cigarette smoking), treatment side effects (such as frequent use of systemic glucocorticoids) or “overspill” inflammation from the lungs
remains uncertain [60]. The association between varying degrees of systemic inflammation and vascular endothelial dysfunction commonly seen in patients with COPD is also not well characterised and under intense research scrutiny [61, 62]. Beyond doubt however, is the fact that cardiovascular disease (including pulmonary vascular disease, congestive heart failure, coronary artery disease, peripheral vascular disease, lipid and inflammatory marker abnormalities) is a major cause of morbidity and mortality in patients with COPD [59, 63-70].

Specific research into elevated markers of cardiac dysfunction in acute exacerbation of COPD is described in detail later in this review and formed the basis for the chapter on biomarkers and risk prediction in acute exacerbation of COPD.

1.1.3 Diagnosis and Spirometric Classification of Severity

The diagnosis of COPD should be considered in any patient with symptoms of chronic cough, sputum production or dyspnoea and/or a history of exposure to risk factors for the disease. Spirometry is fundamental to making the diagnosis and should be performed where there is clinical suspicion based on history, symptoms or signs. The principal differential diagnosis is asthma, which is characterised by airways hypersensitivity and reversible airflow obstruction [71].

Spirometry is also used to assess the severity of airflow obstruction, guide therapy and predict prognosis [2, 72]. Internationally accepted spirometric classifications of severity and stages of COPD are summarised in Table 1.1. Airflow obstruction is defined as a post-bronchodilator FEV₁/FVC ratio <0.70. An FEV₁ < 80, 50 and 30% of predicted values are
classified as moderate, severe and very severe disease respectively [1-3, 73]. There is still considerable debate concerning global adoption of these criteria. Indeed, consensus in severity criteria between European/British and North American guidelines was only recently achieved with the 2010 update of the NICE guidelines [1]. Studies conceived prior to this date, including those in this thesis, regularly use the 2004 BTS/NICE severity criteria are still prevalent in the current literature [74].
Table 1.1 Summary of COPD stages and spirometric classifications of airflow obstruction severity

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<td>&lt; 0.7*</td>
<td>&lt; 0.7*</td>
<td>≥ 80 %</td>
<td>Mild</td>
<td>Stage 1 – Mild</td>
<td>Stage 1 – Mild**</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.7*</td>
<td>50-79%</td>
<td>Mild</td>
<td>Moderate</td>
<td>Stage 2 – Moderate</td>
<td>Stage 2 – Moderate</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.7*</td>
<td>30-49%</td>
<td>Moderate</td>
<td>Severe</td>
<td>Stage 3 – Severe</td>
<td>Stage 3 – Severe</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.7*</td>
<td>&lt;30%</td>
<td>Severe</td>
<td>Very severe</td>
<td>Stage 4 – Very severe***</td>
<td>Stage 4 – Very severe***</td>
<td></td>
</tr>
</tbody>
</table>

* or FEV₁/FVC < lower limit of normal as defined by value less than the 5th centile of healthy population for age

** Symptoms should be present to diagnose COPD in people with mild airflow obstruction

*** or FEV₁ < 50% with respiratory failure
The Global initiative for chronic Obstructive Lung Disease (GOLD) severity classification is now routinely referred to in the literature [2]. COPD severity is classified from stage I to IV: mild, moderate, severe and very severe (Table 1.1) A fifth category – “Stage 0: at risk” has been removed from the most recent document revision in 2009 as there is insufficient evidence to support that at risk individuals necessarily progress onto other stages of the disease.

As alluded to above, there is considerable debate concerning the use of these criteria. It is important to note that while the specific spirometric cut-points are commonly used in the literature, they have not been clinically validated [2, 75]. FEV₁/FVC ratio is also dependent on age, sex, height and ethnicity, and the use of a fixed ratio tends to over-diagnose COPD in older people while under-diagnosing younger people [76-80]. For these reasons, defining airflow obstruction as FEV₁/ FVC less than the lower limit of normal ratio has been proposed [75, 81, 82]. Wider implementation of this definition is limited by the lack of well-validated predictive equations and reference values [83-85]. Predicted values in adults also need calibration for different populations and ethnic groups [86-88].

1.1.4 Prevalence and Disease Burden

Estimating the societal burden caused by COPD is challenging because of the existence of co-morbid conditions and the strong association with aging. Despite this, COPD is well recognised as a leading cause of morbidity and mortality and a major cost to health care organisations and society. In 2001, the WHO Global Burden of Disease Project estimated that COPD was the fourth leading cause of premature death worldwide and will become the third leading cause by 2020 [89, 90]. More recently, the Burden of Obstructive Lung Disease
(BOLD) Initiative assessed 9425 participants from 12 sites internationally and reported the prevalence of stage II or higher COPD was 10.1% (SE 4.8) for men and women over 40 years of age [91]. Other international studies of COPD epidemiology have reported similar disease prevalence [92, 93].

COPD prevalence and mortality rates have continued to increase during the last four decades in most regions of the world [94, 95]. This is in contrast to cardiovascular disease, the prevalence of which has been decreasing in the western world since the 1970’s [96-100]. In developing countries, the increase in prevalence of COPD and associated mortality has grown with increasing cigarette smoking [101, 102]. Encouragingly, there is now emerging evidence to indicate that the peak of tobacco-related COPD incidence and prevalence has been reached in some developed countries [103].

Locally, the 2006/07 New Zealand Health Survey found that 6.6% (95%CI 5.9-7.3) of people over 45 years have been told by a doctor that they have COPD (emphysema or chronic bronchitis) [104]. In contrast to international trends, this survey found that women (7.4%, 95%CI 6.5-8.4) were more likely than men (5.6%, 95%CI 4.4-6.7) to report the diagnosis (p < 0.05). Although this finding may reflect the increased rates of tobacco use by New Zealand women compared to men, the data need to be interpreted with caution. The study was a cross-sectional survey with appropriate weighting to reflect the gender, ethnicity and age of the population. However, as with any questionnaire based analyses, the results reflect self-reported health states and diagnoses rather than objectively measured disease.

More recently, Shirtcliffe et al reported results of a random populational survey of urban-dwelling (Wellington) adults [105]. This is the largest spirometry-based COPD prevalence
survey done in New Zealand to date. 749 adult volunteers underwent pre- and post-bronchodilator spirometry, skin-prick allergy testing and detailed respiratory questionnaire. The prevalence of COPD defined by GOLD criteria (post-bronchodilator FEV₁/FVC < 0.7) [2] was compared to the lower limit of normal criteria proposed by the 2004 ATS/ERS Task force (using a cut-off value for FEV₁/FVC ratio set at the fifth percentile of the normal distribution)[3]. This study found the prevalence of GOLD-defined COPD in adults aged greater than 40 years was 14.2% (95%CI 11.0-17.0) with greater prevalence in men (19.7%, 95%CI 16.0-23.9) than women (10.5%, 95%CI 7.5-14.2). Interestingly, the overall prevalence of COPD was slightly less when airflow obstruction was defined by FEV₁/FVC less than the fifth centile (9.0%, 95%CI 6.7-11.3) and this difference in prevalence as defined by the two methods became more prominent with age. Regardless of the exact spirometric criteria used, this study nevertheless reaffirmed that COPD is a major cause of morbidity and mortality in New Zealanders.

The burden of COPD consists of several overlapping components: the proportion of the population that is symptomatic of the disease; the effects of the disease on each affected individual; the costs to society incurred by patients with the disease. Within individuals, respiratory symptoms, co-morbidities and side effects of treatment lead to poor health status, impaired exercise and performance capacity; increased visits to primary health providers and the emergency departments; increased use of medications and requirements for functional support; increased rates of hospitalisation and ultimately, increased mortality [4, 65, 106-109]. Premature death is common in COPD. People with moderate to severe disease die earlier than those with normal lung function, both as a result of respiratory causes and co-morbid conditions such as malignancies and stroke [110]. Despite the
substantial impact of COPD on individuals and society, it is often under-diagnosed and under-treated. The true disease burden of COPD is likely to be under-estimated because it is usually only recognised when it is clinically apparent and moderately advanced. In addition, the indirect costs of COPD to society are generally under-estimated as the economic value of work days lost by the patient or care-giver (such as a family member) are frequently unacknowledged.

1.1.4.1 COPD in Māori

Māori now make up 15-20% of the total population of New Zealand [111]. Māori have on average the poorest health status of any ethnic group in New Zealand like many other indigenous minority groups in other parts of the world [112-114]. This is demonstrated across a range of key health indicators such as increased infant mortality; poor socio-economic status associated with residential over-crowding and reduced access to health care; reduced use of preventative health services such as immunisation and cervical and breast cancer; higher rates of modifiable risk factors for chronic disease such as smoking, obesity and diabetes; and increased rates of disability due to poor health [115]. Overall, this translates into reduced life expectancy at birth (in 2006) of about 8 years than that for non-Māori, with 70.4 years for Maori men versus 79.0 years for non-Maori men and 75.1 years for Maori women versus 83.0 for non Maori women [111].

Part of this mortality discrepancy is attributable to higher COPD prevalence and severity in Māori. The 2006/07 New Zealand Health Survey found the age standardised rates of COPD were almost two times greater in Māori men and women compared to the general population (12.8%, 95%CI 9.2-16.13 and 5.9%, 95%CI 5.2-6.7 respectively) [104]. This is
largely attributable to the higher rates of tobacco and second hand smoke exposure in Māori. The same survey found that the rate of current smokers was 40.4% (95%CI 38.3-42.4) in Māori and 18.0% (95%CI 16.9-19.2) in non-Māori and Māori were more likely to have never considered quitting. Māori also experience greater degrees of social deprivation, occupational exposure and have higher rates of childhood respiratory infections. All of these factors have been independently linked to the development of obstructive lung disease [116-121].

These statistics translate into markedly elevated mortality rates from COPD in this population. The age-standardised mortality from COPD is < 20 per 100,000 in non-Māori New Zealanders but 64.8 (95%CI 52.5-77.2) per 100,000 in Māori men and 71.9 (95%CI 59.7-84.1) per 100,000 in Māori women. Furthermore, the COPD mortality rate in Māori women has risen from 51.0 per 100,000 population in 1981 to 71.9 per 100,000 in 2004. To put this in perspective, in Europe the age-adjusted mortality rate is < 20 per 100,000 in Sweden, Iceland and Norway but more than 80 per 100,000 in former Eastern-bloc countries such as the Ukraine and Romania [122].

Taken together, COPD is an important and rapidly growing cause of morbidity and mortality in the Māori population of New Zealand. However, the exact prevalence by spirometric criteria remains unexplored in this population as the only large scale survey to date included only a small number of Māori people (n = 26) [105]. Moreover, targeted service delivery, risk factor reduction and prevention strategies remain poorly developed. The rate of exacerbation and outcome of these patients are unknown but presumed to be poorer than average COPD patients. No published data document the rate of hospitalisation and
outcome in Māori with acute exacerbations of COPD. Clearly this is an area requiring further research. *Chapter two of this thesis describes the findings of a retrospective study of patients hospitalised for COPD exacerbations and their outcome in relation to ethnicity.*
1.2 Acute Exacerbations of COPD

A significant portion of the social and economic burden of COPD is associated with exacerbations. Exacerbations frequently lead to unscheduled doctor visits, escalation in medication use and hospital stays and may lead to reduced quality of life and/or death. Exacerbations are estimated to account for 50-75% of the cost of healthcare services for COPD [3]. A recent systematic review of the literature examining the direct and indirect costs of COPD exacerbations found only 11 relevant studies [123]. The estimated costs of exacerbations varied widely across studies – from $88 to $7,575 (2007 US Dollars) per exacerbation. However, hospitalisation was consistently the largest component of total cost of COPD exacerbations across countries and study sites. Furthermore, costs are closely related to exacerbation severity – which often determines whether hospitalisation is required. This review illustrated the importance of correctly defining, diagnosing and treating COPD exacerbations.

The benefits of timely and appropriate management of acute exacerbations of COPD extend beyond basic health economics. A growing body of evidence now support the concept that patients who experience frequent exacerbations appear to be a distinct phenotype. They are susceptible to a more rapid decline in lung function, poorer quality of life and increased mortality [124-128]. Even amongst patients with relatively mild COPD by spirometric criteria, those who have frequent exacerbations have a worse outcome. Not surprisingly, this group of patients contribute disproportionately to the health burden of COPD [129].
1.2.1 Definition of an Exacerbation and Assessment of Severity

Until the recent widespread adoption of the GOLD definition, interpretation of research into acute exacerbations of COPD was somewhat hindered by the lack of standardised diagnostic criteria [2]. An acute exacerbation of COPD is defined in the GOLD consensus statement as “an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.” This definition recognises a number of features: that a patient’s stable state may fluctuate from day to day without signifying an exacerbation; that an exacerbation should be acute in onset (as the natural history of the disease is usually chronically progressive); and that the change in condition necessitates a change in treatment.

Despite the adoption of this consensus definition, COPD remains a clinical diagnosis with no established criteria for assessing severity. Following the 1999 Aspen Lung Conference dedicated to COPD, a panel of North American and European respiratory physicians proposed a severity staging system to sub-classify COPD exacerbations based on health-care utility [130]. A patient who is able to manage in his/her own environment is classified as mild and a patient who requires hospitalisation is classified as having a severe exacerbation. While easy to apply, this staging system adds little to practical clinical management.

Prior to the GOLD document, the most commonly used definition of COPD was provided by Anthonisen et al, based on the presence of increased dyspnoea, sputum volume and purulence in a patient with COPD [131]. Depending on whether one, two or all three symptoms are present, the exacerbations were classified Anthonisen Type I, II or III. The
Anthonisen criteria were particularly used to describe patient symptoms in studies examining antibiotic utility [132]. However, as clinicians are unlikely to withhold antimicrobial therapy in any acutely unwell COPD patient even without signs and symptoms overtly suggestive of bacterial infections, the Anthonisen sub-classifications were not commonly used outside of research settings.

More recent consensus guidelines from North America, Europe and Australasia recommend assessment of COPD severity based on multiple inputs including the patient’s pre-exacerbation status, other co-morbidities, physical examination, arterial blood gas measurements and other laboratory test results [1, 2, 133, 134]. Suggested criteria for hospital-based treatment include increased symptom intensity, severe underlying COPD, evidence of cardiac or respiratory failure, failure to respond to initial treatment, older age and poor social support. However, apart from the presence of respiratory acidosis, altered mental status and the need for ventilatory support, these criteria are predominantly based on expert panel consensus and retrospective observations (levels B to D evidence) rather than outcome-based controlled trials (level A evidence). Accordingly, all of these consensus documents acknowledge that the major outstanding issue of when to treat an exacerbation at home and when to hospitalise the patient remains unsatisfactorily answered and currently clinicians still have to rely on clinical acumen to determine the diagnosis and optimal treatment.

1.2.2 Summary of Current Treatment of Acute Exacerbations

The cornerstones of COPD exacerbation management are inhaled bronchodilators, systemic corticosteroids, antibiotics, oxygen and ventilatory support. However, reviewing data from
the original trials of these commonly used therapies does challenge our rationale for their use as these often quoted seminal studies had significant methodological flaws and involved small numbers of patients. Meta-analyses of these small trials are available summarising the benefits of most recommended treatments in COPD exacerbations. A brief summary of the evidence supporting current guidelines is as follows:

1.2.2.1 Systemic Corticosteroids

Systemic glucocorticoids have been shown to improve symptoms and lung function, reduce the length of hospital stay and the proportion of treatment failures [135-137]. The Veterans Affairs Cooperative Study of Systemic Corticosteroids in COPD Exacerbations (SCCOPE) randomised 271 patients with a COPD exacerbation to receive either 2 weeks of systemic corticosteroids, 8 weeks of systemic corticosteroids or placebo and found that systemic therapy significantly reduced the treatment failure rate as defined by physician assessment (23% versus 33%, p = 0.04) and hospital stay (8.5 versus 9.7 days, p = 0.03) compared to placebo. The 8-week course was not superior to the 2-week course but patients receiving longer courses experienced more steroid related side effects. There was no difference between the treatment groups at 6 months post exacerbation [136].

A meta-analysis including 10 studies and 959 patients found that the method of administration (oral or parenteral) did not modify the beneficial effects of corticosteroids [138]. This is not surprising as oral corticosteroids are rapidly absorbed (peak effect within 1 hour of ingestion) with good bioavailability. However, intravenous formulations are still commonly given in patients with severe exacerbations or poor oral intake. A recent Cochrane meta-analysis including 11 studies and more than 1000 patients found similar
symptomatic benefits and no significant difference in overall mortality between these routes of administration. This analysis also concluded that the optimal dose and duration of corticosteroid treatment is still to be determined [137].

1.2.2.2 Bronchodilators

Inhaled short-acting beta-2 adrenergic agonists are the treatment of choice for relief of dyspnoea with the addition of an anticholinergic agent if required [1, 2, 133]. Even though these bronchodilators are recommended in major guidelines and ubiquitously used in patient treatment, the evidence of their benefits arise from largely from clinical experience and a handful of studies involving small numbers of patients. A meta-analysis performed in 2001 found only 14 randomised studies addressing the use of bronchodilators in this setting [139]. The authors concluded that the bronchodilation effects (as measured on spirometry) of inhaled short acting beta-2 agonists and anticholinergics are comparable but both agents are more effective than intravenously administered bronchodilators (e.g. methylxanthines and sympathomimetics). The effect of adding an anticholinergic to a $\beta_2$ agonist was small and the toxicity profile of intravenously administered methylxanthines renders this class of drug potentially harmful without significant benefits. No significant difference in delivery modality for inhaled bronchodilators (nebulisers versus metered-dose inhalers) was found.

A Cochrane meta-analysis performed by the same group in 2002 assessed the efficacy of anti-cholinergic agents compared to short-acting $\beta_2$ agonists in treating acute exacerbations of COPD [140]. Four studies (n=199) were included in the analysis, which found no significant differences in the improvement of short term or overnight FEV$_1$, PEFR or PaO$_2$
between the two agents. No significant additional increase in lung function was found with combination treatment compared to either agent alone.

The optimal dose of salbutamol was only recently examined in a randomised controlled fashion by Nair et al in 2005. Dose-response curves were compared following regular nebulisation of 2.5 or 5mg of salbutamol in 86 patients hospitalised for acute exacerbation of COPD [141]. The study found no significant differences in maximal bronchodilation, rates of recovery (as measured by lung function) or lengths of hospital stay. However, this study did not include salbutamol at doses less than 2.5mg and the optimal therapeutic dose may well be less than this.

More recent research has focused on the effects of long acting bronchodilators such as formoterol and tiotropium bromide. A small pilot study found synergistic effects of these two agents following 24 hours of drug administration during mild to moderate exacerbation [142]. Whether longer acting formulations provide acute benefits compared to short acting agents is not known.

1.2.2.3 Antibiotics

Antibiotics are frequently prescribed in acute exacerbations although their benefits, particularly in patients without purulent sputum, are still controversial [133]. Current literature suggests that 50-70% of all exacerbations are due to respiratory infections (including bacterial, atypical organisms and viral) [143-146]. Bronchoscopic sampling of the lower respiratory tract has found 30-50% of exacerbations are associated with pathogenic bacteria, most commonly *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella*
*catarrhalis*, *Haemophilus parainfluenzae* and *Pseudomonas aeruginosa* [147-150]. Bacterial involvement, particularly with gram negative rods (such as *enterobacter* and *Proteus* species), are more common in patients with severe exacerbations and requiring ventilatory assistance [151].

A meta-analysis of nine randomised, placebo-controlled studies of antibiotic treatment found a small but statistically significant reduction in duration of symptoms and days lost from work with antibiotic treatment [152]. A Cochrane review on this topic published in 2006 included only two further randomised studies conducted in the last decade [153]. Ram et al concluded in this review that any antibiotic therapy significantly reduced mortality (RR 0.23, 95%CI 0.10 – 0.52) and treatment failure (RR 0.47, 95% CI 0.36- 0.62) in moderate to severely ill patients. This translated into a number-needed-to-treat of 8 patients to prevent one death. Diarrhoea was the most common adverse effect.

The above findings should be interpreted with caution as there was significant heterogeneity in patient selection, antibiotic choice and standardisation of other treatments that may have influenced outcome (such as the use of systemic corticosteroids).

Furthermore, many of the studies included in the above meta-analyses are more than 20 years old, prior to the emergence of multi-resistant respiratory pathogens.

Two large retrospective studies were recently published that also provide supporting evidence for the use of antibiotic treatment in acute COPD exacerbation. Roede et al identified 842 patients with COPD exacerbations via the Second Dutch National Survey of General Practice (2001-2005) and found that adding oral antibiotics to systemic
corticosteroid therapy significantly reduced time to subsequent exacerbations, particularly in patients with frequent exacerbations [154]. This study, which was a retrospective database study and therefore susceptible to treatment selection and recording bias, also found that all cause mortality was reduced in patients treated with both antibiotics and corticosteroids compared to patients treated with antibiotics alone.

More recently, Rothberg et al conducted a large retrospective cohort study to compare outcomes of patients treated with antibiotics in the first 2 days of hospitalisation compared to those treated later or not at all [155]. The authors identified 84,621 patients hospitalised in American health care facilities via ICD-9 codes and defined treatment failure with a composite endpoint of: initiation of mechanical ventilation, in-patient mortality, or readmission for acute exacerbation of COPD within 30 days of discharge. After multivariable adjustment, the risk of treatment failure was lower in antibiotic-treated patients (OR 0.87, 95%CI 0.82-0.92) compared to not treated patients, but had a higher rate of readmission for Clostridium difficile (0.2 and 0.1% respectively).

Although this study was retrospective and cannot account for all potential sources of bias, it nevertheless provided the first large scale, robust evidence of the benefits of antibiotics in a large, unselected group of patients. A randomised trial is unlikely to be conducted from this point forward as it may not be considered to be ethical given the results of the studies described above. The research focus now needs to be directed towards identifying patients at higher risk of bacterial involvement who would benefit most from antibiotics. Several recent studies have focused on using biomarkers such as C-reactive protein and procalcitonin for this purpose with some success [156-158]. A later chapter in this thesis
explores the use of clinical scores and cardiac biomarkers for risk stratification in COPD exacerbation. This is an approach that may lead to targeted antibiotic therapy. In the meantime antibiotic use appears to be appropriate for almost all hospitalised patients with COPD exacerbations.

1.2.2.4 Supplemental Oxygen and Non-Invasive Ventilation

Logically supplemental oxygen therapy may provide significant benefits to hypoxaemic patients with acute exacerbations of COPD. Supplemental oxygen relieves pulmonary vasoconstriction and right heart strain, lessens myocardial ischaemia and thus improves cardiac output and systemic oxygen delivery. Much of the literature supporting the use of emergency oxygen therapy for patients with dyspnoea or respiratory failure is more than 30 years old [159-161]. Remarkably, a review of the literature revealed few randomised controlled studies directly assessing oxygen titration in acute exacerbation of COPD. In a prospective crossover study, Agusti et al administered oxygen via nasal prongs (2-4L/min) or Venturi mask (24-28%) to 18 patients with acute respiratory failure secondary to exacerbation of COPD. Both methods of administration improved arterial oxygen saturation to >90% immediately without causing significant adverse events [162].

There is substantial interest in the risk of developing hypoventilation and worsening hypercapnia following supplemental oxygen therapy in patients with existing chronic respiratory disease. Various mechanisms have been put forward to explain this phenomenon – including depression of respiratory drive, ventilation/perfusion mismatch and the Haldane effect [163, 164]. The above mentioned cross-over study by Agusti et al and a number of other observational studies have shown that hypercapnic respiratory
failure secondary to oxygen administration is a rare adverse event. However, controlled oxygen with blood gas monitoring is preferable to high flow oxygen therapy to reduce this risk [133, 162, 165, 166].

Non-invasive ventilation (NIV) is now the treatment of choice in patients with type II respiratory failure during an exacerbation of COPD [1, 2, 133]. This is supported by high quality evidence based on randomised controlled studies [167-170]. The Cochrane review on this issue (updated in 2004) assessed 14 randomised controlled studies including 758 patients and found that compared to usual medical care, NIV reduced overall mortality (RR 0.52, 95%CI 0.36-0.76), rate of treatment failure (RR 0.48, 95% CI 0.37 – 0.63), length of intensive care and hospital stay and improved blood gas and ventilatory parameters [171]. Patients that do not respond adequately to NIV require intubation and mechanical ventilation and clear management guidelines are in place for these patients [2, 133].

1.2.3 Current Standards of Care during Hospitalisation

In 1987, the American Thoracic Society became the first national special interest group to produce clinical practice guidelines for the management of COPD exacerbations [172]. Since then a number of guidelines have been developed based both on available evidence and, when this is lacking, expert panel consensus [2, 71, 133]. Despite their availability, there has been minimal published research into whether they are adhered to in clinical practice. Other important questions also remain, including: whether regional differences in treatment exist; whether there is a positive relationship between patient volumes and the quality of care; whether any disparities in treatment exist between sexes or among ethnic groups;
whether care provided by respiratory specialists is better than generalists and whether adherence to guidelines improves patient outcome.

Most available data paints a disappointing picture with wide variations in clinical assessment and treatment and inadequate medical documentation. The BTS Standards of Care subcommittee audited 1400 admissions for acute exacerbation of COPD from 38 hospitals in 2001 [173]. They demonstrated significant deficiencies in both the assessment and treatment of patients hospitalised with acute exacerbations of COPD compared to the recommended BTS guidelines. Only 53% of all cases had confirmation of clinical diagnosis by spirometry, 79% had arterial blood gas assessments, 65% were assessed by chest radiography, formal prescription of oxygen was documented in only 64% and fewer than 15% of patients in acidotic hypercapnic respiratory failure received ventilatory support. Large variations between centres were also found. For example, a comment on chest radiograph was recorded in 98% of cases in one centre and in no cases in another. The greatest variations from the guidelines were noted in patients not under the care of a specialist respiratory physician. The authors concluded that the general standards of care in this audit fell below guideline recommendations and that there was substantial room for improvement in clinical practice. The data from this study were also analysed for predictors of poor outcome and these results will be discussed separately in section 1.3.1 [174].

Similar variations in care have also been reported by Irish, Australian and a number of North American centres [175-177]. The largest retrospective cohort study to examine the appropriateness of care received by patients to date was reported by Lindenauer et al in 2006 [178]. Nearly 70,000 patients hospitalised for acute exacerbations of COPD in 360 US
hospitals in 2001 were identified by ICD-9 coding. Most patients underwent chest radiography (95%), received supplemental oxygen (91%), bronchodilators (97%), systemic corticosteroids (85%) and antibiotics (85%). Overall 33% of patients received “ideal care”, which was arbitrarily defined a priori as all 5 of the recommended care elements (chest radiography, oxygen, bronchodilators, corticosteroids and antibiotics) and none of the non-recommended ones (mucolytics, methylxanthines and chest physiotherapy). This study also observed a wide variation in adherence to guidelines between units. Interestingly, hospitals in the western parts of the United States were far more likely to provide ideal care but neither teaching status nor annual patient throughput were associated with appropriateness of care. Hospitals where the patient population was predominantly black performed poorly and accounted for nearly all of the ethnic disparities seen in this study.

In New Zealand, the only study to examine the care of patients admitted for COPD exacerbation was performed more than 15 years ago. Neill et al audited 95 consecutive cases admitted to Christchurch Hospital and compared the care received by patients against local treatment recommendations [179]. The majority of patients were documented to have received recommended treatment: oxygen therapy 87%, bronchodilator therapy 90%, antibiotics 77%, corticosteroids 95%. However, significant deficiencies in patient assessment, diagnosis and documentation were identified. Importantly, this study lacked information on patient baseline characteristics and disease severity, and was thus unable to judge if the treatment was appropriate and compares their findings against international norms.
In summary, most guidelines recommend that patients who present with an acute exacerbation of COPD undergo diagnostic evaluation that includes chest radiography and arterial blood gas analysis, followed by treatment with controlled supplemental oxygen, short-acting bronchodilating agents, systemic corticosteroids, antibiotics and when required, non-invasive positive pressure ventilation. Mucolytic agents, sputum examinations, methylxanthine bronchodilators and chest physiotherapy are of uncertain or no benefit based on current evidence.

There is remarkably little data available on clinical adherence to the guidelines and current information suggests that there is a wide variation in adherence. As the guidelines are evidence based to maximise patient outcome, one might infer that poor guideline adherence may lead to poorer patient outcome. Locally, the only available statistics are nearly two decades out of date, and have not been compared with internationally recommended standards. Furthermore, substantial advances to COPD treatment has been made since the study by Neill et al was published. Chapter two of this thesis outline the results of a retrospective study designed and conducted to accommodate some of these criticisms. The local data are compared to available international cohorts in this chapter.
1.3 Risk Prediction in COPD

Morbidity and mortality prediction in COPD is fraught with difficulties. COPD is an umbrella term that includes a diverse spectrum of disease phenotypes (such as predominant bronchitis, predominant emphysema and frequent exacerbators) and heterogeneous systemic manifestations. By nature of the risk factors of the disease, such as smoking and age, there are also often numerous co-morbidities causing increased morbidity and mortality [66]. Indeed, a large proportion of patients with COPD die from cardiovascular causes rather than decompensated respiratory failure [110, 180]. Despite this, COPD is still associated with a very high mortality both with exacerbations in the short term as well as with chronic disease so a practical risk prediction model could be very useful to help direct treatment and resources and help with advice to patients.

Airflow obstruction (as defined by reduced FEV$_1$ and FEV$_1$/FVC ratio) is commonly used to measure severity in COPD. However, this measure by itself is a poor predictor of mortality because of substantial disease heterogeneity. For example, a recent review of more than 2000 patients with COPD found only a weak correlation between FEV$_1$ and both mortality and need for hospitalisation [181]. Apart from severe airflow obstruction, a number of other clinical and functional characteristics have been used to classify COPD severity and predict poor prognosis. These include dyspnoea [182], malnutrition [183], muscle mass [184], health-related quality of life [185], presence of hypoxaemia or hypercapnia, reduced exercise capacity [186] and physical activity [187, 188], inspiratory capacity [189],
hospitalisation related to COPD exacerbation [126] and the degree of pulmonary hypertension [190].

Celli et al hypothesised that a multi-dimensional grading system would be a better outcome predictor than airflow obstruction alone in a multi-centre landmark study published in 2004 [191]. They first retrospectively evaluated 207 outpatients with stable COPD and determined that the four factors that best predicted mortality were BMI (B), airflow obstruction (O) measured by the percentage of predicted post-bronchodilator FEV$_1$, reports of dyspnoea (D) assessed by the modified Medical Research Council (MMRC) score, and exercise tolerance (E) quantified by 6 minute walk distance. The variables were graded from 0 to 3 (0 or 1 for BMI) and a composite score out of 10 was termed the BODE Index. The index was then prospectively evaluated in a cohort of 625 patients (median follow up 28 months). The hazard ratio per point increase in the BODE index was 1.34 (95% CI 1.26-1.42, $p < 0.001$) for all cause mortality and 1.62 (95% CI 1.48-1.77, $p < 0.001$) for respiratory-related mortality. In this cohort, the BODE index better predicted death than FEV$_1$ alone (the area under the receiver operator characteristic curve was 0.74 for BODE score and 0.65 for FEV$_1$ alone).

Along the same lines, Estaban et al developed the Health-Activity-Dyspnoea-Obstruction (HADO) score after prospectively analysing the characteristics and outcome of 611 stable COPD patients over 3 years [192]. Unlike the BODE index which requires an objective exercise test, patient perceived overall health and physical function were assessed by questionnaire. Airflow obstruction was assessed by spirometry. The score correlated well with health-related quality of life parameters as measured by the generic SF-36 Healthy
survey [193], the St George Respiratory Questionnaire [194] and the Chronic Respiratory Questionnaire [195]. Although easier to use than the BODE index, the mortality predictive value for the HADO score was only marginally better than FEV$_1$ alone (c-statistic for mortality at 3 years = 0.682 for HADO score and 0.647 for FEV$_1$ alone). Indeed, the superior predictive value of the BODE index particularly for patients with more severe COPD (FEV$_1$ less than 50% predicted) was demonstrated in a recent head-to-head longitudinal comparative study based on stable outpatients [196].

A number of other multi-dimensional indices have subsequently been proposed for prognostic purposes in stable COPD. These include modifications of the BODE index – the mBODE (replaces 6 minute walk distance with $V'\dot{O}_2$ [197], e-BODE (BODE plus exacerbations) [198], and ADO (age, dyspnoea and FEV$_1$), which have all shown better predictive value for mortality than FEV$_1$ alone [199]. The main barrier to most BODE index based scoring systems is that objective exercise capacity, whether by 6 minute walk distance or other testing, is relatively resource intensive and not always practically obtainable. Furthermore, the BODE index was developed using mortality as the sole outcome without taking into consideration events such as exacerbations and hospitalisations which have important implications both for the patients’ quality of life or health-related costs.

These limitations led to the development of non-exercise test related prognostic models. Briggs et al proposed the COPD Prognostic Index (CPI) in 2008 based on pooled data from 12 randomised controlled trials involving over 8800 patients [200]. The CPI is a composite score from quality of life, FEV$_1$, age, sex, BMI, exacerbation and cardiovascular disease history and was predictive of mortality, hospitalisation and exacerbation frequency.
However, the relatively complex calculations required to obtain this score has translated into low clinical utility. The CPI also has yet to be prospectively tested beyond the initial derivation and validation cohorts.

Most recently, Jones et al proposed the DOSE index (dyspnoea measured by MRC dyspnoea scale, airway obstruction measured by FEV₁, smoking status and prior exacerbation history) after retrospectively examining 5 multinational general practice datasets involving 1200 patients [201]. Using a cut-off of four points or less, higher DOSE scores are predictive of mortality, hospitalisation, rates of exacerbation and rescue treatment requirements. Again, the DOSE index has yet to be externally tested. However, a recently published small pilot study (n=11) using the DOSE index to guide outpatient management has shown a non-significant reduction in the number of hospital admissions and total bed days compared to the same reference period in the previous year [202]. Clearly, more robust evidence of clinical benefit is required.

All of these clinically practical risk prediction tools are still being developed and validated in stable COPD. However, the need for a similar bedside scoring tool in the management of acute exacerbations remains unfilled. The reality is that most health care resources are used during exacerbations of COPD and optimised management of these patients remains one of the most challenging aspects in the COPD treatment. Further, most of the above described prediction models require components such as exercise tolerance or lung function tests that are unlikely to be available to physicians when evaluating patients in the emergency department.
Ideally, a clinical risk prediction model for COPD exacerbation should have the following characteristics: reliability and accuracy, information routinely or easily obtainable in the emergency department and does not require invasive testing, complex calculations or expensive data collection.

1.3.1 Currently existing risk prediction in Acute Exacerbation of COPD

Although an exacerbation of COPD is now conventionally defined as a “sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment” [130, 203], there is no diagnostic gold standard. Severity criteria that are applicable in stable disease (such as spirometry) may be inappropriate or unavailable in the acute setting. Currently, clinicians mainly rely on clinical acumen to determine the diagnosis and optimal treatment.

Patients commonly present with a wide range of symptoms and severity, and treatment requirements may range from unscheduled primary care visits to emergency department presentations to in-patient or intensive care. Hospitalisation for COPD exacerbations usually occurs during advanced stages of disease and the mortality is between 5 to 15% [4, 204, 205]. Moreover, many patients with COPD have other concomitant medical conditions and are thus at higher risk of morbidity and mortality [66]. Objective assessments of exacerbation severity and risk are useful to better direct clinical resources, facilitate discussions between patients and their families and may lead to improved patient outcome. Indeed, current international clinical guidelines recommend consideration of symptom severity and presence of co-morbidities when deciding whether a patient should be hospitalised for acute exacerbation of COPD [133, 206]. However, no prospectively tested
risk stratification framework is available and these recommendations are based on level D evidence (Panel Consensus) only.

A number of patient and disease characteristics associated with poor outcome in acute exacerbations have been identified primarily in previous cohort studies. A summary of the key studies is as follows:
The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT) was a prospective cohort study involving five US centres and 8,300 patients [207]. One of the nine disease groups included in SUPPORT were hypercapnic patients in acute respiratory failure secondary to severe exacerbation of COPD. Subgroup analysis of these patients (n=1,016) identified high APACHE score, low BMI, older age and poor functional status as important predictors of poor outcome (death and dependency status) at 180-day follow up [204]. The authors developed a model for computing survival probability following severe exacerbation of COPD based on characteristics of the first 600 consecutive patients and validated the model on the next 416 patients (Figure 1.1). Even though the prediction formula was too cumbersome to adopt for clinical use, this study provided the first high quality evidence that probability of survival can be predicted from readily available clinical information in this group of patients. This study provided important credibility to the concept that prognostication models may provide useful information to patients and their physician when making health-care decisions.
**Figure 1.1** Formula for computing the probability of survival following acute exacerbation of COPD as proposed by Connors et al.

\[
\text{Probability (} T \geq t \text{)} = S(t)^{X\beta}
\]

Where \( T \) = survival time in days, \( t \) = an arbitrary time, \( e \) = the base of the natural logarithm.

\[X\beta = 0.967886 + (0.028876 \times \text{acute physiology score}) + (0.016583 \times \text{age}) - (0.050168 \times \text{PaO}_2/\text{FiO}_2) - (0.058050 \times \text{BMI}) - (1.417586 \times \text{normal BMI}) + (0.155408 \times \text{the Katz Activities of Daily Living scale score}) - (0.257863 \times \text{albumin}) - (0.362817 \times \text{congestive heart failure as cause}) - (0.397354 \times \text{cor pulmonale}) + (0.110696 \times \text{number of comorbid illnesses}).\]

The baseline probability, \( S(t) \), is estimated for the following intervals:

- 30 days \quad 0.8807
- 60 days \quad 0.8294
- 90 days \quad 0.7815
- 120 days \quad 0.7539
- 150 days \quad 0.7250
- 180 days \quad 0.6996

From the paper appendix of Connors *et al* [204]
One of the largest cohorts to exclusively examine COPD exacerbations was reported by Roberts *et al* on behalf of the BTS standards of care subcommittee in 2002 [174]. 1400 admissions for acute exacerbations (identified from coding) from 38 hospitals were audited for patient characteristics, investigation findings, clinical management and outcome. Predictors for increased hospital length of stay, risk for readmission and mortality at 3 months after admission were assessed by logistic regression. The three most important independent predictors for mortality were poor performance status, deranged arterial pH on admission and the presence of bilateral leg oedema. Other predictors of mortality included age 70 years or more, arterial oxygen saturation <86% on oximetry and use of assisted ventilation. Poor performance status and older age also strongly predicted increased length of stay, alongside reduced FEV₁. The authors acknowledged that there were likely other important predictors of poor outcome that were not assessed in this study – as the 3 most important prognostic factors only accounted for 15% of the variability in mortality. The main limitation of this study was its retrospective nature, and any inclusion and data collection bias associated with this study design. It is also important to note the substantial advances in acute COPD exacerbation treatment, particularly the widespread adoption of non-invasive ventilation since these data were collected in September 1997 [167, 168, 208]. Only 13% of potentially eligible patients received ventilatory support in the cohort and this likely negatively impacted on the prognosis of the patients. However, despite these limitations, the scope of the cohort in terms of the large number of patients and hospitals involved means that it is still the benchmark against which standards of care and patient characteristics of future cohorts are compared.
Since then, multiple (predominantly retrospective) cohorts and cross-sectional studies have reported similar albeit inconsistent findings. Increased mortality in hospital or following hospitalisation for acute exacerbation of COPD has been reported in association with a number of disease and patient characteristics. These include indicators of chronic disease severity and reduced physiological reserve: advanced age [126, 209-214], reduced lung function, long term oxygen [215] and corticosteroid therapy[209], reduced BMI [210, 214, 216, 217] and reduced serum albumin [217, 218]; markers of exacerbation severity: APACHE score [210, 218-220], PaCO₂[126, 209, 217, 221], FiO₂/PaO₂ ratio[217], dyspnoea grade [211, 216, 221], requirement for mechanical ventilation [210, 219]; and other independent factors such as social isolation and quality of life [215, 222], income status [212] and existing co-morbidities [212, 214, 222]. However, the risk factors and their impact varied significantly from cohort to cohort and no consistent risk assessment system has been developed.

There are few prospective studies designed to directly address risk prediction in this population. Groenewegen et al prospectively recruited all patients admitted in 1999 to the pulmonology ward of the University Hospital Maastricht for acute exacerbations of COPD [209]. The in-hospital mortality was 8% (n = 13 of 171 patients) and 1-year mortality was 23%. Independent predictors of survival were identified by Cox regression, which found long-term oral corticosteroid use to be the most important predictor of mortality (relative risk = 5.07, 95% CI 2.03 – 12.6, p = 0.0005) followed by blood gas derangement (both PaCO₂ & PaO₂) as well as advanced age. Lung function, BMI, and other co-morbidities were not significant predictors after multi-variate adjustments. In contrast, a Turkish cohort of 205 prospectively recruited patients with similar baseline characteristics and overall survival (in-
hospital mortality of 8.3%) reported reduced BMI and serum albumin to be important parameters associated with poor outcome alongside blood oxygen tension and duration of disease history [217]. Neither study was able to make specific recommendations in regards to management decisions from their results. The results from these two recent prospective cohorts demonstrate the problems and inconsistencies seen in the literature thus far.

The COPD and Asthma Outcome Study (CAOS) was a prospective multi-centre cohort study conducted in the United Kingdom across 92 intensive care units and 3 respiratory high-dependency units involving 832 patients [223]. Although initially designed to assess quality of life after discharge from ICU, the authors were able to develop a prediction model for prognosis using the data collected [224]. The primary endpoint was survival at 180 days post admission to ICU. Multivariate analysis found older age, male sex, longer time in hospital prior to critical care admission, poorer functional status, mid-arm circumference ≤ 25cm and increased acute physiology score were significantly predictive of mortality. The final prediction model incorporated varying weightings of these factors to give a 180-day mortality risk of between 1.9% (lowest possible risk) and 97.2% (highest possible risk) (Figure 1.2).

The CAOS study acknowledged that reversible and irreversible airways obstruction may be difficult to differentiate in the acute setting and accommodated for this uncertainty by allowing clinicians to include all patients with airways obstruction and make a clinical categorization (of either asthma or COPD or a mixture of both) upon study entry. 635 out of 832 (76%) patients recruited were categorized as having “pure COPD” (n = 80 for “pure asthma” and n = 117 for “mixture of asthma and COPD”) and patients with “pure COPD” had
worse prognosis compared to other patients (RR = 3.01, 95% CI 1.38 – 6.59). The inclusion of this clinical categorization is important because this gave the study results practical clinical applicability and made the subsequent results more generalisable than other carefully selected “pure COPD” cohorts.

Interestingly, the CAOS study design also included the prospective estimation of 180-day survival rate by the clinician within 24 hours of admission to ICU. Compared to actual survival rates, clinicians tended to underestimate the probability of a favourable outcome particularly for patients with the worst prognosis. In fact, for the 10% of patients with the poorest prognosis – clinicians predicted a 180-day survival of only 3% compared to the actual survival of rate of 36% [225]. The impact of prognostic pessimism on clinical decision-making and patient outcome is unknown. However it is plausible that some patients may be inappropriately excluded from intensive care or a trial of ventilation on the basis of such prognostic pessimism. This possibility and the survival results from the CAOS study highlight the importance of having a workable and accurate bedside prognostic tool to aid clinical decision making in this group of patients.

The risk prediction tool proposed by the CAOS authors still requires external validation. The model is also untested against other existing prognostic models such as the APACHE score or the SUPPORT model. The other major limitation of this study is the lack of complete data collection. Although recruitment and entry into the UK Case Mix Programme database were prospective, the information was extracted retrospectively and there were thus a moderate number of missing data. Finally, although the authors were able to design a prognostic score sheet that simplified the risk calculations, the prediction tool still involved 9
Figure 1.2 COPD outcome prediction model for likelihood of death within 180 days of admission to ICU as proposed by the CAOS study authors [224].

\[
\text{Risk} = \frac{e^{-3.95 + 0.0375 \times S}}{1 + e^{-3.95 + 0.0375 \times S}}
\]

Where \( S = 25 \) if diagnosis = COPD, or 18 if COPD-or-asthma
+10 if sex = male
+45 if function = bed/chair bound or 17 if housebound or 11 if restricted
+11 if has atrial fibrillation
+4.5 \times \) days since hospital admission (up to a maximum of six)
+1.8 \times \) years of age over 70
+2.6 \times \) cm mid-arm circumference less than 30
+1.6 \times (15–Glasgow coma score, i.e. difference between best possible and actual)
+COPD acute physiology score

(continued over page)
Figure 1.2 cont.
The authors also provided a scoring sheet for practical use:

For each variable in T1 (diagnosis, sex etc), write in the ‘Score’ column the weight given to the patient’s category.

For each variable in T2 (days since admission etc), write the patient’s value in the ‘raw value’ column. Transform to the ‘new’ value using the rules given. Thus:
   - A ‘raw’ number of days of eg 3 is unchanged; anything above 6 becomes 6 (the maximum)
   - A ‘raw’ age of eg 75 becomes 75–70 = 5; anything below 70 becomes 0 (the minimum)
   - A raw MAC of eg 20 becomes 30–20 = 10; anything above 30 becomes 0 (the minimum).
   - A raw Glasgow Coma Score of eg 12 becomes 15–12 = 3.

Multiply each ‘new’ value by its weight and put the answer in the ‘Score’ column.

For Acute Physiology Score in T3 there is no weight; just write the APS in the ‘Score’ column.

Calculate the Total Score and read off the estimated risk from T4.

<table>
<thead>
<tr>
<th>T1</th>
<th>Category</th>
<th>Weight (pick one)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis at time of decision to admit to critical care</td>
<td>COPD</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COPD + asthma</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>asthma only</td>
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<td></td>
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<tr>
<td>Sex</td>
<td>male</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Physical function in 2 weeks before hospital admission</td>
<td>bedbound or chairbound</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>housebound¹</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>restricted²</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>fully mobile and living without assistance</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
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<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>0</td>
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</table>

<table>
<thead>
<tr>
<th>T2</th>
<th>Raw value</th>
<th>Transform</th>
<th>New value</th>
<th>Weight (multiply)</th>
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</thead>
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<tr>
<td>Days since hospital admission</td>
<td>(maximum 6)</td>
<td>4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Age – 70 (minimum 0)</td>
<td>1.8</td>
<td></td>
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</tr>
<tr>
<td>Mid arm circumference (cms)</td>
<td>30 – MAC (minimum 0)</td>
<td>2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>15–GCS</td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| T3 | COPD Acute Physiology Score | |

**T4**

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>10</td>
<td>2.7%</td>
</tr>
<tr>
<td>20</td>
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<td>75</td>
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<tr>
<td>190</td>
<td>96.0%</td>
</tr>
<tr>
<td>200</td>
<td>97.2%</td>
</tr>
</tbody>
</table>

1. Cannot get out of house unassisted or gets out of the house rarely; able to perform self-care but unable to do heavy chores such as house cleaning; cannot live alone; may be institutionalized
2. Able to live on their own and get out of the house to do basic necessities but severely limited in exercise ability
parameters from a detailed medical history and examination and 7 further parameters from venous and arterial blood sampling. While arguably less cumbersome than the calculations required for the SUPPORT model, the CAOS prediction tool has so far failed to gained wide spread acceptance partly because it is considered too unwieldy for use at the bedside. Furthermore, as the CAOS study only included patients admitted to intensive care, it is unlikely to be generalisable to most exacerbations.

Thus, at beginning of the new millennium, clinicians are still predominantly relying on clinical acumen to determine diagnosis and base treatment decisions when assessing patients with acute exacerbations of COPD. Several risk factors for poor prognosis are known but the only risk prediction models available have yet to be externally validated and are too complex to translate into everyday use at the bedside. Clinician prognostic pessimism remains a concern and therefore an objective tool to predict risk may improve outcome in the patients who may otherwise be under-treated. Compared to other acute respiratory conditions such as community-acquired pneumonia, assessment and prognosticating in acute exacerbation of COPD still has much room for development.

1.3.2 Risk Prediction in Community Acquired Pneumonia

Risk prediction and stratification models are much better established in community-acquired pneumonia than COPD. Like COPD, patients with community acquired pneumonia present with a spectrum of disease severity (from mild and self-limiting to potentially life threatening) and timely risk stratification and implementation of appropriate treatment is perhaps the single most important clinical decision in the overall management of this disease. Accurate assessment of illness severity can also help direct limited health
resources and may potentially reduce inappropriate hospitalisation and associated morbidity and costs. For these reasons, the routine use of risk prediction models are now incorporated into conventional treatment guidelines for community acquired pneumonia and there is ongoing research interest into the role of prediction models in patient management and their impact on outcome [226, 227].

The two main models in use are the Pneumonia Severity Index (PSI), which is widely used in North America and Australia, and the modified British Thoracic Society (BTS) assessment tool, which has been more commonly adopted in Europe and New Zealand.

The PSI is a two-step scoring system using 20 variables and was developed for identifying low-risk patients or potential candidates for outpatient treatment [228]. It was based on derivation and validation cohorts of more than 14,000 and 38,000 hospitalised patients with community acquired pneumonia respectively and its ability to predict mortality has been confirmed in multiple subsequent studies [229-232]. The PSI stratifies patients into 5 mortality risk classes, and on the basis of associated mortality rates, it has been suggested that risk class I and II patients should be treated as outpatients and risk class IV and V patients should be treated as inpatients [227]. More recent studies assessing the impact of using the PSI on guiding treatment decisions and hospitalisation found significantly reduced rates of hospitalisation but no differences in overall mortality [229-233].

The modified BTS assessment tool is better known as the CURB65 score and relies on five clinical parameters for scoring. It was originally proposed by the BTS in 1987 after a prospective study in 25 British hospitals involving 453 patients [234]. Patients with any two of the following had a 21-fold increased risk of death at 30 days compared to patients with none of these risk factors: respiratory rate ≥ 30/min, diastolic BP ≤ 60mmHg and urea >
7mmol/L. Neill et al formalised this into the CURB score in 1996 after prospectively
assessing 255 consecutive patients admitted to Christchurch Hospital with community
acquired pneumonia [235]. Using four simple criteria, patients can be classified into severe
or non-severe groups and the score predicted mortality with an overall sensitivity of 95%
and specificity of 71%. Most recently, Lim et al coined the name “CURB65” score after
enrolling 1068 patients (from the United Kingdom, New Zealand and the Netherlands) with
community acquired pneumonia to derive and internally validate the prediction rule [236].
The CURB65 score assigns less prognostic importance to co-morbid illnesses and uses 5
simple variables (four bedside observations and one blood test) to assign a score on a six-
point scale (0 to 5). The presence of confusion, elevated serum urea > 7mmol/L, respiratory
rate ≥ 30/min, low systolic (<90mHg) or diastolic (<60mmHg) blood pressure and age > 65
years were each assigned one point. Scores less than two are considered to indicate low
risk, with a 30-day-mortality rate of 0-2.1%; a score of two is considered intermediate risk,
with a 30-day mortality of 5-9.2%; and a score of greater than two is considered high risk,
with a 30-day mortality of 14-57%. Scores in the high risk group predicted mortality with an
overall sensitivity of 75.0% and specificity of 74.9%. The authors suggested that patients
with low risk scores may be treated as outpatients, and those with scores of more than 3
may require intensive care.

A simplified version that does not include urea and thus does not require laboratory testing
is the CRB65 score [237]. This and other adaptations of the CURB65 score have been shown
to perform similarly in terms of prediction of in-hospital death with some performing better
in specific patient populations. For example, the Severe Community Acquired Pneumonia
(SCAP) score, which also takes into account blood gas derangement and multi-lobar
consolidation, has been shown to be better at identifying patients evolving towards more severe disease [238]. Similarly, specific scores such as SOAR – systolic blood pressure, oxygenation, age and respiratory rate [239]; CURSI and CURASI – confusion, urea, respiratory rate and (adjusted) shock index [240] have been developed that may be more sensitive in older patients or patients from residential care.

Direct comparisons of predictive values between various CURB65 models and the PSI have generally shown that the PSI is more sensitive but less specific than the CURB65 score with higher positive predictive values [237, 241-244]. This is confirmed in a recent meta-analysis which included 23 studies and more than 23,000 patients [245]. The analysis found the pooled sensitivity for mortality were 90% (95% CI 87-92%) and 62% (95% CI 54-70%) for the PSI and CURB65 score respectively while the pooled specificity were 53% (95% CI 46-59%) and 79% (95% CI 75-83%) respectively. The area under the receiver-operating characteristic curve was 0.81 for PSI and 0.76 for CURB65 score. The negative predictive values were similar - 98% (95% CI 98-99%) for the PSI and 95% (95% CI 93-97%) for CURB65, indicating that the clinical difference when applying these scores as “rule-out” tests are likely to be small. This is important because it directs decisions on which patients can be managed as outpatients.

Although in theory the poorer sensitivity of CURB65-based scores suggest that some patients may be under-diagnosed and managed as non-severe when they are in fact at higher risk of death, this has to be weighed against the practical aspects and resource implications of implementing the two different scores. The PSI requires the clinician to gather 12 parameters from a detailed medical history and physical examination, and then
derive 7 parameters from venous and arterial blood sampling and chest radiography. Although most of these parameters are available in hospital settings and can be negotiated through a computer-based calculator, estimating the PSI still present significant practical challenges to the time-poor clinician. In contrast, the CURB65 score only requires one blood test and 4 other clinically based observations and is easily calculable using fingers on one hand. However, unlike the PSI, the impact of using CURB65 based scores on guiding treatment and deciding whether a patient should be hospitalised has not yet been prospectively assessed.

Locally, the Australian Community Acquired Pneumonia study prospectively assessed 882 presentations and developed a model via multiple logistic regression to predict the need for intensive ventilatory and/or vasopressor support [246]. Acronymed SMART-COP, the tool included low systolic blood pressure (2 points), multilobar chest radiography involvement (1 point), low albumin level (1 point), high respiratory rate (1 point), tachycardia (1 point), confusion (1 point), poor oxygenation (2 points) and low arterial pH (2 points). Although SMART-COP out-performed both the PSI and the CURB65 score when predicting the need for ventilatory or cardiovascular support in this cohort, it was not better at predicting mortality. Moreover, this prediction model also requires further external validation.

A major criticism of risk prediction rules in community acquired pneumonia is the lack of evidence that making treatment decisions based on these scoring systems improve patient outcome. However, as these scores are predominantly designed to identify patients who are at low risk of death, a better measure of success may be improved health economics without compromising patient outcome. There is now fairly robust evidence supporting the
safety of using the PSI to support discharge decisions in hospital emergency departments for patients presenting with community acquired pneumonia. Multiple prospective cohorts and randomised controlled studies have documented reduced hospitalisation rates and improved patient satisfaction while observing no change in mortality or complication rates [229-233].

These prediction rules are useful adjuncts to help clinicians in the choice of site for treatment but they are not a substitute for good clinical judgement. As with all clinical situations, factors other than predictors included in prognostic model may be important when making an admission decision. For example, low risk patients may have other medical or psychosocial contraindications to outpatient therapy. Patient preference, ability to maintain oral intake, cognitive impairment and social support all influence clinical decision making. Finally it is important to recognise that these prediction rules are only applicable to adult populations with community acquired pneumonia, and their development excluded children, pregnant women, immunocompromised patients and patients with hospital acquired or aspiration pneumonia.
1.3.3 Applicability of community acquired pneumonia scoring systems to acute exacerbations of COPD

Risk predictions in community-acquired pneumonia may provide useful insights into risk prediction in acute exacerbation of COPD. Importantly, the two conditions share common aetiological and pathophysiological features. Microbiological infection of the lung and subsequent breakdown of host defences underpin the pathology of community-acquired pneumonia [247, 248]; and although host-pathogen interactions in COPD exacerbation are still incompletely understood, infections undoubtedly play a significant role. Bacterial inflammation – both via new strain acquisition and increased pathogen load of pre-existing strains, are implicated in a significant proportion of COPD exacerbations [149, 249] and are associated with more intense pulmonary and systemic inflammation compared to non-bacterial episodes [250]. COPD itself is a predisposing risk factor in the development of community acquired pneumonia with colonisation of potentially pathogenic organisms in the respiratory tract, poor host defence systems such as impaired mucociliary clearance and abnormal inflammatory response to insults [251, 252]. Similarly, risk factors for community acquired pneumonia such as cigarette smoking, pre-existing heart and lung disease, inhaled glucocorticoid therapy and chronic bronchitis often co-exist in patients with COPD [253, 254].

Many components in existing prediction rules for community-acquired pneumonia indicate existing or impending cardiorespiratory decompensation. This is a common end pathway to poor outcome that may also result from other pathologies. It is therefore plausible to extrapolate that a score composed of such components may also be predictive of mortality in acute exacerbations of COPD. This hypothesis was explored in the retrospective study.
described in chapter two of this thesis. A study was then designed to prospectively test the risk prediction score. These results are outlined in chapter three.
1.4 Biomarkers of Cardiac Dysfunction in COPD

Many patients with chronic obstructive pulmonary disease (COPD) also have cardiovascular disease and have a high risk of cardiovascular mortality [255-260]. The complex interplay between systemic inflammation, airflow obstruction and their extra-pulmonary effects in COPD are incompletely understood. Circulating biochemical markers of inflammation/infection, cardiac and other end-organ dysfunction have been investigated in chronic stable disease and acute exacerbations. Measurement of these biomarkers in peripheral blood of COPD patients has emerged as a new tool with multiple potential utilities: i) they may improve patient care by facilitating severity assessment and help track response to treatment; ii) they may contribute to the understanding of disease pathophysiology; and iii) repeatable, reliable and accurate biomarkers may be used as surrogate endpoints for disease state or quality of life in intervention-related research and enable shorter “proof of concept” studies.

1.4.1 B-Type Natriuretic Peptide and Its Derivatives

B-type or brain natriuretic peptide (BNP) was originally isolated from porcine brains after observations of its potent relaxant effect on chick rectum [261]. In humans, like atrial natriuretic peptide (ANP), this family of peptides are synthesized by human cardiomyocytes in response to ventricular wall stretch due to pressure and volume overload [262]. Natriuretic peptides have several actions: i) down-regulating the sympathetic and the renin-angiotensin-aldosterone system; ii) increasing renal diuresis and natriuresis through direct effects on the distal tubules; iii) promoting vasodilatation via smooth muscle relaxation thus reducing peripheral vascular resistance; and iv) inhibiting cardiac remodelling by inhibiting
myocyte hypertrophy [263-266]. The human BNP gene is located on chromosome 1 and encodes the 108 amino acid prohormone – proBNP. The prohormone is cleaved into the biologically active 32 amino acid C-terminal BNP and the inactive N-terminal segment (NT-proBNP) [264]. NT-proBNP has a longer plasma half-life than BNP (approximately 120 minutes and 20 minutes respectively) and is also commonly measured via immunoassay [267]. Apart from receptor binding, the main mechanism of eliminating circulating BNP and NT-proBNP is renal clearance [264].

1.4.1.1 BNP and NT-proBNP in Cardiac Disease

Elevated BNP /NT-proBNP levels are now well established as markers of left ventricular dysfunction. The landmark Breathing Not Properly multi-national study established BNP as an accurate diagnostic tool for congestive heart failure in acutely dyspnoeic patients presenting to the emergency department [268]. In that study, BNP levels < 100pg/mL carried an 89% negative predictive value for excluding heart failure and by themselves were more accurate than any other single clinical or laboratory feature when compared to a clinical gold standard. NT-proBNP has demonstrated similar diagnostic accuracy in this setting and in a large prospective study, NT-proBNP levels <300pg/mL carried a 99% negative predictive value for ruling out cardiac failure [269].

In addition, BNP/ NT-proBNP are strong prognostic markers in patients with varying degrees of left ventricular failure. A large systematic review pooled results from 19 studies and found that in patients with left ventricular failure, the relative risk of death increased by 35% for every 100pg/mL increase in BNP [270]. This linear relationship between BNP levels and risk is present in chronic stable patients both before [271, 272] and after [273-275]
Natriuretic peptides also have prognostic value in coronary artery disease. In acute coronary syndrome, multiple studies have demonstrated that both BNP and NT-proBNP are powerful predictors of early and late mortality [280-282]. This risk is additive and independent to that indicated by increased troponins [283] and has been linked to the degree of myocardial ischaemic burden [284]. Interestingly, the prognostic value of BNP and NT-proBNP have also been demonstrated in patients with chronic stable coronary disease[285] and patients who are at risk of, but have not developed symptoms of heart disease [286]. Furthermore, multiple cohorts have observed BNP elevation in a range of other primary cardiac problems including cardiac amyloidosis [287], restrictive cardiomyopathy and pericarditis [288], atrial fibrillation (independent of left ventricular dysfunction) [289] and valvular heart disease [290-292].

1.4.1.2 BNP and NT-proBNP in Right Ventricular Dysfunction and Lung Disease

Natriuretic peptide elevations in association with right ventricular dysfunction and pulmonary disease have been less well explored. In the absence of significant left heart disease, BNP/ NT-proBNP levels are directly associated with right ventricular work load and levels of these cardiac biomarkers increase with the degree of right ventricular dysfunction [293, 294]. Specifically, elevated levels of BNP/NT-proBNP have been identified in right ventricular pressure and volume overload secondary to pulmonary hypertension, pulmonary thromboembolic disease and undifferentiated end-stage lung disease and hypoxaemia [295-
Further, increased levels of BNP/NT-proBNP are associated with a poorer prognosis in patients with pulmonary arterial hypertension and pulmonary thromboembolic disease [298-300].

Subsequently, Leuchte et al prospectively recorded BNP levels in 176 consecutive patients undergoing right heart catheterisation with clinically stable chronic lung disease [300]. Approximately half of the cohort had predominant chronic obstructive ventilation impairment (n = 82), and the other had predominant restrictive ventilation impairment (n = 94). Elevated BNP levels (expressed as normalised BNP ratio > 1 after adjusting for age and sex) identified significant pulmonary hypertension (mean pulmonary artery pressure > 35mmHg) with a sensitivity of 85% and specificity of 88%. During a mean follow-up period of 10.6 ± 0.68 months, 31 patients (18%) died, and more non-survivors had elevated normalised BNP ratios than the survivors (55% and 25% respectively, p = 0.01). Moreover, BNP remained an independent predictor of death after adjustments for lung function, the degree of hypoxaemia and pulmonary arterial hypertension. This study concluded that elevated BNP is an useful marker for pulmonary hypertension in chronic lung disease and may reflect impending right heart failure. The authors postulated that secretion of BNP may be driven by its natriuretic effects as well as its direct vasodilative and anti-proliferative properties in response to pulmonary hypertension.

1.4.1.3 BNP and NT-proBNP in Chronic Obstructive Pulmonary Disease

In patients with COPD, there is often concomitant left and right heart dysfunction. Many patients have co-existing atherosclerotic disease due to shared risk factors such as advanced age and tobacco smoking [66]. In parallel, chronic respiratory insufficiency and cor
pulmonale can eventually lead to biventricular failure. Indeed, differentiating between a predominantly cardiac and pulmonary cause of dyspnoea remain challenging yet critical to the attending physician, as opposite treatments such as β-blockers or β-agonists may be prescribed depending on the diagnosis.

As discussed previously, BNP and NT-proBNP were initially established as diagnostic tools for cardiac dysfunction in dyspnoeic patients who are at risk of both processes. A post-hoc subgroup analysis from the Breathing Not Properly study found that using a cut-point of 100pg/mL, BNP measurements carried a sensitivity of 93% and specificity of 77% for the diagnosis of congestive heart failure in patients with a history of obstructive pulmonary disease [301]. This was prospectively confirmed by Morrison et al [302] who compared the utility of BNP levels against a diagnosis of CHF confirmed by two independent cardiologists (who were blinded to BNP results) based on the Framingham criteria [303]. They found similar diagnostic statistics – BNP > 94pg/mL carried a sensitivity of 86% and specificity of 98% for ruling out congestive heart failure, and the area under the receiver operating characteristic curve for sensitivity and 1-specificity was 0.97. However, the authors pointed out patients with marked cor pulmonale were likely to have higher BNP values than patients who do not have heart failure and suggested higher cut-points (such as 300-600pg/mL) to increase the negative predictive value in this subgroup of patients. In the general population, it is accepted that levels of 100pg/mL for BNP and 450pg/mL for NT-proBNP are accurate for ruling in the diagnosis of acute congestive heart failure and 50pg/mL for BNP and 300pg/mL for NT-proBNP are accurate for ruling out this diagnosis [304].
Christ et al showed that regardless of the cause of acute dyspnoea, BNP levels are strong and independent predictors for poor outcome [305]. Long term follow up data from the B-type natriuretic peptide for Acute Shortness of Breath EvaLuation (BASEL) study found the risk of death is strongly associated with increased BNP levels at initial presentation to the emergency department in both patients with cardiac related dyspnoea (n=236, log rank p = 0.001) and non-cardiac related dyspnoea (n = 217, log rank p < 0.001). Although patients with cardiac causes of acute dyspnoea had higher levels of BNP (mean BNP 297pg/mL and 138pg/mL respectively, p < 0.001), relative risk of death for patients with plasma BNP levels > 500pg/mL was 4.0 at 18 months (95% CI: 2.3 – 6.8, p <0.001) even in patients with non-cardiac causes of dyspnoea. This suggests that an elevated BNP may be a reflection of overall ill health (and thus increased cardiac demand) rather than cardiac disease alone.

Very high NT-proBNP levels have been observed in a cohort with severe COPD exacerbations (requiring mechanical ventilation) and co-existing left ventricular dysfunction [306]. Abroug et al prospectively examined 148 patients admitted to intensive care with an exacerbation of COPD and determined any associated cardiac dysfunction via standardised echocardiography and right heart catheterisation in selected patients. They found that although higher levels of NT-proBNP were observed in patients with associated left ventricular dysfunction, there was also supraphysiological release of these peptides in patients with severe AECOPD but no evidence of left ventricular dysfunction. The authors postulated an additive effect with both left and right ventricles contributing to the natriuretic peptide levels found in acute exacerbation of COPD and suggested NT-proBNP levels of < 1000pg/mL to rule-out left ventricular dysfunction and > 2500pg/mL to rule-in left ventricular dysfunction in this group of patients.
Building on this work, Stolz et al examined plasma BNP levels during acute exacerbation and post recovery [307] in patients enrolled in the Procalcitonin Guidance of Antibiotic Therapy in COPD Study [308]. BNP levels were significantly elevated during acute exacerbation compared to recovery (65pg/mL and 45pg/mL respectively, p <0.001.) and were significantly higher in patients requiring ICU treatment compared to those who did not (105pg/mL and 60pg/mL, p = 0.007). BNP levels also correlated well with the duration of ICU stay (rho = 0.218, p = 0.005) and in-hospital stay (rho = 0.242, p= 0.002). Interestingly, BNP levels did not discriminate between those patients with more severe disease at baseline as defined by GOLD classes (p = 0.180), type of exacerbation according to Anthonisen criteria (p = 0.188), or patients with positive and negative sputum bacterial cultures (p = 0.511).

In contrast to the authors’ expectations, this study did not find a statistically significant correlation between BNP level and mortality at any time points after the acute exacerbation. The authors hypothesised that this may be due to a lower prevalence of pulmonary arterial hypertension and right ventricular dysfunction in patients with COPD compared to other respiratory conditions. The study did however have a major limitation - only patients included were those randomised for the procalcitonin guidance of antibiotic therapy study rather than an unselected group of patients diagnosed with AECOPD. Of 288 patients identified during the study period, 208 patients were enrolled. More unwell patients with multiple co-morbidities were more likely to be excluded from randomisation and thus not included in the analysis [308]. This selected population likely has less co-morbidities compared to the general COPD population. Indeed, this may explain the cohort’s low mortality rate (in hospital deaths, n= 5 (2%) and the low proportion of deaths attributable to cardiac causes (15%) over the two-year follow up period.
Plasma BNP levels in patients with stable COPD were explored in two small cross sectional studies. In the first, Rutten et al examined BNP and NT-proBNP levels using different assays in elderly patients with COPD [309]. They found overall mildly raised levels of natriuretic peptides. More recently, Inoue et al compared BNP levels in patients with stable COPD to those in asthmatics and healthy controls. Mean plasma BNP was higher in COPD patients than in normal subjects or patients with asthma (41pg/mL, 15pg/mL and 17pg/mL respectively, p < 0.0001). There was no correlation between BNP levels and pulmonary function or hypoxia but moderate correlation with cardiac ejection fraction (rho = 0.4, p = 0.019) and pulmonary artery systolic pressure (rho = 0.5, p = 0.004). Importantly, patients with higher BNP levels (defined as 2 standard deviations above normal mean i.e. > 34pg/mL in this cohort) had shorter times to next exacerbation (p = 0.029). BNP levels during exacerbations were also higher than during stable disease (80pg/mL and 41pg/mL respectively, p = 0.004). This study did not observe a statistically significant correlation between BNP elevation and overall mortality. However, it was limited by the small sample size (n = 60, 10 and 30 for COPD, asthma and healthy controls respectively) and the small number of events during the 3-year follow up period (13 patients with COPD had exacerbations).

Finally, a small physiological study that measured plasma BNP levels during rest and exercise found a transient rise in COPD patients with normal right ventricular function (21pg/mL and 38pg/mL before and after exercise respectively, p < 0.05) but no change in healthy age-matched controls (13pg/mL and 15pg/mL before and after exercise respectively, p > 0.05) [310]. Interestingly, the exercise capacity did not differ significantly between groups. Although limited by the small sample size and lack of information on pulmonary
haemodynamic response during exercise, the results of this study suggest that increases in BNP in may signal reduced cardiac physiological reserve in patients with COPD.

In summary, BNP and NT-proBNP act as markers of severity in COPD exacerbations where raised levels correlate with an increased requirement for ventilation and intensive care admissions. The only published prospective study to examine the relationship between BNP levels and mortality was limited by selection criteria and a small number of deaths and did not find a correlation. Other studies to date have been limited by retrospective data collection and small sample size. It is still unknown whether elevations in BNP/ NT-proBNP levels in these patients are due predominantly to left or right ventricular overload. However, there is evidence to suggest that an elevated BNP in an acute exacerbation of COPD is a marker of abnormal cardio-respiratory reserve.
1.4.2 Cardiac Troponins

Troponin is a complex of three regulatory proteins located on the actin filament and is integral to calcium mediated cardiac and skeletal muscle contractions [311]. Specific isoforms of Troponin I (acts by inhibiting actin activated myosin ATPase activity) and Troponin T (acts by binding tropomyosin) are specific to cardiac muscles and can be detected by highly specific antibodies [312]. Hence these proteins can be used as specific markers for cardiac damage. The cardiac isoform of Troponin C (acts by binding calcium ions) also occurs in slow-twitch skeletal muscles, thus is not used in assays for the diagnosis of cardiac injury [313].

Cardiac Troponin I and T are released from cardiac myocytes during prolonged ischaemia with degradation of the cell membrane and have now supplanted creatinine phosphokinase-MB isoenzyme (CK-MB) as the analytes of choice in acute coronary syndrome [314]. Indeed, a joint committee of the European Society of Cardiology and American College of Cardiology in 2000 issued new criteria that acknowledged elevations in troponins as fundamental to the diagnosis of acute myocardial infarction [315, 316].

Although highly sensitive, it is well recognised that troponin elevation is not synonymous with cardiac damage from atherosclerotic coronary artery disease [317, 318]. Elevated troponin levels have been observed in many other conditions including and not limited to: atrial fibrillation and other tachyarrhythmias [319, 320], congestive heart failure [321-324], myocarditis [325], pericarditis [326], cardiac toxins [327, 328], direct cardiac trauma[329, 330], cardiac infiltrative disorders [331], sepsis [332-334], pulmonary embolism [335, 336], stroke [337], pneumonia [338] and COPD [339].
Troponin elevations in these conditions are likely due to general myocardial injury rather than acute coronary arterial thrombosis and can be broadly categorised into i) demand ischaemia - where there is an oxygen supply-demand mismatch due to increased cardiac work; ii) myocardial supply ischaemia – where there is a supply-demand mismatch due to reduced myocardial supply; iii) direct myocardial damage such as trauma and cardiac toxins and; iv) myocardial strain causing ventricular wall stretch [317, 318].

1.4.2.1 Elevated Troponins in Respiratory Disease

In respiratory disorders, abnormal serum troponins have particularly been observed in association with pulmonary thromboembolic disease and there is on-going research into the role of troponin-based risk stratification in this setting. Two recent meta-analyses have yielded comparable results. In the first, Becattini et al analysed short term mortality of 1985 patients from 20 studies presenting with acute pulmonary embolism [340]. Overall short term mortality was higher in patients with elevated cardiac troponins compared to patients with normal troponins (19.7% and 3.7% respectively, OR 9.44, p < 0.00001) and the results were consistent for troponin I or T and in prospective as well as retrospective studies. However, this analysis was criticised for pooling data of haemodynamically unstable and normotensive patients, as systemic hypotension is a well established risk factor associated with high short-term mortality [341].

More recently, Jiménez et al specifically examined the prognostic value of troponins in normotensive patients with acute symptomatic pulmonary emboli [342]. Pooled results from 9 studies including 1366 patients found that elevated troponin levels were associated
with a 4.3-fold increased odds of overall mortality (95%CI 2.13 – 8.50). The results were consistent for both troponin I (OR 2.65, 95%CI 1.26 -5.56) and troponin T (OR 8.60; 95% CI 1.56 – 6.45). Although this meta-analysis confirmed the association between elevated serum troponin levels and adverse outcomes, the authors noted that neither the positive nor the negative likelihood ratio of an elevated or normal troponin level in a haemodynamically stable patient with acute PE is extreme enough to alter management.

1.4.2.2 Elevated Troponins in COPD

In patients with acute exacerbations of COPD, elevated serum troponins are not uncommon. In a database review of 144 patients with elevated cardiac troponins but normal coronary arteries on cardiac catheterisation, 4% were identified as having COPD exacerbation as the cause of troponin rise, compared to 1.4% due to acute pulmonary emboli and 8% due to congestive heart failure [317].

Harvey et al reviewed consecutive patients admitted to hospital for treatment of COPD over a 12 month period and found troponin elevation in 58 of 235 (25%) presentations in which troponin was measured [339]. Despite the troponin result, only 7 of the 58 patients were diagnosed with acute coronary syndrome and new ischaemic ECG changes were uncommon. Although there was no difference in baseline lung function, patients with elevated troponins had greater abnormal measures of ventilatory function compared to patients with normal troponins, with lower pulse oximetry (86% and 90% respectively, \( p = 0.003 \)), more acidosis (pH = 7.34 and 7.40 respectively, \( p = 0.002 \)), and more hypercapnia (pCO\(_2\) = 58mmHg and 49mmHg respectively, \( p = 0.04 \)). Patients with elevated troponins also had a longer hospital length of stay (mean days = 5 and 3 respectively, \( p < 0.001 \)). The
authors speculated that acute COPD exacerbations may lead to myocardial injury and troponin release and that detectable elevation of troponins may reflect the severity of the underlying exacerbation and systemic stress.

These results have been replicated in other retrospective cohorts: Brekke et al examined the largest of these, which included 897 patients hospitalised for acute exacerbation of COPD identified by discharge coding and analysed mortality data from a national registry [343]. Elevated troponin T (as defined by values ≥ 0.04µg/L) was significantly associated with increased all-cause mortality during and after hospitalisation (hazard ratio = 1.64, p = 0.006; median follow up = 1.9 years). Importantly, there was a difference in survival between patients who had troponin T measured and those who did not (univariate hazard ratio = 1.25, p = 0.04) and the multivariate analysis employed an exposure propensity score in order to adjust for this. Patients who had troponin T measurements also had poorer lung function (p = 0.016), increased pulmonary congestion on chest radiograph (p = 0.003), and were more likely to report a history of ischaemic heart disease (p = 0.002) and aspirin prescription (p = 0.016).

Similar results correlating cardiac troponin I elevation and long term survival have been observed recently in Israeli and Portuguese COPD cohorts [344, 345]. The main limitation of these retrospective observations is possible sampling bias – patients were more likely to have troponin measured if they had clinical evidence of cardiac dysfunction. Indeed, the separation in survival between patients who had troponin measurements and those who did not as reported by Brekke et al suggest strongly that this is the case. Given this clinician introduced sampling bias, the utility of troponins in acute exacerbation of COPD is difficult
to discern from existing retrospective data and prospective studies including unselected patients are needed.

The only study to date to prospectively assess cardiac troponins in exacerbation of COPD has been limited to critically ill patients [346]. Baillard et al recorded troponin I levels in 71 consecutive admissions to intensive care and found elevated levels in nearly 1 in 5 patients. Positive troponin I (defined as > 0.5µg/L) was a strong predictor of in-hospital death independent of ventilation parameters, cardiovascular history or treatment strategies (odds ratio 6.52, p = 0.03). However, whether these findings can be generalised to all patients presenting with an exacerbation of COPD is not known, as the cohort mainly consisted of severely ill patients requiring ventilatory support - 51% non-invasive ventilation, 34% invasive ventilation and only 15% received no ventilation. This study has also been criticised for not taking markers of acute heart failure into account [347]. Nevertheless, this small study provides the first prospective evidence that troponin elevation on admission is a strong prognostic factor independent to previously known risk factors and may indicate a new avenue of disease treatment.

In summary, elevated levels of cardiac troponins and natriuretic peptides appear to indicate increased COPD severity and perhaps need for intensive treatment. The prognostic value of these cardiac biomarkers was investigated in a prospective cohort study. Chapter four of this thesis outline the findings of the study.
1.5 The β-adrenergic Receptor and Treatment Implications in COPD

COPD and cardiovascular disease are both common. They share a number of risk factors, including tobacco smoking, which is the major modifiable risk factor for both conditions. Because of their prevalence and common risk factors, a large number of patients have COPD and co-existing cardiovascular disease. Current prevalence estimates of 25-33% of COPD in patients with chronic heart failure is set to increase with the rising prevalence of chronic airways disease [348, 349].

The use of pharmacological agents targeting the β-adrenergic receptor is a source of ongoing controversy in these patients. β-blockers (agonists) are used widely to treat cardiovascular disease while β-agonists are commonly used to treat airways obstruction. Traditionally patients with obstructive airways disease have been excluded from β-blocker therapy and consequently, their potential cardiovascular benefits. This section of the review examines the physiological basis for this concern, recent evidence that supports the use of β-blockers in this group of patients and potential interactions with concomitant use of these agents.

1.5.1 The Human β-adrenergic Receptor

β-adrenergic receptors belong to the seven subunit transmembrane family of G-protein coupled receptors that bind to catecholamines and initiate a sympathetic signalling cascade [350, 351]. Three subtypes of β-adrenergic receptors have been identified in humans: β₁, β₂ and β₃. Homology between subtypes is high, with 65 to 70% amino acid and structural components being identical [352].
1.5.1.1 \( \beta \)-adrenergic receptors and human airways

\( \beta_2 \)-adrenergic receptors are widely distributed in smooth muscle cells in the human airway. They are also found in other sites of the pulmonary system including cells that mediate inflammatory and innate immunity and type I and type II alveolar cells [353]. \( \beta_2 \)-receptor stimulation leads to airway smooth muscle relaxation. However, prolonged stimulation causes a reduction in receptor responsiveness seen in vivo as desensitisation [354]. \( \beta_1 \)-adrenergic receptors are present submucosal glands within the airways and alveolar walls [355].

1.5.1.2 \( \beta \)-adrenergic receptors and the human cardiovascular system

\( \beta_1 \)-receptors are found in both atrial and ventricular myocytes and cardiac electrical conduction tissues. They are key participants in triggering and regulating cardiac contractility. Stimulation of these receptors leads to an increased cardiac chronotropic and inotropic state. \( \beta_1 \)-stimulation also facilitates renin release from juxtaglomerular cells. Renin is a potent vasoconstrictor, thus \( \beta_1 \)-stimulation can indirectly causes systemic vasoconstriction [351, 356].

\( \beta_2 \)-receptors are also present in normal hearts. The ratio of \( \beta_1:\beta_2 \) receptors is approximately 70:30 in the atria, 80:20 in the ventricles and approaching 50:50 in the sino-atrial node [357, 358]. This is consistent with physiologic studies that implicate \( \beta_2 \)-receptors as important regulators of cardiac chronotropism [359, 360].
1.5.2 β-adrenergic receptors as therapeutic targets

Modulation of β-receptor function has long been a therapeutic target for pulmonary and cardiac disease. Traditionally, the β-adrenergic based therapies for obstructive lung disease and cardiovascular disease were viewed as completely antagonistic.

In obstructive lung diseases such as asthma and COPD, volumes of published evidence support the use of both short-acting and long acting β2-agonists to induce bronchodilation [2, 361-363]. In patients with stable COPD, β2-agonists alone and when used in combination with inhaled corticosteroids, improve quality of life and exercise capacity and reduce the frequency and severity of exacerbations [180, 364]. As discussed previously in this review, bronchodilation therapy with β2-agonists is an important component of standard treatment in acute exacerbation of COPD [2, 133].

On the other hand, β-blockade is a major therapeutic approach for the management of a number of cardiovascular disorders, including hypertension [365], acute coronary syndrome [366-368], congestive heart failure [369, 370] and cardiac arrhythmias [371]. Indeed, commenting on Sir James Black’s Nobel-winning work to discover propranolol, the first β-blocker, the Nobel Committee in 1988 reminded us that these agents were “the greatest breakthrough when it comes to pharmaceuticals against heart illness since the discovery of digitalis 200 years ago” [372]. β-blockade may be beneficial through a number of different mechanisms including: reduction of catecholamine exposure; restoration of inotropic and chronotropic responsiveness of the myocardium by upregulating receptor density; reduction of circulating level of vasoconstrictors and thus reducing afterload; improvement in LV remodelling and reduction in myocyte oxygen consumption; reduction in ventricular ectopic
frequency and normalisation of upregulated gene products involved in inflammation and muscle hypertrophy [373-378].

These two diametrically opposed treatment pathways have been somewhat mitigated by pharmacological receptor subtype targeting - the so-called cardio-selective/β₁-blockers and β₂-agonists. However, in practice things are not as simple as one might hope and considerable overlap exists both in receptor subtype selectivity and patient requirements.

Although β₂-agonists have higher affinity for β₂ receptors, they also bind to β₁ receptors. The β₁:β₂ selectivity ratio varies from 1:1 (isoprenaline), 1:120 (formoterol), 1:1375 (salbutamol) to 1:85 000 (salmeterol), thus some β₂-agonists may induce β₁ activity at higher doses [352]. Furthermore, the above described receptor homology and the presence of β₂ receptors in the heart translate into clinically significant cardiac related β-activation seen clinically as tachycardia and palpitations. The classification of cardio-selective and non-selective β₁-blockers is also oversimplified as this selectivity is reduced at large doses and all β₁-blockers may affect the airway when their concentrations are high enough [379, 380]. Some β-blockers also have intrinsic sympathomimetic activity and may down-regulate β-receptors which, in patients with bronchial hypersensitivity, further reduces the bronchodilator responses to any subsequently inhaled β₂ agonists [381, 382]. Table 1.2 and Table 1.3 summarise the effects of different classes of β-blockers and β-agonists.

Thus, despite clear evidence of their effectiveness and mortality benefit, clinicians are often reluctant to prescribe β-blockers in patients with co-existing airways disease [383-385]. This is reflected in practice guidelines which commonly list obstructive airways disease as contra-
indications to β-blocker use and acute cases of bronchospasm after non-selective β-blocker administration are often cited to support this position [386-388]. For example, the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) lists “bronchial asthma or other obstructive lung disorders” as the first contra-indication for all selective and non-selective β-blockers, ahead of other contra-indications such as bradycardia and cardiogenic shock [389]. In the United Kingdom, the British National Formulary advices that β-blockers should not be given to patients with obstructive airways disease except in rare situations, where there is no alternative, a cardio-selective β-blocker may be given under “extreme caution and under specialist supervision” [390].

However, accumulating evidence over the last decade has demonstrated that the theoretical safety concerns for cardio-selective β-blockers (which has a 20-fold affinity for the β₁ receptor compared to the β₂ receptor) are less relevant in the clinical setting when compared to their substantial proven benefits. Salpeter et al examined the effect of these medications in a Cochrane meta-analysis last updated in 2005 by pooling results from 20 randomised controlled studies (n = 278) [391]. They demonstrated that cardio-selective β-blockers, given as a single dose or for longer durations, produced no significant change in lung function (as measured by FEV₁) or respiratory symptoms compared to placebo. Importantly, the findings were unchanged in subgroup analyses of patients with severe COPD (FEV₁ < 1.4L or < 50% of normal predicted values). A meta-analysis examining the effect of these medications in patients with reversible obstructive airways disease have yielded similar results [392].
Table 1.2 Summary of pharmacological properties of selected β₂-agonists

| β₂ agonist | Affinity for β₂ -AR (Ki, nmol/L) | Efficacy at β₂-AR | Potency at β₂-AR || Selective ratio (β₁-AR/β₂-AR) | Approximate onset of action (min) | Approximate Duration of action |
|------------|---------------------------------|------------------|-----------------|-----------------|---------------------------------|--------------------------------|
| Isoprenaline | 200 | (100) | (1) | 1/1 | 2-5 | < 20 min |
| Salbutamol | 2500 | 88 | 1/120 | 1/1375 | 2-3 | 4-6 h |
| Fenoterol | ND | 100 | ND | 1/120 | 2-4 | 4-6 h |
| Terbutaline | ND | 65-85 | ND | ND | 2-4 | 4-6 h |
| Salmeterol | 53 | 63 | 8.5 | 1/85 000 | 30 | > 12 h |
| Formoterol | 76 | 100 | 20 | 1/120 | 2-3 | > 12 h |

AR = adrenergic receptor        ND = no information available

* Relative to isoprenaline as 100%

¶ Relative to isoprenaline
**Table 1.3** Pharmacological characteristics of β-blockers

<table>
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<th>Non-selective (β₁ + β₂ adrenergic receptors)</th>
<th>More selective for the β₁ adrenergic receptor</th>
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<td>No intrinsic sympathomimetic activity</td>
<td>+ intrinsic sympathomimetic activity</td>
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<tr>
<td>Propranolol</td>
<td>Oxprenolol</td>
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<td>Timolol</td>
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<td>Nadolol</td>
<td>Dilevalol</td>
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<td>Sotalol</td>
<td>Prenatelor</td>
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<tr>
<td>Ibutimonide (+ α block)</td>
<td>Labetalol (+α block)</td>
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Intrinsic sympathomimetic activity = partial agonistic effect when bound to the β-adrenergic receptor
Inevitably, the results of these randomised studies and subsequent meta-analyses have been subject to substantial criticism on the basis of potential publication bias, small subject numbers and short duration of study periods. Nevertheless, they provide compelling support that short term cardio-selective β-blockers treatment does not produce adverse respiratory events in these patients. A recent observational study examining β-blocker use in patients hospitalised for exacerbations of COPD has in fact found a mortality benefit. Dransfield et al reviewed admission data of 825 patients admitted for COPD exacerbations and found that in-patient β-blocker use was associated with reduced in-hospital mortality in a multivariate model (OR for death 0.39, \( p = 0.049 \)) [393]. The benefit of β-blockers was observed despite the fact that those who received the drugs were older, had longer hospital stays and a greater prevalence of cardiovascular disease. Standard limitations of a retrospective database review aside, this study suggests that β-blocker use in patients admitted with acute exacerbations of COPD is not harmful and may be associated with benefits. Further prospective assessment is required to examine the potential benefits of β-blockers in this population.

1.5.2.1 Interaction between β-blocker and β-agonist treatments

The impact of prior β-blocker treatment on the response of β₂-agonist bronchodilators is not known. This is an important issue because β₂-agonists are the bronchodilator of choice to relieve symptoms and in treatment of an exacerbation. Since the two agents can competitively bind to the β₂-receptor, it is possible that β-blocker therapy may impede the bronchodilator response to β₂-agonist inhalers. Salpeter et al in the above mentioned meta-analyses found that cardio-selective β-
blockers did not significantly affect airway response to bronchodilators compared to placebo (weighted mean difference 1.12%, 95% CI -4.97–7.20) [391]. However, their analysis was not specifically designed to address this issue and different classes of bronchodilators were included in the analysis. As a β-blocker specifically acts on the β-adrenergic receptor, in theory its use should not impact the effect of other bronchodilating agents such as anticholinergics. The inclusion of these drugs in Salpeter et al’s analysis may have skewed the results towards overall non-significance.

The only study to directly assess bronchodilator response to β2-agonists in this setting was conducted by Van der Woude et al in 2005 [394]. In a double blind, placebo-controlled, crossover study, 15 patients received low doses of a non-selective β-blocker (propranolol 80mg), cardio-selective β-blocker with no intrinsic sympathomimetic activity (metoprolol 100mg), a cardio-selective β-blocker with intrinsic sympathomimetic activity (celiprolol 200mg), or placebo. The non-selective β-blocker significantly reduced the bronchodilator response while both cardio-selective β-blockers did not. However, the doses of the cardio-selective β-blockers were intentionally limited to doses that guaranteed cardio-selectivity – that is, in the lower range of clinically recommended doses. This study design limited the clinically applicability of the findings as many patients are on higher equivalent doses of these cardio-selective β-blockers.

*Chapter five of this thesis describes a double-blind, randomised, three-way cross-over study with a final open-label high dose arm that explores the bronchodilator*
response after selective and non-selective β-blocker treatment in patients with moderate COPD.
Chapter Two

Retrospective Study of Acute Admissions of COPD:

In-patient Management and Outcome

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2.1 Abstract

*Background*

Despite publication of several management guidelines for exacerbations of chronic obstructive pulmonary disease (COPD), there is little information on standards of care in clinical practice. The aim of this audit was to examine the assessment, management and outcome of COPD admissions to a secondary New Zealand hospital during two different seasons. Compliance to current recommendations was examined and compared to available international literature.

*Methods*

All cases of COPD related admissions to Waikato Hospital during the months of May and October 2004 were reviewed. 94 cases (from 84 patients) were audited.

*Results*

General characteristics, clinical features and lung function tests were similar to that of other cohorts. 23% of admissions were Māori and the mean age of Māori admissions were significantly less than that of the non-Māori admissions (57 years and 72 years respectively, \( p = 0.0001 \)). The mean length of stay was 3.4 days, which is significantly less than most other reported hospital lengths of stays related to exacerbations of COPD. 55% of the cohort was admitted more than once for COPD in the 12 months before the index admission. 13% of all admissions received assisted ventilation. Overall 30-day mortality was 8% and 12-month mortality was 31%. Decreased body-mass index was identified as a risk factor for death as was
increased CURB65* score – a simple bedside assessment score which has previously been used to predict mortality in patients with community acquired pneumonia.

**Conclusion**

This audit documented the general patient characteristics, assessment, management and outcome of COPD admissions to a secondary New Zealand hospital. Further investigations into factors contributing shorter length of stay and predictors of mortality are needed.

*CURB65 = one point each for Confusion, Urea > 7mmol/l, Respiratory rate ≥ 30/min, low Blood pressure (systolic <90mmHg or diastolic <60mmHg), age ≥ 65 years.*
2.2 Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in New Zealand. Exacerbation of COPD is a common cause of acute hospital admission and patient outcomes are variable [395]. Previous studies have suggested that variable outcomes in this group are dependent upon patient characteristics and the medical care received [204, 396]. This has lead to the introduction of clinical management guidelines for exacerbation of COPD [133, 172]. However, there have been little validation studies since the publication of such guidelines to confirm actual standards of care in clinical practice.

Hospitalisation for acute exacerbation of COPD usually occurs during advance stages of disease and conveys a high mortality [204, 222]. Various risk factors for poor outcome have previously been identified. In non-ventilated patients however, these have primarily focused on performance status and pulmonary function [174, 209, 212]. These are usually difficult to assess objectively at the bedside of an acutely unwell patient. Risk prediction modelled on data obtained during the initial assessment of an acute presentation (and therefore readily available to the clinician) are more likely to be helpful in the acute assessment phase.

This study examined the characteristics, assessment, management and outcome of COPD admissions to a secondary New Zealand hospital during two different seasons. The results are compared to current recommendations and available data from other cohorts in international published work.
2.3 Methods

Retrospective review was carried out on all cases of COPD-related admissions to Waikato Hospital during the calendar months of May (Autumn) and October (Spring) 2004. Waikato Hospital is a secondary and tertiary referring hospital that covers the central North Island of New Zealand. The secondary referring population is 330,000 and the tertiary population 780,000 [111]. For the purposes of this study, only patients from the secondary catchment area were included. Adult patients admitted with COPD related diagnoses (COPD, emphysema, asthma over the age of 50 and bronchitis) during the calendar months of May and October 2004 were identified using International Classification of Disease (ICD-10) codes (J42-45). The months of May and October were chosen because in a review of overall COPD admissions during 2002-2004, these months appeared to give a representative seasonal snapshot of the population.

All admissions (including re-admissions) were reviewed and those with a physician diagnosis of exacerbation of COPD were included in the analysis. The notes were reviewed retrospectively and data were entered into a customised database (Microsoft Access 97 SR-II, Redmond, USA). Out-of-region and incomplete cases were excluded from analysis and the denominator was altered accordingly. Results are expressed as percentages of either total number of patients or episodes where appropriate. Categorical data were compared using $\chi^2$ or Fisher’s exact tests. Outcome data and 1-year mortality results were obtained from hospital notes and general practitioner records. In cases of ambiguity, follow-up phone calls were made
to the patient and/or their family. Length of stay data were log transformed to approximate a normal distribution.

Patient characteristics and outcome were then compared with studies of similar cohorts in the available published work. Clinical assessment and management were audited against existing guidelines endorsed by local respiratory physicians, which were based on British Thoracic Society (BTS) recommendations [133].
2.4 Results

2.4.1 Patient Characteristics

105 patients were identified using the ICD-10 codes. All case records were obtained and 21 cases were excluded from final analysis as on review of the notes they were incorrectly coded. Overall, 94 admissions involving 84 patients were included in the study. 45 and 49 admissions were identified for May and October 2004 respectively. No patient was lost to follow-up.

General patient characteristics are listed in Table 2.1. 77% (65/84) patients were of European ethnicity while the remainder 23% (19/84) were Māori. Most patients are elderly; the mean age was 69 years (range 39-93 years). More than half were men (57%). There was no significant difference in age between the sexes, however Māori tended to be much younger (mean age 57 years) than their European counter-parts (mean age 72 years). Most patients had a history of smoking (55%) or were current smokers (38%).

Lung function tests were obtained in 78 patients (93%) within 3 months of the admission (before, during or after). The mean FEV\textsubscript{1} was 36% predicted. According to the National Institute for Health and Clinical Excellence (NICE) and BTS criteria current at the time of study, 32% had severe airway obstruction (FEV\textsubscript{1} < 30% predicted), 44% moderate airway obstruction (FEV\textsubscript{1} 30-50% predicted) and the remaining 24% mild airway obstruction [133].
Most patients (71%) had previously been hospitalised for COPD related symptoms and co-morbidities are common. 71% of patients had two or more co-morbidities and the median number of co-morbid conditions was 2.2. The most common co-morbid conditions were cardiovascular (ischaemic heart disease and hypertension, 52% and 18% respectively), anxiety and depression (20%), diabetes mellitus (17%) and malignancies (17%). Of the 67 patients that were known to have COPD, 51 (76%) were diagnosed by the local respiratory outpatient service. The remaining were known their general practitioners. 16 patients were on home oxygen.

Reported health care use for COPD in the 12 months prior to the index admission was also audited. These included primary health care practitioner visits, emergency department visits or hospital admissions. 135 events were recorded. Patients with other COPD-related hospital admission in the last 12 months (55% of total population) were identified to be “frequent users” and these patients accounted for 93% of all episodes of health care resources audited.

### 2.4.2 Assessment and Treatment

The audit examined the presenting complaints documented; “increased dyspnoea”; “increased sputum production”; “increased sputum purulence” and “social issues”.

Other presenting complaints were also counted. Most patients (93%) complained of increased dyspnoea but only about 40% had changes to sputum characteristics (Table 2.2). Social complications from respiratory illness were also common (35%), followed by cough (23%), chest pain (21%) and fever (19%).
A chest radiograph was obtained in 95% (89/94) of admissions. Infective changes less than segmental consolidation were seen in 22% (20/89) of these. An arterial blood gas was carried out in 70% (66/94) of admissions. Reasons for obtaining this were poorly documented. No correlation was found between oxygen saturation as documented by oximeter on presentation and whether an arterial blood gas was carried out. Arterial blood gas results are listed in Table 2.2.

Antibiotics and supplemental oxygen were administered to 80% and 79% of the patients respectively (Table 2.3). The rationale for oxygen administration was poorly documented. No correlation was found between initial supplemental oxygen administration and blood arterial oxygen saturation by oximetry or the results of arterial sampling (rho = 0.05 to 0.16). 78 (83%) patients received steroid therapy. This consisted of oral prednisone (100% of all who received steroid therapy) and intravenous hydrocortisone (11% of group). The median total steroid course length was 4 days.

Twelve (13%) patients required ventilatory support; 2 were intubated and 10 required non-invasive ventilation. Ventilation was more likely in the acidotic patients. Most patients (97%) were treated with inhaled bronchodilators. These include inhaled ipratropium bromide (83%) and salbutamol (94%). A significant proportion received their bronchodilators through spacers (43%). Nebulisers were used in 31% of the patients.
Management of patients was not limited to medical staff. Most patients had documented input by respiratory physiotherapists (65%) as well as specialist respiratory nurses (63%). Approximately 25% of patients were also seen by the clinical dietitian while in-hospital.

A significant proportion of patients were discharged on oral antibiotics (50%) and oral corticosteroids (30%). 15% of patients living at home were discharged to residential-care facilities.

### 2.4.3 Outcome

94% of patients were admitted directly under a specialist respiratory physician. The geometric mean length of stay was 3.4 days. Patients admitted under non-respiratory specialists tended to stay longer (geometric mean 4.9 days). Total in-hospital mortality was 5%, 30-day mortality was 8% and the overall 12-month mortality is 31%.

A low BMI on admission was identified as a risk factor for death. 12-month mortality was compared to BMI on admission (Table 2.4). The mean BMI for patients still surviving at 12 months was 26.6kg/m². The mean BMI for patients who died within 12 months of the index admission was 20.9kg/m².

The CURB65 score developed by Lim et al was retrospectively calculated for each admission [236]. CURB-65 is a six point score, one point each for the presence of
Confusion, Urea > 7 mmol/l, Respiratory rate ≥ 30/min, Blood pressure systolic(<90 mmHg) or diastolic ≤ 60 mmHg), age ≥ 65 years; based on information available at initial hospital assessment. Insufficient data were available to calculate the score for four patients. Patients were stratified into three groups: low-risk (CURB65 = 0-1), medium risk (CURB65 = 2) and high risk (CURB-65 ≥ 3). For patients in this audit, the in-hospital mortality for each of these groups was 0%, 5% and 13% respectively (p = 0.08) and the 12-month mortality was 15%, 30% and 47% respectively (p = 0.04) (Table 2.5). The differences in mortality between the high risk and low risk groups remained significant if age was removed from the score (Table 2.6). Logistic regression analyses were also carried out with BMI and CURB65 score as independent variables for death. This showed the CURB65 score was a better predictor of mortality than BMI. Those with higher CURB65 scores (>2) were more likely to die with an odds ratio of 14.9 for in-hospital death, 10.1 for 30-day mortality and 5.2 for 12-month mortality. Conversely, when adjusted for CURB65 score, BMI was not a significant predictor of death.
2.5 Discussion

COPD is a common cause of acute hospital admissions with variable outcomes. This study of COPD-related admissions to a large New Zealand hospital achieved several goals. Comparisons of patient characteristics and baseline lung function show little difference to other international in-patient cohorts[173, 222, 397]. This suggests that disease severity was similar in the patients of our study and in those of the others. Thus, comparisons of standards of care and outcome can be made.

Of interest is that the Māori patients were significantly younger than Europeans in this cohort of COPD admissions. Potential contributors to this may be the higher rate of cigarette smoking and poor primary health access in the indigenous Māori population. However, the underlying reason(s) is probably complex and warrants further investigation.

This audit examined the standards of care with regards to currently accepted management guidelines for acute exacerbation of COPD [133]. Comparisons were also made with a large British audit published in 2001 and similar standards are achieved in most areas [173]. Diagnosis by spirometry was attempted in most patients (93%) within 3 months of admission compared with 53% found in the BTS Audit. As recommended, high proportions of patients were assessed with a chest radiograph (95%) and arterial blood gas analysis (70%). However, inspired oxygen levels were not frequently noted and bedside peak expiratory flow measurements
were seldom done. Type II respiratory failure was common and a relatively large proportion of patients received ventilatory support (Table 2.7). Previous approaches to COPD-related hypercapnic respiratory failure had often been nihilistic and therefore may be sub-optimal [398, 399]. The BTS audit noted that only 13% of those with acidosis and hypercapnoea received ventilatory support while in our cohort this figure approach 90% [173].

Although our cohort’s in-patient mortality is similar to others reported – 5% versus 2.5 - 11% our cohort’s length of stay is significantly shorter than other reported lengths of stay (mean 3.4 versus 8 – 12 days) [204, 209, 212, 400]. Overall lengths of hospital admission for COPD appear to have decreased in recent years; however, the lengths of stay in this study were still shorter than contemporary similar centres. Data from the NZ Health Round Table report that the mean length of stay of 9 major hospitals around NZ (including Waikato Hospital) for exacerbation of COPD was 5.8 days in Dec 2004 [401]. This we attribute to a number of factors: a) we are more aggressive in regards to treatment of hypercapnoic respiratory failure with assisted ventilation – whether invasive or non-invasive; b) the mean length of steroid use was 4 days in this cohort, which is significantly shorter than other in-patient groups; c) only 31% of patients received bronchodilators by nebuliser in contrast with 91% found in the BTS audit; and d) our multi-disciplinary approach to patient management.

This study highlights the potential of the CURB65 score as a simple bedside scoring tool for risk stratification in acute exacerbations of COPD. A score to rapidly assess
the severity of community-acquired pneumonia was originally developed by the BTS in 1987 and modified by Neill et al into the CURB score in 1996 [234, 235]. This was developed into the CURB65 score in 2003 for greater sensitivity [236]. CURB65 scores have not previously been used to predict outcomes of COPD-related hospital admissions. However, given the significant role that respiratory tract infections play in COPD exacerbations and the use of anti-microbial therapy in treatment, the CURB65 score appears to be an ideal starting point to develop a specific risk stratification tool for COPD. Indeed, in some cases the only difference between the diagnosis of COPD exacerbation and community-acquired pneumonia is the amount of consolidation seen on the chest radiograph.

The prime advantage of the CURB65 score is its simplicity and the ease of application at the bedside. Although other risk factors for poor outcome have previously been described, these have primarily focused on performance status and lung function – which are difficult to assess objectively in the acutely unwell patient [174, 209, 212]. Further prospective studies are needed to confirm the role that the CURB65 score may play in COPD risk-prediction.

There are several limitations to our study that should be acknowledged. The retrospective nature of this review may cause selection bias. Given that almost one-fifth of patients initially identified were excluded because of coding error, it is possible that some patients with COPD exacerbation may not have been identified. Relatively small patient numbers also limit the study – although most results do achieve statistical significance. Finally, because of seasonal variability in respiratory
admissions, the two selected ‘representative’ months may not be truly representative of admissions at other times of the year.

In conclusion, this study documents the general characteristics, assessment, management and outcome of COPD admissions to a secondary New Zealand hospital. An analysis of patient investigations and treatments show that international guidelines were well followed and outcomes were the same as those in other similar cohorts. Further investigations into factors contributing to length of stay and predictors of mortality are needed and a prospective study is underway to further address these issues.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value , n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (57)</td>
</tr>
<tr>
<td>Female</td>
<td>36 (43)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>65 (77)</td>
</tr>
<tr>
<td>Maori</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>69.5 ± 12</td>
</tr>
<tr>
<td>European</td>
<td>72</td>
</tr>
<tr>
<td>Maori</td>
<td>57</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>36 (38)</td>
</tr>
<tr>
<td>Ex-Smoker</td>
<td>52 (55)</td>
</tr>
<tr>
<td>Never</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Lung Function</td>
<td></td>
</tr>
<tr>
<td>FEV$_1$ (L)</td>
<td>0.81 (0.33 – 2.19)</td>
</tr>
<tr>
<td>FEV$_1$ (% predicted)</td>
<td>36 (14 – 83)</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>43</td>
</tr>
<tr>
<td>First Admission (%)</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Co-morbid Illnesses, No (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (11)</td>
</tr>
<tr>
<td>1</td>
<td>17 (18)</td>
</tr>
<tr>
<td>2</td>
<td>30 (32)</td>
</tr>
<tr>
<td>3</td>
<td>19 (20)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>14 (15)</td>
</tr>
<tr>
<td>5</td>
<td>3 (3)</td>
</tr>
<tr>
<td>6</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mean</td>
<td>2.2 ± 1.35</td>
</tr>
</tbody>
</table>

BMI, mean (kg/m²) (range) 24 (12.6-52.3)
Table 2.2  Assessments and Measurements Performed on Admission

<table>
<thead>
<tr>
<th>Assessment</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting Complaint</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>87 (93%)</td>
</tr>
<tr>
<td>Increased sputum production</td>
<td>39 (41%)</td>
</tr>
<tr>
<td>Increased sputum purulence</td>
<td>37 (39%)</td>
</tr>
<tr>
<td>Social Issues*</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Other</td>
<td>64 (68%)</td>
</tr>
<tr>
<td>Chest Radiograph</td>
<td>89 (95%)</td>
</tr>
<tr>
<td>Infective Changes</td>
<td>20 (22%)</td>
</tr>
<tr>
<td>Arterial Blood Gas (range)</td>
<td></td>
</tr>
<tr>
<td>Median pH</td>
<td>7.38 (7.07-7.54)</td>
</tr>
<tr>
<td>Median PaCO₂, mmHg</td>
<td>54 (24 – 191)</td>
</tr>
<tr>
<td>Median PaO₂, mmHg</td>
<td>59 (22 - 529)</td>
</tr>
</tbody>
</table>

* Social circumstances were believed to contribute to the need to admit these patients. These include living alone, poor social support system, no access to telephone/emergency contact, geographic remoteness and poor access to health care at home.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplemental Oxygen</td>
<td>74/94 (79)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>75/94 (80)</td>
</tr>
<tr>
<td>Steroid therapy</td>
<td>78/94 (83)</td>
</tr>
<tr>
<td>Oral</td>
<td>78/78 (100)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>8/78 (11)</td>
</tr>
<tr>
<td>Ventilation</td>
<td>12/94 (13)</td>
</tr>
<tr>
<td>Intubation</td>
<td>2/94 (2)</td>
</tr>
<tr>
<td>Non-invasive Ventilation</td>
<td>10/94 (11)</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>78/94 (83)</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>89/94 (94)</td>
</tr>
<tr>
<td>None documented</td>
<td>3/94 (3)</td>
</tr>
<tr>
<td>Nebulised</td>
<td>29/94 (31)</td>
</tr>
<tr>
<td>Spacers</td>
<td>40/94 (43)</td>
</tr>
</tbody>
</table>
Table 2.4 BMI on admission and 12-month mortality

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>No. of Patients*</th>
<th>12-month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>16</td>
<td>50%</td>
</tr>
<tr>
<td>20-25</td>
<td>41</td>
<td>40%</td>
</tr>
<tr>
<td>26-30</td>
<td>13</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;30</td>
<td>11</td>
<td>14%</td>
</tr>
</tbody>
</table>

* BMI on admission obtained in 81 out of 84 patients.
Table 2.5  CURB65 score and Mortality

<table>
<thead>
<tr>
<th>Mortality, % (n)</th>
<th>CURB65 Score</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 and 1</td>
<td>2</td>
<td>≥ 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Hospital</td>
<td>0 (0/34)</td>
<td>5 (1/20)</td>
<td>13 (4/32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-Day</td>
<td>0 (0/34)</td>
<td>15 (3/20)</td>
<td>22 (7/32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-Month</td>
<td>15 (5/34)</td>
<td>30 (6/20)</td>
<td>47 (15/32)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Differences between groups are assessed by Fisher’s exact tests
**Table 2.6** CURB score (excluding age) and mortality

<table>
<thead>
<tr>
<th>Mortality, % (n)</th>
<th>CURB score</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 and 1</td>
<td>2</td>
<td>13</td>
<td>(5/39)</td>
</tr>
<tr>
<td>In-hospital</td>
<td></td>
<td>p = 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-Day</td>
<td>2</td>
<td>(1/55)</td>
<td>23</td>
<td>(9/39)</td>
</tr>
<tr>
<td>12-Month</td>
<td>20</td>
<td>(11/55)</td>
<td>46</td>
<td>(18/39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p &lt; 0.001</td>
<td>p = 0.003</td>
<td></td>
</tr>
</tbody>
</table>

Differences between groups are assessed by χ² tests
### Table 2.7  Arterial Blood Gas Analysis and Ventilation

<table>
<thead>
<tr>
<th>pH</th>
<th>Current Study</th>
<th>BTS Audit [173]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7.25</td>
<td>86%</td>
<td>15%</td>
</tr>
<tr>
<td>7.26 – 7.34</td>
<td>43%</td>
<td>11%</td>
</tr>
<tr>
<td>&gt; 7.35</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Chapter Three

Predicting Early Mortality in

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

using CURB65 scores

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Published as Chang et al.

Respirology, 2011: 16:146-151
3.1 Abstract

**Background and Objectives**

Hospitalisation for exacerbation of Chronic Obstructive Pulmonary Disease (COPD) is associated with a high risk of mortality. A risk-prediction model using information easily obtained on admission could help to identify high-risk individuals. The CURB65* score was developed to predict mortality risk in community acquired pneumonia. A retrospective study found that this score was also associated with mortality in COPD exacerbations. We conducted a prospective study to assess the utility of the CURB65 score in acute COPD exacerbations.

**Methods**

Consecutive patients with physician diagnosed COPD exacerbations admitted to a public hospital during a one year period were studied prospectively. CURB65 scores were calculated from information obtained at initial hospital presentation.

**Results**

30-day mortality data were available for 249 of 252 patients. CURB65 scores on admission significantly predicted risk of death during the hospital admission and at 30 days. The 30 day mortality by score groups were: low risk (scores 0-1) 2.0% (2/98), moderate risk (score 2) 6.7% (6/90) and high risk (scores 3-5) 21.3% (13/61). CURB65 scores were not predictive of one year mortality.
Conclusion

A simple six point score based on confusion, blood urea, respiratory rate, blood pressure and age can be used to stratify patients with COPD exacerbation into different management groups. The CURB65 score was as effective in predicting early mortality in our cohort of acute COPD exacerbations as it was in previous cohorts with community acquired pneumonia. Our findings suggest that CURB65 can help clinicians to assess patients with exacerbation of COPD.

*CURB65 = one point each for Confusion, Urea > 7mmol/l, Respiratory rate ≥ 30/min, low Blood pressure (systolic <90mmHg or diastolic <60mmHg), age ≥ 65 years.
3.2 Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of disability, hospital admissions, and mortality. The burden of this disease is predicted to increase further as the population ages[4]. Hospitalisation for COPD exacerbation usually occurs during advanced stages of the disease and the outcome is often poor [204, 205].

Despite the high incidence of COPD related hospitalisations, relatively little is known about the determinants of mortality and outcome. Scoring systems have been developed to predict mortality in chronic stable COPD[191]. In the setting of acute exacerbations, studies have also shown that low body mass index, age, poor functional status, long-term oral corticosteroids use, respiratory rate, PaCO₂ and other co-morbidities are associated with increased mortality[174, 209, 222]. Despite this, there are no prognostic models which can be used at the bed-side to predict risk for mortality following an acute exacerbation. Prognostic scoring systems have been developed for other acute respiratory conditions such as community acquired pneumonia and are widely used[227, 236, 402, 403]. A similar model to identify individuals at high risk of death from COPD exacerbation may be equally useful.

One of the more widely used severity scores for community acquired pneumonia is the British Thoracic Society (BTS) CURB65 score. This is a simple six point score (one point each for Confusion, Urea > 7mmol/L, Respiratory rate ≥ 30/min, Blood
pressure systolic < 90mmHg or diastolic < 60mmHg and age > 65 years) that has shown good discriminatory value in validation studies involving over 11,000 patients[404]. Given the significant role that respiratory tract infections play in COPD exacerbation and the common use of antimicrobial therapy in this condition, we hypothesised that this same score could also be used in COPD risk-assessment. A retrospective study by the authors found the CURB65 score was associated with mortality from COPD exacerbations with 30-day mortalities for those with low (0-1), moderate (2) and high risk (3-5) CURB-65 scores of 0%, 15% and 22% respectively[405].

The present study was designed to prospectively assess the ability of CURB65 score to predict mortality in acute COPD exacerbation requiring hospitalisation.
3.3 Methods

The study was performed at Waikato Hospital, an urban secondary and tertiary teaching hospital that services the central North Island of New Zealand. The secondary referral population is 380,000 and the tertiary population is 790,000[111]. All patients with acute respiratory conditions are routinely admitted under a respiratory physician. We prospectively recruited all adult patients requiring hospitalisation to the respiratory service for exacerbation of COPD between July 10th 2006 to July 9th 2007. This study was approved by the Northern Y Regional Ethics Committee of New Zealand and informed consent was obtained from all participants.

The inclusion criterion was COPD exacerbation requiring hospitalisation. Exacerbations were diagnosed by the admitting physicians and were defined as: dyspnoea, cough or sputum purulence severe enough to warrant hospitalisation; respiratory failure (pO2 < 60mmHg or pCO2 > 45mmHg) or change in mental status due to COPD. Whenever possible COPD was confirmed by spirometry, which performed when the patients were stable.

Exclusion criteria included a history of other respiratory illnesses such as acute asthma, bronchiectasis or interstitial lung disease; consolidation on chest radiograph (i.e. pneumonia) as reported by either the respiratory physician or radiologist; and hospitalisation for reasons other than COPD exacerbation. The primary end-points were in-hospital and 30-day mortality.
Only the first admission for each patient was included in the analysis, even if the patient was hospitalised more than once during the study period. Management of patients during hospitalisation was unchanged and was undertaken according to the unit protocol which is based on BTS recommendations[133] and included corticosteroids, bronchodilating agents, oxygen, antibiotics and ventilation (invasive and non-invasive) as required. CURB65 score was calculated using the information from the initial assessment in the emergency department and where multiple measurements of blood pressure and respiratory rate were taken, the first recording was used. Confusion was assessed by the admitting clinician. The patient was then followed until discharge or death. Survival at 30 days and one year confirmed via a phone interview with the patient, their family, or their general practitioner. Mortality was compared between groups with different CURB65 scores using Chi-squared or Fisher’s exact tests. Further analyses used logistic regression to adjust for other known risk factors (by stepwise addition of each risk factor to the analysis). p-values < 0.05 were considered statistically significant. The area under the receiver-operating characteristic (ROC) curve for different CURB65 scores was calculated. Analyses were performed using STATA10 (College Station TX).
3.4 Results

3.4.1 Patient Characteristics

General patient characteristics and demographics are listed in Table 3.1. Of the 252 patients admitted, follow-up information was available for 249 (99%) at 30 days and 228 (90%) at one year. The 3 patients lost to 30-day follow up were excluded from subsequent analysis (2 were overseas visitors). Most patients (74%) had had prior contact with the local respiratory service with existing diagnosis of COPD confirmed by spirometry. Our unit protocol also included standard outpatient clinic review and spirometry at 6 weeks following admission for COPD exacerbation. Thus, lung function tests performed within 6 months before or shortly after the index admission were available for 244 patients (98%). As defined by the NICE and GOLD guidelines[74, 206], 37% had severe airway obstruction (FEV₁ < 30% predicted), 44% had moderate airway obstruction (FEV₁ 30-50% predicted) and the remaining 19% had mild airway obstruction. Nine patients did not meet both of the spirometric criteria for COPD (fixed airflow obstruction as indicated by reduced FEV₁ to less than 80% predicted and reduced FEV₁/FVC to less than 70%)[74] although all but one of these had FEV₁ values < 80% predicted. Excluding these patients from the analysis made no material difference to the findings. Lung function tests were not obtained in 7 patients due to inpatient death (n=2) or inability to perform spirometry (n=5).

3.4.2 Mortality and CURB65 Score

12/249 patients died in hospital (4.8%) and the 30-day mortality was 8.4% (21/249). CURB65 score was recorded in all patients. There were fewer patients with scores of 4 or 5 so these groups were combined for analysis (Table 3.2). The risk of both in-
hospital and 30-day mortality was significantly different between groups and increased with higher CURB65 scores.

Patients were further stratified into 3 risk groups by CURB65 scores using the groups previously established for community acquired pneumonia[402]: low risk (scores 0-1), intermediate risk (score = 2) and high risk (scores 3-5). Both in-hospital and 30 day mortality significantly differed between these groups and increased with risk categories (Table 3.2).

CURB65 score was independently predictive of 30 day mortality (crude odds ratio 1.89, adjusted odds ratio 1.71, p=0.013) after correcting for other putative risk factors of poor outcome (baseline FEV₁, BMI, pH, PaCO₂ and PaO₂)[174, 209, 222]. A lower pH (or higher PaCO₂) was also an independent predictor of 30 day mortality (p < 0.001) whereas BMI, FEV₁ and PaO₂ were not (p values > 0.2). CURB65 risk group (low, intermediate or high) was also independently predictive of 30 day mortality (crude odds ratio 3.05, adjusted odds ratio 3.24, p < 0.001). Apart from low blood pressure, each successive individual CURB65 component increased the predictive value of the overall score (AUC = 0.73) (Figure 3.1). Respiratory rate ≥ 30/min was the most significant contributor to CURB65 predictive value by logistic regression (adjusted odds ratio 2.40, p = 0.017).

CURB65 scores were not predictive of one year mortality after excluding deaths in the first 30 days (Table 3.2). There was no difference in one year mortality either across CURB65 score (p = 0.351) or risk groups (p = 0.406). ROC analysis of the score
showed poor discriminating value for mortality at 1 year after COPD exacerbation (AUC = 0.53) (Figure 3.2).

3.4.3 Mortality and CRB65 Score

CRB65 score is a simpler model that does not require laboratory measurement of urea and is a useful tool for assessing community acquired pneumonia outside hospital as it only uses clinical parameters for scoring (confusion, respiratory rate, blood pressure and age)[236, 243]. In this cohort of COPD exacerbations, the risk of 30-day mortality also increased with higher CRB65 scores. (Table 3.3)
3.5 Discussion

To our knowledge, this is the first study to prospectively assess the utility of CURB65 scores in COPD patients. It is also the first study to prospectively assess a prognostic scoring system in the setting of an acute COPD exacerbation. This study demonstrates that the CURB65 score obtained on hospital admission significantly predicts both in-hospital and 30 day mortality in these patients. Many other variables including a low body mass index, high APACHE score, severity of airflow obstruction, raised PaCO₂, the presence of pre-existing co-morbidities and cor pulmonale have previously been associated with reduced survival following acute exacerbation[174, 204, 209, 222]. However, prior to this study, there has not been a prospectively validated mortality prediction model in this population. The current guidelines from both the British Thoracic Society/NICE[133] and American Thoracic Society/GOLD[206] suggest consideration of symptom severity and presence of co-morbid conditions when deciding if an exacerbation is severe enough to warrant hospitalisation but do not provide a prospectively-tested risk stratification framework. Further, these recommendations are based on level D evidence (Panel Consensus) only.

Our previous retrospective study demonstrated an association between CURB65 score and mortality in COPD exacerbations[405]. Since then, Tabuk et al have reported a retrospective database analysis based on ICD-9 discharge codes and developed a risk prediction score for patient death and mechanical ventilation in this population[406]. Importantly, this study incorporated 3 of the 5 CURB65 criteria,
including high serum urea, acute mental status change and age > 65 years. It also included tachycardia. Our findings add weight to the concept that a score based on clinical markers that signal end-organ dysfunction can be a powerful tool for risk stratification in acute exacerbation of COPD.

One of the advantages of the CURB65 score lies in its simplicity. The variables are simple to obtain at the time of admission and the risk group divisions are easy to follow (less than two risk factors, equal to two risk factors and greater than two risk factors). This simplicity is one reason for its widespread use in assessing mortality risk in community acquired pneumonia. Our study demonstrated that the CURB65 score was as effective in predicting mortality in our cohort of acute COPD exacerbations as it was in previous cohorts with community acquired pneumonia. In fact, the area under the ROC curve in our cohort, is similar to previously published community acquired pneumonia cohorts using the CURB65 score[243] (Figure 3.1). Indeed, the mortality rates that we found for COPD exacerbations in each risk group are remarkably similar to those observed in previous cohorts with community acquired pneumonia (Table 3.4).

There are several reasons why the CURB65 score may work as well in mortality prediction in exacerbation of COPD as it does in community acquired pneumonia. Firstly, the two conditions share important aetiological and pathophysiological features. Although the host-pathogen interactions in COPD exacerbation are still poorly understood, infections undoubtedly play a significant role. Both new strain acquisition as well as increased pathogen load of pre-existing strains have been
implicated as mechanisms of increased inflammation leading to exacerbations[149, 249]. Although bacterial inflammation is not implicated in all COPD exacerbations, there is evidence that exacerbations associated with new bacterial strains are associated with more intense airway and systemic inflammation than those with pre-existing strains and non-bacterial episodes[250]. Further, risk factors for community acquired pneumonia such as cigarette smoking, pre-existing heart and lung disease, inhaled corticosteroid and bronchodilator use as well as pre-existing chronic bronchitis are also commonly found in patients with COPD[253, 254, 407].

Secondly, there is often considerable overlap in the clinical presentation of COPD exacerbation and pneumonia. Patients with both conditions may present with dyspnoea, cough, sputum, fever and leucocytosis. Often the main feature separating the two diagnoses is the chest radiograph where the presence of consolidation is still considered the “gold standard” for pneumonia diagnosis[227]. However, it is well recognised that many patients who present with symptoms and clinical findings suggestive of community-acquired pneumonia lack the radiographic finding at the time of presentation[408]. In a large case series of 2706 patients hospitalised with clinical features suggestive of pneumonia, one third (911/2706) had no consolidation on chest radiography. There was no significant difference in mortality between the radiographic confirmation and the non-confirmation groups[409].

A strength of this study is that it was designed to prospectively assess a risk-prediction score previously identified in a retrospective study[405]. Follow-up was completed for all but 3 of the 252 participants in an unselected cohort of patients
requiring admission to hospital. Although the clinicians treating the patients were not blind to the CURB65 score and were aware of the findings of the previous retrospective study, it seems unlikely that this would significantly bias the outcome of mortality. Our results represent the outcome of a modest number of patients from a single centre, and the generalisability of our findings require further confirmation with larger numbers of patients and at other centres. Our findings also suggest that the CRB65 score may be useful outside the hospital setting where laboratory facilities may not be available, but this needs to be confirmed.

This study reaffirms that exacerbation of COPD requiring hospital admission carries considerable risk with an overall 30 day mortality of 8.4%. This is similar to the mortality reported by others[174, 209, 222]. We believe that a scoring system to predict mortality would be as useful for clinicians managing patients with COPD exacerbations as they are for those with community acquired pneumonia[227, 402]. The advantage of CURB65 score is that it can be used for both conditions and provides similar prognostic information. This, and its overall simplicity, is likely to facilitate its use by medical staff.

Although CURB65 score was a good predictor of in-hospital and 30 day mortality, it did not predict mortality between 30 days and one year outcome in our cohort (Table 3.2). This is important because it suggests that CURB65 score is not simply a measure of overall frailty and poor health but signals significant end-organ dysfunction and is indicative of the acute exacerbating process that may lead to death.
Better prognostic information for acute exacerbations of COPD would have a number of advantages. Although it may not necessarily lead to improved patient outcome, it may facilitate discussions between clinicians, patients, and their families and inform management decisions. For service providers, information on severity may help to assess the needs of different patient populations. Finally, risk stratification would be very helpful to researchers aiming to compare and improve the treatment of COPD exacerbations.

In summary, we have found that the CURB65 score predicts short term mortality following an exacerbation of COPD requiring admission to hospital. This is the first time that a risk stratification score has been demonstrated to be successful for acute exacerbations of COPD. Our findings suggest that CURB65 can help clinicians to assess patients with this condition.
### Table 3.1 Cohort Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>113 (45)</td>
</tr>
<tr>
<td>Female</td>
<td>139 (55)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>199 (79)</td>
</tr>
<tr>
<td>Maori</td>
<td>43 (17)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Age, mean in years (range)</td>
<td>71.7 (41-95)</td>
</tr>
<tr>
<td>European</td>
<td>73 (41-95)</td>
</tr>
<tr>
<td>Maori</td>
<td>67 (44-83)</td>
</tr>
<tr>
<td>Smoking Status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>83 (33)</td>
</tr>
<tr>
<td>Ex-Smoker</td>
<td>160 (63)</td>
</tr>
<tr>
<td>Never</td>
<td>9 (3.6)</td>
</tr>
<tr>
<td>Lung Function, mean (range)</td>
<td></td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.81 (0.12 – 2.49)</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>35 (7 – 87)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>44 (16-83)</td>
</tr>
<tr>
<td>BMI, mean kg/m² (range)</td>
<td>25.3 (13.0-45.2)</td>
</tr>
<tr>
<td>Presence of CURB65 characteristics, n (%)</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>36 (14)</td>
</tr>
<tr>
<td>Urea &gt; 7mmol/L</td>
<td>111 (44)</td>
</tr>
<tr>
<td>Condition</td>
<td>Count</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Respiratory rate ≥ 30/min</td>
<td>103</td>
</tr>
<tr>
<td>Blood pressure &lt; 90mmHg (systolic) or &lt;60mmHg (diastolic)</td>
<td>37</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>197</td>
</tr>
</tbody>
</table>

### Treatment, n (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic corticosteroids</td>
<td>247</td>
<td>98</td>
</tr>
<tr>
<td>Antimicrobial therapy</td>
<td>243</td>
<td>96</td>
</tr>
<tr>
<td>Bronchodilating agents</td>
<td>252</td>
<td>100</td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
<td>24</td>
<td>9.5</td>
</tr>
<tr>
<td>Ventilation via endo-tracheal tube</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Intensive/High Dependency Care Admission</td>
<td>15</td>
<td>6.0</td>
</tr>
</tbody>
</table>
Table 3.2 In-hospital and 30-day mortality by CURB65 score and risk groups

<table>
<thead>
<tr>
<th>CURB65 Score</th>
<th>N</th>
<th>In Hospital Deaths</th>
<th>%</th>
<th>30 Day Deaths</th>
<th>%</th>
<th>N</th>
<th>1 Year Mortality</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>27</td>
<td>1</td>
<td>3.7</td>
<td>1</td>
<td>3.7</td>
<td>26</td>
<td>6</td>
<td>23.1</td>
</tr>
<tr>
<td>1</td>
<td>71</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.4</td>
<td>66</td>
<td>11</td>
<td>16.7</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>4</td>
<td>4.4</td>
<td>6</td>
<td>6.7</td>
<td>86</td>
<td>12</td>
<td>14.0</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>4</td>
<td>8.7</td>
<td>9</td>
<td>19.6</td>
<td>35</td>
<td>7</td>
<td>20.0</td>
</tr>
<tr>
<td>4 and 5</td>
<td>15</td>
<td>3</td>
<td>20.0</td>
<td>4</td>
<td>26.7</td>
<td>15</td>
<td>6</td>
<td>40.0</td>
</tr>
</tbody>
</table>

*p* = 0.013

(continued over page)
Table 3.2 cont. In-hospital and 30-day mortality by CURB65 score and risk groups

<table>
<thead>
<tr>
<th>CURB65 Risk Group</th>
<th>Early Mortality (within 30 Days)</th>
<th>Late Mortality (after 30 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>In Hospital Deaths</td>
</tr>
<tr>
<td><strong>Low Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt; 2)</td>
<td>98</td>
<td>1</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risk (= 2)</strong></td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt; 2)</td>
<td>61</td>
<td>7</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

* difference between groups are assessed by χ² test.
Table 3.3  In-hospital and 30-day mortality by CRB65 risk groups

<table>
<thead>
<tr>
<th>CRB65 Risk Group</th>
<th>N</th>
<th>In Hospital Deaths</th>
<th>%</th>
<th>30 Day Deaths</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (  =0)</td>
<td>30</td>
<td>1</td>
<td>3.3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate Risk (1-2)</td>
<td>199</td>
<td>7</td>
<td>3.5</td>
<td>15</td>
<td>7.5</td>
</tr>
<tr>
<td>High Risk (&gt; 2)</td>
<td>20</td>
<td>4</td>
<td>20.0</td>
<td>5</td>
<td>25.0</td>
</tr>
</tbody>
</table>

p* = 0.02

* difference between groups are assessed by Fisher’s exact probability test.
Table 3.4  Comparison of 30 Day Mortality by CURB65 Risk Groups in COPD Exacerbation and Community Acquired Pneumonia

<table>
<thead>
<tr>
<th>CURB65 Risk Group</th>
<th>30 Day Mortality after COPD Exacerbation</th>
<th>30 Day Mortality after CAP&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (&lt; 2)</td>
<td>2.0 %</td>
<td>1.5 %</td>
</tr>
<tr>
<td>Intermediate Risk (= 2)</td>
<td>6.7 %</td>
<td>9.2 %</td>
</tr>
<tr>
<td>High Risk (&gt; 2)</td>
<td>21.3 %</td>
<td>22.3 %</td>
</tr>
</tbody>
</table>

CAP = Community acquired pneumonia
**Figure 3.1** Receiver operating characteristic (ROC) curve for CURB65 score in 30-day mortality prediction.

The area under the ROC curve = 0.7334
Figure 3.2 Receiver operating characteristic (ROC) curve for CURB65 score in 1-year mortality prediction.

The area under the ROC curve = 0.5317
Chapter Four

Biochemical Markers of Cardiac Dysfunction

Predict Mortality in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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4.1 Abstract

Background

Retrospective studies suggest that blood levels of NT-proBNP and cardiac troponin T are often elevated in patients with acute exacerbations of COPD and are associated with increased mortality. We investigated these cardiac biomarkers in an unselected cohort of patients admitted to hospital with exacerbations of COPD.

Methods

Consecutive patients with physician diagnosed COPD exacerbation but without clinical evidence of acute cardiac disease admitted to a public hospital over a one year period were studied prospectively. NT-proBNP and troponin T were measured on admission. The primary end-point was all-cause mortality at 30 days.

Results

Elevated NT-proBNP (>220pmol/L) was present in 65/244 patients (27.5%) and significantly predicted 30 day mortality (OR=9.0, p<0.001). Elevated troponin T (>0.03μg/L) was found in 40/241 patients (16.6%) and also predicted 30 day mortality (OR=6.3, p<0.001). These associations persisted after adjusting for other clinical and laboratory predictors of mortality (PaCO2, BMI, CURB65 score). NT-proBNP and troponin T levels appeared to have additive associations with mortality: 30 day mortality among patients with abnormalities of both NT-proBNP and troponin T was 15 fold higher than among patients with normal values.
Conclusion

Elevated levels of NT-proBNP and troponin T are strong predictors of early mortality among patients admitted to hospital with acute exacerbations of COPD independently of other known prognostic indicators. The pathophysiological basis for this is unknown, but indicates that cardiac involvement in exacerbations of COPD may be an important determinant of prognosis.
4.2 Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of disability, hospital admissions and mortality[4]. Hospitalizations for acute exacerbations of COPD usually occur in advanced disease and are associated with a high mortality[222].

Cardiovascular disease is common in patients with COPD[66, 222] and is associated with poorer prognosis in COPD exacerbations[65, 410]. The degree to which cardiac disease contributes to mortality during acute exacerbations of COPD is unknown but there is accumulating evidence that this is substantial. In COPD exacerbations severe hypoxemia[209], pulmonary hypertension[214] and systemic inflammation[157, 411] are associated with poorer prognosis and may impact on cardiac function, but the interplay of these factors and their cardiovascular effects in COPD are incompletely understood.

Brain Natriuretic Peptide (BNP) and its inactive cleavage product, N-terminal pro-BNP (NT-proBNP) are released by cardiomyocytes in response to ventricular wall stretch due to pressure or volume overload[262]. These are established markers of left ventricular dysfunction and are associated with increased mortality in acute[280] and stable[285] heart disease. BNP and NT-proBNP levels are also increased with right ventricular pressure overload[293, 294] and are associated with a poor prognosis in patients with pulmonary arterial hypertension[298] and pulmonary thromboembolism[299].
Cardiac troponins are highly specific markers of myocardial necrosis and commonly used to diagnose myocardial infarction[316]. Elevated troponin levels have also been observed in many other conditions including pulmonary thromboembolism[335], congestive heart failure[321], tachyarrhythmias[317], myocarditis[325], pericarditis[326], sepsis[332] and stroke[337]. Troponin elevations in these conditions probably reflect general myocardial injury rather than coronary arterial occlusion. In a previous retrospective study, we observed that cardiac troponins are frequently raised in COPD exacerbations and appear associated with the severity of the exacerbation[339]. There are few prospective data on the prognostic value of cardiac troponins in patients with acute exacerbations of COPD.

To further investigate the extent of cardiac involvement in acute exacerbations of COPD, we analysed the associations between NT-proBNP and troponin T levels and mortality in a prospective cohort of consecutive patients admitted to hospital with acute exacerbations of COPD.
4.3 Materials and Methods

4.3.1 Study Design
Consecutive patients admitted to hospital with a primary diagnosis of an exacerbation of COPD over 1 year (10th July 2006 to 9th July 2007) were recruited. Informed consent was obtained from all participants or their next of kin. The study was approved by the Northern Y Regional Ethics Committee.

4.3.2 Setting
The study was performed at Waikato hospital, an urban secondary and tertiary teaching hospital in the central North Island of New Zealand. All patients with acute exacerbations of COPD are routinely admitted under the care of a respiratory physician.

4.3.3 Inclusion and Exclusion Criteria
Acute exacerbations of COPD were diagnosed by the admitting physicians. These were defined as: dyspnoea, cough or sputum purulence, respiratory failure (pO₂ <60mmHg or pCO₂ >45mmHg) or change in mental status due to COPD.

Patients were excluded if there was evidence of another acute respiratory illnesses such as acute asthma, exacerbation of bronchiectasis or interstitial lung disease, or consolidation on chest radiograph (i.e. pneumonia) reported by either the respiratory physician or radiologist; and hospitalization for reasons other than COPD exacerbation. Patients with a diagnosis of an acute coronary syndrome based on symptoms and electrocardiogram changes were also excluded. For patients
admitted for more than one exacerbation of COPD during the study period, only the first admission was included in the analysis.

4.3.4 Treatment

Patients were treated by the admitting physician according to standard hospital protocols which included corticosteroids, bronchodilators, oxygen, antibiotics and ventilation (invasive and non-invasive) as required. Treatment was not influenced by participation in this study.

4.3.5 Data Collection

The following data were recorded: medical history, smoking status, ethnicity, blood pressure, pulse rate, respiratory rate, temperature, percutaneous oxygen saturation, arterial blood gases, complete blood count, serum urea, body-mass index (BMI), requirement for mechanical ventilation, length of hospital stay and all-cause mortality. Lung function was measured at disease stability (defined as either within 6 months prior to the exacerbation or within 6 weeks after recovery). The clinical data on admission were used to compile two clinical prognostic scores: BAP65[406] (scored from raised blood urea, acute mental status change, pulse >109/min and age over 65) and CURB65 [405, 412](scored from confusion, blood urea, respiratory rate ≥30/min, low blood pressure and age over 65).

Blood samples for NT-proBNP and troponin T were obtained within 24 hours of admission. Levels were determined by quantitative electrochemiluminescence assay (Elecsys proBNP and Troponin; Roche Diagnostics Corporation, IN, USA). The
detection limits were 0.6pmol/L for NT-proBNP and 0.01μg/L for troponin T. Values of NT-proBNP >220pmol/L and troponin T > 0.03μg/L are considered abnormal for the local population (laboratory communication).

Survival at 30 days and one year was ascertained from a phone interview with the patient, their family or their general practitioner.

4.3.6 Statistical Analysis

The primary end-point was 30-day mortality. Subsequent mortality between 30 days and one year was a secondary end-point. Neither NT-BNP nor troponin T were normally distributed and values were therefore categorised as normal or elevated. Logistic regression analysis was used to adjust associations between NT-proBNP, troponin T and mortality for potential confounders including age, lung function, arterial blood gases, CURB65 score, BAP65 score, and BMI. To limit the number of event-per-variables, only variables with univariate associations of $p \leq 0.05$ were included in the multiple logistic regression models.

Kaplan-Meier cumulative survival curves were constructed and compared with the log-rank test for elevated levels of NT-proBNP and troponin T. Mortality in patients with different cardiac marker status (normal, elevated NT-proBNP & normal troponin T, normal NT-proBNP & elevated troponin T and both elevated NT-proBNP & troponin T) was compared using Chi-squared tests. SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. $P$ values $\leq 0.05$ were regarded as statistically significant.
4.4 Results

4.4.1 Patient Characteristics

251 consecutive patients met inclusion criteria of which 250 consented to participate. Two overseas visitors were lost to 30-day follow-up and were excluded from the analysis. Follow-up information was available for 248 (99%) at 30 days and 227 (91%) at 1 year. Patient characteristics are shown in Table 4.1. 37% had severe airway obstruction (FEV₁ < 30% predicted), 44% had moderate airway obstruction (FEV₁ 30-50% predicted) and the remaining 19% had mild airway obstruction[206]. Lung function was not measured in 7 patients due to in-patient death (n=2) or inability to perform spirometry (n=5). Nine patients did not meet both of the spirometric criteria for COPD (FEV₁ <80% predicted and FEV₁/FVC <70%)[206]. Twenty-six (10.4%) patients received ventilatory support. The overall in-hospital, 30 day, and one year mortality were 4.8% (12/248), 8.5% (21/248), and 18.5% (42/227) respectively.

4.4.2 NT-proBNP

NT-proBNP levels were available for 244 (98%) patients. The median level was 66.5pmol/L (range 2–3900). 65 patients (27.5%) had elevated levels (>220pmol/L). Elevated NT-proBNP levels predicted mortality at 30 days (OR = 9.0, p<0.001) (Table 4.2) but did not predict deaths between 30 days and one year of follow-up (p=0.27) (Figure 4.1).
4.4.3 Troponin T

Troponin T levels were available for 241 (97%) patients. The majority (74%) were at or below the lower limit of detection at 0.01μg/L. Troponin T level was elevated (>0.03μg/L) in 40 (16.6%) patients. Elevated troponin T levels predicted mortality at 30 days (OR = 6.3, p <0.001) (Table 4.2) but did not predict deaths between 30 days and one year of follow-up (p=0.63) (Figure 4.1).

NT-proBNP and troponin T levels were moderately correlated (Spearman’s rho = 0.46, p<0.001). In logistic regression analyses using both of these biomarkers, a raised NT-proBNP predicted 30 day mortality (OR=6.71, p=0.001), but raised troponin T levels were of borderline statistical significance (OR =2.74, p=0.066). Patients with both raised troponin T and raised NT-proBNP had the highest risk of 30-day mortality (Figure 4.2).

4.4.4 Multivariate Analysis

In univariate analyses, pH, PaCO₂, BMI, and CURB65 scores also predicted 30-day mortality whereas lung function (FEV₁%predicted, FEV₁/FVC), PaO₂, BAP65 score and age did not. PaCO₂ and pH were highly correlated with each other (Spearman’s rho=0.76) and did not predict mortality independently of each other.

In multivariate analysis a high NT-proBNP remained a significant predictor of 30-day mortality independently of PaCO₂ (or pH), BMI, and CURB65 score (OR=9.2, p=0.001) (Table 4.2). A high troponin T was also a significant predictor of 30-day mortality independently of PaCO₂, BMI, and CURB65 score (OR=5.1, p=0.003), but failed to
achieve statistical significance if NT-proBNP was included in the analysis (Table 4.2).

A past history of cardiovascular disease was associated with high NT-proBNP levels ($\chi^2 = 9.1, p=0.003$) but did not predict 30-day mortality. Troponin T levels were not associated with a past history of cardiac disease ($\chi^2 = 0.11, p=0.74$).
4.5 Discussion

Elevated NT-proBNP and Troponin T were strongly associated with increased early mortality in this unselected cohort of patients admitted to hospital with acute exacerbations of COPD. These cardiac biochemical markers appeared to have an additive association with risk: patients with abnormalities of both NT-proBNP and troponin T had a 15-fold higher mortality at 30 days than patients with normal values for both markers (Figure 4.2). The pathophysiological processes underlying the derangements in these cardiac biochemical markers and how they relate to increased mortality in exacerbations of COPD are unknown. However, patients without abnormalities of NT-proBNP or Troponin T had a low mortality and this suggests that cardiac involvement in acute exacerbations of COPD may be an important determinant of prognosis.

Although NT-proBNP and troponin T predicted mortality independently of other prognostic indicators, it remains unclear whether cardiac involvement is a direct cause of mortality or whether these biomarkers just reflect the severity of the exacerbation. In severe COPD, hypoxia and associated pulmonary vasoconstriction can cause pulmonary hypertension and right ventricular dysfunction[413]. Tachycardia, increased ventilation-perfusion mismatch and respiratory muscle fatigue also contribute to cardiac stress, which may be further exacerbated by an increased oxygen cost of breathing and increased left ventricular afterload from dynamic hyperinflation. Perhaps surprisingly, there was no evidence that oxygen tension on arterial blood gas measurement was associated with either elevated
cardiac biomarkers or mortality. However, we cannot rule out the possibility that hypoxaemia earlier in the exacerbation may have contributed to these: in practice many patients are treated with supplemental oxygen prior to hospitalisation and the arterial oxygenation measurements made on admission could have been influenced by this.

Alternatively, cardiac involvement may be due to a parallel process: many patients with COPD have co-existing coronary artery disease due to shared risk factors such as tobacco smoking[66]. Mounting evidence also suggests that systemic inflammation is associated with endothelial dysfunction and a procoagulant state[62, 414]. Hence, coronary ischemia may be more likely to occur in the setting of an acute COPD exacerbation[415]. However, none of the patients in our cohort had a clinical diagnosis of acute coronary syndrome. Moreover, there was only a weak correlation between blood C-reactive protein levels and NT-proBNP (Spearman’s rho = 0.16, p=0.01) and no correlation between C-reactive protein and troponin T (rho = 0.07, p=0.3) indicating that the severity of the systemic inflammatory response was not a major determinant of cardiac involvement.

Elevated levels of NT-proBNP and troponin T were associated with early (30-day) mortality but did not predict subsequent deaths between 30 days and one year. This suggests that these biomarkers reflect the acute pathology of a severe exacerbation rather than general frailty. In keeping with this, NT-proBNP and troponin T predicted 30 day mortality independently of markers of chronic disease severity and reduced
physiological reserve (lung function, BMI, age) as well as clinical and laboratory indicators of exacerbation severity (PaCO₂, severity score).

Previous research has found that BNP and NT-proBNP may be elevated in patients with right ventricular pressure overload due to pulmonary arterial hypertension[298], pulmonary thromboembolism[297], undifferentiated chronic lung disease[294] and respiratory failure[416] where they are also associated with a poor prognosis[300]. In severe acute exacerbations of COPD requiring ventilatory support, high levels of NT-proBNP are associated with left ventricular dysfunction[306]. Stolz et al previously found that elevated levels of BNP during COPD exacerbation predicted the need for intensive care[307]. They did not find an association between raised BNP and mortality, but this may be attributed to the small number of early deaths in the cohort. Levels of BNP observed in that study were also lower than values typically found in patients with left ventricular failure. This is confirmed in our study in which elevated levels of NT-proBNP were generally much lower than levels found in left ventricular failure[417].

Elevated cardiac troponins have been observed in retrospective studies of COPD exacerbations and were associated with adverse outcomes[339, 343-345]. These retrospective observations are limited by the potential for measurement bias – patients may be more likely to have troponins measured if they had a history of cardiovascular disease or evidence of cardiac dysfunction. Only one other prospective study has assessed the prognostic significance of cardiac troponins in exacerbations of COPD but this was limited to critically ill patients admitted to
intensive care[346]. It also found that elevated troponins predicted increased mortality.

The strengths of the present study include the prospective design and the recruitment of all but one patient hospitalized for exacerbation of COPD during the study period. To our knowledge, this is the first time that markers of ventricular overload (NT-proBNP) and myocardial necrosis (troponin T) have been jointly assessed in an unselected cohort of patients with acute exacerbations of COPD. None of the patients were clinically diagnosed or treated for acute coronary syndromes or acute cardiac failure, although we cannot rule out the possibility that these conditions contributed to their admissions. Although this was a non-intervention study, the clinicians were not blinded to the results of the cardiac biomarkers and it is possible that patient treatment were influenced by these. However, since treatment would be expected to improve patient outcomes, any treatments would be more likely to cause an under-estimation of the difference in mortality. Although we were unable to confirm COPD in a small number of patients, either because they did not have spirometry or their spirometry did not meet strict GOLD criteria[206], excluding these patients from analysis made no material difference to the findings. Finally, we only included the 3 most significant prognostic co-factors in our multivariate analysis to avoid over-fitting the model due to the relatively small number of deaths.

Should patients with elevated NT-proBNP or troponin T but no clinical evidence of acute cardiac dysfunction be treated differently to patients with normal values? Increasing circumstantial evidence suggests they should. A recent autopsy series of
43 consecutive patients who died within 24 hours of hospitalisation for acute exacerbation of COPD found that cardiac failure was the leading cause of death[418]. Surprisingly, respiratory failure secondary to COPD was the main cause of death in only 6 patients. The authors emphasised that COPD is a multi-system disorder often accompanied by serious co-morbidities and complications that should be addressed in a comprehensive treatment plan. There is observational evidence to support β-blocker treatment in stable COPD [392, 419]. Patients receiving β-blockers appear to have lower risk of COPD exacerbations[420] and a lower mortality from exacerbations[393]. Other cardioprotective treatments including statins and angiotensin converting enzyme inhibitors may also be beneficial in COPD patients[421, 422]. Our data suggest that cardiac involvement occurs frequently in acute exacerbations and that its presence predicts a poor prognosis. It is possible that active treatment of cardiac disease would improve outcomes but, as far as we are aware, there are no published trials of acute cardiac treatment in this setting. Taken together, these findings point to an urgent need to further investigate the role of cardiac dysfunction and its treatment in COPD exacerbations. Meanwhile, measurement of NT-proBNP and troponin T may help clinicians to assess prognosis.

In summary, elevated levels of NT-proBNP and Troponin T predict early mortality in patients with acute exacerbations of COPD independently of other known prognostic factors. The pathophysiological basis of this is unknown but the findings indicate the importance of cardiac dysfunction in these patients. NT-proBNP and troponin T may help clinicians to assess prognosis in exacerbations of COPD, but further research is needed to determine if they should influence treatment.
<table>
<thead>
<tr>
<th>Table 4.1 Cohort Characteristics</th>
</tr>
</thead>
</table>

**Sex, n (%)**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>112 (45)</td>
</tr>
<tr>
<td>Female</td>
<td>138 (55)</td>
</tr>
</tbody>
</table>

**Ethnicity (%)**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>197 (79)</td>
</tr>
<tr>
<td>Maori</td>
<td>43 (17)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (4)</td>
</tr>
</tbody>
</table>

**Age, mean in years (range)**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>71.7 (41-95)</td>
</tr>
<tr>
<td>Maori</td>
<td>67 (44-83)</td>
</tr>
</tbody>
</table>

**Smoking Status (%)**

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Smoker</td>
<td>83 (33)</td>
</tr>
<tr>
<td>Ex-Smoker</td>
<td>159 (63)</td>
</tr>
<tr>
<td>Never</td>
<td>8 (3.2)</td>
</tr>
</tbody>
</table>

**Lung Function – mean (range)**

<table>
<thead>
<tr>
<th>Lung Function</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (L)</td>
<td>0.81 (0.12 – 2.49)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (% predicted)</td>
<td>35 (7 – 87)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC (%)</td>
<td>44 (16-83)</td>
</tr>
<tr>
<td>Description</td>
<td>Count (Percentage)</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>BMI – mean (range)</strong></td>
<td>25.3kg/m² (13.0-45.2)</td>
</tr>
<tr>
<td><strong>Comorbidities, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>22 (8.8)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>23 (9.2)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>75 (30.1)</td>
</tr>
<tr>
<td>Cerebral vascular disease</td>
<td>28 (11.2)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>None of the above</td>
<td>141 (56.6)</td>
</tr>
<tr>
<td><strong>Treatment, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>245 (98)</td>
</tr>
<tr>
<td>Antimicrobial therapy</td>
<td>241 (96)</td>
</tr>
<tr>
<td>Bronchodilating agents</td>
<td>250 (100)</td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
<td>24 (9.6)</td>
</tr>
<tr>
<td>Ventilation via endo-tracheal tube</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Intensive/High Dependency Care Admission</td>
<td>15 (6.0)</td>
</tr>
</tbody>
</table>
Table 4.2  Univariate and logistic regression analyses of risk factors for death at 30 days in patients hospitalised for acute exacerbation of COPD.

Multivariate logistic regression was performed only on risk factors significant in univariate analyses (BMI, pCO$_2$, CURB65 score, high NT-proBNP and high Troponin T). Results for elevated NT-proBNP and Troponin T are presented before and after adjustments for each other. Odds ratios refer to the change in odds of mortality at 30 days associated with an increase in the predictor variables by 1 of the respective units.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Logistic Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>P value</td>
</tr>
<tr>
<td>Age, year</td>
<td>1.032</td>
<td>0.171</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>0.925</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Lung Function

$FEV_1$, L                | 0.504      | 0.392   |

$%predicted FEV_1$, %     | 0.998      | 0.923   |

$FEV_1/FVC$, %            | 1.0        | 0.998   |

(Continued over page)
Table 4.2 cont.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
<th>Estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$pCO_2$, mmHg</td>
<td>1.049</td>
<td>0.001</td>
<td>1.041</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>$pO_2$, mmHg</td>
<td>0.996</td>
<td>0.083</td>
<td>1.162</td>
<td>0.249</td>
<td></td>
</tr>
<tr>
<td>$CRP$, mg/L</td>
<td>1.05</td>
<td>0.949</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
<th>Estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAP65, increment by 1</td>
<td>1.665</td>
<td>0.065</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CURB65, increment by 1</td>
<td>2.171</td>
<td>&lt;0.0001</td>
<td>1.684</td>
<td>0.075</td>
<td></td>
</tr>
</tbody>
</table>

Past medical history

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease</td>
<td>0.701</td>
<td>0.504</td>
</tr>
<tr>
<td>Cerebral vascular disease</td>
<td>1.990</td>
<td>0.248</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0.466</td>
<td>0.467</td>
</tr>
</tbody>
</table>

Biochemical markers of cardiac dysfunction

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
<th>Estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP &gt; 220pmol/L</td>
<td>9.034</td>
<td>&lt;0.0001</td>
<td>7.455</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Troponin T &gt;0.03ug/L</td>
<td>6.333</td>
<td>&lt;0.0001</td>
<td>2.468</td>
<td>0.138</td>
<td></td>
</tr>
</tbody>
</table>

*Analyses include all other variables in the multivariate model except elevated Troponin T.

† Analyses include all other variables in the multivariate model except elevated NT-proBNP.
**Figure 4.1** Kaplan-Meier survival curve for patients with acute exacerbation of COPD stratified according to cardiac biomarker status

Survival was worse in patients with both biomarkers elevated compared to patients with normal biomarkers (log-rank test, p<0.0001). Survivals in patients with elevated NT-proBNP and cardiac Troponin T alone are also significantly different from patients with neither biomarkers elevated (log-rank test, p<0.001 and p=0.004 respectively).
Figure 4.2 30-Day Mortality after Exacerbation of COPD according to markers of cardiac dysfunction status (%)

30-day mortality was significantly lower in patients who had normal NT-proBNP and troponin T levels (3 deaths among 163 patients) compared with patients who had elevated troponin T alone (2/14, p = 0.05), elevated NT-proBNP alone (7/42, p = 0.0007) and both elevated troponin T and NT-proBNP (7/25, p < 0.0001). Mortality between groups were compared using Chi-squared test.
Chapter Five

Cardio-selective and Non-selective β-blockers in COPD:

Effects on Bronchodilator Response and Exercise

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Department of Respiratory Medicine, Waikato Hospital,

Hamilton, New Zealand

Published as Chang et al

5.1 Abstract

Background
Patients with COPD often have co-existing cardiovascular disease and may require β-blocker treatment. There are limited data on the effects of β-blockers on the response to inhaled β₂-agonists and exercise capacity in patients with COPD.

Objective
To determine the effects of different doses of cardioselective and non-selective β-blockers on the acute bronchodilator response to β-agonists in COPD, and to assess their effects on exercise capacity.

Methods
A double-blind, randomized, 3-way cross-over (metoprolol 95mg, propranolol 80mg, placebo) study with a final open-label high dose arm (metoprolol 190mg). After 1 week of each treatment, the bronchodilator response to salbutamol was measured after first inducing bronchoconstriction using methacholine. Exercise capacity was assessed using the incremental shuttle walk test.

Results
11 patients with moderate COPD were recruited. Treatments were well-tolerated although two did not participate in the high-dose metoprolol phase. The area under the salbutamol-response curve was lower after propranolol compared to placebo ($p=0.0006$). The AUC also tended to be lower after high dose metoprolol ($p=0.076$).
The percent recovery of the methacholine-induced fall was also lower after high dose metoprolol ($p=0.0018$). Low dose metoprolol did not alter the bronchodilator response. Oxygen saturation at peak exercise was lower with all $\beta$-blocker treatments ($p=0.046$).

**Conclusions**

Non-selective $\beta$-blockers and high doses of cardio-selective $\beta$-blockers may inhibit the bronchodilator response to $\beta_2$-agonists in patients with COPD. $\beta$-blockers were also associated with lower oxygen saturation during exercise. The clinical significance of these adverse effects is uncertain in view of the benefits of $\beta$-blocker treatment for cardiovascular disease.
5.2 Introduction

Many patients with chronic obstructive pulmonary disease (COPD) also have cardiovascular disease and have a high risk of cardiovascular mortality [255-260]. β-adrenergic blocker therapy reduces mortality and has symptomatic benefits for many forms of cardiovascular disease [365, 423-427]. Although patients with COPD also appear to benefit from β-blocker treatment for their cardiovascular disease[428], they are often avoided in patients with concomitant airways disease because of fear of drug-induced broncho-constriction [429].

The airway effects of β-blockers are likely to vary substantially between different classes of the drug. Cardio-selective or β₁-adrenoceptor blockers have a negligible effect on β₂-adrenoceptors, except at very high doses [380], and therefore pose less risk of broncho-constriction than non-selective β-blockers [430]. Indeed, the safety of cardio-selective β-blockers in stable COPD (in terms of respiratory function) has been demonstrated in multiple studies [391, 431] and a recent observational study suggested that β-blockers may even be associated with reduced mortality from COPD exacerbations [393]. However, the effects of β-blockers on the airway during an exacerbation of COPD are not known. In particular, the interaction between β-blockers and β₂-agonist bronchodilators has been poorly studied. This is of considerable clinical importance because β₂-agonists are one of the first-line treatments for COPD exacerbations [133]. Since β-blockers and β₂-agonists can competitively bind to the β₂-receptor, β-blocker therapy may impede the bronchodilator response of β₂-agonist inhalers.
Van der Woude and colleagues found that a non-selective β-blocker (propranolol 80mg) reduced the bronchodilator response to β-agonist while the selective β-blockers (metoprolol 100mg and celiprolol 200mg) did not [394]. This study used low doses of cardio-selective β-blockers in order to ensure cardio-selectivity. As β₁ selectivity is a dose dependent phenomenon [380], the effects of cardio-selective β-blockers on the airway at higher doses remain unknown.

In addition to the possible antagonism between β-blockers and β-agonists, there are other potential concerns with the use of β-blockers in COPD. A reduced capacity for exercise is an important cause of disability in COPD and exercise training improves symptoms and health-related quality-of-life [432]. In patients with a low respiratory reserve, cardiac output is an important compensatory mechanism for the increased oxygen demand of exercise. It is plausible that β-blockade may reduce this compensation through its effects on heart rate and sympathetic tone and thus reduce exercise capacity. On the other hand, β-blockers reduce exercise dyspnoea and prolong exercise time in patients with heart failure, although they have no effect on measured exercise capacity or 6 minute walk distances [433]. We are aware of only one study to directly address this issue in COPD - this found no evidence that the cardio-selective β-blockers atenolol and metoprolol reduced the exercise capacity of patients with COPD [434].

This study was designed to assess the effects of clinically-relevant doses of cardio-selective and non-selective β-blockers on the acute bronchodilator response to β-agonist in COPD. Bronchodilator responses to salbutamol were measured in the
setting of methacholine-induced bronchoconstriction using the “challenge-rescue” technique [435]. In addition, the effect of β-blockers on exercise capacity was measured using the incremental shuttle walking test.
5.3 Methods

5.3.1 Subjects

All participants had stable COPD diagnosed by a respiratory physician. Inclusion criteria were: fixed airflow obstruction (post bronchodilator FEV₁/FVC <70%, FEV₁ <80% predicted, reversibility <15% of baseline FEV₁ after inhalation of 200µg of salbutamol); lifetime history of cigarette smoking >15 pack years; ≥40 years of age; and ≥20% fall in FEV₁ with a cumulative methacholine dose (PD₂₀) of <7.5mg.

Exclusion criteria were: current β-blocker use or contraindication to β-blocker use, history of asthma, current use of tiotropium bromide or long-acting β-agonist, and contraindications to methacholine inhalation including severe COPD (FEV₁ <30% predicted or <1.0L).

5.3.2 Study Design

This was a randomized, placebo-controlled, double-blinded, 3 way cross-over study with a final open-label high-dose metoprolol arm. Each study period consisted of 7 - 10 treatment days (to ensure adequate loading of study drug and wash-out from previous treatment) followed by a methacholine provocation test and a shuttle walking test performed on different days. Treatments consisted of slow release once daily propranolol 80mg, metoprolol 95mg, or placebo in random order followed by metoprolol 190mg. All medications apart from the open-label 190mg metoprolol were administered in identical capsules made up by the hospital pharmacy.

Randomisation was generated by an independent hospital pharmacist and unblinding only occurred after all recruitment and treatments were completed. The patients were instructed to take one capsule each morning. During the study,
subjects were asked to withhold all β-agonist inhalers if possible and an ipratropium bromide (20μg) inhaler was provided as rescue medication. Subjects were also instructed to withhold all bronchodilators for at least 8 hours prior to the methacholine challenge tests.

Methacholine challenges were performed using a modified Yan technique [436, 437]. Subjects inhaled doubling doses of nebulised methacholine from 0.0073mg to 3.728mg from a dosimeter and the test was stopped once the FEV₁ had fallen by ≥ 20% from baseline. The PD_{20} (cumulative dose) was calculated by linear interpolation. Salbutamol 100μg, 100μg, and 200μg via metered dose inhaler and Volumatic spacer were given at 0, 5, and 10 minutes after the methacholine challenge respectively. The FEV₁ was measured 5 minutes after each dose of salbutamol, giving a total response time of 15 minutes.

Incremental shuttle walk tests were conducted using the protocol described by Singh et al [438]. Oxygen saturation by pulse oximetry, blood pressure and heart rate were measured at rest before starting the test and at maximal exercise. All patients had a practice shuttle test prior to randomisation to allow for a learning effect.

5.3.3 Ethical Considerations

Given the potential risk of β-blocker induced bronchospasm, arrhythmias, and hypotension, all subjects were given a test dose of short-acting propranolol 40mg prior to entry into the study. Spirometry, blood pressure and an electrocardiogram were measured at 90 minutes after the test dose had been given. The maximal
dose of metoprolol (190mg controlled release) had not been previously studied in COPD and was therefore administered in an open-label arm to enhance safety. The study was approved by the Northern X Regional Ethics Committee of New Zealand. All subjects provided written informed consent.

5.3.4 Analysis

The primary outcomes for the effect of β-blockers on bronchodilator response were:
a) the area under the salbutamol dose-response curve (AUC, expressed as FEV₁ recovery in litres*min) after the methacholine-induced fall and b) the percentage recovery of the FEV₁ after the methacholine-induced fall. These were compared between treatment groups using repeated-measures analysis of variance (ANOVA).

If the initial ANOVA model indicated a significant difference between treatments (p<0.05), each β-blocker was compared with placebo using paired t-tests.

The primary outcomes for the effects of β-blockers on exercise tolerance were the distance walked in the shuttle test and oxygen saturation at maximal exercise. These were compared using ANOVA and paired t-tests as above. The adequacy of β-blockade was determined by analysis of heart rates prior to exercise.
5.4 Results

40 patients were recruited between June 2005 and July 2007 from respiratory outpatient clinics and the local pulmonary rehabilitation programme. 26 patients were excluded after initial screening and 3 more patients withdrew after randomisation 11 patients completed the study protocol and 9 completed the high dose metoprolol arm (Figure 5.1). The treatments were well tolerated but 2 patients elected not to participate in the final phase of the study. The baseline characteristics of the subjects are listed in Table 5.1.

Significant β-blockade was achieved in all active treatment arms compared to placebo with reductions in mean heart rate of nearly 20 beats/min in all active arms (p<0.0001). The mean heart rate was not different between different β-blockers (Table 5.2) (Figure 5.2)

There were no significant differences between baseline FEV₁ (immediately before methacholine inhalation) or PD₂₀ between treatment periods by ANOVA, although baseline FEV₁ tended to be lower following propranolol treatment compared to placebo (p=0.0289 paired t-test) (Table 5.2).

5.4.1 Bronchodilator Response

The area under the salbutamol-response curves was significantly different between treatments (ANOVA p=0.0025). Paired t-tests indicated that the AUC following propranolol was significantly lower than placebo (p=0.0006). The AUC following metoprolol was not significantly different to placebo for the low-dose metoprolol
(p= 0.20) but showed a trend towards a significant difference for high-dose metoprolol (p=0.0760) (Figure 5.3, Table 5.2). The percentage recovery (final FEV₁ as a percentage of the methacholine-induced fall) was also significantly different between treatments (ANOVA p=0.0008). Paired t-tests showed no significant difference in percentage recovery between placebo and low-dose metoprolol treatment (p=0.16) but significant lower percentage recovery in the high dose metoprolol (p=0.0018) and propranolol (p=0.0002) treatment groups compared to placebo (Figure 5.4, Table 5.2).

Previous studies in asthma have indicated that the baseline FEV₁, the fall in FEV₁ induced by methacholine and/or the PD₂₀ methacholine may be significant covariates of the AUC using the challenge-rescue technique [437]. However, none of these were significant covariates when included in the analyses of covariance in this study, and their inclusion made no material difference to the findings.

5.4.2 Exercise Tolerance

The mean distances walked in the shuttle tests at the end of each treatment period are shown in Table 5.2. There was no significant difference overall between treatment groups by ANOVA but there was a trend to lower distances after propranolol treatment than placebo (paired t-test, p=0.0015). Oxygen saturation at the end of exercise was significantly different between groups (ANOVA p=0.046) and was lower in the high dose metoprolol group (paired t-test, p=0.0302) (Table 5.2).
5.5 Discussion

This study provides evidence that the bronchodilator response to salbutamol may be impaired by β-blocker treatment. Predictably, this effect was most apparent for the non-selective β-blocker, propranolol. Indeed, the response to salbutamol after methacholine challenge in the propranolol group was little better than the natural rate of recovery from methacholine, indicating almost complete β₂-receptor blockade (Figure 5.4). However, we also found that high doses of the selective β₁-blocker metoprolol appeared to partially inhibit the bronchodilator responsiveness to β-agonists. There was little difference between the bronchodilator responses after low dose metoprolol compared to placebo.

These results raise potential concerns about the safety of cardio-selective β-blockers at high, but clinically relevant, doses. These findings need to be interpreted with caution - the difference in bronchodilator response was small and only significant in the percentage recovery analysis, although there was a similar trend for the AUC (p=0.076). These findings require confirmation in further studies. Whether other cardio-selective β-blockers have a similar effect to bronchodilator response at high doses is unknown.

The safety of β-blockers in COPD is an important issue. The role of β-blockers in primary and secondary prevention as well as treatment of cardiovascular diseases is well-established and the use of β-blockers is becoming increasingly common in the COPD population. Despite several publications in recent years citing the safety of cardioselective β-blockers in COPD disease, there is very little evidence of their
effects in the setting of an exacerbation of airways disease [391, 431]. In particular the impact of prior β-blocker treatment on the response to β-agonist bronchodilators has received little attention. To our knowledge, the only other study to examine bronchodilator response in this setting found that a non-selective β-blocker (propranolol 80mg) reduced the bronchodilator response to β-agonist while low doses of selective β₁-blockers (metoprolol 100mg and celiprolol 200mg) did not [394]. Although in that study the doses of the cardio-selective β-blockers had been intentionally limited to doses that guarantee cardioselectivity – i.e. in the lower range of clinically recommended doses. Our study also found no significant difference between placebo and low dose metoprolol. However, we found that metoprolol at higher doses did appear to have an effect on bronchodilator response. The subjects in our study also had more severe COPD than those previously studied [394] and therefore may be more representative of the patients with moderate-severe COPD that are most likely to develop cardiovascular co-morbidities and benefit from β-blocker treatment.

Our study used the challenge-rescue technique to measure the response to β-agonists after β-blocker treatment. This technique has now been used in both asthma[435, 437, 439] and COPD [394] and has proven to be a sensitive method to demonstrate functional impairment of β₂-agonist bronchodilation. Measuring the bronchodilator response after methacholine-induced bronchoconstriction attempts to replicate the experience of patients, who use bronchodilators to relieve symptoms caused by bronchoconstriction. Although the airflow limitation associated with exacerbations of COPD is far more complex than simple airway
smooth muscle-induced bronchoconstriction, it is this aspect of airway narrowing that is the main target of β₂-agonist treatment. Methacholine responsiveness is common in COPD [440] and the challenge-rescue technique enabled the measurement of a bronchodilator response in this group of COPD patients who had fixed airflow obstruction with no significant response to β-agonist at screening.

We also observed a trend towards worsening exercise capacity with the non-selective β-blocker propranolol while the selective β-blocker metoprolol made little difference to exercise capacity even at high dose. Although any reduction in exercise capacity is undesirable, it is unclear whether this difference is clinically important. Singh et al estimated the minimum clinically important difference in distance walked for the shuttle test to be 47.5m [441]. In our study, the difference between the mean distances walked during placebo and propranolol treatments was slightly less than this at 45.5m (Table 5.2).

All β-blockers were associated with lower oxygen saturations (measured by pulse oximetry) at peak exercise. This was only statistically significant in the high dose metoprolol group, but there were trends towards lower oxygen saturations in all active treatment groups. This is a novel observation in patients with COPD. A potential explanation is that β-blockade reduces cardiovascular compensation during exercise resulting in reduced oxygen delivery when the respiratory system is impaired. This is supported by evidence that β-blockade exaggerates exercise-induced oxygen desaturation at altitude and reduces cardiovascular oxygen flow in hypoxia [442, 443]. It has been postulated that there is β-adrenoceptor mediated
vasodilation in hypoxic exercise states and that blockade of these receptors may lead to significant tissue hypoxia [444]. The clinical implications of this in the setting of COPD and exercise are uncertain.

The main limitation of this study is the small number of subjects involved. Hence the study may be underpowered to detect small differences between placebo and metoprolol treatment. Despite this, we observed a non-significant trend to a reduced response to bronchodilator with high-dose metoprolol which was statistically significant when analysed as percentage recovery. Based on previous studies in asthma [435, 437, 438], we calculated a sample size of 10 subjects in a cross-over design to provide 80% power to show a 35% reduction in the response to salbutamol. Such a reduction in response is typically seen during regular short- or long-acting beta-agonist therapy [435, 437] and effects smaller than this in response to beta-blocker therapy may be of doubtful clinical significance.

Another limitation is that, for safety reasons, the high-dose metoprolol arm was unblinded and not in random-order. We believe it is unlikely that this introduced bias to the measurement of bronchodilator response since an objective outcome (FEV₁) was used. However, as this open-label arm was conducted last, a learning effect may explain the non-significant trend to an increased walk distance in this treatment arm. The number of patients who were not eligible for this study also raises the issue of the generalisability of its findings. More than half of the potential volunteers were excluded because of their pre-existing treatment (long-acting anti-cholinergic treatment which would preclude methacholine challenges, or long-acting
β-agonists which would induce tolerance to the β-agonist response) or because they had COPD which was either too mild or too severe for the protocol. We believe it is unlikely that these selection criteria have biased the findings.

Although cardio-selective β-blockers appear to be safe in stable COPD, little is known about their effects in exacerbations. This is the first time that the bronchodilator response to β-agonist has been measured after full recommended-dose cardio-selective β-blocker therapy. Our findings confirm that non-selective β-blockers block the bronchodilator response and raise concerns that high doses of cardio-selective β-blockers may partially inhibit the bronchodilator response to β₂-agonists. We also observed lower oxygen saturations during exercise with β-blocker therapy. These findings need to be interpreted in the context of recent studies regarding the safety profile and benefits of cardio-selective β-blockers in chronic stable COPD. Even though cardio-selective β-blockers may provide overall benefit to these patients, our study identifies potential drawbacks to this treatment.
Table 5.1 Study subject baseline characteristics

<table>
<thead>
<tr>
<th>Age, mean (range)</th>
<th>65 years (47-76)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking Status (n)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Smoker</td>
<td>5</td>
</tr>
<tr>
<td>Ex-Smoker</td>
<td>6</td>
</tr>
<tr>
<td>Pack-years, mean (range)</td>
<td>49 (20-100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung Function, (mean (SD))</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td>1.64 (0.53)</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>59% (15%)</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.58 (0.09)</td>
</tr>
</tbody>
</table>

| Heart Rate, beats/min (mean (SD)) | 79.8 (10.0) |
Table 5.2 Variables at the end of each treatment period.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo (n=11)</th>
<th>Metoprolol 95mg (n=11)</th>
<th>Propranolol (n=11)</th>
<th>Metoprolol 190mg (n=9)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Baseline FEV₁, L (SD)</td>
<td>1.60 (0.53)</td>
<td>1.54 (0.58)</td>
<td>1.48 (0.50)*</td>
<td>1.59 (0.55)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PD₂₀, mg (SD)</td>
<td>0.69 (1.03)</td>
<td>0.60 (0.79)</td>
<td>0.45 (0.69)</td>
<td>0.76 (0.84)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean AUC L/min (SD)</td>
<td>3.12 (1.16)</td>
<td>2.55 (1.81)</td>
<td>1.20 (1.32)†</td>
<td>2.31 (1.14)†</td>
<td>p = 0.0025</td>
</tr>
<tr>
<td>Mean recovery, % of fall (SD)</td>
<td>114.1 (54)</td>
<td>97.2 (72)</td>
<td>38.3 (36)**</td>
<td>82.4 (40)∥</td>
<td>p = 0.0008</td>
</tr>
<tr>
<td>Mean Heart rate, beats/min (SD)</td>
<td>78.8 (12)</td>
<td>62.9 (11)</td>
<td>61.2 (11)</td>
<td>61.6 (10)</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Mean ISWT distance, m (SD)</td>
<td>480.9 (181)</td>
<td>458.2 (202)</td>
<td>435.5 (186) §</td>
<td>504.4 (213)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean O₂ Sat after ISWT (SD)</td>
<td>94.2 (5.0)</td>
<td>92.5 (5.0)</td>
<td>91.2*** (6.2)</td>
<td>90.1 (6.8)¶</td>
<td>p = 0.046</td>
</tr>
</tbody>
</table>

Paired T-Tests against placebo value:
* p = 0.0289, † p = 0.0006, ‡ p = 0.0760, ** p = 0.0002, ∥ p = 0.0018, § p = 0.0015, *** p = 0.0830, ¶ p = 0.0302
Figure 5.1 CONSORT flow diagram of trial profile

Eligible for Screening (n = 40)

Excluded after screening (n = 26)
- FEV₁ < 1.0L or 30% predicted n = 8
- Reversibility > 15% after bronchodilator n = 8
- No change to FEV₁ after methacholine inhalations n = 3
- FEV₁ > 80% predicted  n = 2
- Patient declined participation after screening n = 2
- Bronchospasm after test dose of β-blocker n = 1
- Inability to perform shuttle-shuttle walk test n = 1
- Exacerbation of COPD after screening n = 1

Randomized (n = 14)

3 withdrew after randomization
- Exacerbation of COPD (n = 2)
- Other health related (n = 1)

11 completed randomized, double-blinded 3-way cross-over study periods
- (metoprolol 95mg, propranolol 80mg, placebo)

2 withdrew consent

9 completed open-label high dose metoprolol (190mg) study period
Figure 5.2 Effect of β-blocker treatment and exercise on heart rate

ISWT = incremental shuttle walk test.

Error bars indicate standard error.
**Figure 5.3** Mean FEV$_1$ values before and after methacholine challenge and following salbutamol.

![Bronchodilator Dose-Response after Beta-Blocker Treatment](image)

The baseline FEV$_1$ appears higher in the high-dose metoprolol arm because the 2 participants who declined to participate in this arm had baseline lung function below the group mean.
**Figure 5.4** Percentage recovery in response to salbutamol after each treatment (expressed as percentage of the fall in FEV1 induced by methacholine).

The natural recovery curve was obtained at 5, 10, and 15 minutes after the screening methacholine challenge when no bronchodilators were given.
Chapter Six

Discussion
Contrary to what Asimov says, the most exciting phrase in science, the one that heralds new discoveries, is not 'Eureka!' or 'That's funny...', it's 'Your research grant has been approved.'

- John Alejandro King

6.1 Introduction

This research into acute COPD exacerbations examined questions that fall into three general themes:

1. What is the pattern of COPD-related hospitalisations in New Zealand and how well do we manage our patients compared to internationally recognised standards? The data obtained from the retrospective (Chapter Two) and prospective cohort (Chapter Three) studies were analysed to address these questions.

2. Can a simple bedside score such as the CURB65 score be used to predict risk in a patient with an acute exacerbation of COPD? This hypothesis was explored in a small retrospective study (Chapter Two) and then prospectively tested in a larger cohort study (Chapter Three).

3. Are elevated cardiac biomarkers, in particular, Troponin T and pro-NT BNP, indicative of increased risk of mortality in acute exacerbations of COPD? What are the implications of this for our current understanding of exacerbation pathophysiology and treatment? Data
collected from the prospective cohort study (Chapter Four) were used to address the first part of this question. As β-blockers have proven benefits in cardiovascular disease treatment, a randomised controlled study (Chapter Five) was conducted to examine the effect of β-blocker treatment in COPD patients and the effect this may have on their bronchodilator response to β-agonists.

This discussion will address each of these themes in the light of the new information obtained during the conduct of these investigations and other studies published since embarking on these studies. It will also highlight further investigations currently underway, or planned by the author and the research group to which the author belongs as well as any recommendations for clinical practice based on the answers to the author’s research questions.
6.2 The Pattern of COPD Hospitalisations in New Zealand and International Comparisons

COPD is a leading cause of morbidity, mortality and socioeconomic burden. Acute exacerbations of COPD account for the majority of direct and indirect costs of COPD and frequently result in hospitalisations. Suboptimal in-hospital management can lead to increased complications, longer hospital stay, recurrent admissions and increased mortality. Several international clinical practice guidelines are available for the assessment and management of these patients [1, 2, 133]. These are based on the best currently available evidence and are remarkably consistent with few clinically relevant variations [445].

Few practice adherence studies are available in the literature. A recent systematic review examining in-hospital management of COPD exacerbations identified only seven studies (including the author’s own as presented in Chapter Two of this thesis) that were published since the widespread availability of the practice guidelines [446]. Of these, only four included information that was collected in the last decade and only one study recruited patients prospectively. Apart from the author’s own study, only one other study which was small (n = 49) included patients from non-European or non-North American centres [176]. This is remarkably sparse information given the number of patients that present with acute exacerbation of COPD daily. Prior to our study, the only study to examine the care of patients with COPD exacerbations in a New Zealand hospital was conducted more than 15 years ago [179]. This absence of local information is important because different COPD prevalence, phenotypes and microbial patterns have been observed in population-based
studies and this may translate into regional specific clinical presentation and treatment requirements [4, 91].

The available studies that do address clinical management of patients with exacerbations of COPD suggest a wide variation in approach to clinical assessment and treatment in hospitalised patients. One might infer that poor guideline adherence leads to poorer patient outcomes as exacerbation of COPD management guidelines are evidence based current best practice. On the other hand, the evidence on which these guidelines were based is far from robust and sometimes limited to level IV recommendations. One can conjecture that the wide variation in clinical approach is in fact appropriate given the varied patient phenotypes. However, not only does management appear less than ideal in many centres when compared to guidelines, but documentation is often incomplete making it impossible to accurately assess whether any improvements can be made [173].

Chapter Two describes a review of COPD admissions to a secondary New Zealand hospital, while Chapter Three describes a prospective cohort of consecutive COPD admissions for one year to the same hospital. These studies compared local patient characteristics, clinical management practice and patient outcomes with published best practice guidelines and other available international cohort statistics.

The studies found that the general patient characteristics, clinical features and lung function were similar to that of other cohorts. Women make up a substantial proportion of both
studies (43% in the retrospective study and 55% in the prospective study). This is a trend that is increasingly observed in COPD epidemiology research [94, 447, 448]. COPD has traditionally been regarded as a predominantly male condition. However, in the last two decades, the overall prevalence of COPD has increased more rapidly in women than in men, and in many industrialised countries more women than men are dying from COPD [36]. In the USA, the rate of emphysema is approximately equal in men and women but chronic bronchitis now affects twice as many women as men[449]. Recent research has identified increasing sex (biological differences between men and women) and gender (socio-cultural differences ascribed to the two sexes) differences in COPD prevalence, symptoms, diagnosis, self-care, coping strategies and determinants of quality of life [440, 450-453]. Increasing evidence now supports greater rates of decline in lung function associated with smoking and other environmental exposures in women compared to men [454-457]. When these factors are considered together, COPD is expected to become an increasingly major health issue for women worldwide. Despite this most of the available literature has focused on men. This thesis goes a small way in helping address this data deficit, at least in New Zealand women.

Although our overall patient demographics are comparable to other published cohorts, Māori patients were significantly younger than non-Māori New Zealanders. This was a novel, albeit unsurprising finding. Māori have the poorest health status of any ethnic group in New Zealand. It is a disadvantage they share with numerous other ethnic minority groups in other countries around the world. The current gap in life expectancy at birth between Māori and non-Māori New Zealanders is 8.6 years for men and 7.9 for women [111].
However, the age gap between Māori and non-Māori New Zealanders at hospitalisation in the retrospective study was almost twice as wide. The median age at presentation was 57 years for Māori and 72 years for non-Māori. The follow up prospective study also found a statistically significant albeit smaller age gap between Māori and non-Māori patients (7 years). This suggests that Māori are not only dying earlier but may be suffering symptoms of the disease and requiring hospitalisation earlier than their European counterparts. However, as the analysis did not account for whether the admission was a first or recurrent admission, the data need to be interpreted with caution.

Our findings are in keeping with other studies that have found higher rates of respiratory-related hospitalisation in Māori. A 2006 report found that the overall rate of hospitalisation for community-acquired pneumonia was 3.03 times higher among Māori than non-Māori New Zealanders \((p < 0.001)\) [458].

There are likely to be multiple factors contributing to this difference. Perhaps the most obvious is the higher rates of smoking and second-hand tobacco exposure in Māori which has been well documented [104]. If this factor turns out to be the most important factor accounting for this difference then unfortunately this difference looks set to widen. While prevalence of tobacco use is falling in the general population it continues to increase in the Māori population, particularly in Māori women [104]. Other likely contributing factors include: poorer primary health access; higher rates of childhood respiratory infections; higher rates of occupational and environmental exposure and greater social deprivation.
Whatever the underlying factors, our results highlight the discrepancy in health status and identify Māori as an important area of need for targeted service delivery and risk factor strategies.

Our findings also support the concept of the “frequent exacerbator” as a distinct disease phenotype of COPD. It appears that having one exacerbation is itself a risk factor for further exacerbations. In the retrospective study, most patients (71%) had previously been hospitalised for COPD-related symptoms and more than 90% of the health care resources audited was utilised by a small percentage of individuals. These “high user” patients tended to have multiple co-morbidities and often self presented. Indeed, much work has appeared in the literature concerning this group of patients since the publication of our study [128, 459]. Most recently, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators published the results of a large cohort study involving more than 2000 patients with COPD followed over 3 years [460]. This study identified that the single-best predictor of exacerbations, across all GOLD severity stages, was a history of exacerbations. Conversely, a subgroup of patients with severe disease that are relatively resistant to exacerbations was also identified. These findings suggest treatments may potentially be tailored to individuals identified as “frequent exacerbators” and that if successful, targeting these patients may lead to significant health-economic benefits.

The retrospective study also demonstrated that the “social admission” is common in this group of patients. Social issues were listed as one of the predominant presenting
complaints in 35% of all patients, behind dyspnoea and changes in sputum production and/or purulence. The potential influence of social factors on hospitalisations, lengths of stay and readmissions for acute exacerbations of COPD have not been well studied. Previous studies have identified marital status (a single person is more likely to live alone and may have less support to help manage their illness), socio-economic factors and the requirement for social worker input during a hospitalisation to be associated with longer lengths of stay and poorer recovery [461-463]. In our study, 20% of the patients required input from a social worker during their admission and of these, most (n = 14/19 patients) were discharged to living arrangements that were not their own home. Six of the 14 patients required convalescent care while the rest were discharged to community health care or residential care facilities.

The increased support requirements likely reflect a significant decline in functional status in these individuals. How much of this decline can be attributed to their pulmonary disease is difficult to tease out. It is possible that the decline in functional status without overt evidence of pulmonary deterioration may in fact reflect subtle deteriorations with systemic decompensation or changes in social support. Our study found no difference in short-term mortality whether patients were admitted for social reasons or not. In the BTS acute exacerbation audit, poor home circumstances on admission were found to be a significant risk factor for mortality [174]. Whether this heightened risk can be translated into a treatment approach is yet to be seen but further research is warranted. Perhaps a risk assessment approach that takes overall frailty and reduced mental capacity into
consideration may be a useful starting point to investigate this. The value of a rapid bedside assessment tool in these patients will be discussed in the next section.

The frequency of co-morbid illnesses found in our patients deserves some comment. Most (71%) patients had two or more co-morbidities documented at the time of admission (median number = 2.2). By far the most common co-morbidity in our study was ischaemic heart disease. When all cardiac diseases were combined (ischaemic heart disease, hypertension, congestive heart failure, valvular heart disease and cardiac rhythm disorders) 56 of 94 (60%) had one or more cardiac related co-morbidities. This is not surprising given that our cohort is comprised of a selected population of elderly smokers/ex-smokers. However, when compared to other hospital admission cohorts with similar demographics and disease severity indices, such as the Dutch study reported by Groenewegen et al, our patients report significantly higher rates of co-morbid illnesses [209]. Despite this, both of our studies reported a shorter overall length of hospital stay (3.4 days).

The relatively short duration of stay reported in the retrospective study may be attributed to several factors. Firstly, our hospital policy is to admit patients with respiratory illnesses directly under the care of a specialist respiratory physician (94% of all patients) on a respiratory ward (79%). Previous studies in the management of patients with obstructive lung diseases have suggested that specialist respiratory units provide better care than non-respiratory medical specialists [174, 464, 465]. Our study confirms this finding: patients admitted under non-specialist respiratory care, typically had longer lengths of stay and were
less likely to receive input from allied health practitioners such as respiratory physiotherapists. In contrast, the Christchurch study of COPD admissions had equal numbers of admissions to general medical services and specialist respiratory services and also documented a longer length of stay of 9 days [179].

Secondly, all junior medical staff rotating through the respiratory unit attend an one day course at the start of their rotation, on common respiratory presentations and the preferred management guidelines. At the time of this study, these guidelines were based on the 2004 British Thoracic Society guidelines [133]. This course helps standardise investigations and care allowing optimal management to be institute from the time of patient presentation rather than potentially delaying optimal care until respiratory specialist review on the ward-round the following day.

Thirdly, the unit policy recommends that bronchodilators are administered via metered-dose inhalers (usually via a spacer device) and dry powder inhalers instead of nebulisers in all patients if possible. Only 31% of patients in our cohort received bronchodilators via nebulisers in contrast to 90 -100% found in the literature [173, 446]. There is now a body of evidence indicating that wet nebulisers are more expensive, less portable, require more resource and time intensive maintenance and have more varied drug delivery and side-effects compared to metered-dose and dry powder inhalers [466]. Accordingly, major treatment guidelines that recommend the use of bronchodilators now advise against the use of nebulisers when possible [2, 71]. It is plausible that early use of metered-dose and
dry powder inhalers or early conversion to these inhalers from nebulisers facilitates early discharge. The effect on discharge may be two fold, firstly drug delivery may be improved and secondly, through psychological assurance. Patients are likely to have ready access to dry powder or metered-dose inhalers at home but unlikely to have access to nebulised bronchodilators.

Finally, the respiratory unit has access to an open High Dependency Unit for patients in acute respiratory failure requiring non-invasive ventilation. These patients are cared for directly by the specialist respiratory team. Traditionally, therapeutic nihilism (in clinicians as well as patients) and resource constraints have contributed to variations in mortality [225, 398, 399]. Indeed, the BTS acute exacerbations audit noted that only 13% of patients with acidosis and hypercapnoea received ventilatory support compared to nearly 90% in our cohort [174]. Having ready in-house access to a trial of non-invasive ventilation, without necessarily admitting the patient to the Intensive Care Unit, may have increased the rate of use of non-invasive ventilation in our patients.

There are several limitations that must be acknowledged. Firstly, as in many other retrospective cohorts, the patients in the study described in Chapter Two were identified by disease coding (International Classification of Diseases, 10th edition) and therefore subject to the error inherent with the coding process. Further selection bias may have occurred as patients were selected for study from only two representative months of a 12-month period. The small number of patients also limited the retrospective study. Finally, in
retrospect, it may have been interesting to examine the relationship between socio-economic status, ethnicity, hospital length of stay and other service usage. Some of these data were not collected in our study, but these relationships deserve future research.

Despite these limitations, the retrospective study is important. It became the forerunner and allowed better design and statistical planning of a rigorously conducted prospective cohort study that provided data for the bulk of this thesis. This retrospective study also confirmed that the New Zealand in-hospital COPD population is comparable in patient demographics and disease characteristics to international cohorts. It also demonstrated that our health care system is able to deliver treatment to internationally acceptable standards and achieve the same, if not better (in terms of length of hospital stay) outcomes. Both of these findings were also confirmed in the prospective cohort as detailed in Chapter Three. The positive results obtained from the retrospective study examining the CURB65 score as a potential risk predictor in COPD exacerbations encouraged further investigation of this topic in a prospective way (discussed in Chapter 6.3). The frequency of cardiac co-morbidities coupled with the frequent elevation of cardiac biomarkers observed in this group of patients also led to further prospective analysis of these biomarkers (discussed in Chapter 6.4).
6.3 Risk Prediction in Acute Exacerbations of COPD using the CURB65 score:

One Score to rule them all?

Patients with acute exacerbations of COPD commonly present with a wide range of symptoms and severity, and a spectrum of treatment requirements – from unscheduled primary care visits to in-patient and intensive care. In clinical decision-making, the physician has to take into account multiple parameters such as the severity of the underlying lung disease, the severity of the acute exacerbation, the presence of any co-morbidities, and the social and familial context. Early identification of individuals at higher risk and initiation of treatment in the appropriate setting will improve patient care, patient satisfaction and health economics. Previous studies had found increased risk following COPD exacerbations in association with a number of disease and patient characteristics [209-212, 214, 216-218, 221, 222] and a number of complex risk computation models had been developed from large multi-centre cohorts [204, 224]. However, a consistent yet practical risk assessment system had not been established and currently these decisions are still predominantly made on clinical judgement. An easy to use objective risk stratification tool such as those already available in patients with community-acquired pneumonia may be equally useful in patients with acute exacerbation of COPD [228, 236].

The hypothesis that the CURB65 risk prediction score, widely used in assessment of community-acquired pneumonia, can also predict risk in patients with exacerbation of COPD was explored in this thesis. This hypothesis was retrospectively examined in Chapter Two, where we observed that a high CURB65 score was predictive of higher risk of death within
30 days of hospitalisation for COPD. Chapter Three described the prospective cohort study specifically designed to validate this observation.

The retrospective study in Chapter Two was, to our knowledge, the first report of an association between CURB65 score and outcome in patients hospitalised for acute exacerbation of COPD. This study found that patients with low (scores 0 and 1), medium (score = 2) and high (scores >2) CURB65 scores had 30 day mortalities of 0%, 15% and 22% respectively (p = 0.006) (Tables 2.5 & 2.6 p94-5). However, the results need to be considered in context of the limitations inherent in a retrospective study. The patients were identified by disease coding, and therefore may be subject to selection bias. The CURB65 score was calculated from information obtained from the notes and although it was decided a priori to record only data available at presentation, this may still be open to the collector’s interpretation. Four patients did not have sufficient information recorded in the notes for a CURB65 score to be calculated.

With these limitations in mind, the prospective cohort study described in Chapter Three was designed. We recruited consecutive patients with physician diagnosed COPD exacerbations admitted to a public hospital during a 1-year period. The CURB65 scores were calculated at initial hospital presentation and the patients were followed until death or discharge and at 30 days and 1 year after the initial presentation. CURB65 score was independently predictive of 30-day mortality (crude odds ratio= 1.89, adjusted odds ratio = 1.71, p = 0.013) after correcting for other significant risk factors of poor outcome such as lung function,
nutritional status and deranged ventilation parameters. As in community acquired pneumonia assessment, CURB65 scores were grouped into three risk groups: low risk (scores 0-1), intermediate risk (score = 2) and high risk (scores 3-5). CURB65 risk group was independently predictive of 30-day mortality (crude odds ratio = 3.05, adjusted odds ratio 3.24, p < 0.001). These odds translated into risks of death at 30-days after presentation of 2%, 7% and 21% for patients with low risk, intermediate risk and high risk scores respectively. (Table 3.2, p114)

This study prospectively confirmed observations from the retrospective study: that CURB65 score is predictive of mortality in acute exacerbations of COPD. There was remarkable consistency between the mortality rates and risk class in the retrospective and prospective cohorts (Table 6.1, p187) indicating good score reliability. Indeed, the mortality rates found for COPD exacerbations in each risk group were remarkably similar to those observed in previous community acquired pneumonia cohorts [236]. The routine use of risk prediction models such as the CURB65 score or the pneumonia severity index (PSI) have already been incorporated into clinical management guidelines for community acquired pneumonia [228, 402]. Perhaps the CURB65 score might be similarly useful in the management of COPD exacerbations.

This is the first study to prospectively assess a prognostic scoring system in the setting of an acute COPD exacerbation. More recently, confirming the need for a workable clinical risk prediction tool for acute exacerbation of COPD, Tabak et al reported a risk prediction model
developed after retrospectively analysing a large COPD exacerbations database [406]. This
was published after completion of the work described in this thesis. Tabak et al proposed a
risk model based on blood urea nitrogen level > 25mg/dL, acute mental status change, pulse
>109/min and age > 65 years. Termed the BAP65 score, this model stratified patients into 5
risk classes of increasing in-hospital mortality and requirement for mechanical ventilation.
Importantly, this model includes 3 of the 5 CURB65 criteria: mental status, urea and age.
The BAP65 model has yet to be prospectively validated but likely reflects common
underlying physiological changes that our model incorporates and confirms that simple
measures of abnormal physiology can indicate increased risk in acute exacerbation of COPD.

Both the CURB65 and BAP65 models include altered mental status, elevated serum urea,
elevated pulse rate or low blood pressure and age as their component variables. These
markers signal the limit of a patient’s physiological reserve. A decline in mental status may
be due to critical hypoxia and/or hypercapnoea in acute exacerbations of COPD. Chronic
respiratory failure is common in stable COPD and patients often develop a degree of
tolerance to abnormal hypoxia and/or hypercapnoea. Monitoring the body’s response to
the further ventilatory aberrations that occur during an acute exacerbation of COPD may be
a better way to assess severity than actual measurements of arterial oxygen and carbon
dioxide tensions. Similarly, an elevated pulse rate or reduced blood pressure in the
presence of significant cardiopulmonary insult indicates considerable cardiovascular stress
and possible imminent decompensation. Elevated serum urea has consistently appeared to
be an important maker of poor outcome in respiratory disease, particularly community
acquired pneumonia [228, 236]. In acute exacerbation of COPD, it may reflect reduced
volume status from reduced oral intake and hyperventilation or reduced inadequate renal perfusion from cardiovascular distress or increased protein catabolism due to increased metabolic demands.

Taken together, these markers form a model integrating the effects of chronic disease, reduced physiological reserve and acute respiratory insult. Our study and the results reported by Tabak et al add weight to the concept that a score based on these markers can be a powerful tool for risk stratification in acute exacerbations of COPD. Importantly, after excluding deaths that occurred in the first 30 days, CURB65 score was not predictive of late mortality. This indicates that a high score reflects more than simply overall frailty and poor health but rather a measure of the acute exacerbating process that may lead to death.

A clinically usable risk prediction model may be beneficial for a number of reasons:

Firstly, such a model provides an objective assessment of both exacerbation severity and degree of risk that are absent in the current management paradigm. Although all clinical guidelines recommend severity assessment prior to determining the best treatment options and location, there has been no evidence based risk stratification framework available [2, 71, 133]. With the exception of blood gas analysis to detect the acidotic patient with respiratory failure in whom mechanical ventilation is a likely requirement, clinicians still rely on the nebulous entity of “clinical acumen” to determine the diagnosis, severity and optimal treatment when a patient presents with an acute exacerbation. Existing severity criteria that are applicable in stable disease (such as spirometry or exercise tolerance) are often
unobtainable or inappropriate in the acute setting. An accurate and reliable prognostication model in these patients would support clinical decision making and may lead to improved patient outcome. The previous section discussed the suggestion that some patients with COPD exacerbations may be undertreated because of therapeutic pessimism. An objective risk prediction tool may alleviate this pessimism and thus improve treatment access in these patients [225, 398].

Secondly, current research into COPD management has been hampered through the lack of both a unified definition and a severity stratification tool for acute exacerbations. Existing clinical studies are routinely criticised for relying on treatment surrogates such as antibiotic or systemic corticosteroid use. A systematic review addressing the way in which clinical trials count, analyse and report COPD exacerbations found widely varying definitions of COPD exacerbation and measures of severity [467]. The reviewers commented that “without a consistent and standardised definition of an outcome, it is impossible to compare one trial with another – or even one medication against another – to determine the relative efficacy of different therapies in reducing the rate of COPD exacerbations.” An objective, well validated, easy to use severity model would help fill this gap in current research, improve trial design and enable accurate evaluation and comparison of results.

Thirdly, as medicine moves towards “shared decision making” where physicians and patients both actively participate in deciding on choices for diagnostic tests or therapeutic interventions, adequate communication about risks and benefits are pre-requisite. An
objective severity assessment tool can facilitate discussions between clinicians, patients and their families and lead to better-informed management decisions.

Finally, objective information on severity and patient risks can help service providers and health policy makers assess the needs of different patient populations and assist in allocating appropriate resources. This is particularly important given current economic constraints and limited health resources. A robust method of identifying patients at highest risk may aid in more appropriate health utilisation and improve emergency department efficiency.

It remains to be seen whether a risk assessment model for acute exacerbations of COPD will actually lead to these projected benefits. Very recently, the CRB65 score (a simplified model based on the CURB65 criteria but does not require laboratory measurement of serum urea) was independently validated in a retrospective study [468]. This study also found that CRB65 score predicted short-term (in-hospital and 30 days) but not long term (1 year) mortality in patients presenting with acute COPD exacerbations. Again, the proportion of deaths in each risk group is similar to that found in both our retrospective and prospective cohorts (Table 6.1, p187).

CRB65 offers the additional benefit over a new clinical prediction score in that it is a familiar score that is already in use for another common acute respiratory presentation – community acquired pneumonia. In our study cohort, the CRB65 score was as effective in
predicting mortality from acute exacerbation of COPD as it was for predicted mortality from community acquired pneumonia in previous published cohorts. One can envisage the biological plausibility for why the CURB65 score may work equally well in risk prediction for both conditions. Exacerbations of COPD and community acquired pneumonia share important aetiological and pathophysiological factors including respiratory infections, smoking and inflammation [149, 249, 250, 253]. Despite the lack of clarification as to the exact host-pathogen interaction that results in COPD exacerbations, bacterial and viral respiratory tract infections undoubtedly play an important role in most cases [252]. Recent studies have indicated that it is not just the presence of bacteria, but their numbers, acquisition of new strains and probable interaction with viruses that relate to the features of exacerbation [149, 469, 470]. Clinical features for presentations of community acquired pneumonia and COPD exacerbations often overlap, particularly in patients with COPD. Both conditions may present with dyspnoea, cough, sputum, fever and leucocytosis. The primary clinical feature delineating the two has traditionally been parenchymal consolidation seen on chest radiography in patients with pneumonia. This has long been considered the “gold standard” in differentiation [227]. However, many patients who present with symptoms and even clinical findings suggestive of pneumonia lack the typical radiographic findings at the time of presentation [409]. Similarly, patients with COPD often have chronic chest radiographic changes and these may be misdiagnosed as pneumonia on acute presentation. A shared risk stratification pathway may provide a practical way to approach this common diagnostic dilemma.
The beauty of the CURB65 score lies in its simplicity. The variables are simple to obtain at the bedside and the calculations required can be done quickly. Unlike previously proposed risk computation models from the SUPPORT and CAOS studies, the CURB65 score has gained widespread acceptance for community acquired pneumonia and could do the same for COPD particularly if only one score is required for two common respiratory conditions.

Several limitations of this study are acknowledged. Clinicians treating cohort patients were not blinded to the CURB65 results and were aware of the results from the previous retrospective study. It is conceivable that this knowledge influenced treatment or discharge decisions although it seems unlikely that it would alter the primary outcome of 30-day mortality as all patients were treated as per standard unit protocol. The results represent the outcome of a modest number of patients from a single centre and therefore require independent external validation ideally with a larger number of patients. One of the strengths of this study is the comprehensive follow-up rate; 30-day mortality outcomes were available for all but 3 of 252 participants. The study design was simple and the patients were unselected prior to recruitment.

Our findings indicate that CURB65 score predicts short-term mortality following exacerbations of COPD requiring admission to hospital. This finding is novel and needs further validation in an independent manner. Whether the use of a severity assessment tool leads to improved clinical outcome and optimal management strategies can be defined for patients in different prognostic groups requires further research. However, the use of
the CURB65 score to categorise patients into severity groups, may for the first time, allow meaningful comparison between studies and ultimately allow these questions to be answered.
### Table 6.1 Summary of studies that assessed the ability of CURB65/CRB65 scores to predict mortality after COPD exacerbation

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of Publication</th>
<th>Type of Study</th>
<th>Study Population</th>
<th>N</th>
<th>Low Risk (&lt;2)</th>
<th>Moderate Risk (=2)</th>
<th>High Risk (&gt;2)</th>
<th>30 Day Mortality by CURB65 or CRB65 score*</th>
</tr>
</thead>
<tbody>
<tr>
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<td>N</td>
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<td>%</td>
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<td></td>
</tr>
<tr>
<td>Chang [405]</td>
<td>2007</td>
<td>Retrospective</td>
<td>Hospital admissions</td>
<td>86</td>
<td>0/34 0%</td>
<td>3/20 15%</td>
<td>7/32 22%</td>
<td></td>
</tr>
<tr>
<td>Chang [412]</td>
<td>2010</td>
<td>Prospective</td>
<td>Hospital admissions</td>
<td>249</td>
<td>2/98 2%</td>
<td>6/90 7%</td>
<td>13/61 21%</td>
<td></td>
</tr>
<tr>
<td>Leow†</td>
<td>Unpub</td>
<td>Prospective</td>
<td>Hospital admissions</td>
<td>73</td>
<td>0/24 0%</td>
<td>3/27 11%</td>
<td>6/22 27%</td>
<td></td>
</tr>
<tr>
<td>Edwards* [468]</td>
<td>2011</td>
<td>Retrospective</td>
<td>Ambulance retrieval</td>
<td>131</td>
<td>3/67 4%</td>
<td>5/57 9%</td>
<td>3/7 43%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>539</td>
<td>5/223 2.2%</td>
<td>17/194 8.7%</td>
<td>29/122 23.8%</td>
<td></td>
</tr>
</tbody>
</table>

*Edwards *et al* studied CRB65 scores. All other studies used CURB65 scores.

†Personal correspondence, 2011
6.4: Cardiac Dysfunction in Acute Exacerbation of COPD: Potential implications for Risk Prediction and Treatment

Patients with COPD commonly have coexisting cardiovascular disease [42, 471, 472]. The two pathologies can develop in parallel; each influenced by shared major risk factors such as tobacco smoking and advanced age [5, 473, 474]. The two pathologies can also interact in a manner that is likely both complex and bidirectional through both specific and systemic effects. Chronic heart failure may lead to pulmonary vascular congestion, interstitial oedema, and lung capillary and tissue membrane remodelling, which can exacerbate lung disease by further limiting pulmonary diffusion[475, 476]. Chronic lung disease can lead to long term cardiovascular sequelae including ventricular dysfunction via secondary pulmonary hypertension and increased intra-thoracic mechanical loads [45, 477]. COPD-related hypoxia, systemic inflammation and endothelial dysfunction can also contribute to the development and severity of atherosclerotic disease [478]. Although the mechanisms for this are far from clear, a growing body of epidemiological and pathophysiological data now support this association [479].

Poor respiratory function is associated with increased cardiovascular morbidity and mortality in prospective studies [480-483]. After adjustments for traditional cardiovascular risk factors such as total serum cholesterol, obesity, smoking, hypertension and diabetes, patients with COPD still have a two to three-fold increase in risk for cardiovascular events. Reduced FEV₁ appears as powerful in predicting cardiac mortality as total serum cholesterol [484]. Reduced FEV₁ and FEV₁/FVC ratio are also independently associated with increased
arterial stiffness indicative of endothelial dysfunction or atherosclerosis [485-487]. Elevated levels of C-reactive protein (CRP) are also associated with increased cardiovascular mortality [488, 489]. Circulating levels of CRP and other inflammatory and pro-coagulant markers such as tumour necrosis factor (TNF)-α, and fibrinogen are higher in patients with COPD than in control subjects suggesting some underlying inflammatory link between COPD and cardiovascular disease [490-492]. This is reinforced by observations that COPD patients with high levels of inflammatory markers are also at increased risk of atherothrombotic events such as acute coronary syndrome and stroke as well as all cause mortality, after adjusting for age, sex, smoking and lung function [493]. Taken together, these findings suggest that COPD itself helps create a pathophysiological milieu conducive to the development of cardiovascular disease states.

Indeed, in patients with mild to moderate COPD, the leading cause of morbidity and mortality is cardiovascular disease [41]. However, in patients with more severe disease and acute exacerbations, the role of cardiovascular morbidity is less certain. Conventional wisdom is that the terminal event for most of these patients is respiratory failure and that co-morbidities play less important roles. This notion is reflected in current treatment recommendations, although accumulating research is challenging this view [2, 133].

What is not well explored is the degree to which cardiac disease contributes to mortality during acute exacerbations (which usually occurs during later stages of disease). This is important because of the implications it may have on treatment. The cardio-protective
effects of agents such as β-blockers, statins and angiotensin converting enzyme inhibitors are well established with a substantial body of evidence highlighting their morbidity and mortality benefits [494, 495]. If cardiac involvement in acute exacerbations of COPD is an important determinant of prognosis, should these treatments be added to current standard recommended treatment of acute exacerbations?

These questions are addressed in two different ways in this thesis. Chapter Four describes the predictive utility of biomarkers associated with cardiac dysfunction in patients with acute exacerbations of COPD, while Chapter Five examines the effect of β-blocker therapy on simulated acute exacerbations of COPD.

The study described in Chapter Four demonstrated that patients with both elevated levels of NT-proBNP and troponin T had a 15-fold increased risk of death at 30 days compared to those with normal levels of these biomarkers, after hospitalisation for COPD exacerbations (Table 4.2, p 138). The predictive effects of elevated NT-proBNP and troponin T were independent of other established risk factors for poor outcome including lung function and blood gas derangements. Furthermore, the risk indicated by elevation of these biomarkers appeared additive, suggesting that the two markers reflect different aspects of cardiac dysfunction (Figure 4.2, p141). Interestingly, elevated levels of cardiac biomarkers were associated with early mortality, but not with mortality after the first 30 days. This suggests that these biomarkers reflect an acute effect of the exacerbation on the cardiovascular system rather than chronic cardiovascular disease – either due to a more severe
exacerbation or decompensation from a diseased cardiovascular system with less reserve. This contrasts with findings from long term follow up studies in patients with cardiovascular disease, which found increased short and long term mortality in those with elevated cardiac biomarkers [272, 274, 324].

These biomarkers already play important roles in the diagnosis and severity evaluation of primary cardiac disease and are incorporated in established guidelines for diagnosing and treatment of coronary artery disease and left ventricular failure [278, 279, 315, 316]. Increasing evidence also suggest that they are useful markers for pulmonary hypertension (whether primary or secondary to chronic lung disease) and where they reflect the degree of right ventricular dysfunction[293-296, 335]. In patients presenting with acute pulmonary embolism both elevated natriuretic peptides and cardiac troponins confer poor prognosis although the treatment implications of these findings remain unexplored [299, 340, 342].

Prior to the study detailed in Chapter Four, retrospective studies of patients with acute exacerbations of COPD had observed that elevated cardiac biomarkers were common and associated with increased adverse outcomes [306, 307, 339, 343, 346]. However, these studies were limited by small sample size and potential selection bias. Patients may have been more likely to have cardiac biomarker measurements if they gave histories consistent with cardiovascular disease or had clinical evidence of cardiac dysfunction. Chapter Four describes the first study to prospectively assess the value of cardiac biomarkers in unselected patients with acute exacerbation of COPD requiring hospitalisation. Being both
prospective and encompassing all admissions for acute exacerbation of COPD, it provides good evidence to support apparent cardiac involvement as being an important determinant of prognosis.

There were however, limitations to this study. The fact that objective measures of cardiac function such as echocardiography were not available makes it difficult to ascertain whether elevations in these biomarkers corresponded to actual cardiovascular pathology/dysfunction or whether they were merely indicative of severe physiological stress. This is important because both these biomarkers can also be elevated in severe physiological stress such as severe traumatic brain injury even without primary thoracic involvement, where they are associated with worse prognosis [496-498]. A study to specifically address this question is currently underway. It is a case-control cohort study involving patients with acute exacerbations of COPD grouped according to biomarker status and investigated with echocardiography to look for objective signs of cardiac dysfunction [Lee 2010, personal correspondence].

Notwithstanding these shortcomingts, the study in Chapter Four adds valuable knowledge in terms of prognostication and risk stratification for patients admitted with acute exacerbations of COPD and helps clarify the direction of future research in this area. The high rate of patients with elevated NT-proBNP (27.5%) and troponin T (16.6%) is in keeping with emerging data suggesting that most patients hospitalised for acute exacerbations of COPD actually die from a complex network of related co-morbidities, of which cardiac
disease is a major component, rather than simply from progressive respiratory failure [418]. The implication is that in patients with COPD a comprehensive treatment plan that adequately treats these co-morbidities may be beneficial. From a cardiovascular point of view there are a number of available agents with proven benefit [494, 495] and there is already some evidence to suggest a benefit in patients with COPD [422]. Cardiac biomarkers such as NT-proBNP and Troponin T may also provide us with a simple way of targeting the patients with the highest risk and therefore most likely to benefit from these agents.

Simply starting all patients with COPD on the common cardio-protective medications is not a straightforward option. Pharmacotherapies targeting the β-adrenoceptor are mainstays of both COPD and cardiovascular disease although with opposing agents. β-agonists are used widely to treat airways obstruction in stable COPD and acute exacerbations while β-blockers (antagonists) are now first-line therapy for patients with numerous cardiovascular diseases. β-blockers have been shown in randomised clinical trials to reduce morbidity and mortality in a wide range of cardiovascular disorders including (and not limited to) acute coronary syndrome, left ventricular dysfunction, hypertension and malignant arrhythmias [427, 499-504]. Despite clear evidence of their efficacy and clinical benefits, this class of medications are often avoided in patients with co-existing obstructive airways disease due to concerns of drug-induced bronchospasm [383, 385, 505]. Indeed, in a recently published European survey, COPD was the most powerful predictor of β-blocker under-prescription or even drug withdrawal in heart failure patients [506]. Further complicating the issue is that, clinical trials demonstrating the benefits of β-blockade may not be applicable to patients who have co-existing obstructive airways disease because such patients are usually specifically
excluded. This has led to a major gap in high-level, randomised evidence for the use of β-blockers in this population. Current COPD practice guidelines reflect these concerns and specify that β-blockers are relatively contra-indicated in patients with obstructive airways disease [389, 507].

Despite this, growing evidence from short-term randomised and observational studies suggests benefit for at least cardio- (β₁-) selective blockers. The Cochrane analysis of 20 randomised controlled studies of patients with reversible airways disease and COPD exposed to a single dose or continuous treatment (3 to 28 days) with cardio-selective β-blockers found no clinically significant difference in post-bronchodilator FEV₁ or respiratory symptoms compared to placebo [391, 392]. Indeed, of the 80 trials identified, no consistent airways exacerbation was recorded for any cardio-selective β-blockers. These two meta-analyses demonstrated that cardio-selective β-blocker therapy is well tolerated by patients with COPD (at least in the short term), even in those with some reversibility and suggested that they should not be with-held without good reason.

Emerging evidence now suggest that β-blockers are not only well tolerated by these patients, but may be beneficial to their lung disease. A very recent retrospective analysis demonstrated that patients with COPD and concomitant β-blocker treatment have reduced mortality (adjusted HR = 0.64, 95% CI 0.52-0.77) and risk of exacerbations (adjusted HR = 0.64, 95% CI 0.55-0.75), even in patients without overt cardiac failure or myocardial ischaemia at baseline assessment [420]. Furthermore, there is now at least retrospective
evidence that β-blocker use reduces mortality even in patients hospitalised for acute exacerbation of COPD [393]. How these drugs could reduce exacerbations and mortality in COPD is unclear, but some speculations can be made from existing data: murine models suggest that chronic β-blocker administration may paradoxically improve bronchial responsiveness to β-agonists, although the exact mechanism by which this occurs is poorly understood [508]. As bronchial hyperresponsiveness is associated with more rapid lung function decline in COPD, this property of β-blockers can, in theory, provide long term protective effects in this group of patients [509]. More recent reports also suggest that systemic β-blocker administration may reduce airway inflammation and mucus secretion in asthmatic mice [510]. These observations, if also true in humans, may be another pathway by which β-blockers may contribute to the observed benefits. On the other hand, by enhancing cardiac function, reducing the degree of tachycardia and thus enhance pulmonary haemodynamics, β-blockers may also improve symptoms and exercise tolerance in patients with COPD. Finally, as the cause 30-50% of COPD exacerbations are unclear, it is possible that at least some of them may initially be cardiovascular events (such as heart failure or myocardial ischaemia) with similar symptoms (such as cough and dyspnoea) to infective exacerbations. β-blockers may, in theory, reduce the frequency and severity of this type of exacerbations.

Thus, there is now good rationale for putting at least stable COPD patients on β-blockers. However, the effect of β-blockers on the airway during an exacerbation of COPD is not known. In particular, the interaction between selective, non-selective β-blockers and β₂-agonists have been poorly studied. This issue is addressed in Chapter Five of this thesis,
which demonstrated in a double-blinded randomised controlled fashion that non-selective β-blockers and high (but clinically relevant) doses of cardio-selective β-blockers may inhibit the bronchodilator response to β2-agonists in patients with moderate to severe COPD (Figure 5.4, p 163). At the same time, β-blocker therapy is associated with lower oxygen saturations during exercise compared to placebo (Table 5.2, p 159). These results identify a potential drawback of β-blocker treatment in this group of patients – that at higher doses, even the cardio-selective drugs appeared to affect the bronchodilator response of β2-agonists. As β2 agonists remain a cornerstone of COPD acute exacerbation treatment, any concomitant therapy that may impede the full action of these drugs is a concern.

The main limitation of this study was the small number of subjects involved, although most outcomes did reach statistical significance. The number of volunteers that had to be excluded from the study protocol also raises concern of the generalisability of the findings. Most of these patients were excluded because their screening lung function results did not fall within the inclusion criteria – that is, they had either too mild or too severe COPD (patients with FEV1 < 1.0L or 30% of predicted were excluded from participating because it was deemed unsafe for these patients to undergo methacholine challenge testing). However, the resulting physiological response should be similar regardless of baseline lung function. Finally, the high-dose metoprolol (cardio-selective β-blocker) arm of the study was open-label for safety reasons. Although the primary outcome of objective lung function measurement is unlikely to be influenced by this.
Should patients with exacerbations of COPD be started on β-blockers? Even though there remains a paucity of data to properly address this question, we believe that the studies discussed in this thesis have substantially advanced our knowledge base towards the answer. We have identified a subgroup of patients with apparent cardiac dysfunction who are at much higher risk in the short term compared to others. These patients may benefit from cardio-protective therapy such as β-blockers and we have demonstrated that cardio-selective β-blockers, when used at low to moderate doses, does not affect the bronchodilating effects of β-agonists after acute bronchoconstriction. Thus, these two agents may be used concurrently during an acute exacerbation without fear of reducing the effectiveness of airways treatment. Our evidence suggest that the heightened risk reflected by elevated cardiac biomarkers are limited to the acute period, therefore it may be more beneficial to maximise cardio-protective therapy during this time rather than wait until after the exacerbation. Our results also raised concerns for cardio-selective β-blockers at high, but clinically relevant doses, and until further information is available, clinicians should consider avoiding high doses of even cardio-selective β-blockers in this group of patients.

Our research group is currently recruiting patients with acute exacerbations of COPD and examining the correlation between cardiac biomarker status and objective measures of cardiac function. Further 5 year follow up for the patients recruited in the prospective cohort is also underway and he results may give us insight into the long term prediction value of these cardiac biomarkers. Ideally, the next step in our investigations will be a randomised controlled study assessing the use of cardio-protective therapy such as β-blockers in the treatment of COPD exacerbations. This is an exciting avenue of research as
little advances in exacerbation treatment have been made since the advent of non-invasive ventilation more than 15 years ago. Potentially, we may be able to add a number of existing treatments to our arsenal. Furthermore, pursuing this line of research will contribute to our understanding of the complex pathophysiology of this disease. Until then, these biomarkers can be used by clinicians to estimate risk and aid clinical decision-making, and perhaps be used as surrogate outcomes in further research.
6.5 Summary

In summary, this thesis confirms similarity between COPD patients at a secondary and tertiary New Zealand hospital and those internationally. This makes the subsequent studies conducted with patients from this New Zealand hospital more likely to be applicable to first world populations elsewhere. It introduces two new assessment tools for patients with acute exacerbations of COPD, namely the CURB65 score and biomarkers indicating cardiac dysfunction (NT-proBNP and Troponin T) that may aid better allocation of resources and targeting of therapy. Chapter Four also suggests a possible population in whom cardio-protective agents (such as β-blockers) may be particularly beneficial while the final chapter demonstrates that using cardio-selective β-blockers at moderate doses do not reduce β-agonist responsiveness after acute broncho-constriction. This thesis also highlights several new avenues of research that may herald changes in the way we think about and treat patients with acute exacerbations of COPD. The future treatment of acute exacerbations of COPD treatment may involve therapy targeting both the pulmonary and cardiovascular systems.
Bibliography


78. Medbo A, Melbye H. Lung function testing in the elderly--can we still use FEV1/FVC<70% as a criterion of COPD? Respir Med. 2007;101:1097-105.


172. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, November 1986. Am Rev Respir Dis. 1987;136:225-44.


382. Prichard BN. Pharmacologic aspects of intrinsic sympathomimetic activity in beta-blocking drugs. Am J Cardiol. 1987;59:13F-7F.


399. Wildman MJ. Variations in mortality in acute COPD may reflect nihilism as well as resources. Thorax. 2004;59:538; author reply


447. Gan WQ, Man SF, Postma DS, Camp P, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respir Res. 2006;7:52.


