The Short and Longer Term Implications of Beta-Blocker Use in Cardiology Patients with Airways Disease

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A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Medicine

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December 2009

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PREFACE

The research contained within this thesis was conducted initially in the wards of the Royal Prince Alfred Hospital. The study protocol was approved and periodically reviewed by the Central Sydney Area Health Service Ethics Committee. All research subjects gave informed consent prior to participating.

I am responsible for the work represented in this thesis, although many have provided assistance, enabling its completion. The extent to which others have contributed is detailed in the acknowledgements. This work has not previously been presented in application for any other degree.

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Belinda Cochrane

Date

PUBLICATIONS

This thesis contains five chapters presenting original research, Chapters 2 - 6. Research abstracts have been presented at the annual congresses of national and international scientific meetings, as follows:

1. Cochrane B, Cochrane JA, Harris P, Phipps P, Young IH (2004) *Prevalence of Coexistent Airways Obstruction in Patients with Cardiac Disease*

Annual Congress of the Thoracic Society of Australia and New Zealand (oral presentation)
Annual Congress of the Royal Australasian College of Physicians (poster presentation)
Annual Congress of the European Respiratory Society (poster presentation)

2. Cochrane B, Cochrane JA, Harris P, Phipps P, Young IH (2004) *Beta-Blocker Prescription in Patients with Coexisting Cardiac and Obstructive Airways Disease*

Annual Congress of the Royal Australasian College of Physicians (poster presentation)
Annual Congress of the European Respiratory Society (poster presentation)

3. Cochrane B, Cochrane JA, Walters HE, Phipps P, Harris P, Young IH (2007) *Prolonged Beta-Blocker Treatment in Subjects with Comorbid Cardiac and Obstructive Airways Disease*

Annual Congress of the Asian Pacific Society of Respirology (oral presentation)

In addition, the findings of this thesis were presented in a talk; *Heart Disease in COPD and Issues Related to Medication* during a session entitled “Heart-Lung Interdependence in COPD” at the invitation of the organisers of the biennial Airways Scientific Meeting 2008.

As yet, none of the material contained within this thesis has been published elsewhere.

ACKNOWLEDGEMENTS

In clinical research results are never achieved without the help and support of others. The research represented in this thesis has benefited through the cooperation and contributions of many people. Particular acknowledgement is due the following:

My research subjects, who were recruited from amongst the Cardiology Unit inpatients at Royal Prince Alfred Hospital. Most of them commenced the study protocol whilst unwell, but nevertheless participated, eager to contribute their own personal results to my research. Many returned for review assessments despite advanced age, physical disability and inconvenience, and without any remuneration. Their enthusiasm often provided inspiration when my own was lacking.

I am grateful to the Royal Prince Alfred Hospital cardiologists, who allowed me to approach their inpatients for study recruitment and to undertake the initial stages of the study protocol during a period of inpatient stay. The junior medical staff, nursing and allied health staff and the clerical staff of the Coronary Care Unit and Cardiology Ward also provided much-valued assistance.

I have had various supervisors, during different stages of this work, who include Iven Young, Philip Harris, Haydn Walters and Paul Phipps. I am indebted to Iven and Phil, who encouraged my research concepts from the outset, and have maintained an untiring level of support, optimism and guidance, ensuring that I learnt to overcome the frequently-encountered challenges of translating research ideas into practical,

achievable results. Along the way, Iven has become an esteemed colleague and source of advice about clinical medicine and professional issues, not only research. All supervisors have provided invaluable advice and support at various points along the way, but in recent times I must thank Iven, Phil and Haydn for generously donating sparse free time to review and provide opinion on my writing.

Much of my research output has been dependent on the effective use of computers, computer programs and statistics. Here I must give due acknowledgement to Brad Anderson, for assistance with the initial Filemaker Pro database set up and for willingly providing round the clock computing expertise during the initial years. Although the statistical analyses from the initial research chapters did not require supervision or specialised input, Chapter 6 called for complex statistical analyses. Hence, the reported results from Chapter 6 are the outcome of extensive consultation, discussion and revision under the supervision of Menzies Research Institute statistician, Steve Quinn. I have to credit him for his patience and perseverance, under particularly challenging circumstances, since our interchanges were almost entirely by email and telephone, due to the substantial geographical separation between us.

My research would not have been possible without the generosity of Niche Medical, who loaned the hand-held spirometer and software used for the initial 12 months of the study protocol. This was provided, along with back up technical support for the equipment, at no cost.

A completed thesis certainly represents the author's hard work, but in terms of family and friends there are costs never reconciled and contributions, the extent of which can never be measured or adequately attributed. To this end, I must thank my clinical colleagues, for their enduring patience and gracious support, while I have attempted to divide my attentions between research and my clinical responsibilities. I must apologise to my close friends and family for an often grumpy (and undeserved) demeanour and for distancing myself behind closed doors, seemingly preferring a hermit's life, and my computer's company to their own. I must also thank my partner Tony, who has devoted many hours to the aesthetics of this document. His patient attention to formatting, diagram modification and consistency has been woefully underappreciated.

Finally, thank you to my mum. She has without fail provided a listening ear, love, and advice, even when I have been at my most objectionable. It was she who persuaded me to strive for a higher degree, in the first place. However, having endured my late father's PhD, and her own career being in medical research, my Mum knew more than most what was ahead. I am indebted to her for providing her advice and insights into database design and data management, into questionnaire design and for volunteering to help with subject recruitment during the first few weeks – I know that she remembers this as a thoroughly exhausting experience!

THESIS ABSTRACT

Coronary atherosclerosis and chronic obstructive pulmonary disease (COPD) are highly prevalent, and two of the commonest causes of morbidity and mortality in the Australian population. They share cigarette smoking as an important risk factor, and frequently coexist. Drugs which act on the beta-adrenergic receptor are important therapeutic tools in both diseases. However, beta-receptor antagonists, which are commonly used to treat cardiac disease, theoretically may cause adverse respiratory effects and are traditionally avoided in patients with obstructive airways disease. This work seeks to explore the short and longer term effects of beta-blocker medications, when used for treatment of cardiac disease in patients with coexisting obstructive airways disease. Specifically, the aims of this research are:

1. To estimate the prevalence of coexisting obstructive airways disease amongst patients with cardiac disease
2. To investigate current beta-blocker prescribing practice in patients with obstructive airways disease
3. To document adverse respiratory effects of beta-blocker medications, in terms of symptoms, lung function and other longer term health outcomes.

Within 24 hours of hospital admission for suspected cardiac disease, patients were screened for airways obstruction, using spirometry. Spirometry results demonstrated a high level of coexistence of cardiac disease and obstructive airways disease, about twice that cited in previously published estimates. Documentation of beta-blocker

prescribing practices within the Royal Prince Alfred Hospital's Cardiology Unit revealed minimal prescription of these medications to patients with previously diagnosed chronic obstructive airways disease and asthma, despite limited evidence of adverse effects of beta-blocker use in such patients. This notably occurred even when guidelines recommended beta-blockade as first line therapy, and where survival benefit was established. However, many patients with obstructive spirometry, but no formal diagnosis of obstructive airways disease, did receive beta-blockers. Longitudinal analysis of symptom assessment, lung function and health outcomes was performed. Lung function and respiratory symptoms data were collected over a twelve month period and data pertaining to beta-blocker discontinuation, respiratory exacerbations, acute cardiac events and survival were collected over almost six years. There was no indication of a statistically significant adverse beta-blocker effect on lung function, respiratory symptoms or survival but beta-blocker medications did appear to increase respiratory exacerbation rates.

This work confirms the very high frequency of obstructive airways disease existing in combination with cardiac disease in an Australian urban population, which had been suspected but not previously documented. However, its major contribution is to provide prospective long term respiratory health outcome data for the use of beta-blocker medications in this group.

CHAPTER 1

LITERATURE REVIEW

CHAPTER 1: LITERATURE REVIEW

Coronary atherosclerosis and chronic obstructive pulmonary disease (COPD) are highly prevalent, and two of the commonest causes of morbidity and mortality in the Australian population. Prevalence of both medical conditions increases with increasing age. Coronary artery disease prevalence estimates in Australia, for patients older than 65 years, approached 66% in 2001 (1). Measures of COPD prevalence, until very recently based on doctor diagnosis and inhaled medication prescriptions, have been considered inexact and greatly underestimated. Despite ongoing debate surrounding the diagnostic criteria used, recent publication of the Burden of Obstructive Lung Disease (BOLD) Study (2), an international prevalence study of COPD in adults aged beyond forty years has provided a basis for more precise estimates. The Australian section of the BOLD Study found COPD (GOLD stage II or greater) in 9.3% males and 11.29% females. GOLD stage II is defined as FEV1/FVC ratio less than 0.70 and percentage predicted FEV1 (forced expiratory volume in one second) from 50% to less than 80% (3). Reflecting global estimates, ischaemic heart disease is the leading documented cause of mortality in Australia, with COPD ranking fifth in men and seventh in women (1, 4). In terms of morbidity, when defined as disability sufficiently profound to limit core daily activity, COPD marginally outranks ischaemic heart disease, with them lying in third and fourth places, respectively (5). The import of high disease prevalence and the major impact on disease burden, when these two diseases are assessed individually, is that clinicians potentially face enormous patient numbers having the disease combination, due to population ageing and the shared main risk factor, cigarette smoking. Drugs

acting on the beta-adrenergic receptor play important therapeutic roles in the treatment of both diseases. However, beta-agonist agents are used in the obstructive airways diseases and it is antagonist agents that are most beneficial in the common forms of cardiac disease. The clinician then must reconcile the apparent therapeutic dilemma.

1.1 The Beta-Adrenergic Receptor

Beta-blocker drugs target the beta-adrenergic receptor (B-AR), of which there are three subtypes, distributed predominantly as follows: the beta-1 receptor to myocardium, the beta-2 receptor to glands and smooth muscle of the airways, myocardium, blood vessels, uterus, bladder and gut, and the beta-3 receptor (6) to adipose tissue, gastrointestinal tract and myocardium.

Activation of the beta-1 subtype causes increases in chronotropy, atrioventricular (AV) node conduction and myocardial contractility, and reduction in the AV node refractory period. Stimulation of the beta-2 subtype results in bronchodilation, mucus secretion and surfactant production, peripheral vasodilation and relaxation of other organ-related smooth muscle. Less is known about the beta-3 receptor subtype. It is thought to have a role in fat metabolism, regulating lipolysis and thermogenesis in visceral adipose tissue (7).

At the cellular level, the B-ARs exert their effects via cyclic Adenosine Monophosphate (cAMP)-mediated activation of protein kinase A, and may also have cAMP-independent effects on calcium-activated potassium channels (7-9). B-AR

activity is subject to tight regulation. This is not only achieved through the direct effects of agonist, inverse agonist and antagonist substances. There exists a negative feedback system, whereby ongoing beta-agonist stimulation leads to a decrease in receptor density and substrate affinity in a process termed “desensitisation”. In the short term, the receptor can be made relatively insensitive to agonist stimulation by a process known as “uncoupling”, with receptor conformational change preventing effective molecular interaction between the receptor and cAMP. Less immediately, there is regulation of surface cell membrane B-AR numbers, by receptor internalisation and degradation and regulation of B-AR messenger RNA (mRNA) transcription. There are both immediate and longer term regulatory processes involving cross interactions with other neurotransmitter systems (such as the cholinergic system) and inflammatory mediators. Beta-2 receptors are up-regulated and down-regulated by endogenous substances such as hormones and cytokines, and by exogenous agents. They are down-regulated rapidly in response to agonist agents, certain viruses and pro-inflammatory cytokines (8, 10, 11). There is an up-regulatory beta-2 receptor response to oral corticosteroids (8, 12, 13).

To complicate matters further, as with other complex constituent cellular proteins, B-ARs, both beta-1 and beta-2 subtypes, are subject to genetic polymorphism, that is, distinct forms existing within the same population, differing at an allelic locus, and occurring more commonly than can be accounted for by chance mutation. There are several documented polymorphisms of each B-AR subtype, which may have differing effects on disease manifestations, clinical severity and susceptibility to receptor-active drugs.

1.2 Beta-Blocker Medications

Beta-blocker medications are competitive inhibitors of catecholamines at the B-AR. They may act as antagonist drugs, by blocking an agonist-mediated receptor response, without themselves provoking a biologic receptor response, but may also have inverse agonist properties, exerting a pharmacologic effect on receptor binding, opposite to that of receptor agonist drugs. They exist as racemic mixtures of optical isomer compounds, although, except in the case of sotalol, it is the levorotatory (L) isoform which is more active, and therefore more clinically useful. Beta-blockers have a well-established side effect profile. The most commonly cited adverse side effects include bronchospasm, hypotension, bradycardia, impotence, exacerbation of heart failure or peripheral vascular disease, hypoglycaemia (or loss of alerting symptoms), fatigue, depression, hallucinations, insomnia and bad dreams. The central nervous system (CNS) and psychiatric affects may be seen more commonly with drugs subject to hepatic metabolism, such as propranolol and metoprolol, and may reflect enhanced lipid solubility and high CNS concentrations. The water soluble agents, such as atenolol and sotalol, are renally excreted via the urine and have more reliable bioavailability and longer plasma half lives. Esmolol is an ultra short acting agent which is rapidly metabolised in blood, tissues and liver. Its half life of ten minutes makes it useful as a test agent and predictor of subsequent beta-blocker tolerance, particularly when there are concerns about life-threatening adverse effects (14).

Beta-blockers can be classified in terms of their “cardioselectivity”, or beta-1 receptor affinity. Selectivity is not an absolute phenomenon, and diminishes as drug

dose escalates. This is attributable to the distribution of B-AR subtypes, which is not entirely exclusive to tissue type, and also to variations in receptor density between tissue types. A sufficiently high dose will affect all B-AR subtypes. Extended release drug formulations may enhance selectivity (15). The reason for this relates to the pharmacokinetics of extended release formulations; peak serum levels are much lower in comparison with short acting agents at equivalent dose. Most of the beta-blocker agents now in common use, such as atenolol, bisoprolol and metoprolol, are relatively beta-1 selective. Carvedilol and propranolol are regarded as non-cardioselective.

Beta-blockers are also classified as to intrinsic sympathomimetic activity (ISA), which is the extent of partial beta-agonist effect. A compound may actually exert an antagonist effect at one receptor subtype, and yet have an agonist interaction at a different receptor subtype (16). Pindolol, labetalol and acebutolol are agents with significant ISA properties. Partial agonist activity may cause a reduction in the desired pharmacologic effect.

Alpha-adrenergic receptor blockade results in coronary and peripheral vasodilation. Some beta-blocker medications have additional alpha-adrenergic receptor activity (labetalol and carvedilol) or alternatively-mediated vasodilatory actions (bucindolol). In the case of carvedilol, a newer agent with blocking effects at the beta- and alpha-1 receptors, but without cardioselectivity or ISA, this property is utilised in the treatment of heart failure. It has been suggested that the alpha-receptor effects may ameliorate, or to some extent counter, any potential bronchoconstrictive effect seen at the beta-2 receptor (17).

Table 1.1: Characteristics of Beta-Blocker Agents in Common Use

Beta-Blocker	Beta-1 Selective	ISA	Alpha-Blockade
Metoprolol	Yes	No	No
Propranolol	No	No	No
Atenolol	Yes	No	No
Bisoprolol	Yes	No	No
Esmolol	Yes	No	No
Labetolol	No	Yes	Yes
Carvedilol	No	No	Yes

1.2.1 Therapeutic Uses

B-AR antagonists are important drugs in the treatment of cardiac disease, including left ventricular dysfunction and myocardial ischaemia. They are long established antihypertensive agents and are effective in prevention of peri-operative myocardial events (18). They are useful in treatment of cardiac arrhythmia, as well as in hyperthyroidism and portal hypertension. Significant survival benefit is established for their use after myocardial infarction and in the setting of left ventricular dysfunction.

Their beneficial effects in cardiac disease are thought to occur through the following mechanisms:

- Reduction in myocardial oxygen demand, with negative chronotropic and negative inotropic effects resulting in reduced cardiac workload

- Bradycardia, prolongation of diastole and enhanced coronary flow

- Interruption the sympathetic nervous system (SNS) and renin-angiotensin system (RAS) stimulation, that accompanies heart failure, with reduction in circulating levels of vasoconstrictor substances, and hence reduction of cardiac afterload and enhancement of coronary perfusion

- Membrane stabilisation effects, with reduction in ventricular ectopy and sudden cardiac death

In addition, in the long term, the following mechanisms are felt to be important with more prolonged beta-blocker treatment:

- Reduction in detrimental post infarct myocardial remodelling, with preservation of ventricular function

- Reversal of long term consequences of chronic SNS and RAS overactivity, with B-AR up-regulation and restoration of the myocardial contractile response

1.2.1.1 Heart Failure

Heart failure is a state of impaired cardiac pump function, which results in suboptimal perfusion of peripheral tissues. It is characterised by overactivity of the SNS and RAS, which has the initial effect of improving hypotension and peripheral

perfusion but the longer term consequences of B-AR desensitisation and decreased myocardial beta-1 density.

Left ventricular dysfunction is probably the most compelling current indication for beta-blocker treatment, although these drugs were formerly felt to be contraindicated due to their negative inotropic effects. The impact on survival, even in the setting of other effective treatment strategies, with known survival benefit, such as Angiotensin Converting Enzyme Inhibitor (ACEI) or Receptor Blocker (ARB) agents, is certainly marked. An attributable reduction in mortality risk of greater than 30% has been cited (19). A more recent meta-analysis (20) has also shown clear improvement in survival. They quote a combined odds ratio (OR) of 0.65 (95% confidence interval 0.53 – 0.80) for survival in patients with predominantly class II – III New York Heart Association (NYHA) heart failure. NYHA class refers to an incremental disability scale used to express severity of symptoms due to heart failure, where class I represents no symptomatic limitation and class IV represents symptomatic congestive cardiac failure whilst at rest and implies inability to perform any physical activity without discomfort. The meta-analysis reviewed 22 trials, comprising a total of 10135 subjects. The majority of the patients included in the meta-analysis were already established on ACEI therapy, or equivalent. The clinical impact of the meta-analysis' cited survival benefit translates to 3.8 lives saved, per one hundred patients, per year. There was also a significant reduction in requirement for hospitalisation. Survival benefit has been demonstrated in patients with severe heart failure (21) and in studies of individual agents: sustained release metoprolol (22), bisoprolol (23) and carvedilol (21, 24). Studies of sotalol and beta-blocker drugs with ISA were not

included in the meta-analysis, as these agents have been found to be detrimental in the setting of heart failure.

Guidelines for management of heart failure, issued by the Cardiac Society of Australia and New Zealand (25), now recommend beta-blocker therapy, early after myocardial infarction (MI), regardless of left ventricular dysfunction (Level II recommendation), in patients with systolic heart failure, with mild to moderate symptoms despite the use of ACEI and diuretics (Level I recommendation) and in advanced congestive cardiac failure (Level II recommendation). Level of evidence is here quoted according to the National Health and Medical Research Council (NHMRC) designations, which associates each recommendation with the extent and quality of existing supporting medical evidence, as here detailed (26):

- Level I – evidence from a systematic review of all relevant randomised, controlled trials
- Level II – evidence from at least one properly-designed randomised, controlled trial
- Level III – evidence from:

(a) well-designed, pseudo-randomised, controlled trials
(b) cohort studies, case control studies, interrupted series with a control group
(c) comparative studies with historic control, two or more single arm studies, interrupted time series with no parallel control group

- Level IV – evidence from case series

- Level EO – based on opinion of respected authorities, descriptive studies, and expert committee reports

Likewise, the American Heart Association Guidelines (27) recommend beta-blocker and ACEI therapy in patients with recent or remote myocardial infarction, regardless of left ventricular ejection fraction (LVEF) or heart failure (Class I recommendation, Level A evidence), and state that beta-blocker treatment is indicated in all patients without previous myocardial infarction if LVEF is reduced, even if symptoms of heart failure are mild or absent (Class I recommendation, Level C evidence in the absence of symptoms of cardiac failure). For patients with current or prior symptoms of heart failure they recommend beta-blocker therapy and specify the three agents with proven survival benefit in this setting (Class I recommendation, Level A evidence). The strength of the recommendations are here qualified using the American College of Cardiology and American Heart Association classification system, which reflect the level of supporting medical evidence, with recommendations classed I-III, and level of evidence A-C:

- Class I – evidence or general agreement that treatment is beneficial/ effective

- Class II – conflicting evidence or divergent opinion as to efficacy/ benefit of treatment

(a) weight of evidence is in favour of treatment
(b) evidence or opinion is less established

- Class III – evidence against treatment efficacy or suggesting that treatment may be harmful

- Level A – derived from multiple randomised clinical trials or meta-analysis
- Level B – derived from single randomised trial or non-randomised studies
- Level C – derived from consensus expert opinion, case studies or standard-of-care

Heart failure is prevalent in the Australian population, and has high associated morbidity and mortality. Finding this magnitude of benefit with a relatively inexpensive drug treatment is clinically important. Beyond drug therapy, alternative treatment strategies, such as cardiac transplantation, surgical procedures to augment ventricular contraction, and, in selected patients, implantable defibrillators, are of high cost and therefore are associated with limitations in terms of availability and practical clinical utility.

1.2.1.2 Ischaemic Heart Disease

Although in recent times research investigating treatment of acute coronary syndromes has concentrated on timely myocardial reperfusion techniques, stent technology and anti-thrombotic strategies, beta-blockers have long held a place in the management of myocardial ischaemic syndromes. Beta-blocker therapy is known to improve survival following myocardial infarction. This is well established for ST elevation myocardial infarction (STEMI) (28, 29). Yusuf's meta-analysis looked at beta-blocker use after MI. Pooled results of 23 trials of long term beta-blocker use

after MI, showed a 20% reduction in mortality and the results of 24 pooled trials showed a 25% reduction in non-fatal reinfarction. These results are impressive, given intention to treat analysis, and comparison with the aspirin mortality effect in this setting, which is cited at 15% (30). The mortality benefit has been shown with beta-blockers of different types, both selective and non-selective, but notably does not extend to beta-blockers with ISA.

The evidence is less robust for non ST elevation myocardial infarction (NSTEMI). The National Heart Foundation of Australia: Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (31) stratify patients into categories of risk (for subsequent adverse cardiac outcomes) on the basis of clinical presentation and adverse clinical prognostic factors; electrocardiogram and biomarker results, prior coronary intervention and the specific medical comorbidities of diabetes mellitus and chronic renal insufficiency. These guidelines recommend beta-blocker therapy for high risk patients unless there is an existing contraindication. This is a recommendation supported by another meta-analysis (32). Although interpretation is complicated by the recent changes in terminology for acute coronary syndromes and the widespread adoption of the troponins as biomarkers for myocardial damage, this meta-analysis demonstrated 13% reduction in progression to myocardial infarction in the clinical setting of "threatened myocardial infarction" (characteristic ischaemic chest pain and ECG normal or with ST depression). The results are a summary of five randomised trials, comprising a total of 4700 subjects. The same guidelines also recommend beta-blocker therapy for most patients after confirmed myocardial infarction, with a view to indefinite use in those at high risk of further coronary events. The corresponding

American Heart Association Guidelines (33) advocate prompt administration of beta-blocker in the setting of STEMI, and continuation unless adverse effects preclude continued use (Class I recommendation, Level A evidence). They also recognise a role for beta-blockers in secondary prevention, after the acute phase, for all but low risk patients and those with contraindications. For NSTEMI or unstable angina, judged to be a threatened or evolving MI, beta-blocker therapy is recommended, once again on the strength of the Yusuf 1988 meta-analysis results.

There are no trials of sufficient power evaluating beta-blocker efficacy for similar end points in the clinical setting of stable angina. However, given the evidence for beta-blocker use in STEMI and threatened MI, and an established survival benefit for their use in treatment of hypertension, a major risk factor for adverse cardiovascular events, beta-blockers are recommended also for patients with stable angina. Goals for treating patients with stable angina must provide the best strategy to improve survival and prevent adverse cardiac outcomes, but also should address symptoms and exercise performance. There is some evidence that beta-blockers improve symptoms in exercise-induced angina, with increased in exercise tolerance (34-36), reduced frequency of angina episodes (34, 36) and reduced use of medications used to relieve angina symptoms (34, 36, 37). In studies using exercise testing and cardiac monitoring, reduction of both symptomatic and asymptomatic myocardial ischaemia (34, 37-39) has been shown. Because of these factors, beta-blocker therapy is recommended, in addition to aspirin and lipid lowering therapy, for these patients by the American Heart Association Guidelines (40).

1.2.2 Perceived Beta-Blocker Contraindications

Despite increasing and compelling indications for beta-blocker use, concern remains regarding potential adverse side effects, and this is reflected in low prescription rates amongst patients who might otherwise benefit from beta-blocker therapy. Underprescription particularly affects the elderly, females, and patients with obstructive airways diseases, cardiac failure, diabetes and peripheral vascular disease (41-48). Contraindications to beta-blocker medications have previously included bradycardia and conduction abnormalities, hypotension, left ventricular insufficiency, chronic obstructive airways disease and asthma, diabetes mellitus, peripheral vascular disease, advanced age and depression. However, the recently accumulated evidence for beta-blocker use in cardiac disease mandates a thorough reassessment. Left ventricular dysfunction has become an indication for beta-blocker treatment. Many of the other listed conditions are no longer regarded as contraindications, or have been demoted to relative contraindications, with the provision of careful monitoring whilst on therapy.

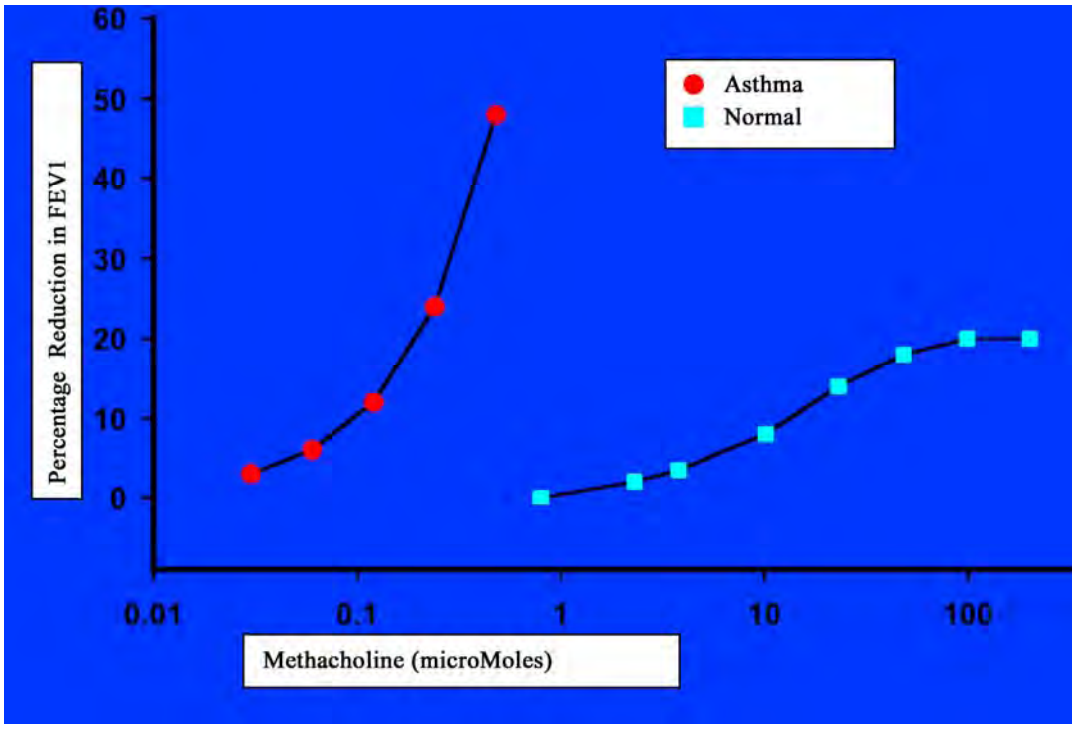
1.2.3 Potential Adverse Respiratory Effects

The obstructive airways diseases are most commonly cited as reason for withholding beta-blocker medications after myocardial infarction in elderly patients (45). Beta-blocker medications have been traditionally avoided in COPD and asthma due to a potential to precipitate severe, and sometimes fatal, bronchoconstriction. Early experiences were of acute bronchoconstriction associated with use of non-cardioselective beta-blockers. Subsequently, even cardioselective beta-blockers have

caused respiratory symptoms and deterioration of lung function in selected cases (49). In fact, obstructive airways diseases are traditionally treated with beta-agonist medications, with the aim of inducing bronchodilation.

Patients with bronchial hyperresponsiveness (BHR) or asthma theoretically are more at risk of adverse reactions to beta-blockers, due to increased airway caliber instability associated with exposure to certain provocative stimuli. The concern with asthmatic patients is that the airway narrowing response to the stimulus (often measured as FEV1) does not plateau with increasing levels of stimulus exposure, as it does in non-asthmatics. Use of beta-blockers in these patients potentially raises safety issues and seems counter-intuitive. Hence, the risk of precipitating bronchospasm in patients with reactive airways disease is a significant deterrent to using beta-blockers.

Graph 1.1: Bronchial Hyperresponsiveness – Comparison of Asthmatic and Normal FEV1 Response to Methacholine Challenge (50)



The conventional view is that acute bronchoconstriction seen with beta-blocker use in asthmatics, results from competitive antagonism of the beta-2 receptor and prevention of bronchodilating effects of endogenous catecholamines or interruption of constitutive receptor activity. However, Bond (51) has noted the following inconsistencies in traditional theory: that a significant degree of beta-2 receptor antagonism can be achieved without any demonstrable change in airway diameter, lacking evidence for a link between beta-blockade and mast cell degranulation, reversal of beta-blocker induced airway constriction by anticholinergic drugs, and frusemide, whose main mechanism of action occurs at a cell membrane ion exchange transport protein, but not by pre-treatment with pranlukast, a leukotriene receptor antagonist, or by the corticosteroid, beclomethasone. He proposes that a more complete explanation also involves contribution from other beta-blocker actions, including inverse agonist activity and cross-interactions with other neurotransmitter and cellular pathways.

There is some support for his suggestions. McGraw's group (52) sought an explanation for the phenomenon of increased bronchial hyperresponsiveness seen with chronic beta-agonist use, using two groups of genetically altered mice: those deficient of B-AR and those overexpressing airway smooth muscle. They showed airway smooth muscle responsiveness to methacholine, in terms of lung function measured by plethysmography, and tracheal ring contractility, to be reduced in the first group, and increased in the second. These changes were replicated when the challenge agent, methacholine, was replaced with stimulatory agents specific to other G-protein coupled pathways, such as the prostaglandin and serotinergic pathways. Their results suggest that the B-AR has regulatory effects on bronchial smooth

muscle tone, independent of direct bronchodilatory effects. Measuring inositol phosphate as a downstream representative of G-protein receptor activation, and finding corresponding decreased and increased levels, respectively, in the two mouse groups, they proposed a mechanism of receptor pathway "cross-talk", through a final common pathway substance, which they identified as phospholipase C-beta1, by Western blot analysis. Their study provides additional explanation for seeming inconsistencies in the traditional understanding of B-AR mediated airway caliber effects and has the implication of providing an alternative potential therapeutic target in the treatment of obstructive airways diseases.

1.2.4 Evidence for Adverse Respiratory Effects

One approach is to examine the available major beta-blocker trials for evidence of airway-specific adverse drug reactions. Many of the therapeutic trials of beta-blockers in cardiology excluded subjects with obstructive airways disease, both COPD and asthma. Adverse reactions mentioned in the major trials of cardioselective beta-blocker use for acute coronary syndromes and cardiac failure were predominantly cardiac or haemodynamic. For the most part, permanent treatment withdrawals were similar in beta-blocker and placebo-treated groups (21-24, 53, 54). Airways obstruction or bronchospasm was uncommonly mentioned as an adverse effect, although the Metoprolol in Acute Myocardial Infarction (MIAMI) Trial did specify "significant airway obstruction not responsive to beta-2 stimulating therapy" as a criterion for treatment withdrawal. The investigators of First International Study of Infarct Survival (ISIS) 1 (55) provided for dose omission or reduction in their beta-blocker protocol in the setting of an adverse response to

treatment. However, it would appear that less than 1% of their randomised subjects required any dosage amendment on the basis of bronchospasm or airways obstruction. Albeit using a non-selective beta-blocker, in the Norwegian Multicentre Study Group trial of timolol after myocardial infarction, not only was there a significantly increased incidence of airways obstruction, reported as an adverse drug reaction in the active treatment group, but there was also a significant increase in the rate of respiratory infections, bronchitis and pneumonia (56).

In 2002-2003 a pair of Cochrane meta-analyses assessed cardioselective beta-blocker use, both in patients with chronic obstructive airways disease (57) and in those with reversible airways disease (58). The meta-analyses were limited to cardioselective beta-blockers only, since most of the agents in common use are cardioselective, and since these agents have twenty fold increased affinity for the beta-1 as opposed to the beta-2 receptor. For inclusion, trials had to be randomised, blinded, controlled trials. Only published data were examined. The meta-analyses comprised single dose and longer duration studies.

The first meta-analysis included trials of cardioselective beta-blockers, with or without ISA, in patients with reversible airways disease, which was defined as 15% FEV1 response to beta-agonist, positive methacholine challenge or asthma, as defined by the American Thoracic Society (ATS). Trials were to report beta-agonist use, respiratory symptoms or FEV1 response to beta-blocker (beta-agonist medication was to be withheld at least eight hours prior to measuring spirometry). Predetermined subgroups included COPD, comorbid cardiovascular disease or hypertension, and beta-blockers with ISA. The COPD subgroup was defined by

having baseline FEV1<80% predicted, less than 1.8L, or as defined by ATS guidelines. Of 104 potentially eligible trials, only 29 met inclusion criteria. The trial results were homogenous, in all but the subgroup analysis for beta-agonist response in beta-blockers without ISA, but no trial completely met the predetermined methodology quality criteria. There were 19 single dose trials (240 patients), with 79% male subjects. The pooled results showed a statistically significant reduction in FEV1 (mean 7.46%) and increase in beta-agonist FEV1 response (mean 4.63%), but no change in respiratory symptoms. Ten longer duration trials (141 patients) were included, with 77% male subjects. Five of these had no FEV1 data. Trial duration ranged from 3 to 28 days. There was no significant effect seen on FEV1, respiratory symptoms or inhaler use. Beta-agonist response was significantly increased (mean 8.74%). The COPD and cardiovascular subgroups reflected the results of the group as a whole. The subgroup treated with beta-blockers possessing ISA showed some differences. The differences are not discussed here as beta-blockers with ISA are rarely used in the treatment of cardiac disease, the most common setting of clinical use being for the treatment of hypertension in pregnancy.

A separate meta-analysis for COPD was deemed important because, compared to patients with asthma, these patients generally have a greater risk for cardiovascular disease and more severely impaired lung function. Hence, they may have adverse effects from even small changes in lung function. Included studies assessed the effects of cardioselective beta-blockers on FEV1 or respiratory symptoms in patients with COPD. COPD was defined by baseline predicted FEV1<80%, or according to ATS guidelines. The parameters examined were FEV1, symptoms and FEV1 response to beta-agonist. Eleven single dose studies (141 subjects) met inclusion

criteria. Eighty percent of subjects were male. Four of these trials had FEV1 data, two had FEV1 response data and nine were placebo-controlled. Symptoms assessed were “shortness of breath”, “dyspnoea” and “wheeze”. Eight longer duration studies (126 subjects) met inclusion criteria. 77% of subjects were male. The duration of the studies ranged from two days to twelve weeks (mean 1.1 month). Four of these studies had FEV1 data, seven assessed symptoms, and one assessed beta-agonist response. The symptoms assessed were “shortness of breath”, “increase in respiratory symptoms” and “asthma attacks/ COPD exacerbations”. Trial results were homogeneous. As in the meta-analysis looking at reversible airways disease, all trials used a beta-blocker dose sufficient to achieve a therapeutic response. However, five of the trials included patients with COPD diagnosis, based on “clinical grounds”. No significant effect of cardioselective beta-blockers on FEV1, symptoms or FEV1 response was found in either the single dose or longer duration studies. This held even for the predetermined subgroups with severe airways obstruction (FEV1 < 50% or 1.4L), baseline demonstrable bronchodilator response (increase in FEV1 of 15% after beta-agonist), and with comorbid hypertension or angina. However, amongst the longer term trials, prevalence of symptoms was very low indeed, with only one subject reporting symptoms in each of the treatment and placebo groups. There were no hospital admissions and respiratory exacerbations, though all studies claimed to report them. Several of the included studies defined reversible airways disease in terms of FEV1 response, using percentage criteria, but without regard to actual magnitude of the FEV1 increase. This should not be critical in patients with moderate airways disease but might have resulted in incorrect classification in subjects with more severe disease.

The authors' conclusions were that, according to available evidence, the use of cardioselective beta-blockers was probably safe in patients with COPD, as well as in those with less than severe reversible airways disease, and that these agents should not be withheld in clinical circumstances where benefit is established. A proviso of "close monitoring" and medication withdrawal on suspicion of adverse respiratory consequences was made. However, there has been hesitance to embrace these conclusions, due to reservations regarding the size and quality of the individual trials, the small absolute numbers of patients involved, the paucity of long term beta-blocker exposure data, even amongst "longer duration" studies, and due to under-representation of minority groups, especially females, patients with severe disease and the elderly. There is little data on long term respiratory morbidity outcomes, such as respiratory exacerbations and hospital admissions, and there is doubt that the conclusions can be extrapolated to situations of potential respiratory instability, such as respiratory infections or exacerbations. Subsequent to these two Cochrane meta-analyses, some preliminary work on long term beta-blocker treatment in patients with obstructive airways disease has been presented. Treatment observation periods for these studies extend beyond twelve months and outcomes reported include lung function (59), tolerance of beta-blocker treatment (60), airways-related medical encounters and respiratory exacerbation rates (61). Despite potential criticisms as to methodology, need for further clarification (61) and some reporting ambiguity (59) no adverse results attributable to beta-blocker treatment were found. However, Kotlyar's group did report high rates of beta-blocker intolerance in their small subset of patients with asthma. More detailed discussion of these studies is provided in context in Chapter 6.

There have been other attempts to examine whether beta-blocker treatment adversely impacts on respiratory exacerbations (62, 63). Brooks' study used an electronic medical record database to identify 11592 patients with asthma and COPD, taking beta-blocker medications for at least 30 days, between August 1997 and December 2005. Patients with asthma were found to have increased emergency department encounters and hospital admissions. Beta-blockers were actually protective against medical encounters in COPD, under some circumstances. As a retrospective observational cohort study, the study has important limitations, which are acknowledged by the authors. These include the reliance on a disease coding system (the International Classification of Diseases, Ninth Revision) for diagnosis of asthma and COPD, use of surrogate markers to imply disease severity, potential under-reporting of emergency department visits, and having a treatment group, the group taking non-cardioselective beta-blockers, significantly different from the beta-1 selective treatment group and the control group in terms of baseline characteristics. In a veteran subject population, Barnett's study had similar limitations, although in this instance the subject groups were comparable at baseline. They reported no excess of hospital admissions or hospital length of stay, and fewer airways-related outpatient clinic visits in association with beta-blocker use. The results did not differ according to cardioselectivity of the beta-blocker agent used. However, since subjects could be included solely on the basis of one beta-blocker prescription, it cannot be assumed that the study results represent accurately the situation seen in long term beta-blocker therapy.

The Cochrane pooled data on patients with reversible airways disease suggest an initial reduction in FEV1 after exposure to cardioselective beta-blocker treatment,

which is accompanied by an increase in beta-agonist response. While the beta-agonist response is sustained over continued treatment, the reduction in FEV1 is not. The authors postulated that this might be related to beta-blocker effects on receptor regulation. Recent research by Callaerts-Vegh (64) also suggests a differential airway response between single dose and prolonged beta-blocker exposure. This research group noted that the beneficial effects of B-AR active drugs in the clinical setting of cardiac failure are dependent on timing and duration of therapy. They postulated the existence of a parallel situation in the airways. Using a murine asthma model, they assessed airway responses to acute and chronic B-AR drug exposures, in terms of B-AR density, airway caliber indices using forced oscillation technique, bronchial reactivity using methacholine challenge, and airway cellular responses using bronchoalveolar lavage. Chronic responses were assessed after an exposure duration of 28 days. Acute exposure to partial agonist agents, salbutamol and alprenolol, caused some increased airway resistance in the non-constricted state, decreased airway resistance after methacholine challenge, and increased B-AR density to a level, the equivalent of non-asthmatic controls. Administered chronically, these effects were not seen. Whereas, acute exposure to beta-antagonists, nadolol and carvedilol, caused no airway caliber response in the non-constricted state but caused an increased bronchial constriction response to methacholine. Chronic exposure caused a marked reduction in the bronchial constriction response to methacholine (with the response to nadolol, similar to that seen with acute salbutamol exposure), and a significant increase in B-AR density. While absolute subject numbers were small, and while the murine asthma model may not accurately represent the asthmatic condition in humans, the idea that drugs may show duration-dependent effects, via modulation of B-AR numbers or activity, warrants further assessment in

humans and may have significant therapeutic implications.

"Paradox pharmacology", a phrase coined by Bond (65), is an intriguing possibility for the future treatment of obstructive airways diseases. The concept has been demonstrated already in the treatment of chronic heart failure. Acutely in cardiogenic shock, beta-agonist provides an immediate improvement in haemodynamics, and beta-blockade an immediate worsening. In the chronic situation, beta-agonist treatment results in increased mortality, but beta-blockade, despite long being avoided in the setting of heart failure, actually improves survival. Whether important parallels exist, with regard to beta-blocker airway effects, remains to be seen. Certainly, beta-agonist drugs provide effective bronchodilation when used in the acute setting. Also, since the 1950s, concerns have been expressed about potential detrimental effects, including deaths and refractory asthma, associated with prolonged, regular beta-agonist use in asthma (66-70). These concerns arose during two periods of increased asthma death rates, during the 1960s in six western countries (including Australia) and during the 1970s in New Zealand, when the surplus of deaths could not be attributed to a sudden increase in disease incidence or prevalence, or diagnostic inaccuracy, and hence changes in asthma treatment practices were implicated.

Detrimental effects of chronic beta-agonist use is more difficult to demonstrate in asthma, than in heart failure, as asthma patients are generally younger, and mortality is less frequent. In asthmatics, frequent beta-agonist use may reflect disease severity, patient non-compliance, delay in medical intervention or poorly-treated disease, thus confounding the issue of any direct drug effect. Concerns about beta-agonist safety

resurfaced with the introduction of long-acting beta-agonist (LABA) drugs to obstructive airways disease treatment in the1990s and never have been completely dispelled. Regular beta-agonist use does seem to confer mortality risk, at least in some patients, but evidence is still insufficient to differentiate responsibility from association. Issues of drug tolerance, masking of deteriorating asthma control, loss of bronchoprotection, tolerance of increased allergen load and increased bronchial hyperresponsiveness have been raised with regular use of beta-agonist medication (51, 67). Hence, America's Food and Drug Administration (FDA) and Australia's Therapeutic Goods Administration (TGA) made recommendations that LABA should not be used as monotherapy for asthma. To this end, current asthma treatment guidelines (71) have inhaled steroids as first line treatment for any asthmatic with regular symptoms and LABA introduced only as a subsequent therapeutic option.

Detrimental effects of chronic beta-agonist treatment have been less extensively studied in COPD. Nevertheless, a meta-analysis reviewing the clinical outcomes of "severe exacerbation", mortality and "respiratory death" in COPD, for chronic use of beta-agonist, anticholinergic bronchodilators and inhaled corticosteroids (72), suggested that beta-agonist use was associated with increased respiratory deaths and comparatively worse outcomes than the alternative therapeutic modalities. Two major barriers to interpretation of these results were that trials investigating short-acting beta-agonist (SABA) and LABA were pooled and that most beta-agonist trials allowed beta-agonist use to alleviate acute symptoms even in the placebo arms. In contrast, the recent Towards a Revolution in COPD Health (TORCH) Study (73) was designed to investigate the question of mortality benefit and included regular LABA treatment in two treatment arms: salmeterol alone and in combination with

fluticasone. No significant difference in mortality was seen when LABA-containing treatment arms were compared with the placebo treatment arm. Particular issues in this study were the overall low mortality rate and the high rate of attrition in the placebo arm, with conversion to open label active treatment, in the context of efficacy analyses being performed under the intention-to-treat principle. Therefore, also in the setting of COPD it is not certain whether beta-agonists exert adverse effects, and if so, whether adverse effects are restricted primarily to short-acting agents.

Although a controversial idea, it may be that the same therapeutic reversal, seen already in the approach to treatment of heart failure with beta-blockers, could be a future strategy for the treatment of obstructive airways diseases. The first steps in this direction have already been taken. There is currently in publication, a pilot study of nadolol, a non-selective beta-blocker, used as chronic treatment of mild asthma (74). It is an eleven week, open-label, prospective study of ten subjects with mild asthma. Results to date show a shift in PC_{20} methacholine comparable to other disease-modifying therapies, including inhaled corticosteroids, although this is accompanied by a small, but statistically significant, sustained reduction in mean FEV1. This work was primarily planned as a safety study. However, on the strength of these results, further studies comprising much larger subject numbers will no doubt ensue.

1.3 Areas of Knowledge Deficiency

1.3.1 Extent of Coexistence of Cardiac Disease and Obstructive Airways Disease

Chronic obstructive airways diseases and ischaemic heart disease are prevalent and provide a major contribution to morbidity and mortality. Both global and Australian estimates rank ischaemic heart disease as the leading cause of mortality and of disease burden. COPD is ranked amongst the world's top ten causes of mortality and disability. In Australia, COPD ranks as the third highest cause of disability, and asthma is also included amongst the top ten causes (5, 75, 76). The Australian Institute of Health and Welfare report's 2006 figures differ slightly in the category of information presented, but convey a consistent message (4): ischaemic heart disease is the largest cause of mortality in both sexes, with other forms of heart disease also holding a ranking in the top five causes of death in both men and women. COPD also causes significant mortality, being ranked fifth in men and seventh in women, and being responsible for ten percent of deaths in people beyond 65 years of age. In terms of disability sufficiently "profound or severe to cause core activity limitation", heart disease ranks fourth and "asthma" thirteenth in the age-standardised rankings. However, the term "asthma" is not defined and COPD is not mentioned amongst these figures, suggesting that this term might in fact encompass a broader spectrum of obstructive airways disease. The reported death rate trends in this work are encouraging, in that they show a trend of reducing death rates from cardiovascular and respiratory diseases. This notwithstanding, both ischaemic heart disease and the obstructive airways diseases have a heavy current contribution to the health burden in Australia, even in the setting of likely underestimation of COPD from inaccuracies

of death certification and documentation of comorbidities. The burden is predicted to increase, due to the combined effects of population ageing and a large increase in smoking during the 1970s and 1980s, auguring a significant increase in the burden of all smoking-related diseases (75, 77, 78).

The recently-introduced GOLD Guidelines (3, 77) have encouraged population spirometry screening of smokers, facilitating diagnosis prior to symptom onset, and hence at an earlier stage of disease severity, in the hope that effective preventive interventions can be instituted. There is preliminary information that this approach does at least increase COPD diagnosis rates and increase treatment prescription rates, both pharmacologic and non-pharmacologic. A recent study by Walker in Liverpool, United Kingdom (79), made available spirometry for use in a primary care setting between 1999 and 2003. Of 1508 subjects referred for spirometry, over 50% received a new diagnosis on the basis of combined clinical and spirometric assessment, and significantly increased rates of treatment with anticholinergic, LABA, inhaled corticosteroids and smoking cessation advice, were reported.

Smoking is an important risk factor both for ischaemic heart disease and for COPD. High rates of coexistence are likely, due to the high individual estimates of prevalence for both conditions, and their shared major risk factor. A study of fatal adverse drug events supports this, reporting the presence of heart disease in 74% of autopsied COPD patients (80). While the authors did not specify as to type of heart disease, they did comment that extensive coronary disease was virtually always present in COPD patients who underwent autopsy. It must be remembered that such patients may well represent a group with unique characteristics. However, previous

reports of obstructive airways disease prevalence amongst living cardiology patients is quite low, at 7-28% (48, 81-84). Even so, the prevalence of 7% reported in Behar's study of 5800 survivors of acute myocardial infarction (AMI) is about 50% higher than prevalence estimates for the general population. Such estimates have been based on clinical diagnosis or surrogate measures such as inhaled bronchodilator use, and are mostly unsupported by measures of lung function. Because of reliance on clinical assessment or clinical surrogates, and the lack of data on objective lung function measures, which provide a more sensitive diagnostic tool, it is likely that the previously cited prevalence figures are underestimates. Patients with coronary atherosclerosis, who usually have higher smoking exposure rates than the general population, have a higher risk of COPD. Therefore the underestimation of COPD prevalence, which is seen in the general population, may be even more marked in this subgroup.

1.3.2 Beta-Blocker Prescription Practice Amongst Patients with Obstructive Airways Diseases

Traditionally beta-blocker therapy has been avoided in patients with obstructive airways disease, both COPD and asthma. This group is one in which beta-blocker medications have been previously underprescribed (42-46). Now, with convincing indications for beta-blocker therapy in certain types of cardiac disease and the encouraging statements made by the Cochrane collaboration (57, 58), there may have been significant alterations to beta-blocker prescribing practice. The study by Heller (45), would suggest this to be the case, at least in their Pennsylvanian study population. Their subjects were predominantly female (71.8%); the result of

recruitment from an income-eligible prescription assistance scheme. This factor alone makes the study unusual and interesting, as females are a subgroup in which beta-blocker underprescription has been previously documented, and as most beta-blocker studies have a majority of male participants. Beta-blocker prescription after myocardial infarction was investigated in nearly 10000 elderly patients between 1994 and 1997. Comparing groups with and without traditional beta-blocker contraindications, they found an increase in beta-blocker prescription over the study period in both groups, which was more pronounced in the group with contraindications. Between 1994 and 1997 prescription rates increased from 34.1% to 53.4% in this group. Prescription was more likely if the prescriber was a cardiologist (odds ratio 1.52, P=0.0001), but less likely in COPD (odds ratio 0.49, P=0.0001), or asthma (odds ratio 0.32, P=0.0001). Work more recently completed, whilst still showing that the elderly and patients with obstructive airways disease are underrepresented with regard to beta-blocker prescription, does show a sustained increase in overall prescription rates (48), albeit in a specialist cardiology practice setting. Within the American Heart Association Guidelines (27), the issue merits mention: “in reference to beta-blocker use in patients with obstructive airways disease, these guidelines suggest that when beta-blocker therapy is indicated, COPD patients are mostly suitable”. The guidelines recommend that beta-blocker therapy be considered also for patients with reactive airways disease. Asthma guidelines too have incorporated the findings of the 2002 Cochrane meta-analysis of cardioselective beta-blockers in reactive airways disease; the 2007 version of the National Heart, Lung, and Blood Institute’s guidelines (85) indicate that these agents may be used for the treatment of cardiovascular disease after careful evaluation.

With high rates of occult obstructive airways disease present in the community, it is likely that large numbers of these patients already receive beta-blocker therapy prior to a diagnosis of airflow limitation. Experience would suggest that adverse respiratory complications only rarely occur in this group. It has not been standard practice to screen patients for obstructive airways disease, prior to commencement of beta-blocker drugs, nor to monitor patients during therapy. Currently what generally occurs in clinical practice is a “therapeutic trial”, with medications being commenced, and only withdrawn with the onset of adverse symptoms, believed to be attributable to the beta-blocker medication. The existing alternative options for assessment would be measurement of spirometry, response to bronchodilator, and/ or bronchial hyperresponsiveness prior to beta-blocker commencement. These tests could also be performed during ongoing therapy, in conjunction with assessment for changes in respiratory symptoms and clinical examination findings. It is uncertain whether any of these tests gives a reliable prediction of adverse respiratory effects. Should such testing be adopted in the clinical setting, no current guidelines exist as to what level of abnormal result (if any) should preclude beta-blocker use. It is therefore necessary to firstly obtain more clinical data as to the utility of such testing, in order to develop evidence-based guidelines, prior to incorporating any of these tests into routine clinical practice, when initiating and monitoring beta-blocker therapy.

1.3.3 Cardiac Benefit of Beta-Blocker Medications in Patients with Obstructive Airways Disease

COPD is a leading cause of mortality and morbidity worldwide, but death is more

often due to comorbid cardiovascular disease, than to COPD itself. However, the cause of death in COPD does vary according to disease severity, with CVD and lung cancer being responsible for most deaths in patients with COPD of mild to moderate severity (86, 87) and respiratory failure being the prime cause in those with advanced disease (87, 88). Review of death certificate information shows quite consistent rates of death certificate mention of obstructive lung disease in European and United States' surveys (89), despite inherent inaccuracies in death certification, with under-reporting of milder disease and in women (90). Obstructive lung disease is cited as the actual cause of death less commonly in the surveys from the United States, and this has been attributed to more stringent documentation of comorbidities, more thorough training in death certification and utilisation of more aggressive diagnostic and medical management strategies. (89). In Hansell's study, using electronic database information for England and Wales between 1993 and 1997 from the Office of National Statistics, mention of obstructive lung disease was made in 8% of all death certificates, with causality attributed in 59.8% of these. In patients classified on the certificate as having obstructive lung disease but an alternate cause of death, cause was most commonly, in descending order of frequency, ischaemic heart disease, lung cancer, bronchopneumonia and congestive cardiac failure. Comparison with the major United States' study from the same period, showed that the most common causes of death, not related to airways disease, were similar, although the percentage attributed to obstructive lung disease per se, was less, at about 43% (91). The 1997 study by Vilkman (92), documenting cause of death in a Finnish COPD cohort, found a high mortality rate. Their group was a worse prognostic category, comprising patients after their first hospital admission for COPD, who were recruited between 1986 and 1990. Median survival was 5.71 years, which was considerably

less than the life expectancy for the corresponding age group in the general Finnish population (12.24 years in men and 15.89 years in women). The National Research and Development Centre for Welfare and Health provided their database and recorded cause of death as cardiovascular or circulatory in 37.3%, and COPD-related in 30%. Similar figures were quoted by Kuller's group (93), in their United States' multicentre study of determinants of COPD mortality, using the Multiple Risk Factor Intervention Trial data set (94): namely, 34% deaths from COPD and 37% deaths from cardiovascular causes. Zielinski's retrospective multicentre European study of COPD patients with more advanced respiratory disease and type 1 respiratory failure (88), attributed 38% deaths to an exacerbation of respiratory failure, and 42% to cardiovascular causes, but commented that pulmonary thromboembolism may well be under-recognised as cause of death in their group of oxygen dependent patients, given its relatively frequent discovery at autopsy.

Evidence has accumulated, that measures of respiratory morbidity have an adverse association with cardiovascular health. Myocardial ischaemia occurring in the setting of recent influenza-like symptoms or respiratory infection is a clinically recognised entity. There is also evidence in the literature that symptoms of chronic bronchitis (95, 96), and acute respiratory infections (97-99) are associated with adverse cardiovascular events and cardiac mortality. However, dyspnoea, a symptom not specific to the respiratory system, is the only "respiratory" symptom consistently found to be related to cardiovascular mortality (96, 100-102).

Although not generally recognised as a traditional cardiovascular risk factor, impaired lung function has also been associated with cardiovascular morbidity and

mortality, and is a powerful predictor of mortality, rivalling serum cholesterol and hypertension as an independent risk factor (103). The association is not attributable to cigarette smoking and has been demonstrated for never smokers. An association has been found to exist for bronchial hyperresponsiveness (104) and inverse relationships have been demonstrated for peak expiratory flow (105), FEV1 (96, 100), FEV1/FVC ratio (forced expiratory ratio, FER) and forced vital capacity (FVC) (106-108). Some of the early studies failed to express lung function results with reference to population predicted values; with knowledge of age, height, gender and race, expected results can be calculated from mean normal population results for non-smokers - now the widely accepted mode of reporting lung function data. However, more recent work yields consistent results. Sin (109) reviewed four studies published subsequent to 1990 (102-104, 110), examining FEV1 and risk of cardiovascular mortality, which reported statistically significant relative risks (RR) ranging between 1.1 and 2.11 for males and between 1.07 and 1.88 for females, corrected for all other major vascular risk factors, most particularly smoking. Their overall interpretation was that for each 10% decrease in predicted FEV1, there was a 14% increase in overall mortality, a 28% increase in cardiovascular mortality and a 20% increase in non-fatal coronary events. Attempts to further elucidate the relationship between lung function and cardiovascular events continue, with Engstrom's recent prospective Swedish cohort study (111), once again showing reduction both in predicted FEV1 and FVC, to be associated with coronary events. The relationship was stronger for fatal than non-fatal events. Not surprisingly, rapid rate of FEV1 decline, again independent of smoking and other vascular risk factors, is also a strong predictor of excess cardiovascular events and mortality (112, 113).

Proposed mechanisms for the links between measures of lung function and cardiovascular outcomes include smoking and systemic inflammation as shared risk factors, cardiopulmonary pathophysiologic interdependence, cardiac arrhythmia and, in patients with advanced lung disease, hypoxaemia. The physiology of the cardiovascular and respiratory systems is interdependent, and this becomes a crucial factor in pathologic states. For example, a respiratory exacerbation can exert excess strain on the heart via increased work of breathing and relative hypoxaemia, whilst an acute coronary syndrome, decompensated arrhythmia or cardiac failure, can increase the respiratory burden via increased airways resistance and impaired end-organ gas exchange. Not only that, but the medications used in treatment of a respiratory exacerbation have potential to destabilise the cardiac status, and vice versa.

Cardiac arrhythmia, both supraventricular and ventricular, is commonly seen in patients with established COPD, both during periods of respiratory stability, and during exacerbations. During exacerbations it is an adverse prognostic factor. From the Copenhagen City Heart Study data, it would appear that new onset atrial fibrillation is significantly increased in patients whose FEV1 is reduced in comparison with population predicted results (114), although the relationship is more complex in populations with pre-existing coronary or valvular heart disease and in recurrent fibrillators. Earlier work by Engstrom's group (115) studying "men born in 1914" examined the situation in ventricular arrhythmia. They looked at categories of ventricular arrhythmia seen in 24 hour electrocardiogram (ECG) monitoring in a Swedish cohort of healthy 68 year old men, stratified according to lung function and followed over a 14 year period. They managed to achieve an autopsy rate of near

60%, which adds significantly to the accuracy of their cause of death records. The severity category of dysrhythmia was inversely associated with FEV1, FVC and FER. In the setting of increased frequency of ventricular arrhythmia in the normal elderly population, there was significantly higher risk of adverse outcome, that is, cardiac event or death, for subjects with the more severe dysrhythmia category of frequent or complex ventricular arrhythmia, if lung function measures were below the population median. The risk combination was additive for FVC, but synergistic for FER and FEV1 - measures more representative of the degree of airways obstruction.

Much of the evidence for beta-blocker use in cardiac disease was produced at a time when beta-blocker medications were considered contraindicated in patients with COPD and asthma. Accordingly, many of the landmark cardiology trials excluded these patients, raising doubts as to whether the beneficial effects of beta-blockers extend to patients with obstructive airways disease. The MIAMI trial (53), for example, excluded 3.1% evaluated subjects on the basis of “severe chronic obstructive airways disease”, the Beta-blocker Heart Attack trial (116) excluded patients with obstructive airways disease, who required regular treatment, and two of the major trials of beta-blockers in the setting of AMI, centred in Scandinavia (54, 56) excluded patients on the grounds of COPD and asthma, respectively. The investigators of ISIS-1 (55) considered “bronchospasm” a factor on which to exclude subjects who were otherwise eligible. Even Soumerai’s work (47), looking at beta-blocker under-prescription in the elderly after myocardial infarction, excluded 8.5% of potential subjects because of COPD or asthma. This trend has continued in the more recent trials of beta-blocker use for left ventricular dysfunction, with patients

being excluded on the basis of "ongoing requirement for inhaled beta-agonist or steroid" in the Capricorn trial (117), "reversible obstructive lung disease" in Cardiac Insufficiency Bisoprolol Study (CIBIS) II (23), "obstructive lung disease requiring oral bronchodilator or steroid therapy" in the Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) Trial (24), "severe primary pulmonary disease" in Packer's study of subjects with severe heart failure (21) and "contraindication to beta-blocker therapy" in the Metoprolol Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) Study (22). It is uncertain whether these exclusions amount to significant numbers of patients, as very few of the studies reported actual numbers or proportions of subjects excluded for reasons of obstructive airways disease. Although the exclusion criteria were not necessarily specific as to disease type (that is, reversible airways disease versus COPD), most of these studies did attempt to differentiate by disease severity, often using surrogates markers, such as the need for regular airway-directed medication.

However, there are trials of beta-blocker use in patients with coexisting obstructive airways disease, suggesting that patients with obstructive airways disease do benefit from beta-blocker treatment (42, 43, 118-120). Unfortunately, none of these are randomised controlled trials. Gottlieb's analysis of two year mortality in 200000 patients after myocardial infarction, according to beta-blocker prescription at hospital discharge, found that mortality was lower in beta-blocker treated patients in every subgroup, including those with COPD and asthma. The COPD subgroup had a mortality benefit equivalent to that of patients with uncomplicated myocardial infarction. Almost certainly, prescription bias was operating, in that patients who did not receive beta-blockers were a "sicker" category of patient, or were considered less

likely to tolerate treatment. The authors did try to compensate for this potential bias by stringently controlling for other risk factors for cardiovascular mortality. Chen's study of 55000 elderly patients after myocardial infarction utilised United States' data from the Cooperative Cardiovascular Project, and examined one year mortality in the context of beta-blocker prescription at time of hospital discharge, with the purpose of identifying any differential beta-blocker effect according to severity status of obstructive lung disease. They defined severity in terms of medication requirements and prior hospital admissions. They reported a relative risk reduction of 14% in patients with obstructive airways disease and no regular beta-agonist use, which was equivalent to patients without airways disease. The risk reduction was not statistically significant for patients using regular beta-agonist and was not apparent for those with severe disease. At six months, there was no increase in hospital admissions for any of the beta-blocker treated groups. Au's group looked at mortality as a primary outcome in 1966 veteran's affairs patients with coexisting COPD and hypertension. The study population was predominantly male. Compared with calcium channel blockers, beta-blockers conferred a mortality benefit of near 50%, after adjustment for medical comorbidity and some measures of lung disease severity. The mortality benefit was similar, but not statistically significant, when comparison was made with other categories of antihypertensive agents. Pre-existing cardiac disease seemed to account for the beta-blocker effect. The study examined respiratory exacerbations as a secondary outcome. There was no evidence for an increase in exacerbations in patients treated with beta-blockers. Unfortunately, these studies all suffer from the inherent limitations of retrospective cohort studies, particularly in terms of potential for confounding. COPD diagnosis and severity estimates were variously based on self report, prescribed treatments for airways

disease and medical record scrutiny. Corroboratory lung function measures, with which to better define disease reversibility and severity, were not provided in any of the studies. Although Au's group did attempt to improve compliance by using an estimated antihypertensive regimen adherence of 80% as part of their inclusion criteria, the other studies had no measure of patient or doctor-initiated dose reduction or drug discontinuation, following hospital discharge.

Concurrent use of beta-agonist and beta-blocker medications has also raised concerns. Theoretically, sharing the B-AR as target could result in compromise of one or both drugs' individual effects. While there is good evidence for a maintained bronchodilator response (beta-agonist effect) with most cardioselective beta-blockers, the converse situation is more controversial. There remains concern that in patients who require regular beta-agonist medication, an attenuation of beneficial beta-blocker effects will occur, due to simultaneous opposing B-AR effects. A study by Au and his colleagues in 2002 suggested that concurrent beta-blocker use was protective against an excess of acute coronary syndromes seen in those prescribed beta-agonist medications (121). In a later study, the cardiovascular benefits attributable to beta-blockers were preserved in those patients already taking beta-agonist medication, that is, those who had had scripts filled for SABA in the preceding 6 months (118). However, Chen's group failed to show any significant mortality benefit for beta-blockers, amongst those patients requiring regular beta-agonist medication or those with more severe disease (43). Requirement for beta-agonist medication can be a surrogate marker for disease instability, severity, age or bronchial reactivity, which may confound the interpretation of such results. Hence, although it is known that patients with obstructive airways disease have high rates of

comorbid cardiac disease, and it is very likely that they benefit from beta-blocker medications, when used for treatment of cardiac disease, it is still unclear whether the benefit extends to all severity categories, to those with airway hyperreactivity and those who use beta-agonist medications on a regular basis.

1.3.4 Adverse Respiratory Outcomes Related to Beta-Blocker Use

Beta-blocker medications have been extensively studied with regard to their effects on standard respiratory function tests, particularly spirometry, and respiratory symptoms, mainly in single dose and short duration study protocols. The Cochrane meta-analyses (57, 58) provide a overview of these collated results, subject to the limitations of the included studies and the meta-analysis technique. Overall there is little evidence of adverse effects of cardioselective beta-blockers on lung function, in patients with reversible or fixed obstructive airways disease, but there is a paucity of data with regard to patients with disease of more than moderate severity and all other minority subgroups, including the elderly. There is even less available information about the effects of long term beta-blocker use on disease progression and other respiratory morbidity outcomes, such as frequency of respiratory exacerbations, or hospital presentations and admissions.

Most existing work has concentrated on beta-blocker use in the stable patient and has not clearly defined the categories of respiratory patient, in whom the clinician must adopt a more cautious approach. Traditionally, beta-blocker agents are ceased during acute exacerbation, and this may still be prudent clinical practice. In the setting of respiratory precipitating factors, such as viral infection, the situation with regard to

beta-blocker tolerance may be quite different. The airways may exhibit more reactivity and the response to beta-blocker agents may be more unpredictable. Most clinicians would also exercise discretion before introducing beta-blocker agents in the setting of suboptimal asthma control or instability and in cases of severely compromised lung function. Despite the long held clinical beliefs and the clinical practices here described, there exists surprisingly little medical documentary evidence supporting this approach. Perhaps this is because there have been appropriate alternative medical treatment options available, and hence until now the need to use beta-blocker medications in airways disease patients has not been a pressing issue. However, there do exist three reported cases in the paediatric medical literature of status asthmaticus occurring during respiratory infection in patients requiring chronic beta-blocker treatment for prolonged QT syndrome (122). It is more difficult to find comparable information for COPD. Although the Norwegian multicentre study of timolol after myocardial infarction (56) excluded COPD patients prior to study entry, the significant increase in “pneumonia and bronchitis” events in their treatment group, possibly could be due to occult COPD and disease destabilised in the setting of infection. A recent study (119), though a retrospective cohort study, with only limited information about lung function by which to infer disease severity, provides more reassurance in the setting of chronic beta-blocker therapy and acute COPD exacerbation. Dransfield’s group reviewed medical records for the period October 1999 till September 2006, assessing 825 patients who met their inclusion criteria: admission diagnosis of acute exacerbation of COPD, with or without respiratory failure. Their primary focus was to define the factors associated with beta-blocker use and to establish whether use was associated with mortality. After multivariate analysis, and attempting to correct for any discrepancy in COPD

severity between the groups and for prescription propensity for those with cardiac disease, they found increased survival to hospital discharge in the group treated with beta-blockers. Van Gestel's study (120), another retrospective observational study, is also reassuring. It targets a population known to exhibit high rates of ischaemic heart disease, those undergoing major vascular surgery. They reported significant mortality benefit of cardioselective beta-blockers in COPD patients, at 30 days and long term, stratified by severity of COPD as measured by spirometry. These authors also attempted to adjust for bias by indication by using a propensity score. However, the duration and maintenance of beta-blocker therapy is unclear, both at study entry and over the long term follow up, which does significantly limit interpretation of the long term beta-blocker effects.

1.4 Objectives

1.4.1 The Prevalence of Obstructive Airways Disease

We sought to estimate prevalence of obstructive airways disease and bronchodilator reversibility, amongst a population of patients with cardiac disease, using objective measures of lung function. We recruited from amongst patients admitted to Royal Prince Alfred Hospital's Cardiology Unit for the assessment and management of cardiac disease. We obtained sequential measures of spirometry and bronchodilator responsiveness over twelve months and used these results to identify subjects with objectively-defined airways obstruction and asthma. Information from an initial interviewer-administered questionnaire further characterised our subject population

in terms of demographics, occupation, known medical comorbidity and medication use (Appendix 1).

1.4.2 Investigate Beta-Blocker Prescription

Past research has demonstrated physician reluctance to use beta-blocker medications for recognised therapeutic indications in certain subgroups of patients, including the aged, females and the medically frail, in particular those with heart failure, obstructive airways diseases and diabetes. More recently, the medical literature reflects increased prescribing, although this has most affected patients with heart failure, following recognition that beta-blocker treatment in this group confers survival benefit. We sought to document the prevailing prescribing practice amongst Royal Prince Alfred Hospital's cardiologists, with regard to beta-blockers, in our study population, recording for each subject whether beta-blocker medication was indicated, whether such medication was considered first line treatment, and any reasons for withholding beta-blocker treatment. Of particular interest to us was a comparison of beta-blocker prescription practice between subjects with previously diagnosed or "known" obstructive airways disease and subjects without an established diagnosis, but who demonstrated airways obstruction or bronchodilator responsiveness on spirometry.

1.4.3 Investigate Adverse Respiratory Effects

Beta-blockers may cause bronchoconstriction via interaction with airway beta-2 receptors, and hence have significant potential for adverse effects in patients with

obstructive airways disease. Nevertheless, the existing medical literature examining beta-blocker use in patients with COPD and reactive airways disease would suggest that beta-blocker use is safe in most instances. However, there is a paucity of information about the respiratory effects of longer term beta-blocker use, which is particularly important in obstructive airways diseases, as they are punctuated by periods of worsening symptoms or "exacerbations", adversely affecting prognosis. In fact, most of the reported research available to clinicians about this topic is retrospective. In the recent Cochrane meta-analyses investigating this topic (57, 58), the longest duration prospective study of cardioselective beta-blockers in obstructive airways disease targeted COPD patients and lasted only 3 months. Therefore we sought to investigate the longer term respiratory effects of beta-blocker use on lung function, symptoms and exacerbations. Specifically, over twelve months we serially assessed respiratory symptom severity scores and spirometry for evidence of deterioration in chronic symptom morbidity and lung function. We collected data pertaining to beta-blocker cessation, respiratory exacerbations, acute cardiac events, hospital admissions for treatment of acute cardiac or respiratory disease and deaths over six years' duration. We sought to ascertain whether there existed a relationship between long term beta-blocker use and risk of respiratory and cardiac events. The effect of beta-blocker use on survival was also investigated.

1.5 Summary

Two of the commonest diseases in the Australian community, ischaemic heart disease and COPD, share cigarette smoking as a most important risk factor. It is therefore likely that a high proportion of patients with cardiac disease have

coexisting obstructive airways disease. Beta receptor antagonist drugs are the appropriate therapeutic choice in many patients with cardiac disease, and the indication for their use after myocardial infarction and for left ventricular dysfunction is compelling. Concern remains about the safety of beta-blocker use in patients with obstructive airways diseases, both COPD and asthma, due to potential for precipitating life-threatening bronchoconstriction. It is possible to monitor lung function and bronchial reactivity in these patients, but there is no assurance that such monitoring is predictive of adverse respiratory consequences. The research represented here for this thesis seeks to:

- Determine the proportion of cardiology patients who have coexisting airways disease

- To document current practice with regard to beta-blocker prescription

- To assess for adverse respiratory effects over a prolonged duration of beta-blocker treatment

CHAPTER 2

THE STUDY PROTOCOL

CHAPTER 2: THE STUDY PROTOCOL

2.1 Recruitment

For a total recruiting period of four weeks, we reviewed all patients who met the eligibility criteria. The patients were recruited consecutively from amongst admissions to the Cardiology Unit of Royal Prince Alfred Hospital, a tertiary teaching hospital, during designated recruitment weeks. Subjects were identified using the hospital computerised listing of Cardiology Unit inpatients. Subjects were considered eligible if accepted for admission under a cardiologist at the hospital, for assessment and/or treatment of an acute cardiac problem. Thus acceptance for admission under a cardiologist was used as a surrogate marker for bone fide cardiac disease, given that often the cardiac diagnosis was not apparent at the time of hospital admission, and was not always confirmed by the time of hospital discharge.

Inclusive selection criteria were deliberately chosen, in order to broaden the applicability of the results obtained. The target population was to be a sample of the Australian resident population. Patients with acute cardiac disease were selected because of the high likelihood that beta-blocker therapy would be used in acute treatment or be considered in chronic management. As ischaemic heart disease is the most common form of acute cardiac morbidity in Australia, and shares with obstructive airways disease, smoking as a major risk factor, we felt that this selection was likely to provide us a study population with high potential for coexisting heart disease and obstructive airways disease, in which to examine the respiratory effects and impact of beta-blocker therapy.

The following exclusion criteria were applied:

- Inability to communicate in English, due to insufficient interpreter resources

- Impaired cognition, sufficient to compromise informed consent.

- Illness severity, sufficient to preclude informed consent or completion of the study protocol. Subjects were also excluded if enrolment in the study protocol was likely to interfere with timely medical investigation and treatment.

- In the initial stages, subjects were excluded if their current place of residence was of sufficient geographic distance from the hospital to preclude return for follow up assessments. This exclusion also applied to those whose physical impairment or social circumstances prevented them from being available for the follow up interviews. However, early during the recruitment period, it became apparent that high numbers of subjects were being excluded on these grounds. Subsequently, the protocol was amended so that those subjects, who were to be excluded purely because of anticipated follow up difficulties, were recruited for an amended version of the protocol.

2.2 Statistical Power

There were insufficient previous research data available for a formal statistical power calculation. Firstly, this is because previously quoted prevalence figures (48, 81-84) for airways obstruction amongst patients with ischaemic heart disease have not used

spirometry for diagnosis. Instead they have relied upon clinical diagnosis and surrogate measures, such as inhaled medication use. These are much less sensitive measures of airways obstruction, incapable of detecting subtle disease. COPD is now precisely defined by spirometric criteria (77).

Secondly, our subjects were recruited from a population of cardiology patients, who did not exclusively have ischaemic heart disease. Although this category of cardiac disease is the most common in the Australian population, our inclusion of patients with non-ischaemic cardiac morbidity meant that the study population was not necessarily comparable to those populations from which the previous prevalence figures have been derived. Neither is it possible to make comparison with the general population, as its COPD prevalence is likely to be much lower. In this setting, any attempt at statistical power calculation would result in compromise of accuracy due to the degree of extrapolation required. A recruitment target of 50 subjects was set for this pilot project.

2.3 Abbreviations

Abbreviations which have been frequently used in this work include the following:

- ACS = acute coronary syndrome
- B-AR = Beta adrenergic receptor
- BDR = Bronchodilator reversibility

- BMI = Body mass index
- CAD = Coronary artery disease
- CI = Confidence intervals
- COPD = Chronic obstructive pulmonary disease
- CVD = cardiovascular disease
- FEV1 = Forced expiratory volume in one second
- FVC = Forced vital capacity
- FEV1/FVC = FER= Forced expiratory ratio
- IHD = Ischaemic heart disease
- LABA = long-acting beta-agonist
- % P FEV1 = Forced expiratory volume in one second expressed as a percentage of the predicted value
- % P FVC = Forced vital capacity expressed as a percentage of the predicted value

- PC_{20} = The provocative concentration of an agent that caused a 20% drop in FEV1

- SABA = short-acting beta-agonist

- STEMI = ST elevation myocardial infarction

- NSTEMI = non ST elevation myocardial infarction

2.4 Methods

The study was approved and monitored by the Ethics Review Committee of Sydney South West Area Health Service, RPAH Zone. At time of recruitment, informed consent was obtained. Beta-blocker treatment was determined by the treating cardiologist. The subjects then completed an interviewer-administered questionnaire (Appendix 1). Information was collected as to demographics, acute cardiac diagnosis, previously made cardiac and respiratory diagnoses, medical comorbidity, medications, including beta-blocker and beta-agonist use, smoking status, previous respiratory exacerbations and potential markers of socio-economic status, including ethnicity, employment and health insurance status. After receiving training in performance of the forced expiratory manoeuvre and observing a demonstration by the study investigator, spirometry was performed, according to American Thoracic Society guidelines (123), using a hand-held EasyOne^{TM} spirometer. This included an assessment for response to inhaled bronchodilator. Patients were subsequently reviewed at day 3 of admission or hospital discharge, and then again at 6 and 12

months. At each review, the subject completed an interviewer-administered questionnaire about smoking habits, respiratory symptoms, respiratory and general health (Appendices 2 and 3), and performed spirometry. Subjects who would have been excluded on the basis of geographic factors, but who participated in the amended version of the study protocol, were required to complete the first and second reviews only. All subjects were then recontacted five years after study commencement and asked to complete a postal questionnaire (Appendix 7), in order to capture long term respiratory health outcomes data; survival, respiratory exacerbations, cardiac events and hospital admissions related to exacerbation of respiratory or cardiac disease.

Spirometry is the timed measure of dynamic lung volumes during forced expiration and inspiration to quantify how effectively and how quickly the lungs can be emptied and filled (124). Important measurable variables include FEV1, FVC and FEF 25-75%. Daily spirometer calibration testing is recommended (123), although the EasyOne^{TM} spirometer has demonstrated performance stability, without need for repeated calibration checks, over prolonged periods, up to 26 weeks (125). Calibration checks were performed daily using a "biologic standard" (testing performed using a subject of known and stable spirometry parameters) and weekly using a 3L calibration syringe, to accuracy within 3%. All spirometry was performed with subject seated upright, facing directly ahead, and both feet flat on the floor. During the manoeuvre supervision and enthusiastic encouragement was provided by a medically-trained study investigator. Subjects were asked to inhale fully and briskly, to insert the spirometer mouth-piece (if not already inserted at start of inspiration) so that the lips formed an airtight seal, and then to forcefully expel or

"blast" the air from their lungs, as hard and fast as possible, until their lungs felt completely empty. At this point, they were asked, whilst remaining with mouthpiece in situ, to breathe in fully – the completion point of the manoeuvre. Subjects were warned about dizziness during the expiratory phase and instructed to breathe in via the mouth piece (and terminate the manoeuvre) should this occur. Repeated manoeuvre attempts were requested until performance acceptability and reproducibility was demonstrated, until eight successive manoeuvres had been attempted, or until tiring, as indicated by the subject or as evidenced by progressive deterioration in spirometry performance.

Each manoeuvre was evaluated for acceptability. The spirometer possessed a computer-based system which assessed start of test (using back extrapolated volume not greater than 0.15L or 5% FVC and time to peak flow not greater than 150ms) and end of test (expiration lasting less than 2s or volume accumulation not diminished below 0.1L per 0.5s) for non-acceptability criteria. In addition, the study investigator terminated prematurely any manoeuvre where technique was overtly marred by hesitation, air leak, cough, extra breath, submaximal effort, glottic closure or valsalva, mouthpiece closure or otherwise poor technique. At least three manoeuvres were required for test reproducibility. The spirometer's computer-based system possessed a quality grade rating system. An A grading required a difference between greatest two measures of both FVC and FEV1, of less than 0.15L and a B grading to a corresponding difference of 0.2L. Tests were not regarded as reproducible unless quality grade rated as A or B. Published reference values were used to derive predicted values of ventilatory function, given age, gender, ethnicity and height (126). Morris' values were chosen as they cover an age range skewed towards the

very elderly, with wide height range, even though they are based on American, and not Australian, population values.

Ideally bronchodilator medication, both long-acting and short-acting, and smoking should be deferred preceding assessment of bronchodilator response. However, the study investigators were not able to intervene in the prescription of regularly-used medications or in habitually-used recreational drugs, such as nicotine. This was not relevant for long-acting bronchodilators, as none of our subjects were using them. However, the recommended four hour delay for short-acting bronchodilators and the hour's delay for smoking were not able to be imposed. Because of this, the bronchodilator response results were subject to potential underestimation. The bronchodilator medication used was a combination of salbutamol 5mg (short-acting beta-agonist), and ipratropium bromide 0.5mg (short-acting anticholinergic drug), administered undiluted via nebuliser. This combination was chosen because it has a rapid onset of action and is generally safe. It provides two mechanisms of bronchodilation, incorporating pathways of both sympathetic and parasympathetic nervous systems. The drugs employed are widely available and commonly administered in combination via this route of delivery. They are also routinely used for the purposes of determining bronchodilator response. The combination and doses chosen have been used by others for the purpose of establishing the presence or lack of bronchodilator response (79). In addition, the choice of an anticholinergic agent specifically, is recommended in reversing beta-blocker induced bronchospasm. There exists a theoretical benefit using a bronchodilatory pathway not dependent on beta adrenergic receptor function and also some experimental evidence of efficacy in this setting (127). A nebuliser was used for drug delivery in order to easily administer an

adequate dose, and because it is a readily available drug delivery modality in the hospital setting. Repeat spirometry, performed for the purposes of assessing the airways response to bronchodilator, was performed after a delay of 15-30 minutes, a time period which is intermediate between those stated in the current ATS recommendations (128) for assessing bronchodilator response with short-acting beta-agonist (10-15 minutes) or short-acting anticholinergic (30 minutes), due to our decision to use a combination of these bronchodilator types.

Respiratory symptoms were assessed using symptom scores. Subjects were asked to rate symptom severity on a scale, with 0 representing absence of the symptom and 10 representing the worst possible severity. The scores were to reflect the subjects' usual experience of the symptom over the last few weeks (except in the second interview, when subjects were asked to consider the last few days). Scores were recorded for cough, sputum production, dyspnoea and wheeze.

2.5 Definitions

- "Airways obstruction" is defined by the single criterion of FEV1/FVC ratio < 70% (77).

- "Body mass index" of an individual is defined as weight divided by the square of height and is expressed in units kg/m^2.

- "Bronchodilator reversibility" (BDR) is defined as a FEV1/FVC <70% and a 15% post bronchodilator increase in FEV1 of at least 0.2L (129).

- A “pack year” is defined as the estimated average number of cigarettes smoked per day, multiplied by the smoking duration expressed in years, divided by twenty.

- A “regular smoker” is here defined as someone who has smoked at least seven cigarettes per week (or the equivalent in terms of tobacco smoked) for three months or more (130).

- A “respiratory exacerbation” is here defined as an increase in respiratory symptoms (sputum quantity or purulence, cough or dyspnoea) prompting a presentation for medical assessment and/or prescription of either antibiotic or systemic corticosteroid.

- Chronic obstructive pulmonary disease (COPD) is defined as persistence of FEV1/FVC ratio<0.7 after bronchodilator (3)

2.6 Statistical Analysis

Results for normally distributed data have been expressed as mean (standard deviation). Results for non-normally distributed data have been expressed as median (range). A p-value less than 0.05 (two-tailed) was considered statistically significant. Non-normal variables were transformed if necessary to obtain normality and means of normal variables were compared using T-tests when the variances were statistically equal and with the Welch Test (131) when the variances were statistically unequal. Otherwise, Kruskal-Wallis tests were used to compare medians

of non-parametric variables. Chi-squared tests were used to examine differences in proportions and, where the expected cell frequency in the contingency table was below five, levels of significance were reported using Fisher's exact test. Data contained in Chapter 3 "Defining the characteristics of a population of cardiology patients", Chapter 4 "The prevalence of coexistent airways obstruction in patients with cardiac disease" and Chapter 5 "Beta-blocker prescription in patients with coexisting cardiac and obstructive airways disease" were analysed using SPSS 13.0 software.

The statistical analyses used in Chapter 6 "The longer term effects of beta-blocker medications on lung function, respiratory exacerbations and survival in patients with cardiac disease" were performed on intercooled STATA 10.0 for windows (StataCorp LP). Specific to this chapter was the requirement for repeated measures analysis, in the context of multiple missing data points. Longitudinal regression was used for analysis of variables for which repeat measures were available. Because of correlated readings in individual subjects over time, the association of beta-blocker use with lung function parameters and with symptom scores was evaluated using linear mixed models with individual-specific random intercepts. The association between respiratory exacerbations or adverse cardiac events and the use of beta-blockers was analysed using a mixed model Poisson regression, which is a consistent estimator of relative risk (132). Results were reported as risk ratios. Survival outcomes were analysed using a Cox proportional hazards model and hazards ratios were reported. All models were adjusted for potential confounding factors, including age, gender, body mass index (BMI), pack years, steroid score and mean FEV1, where appropriate. Routine residual diagnostics were tested to ensure model validity.

CHAPTER 3

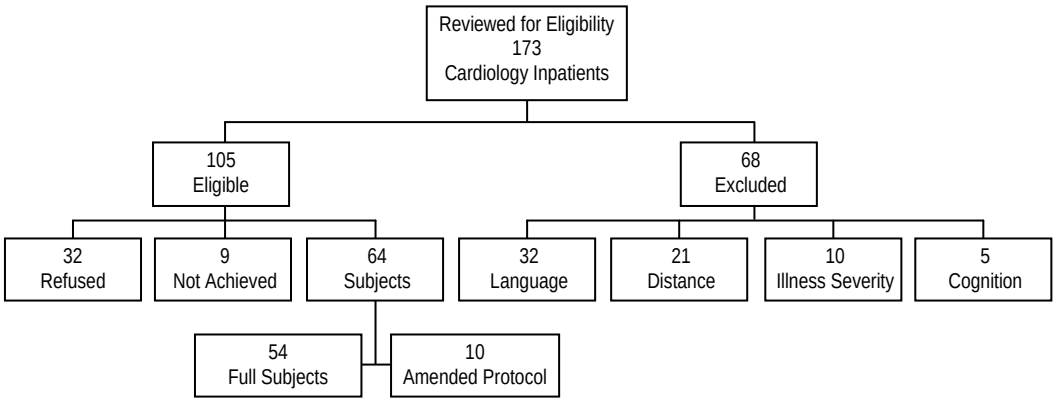
THE STUDY POPULATION

CHAPTER 3: THE STUDY POPULATION

3.1 Recruitment

During the recruitment period, 173 patients were reviewed for eligibility. Of these, 68 (39%) were excluded and 32 (18%) refused to participate in the study protocol. Exclusion criteria were divided as follows: 32 (47%) were non-English speaking, 21 (31%) were excluded due to geographic or transport considerations precluding follow up, ten (15%) were judged too medically unwell to attempt the protocol and five (7.4%) had cognitive or psychiatric impairment sufficient to preclude informed consent. Of the 64 patients (37%) who agreed to participate, 54 were enrolled in the full, and ten in the amended study protocol. The “not achieved” category applied to those patients who were not included in the study, either because of hospital discharge prior to assessment for eligibility, or to patients who were prevented from participating in the study protocol due to unforeseen circumstances, but who had not actually withheld consent. The response rate was calculated to be 61%, based on 64 subjects and 105 eligible patients. Recruitment is illustrated in Figure 3.1.1.

Figure 3.1.1: Recruitment



3.2.1 Demographics

The raw data for results reported in this chapter are presented in Appendix 4 and the characteristics of the subject population are summarised in Table 3.2.1. The subject population was predominantly Caucasian and male, of mean age 65.05 years. Most were overweight, the mean body mass index (BMI) being 27.21 kg/m^2 after reciprocal conversion of data and 9.4% possessed private medical insurance. Nearly all (as detailed in subsequent sections) proved to have bona fide cardiac disease, after medical investigation, and 70.3% either had been diagnosed previously with coronary atherosclerosis, or had an acute coronary syndrome (ACS) as precipitant of the index hospital admission.

Most subjects had previously smoked, or were currently smoking cigarettes on a regular basis. The median pack year smoking history was 18.8, a level sufficient to confer risk of cardiovascular disease and smoking-related lung disease. The pack

year smoking data were strongly right-skewed, with the distribution being influenced by substantial numbers of never smokers and a few subjects with extremely high pack year smoking exposure. Some had previously received a diagnosis of obstructive airways disease, though more had been diagnosed with asthma, than chronic obstructive pulmonary disease (COPD).

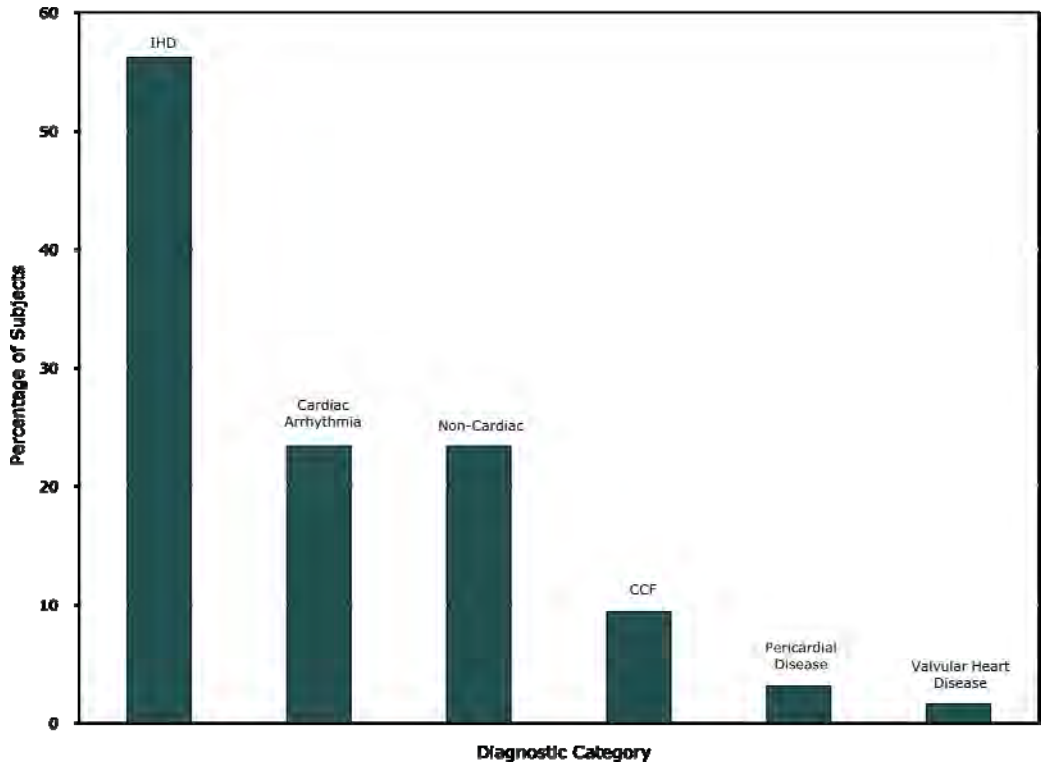
There was a significant proportion of New Caledonian patients amongst the acute cardiology admissions, all of whom were excluded on the basis of language considerations. They comprised 27.7% of the excluded patient population. These patients had been transferred from overseas for treatment under an international agreement. They did not represent Australian resident population, and therefore were not the intended target population of this study. Despite this, compared to the non-participating eligible patients and excluded patients, the subjects were not significantly different in age: median age 67 (range 29-91) years versus 69.5 (range 15-86) years and 68 (range 27-90) years, respectively (Kruskal-Wallis Test: 2 degrees of freedom, $p = 0.736$). A non-parametric statistical test was used for comparison, given the non-normal distribution of age amongst the non-participating, eligible patients. Nor was there any significant difference in gender distribution; 64.1% male, versus 51.2% and 62.1% respectively (Chi-square Test: 2 degrees of freedom, $p = 0.476$).

Table 3.2.1: Study Population Characteristics

Study Population Characteristics	
Mean Age (Years)	65.05 (SD 12.44)
Gender (Male %)	64.1
Caucasian (%)	95.3
Mean Body Mass Index (kg/m^2)	27.21 (SD 13.52)
Diagnosed Coronary Atherosclerosis (%)	70.3
Smoking History (%)	75.0
Median Smoking Exposure (Pack Years)	18.8 (Range 0-228)
Diagnosed COPD (%)	9.4
Diagnosed Asthma (%)	28.1
Beta-Blocker Use (%)	28.1

3.2.2 Cardiac Pathology

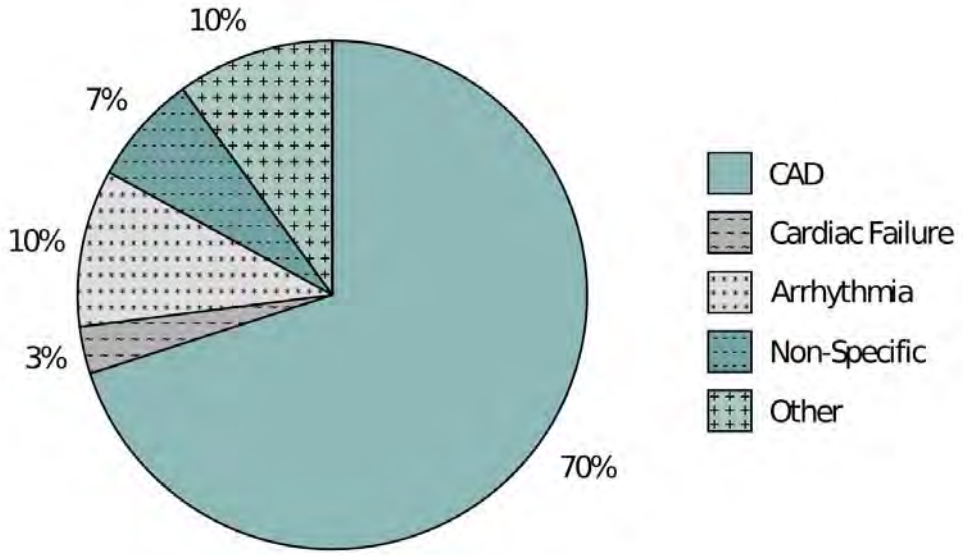
Figure 3.2.1: Acute Diagnosis



The distribution of acute cardiac diagnoses is depicted in Figure 3.2.1. The acute reason for presentation and hospital admission was most often ischaemic heart disease (IHD). Lesser numbers of subjects were admitted for cardiac arrhythmia, non-cardiac or non-specific symptoms, and only small numbers of subjects were admitted because of cardiac failure (CCF), pericardial disease and valvular heart disease. There was a subset of subjects with prior diagnosis of coronary disease, who were admitted for further investigation of chest pain, on suspicion of a coronary cause. A conservative approach was taken and these were included in the "non-cardiac or non-specific" category for acute cardiac diagnosis.

Examination of past medical histories yielded even higher numbers of subjects with a diagnosis of coronary atherosclerosis, with 70.3% having known coronary artery disease (CAD), or else unequivocal evidence of acute myocardial ischaemia during the enrolment admission. In fact, six of the 15 subjects who received no acute diagnosis or who were diagnosed with a non-cardiac condition at hospital discharge, already had established CAD. Table 3.2.2 demonstrates the distribution of cardiac disease in our subject population, judged to be the reason for the acute presentation, after completion of diagnostic investigations.

Figure 3.2.2: Distribution of Cardiac Morbidity*



*When there existed more than one cardiac morbidity category per patient, the one cited is that towards which most investigation and treatment was directed during the hospital admission

After further cardiac investigations, 87.5% subjects had an established cardiac diagnosis at the time of hospital discharge, confirming that despite the use of the potentially non-specific “cardiology unit admission” as the criterion for study eligibility and as a marker indicating cardiac disease, the majority of our subjects did in fact have cardiac disease, which was predominantly ischaemic heart disease. The high proportion of subjects with ischaemic heart disease is consistent with our knowledge that this form of cardiac disease is the most common cause of cardiac morbidity among the Australian population (4).

3.2.3 Comorbid Disease

In terms of respiratory disease, 9.4% subjects had been previously diagnosed with COPD, though more had been labelled as having “asthma” (28.1%). This is in the context of high subject population smoking rates, with 75% having been “regular smokers”. A regular smoker is here defined as someone who has smoked at least seven cigarettes per week (or the equivalent in terms of tobacco smoked) for three months or more (130) . In our subject population this translates into a high level of cigarette smoke exposure, reflected by the population median of 18.8 pack years.

Vascular risk factors and non-coronary vascular disease were prevalent in our subjects, with 18.8% having diabetes mellitus, 17.2% hypertension, and 17.2% having either peripheral vascular disease or cerebrovascular disease. Many patients were also receiving lipid-lowering therapy, although it was not always possible to establish whether therapy had been instituted to treat hyperlipidaemia per se, or whether it had been commenced for risk factor modification and anti-inflammatory effects.

Of other diseases, the most common diagnoses were gastro-oesophageal reflux disease (6.25%) and prostate cancer (4.7%).

3.2.4 Use of Beta-Receptor Active Medication

At the time of hospital admission, 28.1% subjects were using beta-blocker medications. This was in the context of many subjects (42.2%) having a diagnosis,

prior to admission, of ischaemic heart disease, tachyarrhythmia or significant left ventricular dysfunction, all of which are potential indications for beta-blocker therapy.

Twenty-five percent of subjects were using inhaled medications on a regular basis. With one exception (who was prescribed inhaled budesonide only), all of these had been prescribed a short-acting beta-agonist (SABA), such as salbutamol or terbutaline. In 6.25% subjects a short-acting anticholinergic bronchodilator (SAACh) was used in addition to a beta-agonist drug. No subjects were taking either long acting beta-agonist (LABA) or long acting anticholinergic (LAACh) medication. There were several subjects, who took no inhaled medication, despite having known obstructive airways disease, which is in keeping with the episodic nature of reversible airways disease. Conversely, there were also a small number (4.7%) of subjects who used inhaled bronchodilator without any established diagnosis of lung disease. Only one subject was taking both inhaled beta-agonist medication and a cardioselective beta-blocker in combination. Table 3.2.2 shows the use of beta-blockers and inhaled medications in our subject population at study commencement.

Table 3.2.2: Medications

Medication	Number of Subjects (%)
Inhaled Medication	16 (25.0)
SABA	15 (23.4)
AACh	4 (6.2)
Inhaled Corticosteroid	1 (1.6)
Beta-Blocker	18 (28.1)
Beta-Blocker and SABA	1 (1.6)

3.3 Discussion

The subject population was characterised by a high rate of cardiac morbidity. This was important to establish, given that the eligibility criterion “acceptance for cardiology admission” was intended to select patients with heart disease. The population also showed a male predominance, which was expected given the known male predominance of coronary disease in the Australian population. It is possible that the nature of the study favoured selection of patients with respiratory disease, or those who were familiar with the inhaled medications used in treatment of respiratory disease. Informed consent for study participation, specifically included consent for the administration of bronchodilator medications for the assessment of bronchodilator response. This entailed discussion about the potential risk of inducing myocardial ischaemia or cardiac dysrhythmia, through the chronotropic, inotropic and proarrhythmogenic effects of these agents. The scientific literature does suggest an association between use of short-acting bronchodilators, both beta-agonist and anticholinergic agents, and adverse cardiac events, though causality is unestablished (86, 121, 133, 134). Subjects familiar with bronchodilator medications might have been less worried about potential adverse effects and therefore more likely to consent to participation in the research protocol.

Most of the subject exclusions were for reasons of language or because of circumstances precluding follow up outside hospital. The language exclusion was instituted due to a scarcity of interpretation services and because of anticipated difficulty in teaching the spirometry manoeuvre via a foreign language. The language criterion was the reason for excluding all New Caledonian patients, who were

transferred from Noumea and admitted to the hospital under international agreement, for treatment of acute cardiac disease. Inclusion of these patients, given their significant numbers amongst cardiac admissions, would have skewed the ethnic distribution of the study patients, and compromised the intent of studying a population of Australian residents.

During the first week of recruiting it was seen that many patients were being excluded on the basis of anticipated follow up difficulties, especially travel duration from normal place of residence, despite being otherwise eligible for the study. A decision was made to subsequently consent such patients for an amended version of the study protocol, so that the number of patients excluded on this basis represents only those approached early during the recruitment period.

The reasons for withholding consent were frequently not specifically stated and were usually expressed as an unwillingness to contribute the effort required by the protocol whilst still unwell. When a specific reason was given, most often the concerns raised were related to the potential cardiac risks of the bronchodilator medications used in the assessment of bronchodilator response, or reluctance to commit to the planned follow up arrangements.

Because of the nature of cardiac assessment, being reliant on a number of complementary investigations as well as clinical history and examination, information pertaining to the exact cardiac diagnosis often accumulates during the course of time. Hospital protocols at the time of patient recruitment were most directed at excluding coronary disease manifestations, where clinically relevant,

whilst in hospital. Therefore the presence or absence of coronary disease was likely to be confirmed prior to hospital discharge. However, specific investigation of ventricular and valvular function was not always performed in the acute setting. Hence the figures cited with regard to diagnosis of heart failure and valvular heart disease may be underestimated, although these diagnoses were unlikely to have been missed as the reason for the acute presentation.

3.4 Conclusions

The studied population of cardiology patients did prove to have a high rate of bona fide cardiac disease. The subjects were predominantly male, overweight, and average age was 65.6 years. Smoking exposure was significant and there were high reported rates of comorbid respiratory disease and non-coronary vascular disease.

CHAPTER 4

THE PREVALENCE OF COEXISTENT AIRWAYS OBSTRUCTION IN PATIENTS WITH CARDIAC DISEASE

CHAPTER 4: THE PREVALENCE OF COEXISTENT AIRWAYS OBSTRUCTION IN PATIENTS WITH CARDIAC DISEASE

4.1 Aims

Using simple spirometry, we sought to estimate the prevalence of airways obstruction amongst patients admitted to hospital with acute manifestations of cardiac disease.

4.2 Methods

Subject population recruitment, methods and statistical analysis for this observational study are as delineated in Chapter 2. Data collection occurred between April 2003 and July 2004.

4.3 Results

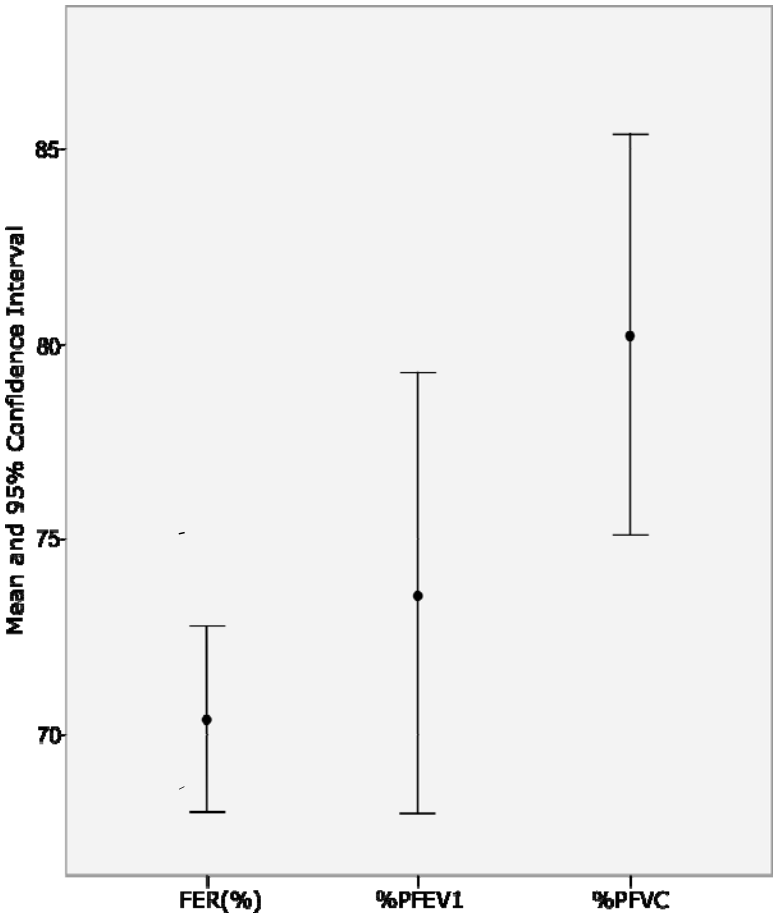
For the purposes of this study, FEV1/FVC ratio < 70% has been chosen as the single criterion defining airways obstruction (77). Bronchodilator reversibility (BDR) is defined as a FEV1/FVC <70% and a 15% post bronchodilator increase in FEV1 of at least 0.2L, as cited by the 1995 American Thoracic Society (ATS) guidelines (129).

Persistence of FEV1/FVC ratio<70% after administration of bronchodilator was regarded as being consistent with a diagnosis of COPD. Given the variable nature of airways obstruction, subjects were classified as having airways obstruction and BDR, if these criteria were met at any of the interview sessions during the twelve month study protocol. Spirometry results which did not meet ATS reproducibility and acceptability criteria (129) were excluded from analysis.

The individual subject data for results reported in this chapter are presented in Appendix 5. By completion of the twelve month study period, four subjects were excluded from the following analyses because of inability to perform acceptable and reproducible spirometry, and one because she withdrew consent prior to her first attempt at spirometry. 30 of 59 subjects (50.8%) met criteria for airways obstruction on one or more occasions. BDR was seen in 17.2% subjects by completion of the protocol. When BDR was assessed as a proportion of those subjects with airways obstruction, ten of the 29 subjects (34.5%) met criteria for BDR on at least one occasion during the study protocol.

For our subject population, on initial assessment, mean percent predicted FEV1 was 73.60 (21.45), mean percent predicted FVC was 80.21 (19.61), mean percent predicted MMEF was 54.92 (27.71) and mean FEV1/FVC ratio was 0.70 (0.09). The reduced FEV1, forced expiratory ratio and MMEF, reflect the relatively high prevalence of obstructive airways disease in this group.

Figure 4.3.2: Mean Subject Population Spirometry Results



Forced expiratory ratio (FER) expressed as a percentage, FEV1 and FVC expressed as percentage of predicted values

As a further guide to the severity of airways obstruction encountered amongst our subject population: GOLD stages II and greater are generally agreed to correlate with clinically significant obstructive airways disease (135). Of our subjects with airways obstruction, 72% had FEV1 within the range of 30-80 percent predicted (GOLD stage II), and 7% had FEV1 < 30% predicted (GOLD stage III). Mean percent predicted FEV1 was 61.79. This is an approximate comparison only, since GOLD stage assessment, strictly applied, pertains only to post bronchodilator spirometry measures. Our group contained both COPD and asthmatic patients, and the quoted

figures represent the most severe measure of obstructive lung function, graded according to FEV1/FVC ratio, seen over the twelve month study duration.

Table 4.3.1: Study Population Characteristics According to FEV1/FVC Ratio

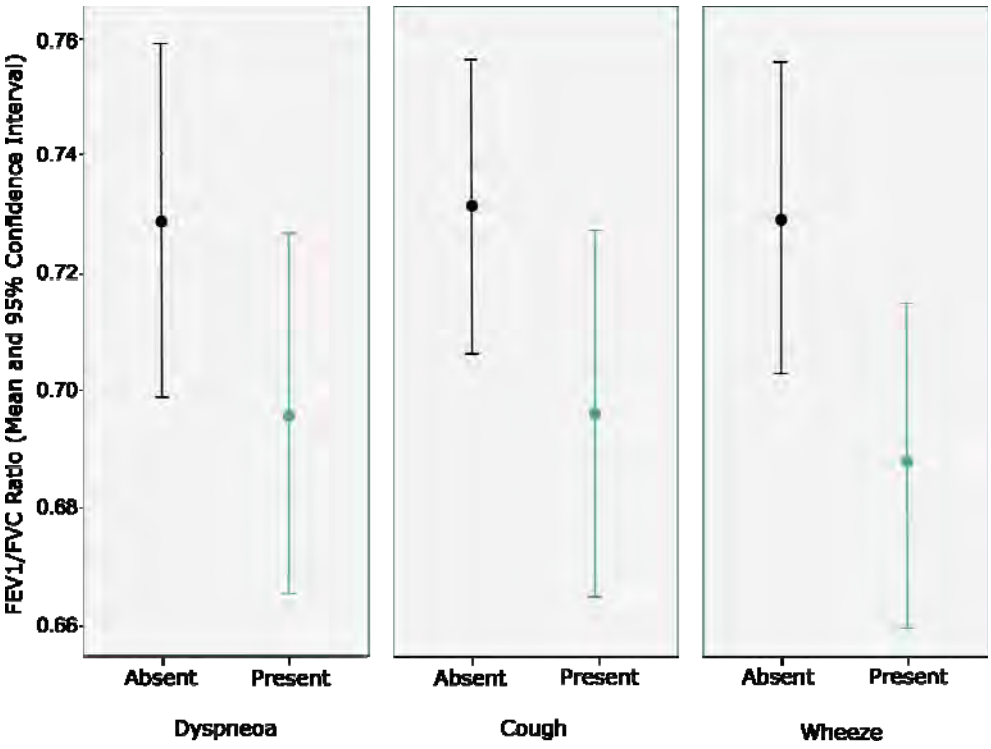
	FEV1/FVC<0.7 (n = 30)	FEV1/FVC>0.7 (n =29)	P Value
Male (%)	60.9	62.9	1.00
Age (year)	69.15 (9.84)	62.03 (12.40)	0.02
Smoker (%)	78.3	74.3	0.974
Mean Pack Years	53.48 (2.23)	10.95 (3.31)	<0.001
Beta-Blocker (%)	43.5	57.1	0.45
Diagnosis COPD (%)	34.8	2.9	0.002
Diagnosis Asthma (%)	34.8	25.7	0.66
IHD (%)	69.6	65.7	0.98
Body Mass Index (kg/m^2)	27.91 (1.24)	27.68 (1.22)	0.48

When patients were divided on the basis of airways obstruction, that is, FEV1/FVC ratio <0.7 or ≥ 0.7 at initial assessment, comparison of patients with and without airways obstruction showed significant differences with regard to age, pack year smoking history and previous diagnosis of COPD. That is, the patients meeting criteria for airways obstruction had accumulated a greater exposure to tobacco smoke and were more likely to have an established diagnosis COPD. These differences were expected: forced expiratory ratio is known to decline with age, there is an established relationship between smoking and airways obstruction, and COPD is a disease defined in part by presence of airways obstruction (77).

That asthmatic patients featured no more prominently in the group with airways obstruction may be due to the episodic nature of their airways obstruction. There was no significant difference between the numbers of subjects taking beta-blocker medications, in each group, which might reflect an absence of medication-related

symptoms or a difficulty in distinguishing symptoms of cardiac disease from those of airways obstruction.

Figure 4.3.3: Symptoms According to FEV1/ FVC Ratio



When a comparison was made of FEV1/FVC ratio between patients reporting the so-called “respiratory symptoms” of breathlessness (SOB), wheeze and cough, and those who did not, the patients complaining of these symptoms did have lower FEV1/ FVC ratios. This difference did not reach statistical significance for any symptom, but was most marked for wheeze.

When the study population was divided on the basis of airways obstruction, those subjects with forced expiratory ratio less than 0.7 were significantly more likely to report wheeze, but this did not apply for breathlessness or cough. Assessment of

these symptoms is part of standard clinical evaluation, used in conjunction with physical examination and results of medical investigations, in an attempt to differentiate obstructive airways disease from other possible causes. Clinical experience suggests that these symptoms are not specific for respiratory disease and that they are unreliable for differentiating respiratory from cardiac disease, which may be accompanied by similar symptoms. In this group of patients with cardiac disease, the clinical impression is supported by our results, with none of the symptoms proving reliable differentiators between airways and cardiac disease.

Table 4.3.2: Symptoms According to FEV1/FVC Ratio

	FEV1/FVC < 0.7 (n = 30)	FEV1/FVC ≥ 0.7 (n = 29)	P Value
Cough (%)	58.3	41.2	0.307
Breathlessness (%)	79.2	67.7	0.504
Wheeze (%)	54.2	23.5	0.035
Any Symptom (%)	95.8	76.5	0.067
All Symptoms (%)	29.2	11.8	0.172

4.4 Discussion

Criteria for diagnosis of airways obstruction using spirometry include assessment of the forced expiratory ratio, in conjunction with the timed forced expiratory flow values, and the appearance of the inspiratory and expiratory phases of the flow volume loop. There is some variation between international guidelines, and hence also some variation in interpretation between observers. There is controversy as to the best method for measuring airflow obstruction, and other methods, such as forced oscillation, are also used. This contributes to difficulty in making comparisons

between studies of airways obstruction. However, spirometry is the technique being implemented in international studies of COPD prevalence (135), is routinely used in clinical assessment of both COPD and asthma, and is intended for use in community screening programmes for COPD.

We elected to use the forced expiratory ratio, obtained during performance of spirometry, to define airways obstruction. Whether airflow obstruction should be defined by a fixed value or a predicted normal value, adjusted for age, is a contentious issue and a subject of current international debate, because the FEV1/ FVC ratio is known to physiologically decline with age. Hence, choosing a fixed value creates potential for over-diagnosis in the elderly and, conversely, under-diagnosis in the young. We chose a value of below 0.7 to define obstruction, given the advanced age of our patient group and given that this would likely represent airflow limitation even in an older population. A value of 0.7 has been chosen in the Global Initiative Guidelines for Chronic Obstructive Pulmonary Disease (GOLD guidelines), for diagnosis of COPD (77) and also in the international BOLD study, for the purposes of assessing the global burden of obstructive lung disease (135). However, the recent lung function interpretation guidelines issued jointly by the European Respiratory Society and the American Thoracic Society (136) advocate the use of predicted normal values for defining an obstructive ventilatory deficit. The 0.7 threshold was initially chosen partly for reasons of pragmatism, to simplify the application of spirometry and facilitate its wider use in the community. The alternative, predicted normal values, are figures derived from large populations of never-smokers. There are strong arguments for using a threshold, rather than mean population values, particularly when the population mean value is demonstrably

unhealthy, as seen with body mass index, for example. There is also the question of whether we should accept age-related changes as normal, as deterioration associated with the ageing process may be associated with significant morbidity, and timely therapeutic intervention may result in improved health outcomes.

Recent work (137) provides some evidence for using the 0.7 threshold: the authors found that even though 54% of their elderly subject group would not have met criteria for airflow obstruction, had predicted forced expiratory ratio values been used, this group (with 0.7>FEV1/FVC ratio > predicted ratio) did have increased mortality and increased risk of COPD-related hospitalisation. Mannino's group sought to determine the mortality and morbidity associated with having FEV/FVC ratio<0.7 but higher than the predicted lower limit of normal, a setting in which GOLD criteria are thought to potentially overestimate COPD diagnosis. Their study population comprised 4965 Cardiovascular Health Study participants, of age greater than 65 years, for whom spirometry results were available as part of the cardiovascular study intake assessment. COPD severity was stratified by two methods: modified GOLD criteria (using FEV1/FVC<0.7 and an additional restriction category) and using predicted FEV1/FVC ratios. Subjects were followed over an eleven year period, with deaths and COPD-related hospital admissions being recorded. After adjustment for potential confounders, application of a Cox proportional hazard regression model, showed that the group "with COPD potentially overdiagnosed" had significantly increased risk of death (hazards ratio 1.3) and of COPD-related hospitalisation (hazards ratio 2.6) after comparison was made with the group having no symptoms and normal lung function. A potential criticism of this study is that GOLD criteria use post-bronchodilator spirometry to define severity

categories of COPD, data which was not available to the study investigators. However, using pre-bronchodilator spirometry would have resulted in potential overclassification of COPD, and so in fact strengthens the significance of the results obtained. The results are persuasive in their implications that, regardless of whether you label it “COPD”, this group of patients having forced expiratory ratio lying below 0.7 and yet above the lower limit of normal predicted values, has significantly increased morbidity and mortality compared to their “normal” counterparts and that recognition of this group as a group at risk of adverse health outcomes, might result in benefit from targeted therapeutic intervention.

The estimated prevalence of obstructive airways disease in our subject population of patients with comorbid heart disease of 50.8%, is higher than previous comparable estimates cited in the medical literature (7-28%)(48, 81-84) and this is reflected by the mean population spirometry results. The reason for this is multifactorial. Until recently, diagnosis of obstructive airways disease has been based on physical assessment and medication use, often without any objective measure of lung function, and so disease prevalence in the general population has been underestimated. Secondly, COPD patients generally present late in the course of disease, with established parenchymal destruction and respiratory function impairment, when respiratory symptoms, such as marked exertional dyspnoea, supervene. This is because impairment of lung function is poorly perceived by patients. Early COPD is often relatively asymptomatic, and hence frequently remains undiagnosed. Use of spirometry increases the sensitivity for detecting early COPD when symptoms are mild or absent (79). This is the basis behind planned community spirometry screening programmes, whose purpose is the introduction of preventive

measures, such as smoking cessation programmes and early medical intervention. However, even spirometry can occasionally be normal in smoking-related lung disease of emphysema-predominant type, where measures of gas exchange or diffusion and high resolution CT imaging may be needed to confirm the diagnosis (138). Thirdly, because of a significant degree of symptom overlap between cardiac and pulmonary disease, diagnosis of obstructive airways disease in patients with known cardiac disease is complicated and often delayed. Lastly, there is the possibility that our recruitment process was affected by selection bias. Our subjects gave consent for spirometry, including assessment of BDR. The process of informed consent required an explanation of potential risks of bronchodilator therapy, and hence all patients approached for enrolment, were told of a small risk of precipitating cardiac arrhythmia or myocardial ischaemia, associated with the use of the bronchodilator agents (121, 133, 134). In some cases, where consent was withheld, this was due to concerns about adverse cardiac effects. It may be that patients who were familiar with bronchodilator agents, experienced less anxiety about untoward effects, and hence were more likely to agree to participate in the study protocol. This could potentially result in overrepresentation of patients with obstructive airways disease amongst our subject group, and result in overestimation of the prevalence of airways obstruction.

General population results from another Australian group, working to establish estimates for the burden of obstructive lung disease in this country (139), are available. This study was comparable with previous studies of adult European populations and has shown airways obstruction in 18.5%, and asthma in 12.5% using very similar criteria to our own, although their population mean age was, younger

(57 years, compared with our mean age 65.6 years). Our much higher prevalence figure does suggest that obstructive lung disease is over-represented amongst cardiology patients, which is part of our original premise. Alternatively, our result might signify the advantage of a longer duration study period, with multiple assessments providing more opportunity for detecting airways obstruction, which has some inherent variability. A recently published British community heart failure clinic study here warrants mention. Shelton's group (59) reports retrospectively on data collected from a group of 513 heart failure patients between September 2001 and July 2003, a period which overlaps with our own data collection period. They report a 34% prevalence of obstructive airways disease, defined by criteria more stringent than our own, namely, FEV1/ FVC < 0.7 and FEV1< 60%. However, they performed spirometry with subjects supine and did not otherwise specify the degree of adherence to spirometry standards of acceptability and reproducibility.

The clinical relevance of our high prevalence figure pertains to the treatment of patients with combined airways obstruction and cardiac disease, where the agents used, despite attempts at attaining beta-receptor subtype selectivity, may have opposing effects, both on the airways and on the myocardium. Beta-blocker medications are crucial agents in the treatment of cardiac disease, with proven survival benefit in left ventricular dysfunction (140) and coronary artery disease (42, 141). They have useful therapeutic effects perioperatively and in other forms of cardiac disease. They should not be withheld unnecessarily, in conditions where their therapeutic effect is established. However, even the cardioselective beta-blocker medications, can have adverse respiratory effects via their beta 2-receptor actions, with potential to precipitate bronchoconstriction. The high prevalence figure implies

large numbers of patients potentially at risk of adverse respiratory effects from beta-blocker medications. Conversely, beta-2 agonist use for the purposes of bronchodilation, in patients with obstructive airways disease, may present potential risk for adverse cardiac effects such as myocardial ischaemia and malignant cardiac arrhythmia (43, 121, 133, 142).

The clinical importance of our prevalence finding is uncertain. Most of our subjects with airways obstruction do have clinically significant impairment of lung function. Further studies will be required to determine whether there are implications for medical management. For now, we propose that screening for obstructive airways disease with spirometry should be considered, ideally prior to commencement of beta-blocker therapy, or soon after treatment is commenced, in patients diagnosed with cardiac disease. The purpose would be to better determine those potentially at risk of adverse airways effects. At the time of beta-blocker commencement or dose escalation, particular attention should be paid to any symptomatic respiratory deterioration, such as breathlessness, cough or wheeze. In such patients, evaluation for symptomatic deterioration should take into consideration the high degree of symptom overlap in cardiac and respiratory disease, as well as the potential of beta-blocker medications to destabilise both obstructive airways disease and heart failure. An attempt should be made to differentiate, using spirometry and the more recently introduced serum marker, brain natriuretic peptide. These tests should be used in conjunction with clinical assessment and conventional investigation tools, such as the electrocardiogram and chest imaging.

4.5 Conclusions

The estimated prevalence of obstructive airways disease in our population of cardiology patients was 50.8%. Of these, 34.5% also had bronchodilator reversibility. This represents a high prevalence of airways obstruction, a higher prevalence than that reported in previous studies, and is likely attributable to clinically occult mild disease, and symptom masking by coexistent cardiac disease. There may be implications for monitoring of respiratory function and the use of beta-blocker and beta-agonist drugs in this population.

CHAPTER 5

BETA-BLOCKER PRESCRIPTION IN PATIENTS WITH COEXISTING CARDIAC AND OBSTRUCTIVE AIRWAYS DISEASE

CHAPTER 5: BETA-BLOCKER PRESCRIPTION IN PATIENTS WITH COEXISTING CARDIAC AND OBSTRUCTIVE AIRWAYS DISEASE

5.1 Aims

This study reviews beta-blocker prescription in Royal Prince Alfred Hospital's Cardiology Unit, stratifying patients according to airways obstruction.

5.2 Methods

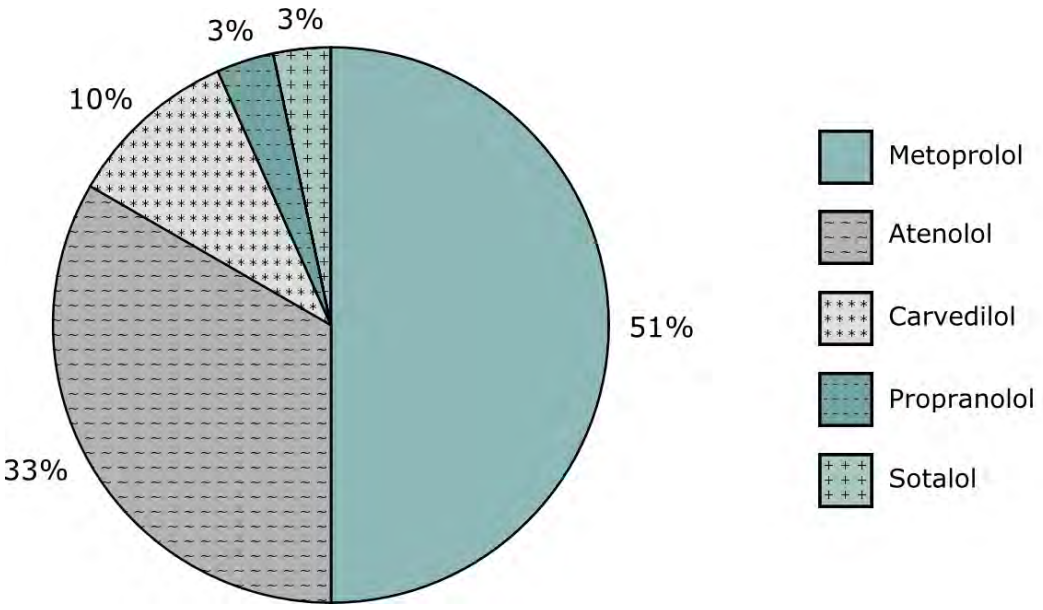
Sixty-four patients, consecutively recruited from acute cardiology unit admissions, completed interviewer-administered respiratory questionnaires and performed spirometry, including assessments of bronchodilator response, as described in Chapter 2. Current medications were recorded and the treating cardiology team were consulted about the role for beta-blocker medications and any existing contraindications to their use.

5.3 Results

Beta-adrenergic antagonist drugs were prescribed in 30 (46.9%) of our subjects. Cardioselective agents were prescribed in 25 (83.3%). The most commonly

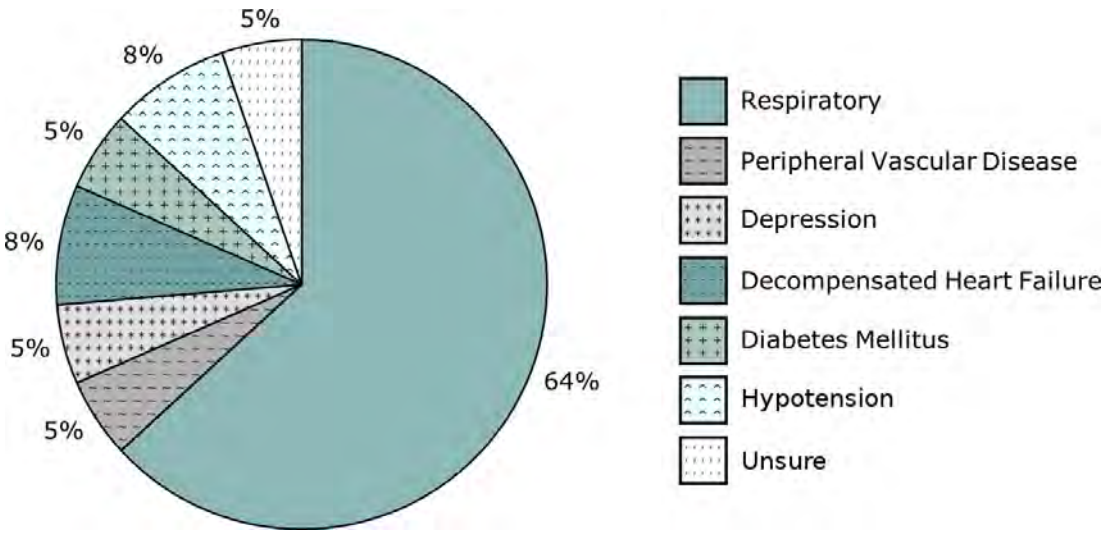
prescribed non-selective beta-blocker was carvedilol. None of the five subjects taking non-cardioselective beta-blocker drugs were taking inhaled medications or had been formally diagnosed with any obstructive lung disease, although one demonstrated both obstructive spirometry and an asthmatic range bronchodilator response on lung function testing. In 13 cases, beta-blocker medication was commenced during the index admission. The agents initially prescribed were beta-1 receptor selective. Metoprolol was chosen in all but one instance.

Figure 5.3.1: Beta-Blocker Prescription



Beta-blockers were considered the cardiac treatment of choice in 48 (75%) patients and were prescribed in 29 (60%) of these. The predominant reason given for non-prescription of beta-blocker medication was the coexistence of respiratory disease. Other reasons included peripheral vascular disease, decompensated heart failure, hypotension, depression and diabetes mellitus.

Figure 5.3.2: Beta-Blocker Contraindications



The group of patients in whom beta-blockers were considered medically indicated were analysed according to beta-blocker prescription status (Appendix 6). Patients who did not receive beta-blockers were more likely to be of female gender, to have been previously diagnosed with obstructive airways disease, and were less likely to have coronary artery disease (CAD), although the differences did not reach statistical significance. These results are consistent with previous studies of beta-blocker prescription. However, unlike previous studies, we found no age difference between the two groups. After logarithmic conversion to achieve normally distributed data, smoking exposure, in terms of pack years, was significantly lower in those subjects who received beta-blocker medications.

Table 5.3.1: Population Characteristics According to Beta-Blocker Prescription

	Prescribed	Withheld	P Value
Mean Age (Years)	65.8 (9.8)	65.7 (14.5)	0.98
Female (%)	43.8	56.3	0.18
Mean Pack Years	14.1 (4.4)	45.4 (2.5)	0.01
Mean BMI (kg/m^2)	28.9 (1.18)	28.0 (1.35)	0.67
CAD (%)	65	35	0.24

Beta-blocker medications were prescribed in only one of five (20%) patients with previously diagnosed obstructive airways disease. A corresponding figure of ten (50%) was obtained for beta-blocker prescription amongst the 20 patients, whose airways obstruction was defined by spirometry. Amongst patients with previously diagnosed asthma, five of 13 (38%) were prescribed beta-blockers. Ten patients demonstrated bronchodilator response (BDR) during the study protocol and five of these (50%), were taking beta-blocker medications.

Although there were fewer patients with a previous diagnosis of asthma in the group prescribed beta-blocker agents, the difference failed to reach statistical significance. In contrast, although very small numbers were involved, the difference with regard to previous COPD diagnosis approached significance. Measured impairment of lung function, both in terms of the obstructive indices, FEV1 and forced expiratory ratio, and FVC (which traditionally reflects restrictive respiratory disease) was markedly worse in those denied beta-blocker treatment. Co-treatment with inhaled bronchodilator medications, another potential marker of obstructive lung disease severity, was also more common in the group which did not receive beta-blockers. Conversely, “respiratory symptoms” were seen more in the group taking beta-blocker medications. The difference was small, but statistically significant. Interestingly,

when each symptom was analysed on an individual basis, breathlessness and wheeze were actually less frequent in the group prescribed beta-blockers, and cough was equally distributed. The difference was only statistically significant in the case of dyspnoea (Chi square test, P = 0.018).

Table 5.4.2: Beta-Blocker Prescription and Obstructive Airways Disease

	Prescribed	Withheld	P Value
COPD Diagnosis (%)	20.0	80.0	0.07
Asthma Diagnosis (%)	38.5	61.5	0.12
Inhaled Medication (%)	23.1	76.9	0.004
Respiratory Symptoms (%)	51.2	48.8	0.032
Mean FEV1/FVC Ratio	0.72 (0.06)	0.66 (0.11)	0.04
Mean Predicted FEV1 (%)	78.2 (18.3)	59.9 (24.4)	0.007
Mean Predicted FVC (%)	83.7 (18.1)	68.1 (21.4)	0.014
Airflow Obstruction (%)	50%	50%	0.16
BDR Positive (%)	50%	50%	0.46

5.4 Discussion

Previous assessments of beta-blocker prescription, mostly in the post myocardial infarction setting, have found low prescription rates (42, 43, 45, 47). Underprescription was found to be most marked in the elderly, females and those with medical comorbidity. Although prescription rates were lower amongst our female subjects, this did not achieve statistical significance, nor did we not find any tendency for older age in the group which did not receive beta-blocker medications. The beta-blocker prescription rate of 60% for our subjects recruited in 2003, in whom beta-blockers were deemed treatment of choice, compares favourably with prescription rates reported previously of 22 – 34% (42, 43), suggesting some

amendment in beta-blocker prescribing practices. Other studies (45, 48) would support this. However, in these studies as well as our own, patients were managed by a cardiologist. This must be taken into consideration, as beta-blocker prescribing rates are known to be higher amongst cardiologists when compared with other physicians (45). The other studies include patients whose medical management was overseen by non-cardiologists.

A number of clinical conditions and medical comorbidities have in the past been perceived as contraindications to beta-blocker use. In Chen's 2001 study, by far the most frequently recorded contraindication was cardiac dysfunction, which accounted for 90%. In Soumeri's 1997 study, 30% of otherwise eligible patients were regarded as having one or more contraindications to beta-blocker treatment: on the basis of cardiac failure or loop diuretic use (63.5%), insulin use in diabetic patients (30.1%) and asthma or inhaled bronchodilator use (8.5%). Their reported 21% prescription rate was in patients without any of the above-mentioned contraindications. In our subjects, obstructive airways disease was the most frequent reason for non-prescription of beta-blockers. It was the cited reason in 64%, compared to decompensated cardiac failure and diabetes mellitus, which were cited in only 8% and 5% of cases, respectively.

Beta-blockers were prescribed in approximately 17% of patients with obstructive airways disease in Chen's study. Their group used a simple clinical severity scale, based on treatments required for airways disease and found that stratified this way, beta-blocker use declined with severity of airways disease, with rates of 37% in mild disease (no regular beta-agonist use) and 12.5% in the most severe category (need for

oral corticosteroid or hospitalisation for obstructive airways disease during preceding year). In Gottlieb's study, prescription rates were 22% for patients with COPD and 18% for those with asthma, whilst in Heller's study prescription rates for patients with obstructive airways disease had increased to 42.3% by 1997 from 26.2% in 1994. Even so, this subgroup had the lowest prescription rates for beta-blockers; the other subgroups being patients with cardiac dysfunction, diabetes mellitus and peripheral vascular disease. The 20% prescription rate seen in our subjects with previously diagnosed COPD is comparable with previous results, although the 38.5% prescription rate in our subjects with a prior asthma diagnosis is interesting, both in terms of comparison with other studies and in terms of the relatively lower prescription rates in COPD patients; patients who might be expected to be more at risk of coronary disease, and to benefit more from beta-blockers, by virtue of their higher rates of smoking. We also found that pack year smoking exposure was significantly higher, regular inhaled medication use more common and lung function indices of obstruction were worse, in patients not prescribed beta-blockers. These are all measures which serve as markers of severity for obstructive airways disease.

Review of our data shows an increased rate of beta-blocker prescription in comparison with older studies. However the higher prescription rates are not attributable to higher rates in patients with obstructive airways disease, but to higher rates in other groups. This may reflect the incorporation of beta-blocker medications into therapeutic regimens for heart failure during the last two decades, after they were shown to have significant mortality benefit for this indication. The reason for the higher beta-blocker prescription rates seen amongst subjects with previous asthma diagnosis compared to those with COPD may be a reflection of the small

numbers involved, or due to non-current disease, as childhood asthma can become quiescent in later life. It could also reflect differing disease severity. By definition, asthma is an episodic disease with fully reversible airflow obstruction. Because the onset of COPD is usually insidious, a diagnosis is often not made until disease is advanced, symptoms are chronic and persistent, and the degree of airflow obstruction is severe, with minimal reversibility.

A substantial proportion of our subjects taking beta-blocker medications had spirometry meeting criteria for airflow obstruction and also for asthmatic bronchodilator response, though only a few had a prior diagnosis of obstructive airways disease. It not possible to determine cause and effect; that is, our study was not designed to show whether the abnormal spirometry results were attributable to the use of beta-blockers, or whether the lung function abnormality actually preceded the use of these medications. A prospective randomised interventional trial would be required to differentiate. However, what can be said is that the low population event rates for severe adverse respiratory outcomes from beta-blocker use, in conjunction with the relatively high frequency of obstructive airways disease diagnosed on the basis of spirometry criteria seen in patients taking beta-blocker medications in our study, would suggest that many such patients may be able to take beta-blockers over the long term without untoward effect.

5.5 Conclusions

In view of compelling indications for beta-blocker use in cardiac disease, there has been amended prescribing practice for these medications, with an increase in beta-blocker prescription rates. The most common contraindication in our subject group was clinical diagnosis of obstructive airways disease, including both COPD and asthma. In this patient category, beta-blocker medications continue to be underutilised. Patients with abnormal lung function, but no formal diagnosis of obstructive airways disease, may receive beta-blockers without untoward effect. Beta-blocker therapy should be considered amongst therapeutic options in patients with obstructive airways disease and comorbid cardiac disease in situations where an established evidence base exists.

CHAPTER 6

THE LONGER TERM EFFECTS OF BETA-BLOCKER MEDICATIONS ON LUNG FUNCTION, RESPIRATORY EXACERBATIONS AND SURVIVAL IN PATIENTS WITH CARDIAC DISEASE

CHAPTER 6: THE LONGER TERM EFFECTS OF BETA-BLOCKER MEDICATIONS ON LUNG FUNCTION, RESPIRATORY EXACERBATIONS AND SURVIVAL IN PATIENTS WITH CARDIAC DISEASE

6.1 Aims

Our initial aims were to assess the longer term respiratory effects of regular beta-blocker therapy by means of serial comparative measures of lung function and symptom severity and respiratory exacerbation rates in a population of cardiology patients over a year's duration. Research aims were subsequently revised and modified so that information regarding respiratory exacerbations, adverse cardiac events and survival was provided for a more prolonged period of close to six years' duration. We hypothesised that beta-blocker use would not be associated with worsening of symptoms, lung function or an increase in the frequency of respiratory exacerbations.

6.2 Methods

Subject population recruitment, methods and statistical analysis for this study have

been previously described in Chapter 2. Permission to extend the study duration for the purposes of further data collection was sought and surviving subjects participated in the final postal questionnaire (Appendix 7). The questionnaire could be self-administered, or interviewer-administered, according to subject preference. Data collection for the extended protocol occurred between April 2003 and May 2008, and included data from between April 2002 until May 2008.

6.3 Statistics

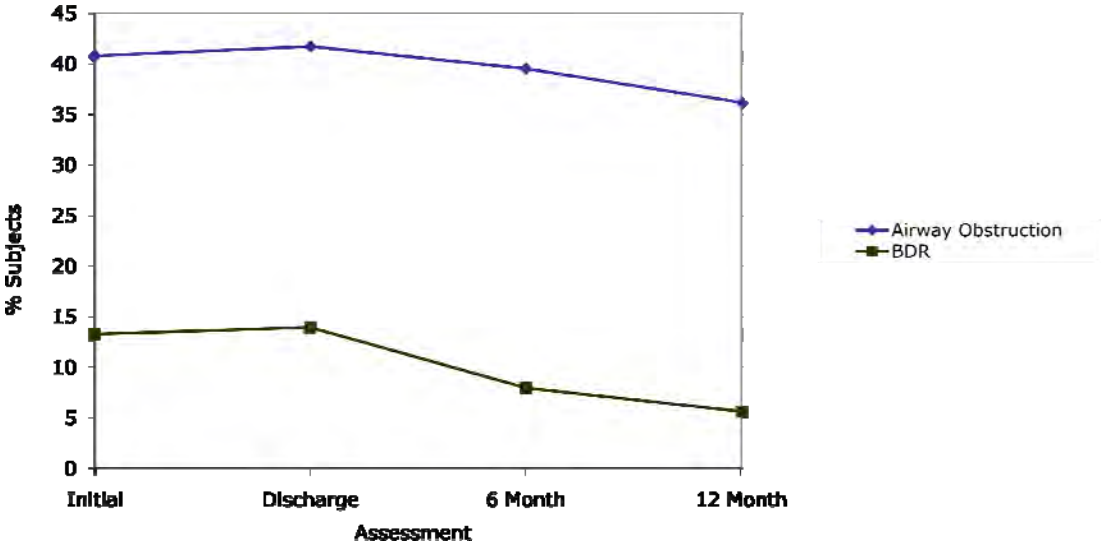
The statistical techniques used in this chapter are described in Chapter 2.

6.4 Results

6.4.1 Spirometry

The proportion of subjects with airways obstruction was stable throughout the twelve month period, with this ranging between 36-42% over the four interviews. The proportion of subjects with BDR diminished for subsequent interviews, from an initial rate of 13.9% to a rate of 5.6% at twelve months. Of the original subject population, 59 subjects have been included in the analysis of airflow obstruction and 58 in the analysis of BDR. Differences between time points were not statistically significant. However, the results should be interpreted with caution due to a substantial amount of missing spirometry data due to subject attrition and technically inadequate spirometry. Individual subject data are presented in Appendix 5.

Figure 6.4.1: Population Results - Subjects with Airways Obstruction and BDR



When the same analysis was made, stratified by beta-blocker status, there were no significant differences between the two groups. The proportion with airways obstruction in each group did not significantly change over the twelve months. There was a tendency for a higher proportion of airways obstruction in the group of patients not taking beta-blockers, which had disappeared at twelve months. The apparent increase in proportion obstructed in the beta-blocker group and decrease in proportion obstructed in the group not taking beta-blockers at twelve months, also did not reach statistical significance.

For BDR the numbers are too small for meaningful statistical comparisons. The observed trend was for the proportion with BDR in both groups to decrease over the twelve month period. However, there was a substantial increase in the proportion with positive BDR amongst subjects taking beta-blockers, which was seen at the discharge assessment only. This warrants further examination in studies with much larger subject numbers. If a reproducible result, in intervention studies of stable-state

COPD patients, this would lend further support to the theory of differential acute and chronic beta-blocker effects on airway beta adrenergic receptors.

Figure 6.4.2: Airways Obstruction According to Beta-Blocker Status

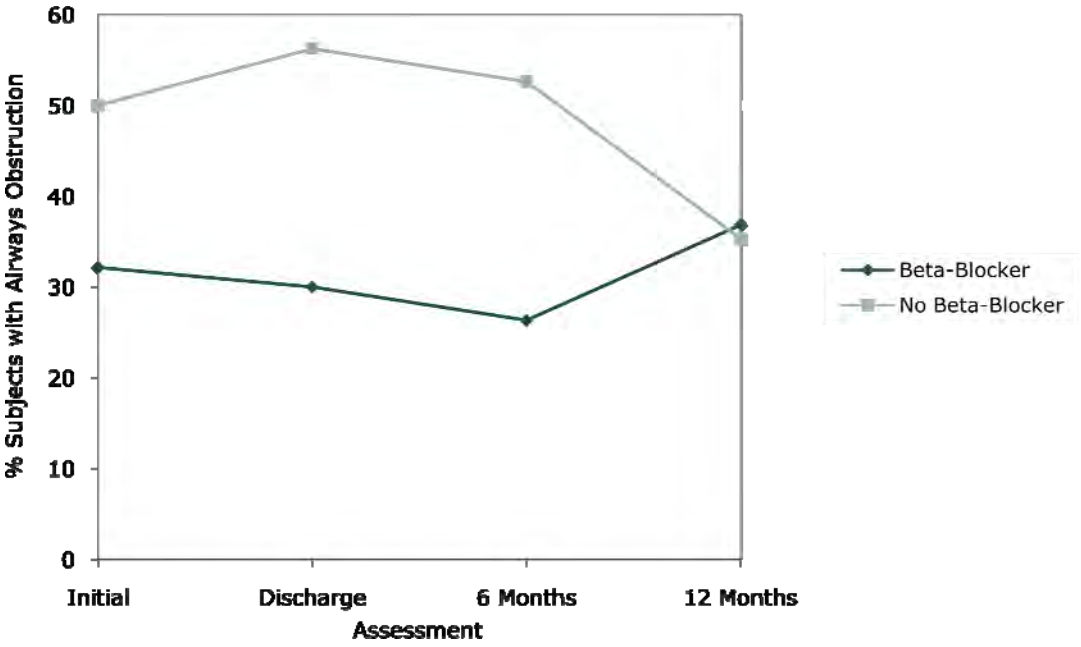
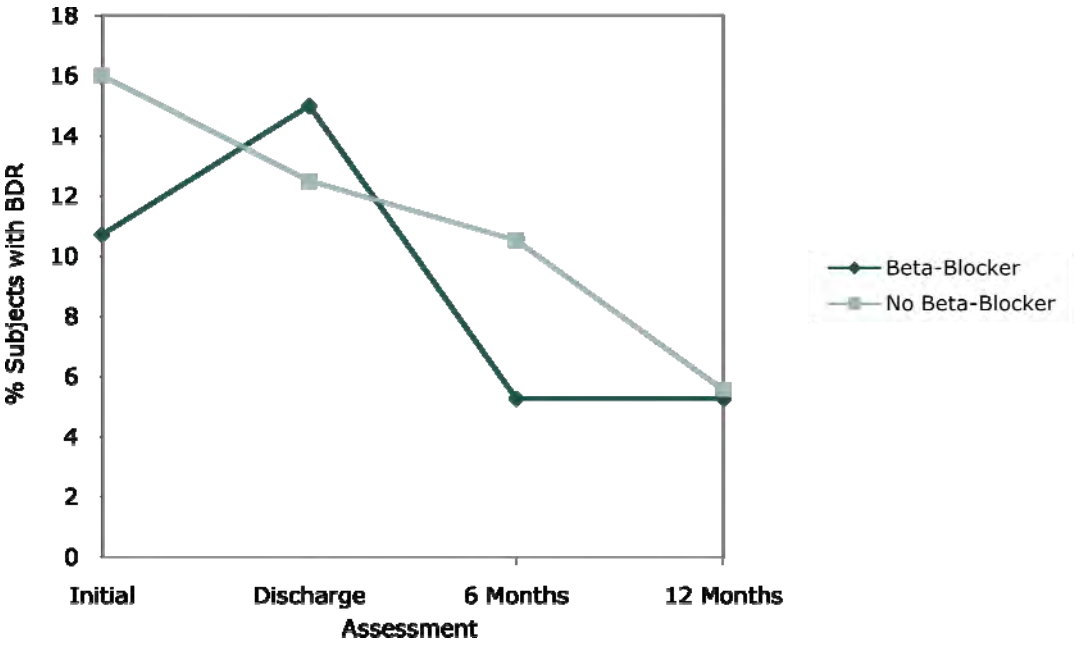


Figure 6.4.3: BDR According to Beta-Blocker Status



For the serial comparisons of lung function data and symptom scores, a non-binary beta-blocker status variable was used, which represented cumulative beta-blocker exposure over the year's study participation. This approach was taken in order to incorporate changes of beta-blocker status during the data collection period. In addition, when adjusting for potential confounders, a variable "steroid score" was used, which represented the number of courses of systemic corticosteroid therapy, whether or not it was combined with antibiotic therapy. It is important to note here that none of our patients was taking continuous corticosteroid therapy over the period in question. Individual subject data are presented in Appendix 7.

Longitudinal analysis over twelve months showed no statistically significant difference in lung function decline related to beta-blocker treatment. Adjustments were made for factors known to influence lung function. That is, age, gender, body mass index, pack years and steroid score in the case of FER, and pack years and steroid score for percentage predicted FEV1 and percentage predicted FVC, as these values already incorporate adjustments for age, gender, height and race. Pack year smoking exposure predicted worsening of lung function for each of the parameters tested. Increased age predicted a worsening of FER.

Table 6.4.1: Longitudinal Analysis of Respiratory Function Parameters, According to Beta-Blocker Status

	Beta Coefficient, β Univariate Analysis N=40	β, adjusted for Pack Years & Steroid Score N=40	β, further adjusted for Age, Gender & BMI[#] N=40
% Predicted FEV1	1.42 (P=0.37)	1.47 (P=0.34)	
% Predicted FVC	1.24 (P=0.40)	1.33 (P=0.36)	
FEV1/FVC	-0.005 (P=0.48)	-0.004 (P=0.61)	-0.002 (0.76)

No further adjustment of predicted values for FEV1 and FVC as age, gender and height are incorporated into prediction equations

Calculating the statistical power of our analysis of percentage predicted FEV1 was complicated due to the characteristics of our data, namely significant quantities of missing data, the variable duration between assessments and the likelihood of correlation between readings for each subject. However, using considerable simplification we have constructed two power calculations, one an underestimate, the other an overestimate, which suggest that at a power of 80% and type I error of 5%, the detectable difference for %PFEV1 lies between 7.6 and 11.2. Importantly, both estimates indicate a detectable difference smaller than the post bronchodilator difference in FEV1 that defines an asthmatic range bronchodilator response.

6.4.2 Respiratory Symptoms

Likewise, when respiratory symptom scores were subject to longitudinal analysis over twelve months, according to beta-blockers status, no statistically significant effect was seen for cough, sputum, dyspnoea or wheeze. In the multivariate analyses, results were again adjusted for factors known to influence respiratory function: age, gender, BMI, steroid score and pack years. These adjustments showed that greater

pack year smoking exposure was associated with worse scores for sputum, higher BMI predicted worse scores for wheeze and that dyspnoea improved over time.

Table 6.4.2: Longitudinal Analysis of Respiratory Symptom Scores, According to Beta-Blocker Status

Respiratory Symptoms	Beta Coefficient Univariate Analysis N=59	Adjusted for Age, Gender & BMI N=59	Further Adjusted for Pack Years & Steroid Score N=59
Wheeze	0.007 (P=0.975)	-0.031 (P=0.89)	0.004 (P=0.98)
SOB	0.17 (P=0.57)	0.18 (P=0.55)	0.25 (P=0.40)
Cough	-0.19 (P=0.49)	-0.15 (P=0.59)	-0.11 (P=0.70)
Sputum	0.22 (P=0.39)	0.11 (P=0.66)	0.16 (P=0.51)

6.4.3 Longer Term Adverse Outcomes

Of the original 64 subjects, 41 completed the final questionnaire and 14 subjects were deceased at the time of attempted recontact. Only three subjects could not be located. Data were collected over almost six years' duration (mean duration 5.72 years for those subjects completing the final questionnaire). Hospitalisations requiring treatment of both acute cardiac and respiratory disease were counted under each individual category.

Comparisons for respiratory exacerbations, acute cardiac events and survival were made according to beta-blocker status. In contrast to results for symptoms scores and lung function, the variables of interest were infrequently occurring events and beta-blocker status information was not available contemporaneously. For Poisson regression models, temporal changes to beta-blocker status were incorporated

directly into the analysis. For survival comparisons, the analysis compared patients using a fixed binary variable for beta-blocker status, and thus we report survival differences in reference to beta-blocker status at the time hospital discharge, for the index hospital admission. Individual subject data for the longer term adverse outcomes reported in this chapter are presented in Appendix 7.

6.4.3.1 Beta-Blocker Discontinuation

After the index hospital admission, beta-blocker medications were discontinued in nine of 31 subjects (29.0%) over the remainder of the study. Only in one case (3.23%) did the reason relate to an adverse drug reaction, and this was non-respiratory. However, there were also five additional subjects who commenced beta-blocker medications, during the study period, after the index hospital admission. One subject commenced, and then later ceased, beta-blocker medication during this period.

6.4.3.2 Respiratory Exacerbations

Respiratory exacerbations were defined as in Chapter 2: an increase in respiratory symptoms (sputum quantity or purulence, cough or dyspnoea) prompting a presentation for medical assessment and/or prescription of either antibiotic or systemic corticosteroid. Two distinct categories were analysed, in attempt to ensure that the condition “respiratory exacerbation” was adequately captured, and that exacerbations of lesser severity were included. One category was defined in terms of

treatment escalation, to antibiotics or systemic corticosteroids or both – “treated respiratory exacerbation”. The other category required an increase in respiratory symptoms of severity sufficient to prompt medical assessment, but there was no requirement for escalation of treatment – “symptom-based respiratory exacerbation”.

The longitudinal multivariate analysis of adverse cardiac and respiratory events is given in Table 6.4.3. At baseline, patients taking beta-blockers were significantly less likely to have required respiratory-related hospital admission (RR 0.23, p = 0.03), although the risk of respiratory exacerbations of both types did not achieve statistical significance, when compared with the reference group of subjects not taking beta-blocker medications. For those taking beta-blockers, the annual risk of an adverse respiratory event was significantly increased for both respiratory exacerbation categories (RR = 1.30, p = 0.001 and RR = 1.37, p = 0.008) and at the conclusion of the study they had an increased risk of exacerbations (RR = 3.67, p = 0.001 and 4.03, p = 0.02) compared to the reference group. All analyses were adjusted for age, gender, pack years, mean FEV1 and BMI. Higher mean FEV1 was an independent protective factor for “symptoms-based exacerbations” and pack years an independent predictor of respiratory-related hospital admissions.

6.4.3.3 Acute Cardiac Events

Acute cardiac events were defined as episodes of angina, chest pain, palpitations or fluid retention, sufficiently severe to prompt a medical presentation, whether or not there was an escalation of treatment. At study outset beta-blocker use was associated with an increased risk of cardiac-related hospital admission (RR 1.86, p = 0.03) but not for overall acute cardiac events (RR 2.12, p = 0.15), when comparison was made

with the reference group who were not taking beta-blockers. Subjects taking beta-blockers had a similar annual risk of acute cardiac events (RR 0.93, p = 0.66) and hospital admissions (RR 0.97, p = 0.80) when compared with the reference group, but at the conclusion of the study were no longer at increased risk of cardiac-related hospital admission (RR 1.54, p = 0.47). All analyses were adjusted for the same covariates as for respiratory exacerbations. BMI and mean FEV1 were significant covariates predicting acute cardiac events, with BMI predictive of increased, and FEV1 of reduced frequency of events.

In detail, beta-blocker use was independently associated with cardiac-related hospital admissions initially (Table 6.4.3). Over the period of the study, those taking beta-blockers experienced a slight but non-significant reduction of risk per year (RR 0.97, p = 0.80), so by the end of the study there was no difference in cardiac-related hospital admission rates between users and non-users (RR 1.54, p = 0.47).

Table 6.4.3: Acute Respiratory and Cardiac Events, According to Beta-Blocker Status

	Baseline		Increase Per Annum		Study End	
	RR (95% CI)	P-Value	RR (95% CI)	P-Value	RR (95% CI)	P-Value
"Symptoms-Based" Exacerbation	0.75 (0.46,1.21)	0.236	1.30 (1.11,1.53)	0.001	3.67 (1.65, 8.18)	0.001
"Treated" Exacerbation	0.62 (0.31,1.23)	0.172	1.37 (1.09,1.72)	0.008	4.03 (1.26, 12.9)	0.019
Respiratory-Related Hospital Admission	0.23 (0.06,0.86)	0.029	1.35 (0.91,2.02)	0.135	1.41 (0.27,7.46)	0.689
Acute Cardiac Events	2.12 (0.76,5.93)	0.152	0.93 (0.66,1.30)	0.663	1.57 (0.73, 3.41)	0.251
Cardiac-Related Hospital Admission	1.86 (1.05,3.29)	0.034	0.97 (0.76,1.23)	0.797	1.54 (0.48, 4.96)	0.469

6.4.3.4 Respiratory Exacerbations – Supplementary Analyses

Because of concerns that the increased risk of respiratory events associated with beta-blocker use might be related to the presence of BDR, we also ran the analysis including BDR as a covariate. BDR did not prove to be an independent predictor of respiratory or cardiac events. Moreover, incorporating BDR into the analysis did not substantially alter the results presented in Table 6.4.3. After adjustment for BDR, the beta-blocker group maintained their increased annual risk of exacerbations of both types (RR = 1.24, P = 0.005, 95% CI 1.07 – 1.44 for symptoms-based exacerbations and RR = 1.33, P = 0.010, 95% CI 1.07 – 1.66 for treated exacerbations). The increased annual risk of respiratory-related hospital admission, associated with beta-

blocker treatment, became statistically significant (RR = 1.53, P = 0.03, 95% CI 1.04 – 2.27). However, at the conclusion of the study, the increased risk of exacerbations associated with beta-blocker treatment, fell short of statistical significance (RR = 2.22, P = 0.072, 95% CI 0.93 – 5.32 for symptoms-based exacerbations and RR = 2.97, P = 0.081, 95% CI 0.87 – 10.09 for treated exacerbations).

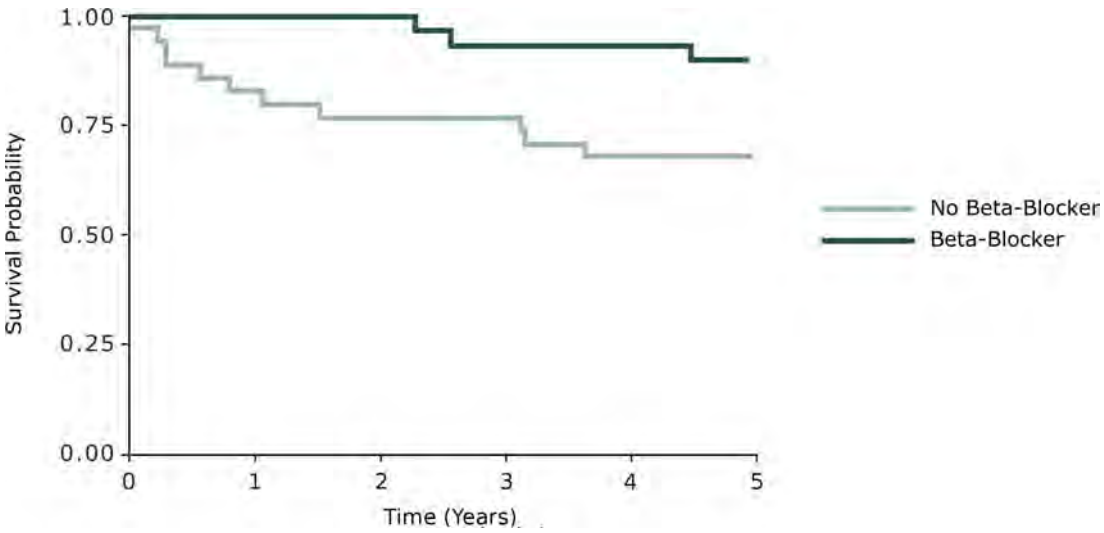
Survival bias is difficult to address in this observational study with small subject population. Obviously the subset of subjects who died during the course of the study may be substantially different from the surviving subjects. In particular, they are likely to have increased severity of medical illness in comparison with the survivors. Of the deceased subjects, eleven of 14 (78.6%) had experienced at least one symptoms-based exacerbation and seven of 14 (50%) had experienced at least one treated exacerbation prior to death. Although it is not possible to accurately predict, either clinically or statistically, what would have happened in terms of cardiac or respiratory events, had these subjects survived, it is possible to demonstrate the potential of survival bias to impact our results. Hence we have performed a sensitivity analysis, in which we investigate the scenario of the deceased subjects each having had one additional respiratory exacerbation. The number of exacerbations per deceased subject is an arbitrary choice. Since only three of the deceased subjects received beta-blocker medications, increasing the number of exacerbations per deceased subject, would be expected to reduce the risk of exacerbation associated with beta-blocker treatment. The results for both types of respiratory exacerbations did not substantially alter after the sensitivity analysis. For symptoms-based respiratory exacerbations the effect sizes reduced marginally, and the increased annual risk and final risk of exacerbations associated with beta-

blockers remained statistically significant at the same level. For treated respiratory exacerbations, small effect size reductions were again seen and the increased risk of exacerbation associated with beta-blocker treatment at the conclusion of the study fell slightly short of statistical significance, although the increased annual risk associated with beta-blockers remained statistically significant.

6.4.3.5 Death

At completion of the study, there had been fourteen subject deaths. The study investigators generally did not have information as to the mode of subject death, except in isolated cases. Cox proportional hazards analysis, investigating the effect of beta-blocker status on survival, was performed. Whilst univariate analysis demonstrated beta-blockers to have a statistically significant protective effect (hazard ratio 0.265, P=0.041), this effect disappeared after adjustment for covariates: age, gender, pack years, BMI and previous hospital admissions for respiratory disease (hazard ratio 0.589, P=0.470). Mean FEV1 was originally included in the model as a covariate, but was found to have a strong inverse correlation with pack years. The concurrent inclusion of both variables in the model was therefore non-contributory. Pack years, and not mean FEV1, was included as a covariate in the survival analysis, given the well-recognised adverse effects of pack years on mortality, which extend beyond cardiovascular and respiratory disease, and given the availability of a complete dataset. FEV1 was not included due to an incomplete dataset, and the necessity to use mean FEV1 as a representative value, because of the potential for variability between measures.

Figure 6.4.4: Survival According to Beta-Blocker Status (adjusted hazard ratio 0.589, P=0.470)



Age, pack years and previous respiratory admissions were independent risk factors for death. Body mass index and gender were not significantly associated. Beta-blocker status was protective, though the loss of statistical significance after adjustment for confounders implies that the association is indirect and dependent on the variable's relationships with the other covariates. Most likely, beta-blocker status was implicated in survival via its association with an intermediary variable, such as age, FEV1, pack years or baseline respiratory admission – a variable having its own influence on survival outcomes. Each of these factors is also associated with severity of obstructive airways disease. The beta-blocker status variable resulted from physician prescription choices, which likely incorporated knowledge of the subjects' medical backgrounds. Physician choice to avoid beta-blocker medications in those perceived to be at higher risk of lung disease, could well result in beta-blockers being less frequently prescribed in these groups, and therefore also contribute to an apparent relationship between beta-blocker status and survival. Our findings in

Chapter 5, which demonstrated that accumulated pack year smoking history was higher, forced expiratory ratio lower, and requirement for regular inhaled treatment more common, in those subjects in whom beta-blockers were not prescribed, provides further support for this theory. Interestingly, we did not find that beta-blocker prescription differed by age, which makes the age covariate less likely as an intermediary for the beta-blocker effect.

An alternative explanation would be that beta-blocker status exerts a favourable influence on one of the other covariates affecting survival. The only variable which is temporally relevant is FEV1. The proposed explanation would require an association of beta-blocker status with improved FEV1, and hence improved survival. However, beta-blocker status is not associated with significant improvement in FEV1 (when adjustment is made for baseline FEV1), and hence this alternative explanation is not supported.

The survival data are demonstrated graphically using Kaplan-Meier curves. Comparative survival profiles have been created, chosen to illustrate the situation as seen in subjects likely to have moderately severe lung disease, looking specifically at parameters of lung function, health service utilisation and smoking exposure. In these profiles the protective effect of beta-blockers on survival is statistically significant, although the data analyses are unadjusted and so the results should be interpreted with caution.

Figure 6.4.5: Survival Profile According to Beta-Blocker Status - Percentage Predicted FEV1 = 50

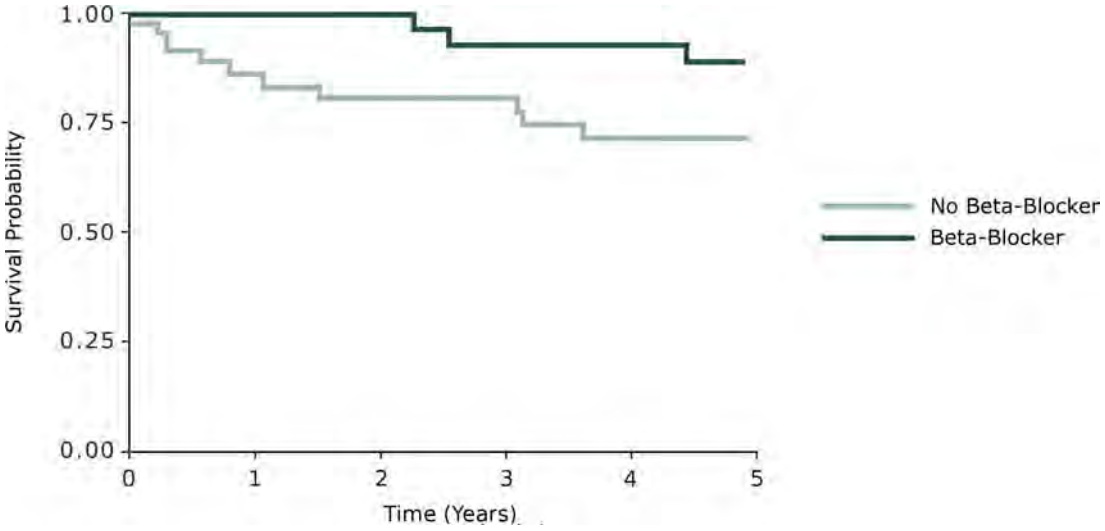


Figure 6.4.6: Survival Profile According to Beta-Blocker Status - Percentage Predicted FEV1 = 80

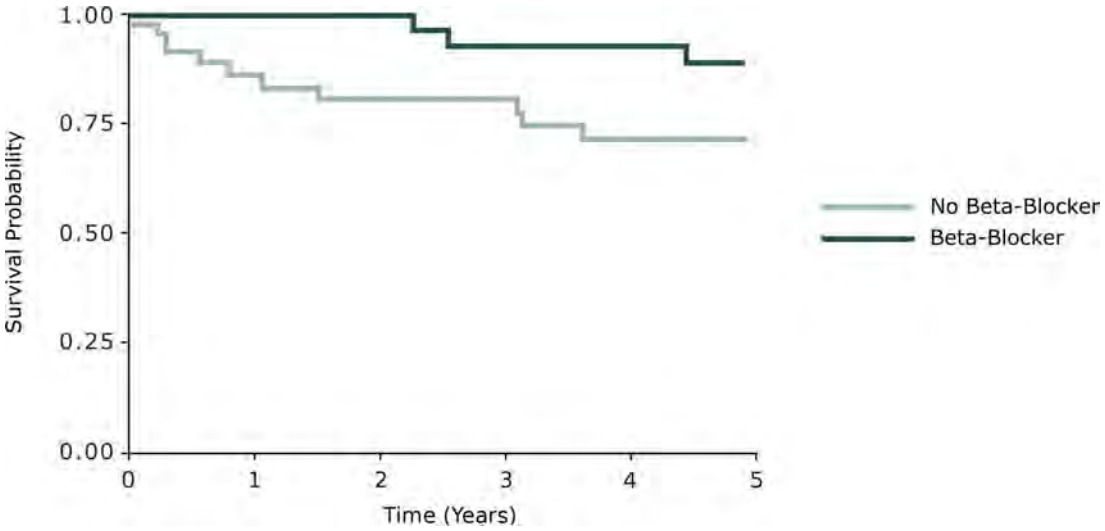
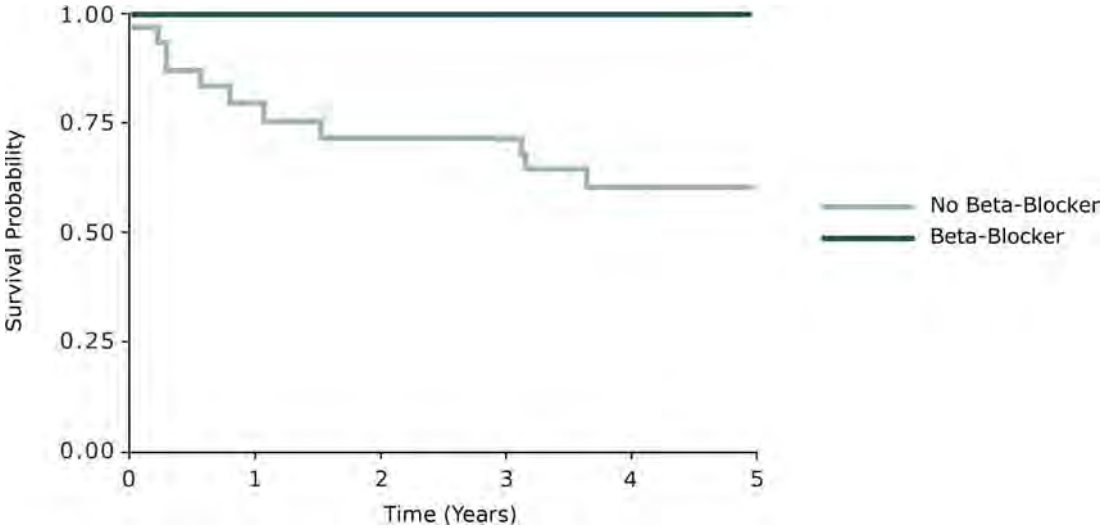


Figure 6.4.7: Survival Profiles According to Beta-Blocker Status - Previous Respiratory-Related Hospital Admissions

(a) Single Previous Hospital Admission



(b) No Previous Hospital Admission

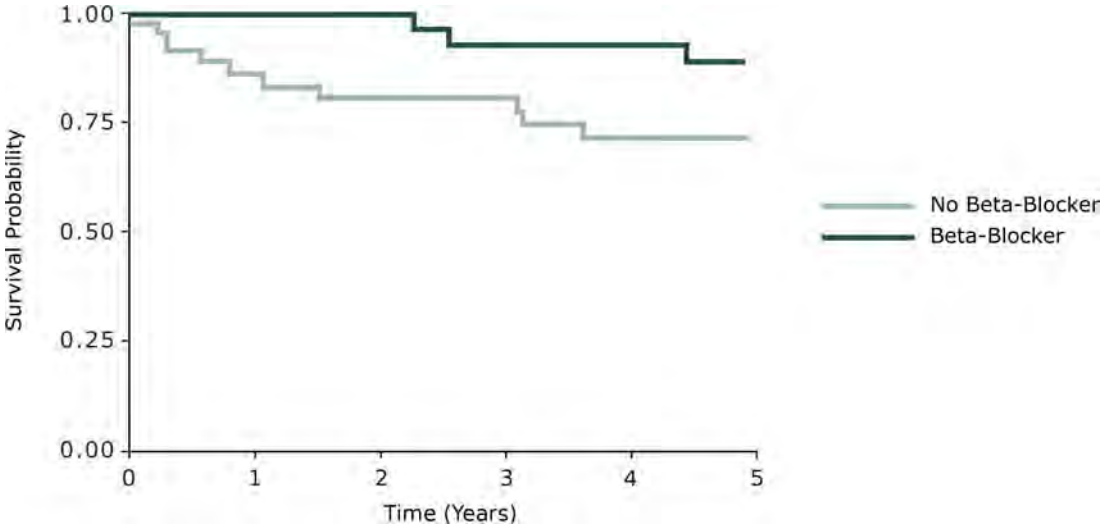
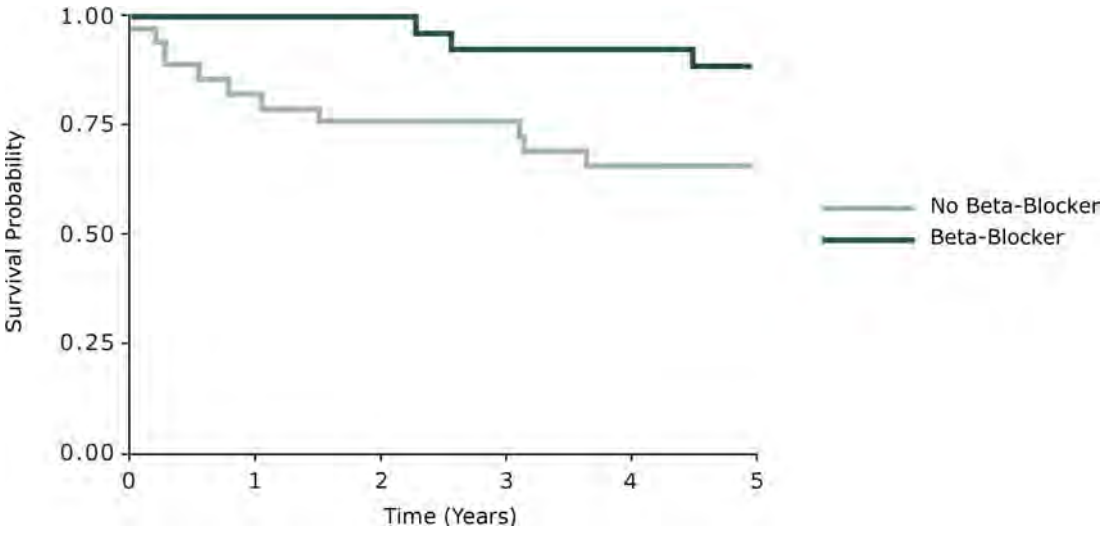
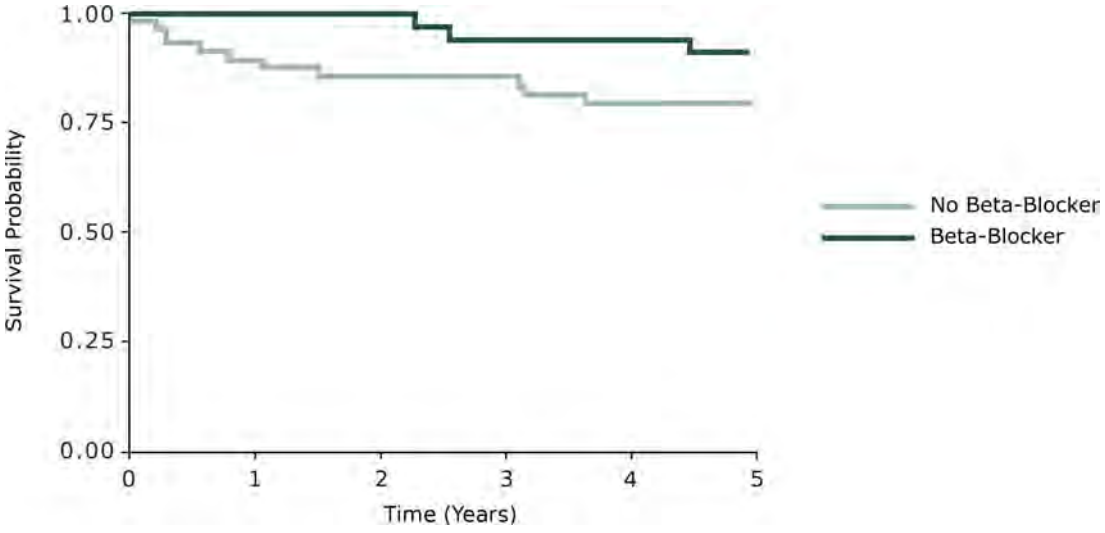


Figure 6.4.8: Survival Profiles According to Beta-Blocker Status - Smoking Exposure

(a) Pack Years = 50



(b) Pack Years = 0



6.5 Discussion

Our study is unique in providing long term prospective data about adverse respiratory outcomes associated with beta-blocker use. We undertook a longitudinal analysis of potential adverse respiratory outcomes related to beta-blocker use, conducted over 12 months for lung function and respiratory symptom measures, and over six years for survival and exacerbation data, in a cohort of cardiac patients, in whom we have previously demonstrated 50.8% prevalence of obstructive airways disease, with diagnosis based on spirometry. Beta-blockers were used by 46.9% of subjects. Use was 50% in subjects meeting spirometry criteria for airways obstruction and also 50% in those demonstrating asthmatic bronchodilator responsiveness. We have demonstrated that beta-blocker use was associated with increased risk for respiratory exacerbations, despite relatively milder respiratory disease in this group. However, although respiratory exacerbations are associated with poor prognosis in COPD and may be associated with an acute deterioration in measured lung function, our results do not support a significant long term detrimental effect on lung function, chronic respiratory symptoms or survival. On these grounds, one cannot unreservedly claim that beta-blocker medications are safe in the subset of cardiac patients with obstructive airways disease, but neither is there sufficient evidence to justify withholding beta-blockers in COPD patients, particularly those in whom comorbid cardiac disease and well-established cardiovascular indications exist. Rather, we would recommend cautious use according to clinical judgement until further evidence, in the form of prospective interventional trials of beta-blocker medications in COPD patients, is available. Our research adds to the existing evidence supporting clinician choice to use these medications where established

clinical indications exist.

This research has some limitations. Consistent with the findings of other groups, we have shown that beta-blocker prescribing is skewed towards patients perceived to be more healthy and robust, and in particular away from those patients known to have obstructive airways disease. With diagnosis of airways obstruction based on spirometry, we could demonstrate that a substantial proportion of subjects with obstructive respiratory disease participating in our study, did receive beta-blockers. Nevertheless, the subjects with clinically apparent disease were likely to have respiratory disease of greater severity, and to have beta-blocker medications withheld on this basis. Such prescribing behaviour may confound the results in our study, but does reflect actual practice in a large cardiology service, and is most likely to bias to null effect rather than the positive results achieved.

For all respiratory exacerbation categories we reported that beta-blockers were associated with a reduced risk of events at the study outset (significant only for respiratory-related hospital admissions), but an increased risk of events over time. The initial result may reflect the avoidance of beta-blocker prescription in subjects with overt airways disease, and the longitudinal results, may reflect an adverse beta-blocker effect seen over time in those with milder disease. The significant beta-blocker effect that we have demonstrated is likely to be underestimated because of this. This effect of prescribing bias is likely to be particularly important for the "treated" and respiratory-related hospital admission categories of respiratory exacerbation, as for an admission to be labelled respiratory, or for prescription of either corticosteroid or antibiotic in the setting of escalated respiratory symptoms, the

implication is that the subject's obstructive airways disease may have been previously recognised. However, in attempting to interpret these results one must also remember that categories of patients with established indication for beta-blockers, such as heart failure and myocardial infarction (and hence confirmed cardiac disease), are known to have poorer prognosis from comorbid obstructive airways disease. A prospective interventional study is needed to clarify these issues. Nevertheless, the finding of an elevated risk of respiratory exacerbation associated with long term beta-blocker use, appears to be consistent, and holds whether respiratory exacerbation is defined by symptoms or requirement for treatment. Therefore, this probably represents a true adverse beta-blocker effect.

In addition, at study outset, we reported that subjects taking beta-blockers were more likely to have cardiac-related hospital admission. In the longer term, although there was no effect of beta-blockers on annual risk of cardiac-related events, risk of cardiac-related hospital admissions was no longer elevated at the conclusion of the study. Even though beta-blockers have been extensively studied in the cardiac setting and have been shown to improve survival and reduce rates of reinfarction, we did not show a significant protective effect of beta-blockers on cardiac events. It would be logical to assume that beta-blockers were avoided in patients with severe heart disease, particularly those with congestive cardiac failure but our prescribing data do not support this. Prescription bias may have been operating, such that patients who received beta-blockers were indeed likely to have established cardiac disease and therefore likely to be at risk of cardiac events. It is also likely that our study lacks sufficient power to show a beneficial effect of beta-blockers on cardiac events, due to small subject numbers. The trials demonstrating survival benefit after myocardial

infarction and in left ventricular dysfunction were of much greater magnitude than our study (21-23, 53, 55). Nevertheless, our results raise again the question of whether patients with obstructive airways disease do receive the equivalent benefit from beta-blocker medications when compared with other patients with cardiac disease. This question is important since our subject population had 50.8% prevalence of airways obstruction, even though subjects were selected for the presence of cardiac disease. Of note, the large cardiology trials establishing the role of beta-blockers in cardiac disease have largely excluded patients with obstructive airways disease (54).

There was substantial subject attrition in our study. Although survival data outcomes were determined for 62 out of 64 subjects, 14 subjects died during the study and 41 of 52 remaining subjects provided longitudinal event information for the final data collection. With seven subject deaths occurring during the first year, 40 of 57 subjects provided spirometry data for the longitudinal analysis of lung function; at least two valid attempts over the twelve months, and interval between tests of six months, were required. Subjects who provided data for follow up may represent a biased sample of subjects who were well and able-bodied enough for ongoing participation. This assertion does not so much apply to survival data, exacerbation and hospitalisation data, as data collection for these outcomes could occur by telephone or correspondence. Hence, evidence of a “healthy survivor effect” was sought by making a correlation of FEV1 outcomes with leaving the study. No association was found. It is therefore less likely that health bias is affecting our results. Factors related to the duration of the study, the age and general frailty of our subjects, were responsible for a substantial amount of missing data, and whilst the

statistical strategies utilised, accounted for this problem to a large extent, this may have compromised the achievement of statistically significant results through type II error.

Lastly, the potential for recall bias needs to be considered. The last data collection was timed nearly four years after the penultimate study assessment, so that subjects had to rely on memory over a prolonged period. Some subjects may have incorrectly estimated both the timing and frequency of events. This could not be routinely cross-checked, but the general practitioner or hospital records were consulted, if the subject expressed uncertainty, and/or requested that confirmatory information be sought.

Our spirometry results suggested no significant deterioration in FEV1, FVC or FER associated with long term beta-blocker use. It may be that because of the tendency to avoid beta-blockers in patients with obstructive airways disease, our results describe a group with hitherto undiagnosed airways obstruction and hence much milder disease. However, there do exist some reports of results in keeping with our own. A small study from 1978 (143), reported on chronic dosing with metoprolol in 14 patients with current or previous asthma. Comparison of mean FEV1 at study entry and exit, a mean duration of 243 days, showed no significant difference.

In Shelton's 2006 study of beta-blocker treatment in 513 heart failure patients (59) beta-blocker drugs were considered contraindicated in COPD requiring regular use of bronchodilator medication, and asthma, although COPD diagnosis per se was not considered a contraindication. Spirometry was included in their protocol, with measures taken at baseline and at twelve months. The manoeuvre was performed

supine. Unfortunately, the degree of adherence to spirometry standards of acceptability and reproducibility, and the choice of predicted reference values used, is unclear, and results are difficult to directly compare with our own, as they are inconsistently reported in terms of actual measures and percentage predicted values. They reported a 34% prevalence of "more than mild" obstructive airways disease, defined as FEV1/FVC ratio < 0.7 and FEV1 < 60% predicted value, amongst their subject group, with outcomes reported in terms of beta-blocker prescription and changes in lung function. At one year, of their 11.5% patients not taking beta-blocker medication, 58% had airways obstruction. The most common specified reasons for beta-blocker cessation or dose reduction were worsening symptoms of heart failure (26%) or COPD symptom exacerbation (11%). They reported FEV1 and percentage predicted FVC to be worse in the group not taking beta-blockers. Comparative interpretation is difficult for the FEV1 results, given that predicted values have not been reported. Although they have not made specific comment, their reported spirometry results, for patients with airways obstruction and taking beta-blockers, actually appear to show a statistically significant improvement in FEV1 measures between baseline and 12 months (1.1L versus 1.5L, P< 0.01). Lastly, they reported a slight increase in bronchodilator medication use (from 12.1% to 14%) but no hospitalisations amongst their subjects, for either decompensated heart failure or COPD exacerbation.

Our research experience was that intolerance of beta-blocker medication was a rare occurrence. The one adverse drug reaction observed was a non-respiratory side effect. Beta-blocker medication had not been withdrawn in any subject for reasons of respiratory compromise. Kotlyar's group (60), on the other hand, found beta-blockers

to be less well tolerated in asthma as compared to COPD. Their 43 subjects were a subset of heart failure patients, recruited between 1996 and 2000, at time of commencement of carvedilol. The subjects were divided into 31 with COPD and twelve with asthma, according to lung function criteria. Severity assessment was based on percentage predicted FEV1 (in conjunction with criteria defining airways obstruction), with mean predicted FEV1 of 62% for the COPD patient subgroup, designated "moderate severity". Although the patients were followed for 24 months, changes from baseline lung function were only assessed in about half their subjects, using pre and post beta-blocker dose peak flow values and only within 48 hours of drug commencement. However, they reported six month beta-blocker tolerance rates as well: 84% for their COPD patients but only 50% for their asthma patients. The reason for beta-blocker discontinuation was related to wheezing in 50% withdrawn asthma patients and to acute exacerbation in 3% withdrawn COPD patients, indicating quite good beta-blocker tolerance in the patients with COPD.

We found a significant increase in respiratory exacerbations and hospitalisations related to beta-blocker treatment in our longitudinal analysis. To date, there is little published research on the effects of beta-blocker use on frequency of respiratory exacerbations. Peters' group (61) retrospectively analysed data collected over 18 months for 1067 heart failure patients. They analysed the frequency of respiratory exacerbations in subgroups with COPD and asthma, according to beta-blocker status, finding no significant increase in medical encounters, respiratory exacerbations or hospital admissions. They also found no difference in these results according to beta-blocker cardioselectivity. Unfortunately, published as yet only in abstract form, limited information is provided as to definitions used for COPD, asthma and

respiratory exacerbations and as to any measured disease severity indices. This information is crucial to be sure that these encouraging results are not due to confounding. Brooks' (63) retrospective cohort study, used an electronic database to identify patients with International Classification of Diseases, Ninth Revision (ICD-9) diagnosis of asthma and COPD, and at least 30 days of treatment with beta-blocker medication between August 1997 and December 2005. Unfortunately reliance on a disease coding system, and surrogate factors to classify disease severity, with one treatment group being statistically different for baseline factors when compared with the remaining treatment and control groups, poses significant limitations. However, they report an excess of emergency department presentations and hospital admissions related to beta-blocker treatment in asthma patients, which was not seen for COPD. In fact, beta-blocker treatment in the COPD patients was found to be protective against medical encounters under certain circumstances.

Fourteen deaths were confirmed during the extended study protocol, and the data were analysed for an effect of beta-blocker status on survival. Beta-blockers were found to be protective, but not independently so, and the effect seen is via an intermediary covariate with significant impact on mortality, such as pack years or FEV1. Most likely there is contribution from prescription bias, in which beta-blockers are withheld from those most likely to have severe respiratory disease. However, at least the data do not seem to suggest any negative effect of beta-blockers on survival, even in patients with moderately severe lung disease. Kaplan-Meier profiles, created to represent patients likely to have moderate respiratory disease, based on high cumulative smoking exposure (pack years = 50), lung function (predicted FEV1 = 50%), and previous respiratory-related hospital

admission, all groups represented amongst the subject population, appear to support this, with curves showing significantly increased survival in the subjects taking beta-blocker medications. However, the profiles present unadjusted results and so should be interpreted cautiously. To date, published research looking at beta-blocker use and survival in patients with obstructive airways disease is scant, and none is prospective. However, Gottlieb's study (42) of two year mortality after myocardial infarction demonstrated that the survival benefit of beta-blockers in this setting extended to include patients with obstructive airways disease. More recently, Dransfield (144) performed retrospective multivariate regression analysis of in-hospital survival outcomes of patients hospitalised with COPD exacerbation, both with and without respiratory failure, according to beta-blocker use. With 825 eligible patients, they controlled for a beta-blocker propensity score and found beta-blocker use to be associated with advanced age, increased duration of hospital admission, cardiac failure and cerebrovascular disease. It proved an independent predictor of survival status, after adjustment for other independent predictors, including age, hospital stay, previous respiratory exacerbation history, respiratory failure, cardiac failure, cerebrovascular and liver disease (hazard ratio 0.39, 95% confidence intervals 0.14-0.99). Although they had available only a partial dataset for spirometry results (34% subject population), the available results indicated severe disease, with percentage predicted FEV1 about 40% and were comparable between the two groups, as were other predictors of disease severity such as prior respiratory-related hospitalisations and respiratory failure. Adding to this reassurance is another retrospective observational study, which looked at mortality outcomes related to beta-blocker use in perioperative vascular patients with COPD (120). This group also used a propensity score, given their population's known high incidence of comorbid

coronary disease, and stratified results by severity of lung disease, using spirometry. The authors reported improved 30 day and long term survival associated with beta-blocker use, with evidence of a dose-response relationship. However, the duration and continuity of beta-blocker treatment was unclear, which complicates the interpretation of long term results.

Interestingly, the first prospective interventional trial of beta-blocker medications, used as treatment of obstructive airways disease, was actually a small pilot study in mild asthmatics, without concomitant heart disease (74). Designed largely to examine safety, the results showed reduced bronchial hyperresponsiveness, albeit accompanied by a slight reduction in mean FEV1. Given the shared prime risk factor of smoking, the high likelihood of COPD coexisting with cardiac disease, and the implications of poor prognosis associated with the combination, beta-blockers are even more likely to be contributory to medical management of COPD patients. The data here presented add to the accumulating evidence about the use of beta-blocker medications in this group and justifies the initiation of prospective treatment trials. Our own work would suggest the prudence of careful monitoring of respiratory exacerbation events in this setting. If beta-blockers do indeed prove beneficial, then we will need to more closely investigate their interactions with beta-agonist drugs, which are a staple, standard treatment for the relief of symptomatic bronchoconstriction, to determine whether there are any advantages or adverse effects associated with agonist and antagonist combination therapy.

6.6 Conclusions

An increased risk of respiratory exacerbation seen with long term beta-blocker treatment was not accompanied by an adverse effect on spirometry, respiratory symptom scores or survival. Non-respiratory beta-blocker effects may compensate for the known poor prognostic impact of exacerbations in the obstructive airways diseases. Prospective treatment trials of beta-blockers in populations with cardiac disease and comorbid obstructive airways disease, both COPD and asthma, are needed to clarify these issues.

CHAPTER 7

CLINICAL APPLICATIONS AND IMPLICATIONS

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7.1 The Status Quo

Beta-blocker drugs are efficacious medications with established survival benefit for left ventricular dysfunction and after myocardial infarction. These medications have been traditionally avoided in patients with obstructive airways diseases, COPD and asthma, due to the belief that they can potentially worsen respiratory function and cause adverse respiratory events. Many of the landmark cardiology trials which established the current place of beta-blocker medications in the treatment of cardiac disease, excluded patients who were thought to have significant airways disease. However, in practice, ischaemic heart disease and the obstructive airways diseases often coexist, due to a combination of factors, including the high individual disease prevalences and the shared primary risk factor of smoking. In addition, patients with impaired lung function and with COPD are at much higher risk than the rest of the population for adverse cardiac events, with COPD patients more likely to succumb to cardiovascular death than death from COPD per se. Despite a few existing case reports of severe irreversible bronchoconstriction, after administration of non-selective beta-blocker medications to asthmatic patients, review of the available medical literature would suggest that treatment with beta-1 selective agents is mostly safe and without significant adverse effects on respiratory symptoms, relief beta-agonist use or lung function. It may be that to withhold beta-

blocker medications in patients with airways disease, in the setting of an established cardiac indication is to deny these patients a substantial survival benefit.

7.2 Contribution to Existing Knowledge

Although logic would suggest that the proportion of cardiac patients with coexistent obstructive airways disease is high, our research specifically sought to quantify this relationship using objective lung function testing, in the form of spirometry. Previous estimates of airways disease prevalence in cardiac patients have not used the more objective and stringent measures of lung function, but have relied upon surrogate measures such as inhaler use, symptoms and clinician diagnosis. In our population of patients admitted to the cardiology service at Royal Prince Alfred Hospital we confirmed that 50.8% met criteria for airways obstruction, a reported prevalence which is much higher than the 7-28% (48, 81-84) previously reported in the scientific literature. In addition, one third of our subjects demonstrating airways obstruction also demonstrated an asthmatic range bronchodilator response.

Beta-blockers have traditionally been withheld in large numbers of patients, felt by clinicians to be at high risk for adverse events. Patients with obstructive airways disease are one category, consistently represented among studies of beta-blocker prescription, as a group who less frequently receive beta-blockers as treatment. In our study, we confirmed the tendency to avoid beta-blocker medications in patients with known airways disease, although prescription rates at 60%, were consistent with other

contemporary studies, showing a trend of increasing overall beta-blocker prescription rates (45, 48). Current clinical practice does not include routine lung function assessment prior to commencement of beta-blocker medications. Having access to spirometry data for our subjects, we had the opportunity to assess airways obstruction in many patients who were already taking beta-blocker medication and so could readily demonstrate that beta-blockers are actually prescribed quite frequently to patients with mild airways obstruction on spirometry and previously undiagnosed airways disease. In fact, amongst subjects who were prescribed beta-blocker medication, the proportion with airways obstruction was 50%, which was also the proportion with asthmatic range BDR.

The 2002 Cochrane Reviews (57, 58) of cardioselective beta-blocker use, both in COPD and reversible airways disease, highlighted significant gaps in the medical literature pertaining to this topic. However, based on the limited evidence available, beta-blockers appeared safe in COPD and in those with no more than moderate reversible airways disease. One important area where information is lacking, with reviewed studies not extending beyond three months, was the longer term effects of beta-blockers on outcomes such as lung function, respiratory exacerbations and chronic symptom morbidity. Our work monitored the effect of beta-blocker use on lung function and symptoms over twelve months, and monitored beta-blocker withdrawal, respiratory exacerbations, acute cardiac events, hospitalisations for respiratory and cardiac disease and survival over close to six years. We have shown an increased propensity to adverse respiratory events, related to beta-blocker use, but we have not shown any statistically significant adverse effect of chronic beta-blocker treatment on any of the other

outcomes. These results add to the existing evidence pertaining to chronic beta-blocker dosing in COPD and asthma, but also serve to emphasise the need for prospective randomised trials where uncertainty exists.

Given the pre-existing opinion in medicine that beta-blocker drugs were unsafe in patients with airways disease, until recently it would have been quite difficult to ethically establish interventional trials of beta-blocker medications including these patients. However, our data add to existing evidence base and experience of chronic dosing of beta-blocker medications in COPD and asthma. Hopefully, the increasing experience and also recent reports indicating increased survival seen in the setting of acute COPD exacerbation, associated with beta-blocker use (144), will soon pave the way for prospective trials of beta-blocker medications in COPD and asthma populations, at least for the established cardiac indications of ST elevation myocardial infarction and left ventricular dysfunction.

7.3 Screening and Monitoring

Adjustment of prescribing practice with regard to use of beta-blocker medication in patients with airways disease is hindered by many unanswered questions. The most pressing is to be able to predict those patients in whom beta-blockers will precipitate acute, severe, irreversible bronchoconstriction. To this end, theoretically asthmatics are more at risk, because of their exponential bronchoconstriction response to bronchial provocation. Theoretically also, one would expect that those asthmatics with the greatest

degree of bronchial hyperresponsiveness, seen during asthma challenge testing, to be most likely affected. Unfortunately though, there is no scientifically demonstrated or universally accepted discriminatory level of hyperresponsiveness which can be used for clinical decision-making. The scientific literature seems to indicate that beta-blocker medications are less well tolerated in asthma than in COPD, but the differences are not great and certainly significant numbers of asthmatics do tolerate these medications without untoward effect.

Given these circumstances it is difficult to make practical and sensible recommendations or guidelines, about appropriate monitoring modalities and frequency, to the clinicians responsible for treating such patients. Accordingly, the following recommendations reflect our opinion only. Most often, bronchial provocation testing forms part of the initial assessment and diagnosis of a patient with asthma, and this can be used as a baseline indicating the severity of the bronchial hyperreactivity. If a known asthmatic patient is to start beta-blocker treatment, the clinician's ultimate decision must consider composite factors, including the patient characteristics and disease severity, stability and behaviour. If BHR testing is to be repeated, it should be performed for clinical indication, or after at least 28 days, if being performed to assess for chronic beta-blocker effects. This duration has been chosen because changes in FEV1 bronchodilator response and bronchial hyperresponsiveness associated with chronic dosing are postulated to be due to beta-receptor up-regulation, and the timing required for this to occur is uncertain. However, the longest study duration of the pooled chronic dosing studies in the Cochrane review, which showed restoration of the acute decrease in

FEV1, but preserved bronchodilator response, in patients with reversible airways disease, was 28 days (58). This was also the exposure duration chosen by Callearts-Vegh's group (64) in their study that demonstrated differential acute and chronic beta-blocker effects in asthmatic murine airways. However, we would suggest that monitoring of bronchial hyperresponsiveness in asthma patients commencing beta-blocker medications, whilst being contributory to scientific data accumulation, is not indicated as part of clinical management at this stage, unless there is evidence of clinical deterioration in the patient. For example, in a patient with mild baseline hyperresponsiveness to methacholine challenge, who seemed to be otherwise clinically stable, but who had a significantly decreased PD 20 after commencing beta-blocker treatment, there would not currently be any indication to alter the beta-blocker treatment.

A case could be made for screening patients at risk for obstructive airways disease, with spirometry, in the setting of planned commencement of beta-blockade and also for regular spirometry monitoring in the setting of prolonged beta-blocker therapy. However, beta-blockers are often started in the setting of acute myocardial ischaemia, or tachyarrhythmia, when spirometry is actually inappropriate or inadvisable. Therefore a pragmatic approach is needed. Where possible, it is desirable to have information regarding basic lung function measures, such as spirometry, in patients known to be at risk of obstructive airways disease, prior to beta-blocker commencement, or shortly thereafter. Patients at risk would include those with a significant smoking history, a clinical history suggestive of asthma or COPD or chronic symptoms potentially relevant to respiratory disease, including breathlessness, cough, sputum production and wheeze.

Screening for occult or early obstructive airways disease in this manner can be justified given the existence of effective early intervention that can modify progression of disease. Smoking cessation interventions, if successful, can modify important disease outcomes, including survival, health care utilisation and symptoms in both COPD and asthma. Lung function measures also provide clinicians with additional information as to cardiovascular prognosis, a fact which is not widely recognised, even in the medical community. Once again, regular monitoring of spirometry may contribute to our knowledge and experience of managing chronic beta-blocker therapy, but is probably not required for safely managing airways disease in the setting of clinical symptom stability. However, in the setting of clinical deterioration, we would argue that properly-performed spirometry is not only appropriate, but currently underutilised as a discriminatory tool in determining the source of deterioration, with clinicians being more reliant on electrocardiogram, medical imaging techniques, echocardiography and recent generation biomarker tests, than this simple and inexpensive test.

CHAPTER 8

DIRECTIONS FOR FUTURE RESEARCH

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Despite different inflammatory pathways and pathologic mechanisms, COPD and asthma are generally treated with the same classes of medication: bronchodilators and anti-inflammatory agents. Anti-inflammatory medication, in the form of inhaled corticosteroid, is very effective treatment for most asthma, but there do exist occasional "difficult" or "brittle" asthmatics who are less responsive to steroid treatment. Unfortunately, pharmacotherapy for COPD is much less effective in controlling symptoms and modifying disease progression. Hence, for the majority of COPD patients and the steroid-resistant asthmatics, researchers and clinicians must investigate more novel approaches to management.

A finding of particular interest from the 2002 Cochrane review of cardioselective beta-blocker use in patients with reversible airways disease (58), was a differential effect on lung function dependent on whether dosing was acute or longer term. This manifested as resolution of the decrease in FEV1 seen in the acute exposure studies, with persistence of the increased responsiveness to bronchodilator. Notably, the same was not found in the Cochrane meta-analysis of beta-blockers in COPD (53). Our study was not powered nor designed to specifically investigate this issue. The effect seen in reversible airways disease was postulated to occur via beta-receptor up-regulation pathways, which also occurs during beta-blocker therapy in heart failure. Callaerts-Vegh's group (64) used a

murine asthma model to demonstrate the differential responses seen in acute and chronic exposures to beta-receptor active drugs. For beta-receptor antagonists nadolol and carvedilol, acute exposure caused an increase in airway resistance to methacholine, while chronic dosing beyond 28 days caused a marked (and significant) reduction in airways resistance to methacholine, and an increase in airway beta-receptor density. Such work has paved the way, in the last twelve months, for early pilot trials investigating a potential role for beta-blockers as pharmacotherapy for asthma and revealed the prospect of a future in which, instead of avoiding beta-blockers in our airways disease patients, we are actively and consciously including them in the therapeutic armamentarium (120).

However, medical research has the responsibility to provide answers for a number of questions relating to practical management, before more investigation into mechanisms can be undertaken. Obviously safety is of primary importance. Despite two Cochrane meta-analyses of cardioselective beta-blocker use in patients with obstructive airways disease finding beta-blockers to be generally safe (57, 58), significant doubt remains due to the small absolute numbers of trial subjects, the limited duration of the so-called long term studies, and the lacking information for minority groups and for the setting of respiratory infection or exacerbation. Hence, much of the medical community still regard beta-blockers as potentially harmful to patients with obstructive airways disease. Our work has added to this knowledge base, showing no adverse long term effect of beta-blocker treatment on respiratory symptoms and spirometry measures over twelve months nor on survival over a more prolonged period. However, our work does raise

concerns about an increased rate of respiratory exacerbations, whether defined by therapy escalation or by increased symptoms alone. Therefore, the first task is to establish a sound evidence base of the nature and extent of adverse effects of prolonged beta-blocker use in patients with obstructive airways disease. Adverse effects will need to be quantified so that clinical decision-making is adequately informed about risks and benefits of treatment, particularly in the setting of comorbid cardiac disease. Secondly, although efficacy has been suggested in previous retrospective studies in COPD (42, 43, 118-120), research must also confirm the efficacy of beta-blocker medications when used for their recommended cardiovascular indications in patients with airways disease, through prospective studies. Then finally, the potential role for beta-blockers as a therapeutic option needs to be investigated individually for the two major obstructive airways diseases, COPD and asthma.

8.1 Safety and Efficacy

To ascertain the safety and benefit of beta-blocker medications, prospective trials in asthma and COPD are warranted. Initially, trials should examine their use in treatment of STEMI and left ventricular dysfunction, beta-blocker indications that confer survival benefit. Given the strength of cardiology guideline recommendations (23, 25, 29, 31) and the paucity of evidence for adverse respiratory beta-blocker effects, it would be unethical for trial design to be placebo-controlled. Because of the potential for medical instability in the setting of acute STEMI, a trial in patients with stable heart failure would be preferable in the first instance. However, if no significant safety concerns were

raised, then it would be important to also demonstrate safety and efficacy in STEMI. Treatment groups would need to include patients with COPD and well-controlled asthma, and patients without obstructive airways disease. End points would need to address both efficacy (left ventricular function, reinfarction) and safety (lung function parameters, acute exacerbations of obstructive lung disease and death). Such trials will require substantial resources, and recruiting will need to set targets similar to those seen in the trials establishing beta-blocker efficacy in cardiac disease.

8.2 A Potential Therapeutic Role for Beta-Blockers in the Obstructive Airways Diseases

Firstly considering reversible airways disease, and the reported results of the pooled Cochrane meta-analysis (58) and Callearts-Vegh's murine asthma model (64): it is the airway effects seen in chronic dosing, which are most intriguing, as they suggest a potential role for beta-blockers as a disease-modifying medication, whereby the increase in airway beta-receptors might render the patient more responsive to endogenous beta-agonists and therapeutic beta-agonist bronchodilators, and in this fashion serve to stabilise airway calibre. The first small pilot study did not reveal serious safety concerns and provided some support of the concept behind beta-blocker treatment in asthma, showing a decrease in BHR in association with chronic beta-blocker treatment (74). The path is now paved for further studies in asthmatic humans aimed at clarifying chronic beta-blocker airway effects, including effects on airways function and receptor distribution. Much work has already considered the acute airway effects, but the chronic

airway effects and impact on longer term respiratory outcomes, such as respiratory exacerbations, have not been well-studied. Then, a larger trial of beta-blocker treatment efficacy, which should be placebo-controlled and double blind, studying subjects with stable mild or moderate persistent asthma, whilst taking first-line disease-modifying treatment such as inhaled corticosteroids, should follow. The endpoints of most interest would be BHR and measures of daily asthma control, including relief bronchodilator use and quality of life.

Although the Cochrane meta-analysis of beta-1 selective antagonists in COPD (53) showed no difference between acute and chronic dosing effects, this does not mean that the effect seen in reversible airways disease was not present. In fact, there is no reason to suppose that B-AR up-regulation, the proposed mechanism of increased bronchodilator responsiveness, does not occur in COPD too. However, this might depend on the extent of concomitant beta agonist use, and which effect predominates, as prolonged beta-agonist use is known to down-regulate B-ARs. By definition, COPD is marked by incompletely reversible airways obstruction and so to detect differences in airway reactivity or bronchodilator responsiveness in the more fixed-calibre COPD airways, studies will need to be carefully powered. Although the effects of longer term beta-blocker dosing on lung function and bronchial reactivity could be investigated in an animal model, such as a murine smoke inhalation model, a more direct approach would be to plan human studies to investigate lung function effects. Obtaining human airway tissue from COPD patients is not without risk, but is performed more commonly for clinical management indications than it is in asthma, as COPD patients are more prone

to lung malignancy. Obtaining such tissue during procedures such as bronchoscopy or lung lobe resection performed for clinical management indications, could be justified without compromise of ethical considerations. Lobar resection would limit the potential researcher in terms of subject population disease severity, as patients need to be physiologically robust to be considered for this type of surgery. Probably a combined approach would give the most useful information about the effects of chronic beta-blocker use on B-ARs in COPD airways. Firstly, a bronchial biopsy and receptor study of COPD patients on chronic beta-blocker therapy, and stratified according to regular beta-agonist use, undergoing bronchoscopy for clinical indication could be performed. Secondly, the B-ARs could be assayed at time of lung resection in patients undergoing thoracic surgery for lung cancer. This could form part of a prospective randomised trial of preoperative beta-blocker treatment to prevent perioperative cardiovascular complications. Again, it would be important to consider and control for chronic beta-agonist use.

It is perhaps less controversial to argue a therapeutic role for beta-blockers in COPD than in asthma, even though COPD patients generally have the more severe impairment of lung function. This is because COPD patients have a high incidence of cardiovascular disease, cardiac arrhythmia and an increased risk of cardiovascular death. Moreover, CVD accounts for more COPD mortality and hospital presentations than do respiratory infections or respiratory failure. Beta-blockers have a well-established therapeutic role in the treatment of IHD, heart failure and cardiac arrhythmia. Hence, it is imperative that

CVD is effectively identified and treated in COPD patients and this forms a strong basis of the argument for their use in treatment of COPD.

With CVD such a major determinant of health outcomes in COPD, it seems an obvious next step in clinical practice to incorporate standard cardiovascular risk factor assessment in these patients. It has been further suggested that they might benefit from a cardiopulmonary treatment strategy, utilising such drugs as HMG CoA reductase inhibitors (often referred to as statins) or angiotensin converting enzyme inhibitors and receptor blockers, in order to discover whether their benefits in heart disease extend to improve the prognosis of COPD patients. While statins and drugs affecting the renin-angiotensin system do have theoretical benefits other than the indications for which they are marketed, beta-blockers too, certainly deserve a place in this strategy. To this end, a randomised, controlled trial of beta-blockers in patients with mild to moderate COPD, and no previously documented cardiac disease, would be appropriate. This trial could be placebo-controlled, as COPD is not a recognised indication for beta-blocker medication. An important component of the trial would be to document the results of formal testing for left ventricular dysfunction and myocardial ischaemia, both problems known to be underrecognised in COPD, which would give an indication of how many incidental patients would correctly receive guideline-recommended therapy for heart failure or symptomatic IHD under this blanket treatment strategy. Once again, longer term COPD health outcomes, such as respiratory exacerbations, cardiovascular events and survival will be particularly relevant. In moderate or severe COPD outcomes more indicative of morbidity, such as walking endurance and quality of life assessment would also be quite

justified, since they give a good indication of symptom control, which is an important treatment outcome in patients with more advanced disease.

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APPENDICES

Appendix 1

COPD SURVEY – 1 Hospital MRN: □□□□□□

Date1: □□/□□/□□

Pub 1/Priv 2 □

Demographics

First name: _____Surname: _____Gender: (M/F)

Residential address: Suburb: Postcode:□□□□

Phone: (home) (□□)□□□□□□□□

(business) (□□)□□□□□□□□

(mobile) □□□□□□□□□□

Country of birth: _____Date of birth (age calculated): □□/□□/□□

Occupation(s): _____

Description of tasks:_____

Airborne exposures: _____

GP: Phone:(□□)□□□□□□□□

Contact person, First name: _____Surname:_____

Contact's address: Suburb: Postcode:□□□□

Phone:(□□)□□□□□□□□

Lung Function Testing Details

Race: _____□ Height □□□.□$_{cm}$ Weight □□□.□$_{kg}$

(Caucasian=1, Asian=2, Other=3)

Make BMI calculated field in database or enter here **BMI** □□.□

Have you ever before performed breathing tests/lung function tests? (yes/no)

If yes give dates and place *(Most recent first)*

Lfdate1:□□/□□/□□ *lfplace1*_____

Lfdate2:□□/□□/□□ *lfplace2*_____

Lfdate3:□□/□□/□□ *lfplace3*_____

1. In the month preceding admission to hospital, have you smoked?

cigarettes (yes/no)
tobacco, e.g. pipe , roll your own, etc
(yes/no)
marijuana (yes/no)
other, state (yes/no)

2a. *A "regular Smoker" has smoked at least 7 cigarettes (or the equivalent in terms of tobacco smoked) per week for three months or more.*
Have you ever been a regular smoker? (yes/no)
If no, go to question 4
2b. In total, for how many years have you smoked/ for how many years did you smoke?

0-10[1]
11-20[2]
21-30[3]
31-40[4]
41-50[5]

greater than 50[6] ☐

3. During your period of heaviest smoking, (approximately) how many cigarettes per day would you smoke?

1-10[1]
11-25[2]
26-50[3]
greater than 50[4]

other[5] (specify other e.g. pipe etc_____) ☐

4. Do you regularly experience any of the following symptoms?

Cough, with or without sputum (phlegm) production (yes/no)
Wheeze (yes/no)
Shortness of breath (yes/no)

5a. Before you were admitted to hospital and when you were feeling relatively well, grade each of these symptoms on a scale of 0-10 (0 is least you have ever had and 10 is most that you have ever had)

Cough ☐☐

Sputum production ☐☐

Wheeze ☐☐

Shortness of breath ☐☐

5b. Before you were admitted to hospital this time and when you were relatively well) how many times per day would take an extra puffer or nebuliser dose (in addition to any normal daily inhaled medication) for relief of breathlessness or wheeze?

0[1]
1-2[2]
3-5[3]
>5[4] ☐

5c. At present, grade each of these symptoms on a scale of 0-10 (0 is least you have ever had and 10 is most that you have ever had)

Cough ☐☐
Sputum production ☐☐
Wheeze ☐☐
Shortness of breath ☐☐

5d. At present, how many times per day would you take an extra puffer or nebuliser dose (in addition to any regular daily inhaled medication) for relief of breathlessness or wheeze? *(this includes additional or "prn" medication prescribed by the medical team)*

0[1]
1-2[2]
3-5[3]
>5[4] ☐

6. Have you ever been told that you have

Asthma?	(yes/no)
Emphysema?	(yes/no)
Chronic bronchitis	(yes/no)
Smoking-related lung disease?	(yes/no)
COPD/COAD	(yes/no)
Pulmonary or lung disease?	(yes/no)

7. Do you take inhaled medications or "puffers"? (yes/no)

8. Which inhaled medications do you take?

Salbutamol (Ventolin, Asmol, Epaq) – grey body, blue cap, MDI	(yes/no)
(Airomir) – blue body, grey cap, MDI	(yes/no)
Nebulised?	(yes/no)
Terbutaline (Bricanyl) – white body, blue cap, TH	(yes/no)
(Bricanyl) –blue body, blue cap, MDI	(yes/no)
Salmeterol (Serevent) – turquoise body, green cap, MDI & ACH	(yes/no)
Eformoterol (Oxis) – turquoise base, white body, TH	(yes/no)
(Foradile) – white body, case & base baby blue, ATH	(yes/no)
Orciprenaline – (Alupent)	(yes/no)
Fenoterol – (Berotec)	(yes/no)
Ipratropium bromide (Atrovent) – transparent body, green cap, MDI	(yes/no)
Nebulised?	(yes/no)
(Apoven) Nebulised only	(yes/no)
(Ipratrin) Nebulised only	(yes/no)
(Ipravent) Nebulised only	(yes/no)
Tiatropium (Spiriva) – grey with green button, HH	(yes/no)
Cromoglycate (Intal) – white body, blue cap, MDI	(yes/no)
(Intal forte) – white body, red/pink cap, MDI	(yes/no)
(Tilade) – yellow body with blue button, MDI	(yes/no)
Nebulised (Intal, Cromese Sterinebs)?	(yes/no)
Budesonide (Pulmicort) – white body, brown base, TH	(yes/no)
Nebulised?	(yes/no)
Fluticasone (Flixotide) – orange/red shades body, red cap, MDI & ACH	(yes/no)
Beclomethasone (Qvar) – red/pink holder, MDI	(yes/no)
(Becotide) – brown body brown cap, MDI	(yes/no)
(Becloforte) – yellow body black cap, MDI	(yes/no)
(Seratide) – purple/mauve body, mauve cap, MDI &ACH	(yes/no)
(Combivent) – clear with grey button, MDI	(yes/no)
(Symbicort) – white body, red base, TH	(yes/no)
Other Inhaled Medication_____	(yes/no)

9a. Do you take beta blocker medication on a regular basis? *(include eye drops* (yes/no)

Ask specifically then tick

Atenolol brands	(yes/no)	*Noten*	(yes/no)
		Tenormin	(yes/no)
		Anselol	(yes/no)
		Atehexal	(yes/no)
		Tensig	(yes/no)
		Atenolol	(yes/no)
Metoprolol brands	(yes/no)	*Betaloc*	(yes/no)
		Lopresor	(yes/no)
		Minax	(yes/no)
		Metolol	(yes/no)
		Metohexal	(yes/no)
		Metoprolol	(yes/no)
Carvedilol brands	(yes/no)	*Dilatrend*	(yes/no)
		Kredex	(yes/no)

*Other please state*_____(yes/no)

9b. Duration of any regular beta blocker therapy □□years □□months □weeks

9c. What other medications do you take on a regular (at least 2nd daily) basis?

_____

_____

_____

10. In the last 12 months have you been admitted to hospital? (yes/no)

Details of Hospital Admissions

Admission	Date Admitted	Hospital	Reason	Respiratory Y/N	Cardiac Y/N
1					
2					
3					
4					
5					
6					

11. In the last twelve months how many times have you sought medical attention for your chest symptoms (includes hospital admissions)?
How many times have you been prescribed antibiotics or prednisone (prednisolone/ cortisone) for these increased symptoms?

Consultations	No Antibiotics or Steroids	Antibiotics only Tick if applicable	Steroids only Tick if applicable	Antibiotics & Steroids
1st				
2nd				
3rd				
4th				
5th				
6th				
7th				
8th				
9th				
10th				
Enter Totals				

Appendix 2

COPD SURVEY 2 **Name _____** Hospital MRN: ☐☐☐☐☐☐

Date2 ☐☐/☐☐/☐☐

Please give full discharge diagnosis *(first cardiac)*

_____

_____*Code later if ICD10 codes available*

Beta blocker indicated (Yes/No)

If Yes Beta blocker prescribed_____

If No reason why not_____

1. At present, grade each of these symptoms on a scale of 0-10 (0 is least you have ever had and 10 is most that you have ever had)

Cough ☐☐

Sputum production ☐☐

Wheeze ☐☐

Shortness of breath ☐☐

2. At present, how many times per day would you take an extra puffer or nebuliser dose (in addition to any regular daily inhaled medication) for relief of breathlessness or wheeze? *(this includes additional or "prn" medication prescribed by the medical team)*

0[1]

1-2[2]

3-5[3]

>5[4] ☐

3. While in hospital have you received extra treatment for your chest?

(Yes/No)

Does your extra treatment include antibiotics or prednisone (prednisolone/cortisone) given specifically for your chest problems?

(Yes/No)

Antibiotics ☐

Prednisone ☐

Antibiotic and prednisone ☐

4. Since you enrolled into the study, have you had any changes made to your medications? *Ask specifically about continuation of the beta blocker and newly introduced inhaled medications.*

_____
_____
_____

5. Have your smoking habits changed since enrolment to the study?

Increased [1]
No change [2]
Reduced [3]
Quit [4] ☐

Appendix 3

COPD SURVEY 3/4 **Name**_____Hospital MRN: □□□□□□

SURVEY No. □

Date3/4 □□/□□/□□

1. At present, grade each of these symptoms on a scale of 0-10 (0 is least you have ever had and 10 is most that you have ever had)

Cough □□

Sputum production □□

Wheeze □□

Shortness of breath □□

2. At present, how many times per day would you take an extra puffer or nebuliser dose (in addition to any regular daily inhaled medication) for relief of breathlessness or wheeze? *(this includes additional or "prn" medication prescribed by the medical team)*

0^1

$1\text{-}2^2$

$3\text{-}5^3$

$>5^4$ □

3. Since you enrolled in the study on the □□/□□/□□ *pre-enter date*, have you been readmitted to hospital?

(yes/no)

Details of Hospital Admissions

Admission	Date Admitted	Hospital	Reason	Respiratory Y/N	Cardiac Y/N
1					
2					
3					
4					

4. Since you enrolled into the study
(a) how many times have you sought medical attention for your chest?
(b) how many times have you been given a course of antibiotics or prednisone (prednisolone/cortisone)?

Consultations	No Antibiotics or Steroids	Antibiotics only Tick if applicable	Steroids only Tick if applicable	Antibiotics & Steroids
1^{st}				
2^{nd}				
3^{rd}				
4^{th}				
Enter Totals				

5. Since you enrolled into the study, have you had any changes made to your medications? *Ask specifically about continuation of the beta blocker and newly introduced inhaled medications.*

_____
_____

6. Have your smoking habits changed since enrolment to the study?

Increased [1] No change [2] Reduced [3] Quit [4] ☐

Appendix 4

Table 1: Individual Subject Data – Demographics

Subject ID	Subject Category	Suburb	Insurance Status	Occupation	Gender	Age	BMI	Race
1	Full Protocol	St Peters	Medicare	Data Entry	Female	29.41	31.2213040	Caucasian
2	Full Protocol	Leichhardt	Ineligible	Travel Agent	Female	58.1	23.7386621	Caucasian
3	Full Protocol	Redfern	Medicare	Artist	Male	79.26	22.9590877	Caucasian
4	Full Protocol	Rozelle	Medicare	Manager Automotive Spare Parts, Carer	Male	54.03	23.7714286	Caucasian
5	Amended Protocol	Redfern	Medicare	Vet/Farrier's Assistant	Male	76.11	21.7554685	Caucasian
6	Full Protocol	Petersham	Medicare	Sales Assistant	Female	79.13	20.3125	Caucasian
7	Full Protocol	Darling Point	Medicare	House Wife	Female	84.19	25.4325260	Caucasian
8	Full Protocol	Glebe	Medicare	Company Sales Representative	Male	92.18	25.7439446	Caucasian
9	Full Protocol	Ermington	Medicare	Printer	Male	79.75	23.6712536	Caucasian
10	Full Protocol	Dulwich Hill	Medicare	Carpenter	Male	80.95	29.5157733	Caucasian
11	Amended Protocol	Concord West	Medicare	Builder	Male	72.78	33.2621407	Caucasian
12	Full Protocol	Concord	Medicare	Motor Mechanic	Male	67.55	25.9515571	Caucasian
13	Full Protocol	Stanmore	Medicare	Clerk	Male	62.16	40.7454649	Caucasian
14	Full Protocol	Waterloo	Medicare	Welder	Male	58	31.7417889	Caucasian
15	Full Protocol	Rozelle	Medicare	Receptionist	Female	76.22	25.8396814	Caucasian
16	Full Protocol	St Peters	Ineligible	Latex Manufacturer	Male	45.92	27.7322998	Caucasian
17	Amended Protocol	Waterloo	Medicare	Clerk	Male	64.61	24.0569348	Caucasian
18	Full Protocol	Dulwich Hill	Medicare	Cook	Female	68.41	34.6260388	Caucasian
19	Full Protocol	Glebe	Medicare	Restaurateur, Chef	Female	73.85	22.6912406	Caucasian
20	Full Protocol	Marrickville	Medicare	Clerk	Female	58.2	23.6652444	Caucasian
21	Full Protocol	Petersham	DVA	House Wife	Female	74.93	29.7441999	Caucasian
22	Full Protocol	Enfield	Private	Technical Aide	Female	60.69	29.7575846	Caucasian
23	Full Protocol	Marrickville	Private	Metal Polishing	Male	70.83	30.4779662	Caucasian
24	Full Protocol	Lilyfield	Private	Boat Builder	Male	50.26	24.5351240	Caucasian
25	Full Protocol	Glebe	Medicare	Taxi driver, Finance, IT	Male	45.81	23.9994592	Caucasian
26	Full Protocol	Dubbo	Medicare	Truck Driver	Male	44.28	30.7563678	Caucasian
27	Amended Protocol	Dubbo	Ineligible	Storeman	Male	44.41	46.7128028	Aboriginal
28	Full Protocol	Pyrmont	Medicare	Policeman	Male	68.59	29.6495116	Caucasian
29	Full Protocol	Drummoyne	Medicare	Carpenter	Male	65.84	35.4191263	Caucasian
30	Full Protocol	North Sydney	Medicare	Self Employed	Female	50.72	31.2025637	Caucasian
31	Full Protocol	Rozelle	Ineligible	Real Estate Agent	Male	68.31	31.5179326	Caucasian

Subject ID	Subject Category	Suburb	Insurance Status	Occupation	Gender	Age	BMI	Race
32	Amended Protocol	Dunedoo	Medicare	House Wife	Female	73.11	30.8596074	Caucasian
33	Full Protocol	Dover Heights	Ineligible	Chartered Accountant	Male	76.07	24.0929705	Caucasian
34	Full Protocol	Elanora	Private	Director Media Company	Male	39.68	22.4087868	Caucasian
35	Full Protocol	Croyden	Medicare	Ship's Engineer, Garden Ctr Owner	Male	59.08	35.3218210	Caucasian
36	Amended Protocol	Lakes Entrance	Ineligible	Clothing Trade, Supervisor in Warehouse	Female	76.15	20.9041950	Caucasian
37	Full Protocol	Killara	Medicare	Secretary/ Receptionist, Air Hostess	Female	73.98	20.8299952	Caucasian
38	Full Protocol	Dulwich Hill	Medicare	Construction	Male	70.93	31.2394144	Caucasian
39	Full Protocol	Lewisham	Medicare	Boss General Textiles	Female	82.41	36.6285120	Caucasian
40	Amended Protocol	Redfern	Medicare	Cook, Fruit-Picking, Laundry	Female	73.48	17.8980229	Caucasian
41	Full Protocol	Rozelle	Medicare	Chartered Surveyor, Strata Inspector, Town Planning Consultant	Male	62.4	25.8166302	Caucasian
42	Full Protocol	Summer Hill	Ineligible	Timber Merchant, Glass Factory Worker, Dep't Store, Hospitality, Staffing Agency	Male	68.31	25.3086420	Caucasian
43	Full Protocol	Elizabeth Bay	Ineligible	Accountant, Clerk, Teacher	Female	81.82	22.6666667	Caucasian
44	Full Protocol	Glebe	Medicare	City Council Work, Sweeper Printer	Male	62.84	25.2092014	Caucasian
45	Full Protocol	Marrickville	Medicare	Cook, Shop Assistant, Store Worker	Female	55.7	31.2452370	Caucasian
46	Full Protocol	Redfern	Medicare	Cook, Labourer	Male	61.94	35.2010451	Caucasian
47	Full Protocol	Watsons Bay	Private	Electrical Engineer	Male	68.75	22.8395062	Caucasian
48	Full Protocol	Leichhardt	Medicare	Factory Worker, Electrician	Male	82.33	22.3093564	Caucasian
49	Amended Protocol	Drouin	Ineligible	Clerk, Financial Management, Gardener, Founder Toyworld	Male	75.11	32.0759130	Caucasian
50	Amended Protocol	Lismore	Medicare	Army, Hospital Work, Construction, Asbestos Removal, Merchant, Catering Officer	Male	59.62	32.4100371	Caucasian
51	Full Protocol	Newtown	Medicare	Fish Monger, Golf Club Manufacturer	Male	66.95	25.6895619	Aboriginal
52	Full Protocol	Erskineville	Medicare	Seaman, Cook, Factory Worker	Male	80.61	29.4887039	Asian
53	Full Protocol	Caringbah	Medicare	Mothercraft Nurse	Female	58.47	39.8961195	Caucasian
54	Full Protocol	Turella	Medicare	Fitter and Turner, Machinist, Tool-Maker	Male	65.02	33.5765087	Caucasian
55	Full Protocol	Faulconbridge	Medicare	Bookkeeper, Graphic Artist	Female	49.62	30.6361822	Caucasian
56	Full Protocol	Marrickville	Medicare	Construction Worker	Male	67.83	26.0789715	Caucasian
57	Full Protocol	Drummoyne	Private	Production Manager, News Media, Printing	Male	55.32	24.0493434	Caucasian
58	Amended Protocol	Sussex Inlet	Ineligible	Boilermaker, Timberyard Maintenance	Male	73.51	27.1314118	Caucasian
59	Full Protocol	Botobolar	Ineligible	Postal Clerk	Male	50.33	22.2222222	Caucasian
60	Full Protocol	Croyden	Medicare	Military Intelligence, Translator, Cook	Male	65.02	21.2009914	Caucasian
61	Full Protocol	Earlwood	Medicare	Bookkeeper	Female	54.71	29.9687825	Caucasian
62	Full Protocol	Rose Hill	DVA	Engineer, Maintenance, Seaman, Army	Male	72.02	21.0667433	Caucasian
63	Amended Protocol	Lithgow	Medicare	Bank Officer, Sewing Machinist	Female	52.97	55.078125	Caucasian
64	Full Protocol	Marrickville	Medicare	House Wife	Female	76.9	39.0625	Caucasian

Table 2: Individual Subject Data - Smoking and Respiratory Morbidity

Subject ID	Regular Smoker	Pack Years	Previous Asthma	Smoke-Related Lung Disease	Emphysema	COPD/ COAD	Chronic Bronchitis	Other Lung Disease
1	Yes	37.5	Yes					
2		0						Yes
3		0						Yes
4	Yes	82						
5	Yes	161.2		Yes				
6		0	Yes				Yes	
7	Yes	10						
8	Yes	63.75						
9		0						
10	Yes	65.55						
11	Yes	25.5						
12	Yes	22.5						
13	Yes	68	Yes				Yes	
14	Yes	50						
15		0						
16	Yes	7						
17		0						
18	Yes	42.5	Yes			Yes	Yes	
19	Yes	52.5						Yes
20	Yes	39.6					Yes	Yes
21	Yes	107.5	Yes			Yes		
22	Yes	7	Yes					Yes
23	Yes	10						Yes
24	Yes	3	Yes					
25		0						
26	Yes	26.25						
27	Yes	25						
28	Yes	96						
29	Yes	15						
30	Yes	18.75	Yes					
31	Yes	168					Yes	
32	Yes	21						
33	Yes	47						
34	Yes	0.6	Yes					
35		0						
36	Yes	5						
37	Yes	7.5						
38	Yes	37.5					Yes	
39		0						
40	Yes	123.75	Yes		Yes		Yes	
41	Yes	18.75						
42	Yes	21						
43		0	Yes					
44	Yes	118.25	Yes	Yes	Yes		Yes	Yes
45	Yes	1						
46	Yes	228	Yes				Yes	
47		0	Yes				Yes	
48	Yes	30						
49		0						
50	Yes	105	Yes					
51	Yes	51						
52	Yes	120						
53		0	Yes					
54	Yes	52.5						
55	Yes	6.5	Yes					
56	Yes	82.5						
57	Yes	1.95	Yes					
58	Yes	1.75			Yes	Yes		
59	Yes	49.5						
60		0						
61		0						
62	Yes	12.6						
63	Yes	7.8	Yes					
64		0						

Table 3: Individual Subject Data – Acute Cardiac Morbidity

Subject ID	Acute Coronary Syndrome	Valvular Heart Disease	Congestive Cardiac Failure	Arrhythmia	Pericardial Disease
1					
2				Yes	
3					
4	Yes				
5			Yes	Yes	
6	Yes				
7	Yes				
8	Yes				
9	Yes				
10					
11	Yes				
12	Yes				
13	Yes				
14	Yes				
15		Yes		Yes	
16				Yes	
17	Yes				
18					
19	Yes				
20				Yes	
21	Yes				
22					
23					
24	Yes				
25					
26	Yes				
27	Yes				
28	Yes				
29					
30	Yes				
31	Yes		Yes	Yes	
32	Yes			Yes	
33					
34				Yes	
35	Yes			Yes	
36					
37	Yes				Yes
38	Yes				
39					
40				Yes	
41					
42	Yes				
43					
44					
45				Yes	
46			Yes		
47	Yes				
48					Yes
49	Yes				
50	Yes				
51					
52	Yes				
53	Yes				
54				Yes	
55	Yes				
56	Yes				
57					
58	Yes				
59	Yes		Yes		
60					
61					
62	Yes				
63	Yes				
64	Yes				

Table 4: Individual Subject Data – Chronic Cardiovascular Morbidity and Risk Factors

Subject ID	IHD	Other Primary Cardiac Disease	Hypertension	Dyslipidaemia	Peripheral Vascular Disease	Cerebrovascular Disease	Diabetes Mellitus
1		Cardiomyopathy					
2		Valvular Heart Disease					
3	Yes						
4	Yes						
5	Yes				Yes		
6	Yes						
7	Yes						
8	Yes						
9	Yes						
10							Yes
11	Yes						Yes
12	Yes						
13	Yes						
14	Yes						
15						Yes	
16							
17	Yes						
18	Yes						
19	Yes						
20							
21	Yes						Yes
22							
23	Yes						Yes
24	Yes						
25							
26	Yes						Yes
27	Yes						
28	Yes				Yes		
29	Yes		Yes	Yes			Yes
30	Yes						
31	Yes						
32	Yes						
33			Yes			Yes	
34							
35	Yes						
36			Yes				
37	Yes		Yes	Yes			
38	Yes		Yes	Yes		Yes	
39			Yes			Yes	
40							
41	Yes		Yes				
42	Yes						
43							
44	Yes						Yes
45			Yes				
46							Yes
47	Yes						
48						Yes	
49	Yes				Yes	Yes	
50	Yes		Yes		Yes		
51	Yes						
52	Yes						Yes
53	Yes						Yes
54	Yes						
55	Yes		Yes	Yes			
56	Yes						
57	Yes						Yes
58	Yes						
59	Yes				Yes		Yes
60							
61							
62	Yes					Yes	
63	Yes		Yes	Yes			
64	Yes						

Table 5: Individual Subject Data – Medication Use

Subject ID	SABA	SAACh	ICS	LABA	LAACh	BB
1	Yes					
2						
3						Yes
4						
5						
6	Yes		Yes			
7						
8	Yes	Yes				
9						Yes
10						
11						Yes
12						Yes
13						
14						Yes
15	Yes		Yes			
16						
17						Yes
18			Yes			
19						Yes
20						
21	Yes					
22	Yes					
23						Yes
24	Yes					
25						
26						
27						
28						
29						Yes
30						
31						
32						Yes
33						
34	Yes					
35						Yes
36						
37						
38						Yes
39						
40	Yes	Yes				
41						
42						
43						
44	Yes	Yes	Yes			
45						Yes
46	Yes		Yes			
47						
48						
49						Yes
50	Yes					Yes
51						Yes
52						
53						
54						
55						
56						
57	Yes					
58						Yes
59						
60						
61						Yes
62	Yes	Yes				
63	Yes		Yes			
64						

SABA=short-acting beta-agonist SAACh=short-acting anticholinergic BB=beta-blocker
LABA=long-acting beta-agonist LAACh= long-acting anticholinergic ICS=inhaled corticosteroid

Appendix 5

Table 1: Individual Subject Data – Spirometry

Subject ID	%PFEV1	%PFVC	%PMMEF*	FEV1/FVC
1	98	95	113	0.88
2	43	49	26	0.67
3	45	48	28	0.71
4	79	85	41	0.68
6	49	63	22	0.57
7	101	97	112	0.72
9	85	82	67	0.72
10	46	63	13	0.58
11	89	106	43	0.65
12	85	89	64	0.74
13	49	58	24	0.66
14	80	85	68	0.75
15	74	81	41	0.68
16	88	89	81	0.8
17	80	80	77	0.78
18	62	68	36	0.69
19	55	68	29	0.61
20	84	84	77	0.79
21	38	49	22	0.58
22	83	85	83	0.77
23	74	71	47	0.67
24	78	76	75	0.82
25	101	102	89	0.81
26	94	105	64	0.72
28	88	99	42	0.65
29	81	84	69	0.78
30	95	103	70	0.77
31	31	42	14	0.55
32	100	96	97	0.78
33	92	99	60	0.71
34	81	97	50	0.67
35	76	73	80	0.82
36	72	71	66	0.92
37	92	95	73	0.69
38	82	89	52	0.69
39	55	70	60	0.68
40	45	54	26	0.59
41	84	101	94	0.75
42	66	70	48	0.72
43	102	98	74	0.72
44	42	62	18	0.52
45	115	115	117	0.81
46	44	60	23	0.59
49	103	119	77	0.68
50	74	83	49	0.71
51	68	86	35	0.62
52	66	77	22	0.61
53	63	67	49	0.75
54	24	44	10	0.39
55	94	97	91	0.75
56	58	64	36	0.72
57	71	80	48	0.7
58	74	73	69	0.77
59	57	58	34	0.7
60	33	38	17	0.78
61	89	102	48	0.72
62	90	95	74	0.72
63	102	113	91	0.74

*PMMEF= Predicted Maximum Mid-Expiratory Flow

Table 2a: Individual Subject Data - Obstructive Lung Function

Subject ID	FER1	FER2	FER3	FER4	Obstruction
1					
2	Obstructed	Obstructed			Obstructed
3		n/a	Obstructed	Obstructed	Obstructed
4	Obstructed		Obstructed	Obstructed	Obstructed
5	X	X	Deceased	Deceased	X
6	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
7				Obstructed	Obstructed
8	X	n/a	Deceased	Deceased	X
9					
10	X	Obstructed	Obstructed	n/a	Obstructed
11	Obstructed	a/p	a/p	a/p	Obstructed
12		n/a			
13	Obstructed	Obstructed		n/a	Obstructed
14			n/a	n/a	
15	Obstructed			Obstructed	Obstructed
16			n/a	n/a	
17		a/p	a/p	a/p	
18	Obstructed	Obstructed	Obstructed	n/a	Obstructed
19	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
20		n/a			
21	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
22					
23		X	n/a	Obstructed	Obstructed
24	X				
25		n/a			
26				n/a	
27	X	a/p	a/p	a/p	X
28	Obstructed		n/a	n/a	Obstructed
29		Obstructed			Obstructed
30		n/a			
31	Obstructed	Obstructed	n/a	n/a	Obstructed
32		a/p	a/p	a/p	
33		n/a			
34	Obstructed	X	Obstructed	Obstructed	Obstructed
35					
36		a/p	a/p	a/p	
37		Obstructed	Obstructed		Obstructed
38	Obstructed		n/a	n/a	Obstructed
39	Obstructed	X	Obstructed		Obstructed
40	Obstructed	a/p	a/p	a/p	Obstructed
41					
42					
43					
44	Obstructed	Obstructed	Deceased	Deceased	Obstructed
45		n/a	n/a		
46	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
47	X	n/a			
48	X	X	n/a	n/a	X
49	Obstructed	n/a	a/p	a/p	Obstructed
50		n/a	a/p	a/p	
51	X	Obstructed	Obstructed	Obstructed	Obstructed
52	Obstructed	Obstructed	Deceased	Deceased	Obstructed
53					
54	Obstructed	Obstructed	Obstructed	Obstructed	Obstructed
55					
56	X		Obstructed	n/a	Obstructed
57	Obstructed	n/a	Obstructed	Obstructed	Obstructed
58		a/p	a/p	a/p	
59	Obstructed		n/a	Deceased	Obstructed
60		n/a	Deceased	Deceased	
61					
62		n/a	n/a	n/a	
63		a/p	a/p	a/p	
64	n/a	n/a	Deceased	Deceased	n/a

n/a = not available a/p = amended protocol X=technically inadequate

Table 2b: Individual Subject Data - Bronchodilator Response

Subject ID	BDR1	BDR2	BDR3	BDR4	Overall BDR
1					
2	BDR				BDR
3		n/a			
4					
5	X	X	Deceased	Deceased	X
6	BDR				BDR
7					
8	X	n/a	Deceased	Deceased	X
9					
10			BDR		BDR
11		a/p	a/p	a/p	
12		n/a			
13				n/a	
14			n/a	n/a	
15					
16			n/a	n/a	
17		a/p	a/p	a/p	
18				n/a	
19		BDR			BDR
20		n/a			
21					
22					
23		X	n/a		
24					
25		n/a			
26				n/a	
27	X	a/p	a/p	a/p	X
28			n/a	n/a	
29		BDR			BDR
30		n/a			
31	BDR	BDR	n/a	n/a	BDR
32		a/p	a/p	a/p	
33		n/a			
34		X			
35					
36		a/p	a/p	a/p	
37					
38	BDR		n/a	n/a	BDR
39		X			
40	X	a/p	a/p	a/p	X
41					
42					
43					
44	BDR		Deceased	Deceased	BDR
45		n/a	n/a		
46	BDR	BDR	BDR	BDR	BDR
47	X	n/a			
48	X	X	n/a	n/a	X
49		a/p	a/p	a/p	
50		a/p	a/p	a/p	
51					
52			Deceased	Deceased	
53					
54	BDR	BDR	BDR	BDR	BDR
55					
56				n/a	
57		n/a			
58		a/p	a/p	a/p	
59			n/a	Deceased	
60		n/a	Deceased	Deceased	
61					
62		n/a	n/a	n/a	
63		a/p	a/p	a/p	
64	n/a	n/a	Deceased	Deceased	n/a

n/a = not available a/p = amended protocol X=technically inadequate

Table 3: Individual Subject Data - by Forced Expiratory Ratio

FER	ID	Age	Gender	BMI	Reg Smoker	PY	Asthma	COPD	Inh Med	Beta-Blocker	IHD
0.39	54	65.02	Male	33.58	Yes	42		Yes			Yes
0.52	44	62.84	Male	25.21	Yes	95	Yes	Yes	Yes		Yes
0.55	31	68.31	Male	31.52	Yes	134					Yes
0.57	6	79.13	Female	20.31		0	Yes		Yes		Yes
0.58	10	80.95	Male	29.52	Yes	52					
0.58	21	74.93	Female	29.74	Yes	86	Yes	Yes	Yes		Yes
0.59	40	73.48	Female	17.9	Yes	99	Yes	Yes	Yes		
0.59	56	61.94	Male	35.2	Yes	182	Yes	Yes	Yes	Yes	
0.61	19	73.85	Female	22.69	Yes	42				Yes	Yes
0.61	52	80.61	Male	29.49	Yes	96		Yes			Yes
0.62	51	66.95	Male	25.69	Yes	41				Yes	Yes
0.65	11	72.78	Male	33.26	Yes	20				Yes	Yes
0.65	28	68.59	Male	29.65	Yes	77				Yes	Yes
0.66	13	62.16	Male	40.75	Yes	54	Yes			Yes	Yes
0.67	2	58.1	Female	23.74		0				Yes	
0.67	34	39.68	Male	22.41	Yes	0	Yes		Yes		
0.68	4	54.03	Male	23.77	Yes	66				Yes	Yes
0.68	15	76.22	Female	25.84		0			Yes		
0.68	39	82.41	Female	36.63		0					
0.68	49	75.11	Male	32.08		0				Yes	Yes
0.69	18	68.41	Female	34.63	Yes	34	Yes	Yes	Yes		Yes
0.69	37	73.98	Female	20.83	Yes	6					Yes
0.69	38	70.93	Male	31.24	Yes	30		Yes		Yes	Yes
0.7	57	55.32	Male	24.05	Yes	2	Yes		Yes		Yes
0.7	59	50.33	Male	22.22	Yes	40					Yes
0.71	3	79.26	Male	22.96		0				Yes	Yes
0.71	33	76.07	Male	24.09	Yes	38					
0.71	50	59.62	Male	32.41	Yes	84	Yes		Yes	Yes	Yes
0.72	7	84.19	Female	25.43	Yes	8				Yes	Yes
0.72	9	79.75	Male	23.67		0				Yes	Yes
0.72	26	44.28	Male	30.76	Yes	21				Yes	Yes
0.72	42	68.31	Male	25.31	Yes	17				Yes	Yes
0.72	43	81.82	Female	22.67		0	Yes				
0.72	56	67.83	Male	26.08	Yes	66					Yes
0.72	61	54.71	Female	29.97		0				Yes	
0.72	62	72.02	Male	21.07	Yes	10			Yes		Yes
0.74	12	67.55	Male	25.95	Yes	18				Yes	Yes
0.74	63	52.97	Female	55.08	Yes	6	Yes		Yes		Yes
0.75	14	58	Male	31.74	Yes	40				Yes	Yes
0.75	23	70.83	Male	30.48	Yes	8				Yes	
0.75	41	62.4	Male	25.82	Yes	15				Yes	Yes
0.75	53	58.47	Female	39.9		0	Yes				Yes
0.75	55	49.62	Female	30.64	Yes	5	Yes			Yes	Yes
0.77	22	60.69	Female	29.76	Yes	6			Yes	Yes	
0.77	30	50.72	Female	31.2	Yes	15	Yes				Yes
0.77	58	73.51	Male	27.13	Yes	1		Yes		Yes	Yes
0.78	17	68.41	Male	24.06		0				Yes	Yes
0.78	29	65.84	Male	35.42	Yes	12				Yes	Yes
0.78	32	73.11	Female	30.86	Yes	17				Yes	Yes
0.78	48	65.02	Male	21.2		0					
0.79	20	58.2	Female	23.67	Yes	32					
0.8	16	45.92	Male	27.73	Yes	6					
0.81	25	45.81	Male	24		0					
0.81	45	55.7	Female	31.25	Yes	1				Yes	
0.82	24	50.26	Male	24.54	Yes	2	Yes		Yes	Yes	Yes
0.82	35	59.08	Male	35.32		0				Yes	Yes
0.88	1	29.41	Female	31.22	Yes	30	Yes		Yes		
0.92	36	76.15	Female	20.9	Yes	4					

Table 4: Individual Subject Data - Respiratory Symptoms by Forced Expiratory Ratio

FER	Subject ID	Dyspnoea	Cough	Wheeze
0.39	54	Yes	Yes	
0.52	44	Yes	Yes	
0.55	31	Yes		Yes
0.57	6	Yes	Yes	Yes
0.58	10	Yes	Yes	
0.58	21	Yes		Yes
0.59	40	Yes	Yes	Yes
0.59	56	Yes	Yes	Yes
0.61	19	Yes		
0.61	52	Yes		Yes
0.62	51			
0.65	11	Yes	Yes	Yes
0.65	28		Yes	Yes
0.66	13	Yes	Yes	Yes
0.67	2	Yes	Yes	
0.67	34	Yes		Yes
0.68	4		Yes	
0.68	15			Yes
0.68	39	Yes	Yes	Yes
0.68	49	Yes		
0.69	18	Yes	Yes	Yes
0.69	37	Yes		
0.69	38	Yes	Yes	
0.70	57			
0.70	59	Yes	Yes	
0.71	3	Yes	Yes	Yes
0.71	33	Yes		
0.71	50		Yes	Yes
0.72	7	Yes	Yes	
0.72	9	Yes	Yes	
0.72	26	Yes		
0.72	42			
0.72	43		Yes	
0.72	56	Yes		Yes
0.72	61		Yes	
0.72	62	Yes		
0.74	12	Yes		
0.74	63	Yes		Yes
0.75	14	Yes	Yes	Yes
0.75	23			
0.75	41			
0.75	53	Yes	Yes	Yes
0.75	55			
0.77	22	Yes	Yes	
0.77	30	Yes		
0.77	58	Yes		
0.78	17			
0.78	29	Yes		
0.78	32	Yes		
0.78	48	Yes	Yes	
0.79	20	Yes	Yes	Yes
0.80	16		Yes	Yes
0.81	25			
0.81	45	Yes		
0.82	24			
0.82	35	Yes		
0.88	1	Yes	Yes	
0.92	36	Yes		

Appendix 6

Table 1: Subjects with Cardiac Indications for Beta-Blocker Treatment

Subject ID	Age	Gender	Reg Smoker	Pack Year	BMI	IHD	BB Status
1	29.41	Female	Yes	37.5	31.2213039		
2	58.10	Female		0	23.7386621		Yes
3	79.26	Male		0	22.9590877	Yes	Yes
4	54.03	Male	Yes	82	23.7714286	Yes	Yes
5	76.11	Male	Yes	161.2	21.7554685	Yes	
6	79.13	Female		0	20.3125	Yes	
7	84.19	Female	Yes	10	25.432526	Yes	Yes
8	92.18	Male	Yes	63.75	25.7439446	Yes	
9	79.75	Male		0	23.6712536	Yes	Yes
11	72.78	Male	Yes	25.5	33.2621407	Yes	Yes
12	67.55	Male	Yes	22.5	25.9515571	Yes	Yes
13	62.16	Male	Yes	68	40.7454649	Yes	Yes
14	58.00	Male	Yes	50	31.7417889	Yes	Yes
15	76.22	Female		0	25.8396814		
17	64.61	Male		0	24.0569347	Yes	Yes
18	68.41	Female	Yes	42.5	34.6260388	Yes	
19	73.85	Female	Yes	52.5	22.6912406	Yes	Yes
20	58.20	Female	Yes	39.6	23.6652444		
21	74.93	Female	Yes	107.5	29.7441999	Yes	
23	70.83	Male	Yes	10	30.4779662	Yes	Yes
24	50.26	Male	Yes	3	24.535124	Yes	Yes
26	44.28	Male	Yes	26.25	30.7563678	Yes	Yes
27	44.41	Male	Yes	25	46.7128028	Yes	
28	68.59	Male	Yes	96	29.6495116	Yes	Yes
29	65.84	Male	Yes	15	35.4191263	Yes	Yes
31	68.31	Male	Yes	168	31.5179326	Yes	
32	73.11	Female	Yes	21	30.8596074	Yes	Yes
35	59.08	Male		0	35.321821	Yes	Yes
38	70.93	Male	Yes	37.5	31.2394144	Yes	Yes
40	73.48	Female	Yes	123.75	17.8980229		
41	62.40	Male	Yes	18.75	25.8166302	Yes	Yes
42	68.31	Male	Yes	21	25.308642	Yes	Yes
44	62.84	Male	Yes	118.25	25.2092014	Yes	
45	55.70	Female	Yes	1	31.245237		Yes
46	61.94	Male	Yes	228	35.2010451		Yes
49	75.11	Male		0	32.075913	Yes	Yes
50	59.62	Male	Yes	105	32.4100371	Yes	Yes
51	66.95	Male	Yes	51	25.6895619	Yes	Yes
52	80.61	Male	Yes	120	29.4887039	Yes	
53	58.47	Female		0	39.8961195	Yes	
54	65.02	Male	Yes	52.5	33.5765087	Yes	
55	49.62	Female	Yes	6.5	30.6361822	Yes	Yes
58	73.51	Male	Yes	1.75	27.1314118	Yes	Yes
59	50.33	Male	Yes	49.5	22.2222222	Yes	
60	65.02	Male		0	21.2009914		
62	72.02	Male	Yes	12.6	21.0667433	Yes	
63	52.97	Female	Yes	7.8	55.078125	Yes	
64	76.90	Female		0	39.0625	Yes	Yes

Table 2: Subjects with Cardiac Indications for Beta-Blocker Treatment – Respiratory Factors

Subject ID	Asthma	COPD	Inh Meds	BB Status	FER	Obstruction	BDR	Cough	Wheeze	Dyspnoea
1	Yes		Yes		0.88	No	No	Yes		Yes
2				Yes	0.69	Yes	Yes	Yes		Yes
3				Yes	0.71	No	No	Yes	Yes	Yes
4				Yes	0.68	Yes	No	Yes		
5		Yes						Yes		
6	Yes		Yes		0.57	Yes	Yes	Yes	Yes	Yes
7				Yes	0.74	No	No	Yes		Yes
8			Yes					Yes		Yes
9				Yes	0.72	No	No	Yes		Yes
11				Yes	0.65	Yes	No	Yes	Yes	Yes
12				Yes	0.74	No	No			Yes
13	Yes			Yes	0.66	Yes	No	Yes	Yes	Yes
14				Yes	0.75	No	No	Yes	Yes	
15			Yes		0.68	Yes	No		Yes	Yes
17				Yes	0.78	No	No			
18	Yes	Yes	Yes		0.69	Yes	No	Yes	Yes	Yes
19				Yes	0.61	Yes	Yes			Yes
20					0.79	No	No	Yes	Yes	Yes
21	Yes	Yes	Yes		0.61	Yes	No		Yes	Yes
23				Yes	0.75	No				Yes
24	Yes		Yes	Yes	0.82	No	No			
26				Yes	0.72	No	No			
27										Yes
28				Yes	0.65	Yes	No	Yes	Yes	
29				Yes	0.78	No	Yes			Yes
31					0.55	Yes	Yes		Yes	Yes
32				Yes	0.78	No	No			Yes
35				Yes	0.82	No	No			Yes
38				Yes	0.69	Yes	Yes			Yes
40	Yes		Yes		0.59	Yes	Yes	Yes	Yes	Yes
41				Yes	0.79	No	No			
42				Yes	0.72	No	No			
44	Yes	Yes	Yes		0.57	Yes	Yes	Yes		Yes
45				Yes	0.81	No	No			Yes
46	Yes		Yes	Yes	0.63	Yes	Yes	Yes	Yes	Yes
49				Yes	0.68	Yes	No			Yes
50	Yes		Yes	Yes	0.71	No	No	Yes	Yes	Yes
51				Yes	0.62	Yes	No			
52					0.61	Yes	No		Yes	Yes
53	Yes				0.75	No	No	Yes	Yes	Yes
54					0.45	Yes	Yes	Yes		Yes
55	Yes			Yes	0.79	No	No			
58		Yes		Yes	0.77	No	No			Yes
59					0.7	No	No	Yes		Yes
60					0.67	Yes	No	Yes		Yes
62			Yes		0.72	No	No			Yes
63	Yes		Yes		0.74	No	No		Yes	Yes
64				Yes						Yes

Appendix 7

FOLLOW-UP BETA-BLOCKERS, AIRWAYS DISEASE SURVEY: Part 5

Subject Number: ☐☐

Hospital MRN: ☐☐☐☐☐☐

SURVEY No. ☐

Date ☐☐/☐☐/☐☐

Please read the accompanying letter first and then answer the questions below by putting a number or tick ✓ in the appropriate box.

1. At present, do you use any puffer or nebuliser?

Yes ☐ No ☐

If yes, how many times per day would you use an extra puffer or nebuliser dose (in addition to any <u>regular</u> daily inhaled medication) for relief of breathlessness or wheeze? ***(Only tick one box for this question)***

No extra use of Puffer or Nebuliser	☐
1-2 extra Puffs or Nebuliser doses	☐
3-5 extra Puffs or Nebuliser doses	☐
More than 5 extra Puffs or Nebuliser doses	☐

2. ***Please tick or put a number in just one box for the number of times, and then (if applicable) record the number of hospitalisations for parts (a), (b) and (c).***

Since your last contact with the Study investigators, on __/__/2004,

(a) How many times have you sought medical attention for <u>cough, breathing difficulty or wheeze</u>? ***(include presentations to hospital)***

In 2004 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2005 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2006 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2007 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

(b) How many times have you sought medical attention for chest pain, angina, palpitations or fluid retention? ***(include presentations to hospital)***

In 2004, None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2005, None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2006, None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2007, None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

(c) How many times have you been given a course of antibiotics or prednisone (prednisolone/cortisone) because of difficulty breathing? ***(include presentations to hospital)***

In 2004 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2005 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2006 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

In 2007 None☐ 1-2☐ 3-5☐ 6-10☐ 10+☐ estimated number☐☐

Number of times that hospital admission was required _____

3 (a). Please provide a list of your current regular medications ***(don't forget inhaled medications!)****:*

_____
_____
_____
_____
_____
_____
_____

4. Please provide details of your current smoking status

(a) Never smoked ☐

(b) Former smoker ☐

(c) Current smoker ☐

5. Please supply your local doctor (or general practitioner)'s details. ***(If you don't have a regular GP, please provide the details of the medical practice that you most often frequent)***

(a) Name_____

(b) Practice address_____

(c) Practice telephone or email contact_____

If you wish to add more information please write in the space provided at the end of this survey (overleaf).

Thank you for your time, effort and ongoing participation in this research project.

Table 1: Long Term Beta-Blocker Exposure and Lung Function

ID[1]	Visit	Duration (Year)	Cum BB	Cum Steroid	FER	% FVC	% FEV1	Age[2] (Year)	Gender	BMI[2]	Pack Years
1	1	0	1	0	0.6784	96	82	-10.82661	Male	-4.483396	82
1	2	0.008219	1	0	0.7405079	85	79	-10.82661	Male	-4.483396	82
1	3	0.5	2	0	0.6918892	88	83	-10.82661	Male	-4.483396	82
1	4	1	3	0	0.6699623	92	86	-10.82661	Male	-4.483396	82
2	1	0	0	0	0.8663793	114	110	-35.44661	Female	2.96648	37.5
2	2	0.008219	0	0	0.8783886	95	98	-35.44661	Female	2.96648	37.5
2	3	0.5	0	0	0.8735632	75	82	-35.44661	Female	2.96648	37.5
2	4	1	0	2	0.8346891	88	93	-35.44661	Female	2.96648	37.5
3	1	0	1	0	0.6905	49	43	-6.756612	Female	-4.516162	0
3	2	0.008219	1	0	0.6668527	52	44	-6.756612	Female	-4.516162	0
3	3	0.5	2	0	0.7244898	71	69	-6.756612	Female	-4.516162	0
3	4	1	3	0	0.7016976	72	68	-6.756612	Female	-4.516162	0
4	1	0	1	0	0.7071	48	45	14.40339	Male	-5.295737	0
4	2	0.008219	1	0				14.40339	Male	-5.295737	0
4	3	0.5	2	0	0.6917337	54	57	14.40339	Male	-5.295737	0
4	4	1	3	0	0.6360656	57	56	14.40339	Male	-5.295737	0
5	1	0	0	1	0.5701	63	49	14.27339	Female	-7.942325	0
5	2	0.008219	0	1	0.6126543	72	60	14.27339	Female	-7.942325	0
5	3	0.5	0	1	0.6223022	75	68	14.27339	Female	-7.942325	0
5	4	1	0	2	0.5624212	76	65	14.27339	Female	-7.942325	0
6	1	0	1	0	0.7355199	100	102	19.33339	Female	-2.822301	10
6	2	0.008219	1	0	0.7407278	101	97	19.33339	Female	-2.822301	10
6	3	0.5	2	0	0.7112181	95	99	19.33339	Female	-2.822301	10
6	4	1	3	0	0.677706	88	88	19.33339	Female	-2.822301	10
7	1	0	1	0	0.709637	82	85	14.89339	Male	-4.58357	0
7	2	0.008219	1	0	0.7007874	90	86	14.89339	Male	-4.58357	0
7	3	0.5	2	0	0.7090717	93	102	14.89339	Male	-4.58357	0
7	4	1	3	0	0.714031	95	107	14.89339	Male	-4.58357	0
8	1	0	1	0	0.7441	89	85	2.693393	Male	-2.303269	22.5
8	2	0.008219	1	0				2.693393	Male	-2.303269	22.5
8	3	0.5	2	0	0.7155101	91	95	2.693393	Male	-2.303269	22.5
8	4	1	3	0	0.7357143	92	101	2.693393	Male	-2.303269	22.5
9	1	0	1	0	0.663	58	49	-2.69661	Male	12.49064	68
9	2	0.008219	1	0	0.688067	66	66	-2.69661	Male	12.49064	68
9	3	0.5	2	0	0.7007199	73	72	-2.69661	Male	12.49064	68
9	4	1	3	0				-2.69661	Male	12.49064	68
10	1	0	1	0	0.7517	85	81	-6.85661	Male	3.486964	50
10	2	0.008219	1	0	0.7484904	58	80	-6.85661	Male	3.486964	50
10	3	0.5	2	0				-6.85661	Male	3.486964	50
10	4	1	3	0				-6.85661	Male	3.486964	50
11	1	0	0	0	0.6815	82	74	11.36339	Female	-2.415143	0
11	2	0.008219	0	0	0.7502756	82	90	11.36339	Female	-2.415143	0
11	3	0.5	0	0	0.7305136	74	80	11.36339	Female	-2.415143	0
11	4	1	0	1	0.677947	81	81	11.36339	Female	-2.415143	0
12	1	0	0	0	0.8027	89	88	-18.93661	Male	-0.5225247	7
12	2	0.008219	0	0	0.8072262	92	91	-18.93661	Male	-0.5225247	7
12	3	0.5	0	0				-18.93661	Male	-0.5225247	7
12	4	1	0	0				-18.93661	Male	-0.5225247	7
13	1	0	0	2	0.6917	72	64	3.553394	Female	6.371217	42.5
13	2	0.008219	0	4	0.6825476	68	69	3.553394	Female	6.371217	42.5
13	3	0.5	1	5	0.674175	67	66	3.553394	Female	6.371217	42.5
13	4	1	2	5				3.553394	Female	6.371217	42.5
14	1	0	1	0	0.5914832	73	63	8.993388	Female	-5.563586	52.5
14	2	0.008219	1	0	0.6089239	69	58	8.993388	Female	-5.563586	52.5
14	3	0.5	2	0	0.5965225	68	57	8.993388	Female	-5.563586	52.5
14	4	1	3	0	0.6086547	64	55	8.993388	Female	-5.563586	52.5
15	1	0	0	0	0.769419	84	90	-6.65661	Female	-4.58958	39.6
15	2	0.008219	0	0				-6.65661	Female	-4.58958	39.6
15	3	0.5	1	0	0.7074647	89	84	-6.65661	Female	-4.58958	39.6
15	4	1	2	0	0.709291	93	89	-6.65661	Female	-4.58958	39.6

ID[1]	Visit	Duration (Year)	Cum. BB	Cum. Steroid	FER	% FVC	% FEV1	Age[2] (Year)	Gender	BMI[2]	Pack Years
16	1	0	0	0	0.6122	50	43	10.07339	Female	1.489375	107.5
16	2	0.008219	0	0	0.5818635	49	41	10.07339	Female	1.489375	107.5
16	3	0.5	0	0	0.6076002	58	67	10.07339	Female	1.489375	107.5
16	4	1	0	0	0.6705069	62	60	10.07339	Female	1.489375	107.5
17	1	0	1	0	0.766	88	91	-4.166612	Female	1.502761	7
17	2	0.008219	1	0	0.7761492	94	99	-4.166612	Female	1.502761	7
17	3	0.5	1	0	0.7409152	94	95	-4.166612	Female	1.502761	7
17	4	1	1	0	0.7700743	90	94	-4.166612	Female	1.502761	7
18	1	0	1	0	0.7465	76	83	5.973392	Male	2.223144	10
18	2	0.008219	1	0				5.973392	Male	2.223144	10
18	3	0.5	2	0				5.973392	Male	2.223144	10
18	4	1	3	1	0.6815227	86	87	5.973392	Male	2.223144	10
19	1	0	0	0	0.8104	102	109	-19.04661	Male	-4.255366	0
19	2	0.008219	0	0				-19.04661	Male	-4.255366	0
19	3	0.5	0	0	0.7134524	112	108	-19.04661	Male	-4.255366	0
19	4	1	0	0	0.7459283	111	111	-19.04661	Male	-4.255366	0
20	1	0	1	0	0.7551	111	113	-20.57661	Male	2.501542	26.25
20	2	0.008219	1	0	0.7157746	107	102	-20.57661	Male	2.501542	26.25
20	3	0.5	2	0	0.7387521	115	114	-20.57661	Male	2.501542	26.25
20	4	1	2	0				-20.57661	Male	2.501542	26.25
21	1	0	1	0	0.6525	108	104	3.733386	Male	1.394689	96
21	2	0.008219	1	0	0.740433	113	103	3.733386	Male	1.394689	96
21	3	0.5	2	0				3.733386	Male	1.394689	96
21	4	1	3	0				3.733386	Male	1.394689	96
22	1	0	1	0	0.7654406	91	97	0.9833862	Male	7.164304	15
22	2	0.008219	1	0	0.6980269	85	93	0.9833862	Male	7.164304	15
22	3	0.5	2	0	0.7779764	89	97	0.9833862	Male	7.164304	15
22	4	1	3	0	0.795128	94	105	0.9833862	Male	7.164304	15
23	1	0	0	0	0.7698	100	102	-14.13661	Female	2.947742	18.75
23	2	0.008219	0	0				-14.13661	Female	2.947742	18.75
23	3	0.5	0	2	0.7965162	86	91	-14.13661	Female	2.947742	18.75
23	4	1	0	2	0.849232	74	87	-14.13661	Female	2.947742	18.75
24	1	0	0	0	0.5708	43	36	3.453387	Male	3.263107	168
24	2	0.008219	0	0	0.5496838	47	38	3.453387	Male	3.263107	168
24	3	0.5	1	0				3.453387	Male	3.263107	168
24	4	1	2	0				3.453387	Male	3.263107	168
25	1	0	0	0	0.7069	104	112	11.21339	Male	-4.161853	47
25	2	0.008219	0	0				11.21339	Male	-4.161853	47
25	3	0.5	0	0	0.7292052	89	99	11.21339	Male	-4.161853	47
25	4	1	0	0	0.7304066	94	106	11.21339	Male	-4.161853	47
26	1	0	0	0	0.6735	98	87	-25.17661	Male	-5.846038	0.6
26	2	0.008219	0	0				-25.17661	Male	-5.846038	0.6
26	3	0.5	0	0	0.660835	98	85	-25.17661	Male	-5.846038	0.6
26	4	1	0	0	0.6872815	89	81	-25.17661	Male	-5.846038	0.6
27	1	0	1	0	0.8662198	69	85	-5.776608	Male	7.066995	0
27	2	0.008219	1	0	0.8209893	77	90	-5.776608	Male	7.066995	0
27	3	0.5	2	0	0.7785252	81	90	-5.776608	Male	7.066995	0
27	4	1	3	0	0.7830994	74	83	-5.776608	Male	7.066995	0
28	1	0	0	0	0.7319	96	101	9.123393	Female	-7.42483	7.5
28	2	0.008219	0	0	0.6934546	104	103	9.123393	Female	-7.42483	7.5
28	3	0.5	0	0	0.6630435	112	107	9.123393	Female	-7.42483	7.5
28	4	1	0	0	0.7492224	99	107	9.123393	Female	-7.42483	7.5
29	1	0	1	0	0.6888	98	99	6.07339	Male	2.98459	37.5
29	2	0.008219	1	0	0.7190769	93	98	6.07339	Male	2.98459	37.5
29	3	0.5	1	0				6.07339	Male	2.98459	37.5
29	4	1	1	0				6.07339	Male	2.98459	37.5
30	1	0	0	0	0.6838	71	73	17.55339	Female	8.373689	0
30	2	0.008219	0	0				17.55339	Female	8.373689	0
30	3	0.5	0	0	0.4394904	116	76	17.55339	Female	8.373689	0
30	4	1	0	0	0.709893	65	74	17.55339	Female	8.373689	0
31	1	0	1	0	0.7871323	105	116	-2.456609	Male	-2.438193	18.75
31	2	0.008219	1	0	0.7462977	104	109	-2.456609	Male	-2.438193	18.75
31	3	0.5	2	0	0.7096774	107	107	-2.456609	Male	-2.438193	18.75
31	4	1	3	0	0.7426013	102	107	-2.456609	Male	-2.438193	18.75

ID[1]	Visit	Duration (Year)	Cum. BB	Cum. Steroid	FER	% FVC	% FEV1	Age[2] (Year)	Gender	BMI[2]	Pack Years
32	1	0	1	0	0.7243	72	77	3.453387	Male	-2.946181	21
32	2	0.008219	1	0	0.7071913	76	86	3.453387	Male	-2.946181	21
32	3	0.5	2	0	0.7174245	71	78	3.453387	Male	-2.946181	21
32	4	1	3	0	0.7219235	74	79	3.453387	Male	-2.946181	21
33	1	0	0	0	0.814741	101	127	16.96339	Female	-5.588159	0
33	2	0.008219	0	0	0.7191316	111	123	16.96339	Female	-5.588159	0
33	3	0.5	0	0	0.7765641	88	115	16.96339	Female	-5.588159	0
33	4	1	0	0	0.7289547	104	122	16.96339	Female	-5.588159	0
34	1	0	0	4	0.5681	64	51	-2.01661	Male	-3.045624	118.25
34	2	0.008219	0	4	0.5177278	66	48	-2.01661	Male	-3.045624	118.25
34	3	0.5	0	7				-2.01661	Male	-3.045624	118.25
34	4	1	0	8				-2.01661	Male	-3.045624	118.25
35	1	0	1	0	0.8067	115	123	-9.15661	Female	2.990413	1
35	2	0.008219	1	0				-9.15661	Female	2.990413	1
35	3	0.5	2	0				-9.15661	Female	2.990413	1
35	4	1	3	0	0.8019518	111	121	-9.15661	Female	2.990413	1
36	1	0	1	1	0.6284	63	55	-2.916611	Male	6.946221	228
36	2	0.008219	1	1	0.5854988	62	50	-2.916611	Male	6.946221	228
36	3	0.5	2	1	0.6864511	64	61	-2.916611	Male	6.946221	228
36	4	1	3	1	0.5882968	50	42	-2.916611	Male	6.946221	228
37	1	0	0	0	0.5966425	98	91	15.75339	Male	1.233878	120
37	2	0.008219	0	0	0.6060321	95	89	15.75339	Male	1.233878	120
37	3	0.5	0	0				15.75339	Male	1.233878	120
37	4	1	0	0				15.75339	Male	1.233878	120
38	1	0	0	0	0.7548	68	69	-6.386609	Female	11.64129	0
38	2	0.008219	0	0	0.7688194	78	81	-6.386609	Female	11.64129	0
38	3	0.5	0	0	0.7443946	72	72	-6.386609	Female	11.64129	0
38	4	1	0	0	0.7451254	70	70	-6.386609	Female	11.64129	0
39	1	0	0	0	0.45	45	30	0.1633865	Male	5.321687	52.5
39	2	0.008219	0	0	0.3927975	49	28	0.1633865	Male	5.321687	52.5
39	3	0.5	0	1	0.4411765	67	43	0.1633865	Male	5.321687	52.5
39	4	1	0	1	0.4282568	69	43	0.1633865	Male	5.321687	52.5
40	1	0	1	1	0.7947	96	100	-15.23661	Female	2.381356	6.5
40	2	0.008219	1	1	0.7459038	101	99	-15.23661	Female	2.381356	6.5
40	3	0.5	1	1	0.7991968	95	100	-15.23661	Female	2.381356	6.5
40	4	1	1	4	0.7793083	93	96	-15.23661	Female	2.381356	6.5
41	1	0	0	0	0.6988	82	80	-9.536611	Male	-4.205482	1.95
41	2	0.008219	0	0				-9.536611	Male	-4.205482	1.95
41	3	0.5	0	0	0.6831152	87	84	-9.536611	Male	-4.205482	1.95
41	4	1	0	0	0.6889797	87	85	-9.536611	Male	-4.205482	1.95
42	1	0	0	0	0.783587	39	38	0.1633865	Male	-7.053834	0
42	2	0.008219	0	0				0.1633865	Male	-7.053834	0
42	3	0.5	0	0				0.1633865	Male	-7.053834	0
42	4	1	0	0				0.1633865	Male	-7.053834	0
43	1	0	1	0	0.7151	102	97	-10.14661	Female	1.71396	0
43	2	0.008219	1	0	0.7705314	100	104	-10.14661	Female	1.71396	0
43	3	0.5	1	0	0.7592782	103	105	-10.14661	Female	1.71396	0
43	4	1	1	0	0.8047957	104	112	-10.14661	Female	1.71396	0
44	1	0	0	0	0.7208	97	106	7.163386	Male	-7.188081	12.6
44	2	0.008219	0	0				7.163386	Male	-7.188081	12.6
44	3	0.5	0	0				7.163386	Male	-7.188081	12.6
44	4	1	1	0				7.163386	Male	-7.188081	12.6
45	1	0	0	0	0.6964	66	63	-14.52661	Male	-6.032601	49.5
45	2	0.008219	0	0	0.7748567	59	63	-14.52661	Male	-6.032601	49.5
45	3	0.5	0	0				-14.52661	Male	-6.032601	49.5
45	4	1	0	0				-14.52661	Male	-6.032601	49.5
46	1	0	0	0				16.09339	Male	1.260947	65.55
46	2	0.008219	0	1	0.5789474	63	46	16.09339	Male	1.260947	65.55
46	3	0.5	0	1	0.6397694	51	53	16.09339	Male	1.260947	65.55
46	4	1	0	1				16.09339	Male	1.260947	65.55
47	1	0	1	0				-14.59661	Male	-3.719701	3
47	2	0.008219	1	0	0.8168686	78	87	-14.59661	Male	-3.719701	3
47	3	0.5	2	0	0.7612422	85	88	-14.59661	Male	-3.719701	3
47	4	1	2	0	0.7587903	87	89	-14.59661	Male	-3.719701	3

ID[1]	Visit	Duration (Year)	Cum. BB	Cum. Steroid	FER	% FVC	% FEV1	Age[2] (Year)	Gender	BMI[2]	Pack Years
48	1	0	1	0				2.093387	Male	-2.565263	51
48	2	0.008219	1	0	0.6213115	88	79	2.093387	Male	-2.565263	51
48	3	0.5	2	0	0.6395953	83	79	2.093387	Male	-2.565263	51
48	4	1	3	0	0.6137648	85	78	2.093387	Male	-2.565263	51
49	1	0	0	0				2.973392	Male	-2.175853	82.5
49	2	0.008219	0	0	0.7155664	66	68	2.973392	Male	-2.175853	82.5
49	3	0.5	0	0	0.6665434	67	73	2.973392	Male	-2.175853	82.5
49	4	1	0	0				2.973392	Male	-2.175853	82.5
50	1	0	0	0				3.89339	Male	-5.415317	0
50	2	0.008219	0	0				3.89339	Male	-5.415317	0
50	3	0.5	0	0	0.7574204	82	92	3.89339	Male	-5.415317	0
50	4	1	0	0	0.686618	91	84	3.89339	Male	-5.415317	0
51	1	0	1	0	0.6478	106	89	7.923388	Male	5.007314	25.5
51	2	0.008219	1	0				7.923388	Male	5.007314	25.5
51	3	0.5	2	0				7.923388	Male	5.007314	25.5
51	4	1	3	0				7.923388	Male	5.007314	25.5
52	1	0	1	0	0.7809	83	93	-0.2466095	Male	-4.19789	0
52	2	0.008219	1	0				-0.2466095	Male	-4.19789	0
52	3	0.5	2	0				-0.2466095	Male	-4.19789	0
52	4	1	3	0				-0.2466095	Male	-4.19789	0
53	1	0	1	0	0.7814	96	107	8.25339	Female	2.604783	21
53	2	0.008219	1	0				8.25339	Female	2.604783	21
53	3	0.5	2	0				8.25339	Female	2.604783	21
53	4	1	3	0				8.25339	Female	2.604783	21
54	1	0	0	0	0.9239905	65	77	11.29339	Female	-7.350629	5
54	2	0.008219	0	0				11.29339	Female	-7.350629	5
54	3	0.5	0	0				11.29339	Female	-7.350629	5
54	4	1	0	0				11.29339	Female	-7.350629	5
55	1	0	0	1	0.5882353	54	46	8.623393	Female	-10.3568	123.75
55	2	0.008219	0	1				8.623393	Female	-10.3568	123.75
55	3	0.5	0	1				8.623393	Female	-10.3568	123.75
55	4	1	0	1				8.623393	Female	-10.3568	123.75
56	1	0	1	0	0.6825067	122	127	10.25339	Male	3.821088	0
56	2	0.008219	1	0				10.25339	Male	3.821088	0
56	3	0.5	1	0				10.25339	Male	3.821088	0
56	4	1	1	0				10.25339	Male	3.821088	0
57	1	0	1	0	0.7079	85	84	-5.236611	Male	4.155213	105
57	2	0.008219	1	0				-5.236611	Male	4.155213	105
57	3	0.5	2	0				-5.236611	Male	4.155213	105
57	4	1	3	0				-5.236611	Male	4.155213	105
58	1	0	1	0	0.7415105	75	87	8.653392	Male	-1.123412	1.75
58	2	0.008219	1	0				8.653392	Male	-1.123412	1.75
58	3	0.5	2	0				8.653392	Male	-1.123412	1.75
58	4	1	3	0				8.653392	Male	-1.123412	1.75
59	1	0	0	0	0.7399	113	111	-11.88661	Female	26.8233	7.8
59	2	0.008219	0	0				-11.88661	Female	26.8233	7.8
59	3	0.5	0	0				-11.88661	Female	26.8233	7.8
59	4	1	0	0				-11.88661	Female	26.8233	7.8

[1] Subject ID matched on medical record number, unique to Appendix 7: Tables 1 and 2

[2]Expressed as subject population mean subtracted from individual subject value

Table 2: Long Term Beta-Blocker Exposure and Respiratory Symptoms

ID[1]	Visit	Duration (year)	Cum. BB	Cum. Steroid	Age[2] (Year)	Gender	BMI[2]	Pack Years	Wheeze	Cough	Sputum	SOB
1	1	0	1	0	-10.82661	Male	-4.483396	82	1	5	3	0
1	2	0.008219	1	0	-10.82661	Male	-4.483396	82	1	5	3	0
1	3	0.5	2	0	-10.82661	Male	-4.483396	82	1	5	2	0
1	4	1	3	0	-10.82661	Male	-4.483396	82	1	5	3	0
2	1	0	0	0	-35.44661	Female	2.96648	37.5	1	5	2	8
2	2	0.008219	0	0	-35.44661	Female	2.96648	37.5	1	1	1	5
2	3	0.5	0	0	-35.44661	Female	2.96648	37.5	0	1	0	1
2	4	1	0	2	-35.44661	Female	2.96648	37.5	1	1	0	1
3	1	0	1	0	-6.756612	Female	-4.516162	0	0	8	0	9
3	2	0.008219	1	0	-6.756612	Female	-4.516162	0	0	5	0	7
3	3	0.5	2	0	-6.756612	Female	-4.516162	0	0	5	0	3
3	4	1	3	0	-6.756612	Female	-4.516162	0	0	0	0	7
4	1	0	1	0	14.40339	Male	-5.295737	0	0	7	3	5
4	2	0.008219	1	0	14.40339	Male	-5.295737	0	0	7	5	5
4	3	0.5	2	0	14.40339	Male	-5.295737	0	0	7	3	5
4	4	1	3	0	14.40339	Male	-5.295737	0	0	4	9	5
5	1	0	0	1	14.27339	Female	-7.942325	0	1	2	1	2
5	2	0.008219	0	1	14.27339	Female	-7.942325	0	1	2	1	2
5	3	0.5	0	1	14.27339	Female	-7.942325	0	1	2	1	2
5	4	1	0	2	14.27339	Female	-7.942325	0	1	2	1	2
6	1	0	1	0	19.33339	Female	-2.822301	10	0	5	3	7
6	2	0.008219	1	0	19.33339	Female	-2.822301	10	0	5	3	7
6	3	0.5	2	0	19.33339	Female	-2.822301	10	0	2	2	3
6	4	1	3	0	19.33339	Female	-2.822301	10	0	2	3	3
7	1	0	1	0	14.89339	Male	-4.58357	0	0	5	0	7
7	2	0.008219	1	0	14.89339	Male	-4.58357	0	0	1	0	3
7	3	0.5	2	0	14.89339	Male	-4.58357	0	0	2	0	3
7	4	1	3	0	14.89339	Male	-4.58357	0	0	3	0	3
8	1	0	1	0	2.693393	Male	-2.303269	22.5	0	1	1	9
8	2	0.008219	1	0	2.693393	Male	-2.303269	22.5	0	8	5	9
8	3	0.5	2	0	2.693393	Male	-2.303269	22.5	0	1	1	5
8	4	1	3	0	2.693393	Male	-2.303269	22.5	0	1	2	0
9	1	0	1	0	-2.69661	Male	12.49064	68	3	1	1	5
9	2	0.008219	1	0	-2.69661	Male	12.49064	68	3	1	1	5
9	3	0.5	2	0	-2.69661	Male	12.49064	68	5	1	4	5
9	4	1	3	0	-2.69661	Male	12.49064	68				
10	1	0	1	0	-6.85661	Male	3.486964	50	7	3	3	2
10	2	0.008219	1	0	-6.85661	Male	3.486964	50	7	3	3	2
10	3	0.5	2	0	-6.85661	Male	3.486964	50				
10	4	1	3	0	-6.85661	Male	3.486964	50				
11	1	0	0	0	11.36339	Female	-2.415143	0	6	2	1	8
11	2	0.008219	0	0	11.36339	Female	-2.415143	0	5	2	1	7
11	3	0.5	0	0	11.36339	Female	-2.415143	0	3	2	1	6
11	4	1	0	1	11.36339	Female	-2.415143	0	2	2	0	5
12	1	0	0	0	-18.93661	Male	-0.5225247	7	1	2	2	1
12	2	0.008219	0	0	-18.93661	Male	-0.5225247	7	1	2	2	1
12	3	0.5	0	0	-18.93661	Male	-0.5225247	7				
12	4	1	0	0	-18.93661	Male	-0.5225247	7				
13	1	0	0	2	3.553394	Female	6.371217	42.5	10	10	1	8
13	2	0.008219	0	4	3.553394	Female	6.371217	42.5	7	10	1	8
13	3	0.5	1	5	3.553394	Female	6.371217	42.5	7	8	1	8
13	4	1	2	5	3.553394	Female	6.371217	42.5				
14	1	0	1	0	8.993388	Female	-5.563586	52.5	0	0	0	2
14	2	0.008219	1	0	8.993388	Female	-5.563586	52.5	0	0	0	1
14	3	0.5	2	0	8.993388	Female	-5.563586	52.5	0	0	1	2
14	4	1	3	0	8.993388	Female	-5.563586	52.5	0	0	1	1
15	1	0	0	0	-6.65661	Female	-4.58958	39.6	3	5	2	1
15	2	0.008219	0	0	-6.65661	Female	-4.58958	39.6				
15	3	0.5	1	0	-6.65661	Female	-4.58958	39.6	3	5	2	1
15	4	1	2	0	-6.65661	Female	-4.58958	39.6	3	5	2	1

ID[1]	Visit	Duration (year)	Cum. BB	Cum. Steroid	Age[2] (Year)	Gender	BMI[2]	Pack Years	Wheeze	Cough	Sputum	SOB
16	1	0	0	0	10.07339	Female	1.489375	107.5	8	3	1	10
16	2	0.008219	0	0	10.07339	Female	1.489375	107.5	5	2	0	5
16	3	0.5	0	0	10.07339	Female	1.489375	107.5	1	1	0	0
16	4	1	0	0	10.07339	Female	1.489375	107.5	5	3	1	5
17	1	0	1	0	-4.166612	Female	1.502761	7	0	6	1	7
17	2	0.008219	1	0	-4.166612	Female	1.502761	7	0	4	1	8
17	3	0.5	1	0	-4.166612	Female	1.502761	7	0	0	0	2
17	4	1	1	0	-4.166612	Female	1.502761	7	0	0	0	0
18	1	0	1	0	5.973392	Male	2.223144	10	2	2	0	2
18	2	0.008219	1	0	5.973392	Male	2.223144	10	2	2	0	6
18	3	0.5	2	0	5.973392	Male	2.223144	10				
18	4	1	3	1	5.973392	Male	2.223144	10	0	5	5	4
19	1	0	0	0	-19.04661	Male	-4.255366	0	0	3	2	1
19	2	0.008219	0	0	-19.04661	Male	-4.255366	0				
19	3	0.5	0	0	-19.04661	Male	-4.255366	0	1	5	3	2
19	4	1	0	0	-19.04661	Male	-4.255366	0	0	1	7	1
20	1	0	1	0	-20.57661	Male	2.501542	26.25	1	3	3	1
20	2	0.008219	1	0	-20.57661	Male	2.501542	26.25	1	3	3	1
20	3	0.5	2	0	-20.57661	Male	2.501542	26.25	1	3	2	1
20	4	1	2	0	-20.57661	Male	2.501542	26.25				
21	1	0	1	0	3.733386	Male	1.394689	96	2	3	2	0
21	2	0.008219	1	0	3.733386	Male	1.394689	96	2	3	2	0
21	3	0.5	2	0	3.733386	Male	1.394689	96				
21	4	1	3	0	3.733386	Male	1.394689	96				
22	1	0	1	0	0.9833862	Male	7.164304	15	5	1	5	6
22	2	0.008219	1	0	0.9833862	Male	7.164304	15	5	1	5	6
22	3	0.5	2	0	0.9833862	Male	7.164304	15	5	1	3	6
22	4	1	3	0	0.9833862	Male	7.164304	15	8	6	8	6
23	1	0	0	0	-14.13661	Female	2.947742	18.75	3	1	1	5
23	2	0.008219	0	0	-14.13661	Female	2.947742	18.75	0	1	1	4
23	3	0.5	0	2	-14.13661	Female	2.947742	18.75	1	1	1	0
23	4	1	0	2	-14.13661	Female	2.947742	18.75	3	1	1	3
24	1	0	0	0	3.453387	Male	3.263107	168	0	4	0	10
24	2	0.008219	0	0	3.453387	Male	3.263107	168	0	1	0	6
24	3	0.5	1	0	3.453387	Male	3.263107	168				
24	4	1	2	0	3.453387	Male	3.263107	168				
25	1	0	0	0	11.21339	Male	-4.161853	47	0	1	2	0
25	2	0.008219	0	0	11.21339	Male	-4.161853	47				
25	3	0.5	0	0	11.21339	Male	-4.161853	47	0	2	3	0
25	4	1	0	0	11.21339	Male	-4.161853	47	0	1	2	0
26	1	0	0	0	-25.17661	Male	-5.846038	0.6	3	2	1	5
26	2	0.008219	0	0	-25.17661	Male	-5.846038	0.6	3	2	1	2
26	3	0.5	0	0	-25.17661	Male	-5.846038	0.6	3	6	2	2
26	4	1	0	0	-25.17661	Male	-5.846038	0.6	4	4	3	2
27	1	0	1	0	-5.776608	Male	7.066995	0	10	7	3	10
27	2	0.008219	1	0	-5.776608	Male	7.066995	0	1	1	2	7
27	3	0.5	2	0	-5.776608	Male	7.066995	0	1	1	1	5
27	4	1	3	0	-5.776608	Male	7.066995	0	1	1	1	7
28	1	0	0	0	9.123393	Female	-7.42483	7.5	0	1	0	1
28	2	0.008219	0	0	9.123393	Female	-7.42483	7.5	0	1	0	1
28	3	0.5	0	0	9.123393	Female	-7.42483	7.5	0	3	0	1
28	4	1	0	0	9.123393	Female	-7.42483	7.5	0	5	0	1
29	1	0	1	0	6.07339	Male	2.98459	37.5	0	2	2	8
29	2	0.008219	1	0	6.07339	Male	2.98459	37.5	0	2	2	0
29	3	0.5	1	0	6.07339	Male	2.98459	37.5				
29	4	1	1	0	6.07339	Male	2.98459	37.5	0	1	1	0
30	1	0	0	0	17.55339	Female	8.373689	0	2	5	2	6
30	2	0.008219	0	0	17.55339	Female	8.373689	0	1	0	0	4
30	3	0.5	0	0	17.55339	Female	8.373689	0	1	3	0	3
30	4	1	0	0	17.55339	Female	8.373689	0	0	4	0	3
31	1	0	1	0	-2.456609	Male	-2.438193	18.75	0	0	0	0
31	2	0.008219	1	0	-2.456609	Male	-2.438193	18.75	0	0	0	0
31	3	0.5	2	0	-2.456609	Male	-2.438193	18.75	0	1	0	0
31	4	1	3	0	-2.456609	Male	-2.438193	18.75	0	0	0	0

ID[1]	Visit	Duration (year)	Cum. BB	Cum. Steroid	Age[2] (Year)	Gender	BMI[2]	Pack Years	Wheeze	Cough	Sputum	SOB
32	1	0	1	0	3.453387	Male	-2.946181	21	4	0	2	8
32	2	0.008219	1	0	3.453387	Male	-2.946181	21	0	0	2	2
32	3	0.5	2	0	3.453387	Male	-2.946181	21	0	0	2	2
32	4	1	3	0	3.453387	Male	-2.946181	21	0	0	0	2
33	1	0	0	0	16.96339	Female	-5.588159	0	0	5	0	7
33	2	0.008219	0	0	16.96339	Female	-5.588159	0	0	8	0	8
33	3	0.5	0	0	16.96339	Female	-5.588159	0	0	1	0	3
33	4	1	0	0	16.96339	Female	-5.588159	0	0	1	0	3
34	1	0	0	4	-2.01661	Male	-3.045624	118.25	2	3	2	9
34	2	0.008219	0	4	-2.01661	Male	-3.045624	118.25	0	0	0	7
34	3	0.5	0	7	-2.01661	Male	-3.045624	118.25				
34	4	1	0	8	-2.01661	Male	-3.045624	118.25				
35	1	0	1	0	-9.15661	Female	2.990413	1	0	0	0	9
35	2	0.008219	1	0	-9.15661	Female	2.990413	1				
35	3	0.5	2	0	-9.15661	Female	2.990413	1				
35	4	1	3	0	-9.15661	Female	2.990413	1	0	0	0	2
36	1	0	1	1	-2.916611	Male	6.946221	228	2	5	6	5
36	2	0.008219	1	1	-2.916611	Male	6.946221	228	2	6	6	2
36	3	0.5	2	1	-2.916611	Male	6.946221	228	5	5	7	5
36	4	1	3	1	-2.916611	Male	6.946221	228	7	8	5	9
37	1	0	0	0	15.75339	Male	1.233878	120	4	8	10	4
37	2	0.008219	0	0	15.75339	Male	1.233878	120	2	1	1	1
37	3	0.5	0	0	15.75339	Male	1.233878	120				
37	4	1	0	0	15.75339	Male	1.233878	120				
38	1	0	0	0	-6.386609	Female	11.64129	0	6	6	3	5
38	2	0.008219	0	0	-6.386609	Female	11.64129	0	6	4	0	5
38	3	0.5	0	0	-6.386609	Female	11.64129	0	6	6	3	5
38	4	1	0	0	-6.386609	Female	11.64129	0	4	4	0	5
39	1	0	0	0	0.1633865	Male	5.321687	52.5	1	1	1	10
39	2	0.008219	0	0	0.1633865	Male	5.321687	52.5	1	1	1	5
39	3	0.5	0	1	0.1633865	Male	5.321687	52.5	2	7	5	5
39	4	1	0	1	0.1633865	Male	5.321687	52.5	2	1	2	4
40	1	0	1	1	-15.23661	Female	2.381356	6.5	0	0	0	1
40	2	0.008219	1	1	-15.23661	Female	2.381356	6.5	0	1	1	0
40	3	0.5	1	1	-15.23661	Female	2.381356	6.5	0	2	2	0
40	4	1	1	4	-15.23661	Female	2.381356	6.5	0	5	10	1
41	1	0	0	0	-9.536611	Male	-4.205482	1.95	0	2	0	0
41	2	0.008219	0	0	-9.536611	Male	-4.205482	1.95				
41	3	0.5	0	0	-9.536611	Male	-4.205482	1.95	0	1	0	2
41	4	1	0	0	-9.536611	Male	-4.205482	1.95	1	3	0	2
42	1	0	0	0	0.1633865	Male	-7.053834	0	0	6	1	6
42	2	0.008219	0	0	0.1633865	Male	-7.053834	0	0	6	1	6
42	3	0.5	0	0	0.1633865	Male	-7.053834	0				
42	4	1	0	0	0.1633865	Male	-7.053834	0				
43	1	0	1	0	-10.14661	Female	1.71396	0	0	1	0	4
43	2	0.008219	1	0	-10.14661	Female	1.71396	0	0	1	1	1
43	3	0.5	1	0	-10.14661	Female	1.71396	0	0	1	1	1
43	4	1	1	0	-10.14661	Female	1.71396	0	0	1	0	1
44	1	0	0	0	7.163386	Male	-7.188081	12.6	0	1	1	10
44	2	0.008219	0	0	7.163386	Male	-7.188081	12.6				
44	3	0.5	0	0	7.163386	Male	-7.188081	12.6				
44	4	1	1	0	7.163386	Male	-7.188081	12.6				
45	1	0	0	0	-14.52661	Male	-6.032601	49.5	0	3	1	5
45	2	0.008219	0	0	-14.52661	Male	-6.032601	49.5	0	2	0	5
45	3	0.5	0	0	-14.52661	Male	-6.032601	49.5				
45	4	1	0	0	-14.52661	Male	-6.032601	49.5				
46	1	0	0	0	16.09339	Male	1.260947	65.55	0	5	3	5
46	2	0.008219	0	1	16.09339	Male	1.260947	65.55	0	4	2	3
46	3	0.5	0	1	16.09339	Male	1.260947	65.55	0	0	0	1
46	4	1	0	1	16.09339	Male	1.260947	65.55				
47	1	0	1	0	-14.59661	Male	-3.719701	3	2	1	1	6
47	2	0.008219	1	0	-14.59661	Male	-3.719701	3	2	1	1	6
47	3	0.5	2	0	-14.59661	Male	-3.719701	3	2	1	1	0
47	4	1	2	0	-14.59661	Male	-3.719701	3	2	1	1	0

ID[1]	Visit	Duration (year)	Cum. BB	Cum. Steroid	Age[2] (Year)	Gender	BMI[2]	Pack Years	Wheeze	Cough	Sputum	SOB
48	1	0	1	0	2.093387	Male	-2.565263	51	0	0	3	0
48	2	0.008219	1	0	2.093387	Male	-2.565263	51	0	0	3	0
48	3	0.5	2	0	2.093387	Male	-2.565263	51	0	0	3	0
48	4	1	3	0	2.093387	Male	-2.565263	51	0	0	3	0
49	1	0	0	0	2.973392	Male	-2.175853	82.5	1	2	5	7
49	2	0.008219	0	0	2.973392	Male	-2.175853	82.5	1	2	3	2
49	3	0.5	0	0	2.973392	Male	-2.175853	82.5	1	2	3	2
49	4	1	0	0	2.973392	Male	-2.175853	82.5				
50	1	0	0	0	3.89339	Male	-5.415317	0	0	1	1	0
50	2	0.008219	0	0	3.89339	Male	-5.415317	0	0	1	1	0
50	3	0.5	0	0	3.89339	Male	-5.415317	0	0	0	1	0
50	4	1	0	0	3.89339	Male	-5.415317	0	0	0	0	0
51	1	0	1	0	7.923388	Male	5.007314	25.5	3	5	1	3
51	2	0.008219	1	0	7.923388	Male	5.007314	25.5				
51	3	0.5	2	0	7.923388	Male	5.007314	25.5				
51	4	1	3	0	7.923388	Male	5.007314	25.5				
52	1	0	1	0	-0.2466095	Male	-4.19789	0	1	1	1	1
52	2	0.008219	1	0	-0.2466095	Male	-4.19789	0				
52	3	0.5	2	0	-0.2466095	Male	-4.19789	0				
52	4	1	3	0	-0.2466095	Male	-4.19789	0				
53	1	0	1	0	8.25339	Female	2.604783	21	0	2	0	5
53	2	0.008219	1	0	8.25339	Female	2.604783	21				
53	3	0.5	2	0	8.25339	Female	2.604783	21				
53	4	1	3	0	8.25339	Female	2.604783	21				
54	1	0	0	0	11.29339	Female	-7.350629	5	0	0	0	3
54	2	0.008219	0	0	11.29339	Female	-7.350629	5				
54	3	0.5	0	0	11.29339	Female	-7.350629	5				
54	4	1	0	0	11.29339	Female	-7.350629	5				
55	1	0	0	1	8.623393	Female	-10.3568	123.75	7	7	7	7
55	2	0.008219	0	1	8.623393	Female	-10.3568	123.75				
55	3	0.5	0	1	8.623393	Female	-10.3568	123.75				
55	4	1	0	1	8.623393	Female	-10.3568	123.75				
56	1	0	1	0	10.25339	Male	3.821088	0	0	0	1	1
56	2	0.008219	1	0	10.25339	Male	3.821088	0				
56	3	0.5	1	0	10.25339	Male	3.821088	0				
56	4	1	1	0	10.25339	Male	3.821088	0				
57	1	0	1	0	-5.236611	Male	4.155213	105	2	0	0	9
57	2	0.008219	1	0	-5.236611	Male	4.155213	105				
57	3	0.5	2	0	-5.236611	Male	4.155213	105				
57	4	1	3	0	-5.236611	Male	4.155213	105				
58	1	0	1	0	8.653392	Male	-1.123412	1.75	0	0	0	5
58	2	0.008219	1	0	8.653392	Male	-1.123412	1.75				
58	3	0.5	2	0	8.653392	Male	-1.123412	1.75				
58	4	1	3	0	8.653392	Male	-1.123412	1.75				
59	1	0	0	0	-11.88661	Female	26.8233	7.8	5	1	0	4
59	2	0.008219	0	0	-11.88661	Female	26.8233	7.8				
59	3	0.5	0	0	-11.88661	Female	26.8233	7.8				
59	4	1	0	0	-11.88661	Female	26.8233	7.8				

[1] Subject ID matched on medical record number, unique to Appendix 7: Tables 1 and 2
[2]Expressed as subject population mean subtracted from individual subject value

Table 3a: Long Term Beta-Blocker Exposure and Cardiac Events

ID	Duration	BB Status	BB Ceased	BB Started	Heart 04	Heart 05	Heart 06	Heart 07	Heart 08
1	1813	0			2	0	0	0	0
2	1731	1			0	0	0	4	0
3	1744	1			0	0	0	0	0
4	1764	1			0	0	1	0	0
5	3	0							
6	1730	0			0	0	0	0	0
7	427	1							
8	1	0							
9	1736	1			0	0	0	0	0
10	211	0							
11	1746	1			0	0	0	0	0
12	1731	1			0	0	0	0	0
13	412	1							
14	1807	1	May-04		1	1	1	0	1
15	1757	0			2	0	0	1	0
16	2	0							
17	1761	1			0	0	2	1	0
18	1762	0		Jul-03	1	1	0	3	0
19	407	1							
20	1716	0		Mar-04	0	0	0	0	0
21	1714	0			0	0	0	0	0
22	1750	1	Aug-03		0	1	4	8	0
23	406	1							
24	1762	1	Apr-04		0	0	0	0	0
25	405	0							
26	1736	1	Mar-04		1	0	0	0	0
27	1750	0			0	0	0	0	0
28	390	1							
29	1743	1			0	0	2	0	0
30	1772	0			4	4	8	0	0
31	1704	0		Jun-03	1	0	0	1	1
32	390	1							
33	406	0							
34	1701	0			0	0	0	0	0
35	1743	1			0	0	1	0	0
36	1697	0			0	0	1	0	0
37	1697	0			0	0	0	0	0
38	387	1	Jan-04						
39	389	0							
40	1	0							
41	1687	1			0	0	0	0	0
42	383	1							
43	1688	0			0	0	0	0	0
44	5	0							
45	1687	1			0	0	0	1	0
46	1685	1			1	2	1	0	0
47	1759	0			0	0	0	0	0
48	8	0							
49	1	1							
50	1763	1			1	1	1	1	1
51	1705	1	Mar-06		1	0	0	2	0
52	3	0							
53	1708	0			2	7	5	5	1
54	1679	0		Sep-04	4	4	4	4	0
55	1746	1	Oct-03		0	2	1	0	1
56	1670	0			0	0	0	4	0
57	1683	0			0	0	0	0	0
58	1667	1			2	4	0	4	0
59	348	0							
60	2	0							
61	1706	1	Oct-03		0	0	0	0	0
62	1667	0	Apr-06	Jun-04	0	0	0	0	0
63	1665	0			0	0	1	0	0
64	1	0							

Table 3b: Long Term Beta-Blocker Exposure - Type 1 Respiratory Exacerbations

ID	Duration	BB Status	BB Ceased	BB Started	CAL 02	CAL 03	CAL 04	CAL 05	CAL 06	CAL 07	CAL 08
1	1813	0			0	1	4	1	0	0	0
2	1731	1			0	2	1	0	0	4	0
3	1744	1			2	2	3	2	2	2	0
4	1764	1			0	2	2	0	2	0	0
5	3	0			7	0					
6	1730	0			1	0	1	0	0	0	0
7	427	1			0	1	0				
8	1	0			2	0					
9	1736	1			0	0	0	0	0	0	0
10	211	0			1	1					
11	1746	1			1	0	0	0	0	0	0
12	1731	1			0	1	0	0	0	0	1
13	412	1			0	0	0				
14	1807	1	May-04		0	0	0	0	1	0	0
15	1757	0			2	1	8	2	2	4	0
16	2	0			0	0					
17	1761	1			0	0	0	0	0	0	0
18	1762	0		Jul-03	4	2	3	0	1	0	0
19	407	1			1	0	1				
20	1716	0		Mar-04	1	0	1	0	0	0	0
21	1714	0			0	0	0	0	0	0	0
22	1750	1	Aug-03		0	0	0	0	4	0	0
23	406	1			0	0	1				
24	1762	1	Apr-04		1	0	0	0	0	1	0
25	405	0			0	0	0				
26	1736	1	Mar-04		0	0	0	0	0	0	0
27	1750	0			0	0	0	0	0	0	0
28	390	1			0	0	0				
29	1743	1			0	0	2	4	4	4	0
30	1772	0			2	2	0	0	0	0	0
31	1704	0		Jun-03	0	0	1	0	0	1	1
32	390	1			0	1	1				
33	406	0			0	0	0				
34	1701	0			2	0	0	0	0	0	0
35	1743	1			1	0	1	0	0	2	0
36	1697	0			0	0	0	0	0	0	0
37	1697	0			2	0	0	0	0	0	0
38	387	1	Jan-04		1	0	0				
39	389	0			8	0	1				
40	1	0			5	0					
41	1687	1			0	0	0	0	0	0	0
42	383	1			0	0	0				
43	1688	0			1	1	0	0	0	0	0
44	5	0			4	2					
45	1687	1			2	0	2	2	2	2	0
46	1685	1			10	0	11	1	1	0	0
47	1759	0			1	0	1	0	0	1	0
48	8	0			1	0					
49	1	1			0	0					
50	1763	1			1	0	0	0	0	0	0
51	1705	1	Mar-06		0	0	0	0	0	0	0
52	3	0			2	3					
53	1708	0			9	3	2	1	0	0	0
54	1679	0		Sep-04	0	1	7	4	4	4	0
55	1746	1	Oct-03		2	1	4	1	0	2	1
56	1670	0			3	0	0	4	4	4	0
57	1683	0			0	2	1	0	0	0	0
58	1667	1			12	0	1	4	4	4	1
59	348	0			17	1	1				
60	2	0			0	0					
61	1706	1	Oct-03		0	0	0	0	0	0	0
62	1667	0	Apr-06	Jun-04	5	1	5	0	1	1	0
63	1665	0			2	0	0	0	0	0	0
64	1	0			0	0					

Table 3c: Long Term Beta-Blocker Exposure - Type 2 Respiratory Exacerbations

ID	Duration	BB Status	BB Ceased	BB Started	CAL 02	CAL 03	CAL 05	CAL 06	CAL 07	CAL 08
1	1813	0			0	1	1	0	0	0
2	1731	1			0	0	0	0	0	0
3	1744	1			2	1	0	0	1	0
4	1764	1			0	0	0	1	0	0
5	3	0			0	0				
6	1730	0			1	0	0	0	0	0
7	427	1			0	0				
8	1	0			2	0				
9	1736	1			0	0	0	0	0	0
10	211	0			0	1				
11	1746	1			1	0	0	0	0	0
12	1731	1			0	0	0	0	0	1
13	412	1			0	0				
14	1807	1	May-04		0	0	0	0	1	0
15	1757	0			2	0	0	0	4	0
16	2	0			0	0				
17	1761	1			0	0	0	0	0	0
18	1762	0		Jul-03	1	2	1	1	1	0
19	407	1			0	0				
20	1716	0		Mar-04	1	0	0	0	0	0
21	1714	0			0	0	0	0	0	0
22	1750	1	Aug-03		0	0	0	0	0	0
23	406	1			0	0				
24	1762	1	Apr-04		0	0	0	0	1	0
25	405	0			0	0				
26	1736	1	Mar-04		0	0	0	0	0	0
27	1750	0			0	0	0	0	0	0
28	390	1			0	0				
29	1743	1			0	0	4	4	4	0
30	1772	0			0	2	0	0	0	0
31	1704	0		Jun-03	0	0	0	0	3	0
32	390	1			0	0				
33	406	0			0	0				
34	1701	0			0	0	0	0	0	0
35	1743	1			1	0	0	0	0	0
36	1697	0			0	0	0	0	0	0
37	1697	0			0	0	0	0	0	0
38	387	1	Jan-04		0	0				
39	389	0			2	0				
40	1	0			5	0				
41	1687	1			0	0	0	0	0	0
42	383	1			0	0				
43	1688	0			1	1	0	0	0	0
44	5	0			3	2				
45	1687	1			0	0	1	1	1	0
46	1685	1			4	0	0	0	0	0
47	1759	0			1	0	0	0	1	0
48	8	0			0	0				
49	1	1			0	0				
50	1763	1			1	0	0	0	0	0
51	1705	1	Mar-06		0	0	0	0	0	0
52	3	0			2	3				
53	1708	0			3	3	1	0	0	0
54	1679	0		Sep-04	0	1	0	0	1	0
55	1746	1	Oct-03		1	3	1	0	1	1
56	1670	0			3	0	0	0	1	0
57	1683	0			0	0	0	0	0	0
58	1667	1			3	0	0	1	4	0
59	348	0			0	0				
60	2	0			0	0				
61	1706	1	Oct-03		0	0	0	0	0	0
62	1667	0	Apr-06	Jun-04	2	1	1	1	1	0
63	1665	0			1	0	0	0	0	0
64	1	0			0	0				

Table 3d: Long Term Beta-Blocker Exposure – Cardiac Admissions

ID	Duration	BB Status	BB Ceased	BB Started	2002	2003	2004	2005	2006	2007	2008
1	1813	0			1	1	2	0	0	0	0
2	1731	1			0	3	0	0	0	2	0
3	1744	1			1	1	0	0	0	0	0
4	1764	1			0	3	0	0	1	0	0
5	3	0			1						
6	1730	0			0	0	0	0	0	0	0
7	427	1			0	5	0				
8	1	0			2	1					
9	1736	1			0	1	0	0	0	0	0
10	211	0			0	0					
11	1746	1			0	1	0	0	0	0	0
12	1731	1			0	1	0	0	0	0	0
13	412	1			0	1	0				
14	1807	1	May-04		0	0	0	0	1	0	1
15	1757	0			4	2	2	0	0	1	0
16	2	0			0	1					
17	1761	1			0	2	0	0	2	1	0
18	1762	0		Jul-03	1	1	1	1	0	1	0
19	407	1			0	2	0				
20	1716	0		Apr-04	0	1	0	0	0	0	0
21	1714	0			0	2	0	0	0	0	0
22	1750	1	Aug-03		0	0	0	0	1	0	0
23	406	1			2	1	0				
24	1762	1	Apr-04		1	0	0	0	0	0	0
25	405	0			0	0	0				
26	1736	1	Mar-04		0	1	1	0	0	0	0
27	1750	0			0	1	0	0	0	0	0
28	390	1			0	1	0				
29	1743	1			0	1	0	0	2	0	0
30	1772	0			0	0	0	0	1	0	0
31	1704	0		Jun-03	0	1	0	0	0	1	1
32	390	1			0	1	0				
33	406	0			0	0	0				
34	1701	0			0	1	0	0	0	0	0
35	1743	1			0	1	0	0	1	0	0
36	1697	0			0	0	0	0	0	0	0
37	1697	0			1	2	0	0	0	0	0
38	387	1	Jan-04		0	2	1				
39	389	0			0	0	0				
40	1	0			0	1					
41	1687	1			0	1	1	0	0	0	0
42	383	1			0	1	0				
43	1688	0			0	0	0	0	0	0	0
44	5	0			3	2					
45	1687	1			1	2	0	0	0	1	0
46	1685	1			1	1	1	1	0	0	0
47	1759	0			0	1	0	0	0	0	0
48	8	0			0	1					
49	1	1			1						
50	1763	1			0	0	0	1	0	0	0
51	1705	1	Mar-06		1	1	0	0	0	0	0
52	3	0			1	2					
53	1708	0			2	1	0	1	0	0	0
54	1679	0		Sep-04	0	2	0	0	0	0	0
55	1746	1	Oct-03		0	1	0	0	0	0	0
56	1670	0			0	1	0	0	0	1	0
57	1683	0			0	1	0	0	0	0	0
58	1667	1			0	2	0	2	1	0	1
59	348	0			0	2	1				
60	2	0			0	1					
61	1706	1	Oct-03		0	0	0	0	0	0	0
62	1667	0	Apr-06	Jun-04	0	0	0	0	0	0	0
63	1665	0			0	3	0	0	1	0	0
64	1	0			0	1					

Table 3e: Long Term Beta-Blocker Exposure – Respiratory Admissions

ID	Duration	BB Status	BB Ceased	BB Started	2002	2003	2004	2005	2006	2007	2008
1	1813	0			0	0	2	1	0	0	0
2	1731	1			0	0	0	0	0	2	0
3	1744	1			0	0	0	0	0	0	0
4	1764	1			0	0	0	0	1	0	0
5	3	0			0	0					
6	1730	0			0	0	0	0	0	0	0
7	427	1			0	0	0				
8	1	0			1	0					
9	1736	1			0	0	0	0	0	0	0
10	211	0			0	1					
11	1746	1			0	0	0	0	0	0	0
12	1731	1			0	0	0	0	0	0	0
13	412	1			0	0	0				
14	1807	1	May-04		0	0	0	0	0	0	0
15	1757	0			1	0	2	0	0	1	0
16	2	0			0	0					
17	1761	1			0	0	0	0	0	0	0
18	1762	0		Jul-03	1	2	2	0	1	0	0
19	407	1			0	0	0				
20	1716	0		Apr-04	0	0	0	0	0	0	0
21	1714	0			0	0	0	0	0	0	0
22	1750	1	Aug-03		0	0	0	0	0	0	0
23	406	1			0	0	0				
24	1762	1	Apr-04		0	0	0	0	0	0	0
25	405	0			0	0	0				
26	1736	1	Mar-04		0	0	0	0	0	0	0
27	1750	0			0	0	0	0	0	0	0
28	390	1			0	0	0				
29	1743	1			0	0	0	0	1	0	0
30	1772	0			0	0	0	0	0	0	0
31	1704	0		Jun-03	0	0	0	0	0	1	1
32	390	1			0	0	0				
33	406	0			0	0	0				
34	1701	0			0	0	0	0	0	0	0
35	1743	1			0	0	0	0	0	0	0
36	1697	0			0	0	0	0	0	0	0
37	1697	0			0	0	0	0	0	0	0
38	387	1	Jan-04		0	0	0				
39	389	0			0	0	0				
40	1	0			0	0					
41	1687	1			0	0	0	0	0	0	0
42	383	1			0	0	0				
43	1688	0			0	0	0	0	0	0	0
44	5	0			4	2					
45	1687	1			0	0	0	0	0	0	0
46	1685	1			1	0	1	1	0	0	0
47	1759	0			0	0	0	0	0	0	0
48	8	0			0	0					
49	1	1			0	0					
50	1763	1			0	0	0	0	0	0	0
51	1705	1	Mar-06		0	0	0	0	0	0	0
52	3	0			1	2					
53	1708	0			0	0	0	0	0	0	0
54	1679	0		Sep-04	0	1	0	0	0	1	0
55	1746	1	Oct-03		0	0	0	0	0	0	0
56	1670	0			0	0	0	1	0	1	0
57	1683	0			0	0	0	0	0	0	0
58	1667	1			0	0	0	0	1	1	0
59	348	0			0	0	0				
60	2	0			0	0					
61	1706	1	Oct-03		0	0	0	0	0	0	0
62	1667	0	Apr-06	Jun-04	0	1	1	0	0	1	0
63	1665	0			0	0	0	0	0	0	0
64	1	0			0	0					

Table 4: Long Term Beta-Blocker Exposure and Survival

ID	DOB	Gender	Pack Years	HospResp	BB	Status	Death
1	28/11/69	Female	37.5	0		Living	
2	20/3/41	Female	0	0	Yes	Living	
3	23/1/20	Male	0	0	Yes	Living	
4	15/4/45	Male	82	0	Yes	Living	
5	18/3/23	Male	161.2	1		Deceased	15/08/2003
6	11/3/20	Female	0	0		Living	
7	18/2/15	Female	10	0	Yes	Deceased	16/11/2005
8	22/2/07	Male	63.75	2		Deceased	02/05/2003
9	26/7/19	Male	0	0	Yes	Living	
10	14/5/18	Male	65.55	0		Deceased	21/06/2006
11	17/7/26	Male	25.5	0	Yes	Living	
12	8/10/31	Male	22.5	0	Yes	Living	
13	1/3/37	Male	68	0	Yes	Lost	
14	29/4/41	Male	50	0	Yes	Living	
15	7/2/23	Female	0	2		Living	
16	29/5/53	Male	7	0		Living	
17	21/9/34	Male	0	0	Yes	Living	
18	1/12/30	Female	42.5	1		Living	
19	9/7/25	Female	52.5	0	Yes	Deceased	04/11/2007
20	6/3/41	Female	39.6	0		Living	
21	12/6/24	Female	107.5	0		Living	
22	8/9/38	Female	7	0	Yes	Living	
23	19/7/28	Male	10	0	Yes	Living	
24	13/2/49	Male	3	0	Yes	Living	
25	26/7/53	Male	0	0		Living	
26	7/2/55	Male	26.25	0	Yes	Living	
27	22/10/54	Male	25	0		Living	
28	16/10/30	Male	96	0	Yes	Deceased	01/09/2005
29	18/7/33	Male	15	0	Yes	Living	
30	29/8/48	Female	18.75	0		Living	
31	28/1/31	Male	168	0		Living	
32	8/4/26	Female	21	0	Yes	Living	
33	26/4/23	Male	47	0		Living	
34	14/9/59	Male	0.6	0		Living	
35	20/4/40	Male	0	0	Yes	Living	
36	12/4/23	Female	5	0		Living	
37	15/6/25	Female	7.5	0		Living	
38	2/7/28	Male	37.5	0	Yes	Lost	
39	9/1/17	Female	0	0		Deceased	17/07/2006
40	13/12/25	Female	123.75	0		Deceased	26/03/2004
41	12/1/37	Male	18.75	0	Yes	Living	
42	15/2/31	Male	21	0	Yes	Lost	
43	12/8/17	Female	0	0		Living	
44	6/8/36	Male	118.25	5		Deceased	05/01/2004
45	27/9/43	Female	1	0	Yes	Living	
46	30/6/37	Male	228	0	Yes	Living	
47	8/9/30	Male	0	0		Living	
48	8/2/17	Male	30	0		Deceased	29/01/2007
49	2/5/24	Male	0	0	Yes	Living	
50	28/10/39	Male	105	0	Yes	Living	
51	14/7/32	Male	51	0	Yes	Living	
52	19/11/18	Male	120	2		Deceased	17/09/2003
53	7/1/41	Female	0	0		Living	
54	21/6/34	Male	52.5	0		Living	
55	13/11/49	Female	6.5	0	Yes	Living	
56	29/8/31	Male	82.5	0		Living	
57	5/3/44	Male	1.95	0		Living	
58	26/12/25	Male	1.75	0	Yes	Living	
59	1/3/49	Male	49.5	0		Deceased	25/07/2004
60	24/6/34	Male	0	0		Deceased	17/10/2003
61	16/10/44	Female	0	0	Yes	Living	
62	23/6/27	Male	12.6	0		Living	
63	14/7/46	Female	7.8	0		Living	
64	14/7/22	Female	0	0		Deceased	10/12/2004

Appendix 8: Response to Examiners

Examiner 1

General comments

The examiner notes that the results show an increase in cardiac events associated with beta-blocker use, and no statistically significant survival advantage, despite the fact that beta-blockers are known to substantially reduce cardiac events and mortality in randomised trials. The implication put forward is that potential confounding variables have been omitted in the analysis and the examiner suggests that severity of cardiac disease might be one of these. The examiner also mentions survival bias as a potential source of confounding.

The examiner has valid concerns about two factors which potentially confound the results, and which are acknowledged in the thesis discussion. The analysis of adverse cardiac events shows an increased risk of cardiac events and hospital admissions at study baseline and an annual reduction of cardiac events over the study duration, although by study end the final risk is still greater in the beta-blocker group than in the reference group. Except for the baseline risk of hospital admissions, none of these results achieve statistical significance for a difference between the two groups. The survival results are as the examiner has described; beta-blockers are protective, but statistical significance is lost after adjustment for potential confounding covariates. The results reported here do not appear to contradict the general body of medical literature. The study lacked sufficient power to demonstrate a statistically significant reduction in cardiac events or hospital admissions over time, or to demonstrate improved survival, since the studies which have reported such findings have described them in subject populations of far greater magnitude. It was felt that this was a more important factor.

Cardiac disease severity is indeed likely to be increased in the beta-blocker group. However, it is difficult to precisely quantify and adjust for the increased severity, particularly in a subject group with heterogeneous cardiac disease. One potential choice is to adjust for left ventricular function (a measure which is subjective and was not available for most of the subjects). It was considered that prior cardiac-related hospital admission probably gave some measure of disease severity, but had not generally been used for this purpose in the medical literature. The analyses were adjusted for mean FEV1, which is traditionally a marker of severity and prognosis in respiratory disease. However, FEV1 also has a strong correlation with adverse cardiovascular events, in particular fatal events, and is equivalent to conventional cardiovascular risk factors, including serum cholesterol and hypertension, in predicting adverse cardiac events. Moreover, in this analysis, FEV1 was a predictor for both cardiac and respiratory events. While it is acknowledged that FEV1 may not be the ideal marker of cardiac severity in this study, because of its inherent links with respiratory disease, and because of missing FEV1 data for some subjects, its inclusion as a covariate does afford some adjustment for cardiovascular disease severity. Similar arguments hold for the inclusion of pack years and age as covariates.

The examiner is understandably concerned about the potential for survival bias and has recommended a sensitivity analysis. Survival bias is difficult to address in an observational study of this size. Obviously, the deceased subjects are likely to represent a group of patients with more severe disease than the survivors. This may also apply to subjects who fail to follow up. Since FEV1 is strongly related to survival in both respiratory and cardiac disease, a correlation between FEV1 and leaving the study was sought. None was present and hence this analysis did not suggest the presence of significant survivor bias. In a small study, it is difficult to estimate clinically or statistically, the likelihood of events in the deceased, had they survived. The sensitivity analysis recommended by the examiner cannot account for the survivor bias affecting the study, but does demonstrate the potential impact of survival bias on the results, and hence is included in the results section for Chapter 6 (6.4.3.4 Respiratory Exacerbations – Supplementary Analyses, page 120).

For the sensitivity analysis, we allocated an extra exacerbation to each of the deceased subjects. Allocating extra exacerbations to the deceased subjects is expected to lessen the effect size and significance of the effect of beta-blockers on exacerbations, since only three of 14 deceased subjects received beta-blocker treatment. However, the sensitivity analysis did not substantially change the results for exacerbations of both types. For symptoms-based respiratory exacerbations, the effect sizes were marginally reduced and statistical significance was maintained at the same level, and for treated exacerbations, the effect sizes were marginally reduced, and although the annual risk of exacerbations remained significantly increased in the beta-blocker group, the increased risk at study conclusion, fell short of statistical significance.

Chapter 1: Literature review

The examiner states that the side effects attributed to beta-blockers (1.2 Beta-blocker Medications, page 18) have not been confirmed as being increased in pooled data from randomised placebo-controlled trials.

To be accepted as a “side effect”, an adverse effect may be increased in the population of patients taking the drug, or may be reported in association with a small number of cases and be attributed to the medication in question. The side effects specified in the thesis are those detailed in the product information for most beta-blocker drugs.

A reference is requested for the statement: cardioselective beta-blockers have caused respiratory symptoms and deterioration of lung function in selected cases (1.2.3 Potential Adverse Respiratory Effects, page 28).

The author is able to report this from clinical experience. However, the literature also contains many references. One has been inserted (reference 49).

The examiner comments that the Norwegian Timolol Trial (reference 56) is the only trial of many which has found an association with a beta-blocker drug and respiratory infections. The examiner goes on to mention that a meta-analysis of

cardioselective beta-blockers in patients with reactive airways disease (reference 58) found no effect on respiratory symptoms or respiratory exacerbations.

The examiner's comment refers to a section of the literature review in which the author reviewed the beta-blocker trials in the treatment of cardiac disease and employed this strategy to seek evidence of reported adverse events, or dosage reduction or subject withdrawals due to adverse respiratory events (1.2.4 Evidence for Adverse Respiratory Effects, page 31). There was very little evidence of dose reductions, subject withdrawals or adverse affects, and the Norwegian Timolol Trial (reference 56) is the only one to report adverse events. That was the reason for mentioning it. However, it should be remembered that many of these trials excluded patients with known obstructive airways disease. Discussion about reference 58, including its weaknesses, is deferred until a subsequent paragraph, because the subject group in this case is different; the meta-analysis subjects had reactive airways disease by definition.

The examiner requests the basis of the statement claiming that there has been a hesitance to embrace the conclusions of the two meta-analyses investigating beta-blocker use in patients with chronic obstructive pulmonary disease (COPD) and reactive airways disease (references 57 and 58, respectively).
1.2.4 Evidence for Adverse Respiratory Effects, page 35.

The statement and reasons proffered were intended to reflect opinion and they are presented for the purpose of delineating the author's main criticisms of the two meta-analyses. However, there is some basis in the medical literature for the author's comments. Although the situation has improved, even very recent studies of beta-blocker prescription, after myocardial infarction and in heart failure, describe underprescription in patients with obstructive airways disease (reference 48). Hence, although there is evidence that prescribing practice has changed, it remains suboptimal.

The examiner requests evidence that acute beta-blockade in congestive heart failure causes an immediate worsening of haemodynamics, before the improvement seen with longer term treatment (1.2.4 Evidence for Adverse Respiratory Effects, page 38).

The author agrees that the trials investigating the introduction of beta-blocker treatment for congestive heart failure have shown little evidence of acute haemodynamic worsening in comparison with placebo. Cardiology guidelines for the implementation of beta-blockade in heart failure suggest that this should occur in stable state; bradycardia, hypotension and pulmonary oedema or significant fluid overload are considered relative contraindications. The guidelines recommend commencement with very small doses, and gradual upward titration to the optimal therapeutic dose over a period of several weeks. It is likely that these strategies temper the effects of bradycardia and reduced myocardial contractility that are associated with beta blockade, so that haemodynamic stability is preserved. The author would point out that previous reports of worsening of symptoms or haemodynamic parameters associated with beta-blocker treatment in congestive heart failure may reflect characteristics of the older generation drugs or higher initiation doses. In fact, when Eichhorn and Bristow (1) compared the acute haemodynamic effects of beta-blockade in heart failure reported in 3 studies, greater

adverse haemodynamic effects were seen with older generation, non-vasodilatory agents, with significant reduction in cardiac index after single dose propranolol or metoprolol, but not following single dose bucindolol or carvedilol.

However, the author's statement about acute haemodynamic worsening related to cardiogenic shock, rather than to congestive heart failure (1.2.4 Evidence for Adverse Respiratory Effects, page 38). By definition, in shock haemodynamics are compromised and so this actually represents a different situation. Even today beta-blockers remain contraindicated in this group, except in very exceptional circumstances.

The examiner notes that updated 2007 asthma guidelines from the National Heart Lung and Blood Institute address the issue of beta-blocker treatment in asthma patients with comorbid cardiovascular disease.

This reference has been added to the section of the literature review which discusses beta-blocker prescribing (reference 116).

Chapter 2: The study protocol

Discussion of statistical analysis has been amalgamated in Chapter 2.

Chapter 3: The study population

Textual references to tables and diagrams have been inserted.

Chapter 4: The prevalence of coexistent airways obstruction in patients with cardiac disease

The examiner enquires about the patients with a previous diagnosis of asthma, but normal spirometry.

Asthma is an episodic disease and spirometry is expected to be normal if measured during periods of good asthma control. A measure of asthma was required in the subject population, and a choice between self-reported asthma and objectively measured lung function was considered.

The subject group contained 19 self-reported asthmatics. Only three of these demonstrated positive bronchodilator response (BDR). In fact, BDR was more frequently observed in subjects who had not previously been diagnosed with asthma. It was considered that the self-reported asthmatics probably did not well represent the type of asthmatic typically reported in the medical literature and also that the diagnosis may have been overestimated in this group. For a small number of those reporting asthma, the history was limited to asthma in childhood, and these were not differentiated from the group as a whole. More concerning was that 15 of 18 also reported being regular smokers (Chapter 2, 2.5 Definitions, page 70, and reference 130), eight of 18 had

accumulated more than 20 pack years' smoking history, four of 18 self-reported additional COPD or emphysema and only one of 18 was taking standard first line treatment for asthma, according to international asthma guidelines (2), namely inhaled corticosteroids.

Of the options for diagnosis of asthma with lung function testing, bronchial hyperresponsiveness testing would have provided more sensitive and specific diagnostic information, but was not appropriate in the setting of acute cardiac disease. However, by choosing the presence of BDR to represent asthma in the subject population, there was risk that asthma prevalence would be underestimated. This is especially the case considering that bronchodilator medications could not be withheld prior to testing. The BDR testing demonstrates an unarguable asthmatic presence within the subject population, but the results should be interpreted in the context of likely underestimation. For the reasons stated above, and to maintain consistency, BDR was used as the covariate to represent asthma in some of the statistical analyses performed.

The examiner enquires as to whether prevalence of previously diagnosed cardiac disease or obstructive lung disease was similar in the patients who refused consent in comparison with the study participants.

Prevalence data for the presence of previously diagnosed cardiac and obstructive lung disease in the patients who refused consent are not available.

The examiner questions the author's recommendations for screening cardiac patients with spirometry (4.4 Discussion, page 96), fearing confusion about treatment decisions.

The author's suggestions about spirometry screening are not intended to change treatment decisions in cardiac disease. Treatment decisions should be based on the entire clinical context and not solely on the results of spirometry. The purpose of such screening would be to identify early, patients with cardiac disease and comorbid obstructive airways disease, to prospectively gather information about the characteristics of their lung disease and then to document disease progression or course. It is anticipated that such screening would contribute to the knowledge base for beta-blocker prescribing in this group.

The potential utility of screening spirometry and bronchial provocation testing has also been discussed in Chapter 7 (7.4 Screening and Monitoring, page 142). The author concurs that there is currently insufficient scientific evidence to mandate the use of lung function testing as part of the assessment and treatment of cardiac disease. The purpose of this chapter was to explore the potential implications of the high degree of overlap between the cardiac and obstructive airways disease and how we might better understand their interactions, particularly in the context of beta-blocker therapy. Hence, the suggestions proffered with regard to lung function testing. For now, given the extent of coexisting cardiac and obstructive lung disease, the author would suggest that it is best clinical practice to confirm the presence of one or both diseases, and if possible, to quantify the severity. There is risk that comorbid lung disease will remain undiagnosed

if not specifically sought in patients with cardiac disease because of frequent coexistence, symptom overlap, and the poor discriminatory performance of diagnostic tests. The same holds true for cardiac disease. The main relevance for this last point is that without diagnosis, patients may miss out on disease-modifying therapeutic intervention.

The examiner comments about lacking evidence for utility of the conventional investigation tools, such as the electrocardiogram (ECG) and chest x-ray for risk stratification (4.4 Discussion, page 96).

The intentions of the author were not to recommend that the conventional investigation tools here-mentioned be used for risk stratification, although the ECG is still used for this purpose in coronary artery disease (CAD), in combination with other factors. The point being made in this section was that the cause for deterioration of respiratory symptoms is often difficult to elucidate in patients with combined cardiac and obstructive airways disease. The author was suggesting that clinical assessment; that is, history, careful physical examination and simple, minimally invasive investigations, might help to clarify the cause.

Chapter 5: Beta-blocker prescription in patients with coexisting cardiac and obstructive airways disease

The examiner enquires about beta-blocker prescription data for subjects with cardiac failure and arrhythmia.

The author presented data for the prevalence of CAD in the subset of the subject population in whom beta-blockers were considered treatment of choice, comparing the group prescribed beta-blockers and those who were not. CAD outcomes were reported because this was by far the most common cardiac diagnosis in the subjects, either as the cause of acute presentation or as a previously confirmed diagnosis. The numbers of subjects with heart failure and arrhythmia were rather a small proportion of the subject population, totalling five and twelve, respectively. In addition, two of the subjects diagnosed with arrhythmia had bradyarrhythmia, and hence beta-blockers were inappropriate. Two of five subjects with heart failure and four of ten subjects with tachyarrhythmia had comorbid CAD, and so had been represented in the CAD comparison.

Beta-blockers were prescribed in one of five patients with heart failure, meaning that the proportion with heart failure was 3.4% in the group treated with beta-blockers and 21.1% in the group who were not. For subjects with tachyarrhythmia, beta-blockers were prescribed in 4 of 10 patients; the proportion with tachyarrhythmia being 13.8% in the group receiving beta-blockers and 31.6% in the group who were not. These data show that those given beta-blockers had a lower prevalence of heart failure and tachyarrhythmia.

Chapter 5, Chapter 6: The longer term effects of beta-blocker medications on lung function, respiratory exacerbations and survival in patients with cardiac disease

The examiner suggests that the Cochrane meta-analyses of beta-blocker trials in patients with obstructive airways disease (reference 57 and 58) may have already addressed the question of whether beta-blockers cause airflow obstruction and respiratory exacerbations.

The author believes that the meta-analyses partly address the question of airflow obstruction. The data contained in the meta-analyses are likely sufficient to address this question in the setting of single dose effect, but are insufficient to answer the question in terms of the long term effects, which is relevant to the substantial number of subjects in this current study who entered the study already using beta-blockers over the longer term. In the meta-analysis focussing on reactive airways disease (reference 58), the range of durations of longer term trials was 3 – 28 days, the total number of included subjects was 121 and half of the included trials reported no lung function data. In the meta-analysis for COPD (reference 57), the duration range was 2 – 84 days (mean 1.1 month), included subjects totalled 126 and again half of the included trials reported no lung function data. From preliminary research in a murine asthma model, it has been suggested that beta-blocker effects on the airways may differ between the settings of acute and chronic dosing, and one proposed mechanism is beta-receptor upregulation. Obviously, to capture a difference between single dose and longer term effect on lung function, lung function parameters must be measured and sufficient study duration must be allocated.

For the reasons mentioned above, the author feels that the Cochrane meta-analyses also do not adequately address the issue of beta-blocker effects on respiratory exacerbations. Since exacerbations are infrequent events occurring over time, even the maximal trial duration of 84 days in the meta-analysis for COPD (reference 57) is not adequate to answer this question. The only caveat to this might be if the subject population has frequent exacerbations associated with advanced disease. In the meta-analysis for COPD, there were no exacerbations, although all included trials claimed to report them. The prevalence of symptoms was surprisingly low for a COPD population, with only one patient in each of the treatment and placebo groups reporting any symptoms. This, together with the use of clinical COPD diagnosis in more than half of the trials does raise the question of whether the included subjects truly had COPD, and whether the spectrum of COPD severity was adequately represented by the subject population.

The examiner requests that hazard ratios be reported for the survival analyses.

Accidental omission of the first paragraph of the section 6.4.3.5 Death (page 121) was the reason for the missing hazards ratios. The omitted paragraph also explains that cause of death was unknown for most of the deceased subjects. The paragraph has been reinstated within the thesis text.

The significant benefit of beta-blockers on survival seen in the univariable analysis was not present in the adjusted analysis. Of necessity, the comparative survival profiles are presented unadjusted, although they suggest that beta-blockers do not have an adverse effect on survival, even in those with more severe lung disease; that is, FEV1 50%, previous respiratory-related hospital admission and pack years = 50. However, the

author had decided against reporting hazard ratios for the comparative survival profiles in order to prevent the reader from placing undue weight on the results. Although all of the comparisons are statistically significant, it must be remembered that such profiles require data extrapolation and remain unadjusted for the covariates which converted the overall survival analysis from significant to non-significant.

The examiner requests further explanation of the sequential measures of BDR proportion in the subject population (6.4.1 Spirometry, page 111).

For these results, which are represented graphically, potential for statistical analysis and interpretation was severely limited, due to small numbers and missing spirometry data. Overall, ten subjects demonstrated BDR during the twelve months of serial spirometry measurements. Five subjects were taking beta-blockers, two of whom had been beta-blocker naïve. Initially, of seven subjects demonstrating BDR, three were taking beta-blockers. At the discharge assessment, of five subjects with BDR, three were taking beta-blockers. The trend was for the proportion with BDR to reduce in both groups over the remainder of the study. The author presented these results to stimulate interest in further research. Firm conclusions cannot be drawn. The results may be in keeping with a differential beta-blocker effect between acute and chronic dosing, but ideally research into this requires much larger subject numbers, a subject population which is beta-blocker naive and comparison of sequential spirometry and BDR for individuals, rather than sequential comparison of the population proportions manifesting BDR.

The examiner requests additional information about the longitudinal analysis of adverse cardiac and respiratory events (6.4.3.2 Respiratory Exacerbations, page 116 and 6.4.3.3 Acute Cardiac Events, page 117).

The statistical software used to analyse this data has not provided unadjusted event rates for the Poisson regressions of adverse respiratory and cardiac events. As the examiner points out, determining the event rates from raw data is possible but cumbersome, and it is made more challenging by the incorporation into the analyses of the changes to beta-blocker status of some subjects during the course of the study. However, it is unlikely that the unadjusted event rates will add insight into the true effect. The more important question is whether the statistical strategies utilised, including the adjustments, have been sufficient to account for any bias present – a question which has been debated in an earlier section of this response.

The examiner also enquired as to the proportion of subjects who experienced at least one adverse event. The data are as follows: for acute cardiac events 37.5%, for cardiac hospital admissions 90.6%, for symptoms-based exacerbations 73.4%, for treated exacerbations 54.7% and for respiratory-related hospital admissions 23.4%. To compare these figures, it is necessary to know that the duration of data collection for adverse cardiac events was approximately half that of the other events for which results have been reported.

Chapter 7: Clinical applications and implications

Discriminating the source of deterioration of respiratory symptoms in cardiac patients (7.3 Screening and Monitoring, page 145)

The point here is not to say that spirometry is a better discriminatory tool than the other investigations mentioned in this section. As the examiner points out, none of the tests are particularly good discriminators, and given this situation the astute clinician should gather information from multiple sources before making a decision. In the author's experience, spirometry is rarely utilised in this situation, except only very occasionally in the patient who has known comorbid respiratory disease. Hence, for the patient with undiagnosed airflow limitation, this differential diagnosis may not be considered.

Chapter 8: Directions for future research

The evidence for a beneficial effect of beta-blockers is discussed, despite the finding of increased respiratory exacerbations

The research presented in Chapter 6 shows increased respiratory exacerbations, but no adverse effect on lung function, symptoms or survival. Hence, the results do not imply an overall adverse effect of beta-blockers in the subject population. However, carefully planned, adequate duration, prospective studies are needed to explore the potential for beta-blockers to cause increased respiratory exacerbations.

As an observational study, this study has inherent limitations, some of which have been raised by the examiner. Although the statistical strategies utilised in the analyses of the data have attempted to minimise the effects of bias, some may still be present. Hence, the exacerbation results do not preclude the finding of beneficial beta-blocker effects in future prospective studies of patients with obstructive airways disease or of beta-blockade as a therapeutic intervention in these diseases.

Examiner 2

Minor emendations

The presence of beta-3 adrenoreceptors in the myocardium; the thesis has been amended to describe the distribution of beta-3 receptors in the adipose tissue, gastrointestinal tract and myocardium and a reference has been inserted (1.1 The Beta-adrenergic Receptor, page 16, reference 6).

The reasoning behind enhanced selectivity of extended release beta-blocker preparations (1.2 Beta-blocker Medications, page 19) is clarified within the main body of the thesis and a reference pertaining to this has been inserted (reference 15). The explanation relates to the pharmacokinetics of extended release formulations; peak serum levels are much lower in comparison with short-acting agents at equivalent dose. Beta receptor selectivity is reduced at high doses due to variations in receptor density between tissue types and the tissue distribution of the various receptor subtypes.

Table 1.1 “Characteristics of beta-blocker agents in common use” (page 20) has been altered to aid interpretation. The blank spaces have been labelled “No” to indicate that the characteristic is absent.

The meta-analysis of beta-blockers in congestive cardiac failure (reference 20) reports a combined odds ratio for total mortality of 0.65 (95% confidence interval 0.53 – 0.80), using a Bayesian random effects model. The confidence intervals have been included in the text (1.2.1.1 Heart Failure, page 22).

The definition of COPD provided by the author (2.5 Definitions, page 70) is that accepted internationally and the reference has been provided (reference 3). The examiner’s requirement that FEV1 be less than 80% would define COPD of at least moderate severity and excludes those with mild COPD.

The examiner requests an explanation of reciprocal conversion (3.2.1 Demographics, page 74). This technique was used to transform the BMI data to achieve a normal distribution, so that parametric statistical tests could be applied. To apply statistical tests to non-parametric data, either the data must be transformed using a mathematical application, such as the reciprocal function used here to transform severely right-skewed data, or non-parametric tests must be used. There is some debate as to the best approach, but the non-parametric tests are less powerful detectors of statistically significant differences. Hence, given the small dataset, conversion was used when possible, and non-parametric tests when it was not, as described in Chapter 2, 2.6 Statistical Analysis. The population BMI data were transformed in preparation for statistical comparison in subsequent chapters. However, within Chapter 3 they could have been more simply summarised as median and range.

Discrepancies between text and tabulated results for beta-blocker use have been reconciled (3.2.4 Use of Beta-receptor Active Medication, page 79), and a typing error has been corrected in Table 3.2.1 Study Population Characteristics (page 76).

The subject numbers for the groups FEV<70% and FEV>70% have been clarified in Table 4.3.1 Study Population Characteristics According to FEV1/FVC Ratio (page 88) and Table 4.3.2 Symptoms According to FEV1/FVC Ratio (page 90)

The text accompanying Figure 6.4.1 Population Results - Subjects with Airways Obstruction and BDR (page 110) has been amended to include the subject numbers included in the analysis. Because the author is aware that the substantial amounts of missing spirometry data, due to subject attrition and technically inadequate spirometry, do limit the interpretation of the these results, a caveat to this effect has also been added.

References

1. Eichhorn E, Bristow M. Practical guidelines for initiation of beta-adrenergic blockade in patients with chronic heart failure. American Journal of Cardiology 1997;79:794-8.

2. Global strategy for asthma management and prevention. In: Global initiative for asthma; 2007.