DOCTOR OF MEDICINE

Evaluation of beta-blockers for the treatment of asthma and chronic obstructive pulmonary disease.

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EVALUATION OF BETA-BLOCKERS FOR THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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DEGREE OF DOCTOR OF MEDICINE

MARCH 2014
UNIVERSITY OF DUNDEE

For Louise and Aoife

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ABBREVIATIONS

ACQ	=	Asthma control questionnaire
AHR	=	Airway hyper-responsiveness
ANOVA	=	Analysis of variance
ATP	=	Adenosine triphosphate
AWR	=	Airway resistance
BDP	=	Beclomethasone dipropionate
BP	=	Blood pressure
cAMP	=	Cyclic adenosine monophosphate
COPD	=	Chronic Obstructive Pulmonary Disease
FEF_{25-75}	=	Forced expiratory flow within 25 and 75% of FVC
FEV_1	=	Forced expiratory volume in one second
fres	=	Resonant frequency
FVC	=	Forced vital capacity
GCP	=	Good Clinical Practice
GDP	=	Guanosine diphosphate
GOLD	=	Global Initiative for Chronic Obstructive Lung Disease
GTP	=	Guanosine triphosphate
HIC	=	Health Informatics Centre
HBSIMD	=	Health board specific deprivation index
HR	=	Heart rate
ICD	=	International Classification of Disease
ICS	=	Inhaled corticosteroids
IL	=	Interleukin
IOS	=	Impulse oscillometry

LABA	=	Long-acting beta-agonist
MAP	=	Mitogen-activated protein
MiniAQLQ	=	Mini Juniper Asthma Quality of Life Questionnaire
NHS	=	National Health Service
PDE4D	=	Phosphodiesterase 4D
PEF	=	Peak expiratory flow
PKA	=	Protein kinase A
R5	=	Airway resistance at 5 Hertz
R20	=	Airway resistance at 20 Hertz
SEM	=	Standard error of the mean
SIMD	=	Scottish Index of Multiple Deprivation
SMR	=	Scottish morbidity records
SRM	=	Standardised response mean
TARDIS	=	Tayside Respiratory Disease Information System
TGF-b1	=	Transforming growth factor beta-1
X5	=	Distal capacitive reactance

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I would also like to thank my family, in particular my wife Louise and our daughter Aoife for their love and support.

DECLARATION

I hereby declare that I am the author of this thesis, that all references cited have been consulted by me and that I have carried out the work described in this thesis.

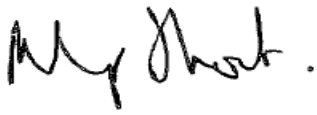
The work contained within this thesis was carried out during my appointment as a Clinical Research Fellow in the Asthma and Allergy Research Group, Division of Cardiovascular and Diabetes Medicine, Medical Research Institute, University of Dundee under the clinical and educational supervision of Professor Brian Lipworth.

I worked with three other research fellows during this period; Dr Peter Williamson, Dr William Anderson and Dr Douglas Elder. Clinical research technicians within the department performed the majority of study visits for the randomised controlled trials included in this thesis. I was principal investigator for all studies included in this thesis.

The chronic beta-blocker dosing study was derived from a Chief Scientist Office awarded to Professor Lipworth and Dr Peter Williamson prior to me starting in the Asthma and Allergy Research Group. I contributed to the study design. I was responsible for study design of the acute beta-blocker dosing study with the support of Professor Lipworth. I was fully responsible for study submission to the relevant regulatory authorities, data analysis and interpretation and write-up of both randomised controlled trials. Dr William Anderson assisted in study recruitment for the chronic beta-blocker dosing study.

For the observational COPD study, Dr Douglas Elder provided statistical advice and support. I was fully responsible for study design, submission, data analysis and interpretation and write-up.

The work described in this thesis has not been previously accepted for a higher degree and I have defined the nature of my contribution to the work described in this thesis.



Philip Short 9th March 2014

SUMMARY STATEMENT

Beta-blockers are avoided in asthma and chronic obstructive pulmonary disease (COPD) due to the potential risk of drug induced bronchospasm. Despite these concerns, beta-adrenoceptor antagonism has recently been associated with potential therapeutics benefits in asthma. Furthermore the use of beta-blockers in COPD patients may potentially result in improved survival due to optimisation of treatment in those with concurrent cardiovascular disease. This thesis evaluates the role of beta-blocker use in asthma and COPD.

The introduction outlines the pharmacological principles associated with the human beta-adrenoceptor and its therapeutic application in the management of asthma and COPD through established treatment strategies including inhaled beta-agonists. The historical literature documenting concerns with beta-blocker use in asthma and COPD is reviewed and critiqued. Finally the hypothesis, on which this thesis is based, that beta-blockers may have a therapeutic role in the asthma and COPD is discussed. Proof of concept studies and preliminary work suggesting potential putative effects of beta-blocker use in asthma, data highlighting the burden of cardiovascular disease in COPD patients and the potential role of beta-blockers are discussed.

New data from two randomised double-blind placebo controlled trials evaluating beta-blocker use in asthma and an observational study investigating the effects of beta-blocker use on mortality in COPD are presented. The first randomised controlled trial, addresses the safety of beta-blocker use in asthma. Using the non-selective beta-blocker propranolol, the study investigated the safety of acute exposure to propranolol in asthmatics, sequentially challenged with histamine to mimic an asthma exacerbation

and evaluated the role of intravenous hydrocortisone in potentiating salbutamol reversibility. The results of this study showed there was no significance difference in salbutamol recovery measured by change in FEV_1 (ml) post histamine challenge following intravenous hydrocortisone verses placebo (mean difference 0.04 (95%CI -0.07 to 0.15), p=0.417).

The study also investigates the degree of bronchoconstriction attributable to oral propranolol in mild-to-moderate asthmatics and uses impulse oscillometry as an alternative method of assessing pulmonary function to conventional spirometry. Following 10 or 20mg of oral propranolol, a mean fall in FEV_1 of 4.7% was observed (95%CI 1.8 to 7.5), p=0.008. Impulse oscillometry showed a greater response to propranolol with an increase of 31.3% (95%CI 15.6 to 47), p= 0.04, 2 hours post propranolol dosing.

The second randomised controlled trial within this thesis, describes the first placebo-controlled trial to assess the effects of chronic dosing with oral propranolol as add-on to inhaled corticosteroids in patients with stable persistent asthma. The study investigated the hypothesis of potential therapeutic benefits of chronic beta-blocker use in asthma by improvements in airway hyper-responsiveness. This study evaluates the effects of oral propranolol on both methacholine and histamine bronchial challenges, in addition to spirometry, impulse oscillometry and inflammatory surrogates including exhaled nitric oxide. Furthermore the effects on asthma control and quality of life post chronic beta-blockade are described. Finally the safety and tolerability of acute cardio-selective beta-blockade with esmolol is compared to acute propranolol dosing and the protective effects of tiotropium are evaluated.

The main result of this study showed chronic propranolol dosing did not affect airway hyper-responsiveness, with no significant difference observed in methacholine challenge PC_{20} following chronic propranolol exposure compared to placebo, geometric mean mg/ml: 2·57 (95%CI 1·13 to 5·85) versus 2·50 (95%CI 1·14 to 5·50), -i.e. a mean doubling dilution difference (DDD) of 0·04 (95%CI -0·56 to 0·63), p=0·89. Furthermore following chronic beta-blocker dosing, FEV_1 showed a fall with propranolol versus placebo amounting to a 4·3% (95%CI -0·6 to 9·2) p=0·08

The final study within this thesis is a large observational cohort study using a disease specific dataset of COPD patients. By means of data linkage using pharmacy prescriptions, hospital admissions and mortality data, the potential effects of beta-blocker use on COPD exacerbations and mortality is examined. This study suggested a potential survival benefit with beta-blocker use amounting to a 22% reduction in mortality (HR 0.78 (95%CI 0.67 to 0.92).

The discussion of this thesis evaluates the results of each study and describes their relevance in the management of patients with asthma and COPD.

CHAPTER 1:

INTRODUCTION

1. BETA-RECEPTOR FUNCTION

a. THE HUMAN BETA-RECEPTOR

In 1948 Ahlquist classified receptors of the sympathetic nervous system into two distinct groups: alpha and beta.[1] Two decades later *Lands et al*. further subdivided the beta-adrenoceptors into subtypes: groups 1 and 2.[2] Latterly the beta-3 subtype has also been identified.[3] Beta-adrenoceptors are distributed throughout the human body with differing effects at each location (see table 1). Although beta-1-adrenoceptors are found in the lungs within alveolar walls and submucosal glands, stimulation of beta-1-adrenoceptors to circulating noradrenaline and adrenaline, predominantly affects the heart resulting in an increased chronotropic and inotropic effect.

Within the human lung, the beta-2-subtype account for approximately 70% of beta-adrenoceptors.[4,5] Autoradiographic mapping has shown that the beta-adrenoceptors seen in airway smooth muscle from both the large and small airways are entirely of the beta-2-subtype.[5] Furthermore beta-adrenoceptors found in airway epithelium and vascular smooth muscle are also entirely of the beta 2-adrenoceptor subtype. There is a uniform distribution of beta-adrenoceptors on the alveolar wall with a ratio of beta-1: beta-2 adrenoceptors of 2:1.[6] These findings are confirmed by *in situ* hybridization studies that have shown a similar distribution of beta-1 and beta-2 adrenoceptor mRNA in human lung tissue.[7,8]

The beta-2-adrenoceptor preferentially binds to adrenaline rather than nor-adrenaline, primarily due to the lack of noradrenergic innervation of human bronchial smooth muscle. Although there is no direct sympathetic innervation of human bronchial muscle, pre-junctionally, the sympathetic neurons lie close to the parasympathetic

neuron and are thought to influence beta-2-adrenoceptors here thus resulting in sympathetic modulation of cholinergic innervation. This phenomenon of beta-2-adrenoceptor and muscarinic receptor crosstalk,[9] may account for the ability of anti-cholinergic medications to inhibit beta-blocker induced bronchoconstriction in asthma.[10] [11]

The affinity to adrenaline is also thought to be due to the size and location of the ligand binding site on the beta-2-adrenoceptor.[12] Although found predominantly in airway smooth muscle, beta-2-adrenoceptors are found throughout human lung tissue, and are also found epithelium, vascular smooth muscle and submucosal glands.[6] Latterly a third group of beta-adrenoceptors has been identified which is different to the beta-1 and beta-2 subtypes. The beta-3-adrenoceptor or "atypical beta-receptors" has been found predominantly within adipose tissue and is yet to be identified within pulmonary tissue.[13]

SUBTYPE	LOCATION	PHYSIOLOGICAL EFFECT
Beta-1	Heart	Increased Myocardial Contractility
	Hypothalamus	Increased Renin Release
	Kidney	(Juxtaglomerular cells)
	Brain and Coronary Vessels	Vasodilatation
	Alveoli	Increased alveolar fluid clearance
Beta-2	Alveolar Epithelium	Increased alveolar fluid clearance
	Bronchial Epithelium	
	Airway smooth muscle	Bronchodilatation
	Skeletal muscle	Increased potassium uptake
	Vascular smooth muscle	Vasodilatation
	Liver	Increased glucose metabolism
		Increased lipolysis
	Uterus	Relaxation
	GI Tract	Decreased motility
	Gall Bladder	Relaxation
	Detrusor muscle (bladder)	Relaxation
	Eye ciliary muscle	Relaxation
		DS
Beta-3	Adipose tissue	Increased lipolysis

Table 1. Subtypes of beta-adrenoceptors

b. ROLE OF THE BETA RECEPTOR IN THE MANAGEMENT OF AIRWAY DISEASE

The human beta-adrenoceptor is a member of the seven-transmembrane family of receptors encoded by a gene on chromosome 5.[14] Through the means of coupling with a Gs protein, (which consists of the subunits α,β, and γ) to adenylate cylase there is a subsequent activation of intracellular cyclic adenosine monophosphate (cAMP). Beta-adrenoceptors exist in both an active and inactive form, and at rest the inactive form is predominant. The beta-adrenoceptor is in the activated form when associated with the α subunit of the G protein in associated with guanosine triphosphate (GTP) and it is through this α subunit that it is coupled to adenylate cyclase.[14] GTP is then replaced by guanosine diphosphate (GDP) which subsequently catalyses the conversion of adenosine triphosphate (ATP) to cAMP. Furthermore the presence of GDP reduces the affinity of the α subunit for the beta-2-adrenoceptor causing it to return to its inactive form.

Within the lung the beta-2-adrenoceptor are found within varying cell types. Predominantly found within airway smooth muscle, they are also found in mast cells, post capillary venular endothelial cells, airway sensory nerves and inflammatory cells (including eosinophils, neutrophils, macrophages and T-lymphocytes). Stimulation of the beta-2-receptor with subsequent effects on cell function can occur primarily by means of binding to endogenous ligands, such as adrenaline or by the use of beta-agonists, such as salbutamol.

Airway smooth muscle relaxation

Release of cAMP causes airway smooth muscle dilatation by activation of protein kinase A (PKA) which causes phosphorylation of several proteins resulting in muscle relaxation.[15] cAMP also results in inhibition of calcium release, due to reductions in intracellular calcium stores, thus resulting in smooth muscle dilatation. Although cAMP is responsible for a significant bronchodilatory effect, pathways independent of cAMP, including interaction of the Gs protein α subunit with potassium channels within the airway smooth muscle result in muscle relaxation.[16] Furthermore beta-receptors can also bind to Gi proteins, resulting in stimulation of the mitogen-activated protein (MAP) kinase pathway with subsequent airway dilatation. [14]

Effects on inflammatory cells

Stimulation of the beta-adrenoceptor, by means of beta-agonists has been shown to inhibit the release of histamine and cysteinyl-leukotrienes within human mast cells.[17] Beta-agonists have also been shown to have a greater bronchoprotective effect against adenosine-monophosphate induced bronchoconstriction, which is mediated by mast cell degranulation in comparison to methacholine, which has direct bronchoconstrictor effects on airway smooth muscle.[18] This finding implies that beta-agonists may have mast–stabilising effects.

Beta-2-adrenoceptors have been identified in eosinophils, neutrophils, T lymphocytes and macrophages.[6,19] Whilst use of acute beta-agonists has been shown to inhibit release of inflammatory mediators, chronic beta-agonist use results in tolerance and down-regulation of the beta-receptor, meaning this benefit cannot be sustained.[6]

Effects on vascular permeability

Leakage of plasma from postcapillary venules is a hallmark of acute inflammation. Although data within asthma and COPD is poorly defined regarding the significance of airway vascular leakage, airway microcirculation is known to be abnormal in asthma.[20] To this effect beta-agonists have been shown to inhibit plasma exudation, suggesting acute anti-inflammatory effects in the airway.[21]

Airway Sensory Nerves

Beta-agonists have been shown to modulate neurotransmission via pre-junctional receptors on airway nerves.[22] Acute beta-agonist use has been shown to inhibit bronchoconstrictor responses from neuropeptides released from sensory nerves mediated via beta-2-receptors in guinea pigs.[23] The importance of sensory nerves with asthma in human subjects is still uncertain.[24]

Epithelial cells

There is a high density of beta-2-adrenoceptors in airway epithelial cells.[25] Epithelial cells can secrete a wide variety of inflammatory mediators in response to allergens and viruses, which may result in airway remodeling.[26] Migration of Th2 helper cells to the lung is key to their inflammatory function in asthma. Th2 helper cells lacking β-arrestin-2, a G protein–coupled receptor regulatory protein, demonstrate impaired migration in vitro. Furthermore in allergen-sensitized mice having a targeted deletion of the beta-arrestin gene do not accumulate T lymphocytes in their airways, thereby having reduced airway inflammation. This evidence supports the possibility of the beta-arrestin pathway being a pro-inflammatory pathway activated by beta-2-adrenoceptors in asthma.[27,28]

Extra-pulmonary effects

Although the major effects of activation of beta-2-adrenoceptors are bronchodilatation of the human airway, stimulation of extra-pulmonary beta-2-adrenoceptors influences the regulation of serum potassium. This is achieved by several mechanisms. Within the kidney, beta-2-adrenoceptor stimulation by circulating catecholamines results in increased renin levels, with subsequent aldosterone synthesis and potassium excretion.[29] Extra-renal augmentation of potassium load is also influenced by beta-2-adrenoceptor stimulation, with increased cellular uptake of potassium occurring predominantly within skeletal muscle.[29] Skeletal muscle regulates extracellular potassium by means of the Na-K-ATPase pump.[30] By means of beta-2-adrenergic stimulation, by either circulating nor-adrenaline or beta-2-agonists, the formation of cyclic AMP, acts through protein kinase A to phosphorylate and activate the Na-K-ATPase pump, leading to the influx of potassium into cells. Conversely the competitive inhibition of the beta-2-adrenoceptor by beta-blockade decreases Na-K-ATPase function and reduces potassium uptake by cells.[31] In a study by Rosa et al, the regulation of potassium homeostasis by beta-adrenergic stimulation was studied. In 9 healthy volunteers, given intravenous potassium, the addition of propranolol augmented and prolonged elevation of serum potassium without decreasing urinary potassium excretion.[29]

c. BETA-AGONISTS AND BETA-BLOCKERS

Receptor pharmacology

There are two fundamental properties requiring clarification prior to discussing adrenoceptor-ligand interactions. Affinity describes the ability of the ligand to bind to the receptor and efficacy describes the ability of the ligand-receptor complex to induce a response. Selectivity to a receptor, for example beta-1 and beta-2 selective medications is based upon the degree of affinity to the chosen receptor.

Ligands at the beta-adrenoceptor are classified as agonists or antagonists based upon the presence of efficacy. Furthermore the degree of efficacy present allows for further classification.

A full agonist has a similar response to that of the endogenous ligand and therefore displays maximal efficacy. A partial agonist also binds and activates the receptor however but only has partial efficacy relative to a full agonist.

A neutral antagonist binds at the receptor but does not have any efficacy, and does not result in any receptor activity. In reality the majority of medications considered to be antagonists do stimulate a response, whether this is as a weak partial agonist or an inverse agonist.[32] A prerequisite for an inverse agonist, is that the receptor must have a degree of constitutional activity in the absence of any ligand. Whilst an agonist increases the activity of a receptor above basal level, an inverse agonist decreases the activity below basal level and essentially “switches off” the receptor, thus displaying negative efficacy (figure 1).

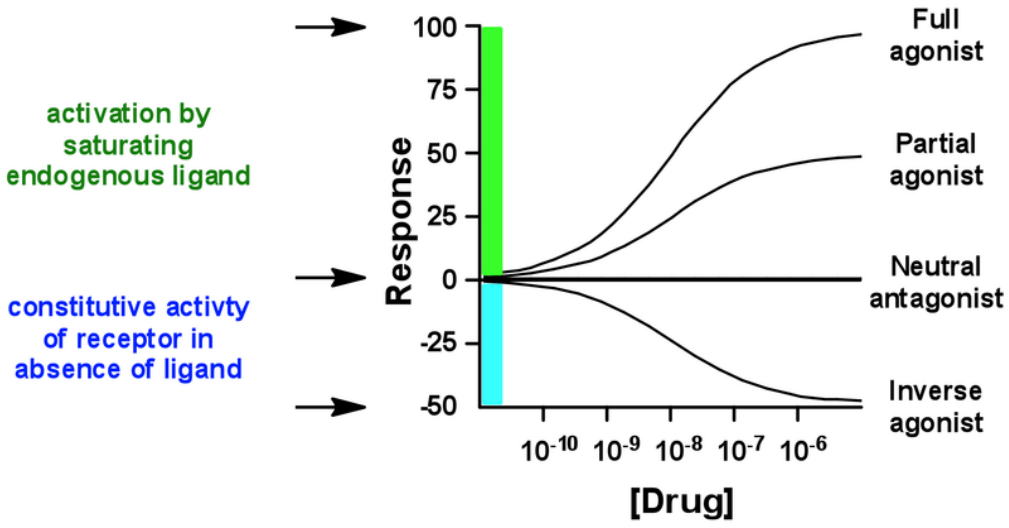


Figure 1. Dose response curves of a full agonist, partial agonist, neutral antagonist and inverse agonist. (Figure from *Wikimedia commons*, *http://en.wikipedia.org/wiki/File:Inverse_agonist_2.png*. *Figure has free license for reproduction.)*

Beta-agonists

The emergence of inhaled beta-2-agonist medications, simulating the effects of endogenous ligands provided a pharmacological means of targeting the beta-2-adenoceptor in the lungs, and thus achieving bronchodilatation. The development of the beta-2-agonist drug class has since become established as a cornerstone in the pharmacological management of asthma and COPD.[33,34]

Following the discovery by Lands et al, regarding the distinction between beta-1 and beta-2 subtypes,[2] investigators began to attempt to develop a medication which exerted bronchodilatory effects on the lungs whilst having minimal effects on the heart. Discovered independently in the late 1960s, salbutamol and terbutaline were the first

beta-2-adrenoceptor agonists found to have significant acute bronchodilatory effects in the absence of significant cardiac stimulation.[35,36]

Whilst salbutamol and terbutaline have relatively short duration of actions, following the search for long acting beta-2-agonists, both salmeterol and formoterol were developed. Whilst salmeterol and formoterol both display similar degrees of affinity for the beta-2-adrenoceptor, formoterol has a higher efficacy thus accounting for its faster onset of action.[32] The development of long acting beta-agonists revolutionised the treatment of asthma and COPD thereby providing means of achieving a sustained bronchodilatory effect of approximately 12 hours in comparison with the approximate 4-6 hours bronchodilatory effects of salbutamol and terbutaline.[37,38]

Whilst long-acting beta-agonists (LABA) undoubtedly improved the treatment of airway disease, there are concerns in asthma that sustained use of long-acting beta-agonists may results in beta-adrenoceptor tachyphylaxis and tolerance. Tachyphylaxis is defined as describing an acute (sudden) decrease in the response to a drug after its administration. Tachyphylaxis can occur both after an initial dose of medication or after an inoculation with a series of small doses. Increasing the dose of the drug may be able to restore the original response. This phenomenon known as tachyphylaxis or desensitization is exhibited upon exposure of cells to beta-adrenergic catecholamines resulting in a progressive, often rapid, loss in subsequent responsiveness of the adenylate cyclase system to further catecholamine stimulation.[39] In addition to desensitization, down-regulation of the beta-adrenoceptor can occur, describing the process of actual receptor loss following persistent catecholamine stimulation.[40]

Beta-adrenoceptor desensitization and down-regulation does have clinical relevance

with chronic beta-agonist therapy in asthmatic subjects resulting in reduction in beta-adrenoceptor density in circulating polymorphonuclear leukocytes and lymphocytes.[41]

Sustained beta-agonist stimulation has also been shown in asthma to cause progressive diminution of the agonist response in the form of a reduced bronchoprotective effect to bronchial challenge testing.[42,43] Furthermore in asthma there has been concern that regular use of LABAs had a detrimental effect on asthma control,[44] whilst the Salmeterol Multi-center Asthma Research trial (SMART study) even reported increased risk of mortality.[45] Whether or not inhaled corticosteroids given concurrently with LABAs mitigate these risks is uncertain.

In a study by Mak et al, the in vivo effects of glucocorticoids on beta-agonist induced down-regulation of beta-1 and beta-2-adrenoceptors were studied.[46] Chronic treatment of dexamethasone was associated with an increased density of beta-1 and beta-2 adrenoceptors and an increase in the transcription rate of the beta-2-adrenoceptor gene. These changes were in comparison with an observed reduction in beta-1 and beta-2 adrenoceptor density following chronic dosing with the beta-agonist, isoproterenol. Combined treatment of glucocorticoids and isoproterenol resulted in no net change in beta-2-adrenoceptor density, thereby implying that glucocorticoids prevent beta-adrenoceptor down–regulation, by augmenting gene transcription which in turn could be suggested to prevent tachyphylaxis.[46] Also in humans, high dose systemic corticosteroids have been shown to re-establish the beta-2-adrenoceptor function following agonist promoted down-regulation. These effects were seen in patients already taking inhaled corticosteroids.[47] These concerns however have resulted in the FDA advising that long-acting beta-agonists should not be given as monotherapy in asthma, suggesting they should only be used in addition to inhaled corticosteroids.[48]

Beta-adrenoceptor polymorphisms have been suggested as a potential cause of variable response to beta-agonists in individuals. The greatest attention has been given to single nucleotide polymorphism causing amino acid substitutions within the beta-2-adrenoceptor at position 16. Individuals homozygous for arginine (Arg /Arg) in comparison with those homozygous for glycine (Gly /Gly) have been found to have an improved peak expiratory flow when chronic dosing with salbutamol has been replaced with the short acting muscarinic antagonist ipratropium.[49] Further evidence of the importance of the Arg16 genotype is seen by in 164 asthmatic children taking inhaled corticosteroids and salmeterol, there was an 3.4 fold (95%CI 1.19 to 9.4) increased risk of asthma exacerbations when comparing Arg16 with Gly16 patients.[50] Although the SMART study did not stratify participants by genotype, it did indicate that the risk of death was greater in those of African American descent. Therefore although it is not possible to draw conclusions with regards to the influence of genotype on mortality within the SMART study, African Americans are known to have an increased frequency of the Arg16 polymorphism.[51]

The LARGE trial published in 2009, attempted to answer conclusively in a placebo randomised controlled trial design whether there was a genotype-specific response to treatment with a long-acting beta-2-agonists in combination with inhaled corticosteroid. The study concluded that there were beneficial effects on pulmonary function in both Arg16 homozygous and Gly16 homozygous participants, with improvements seen in both groups in morning peak expiratory flow in comparison with placebo.[52] However within the study, Gly16 homozygous participants had a 2.4 fold greater improvement in airway hyper-responsiveness (AHR) with salmeterol compared to placebo ($p<0.001$),

while participants homozygous for Arg16 showed no benefit in AHR in comparison to placebo.[52] It could therefore be postulated that in clinical practice, assessing individuals risk by testing individuals for genetic polymorphisms may be important when considering LABA therapy in asthma.[53]

Interestingly no concerns regarding LABA monotherapy exist in COPD, presumably due to the lack of significant airway hyper-responsiveness in the condition. Clinical studies have shown that LABA therapy in COPD improves lung function, reduces symptoms of breathlessness and exercise limitation, health related quality of life and may reduce exacerbations.[38] Furthermore no increased risk of mortality with LABA monotherapy was seen in the, Towards a Revolution in COPD Health (TORCH) study, over a period of 3 years.[54]

Beta-blockers

In 1964 the beta-antagonist (or beta-blocker), propranolol was released for the treatment of cardiovascular disease following its discovery by the late Nobel Laureate Sir James Black.[55,56] Following the sudden death of his father from a presumed heart attack, Sir James wanted to "stop the effects of adrenaline" on the heart, proposing that by blocking the effects of catecholamines would result in a reduction in cardiac stress, with decreased workload and subsequent anti-anginal effects.[57] This discovery revolutionised the management of cardiovascular disease with beta-blockers now routinely given for treatment of hypertension, heart failure and post myocardial infarction.[58]

Beta-blockers are primarily classified based upon beta–receptor affinity. Propranolol has similar affinity for both beta-1 and beta-2 adrenoceptor and therefore is classed as

non-selective.[59] Other examples of non-selective beta-blockers include carvedilol, nadolol and sotalol. However all classed as non-selective each of these medications have a preferential selectivity for the beta-2 adrenoceptor, varying from carvedilol with a 4.5 fold affinity to beta-2, propranolol 8.3 fold affinity and nadolol 23.4 fold affinity.[59] Similarly so called cardio-selective beta-blockers have been developed with varying degrees of beta-1 selectivity.[60] However despite their name, none in clinical use are that beta-1 selective, with bisporolol being the most selective with a 13.5 fold affinity to the beta-1-adrenoceptor.[59,60] This is in comparison with the beta-agonists salbutamol and salmeterol being 28.8 and 2818.4 fold selective to the beta-2-adrenoceptor.[59]

2. HISTORICAL PERSPECTIVE OF BETA-BLOCKER USE

a. BETA-BLOCKER USE IN AIRWAYS DISEASE

Despite the emerging role for beta-blockers in the treatment of cardiovascular disease this was accompanied by concerns regarding beta-blocker use in patients with airway disease. The greatest concern was found in asthmatics due to antagonism of the beta-2-adrenoceptor, resulting in unopposed parasympathetic bronchoconstriction thereby limiting their use. To date prescription of beta-blockers in patients with asthma or COPD would be in contradiction with accepted clinical practice.

The concern regarding beta-blocker primarily in asthma was addressed through a small number of clinical trials looking at the interaction of beta-blockers and asthmatics and a series of case reports illustrating potential adverse effects. These findings have subsequently influenced beta-blocker use in both asthma and COPD.

In 1964 whilst based in Maryfield Hospital (Dundee, UK) McNeill assessed the effects of intravenous propranolol in a group of 10 asthmatic patients.[61] Administration of 5-10mg intravenous doses of propranolol, resulted in a fall in forced expiratory volume in 1 second (FEV_1) on average of 23% (range 6% to 56%). However looking at individual response following propranolol, 60% of patients had no significant fall in their FEV_1 measurements post propranolol when comparing baseline measurements to final measurements that varied from 60-90 minutes post propranolol.[61] Infact with intravenous propranolol having a distribution half-life of approximately 5-10 minutes, comparing the maximal fall in FEV_1 15 minutes post propranolol 60% of participants have FEV_1 falls comparable with the physiological variation of the test (see figure 2).

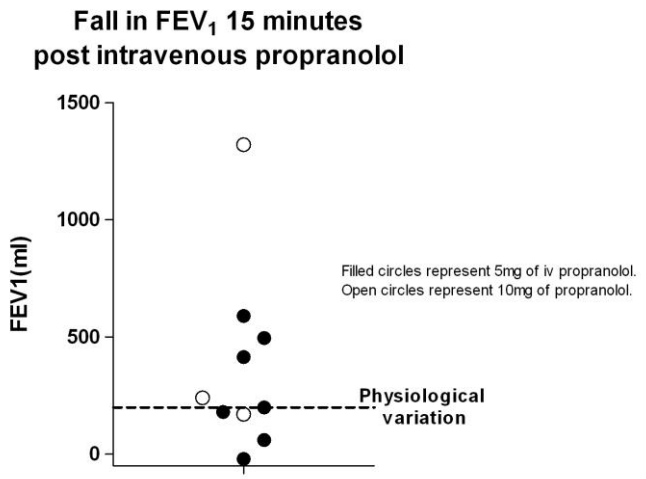


Figure 2. Fall in FEV_1 15 minutes post intravenous propranolol. (Derived from McNeill et al).[61]

Two years later, Zaid and Beall investigated the effects of serial bronchial challenges with histamine and methacholine (mean dose 4.5mg) before and after an intravenous injection of 0.1mg/kg of propranolol.[62] Three distinct patient groups were involved in this study: normal subjects, patients with allergic rhinitis and patients with asthma. Each individual underwent bronchial challenge testing with a fixed dose of histamine or methacholine. Following this their FEV_1 was compared to baseline measurements. Individuals were then allowed to recover and then were administered intravenous propranolol and FEV_1 measurements were recorded, prior to being rechallenged with histamine or methacholine with their FEV_1. Normal subjects and rhinitis patients had no greater sensitivity to histamine or methacholine following either bronchial challenge testing or propranolol. In contrast in the group of asthmatics mean FEV_1 measurements fell by 16.6% after initial challenge testing, 9.1% post propranolol and by 29.6% with the rechallenge that followed propranolol administration (see figure 3).[62]

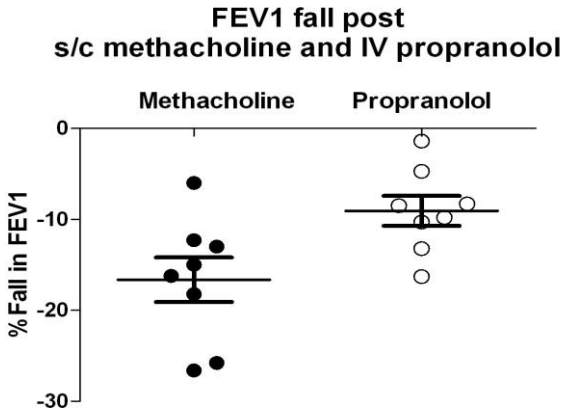


Figure 3. Fall in FEV1 post subcutaneous methacholine versus iv propranolol.

Data displayed as mean (SEM). (Derived from Zaid and Beall).[62]

At this time it was hypothesised that an intrinsic imbalance of beta-adrenergic receptor function may have been the pathophysiological cause of bronchoconstriction. Despite partial beta blockade in healthy controls the lack of increase in bronchial sensitivity to histamine or methacholine allowed the investigators to conclude that beta-blocker induced bronchoconstriction was specific to asthmatic individuals. These findings showed that although beta-blocker induced bronchoconstriction was a major concern in asthmatics, the pathophysiological cause of asthma was more complicated than simple blockade of the beta-receptor.

The study by Zaid and Beall served to highlight the relative falls in FEV_1 following the commonly used methacholine bronchial challenge agent compared to beta blockade.[62] To further demonstrate the comparative effects of methacholine induced bronchoconstriction and propranolol, in a study by Ind et al, showed inhaled propranolol to be less potent at bronchoconstriction than inhaled methacholine with a geometric mean dose causing a 35% fall in airway conductance of 4.7μmol for propranolol compared with 0.48 μmol for methacholine.[10]

The ability to reverse the bronchoconstriction provoked by beta-blockade has been questioned as a major concern with extremely high doses of salbutamol being required.[63] Ind et al however showed that the use of the anticholinergic oxitropium has been shown to reverse the bronchoconstriction caused by acute beta-blockade with propranolol.[10]

The identification of the beta-1 and beta-2 receptor subtypes by Lands et al in 1967, resulted in controlled trials being performed with non-selective beta-blockers which affinity for both beta-1 and beta-2 receptors such as propranolol and specific beta-1-receptor antagonists focussing upon individualised effects on pulmonary function.

Developing on their previous work, McNeill and Colleagues compared the effects on airway resistance of single dosing with intravenous propranolol and an intravenous selective beta-1-antagonist called ICI.50,172. [64] Airway resistance (AWR) measured via body plethysmography and FEV_1 were recorded. Propranolol was shown to be significantly worse in increasing airway resistance with a mean increase of 176% in comparison with 23% with ICI.50,172 (see figure 4). The difference with FEV_1 mirrored the trend seen with AWR with a mean fall in FEV_1 post propranolol of 44% in comparison with a fall of 9% post ICI.50,172.

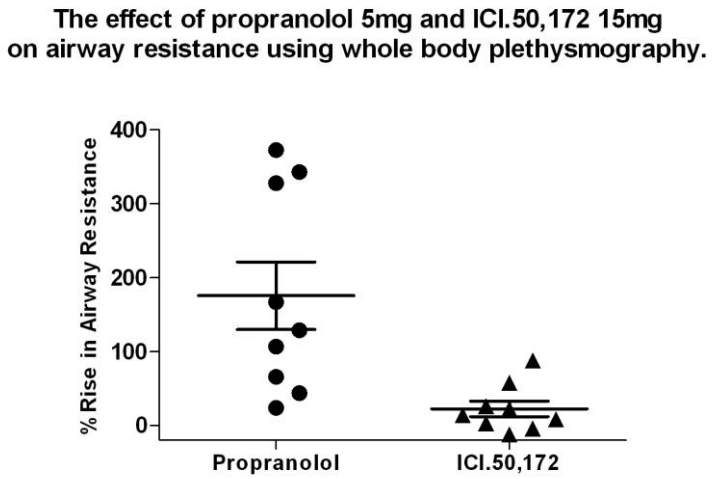


Figure 4. The effect of 5mg propranolol versus 15mg ICI.50,172 on airway resistance. Data displayed as Mean (SEM). (Derived from MacDonald et al).[64]

Johnson et al investigated the effects of intravenous propranolol and the selective beta-1-adrenoceptor antagonist metoprolol against placebo on pulmonary function in asthmatic individuals. The interaction of these drugs with increasing doses of isoprenaline was also studied.[65]

Both propranolol and metoprolol reduced FEV_1 following their administration however the effect was more pronounced following propranolol. The effects of isoprenaline, a highly efficacious non-selective beta-agonist, was also completely blocked post propranolol however were similar to placebo following metoprolol.

Following on from this Greefhorst, compared the relative deleterious effects of the relatively beta 1 selective atenolol, metoprolol and acebutolol.[66] The three beta-blockers caused similar falls in exercise heart rate after two hours ingestion, indicating their equipotency. FEV_1 fell by a significantly by a similar degree with each beta-blocker recovery occurring with the beta-2-agonist terbutaline. The degree of recovery with

acebutolol was less marked which the authors suggested may be due to the lower degree of beta-1 selectivity seen in comparison with the other two beta-blockers.

At this time it was then clear the effects of bronchospasm seen with cardio-selective beta-blockers was less and the bronchodilator activity of beta-2-agonists could be preserved. Through these findings it was postulated that beta-1-adrenoceptor antagonists could potentially be used in asthmatics provided they were combined with beta-2-adrenoceptor agonists.[66]

b. CASE REPORTS AND CONTRAINDICATIONS

Concerns regarding beta-blocker use in asthma and COPD stems from previous case reports and safety of medicines registries.[67-69] As increasing evidence emerged subsequent guidance from the Committee of Safety of Medicines in 1987 stated that beta-blockers whether selective or non-selective should not used in asthmatics due to associated risks of bronchospasm. The Committee on Safety of Medicines reported that 347 cases of bronchospasm and 25 deaths had been reported with beta-blockers with the majority of these events occurring in patients with asthma or obstructive airway disease.[70] The concern regarding beta-blocker prescription remains to this day with a consensus statement from the European Society of Cardiology stating that, a history of asthma should be considered a contra-indication to the use of any beta-blocker.[71] These guidelines are also routinely applied to patients with COPD.

Historically case reports of severe asthma exacerbations and mortality have been reported with beta-blocker use. However it is unclear what severity of asthma these patients had and it could be argued that by today's standards these individuals were

poorly controlled. Two case reports are routinely quoted as evidence for avoiding beta-blockers in asthma.[68,69] In both cases beta-blockers were given in high doses, in a non-observed setting to asthmatics that would now be classed as poorly controlled. It could be argued that based on the potential severity of asthma in these case reports, guidance advising a complete avoidance of beta-blockers in all patients with asthma or COPD was premature.

There is more compelling evidence however of beta-blocker induced bronchoconstriction. In a group of 5 patients classified as "asthmatic bronchitics" the degree of timolol eye drops induced bronchospasm was assessed. In comparison with a group of healthy volunteers in whom there was no associated fall in FEV_1 post timolol, a mean fall of 39% in FEV_1 was seen (range 15% to 56%). This highlights the ability of timolol eye drops to be absorbed directly into the systemic circulation, bypassing first part metabolism and thus reaching the pulmonary circulation in significant concentrations to cause significant bronchoconstriction.[72]

The concerns with timolol eye drops were reaffirmed when the National Registry of Drug-Induced Ocular Side Effects at Oregon University, USA reported 16 deaths following use of timolol eye drops in those with a predisposing history of asthma or COPD.[73]

As a result of these case reports and registries underlining the concerns of use of beta-blockers in asthmatic patients it became established to limit their use in both asthma and COPD patients thereby reducing any potential respiratory side effects from occurring (see table 2).

Reported Adverse Effects of Acute Beta-Blocker Prescription in Asthma
• **1964:** *Mean fall of in FEV_1 of 23% following 5-10mg of intravenous propranolol (n=10).*[61]
• **1965:** *Mean fall of 9.1% in FEV_1 following intravenous propranolol, mean dose 4.5%. (n=8).*[62]
• **1968:** *Mean fall of 44% in FEV_1 following 5mg of intravenous propranolol. (n=9).*[64]
• **1975:** *Mean fall of 120ml in FEV_1 following intravenous metoprolol (0.12mg/kg) and 200ml fall in FEV_1 following intravenous propranolol (0.06mg/kg) (n=7).*[65]
• **1979:** *Two deaths reported with beta-blocker use in patients with airway obstruction (patient details, beta-blocker and dose not given).*[67]
• **1979:** *Mean fall in FEV_1 of 26.5% following 100mg of oral propranolol (n=10) and 53.3% following 10mg of oral timolol (n=5).*[74]
• **1981:** *Mean fall of 350ml in FEV_1 following atenolol (100mg), 360ml fall following metoprolol (100mg) and 270ml fall following acebutolol (400mg).*[66]
• **1981:** *Mean fall of 600ml in FEV_1 following single dose of timolol eye drops (n=5).*[72]
• **1981:** *Near fatal bronchospasm reported following oral nadolol.*[68]
• **1984:***Maximum fall in FEV_1 of 17.6% following intravenous propranolol(n=6) (dose not given).*[75]
• **1984:** *16 deaths reported following timolol eye drops use.*[73]
• **1987:** *347 cases of bronchospasm with 25 deaths (reactions reported to both oral (n=299) and eye-drop preparations (n=48).*[70]
• **2001:** *Bronchospasm reported in 5 asthmatics (2 oral, 3 topical).*[76]

Table 2. Adverse Effects of Beta-Blocker in asthma

c. EMERGING SAFETY DATA

No clear distinction between the potential adverse effects of non-selective and cardio-selective beta-blockers is made by clinical guidelines, with advice suggesting a complete avoidance of beta-blockers regardless of selectivity in asthma and COPD.[71] However limited data suggests that cardio-selective beta-blockers may be tolerated in patients termed to have "reactive airway disease" without any clear evidence of respiratory adverse effects. In a meta-analysis by Salpeter, randomised placebo controlled trials, which studied the effects of cardio-selective beta-blockers in

predominantly patients with COPD were evaluated.[77] In total 19 studies evaluating single dose treatment and 10 studies investigating chronic treatment (range 3 days to 4 weeks) were included. Within the meta-analysis administration of a single dose cardio-selective beta-blocker was associated with a 7.46% (95%CI 5.59 to 9.32) reduction in FEV_1. This was in contrast with the non-significant fall in FEV_1 of -0.42% (95%CI -3.74 to 2.91) seen with chronic treatment. Furthermore a smaller FEV_1 response to beta-agonists was seen with acute treatment at 4.63% (95%CI 2.47 to 6.78) in comparison with chronic treatment of 8.74% (95%CI 1.96 to 15.52).

With the absence of any worsening in symptoms following beta-blocker use demonstrated, this meta-analysis concluded that due to their potential beneficial effects in the treatment of cardiovascular disease, cardio-selective beta-blockers should not be withheld in individuals with mild to moderate reactive airway disease.[77]

The conclusions from this meta-analysis have latterly been supported by a Cochrane review focusing on the effects of cardio-selective beta-blockers in COPD.[78] Within the Cochrane review, 11 studies of single-dose treatment and 11 of treatment for longer durations, ranging from 2 days to 16 weeks, met selection criteria. Cardio-selective beta-blockers, given as a single dose or for longer duration, produced no change in FEV_1 or respiratory symptoms compared to placebo, and did not affect the FEV_1 treatment response to beta-2-agonists.[78]

Despite safety concerns, co-prescription of beta-blockers in asthma patients does occur, with a previous analysis of prescriptions issued in primary care in the Tayside region of Scotland demonstrating that 1.7% of patients receiving a beta-blocker prescription had received a beta-2-agonist in the preceding 30days.[79] In an observational study by

Morales et al, the frequency of oral beta-blocker prescriptions in patients with asthma in general practice was recorded. The main outcome of the study was to determine whether beta-blocker prescriptions resulted in an increased prevalence of severe asthma exacerbations requiring oral steroids use.[80] The incidence of oral beta-blocker prescriptions in patients with asthma was 6.4 per 1000 asthma patients per year with an annual prevalence of 2.2%. Furthermore the study found that the concerns of large increases in the number of patients prescribed rescue oral steroids did not occur following new oral beta-blocker therapy in active asthma.

d. THE ROLE OF BETA-BLOCKERS IN HEART FAILURE

Following the discovery of beta-blockers their benefits in the treatment of cardiovascular disease, immediately became apparent. Propranolol itself was shown to have blood pressure lowering and anti-arrhythmic properties.[81,82] With the development in the number of available beta-blockers came further evidence of their beneficial effects, with beta-blockade post myocardial infarction shown to reduce mortality.[83,84]

Despite initial benefits being seen in the setting of hypertension and post myocardial infarction, acute dosing with beta-blockers in the setting of heart failure was avoided due to their reduction in cardiac contractility and increased risk of acute pulmonary oedema and short term adverse effects. [85] Conversely beta-agonists were routinely used due to their ability to improve myocardial contractility and cardiac output. However despite these acute benefits, chronic beta-agonist use in heart failure was associated with beta-receptor down-regulation and desensitization with ultimately increasing mortality.[86,87] As a result of these concerns, beta-1-agonists, for example dobutamine are now only used in the acute management of heart failure in severely unwell

hospitalised patients. This use of beta-agonists in the management of heart failure is intriguing due to the acute beneficial and chronic deleterious effects of beta agonist use in heart failure patients.

Due to the potential acute deleterious effects it was widely accepted that beta-blockers should not be given to heart failure patients.[88] In 1975 Waagstein et al, published work in congestive cardiomyopathy demonstrating a benefit with chronic beta-blockade.[89] This work represented a change in practice and thinking and would lead on to major multicentre trials including CIBIS-II,[90] COPERNICUS[91] and MERIT-HF[92] all showing an approximate 1/3rd reduction in total mortality after chronic treatment with bisoprolol, carvediolol and extended release metoprolol succinate respectively.

Thus the beneficial effects of chronic dosing overcame concerns of initial deterioration and possible fatal pulmonary oedema following acute beta-blocker use. In order to avoid the potential for decompensating pulmonary oedema, chronic beta-blocker dosing is achieved by gradual dose titration. The evolution of beta-blocker use in heart failure from a contraindicated drug to routine use is intriguing. In fact the use of beta-blockers in heart failure has further evolved that to not give a beta-blocker to a heart failure patient without any contraindication could now be considered unethical.

3. THERAPEUTIC USE OF BETA-BLOCKERS IN ASTHMA

a. THE BETA-BLOCKER HYPOTHESIS

The observed effects of beta-blocker use in heart failure prompted investigators to evaluate the chronic dosing effects of beta-blockers in asthma.[93] Based upon the differing acute and chronic effects of beta-antagonists in heart failure, whilst it was clear that acute beta-blockade in asthma was detrimental, the chronic effects of beta-blockade had not been examined.[94] The concept for putative beneficial effects on airway hyper-responsiveness with chronic beta-blockade in asthma may be plausible when it is considered that in asthma chronic exposure to beta-agonists causes beta-adrenoceptor down-regulation (reduction in receptor density and subsequent desensitisation) with associations to increasing exacerbations and loss of asthma control. This is in contrast to chronic administration of beta-blockers in heart failure with subsequent receptor up-regulation, with associated reductions in mortality (see table 3).[95]

Prolonged treatment with an inverse agonist such as nadolol, carvediolol and propranolol, by reducing constitutive receptor activity, would permit the system to resensitize with subsequent up-regulation of beta-2-adrenoceptors. [96] The process by which beta-adrenoceptor up-regulation occurs with nadolol has previously been studied. In a study by Ohkuma et al, up-regulation of beta-adrenoceptors induced by nadolol is mediated by at least, two different processes, namely an increase in translocation of receptor proteins from cytosol to membrane with no changes in synthesis of receptor proteins and their mRNA and secondly increases in receptor protein synthesis with subsequent increased synthesis of their mRNA.[97] In asthma it was hypothesised that this

beta-adrenoceptor up-regulation may translate into beneficial effects on airway hyper-responsiveness.

Beta-adrenoceptors : Acute vs. chronic therapy				
		Heart failure	**Asthma**	**β-adrenergic receptor expression**
Acute	**Agonist**	**Beneficial (↑contractility)**	**Beneficial (bronchodilation)**	↔
	Antagonist	**Detrimental (↓contractility)**	**Detrimental (bronchoconstriction)**	↔
Chronic	**Agonist**	**Detrimental (↑mortality)**	**Detrimental? (↑AHR/Exac)***	↓
	Antagonist	**Beneficial (↓mortality)**	***Beneficial? (↓AHR)***	↑
*AHR; airway hyper-responsiveness: Exac; exacerbation rate				

Table 3. Effects of acute and chronic beta-adrenoceptor agonism and antagonism. (Derived from Lipworth and Williamson)[95]

b. MURINE MODELS

Callaerts-Vegh et al published the first evidence suggesting potential putative benefits of chronic beta-blockade in asthma in 2004.[98] In mice systemically sensitized to ovalbumin in order to simulate an "asthmatic model", both carvediol and nadolol were found to reduce airway resistance to methacholine bronchial challenge agent and increase beta-adrenoceptor density following chronic 28 day dosing. These findings were in comparison with significant worsening in airway resistance to methacholine demonstrated after acute dosing. [98]

Both carvedilol and nadolol are examples of relatively non-selective beta-blockers with inverse agonist activity (i.e the ability to decrease receptor activity below basal level

and essentially "switches off" the receptor), resulting in the authors concluding that beta-blockers with inverse agonist properties may exert reciprocating effects on cellular signaling dependent on duration of administration.[98]

This study was followed by further data demonstrating an improvement in airway hyper-responsiveness and beta-2-adrenoceptor density in murine models of asthma following chronic administration of nadolol and ICI-118,551 (a highly beta-2-adrenoceptor selective antagonist). This was in contrast with the lack of significant improvements in AHR and adrenoceptor density following chronic metoprolol, a cardio-selective beta-blocker. [99]

In addition to beta-2-adrenoceptor up-regulation, chronic nadolol was associated with down regulation of phosphodiesterase 4D (PDE4D), which is normally associated with cAMP degradation and smooth muscle bronchoconstriction. Thereby providing evidence of a potential chronic bronchodilatory effect with nadolol.[99]

Chronic nadolol and ICI-118,551 in murine models of asthma have been shown to have anti-inflammatory properties. Chronic use for 28 days was associated with reductions in total cell counts, eosinophils, and the interleukins IL-13, IL-10, IL-5, and transforming growth factor beta-1 (TGF-b1) in bronchoalveolar lavage, and attenuated epithelial mucin content (see table 4).[100]

Finally further evidence to support the potential role of beta-blockers in asthma can be derived from beta-2-adrenoceptor knockout mice. Being devoid of beta-2-adrenoceptors these murine models do not develop the asthmatic phenotype of mucous metaplasia,

increased AHR to bronchial challenge testing or inflammatory cells within bronchial alveolar lavage.[101]

Chronic Effects of Nadolol in Murine Model of Asthma
• *Reduced AHR to methacholine.*[98,99]
• *Increased beta-2-adrenoceptor density*[98,99]
• *Decreased total inflammatory cells and eosinophils*[100]
• *Decreased mucous metaplasia*[100]
• *Decreased mucin production*[100]
• *Decreased cytokines (Interleukins 5, 10, 13 and TGF-b1)*[100]
• *Decreased expression of PDE4D*[99]

Table 4. Chronic effects of Nadolol in Murine Models of Asthma

c. PILOT STUDIES

In view of the potential putative effects of beta-blockers demonstrated in murine models, Hanania et al performed the first open label study of chronic non-selective beta-blocker use in asthmatic patients in 2008.[102] Performed in mild steroid naïve asthmatics with an FEV_1 of >80% predicted, 10 participants underwent a dose titration of nadolol over a 6 week period with a further plateau period of 3 weeks once the maximum dose tolerated had been achieved. The maximum dose tolerated varied from 10mg (3 participants), 20mg (4 participants) and 40mg (3 participants). Notably of the 3 participants that only managed to tolerate 10mg, 2 of these participants had significant falls in FEV_1 that prevented further dose titration.

Although designed primarily as a safety study, the effect of chronic nadolol dosing on airway hyper-responsiveness was assessed. Of the 7 participants that tolerated 20mg or 40mg of nadolol, there was a 1.8 doubling dilution shift in methacholine challenge following chronic dosing in comparison with baseline nadolol naïve measurements. This change is comparable with the improvements seen with inhaled corticosteroids.[103] Furthermore there was a dose dependent improvement in AHR was seen with chronic nadolol dosing ($r=0.86$, $p=0.0016$) with a 2.1 doubling dilution shift seen with 40mg of nadolol ($p=0.0042$).

As expected following acute dosing with nadolol there was a significant fall in mean FEV_1 of 7.4 % predicted. Following chronic nadolol dosing a significant fall in FEV_1 was observed with a mean change of 5% in comparison with baseline values ($p<0.05$). However it was noted that all participants were able to tolerate chronic nadolol dosing without any change in respiratory symptoms. Systemic beta-blockade was suggested by a mean fall in heart rate of 7 beats per minute, however this change was not significant ($p=0.051$).

The results of this study were intriguing given the disconnect seen by improvements in AHR with chronic nadolol dosing whilst worsening airway calibre was demonstrated by a significant albeit relatively small fall in FEV_1.

These findings were seen subsequently repeated in another study of 10 mild steroid naïve asthmatics performed by the same group, with a doubling dilution shift (SEM) of 1.79 (0.44), $p=0.004$ seen following methacholine challenge with chronic nadolol dosing over a 13 week period.[104] Interesting within this study 7 out of the 10

participants were able to tolerate the maximal dose of 40mg of nadolol. This is in comparison with 3 out of 10 participants in the first study[102] and may be associated with the longer dose titration period of 10 weeks within this subsequent study.[104]

4. THERAPEUTIC USE OF BETA-BLOCKERS IN COPD

a. MORBIDITY AND MORTALITY OF COPD

Chronic obstructive pulmonary disease is associated with significant morbidity and mortality. Estimated to become the third leading cause of death worldwide by 2020, the presence of concurrent cardiovascular comorbidities within patients with Chronic Obstructive Pulmonary Disease (COPD) are increasingly becoming recognized as modifiable risk factors.[105,106] Furthermore the presence of cardiovascular disease in COPD patients is significantly higher than the rates found in those without COPD. A pooled analysis of two large population-based epidemiological studies by Mannino et al, showed the prevalence of cardiovascular disease (defined as ischaemic heart disease, heart failure, stroke and/or transient ischaemic attack) in COPD patients was found to be 20–22% compared with 9% in subjects without COPD.[107]

COPD and cardiovascular disease are undoubtedly linked due to smoking related atherosclerosis, however evidence suggests that despite this link the prevalence of cardiovascular disease is greater in COPD patients in comparison with matched smoking controls. In the "Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points: (ECLIPSE) study ECLIPSE study, ''heart trouble'' was reported in 26% of 2,164 COPD patients compared with 11% of 337 smoking controls ($p=0.001$).[108] Patients with COPD frequently exacerbate with the risk of subsequent hospital admission independent to the severity of underlying pulmonary function.[109] Furthermore patients admitted with COPD exacerbations have an increased frequency of concurrent myocardial infarction.[110] Therefore early identification of COPD patients at risk of developing cardiovascular disease is of great importance. With the exception of long term oxygen therapy, no therapeutic management in COPD has been associated

with a significant reduction in mortality.[111,112] As a result the treatment of cardiovascular disease within COPD patients provides means of a potential method to improve long term outcome.

b. OBSERVATIONAL STUDIES

With the exception of highlighting the potential concerns with beta-blocker use, clinical guidelines do not differentiate the treatment of cardiovascular disease in COPD patients.[58] Therefore unsurprisingly statins, angiotensin-converting enzymes inhibitors and angiotensin receptor blockers have all demonstrated beneficial effects in the treatment of cardiovascular disease in COPD populations.[113] Beta-blockers have been associated with a reduction in mortality post-myocardial infarction and are now integral in the treatment of cardiovascular disease.[114] The use of beta-blockers in COPD patients however remains controversial and subsequently they are under-utilised in COPD patients.[115] However in addition to the emerging safety data regarding beta-blocker use, several observational studies have now focussed upon the use of beta-blockers in the COPD populations.[78,116-118]

Potential benefits of beta-blocker use in COPD patients have been demonstrated in several observational studies. Dransfield et al performed a retrospective study in patients admitted with an acute exacerbation of COPD as a primary diagnosis, those who with a history of beta-blocker treatment had reduced mortality OR 0.39 (95%CI 0.15 to 0.99)).[119] In patients who underwent major cardiovascular surgery, those with COPD who were treated with cardio-selective beta-blockers had a lower 30-day OR 0.37 (95%CI 0.19 to 0.72) and long-term mortality HR 0.73 (95%CI 0.6 to 0.88) compared with those who did not receive this treatment.[117] A recent study in the Netherlands using general practice electronic records, which included 2,230 patients

Netherlands using general practice electronic records, which included 2,230 patients with a diagnosis of COPD, also suggested that beta-blocker use was associated with decreased mortality HR 0.68 (95%CI 0.56 to 0.83) and exacerbation frequency HR 0.71 (95%CI 0.60 to 0.83).[116] Furthermore a recent meta-analysis has shown an overall beneficial effect on survival in COPD with the nine retrospective studies included resulting in a pooled relative risk of COPD related mortality secondary to beta-blocker use of 0.69 (95%CI 0.62 to 0.78) I2=82%.[120] Although the potential beneficial effect of beta-blocker use in COPD is encouraging, at present no randomised controlled trial exists that examines the use of beta-blockers in COPD to either support of refute these findings.

5. SUMMARY AND THESIS OBJECTIVES

Beta-blockers are avoided in asthma and COPD due to concerns of drug induced bronchospasm. This thesis evaluates the use of beta-blockers in asthma and COPD by means of both randomised controlled trials and observational studies.

a. PROOF OF CONCEPT STUDIES IN ASTHMA

Two randomised controlled trials are included in this thesis. These studies address the safety of acute dosing of both cardio-selective and non-selective beta-blockers and the chronic dosing effects of non-selective beta-blockade.

Patients' safety is paramount when conducting clinical trials with beta-blockers in asthma. Therefore firstly a study was designed to assess the effects of acute dosing of the non-selective beta-blocker, propranolol. The aim of the study was to establish whether ingestion of a single dose of oral propranolol would prevent subsequent salbutamol and ipratropium recovery, following histamine challenge to mimic acute bronchoconstriction present during an asthma exacerbation. The results of this study are discussed in chapter 3. Within the acute doing study, a novel method of assessing airway calibre, namely impulse oscillometry (IOS) was used in addition to standardised spirometry. In a post-hoc analysis of the acute dosing study the relative sensitivities of IOS and spirometry were compared in the assessment of bronchoconstriction to propranolol and bronchodilatation to salbutamol. The results of this analysis are discussed in chapter 4.

The second randomised controlled trial included in this thesis, evaluates the effects of chronic dosing with propranolol in mild-to-moderate asthmatics controlled on inhaled corticosteroids. The aim of this study was to assess whether the putative beneficial effects of non-selective beta-blockade on airway hyper-responsiveness, previously demonstrated in open label studies could be reproduced in a placebo controlled trial in asthmatics controlled on inhaled corticosteroids.[102,104] Furthermore the safety profile of chronic beta-blocker dosing in asthma was assessed. The results of this study are discussed in chapter 5. Within the chronic dosing study, prior to randomisation to propranolol or placebo, a safety visit where participants received an intravenous dose of the cardio-selective beta-blocker, esmolol was performed. The results of this subgroup analysis are discussed in chapter 6.

b. OBSERVATIONAL STUDY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Previous studies have suggested a potential survival benefit with beta-blocker use in COPD.[116,120] These studies have however failed to assess the interaction of beta-blockers with beta-agonists given the theoretical interactions or the interaction with other inhaled bronchodilators. In order to address this an observational study of a National Health Service (NHS) database of COPD patients was performed. This study evaluated the impact of beta-blocker use on mortality, hospital admissions and exacerbations when added to established stepwise inhaled therapy for COPD. The results of this study are discussed in chapter 7.

CHAPTER 2:

METHODS

1. RANDOMISED CONTROLLED TRIALS

Detailed protocols for each analysis will be described in chapters 3 to 6, however many aspects of the methodology are common to all studies, and are therefore are described here.

a. ASTHMA SUBJECT SELECTION

Asthmatic subjects were recruited from the Asthma and Allergy Research Group database. This database includes individuals who have agreed to be contacted with regards to participating in clinical research within the department. Potentially suitable participants were contacted by telephone or post and invited to participate based upon their baseline demographic data held within the database including age, onset of asthma symptoms, lung function, symptom scores, treatment and airway hyper-responsiveness. Further subjects were recruited by the use of local advertising: posters in the hospital and advertisements in local press. Potential participants received a written participant information sheet detailing the individual study requirements and the extent of their participation before attending the department for a screening visit. All patients who entered the studies had a clinical diagnosis of asthma as defined by current guidelines.[121]

All participants were between 18 and 65 years of age. Participants were required to have a normal screening examination, comprising physical examination, urinalysis, and haematology and biochemical screening prior to enrollment. All participants were consented by the principal investigator or appropriate research team member who had the appropriate good clinical practice (GCP) training and was named on the delegation log.

All study protocols and subject information sheets were approved by the Tayside Committee on Medical Research Ethics. All study materials where appropriate were approved by the Medicines and Healthcare Products Regulatory Authority.

b. SPIROMETRY

Spirometry was performed in accordance with the published American Thoracic Society guidelines.[122] Participants were asked to breathe in to total lung capacity and then exhale forcibly to residual volume. This manoeuvre allowed calculation of FEV_1 (forced expiratory volume in 1 second), FEF_{25-75} (forced expiratory flow within 25% and 75% of forced vital capacity) and FVC (forced vital capacity). All measurements were carried out in triplicate. The highest of 3 values for FEV_1, repeatable within 5% was recorded and the percentage predicted (according to sex, ethnicity, height and weight) was calculated. A Micro Medical SuperSpiro (Micro Medical Ltd, Rochester, United Kingdom) was used for all studies.

c. IMPULSE OSCILLOMETRY

Impulse oscillometry (IOS) was performed in accordance with published guidelines.[123] IOS is an effort independent method of assessing airway resistance by the use of small amplitude sound waves being superimposed on normal breathing cycles. Participants supported their cheeks to reduce shunting, whilst impulses were applied during 30 seconds of tidal breathing. This manoeuvre allows airway resistance and reactance to be determined. All measurements were performed in triplicate and means taken. A Jaeger Masterscreen Impulse Oscillometer (Erich Jaeger, Hoechberg, Germany) was used for all studies.

d. BRONCHIAL CHALLENGE TESTING

Airway hyper-responsiveness is usually defined as an increase in sensitivity to a wide variety of airway narrowing stimuli. Both methacholine and histamine bronchial challenge tests are used to measure airway hyper-responsiveness (AHR) in asthma. However airway hyper-responsiveness is a composite of airway hypersensitivity to the inhaled stimulus and the associated reduction in airway calibre observed. Within this thesis a 20% fall in FEV_1 following less than or equal to 8mg/ml of methacholine or histamine is considered evidence of increased AHR.

Methacholine was made up into doubling dilutions with concentrations ranging between 0.03 to 32mg/ml. Histamine was made up into doubling dilutions with concentrations ranging from 0.3125 to 40mg/ml. Solutions were prepared by Tayside Pharmaceuticals (Ninewells Hospital, Dundee) using the diluent benzyl alcohol. Bronchial challenge testing was performed according to recommended guidelines using a validated computer assisted dosimetric method.[124,125] A baseline FEV_1 measurement was taken prior to each challenge test to ensure participant safety. Participants with an FEV_1 less than 60% predicted were excluded from challenge testing as per American thoracic society guidelines.[125] A further FEV_1 was taken following taken following administration of the diluent (benzyl alcohol) alone. This recording was used to derive the subsequent %fall in FEV_1 post methacholine or histamine respectively. Methacholine or histamine were then administered in doubling cumulative doses until a 20% fall from the post-diluent measurement was achieved. The PC_{20} values were calculated by computer-assisted logarithmic interpolation of the dose response curve.[126]

Whilst the PC_{20} value is generally accepted as the standardised measurement of airway hyper-responsiveness, the slope of the dose response curve has also been suggested as providing valuable information when determining airway hyper-responsiveness. When analysing the shape of the dose response curve to either methacholine or histamine, dose-response curves in asthmatic patients have a steeper slope and a higher maximal response at high doses as compared to normal controls. It has therefore been suggested that the term bronchial "reactivity" designated the slope of the curve, as opposed to bronchial "sensitivity" indicating the position (PC_{20}).[127] For the purpose of this thesis, PC_{20} was measured rather than the slope of the curve due to objective nature of this measurement.

e. EXHALED NITRIC OXIDE

Exhaled nitric oxide, a surrogate marker of airway inflammation was recorded using a portable device (NIOX MINO® Airway Inflammation Monitor; Aerocrine AB, Solna, Sweden). All measurements were made prior to measurement of spirometry to ensure accuracy of results. A sustained plateau of at least 8 seconds with a mouth flow rate of 50 ml/s and a pressure of 10 cm H_2O were used. The arithmetic mean was derived according to the current American Thoracic Society recommendations.[128]

f. PERIPHERAL BLOOD MEASUREMENTS

A 5ml blood sample for Full Blood count and a separate 3ml blood sample for measurement of Urea and Electrolytes and Liver Function were taken at respective study screening visits. Within the acute dosing study serial 3ml samples were taken for measurement of serum potassium. All blood samples were processed by the biochemistry department of NHS Tayside, Ninewells Hospital Dundee.

g. QUALITY OF LIFE MEASUREMENTS

The Mini Juniper Asthma Quality of Life Questionnaire (Mini-AQLQ) and Asthma Control Questionnaire (ACQ) were used. These questionnaires have been validated and have been shown to be sensitive markers of asthma control and quality of life.[129,130] The Mini-AQLQ has a total of fifteen questions; each question has a response score ranging from zero to seven. The questions are grouped into four domains; activity limitations, symptoms, emotions and exposure. The Asthma Control Questionnaire has seven questions, five of which are based on symptoms with the remaining two based on FEV_1 and rescue bronchodilator use. The five symptom questions have seven responses. A score of 0.75 indicates well controlled asthma, where as a score of 1.25 indicates poorly controlled asthma.[130] The minimally important difference for both questionnaires is 0.5 units.[131]

h. DOMICILLIARY LUNG FUNCTION MEASURMENTS

Domiciliary FEV_1 and peak expiratory flow were recorded in triplicate both morning and evening using an electronic handheld PiKo monitor (n-Spire Health, Longmont, Collorado, USA) according to manufacturer's instructions.[132]

i. SYSTEMIC MEAUREMENTS OF BETA-1 AND BETA-2- ADRENERGIC RESPONSE

Serum potassium was measured within this thesis as a marker of systemic beta-2-adrenergic response. Within chapter 3, measurement of serum potassium was used to determine the presence or absence of systemic beta-blockade following acute propranolol dosing. As previously described competitive inhibition of the beta-2-adrenoceptor by beta-blockade decreases Na-K-ATPase function and reduces potassium

uptake by cells, thereby resulting in increases in serum potassium.[31] Alternative measurements of systemic beta-adrenoceptor activity include measurement of beta-agonist induced tremor. Previous work in this department has assessed the relevance of these surrogate markers for assessing beta-2-adrenergic activity. When assessing the response to salbutamol, plasma concentrations of salbutamol are significantly correlated to both changes in plasma potassium (Cmax r=0.904; Cav r=0.899) and tremor (Cmax r=0.875; Cav r=0.857).[133] These results highlight the suitability of both surrogate markers of systemic beta-adrenoceptor activity. However due to the complexity of the study visits within the study described within chapter 3, serum potassium was regarded as more practically achievable marker in comparison with measurement of beta-agonist induced tremor.

Within chapter 5, resting heart rate and salbutamol induced chronotropic response were used as markers of systemic beta-blockade. These markers were chosen due to the nature of study visits. However when assessing systemic beta-blockade exercise induced chronotropic incompetence is potentially a more effective marker in comparison with measurement of resting heart rate and salbutamol induced tachycardia.[134]

2. OBSERVATIONAL COHORT STUDY

Detailed methodology with regards to the COPD Observational study included in this thesis is included in chapter 7. An overview of the COPD subject selection and the health informatics infrastructure required for the analysis are discussed here.

a. COPD SUBJECT SELECTION

Since its inception in 2001, the Tayside Respiratory Disease Information System (TARDIS) has enrolled patients with COPD into a structured management programme to support primary care practitioners and secondary care respiratory physicians in managing patients with COPD in Tayside, Scotland. Patients attend annual review visits where data including lung function, symptoms and exercise tolerance are collected. TARDIS thereby provides an unselected disease specific dataset, which has previously been used in observational studies in COPD.[135] Only patients with complete datasets and aged over 50 years at the time entry into TARDIS were included in the study described in chapter 7.

b. HEALTH INFORMATICS

The Health Informatics Centre (HIC) at the University of Dundee, provides a resource whereby several independent clinical datasets can be linked by a common patient identifier. The combined dataset generated is then anonymised and provided to the researcher. Clinical datasets provided by HIC included hospital admission data using Scottish morbidity records (SMR), prescription data from the Tayside Community Prescription database and death records from the General Register Office for Scotland. For this study each dataset was combined the TARDIS dataset, thereby providing a COPD specific dataset with outcome data including mortality, hospital admissions and COPD exacerbations (figure 5).

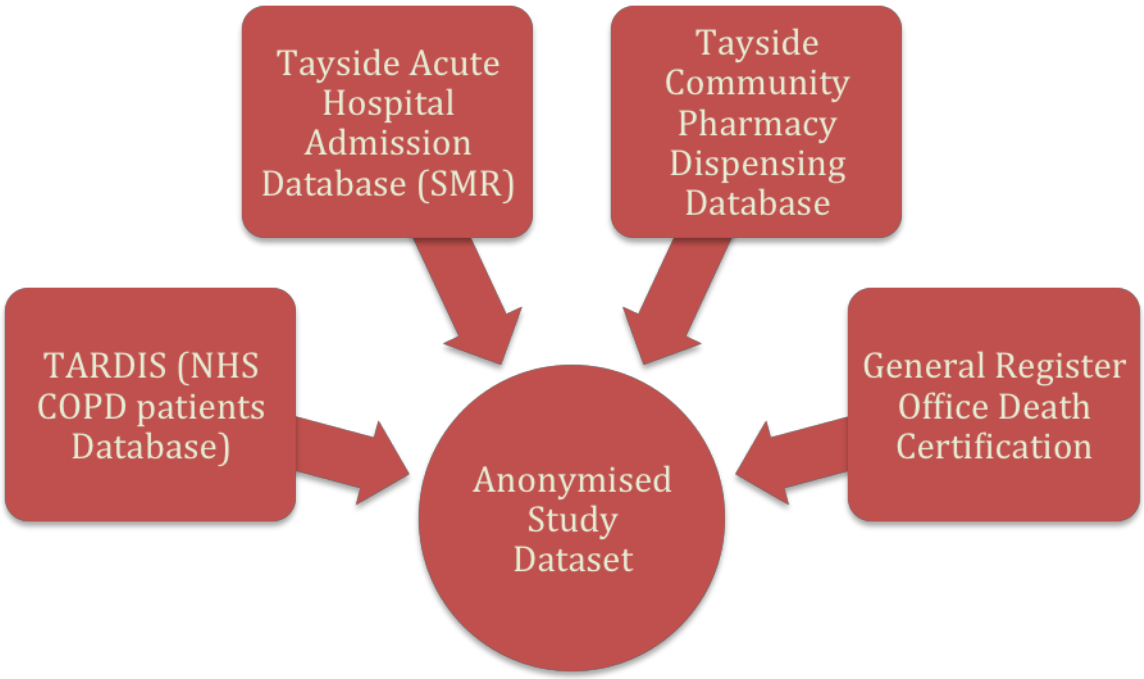


Figure 5. Flow diagram of Health Informatics Centre datasets

CHAPTER 3:

RANDOMISED PLACEBO CONTROLLED TRIAL ASSESSING THE EFFECTS OF HYDROCORTISONE ON ACUTE NON-SELECTIVE BETA-BLOCKER AND HISTAMINE INDUCED BRONCHOCONSTRICTION

Study Aims:

1. **To assess for the presence of bronchoconstriction following acute dosing with oral propranolol in mild-to-moderate asthmatics.**
2. **To establish whether acute propranolol dosing would prevent subsequent salbutamol and ipratropium recovery, following histamine challenge to mimic acute bronchoconstriction present during an asthma exacerbation.**
3. **To determine if acute administration of intravenous hydrocortisone might partially obviate the effects of acute beta-2-blockade and improve the effects of nebulised salbutamol.**

1. INTRODUCTION

Beta-blocker induced bronchoconstriction is most pronounced following the first dose with non-selective drugs due to beta-2-adrenoceptor antagonism. First shown by McNeill, in a group of 10 asthmatic patients, the mean fall in FEV_1 was 23% (range 6% to 56%) following 5-10mg of intravenous propranolol.[61]

Concern regarding beta-blocker use in asthma increased throughout the 1980s with case reports and guidance stating that beta-blockers regardless of selectivity, should not used in asthmatics due to risk of bronchospasm. [68-70] However when applied to larger asthmatic study populations, co-prescription of beta-blockers and beta-agonists has been reported.[79,136]

A meta-analysis has examined cardio-selective beta-blockers use in reactive airways disease. Although FEV_1 mean fall was 7.5% following single dosing, no significant fall was seen with chronic dosing.[77] This disconnect between acute and chronic effects, mirrors the response seen to beta-blocker use in heart failure. Once contraindicated due to concerns following acute dosing, beta-blockers are now established as a main chronic treatment choice for heart failure.[91]

With these reassurances, studies have begun to explore the potential therapeutic benefits of chronic beta-blockade in asthma. The non-selective beta-blocker, nadolol has been shown to reduce airway hyper-responsiveness (AHR) and inflammation and may lead to up-regulation of beta-2-receptors in murine models.[98,99,101] This led to two open-pilot

studies in steroid naïve asthmatics, with chronic nadolol dosing achieving significant improvements in AHR.[102,104]

Patients' safety is paramount when conducting clinical trials with non-selective beta-blockers in asthma.[137] Although salbutamol reversibility has been shown to be preserved following chronic beta-blockade with the non-selective beta-blocker nadolol,[104] concerns remain during the early period of beta-blocker exposure, primarily following the first dose, before any disease modifying activity has occurred. Previous studies have identified it takes approximately 2 weeks for beta-2-adrenoceptor up-regulation to occur, suggesting this would be the theoretical at risk period during up titration with beta-blockade in asthmatics.[138,139]

This study aimed to establish whether ingestion of a single dose of the non selective beta-blocker, propranolol would prevent subsequent salbutamol and ipratropium recovery, following histamine challenge to mimic acute bronchoconstriction present during an asthma exacerbation. Furthermore this study aimed to determine if acute administration of intravenous hydrocortisone might partially obviate the effects of acute beta-2-blockade and improve the effects of nebulised salbutamol due its acute facilitatory effects on beta-2-receptors within 3 hours of administration.[47]

2. METHODS

Study Subjects

Persistent atopic asthmatics, FEV_1 >80% predicted, taking ≤1000µg beclomethasone dipropionate (BDP) dose equivalent of inhaled corticosteroids (ICS), aged 18-65yr who had AHR to histamine challenge were recruited. All participants were non-smokers. Exclusions included resting systolic blood pressure (BP) <100mmHg and heart rate (HR) <60beats-per-minute, history of arrhythmias, diabetes or rate limiting medications. Subjects were invited to participate from a list of known volunteers who had expressed an interest to take part in clinical trials within our department. Potential participants received a written participant information sheet detailing the trial requirements and the extent of their participation before attending for a screening visit.

Study Design

A double-blind randomised placebo controlled crossover study was performed, consisting of an average of 3 (maximum 4) separate laboratory study visits over 3 weeks (see figure 6). The Tayside Medical Research Ethics Committee gave approval before commencement of the trial. The study was registered with www.clinicaltrials.gov (NCT 01070225). Blinding and randomisation of treatment limbs was performed by the Clinical Trials Pharmacy, University of Dundee.

At screening, spirometry, impulse oscillometry (IOS) and histamine bronchial challenge were performed. Participants were issued a peak flow meter (PEF) meter and continued on their regular ICS dose. Long Acting-Beta-Agonist (LABA) therapy was stopped during the study. Combination ICS/LABA was switched to ICS alone. Ipratopium was used a first line reliever therapy with salbutamol restricted to second line if required.

One week post screening visit, participants underwent their first 6 hour laboratory study visit. Following baseline spirometry and IOS, domiciliary PEF was analysed to ensure <20% diurnal variation. Participants ingested 10mg propranolol tablet. Spirometry, IOS, BP and HR were observed. At 2 hours, if fell $FEV_1 \geq$ 10% the study visit continued. If FEV_1 fell <10%, the study visit ended and was repeated on a separate day using 20mg of propranolol.

Two hours post-propranolol (10mg or when required 20mg), participants were randomised to receive 400mg of intravenous hydrocortisone or placebo (0.9% NaCl). At 4 hours post-propranolol, participants underwent histamine challenge (PC_{10}) with reversibility to sequential salbutamol 5mg and ipratropium 500mcg nebulisers. Spirometry and IOS were performed 20 minutes post salbutamol and ipratropium. Serum potassium was measured at baseline, 2, and 4 hours post-propranolol, 20 minutes post salbutamol. A final study visit was performed where treatment limbs were crossed-over (duration between visits 3-5 days). The participant received either intravenous hydrocortisone or placebo (0.9% NaCl) depending on their initial randomisation. At all study visits, the investigator was blinded to the treatment given (hydrocortisone or placebo). The same dose of propranolol was used and the visit was repeated as outlined above.

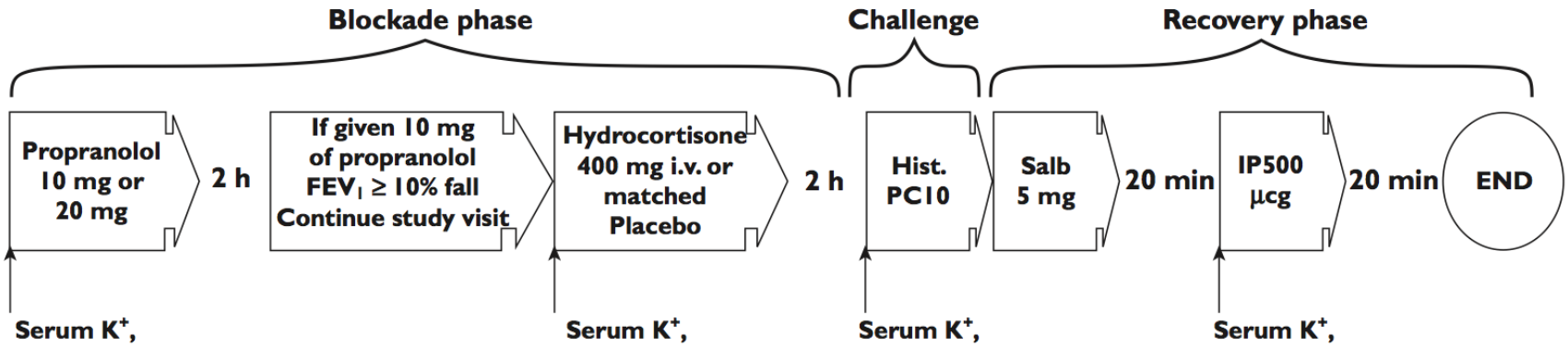


Figure 6. Study Diagram. Hist: Histamine, Salb: Salbutamol, IP: Ipratropium

Measurements

Spirometry was performed in accordance with published guidelines.[122] Impulse oscillometry (IOS) was also performed as an alternative measure of assessing lung function. IOS is an effort independent method of assessing airway resistance by the use of small amplitude sound waves being superimposed on normal breathing cycles and was performed in accordance with published guidelines.[123] The airway resistance at 5 Hz (R5) was recorded. A SuperSpiro spirometer (Micro Medical, UK) and IOS Jaeger Masterscreen (Germany) were used. Histamine Bronchial Challenge (PC_{10}) was performed. A Mefar dosimeter was used with doubling concentrations from 0.3125-to-40mg/ml. The provocative concentration of histamine required to cause a 10% and not the standard 20% fall in FEV_1 was calculated (PC_{10}) in view of safety. We did not use methacholine challenge as this would be directly antagonised by ipratropium. For the purpose of this study, atopy was defined as having a history of one or more positive skin prick tests to common allergens (grasses, trees, weeds, house dust mites, aspergillus, feathers, dog and cat).

Analysis

Data was analysed for normality with Shapiro-Wilk tests and Boxplots. The primary analysis was the difference in salbutamol recovery for hydrocortisone versus placebo. Recovery was determined as change in FEV_1 (ml) post-salbutamol from lowest post histamine FEV_1. A *priori* calculation predicted 13 patients would have an 80% power to detect a difference of 200ml between recovery FEV_1 with a 2-sided significance level of 0.05, assuming a within-patient standard deviation of 150ml. Salbutamol recovery was also assessed by change in FEV_1% predicted, R5 and R5% predicted. Secondary

analysis included assessment of beta-blocker induced bronchoconstriction, the effects of beta-blockade on staged salbutamol and ipratropium reversibility post histamine challenge, and evidence of systemic beta-blockade (serum potassium, HR, BP). Analysis of variance of repeated measures was performed with Bonferroni-correction for pair-wise comparisons with a two tailed α-error set at 0.05. All analyses were performed on a per-protocol basis using SPSS version 17 (SPSS Inc, Chicago, IL).

3. RESULTS

Of 26 participants screened, 15 participants were randomised. A total of 13 participants (7 male, 6 female) completed the study (see figure 7). Mean age (SEM) was 34 (3). 2 participants withdrew as they could not complete the study visits for personal reasons. 11 participants had less than a 10% fall in FEV_1 after 10mg of propranolol and subsequently were given 20mg. There were no adverse events following beta-blocker ingestion (see table 5).

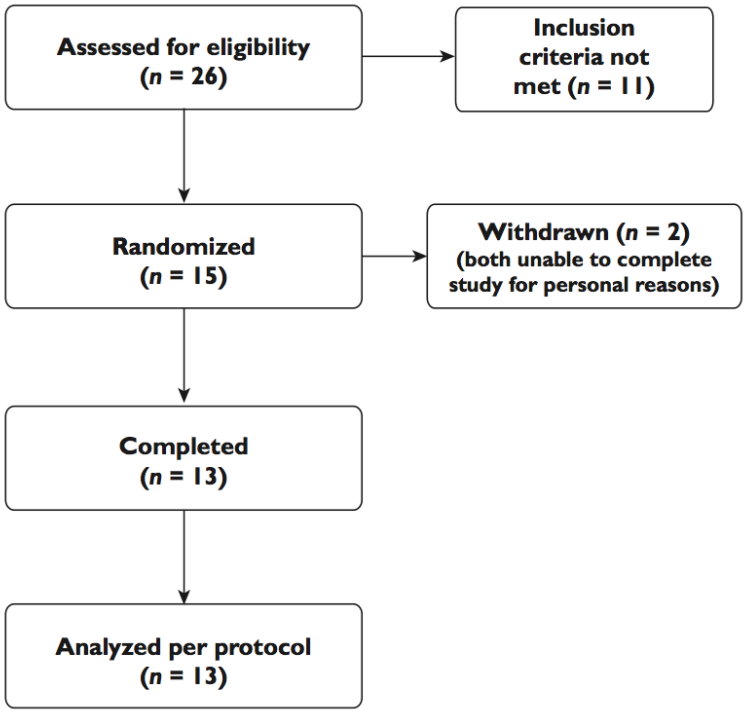


Figure 7. Study consort diagram

Subject/Sex	Age	FEV_1%	R5%	Histamine PC_{10} (mg/ml)	BDP equivalent daily dose(µg)	Duration of asthma symptoms (years)
1/F	20	100	174	0.44	400	10
2/F	40	106	136	8.41	800	6
3/F	42	106	81	7.07	800	15
4/F	19	96	127	0.14	400	12
5/F	44	104	160	1.98	800	30
6/F	23	118	97	8.91	1000	10
7/M	24	86	160	2.18	400	15
8/M	44	92	112	1.89	1000	20
9/M	30	92	89	1.77	400	24
10/M	63	92	114	0.71	200	50
11/M	30	97	153	10.59	800	18
12/M	26	90	183	0.35	400	6
13/M	34	92	169	0.28	800	5
Mean(SEM)	34(3)	98(2)	135(9)	3.44(1.1)	631(75)	17(3)

Table 5. Participant Demographics.
Data shown as % predicted for age, sex, race. FEV_1, Forced expiratory volume in 1 second; R5, Resistance at 5Hz; PC_{10}, Provocative Concentration required to achieve 10% fall in FEV_1; BDP, Beclomethasone Dipropionate.

Comparison between study visits.

There was no significant difference between the histamine PC10 mg/ml on study visits (hydrocortisone and placebo) and the screening visit.

Effect of hydrocortisone on nebulised salbutamol post sequential beta-blockade and histamine challenge.

There was no significance difference in salbutamol recovery measured by change in FEV_1 (ml) post histamine challenge following intravenous hydrocortisone verses placebo (mean difference 0.04 (95%CI -0.07 to 0.15), p=0.417). There was also no change when comparing FEV_1% predicted (mean difference 6.6 (95%CI -5.9 to 19.1), p=0.263), R5 (kPa l-1s) (mean difference 0.03 (95%CI -0.03 to 0.08), p=0.274) and R5% predicted (mean difference 10.9 (95%CI -9.0 to 30.9), p=0.255). Therefore intravenous hydrocortisone did not potentiate the effect of salbutamol recovery post sequential beta-blockade and histamine challenge.

Analysis of beta-blocker induced bronchoconstriction

For the hydrocortisone visit there was a fall in FEV_1% predicted 2 hours post-propranolol of 3.8% (95%CI -0.9 to 8.5), p=0.083, whilst at the placebo visit a significant fall of 4.7% was observed (95%CI 1.8 to 7.5), p=0.008. No significant falls in FEV_1% were observed at 4 hours post-propranolol on either visit (see table 5, figure 8). There was a significant increase in R5% predicted at 2 and 4 hours post propranolol on both visits, with a mean increase of 31.3% on the placebo visit at 2 hours (95%CI 15.6 to 47.0), p=0.04. (see table 6, figure 8).

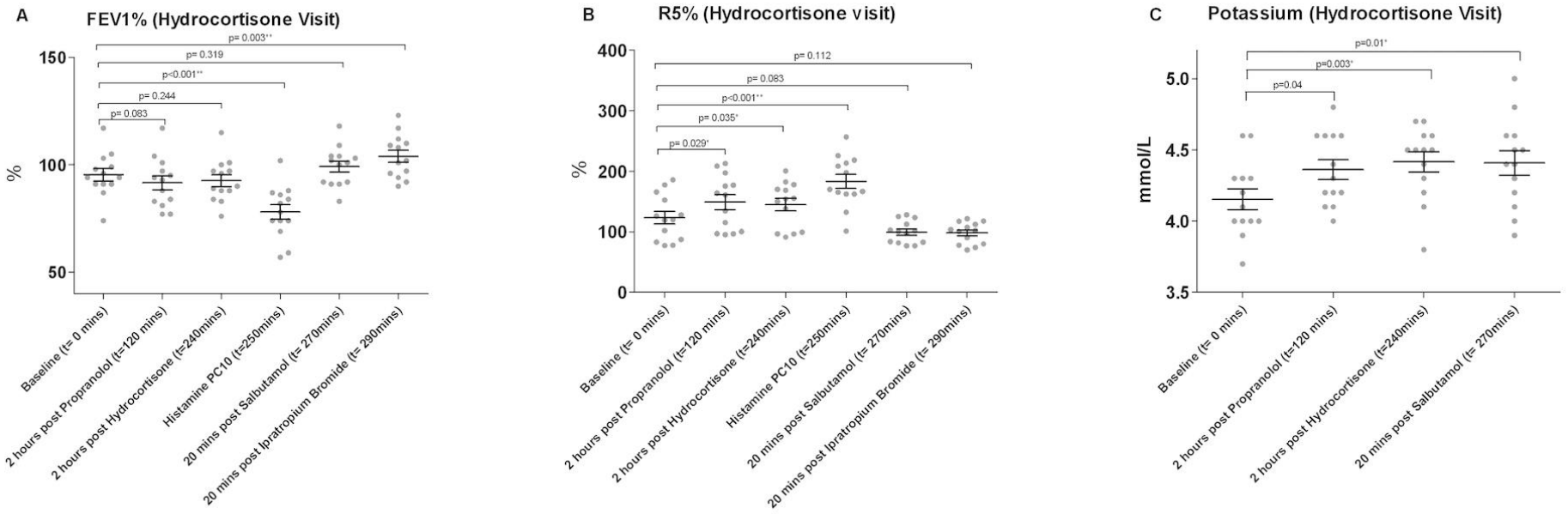


Figure 8. Effect of beta-blockade, bronchial challenge and sequential reversibility with salbutamol and ipratropium on separate study visits (hydrocortisone and placebo). FEV_1% (Panel A and D), R5% (Panel B and E) and serum potassium (Panel D and F). Data displayed as Mean and SEM. Significance calculated by ANOVA of repeated measures with post-hoc bonferroni correction. *Significant difference between time point and baseline , $p<0.05$. **Significant difference between time point and baseline, $p<0.001$.

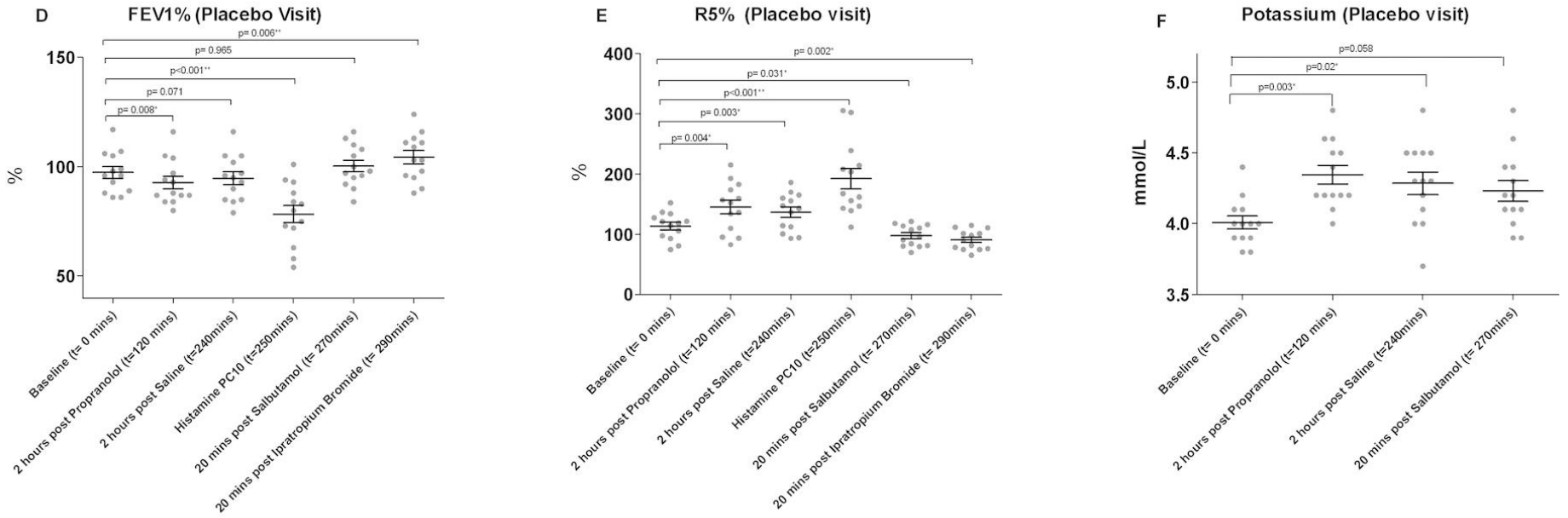


Figure 8 (continued). Effect of beta-blockade, bronchial challenge and sequential reversibility with salbutamol and ipratropium on separate study visits (hydrocortisone and placebo). FEV_1% (Panel A and D), R5% (Panel B and E) and serum potassium (Panel D and F). Data displayed as Mean and SEM. Significance calculated by ANOVA of repeated measures with post-hoc bonferroni correction. *Significant difference between time point and baseline , $p<0.05$. **Significant difference between time point and baseline,$p<0.001$.

Outcome	I.V Hydocortisone Visit (Mean, SEM)	Placebo (I.V 0.9% NaCl) Visit (Mean, SEM)
FEV1 % predicted		
Baseline (t=0mins)	95.4 (2.8)	97.4 (2.6)
2 hours post Propranolol (t=120 mins)	91.6 (3.2)	92.7 (2.9)*
2 hours post i.v Hydrocortisone or Saline (t=240mins)	92.6 (2.8)	94.8 (2.9)
Post Histamine Challenge PC10 (t=250 mins)	78.0 (3.4)**	78.3 (3.9)**
20mins Post Salbutamol (t=270 mins)	99.2 (2.6)	100.3 (2.6)
20 mins Post Ipratropium Bromide (t= 290 mins)	103.9 (2.8)*	104.4 (2.9)*
R5 % predicted		
Baseline (t=0mins)	123.3 (10.5)	113.7 (6.3)
2 hours post Propranolol (t=120 mins)	149.0 (12.35)*	145.0 (11.4)*
2 hours post i.v Hydrocortisone or Saline (t=240mins)	144.8 (10.36)*	136.8 (8.6)*
Post Histamine Challenge PC10 (t=250 mins)	183.3 (11.6)**	192.3 (16.9)**
20mins Post Salbutamol (t=270 mins)	99.6 (5.1)	97.7 (4.9)*
20 mins Post Ipratropium Bromide (t= 290 mins)	98.1 (4.9)	90.6 (4.6)*

Table 6. FEV_1% and R5% throughout study visits

Data displayed as Mean (SEM).
*Significant difference between time point and baseline , $p<0.05$
**Significant difference between time point and baseline, $p<0.001$
Significance calculated by ANOVA of repeated measures with post-hoc bonferroni correction.

Systemic beta-1 and beta-2-blockade

Heart rate was significantly lower 2 hours post-propranolol at the hydrocortisone (mean change 20bpm, (95%CI 14 to 27), $p<0.001$ and placebo visits (mean change 16bpm (95%CI 13 to 20), $p<0.001$. No significant changes were observed with blood pressure post propranolol ingestion. Serum potassium levels were significantly increased at 4 hours post-propranolol on both visits, and did not reverse back to baseline following salbutamol recovery (see figure 8). Thus showing evidence of sustained beta-2-receptor blockade throughout the study.

Reversibility post sequential beta-blockade and histamine challenge

On both visits all spirometry (FEV_1, FVC) and IOS measurements R5 (total airway resistance), R20 (central airway resistance), R5-R20 (peripheral airway resistance), X5 (lung reactance) either returned back to baseline values or significantly improved in comparison with baseline after nebulised salbutamol, with only small further improvements seen following ipratropium (see figure 8, tables 6-8).

Reliever Use

Throughout the study visits, on requirement of reliever therapy, participants were administered ipratropium bromide in preference to salbutamol. Salbutamol was however used if ipratropium was deemed to be ineffective. No participant required salbutamol to be administered during study visits. Furthermore there was no significant greater use of ipratropium throughout the study in comparison with normal reliever requirements ($p> 0.05$).

Time Point	Outcome							
	R5 (kPa l^{-1}s)		R20 (kPa l^{-1}s)		R5-R20		X5 (kPa l^{-1}s)	
	Hydrocortisone Visit	Placebo Visit	Hydrocortisone Visit	Placebo Visit	Hydrocortisone Visit	Placebo Visit	Hydrocortisone Visit	Placebo Visit
Baseline (t=0 mins)	0.363(0.025)	0.341(0.025)	0.313(0.019)	0.316(0.018)	0.050(0.014)	0.025(0.014)	-0.103(0.014)	-0.098(0.01)
2 hours post Propranolol (t=120 mins)	0.455(0.039)**	0.440(0.033)**	0.360(0.020)*	0.351(0.020)**	0.095(0.024)*	0.089(0.023)*	-0.143(0.021)*	-0.139(0.019)*
2 hours post i.v Hydrocortisone or Saline (t=240 mins)	0.442(0.033)**	0.416(0.026)**	0.354(0.021)	0.338(0.015)*	0.088(0.020)*	0.078(0.019)**	-0.137(0.019)	-0.127(0.017)
Post Histamine Challenge PC10 (t=250 mins)	0.555(0.033)***	0.580(0.043)***	0.372(0.018)*	0.360(0.016)**	0.183(0.028)***	0.219(0.043)**	-0.211(0.031)**	-0.216(0.03)**
20mins Post Salbutamol (t=270 mins)	0.305(0.019)	0.300(0.019)	0.280(0.018)	0.277(0.015)**	0.025(0.009)	0.023(0.012)	-0.084(0.01)	-0.085(0.01)
20 mins Post Ipratropium Bromide (t=290 mins)	0.299(0.017)	0.278(0.017)*	0.275(0.019)	0.261(0.014)**	0.024(0.008)	0.017(0.012)	-0.082(0.01)	-0.083(0.01)

Table 7. Impulse Oscillometry (R5, R20, R5-20, X5) throughout study visits

Data displayed as Mean (SEM). * $p < 0.05$ compared with Baseline, ** $p < 0.01$ compared with Baseline, *** $p < 0.001$ compared with Baseline. Significance calculated by ANOVA of repeated measures with post-hoc bonferroni corrections

Time Point	Outcome					
	FEV_1 (L)		FVC (L)		FEF_{25-75} (L)	
	Hydrocortisone Limb	Saline Limb	Hydrocortisone Limb	Saline Limb	Hydrocortisone Limb	Saline Limb
Baseline (t=0 mins)	3.23 (0.18)	3.3 0 (0.19)	4.19 (0.22)	4.20 (0.23)	2.68 (0.21)	2.80 (0.22)
2 hours post Propranolol (t=120 mins)	3.10 (0.18)	3.14 (0.18)*	4.00 (0.19)	4.05 (0.23)	2.56 (0.23)	2.59 (0.18)
2 hours post i.v Hydrocortisone or Saline (t=240 mins)	3.14 (0.18)	3.20 (0.17)	4.02 (0.21)	4.10 (0.22)	2.59 (0.18)	2.70 (0.19)
Post Histamine Challenge PC10 (t=250 mins)	2.64 (0.16)***	2.62 (0.15)**	3.57 (0.22)**	3.60 (0.22)**	2.05 (0.14)**	2.01 (0.14)**
20mins Post Salbutamol (t=270 mins)	3.37 (0.19)	3.39 (0.17)	4.14 (0.22)	4.30 (0.18)	3.10 (0.14)	3.10 (0.24)
20 mins Post Ipratropium Bromide (t=290 mins)	3.51 (0.18)**	3.52 (0.18)**	4.24 (0.19)	4.27 (0.20)	3.39 (0.26)**	3.42 (0.25)**

Table 8. Spirometry (FEV_1, FVC, FEF_{25-75}) throughout study visits

Data displayed as Mean (SEM). * $p < 0.05$ compared with Baseline, ** $p < 0.01$ compared with Baseline, *** $p < 0.001$ compared with Baseline. Significance calculated by ANOVA of repeated measures with post-hoc bonferroni corrections

4. DISCUSSION

The major issue when conducting clinical trials using beta-blockers in asthma is patient safety. Whilst salbutamol has been shown to reverse bronchial challenge induced bronchoconstriction following chronic beta-blockade, this has not been reported following acute beta-blockade.[104] This study has demonstrated that nebulised salbutamol is able to reverse sequential single dose propranolol and histamine induced bronchoconstriction in this study cohort.

The primary study endpoint was to assess if acute administration of intravenous hydrocortisone might partially obviate the effects of acute beta-2-blockade and improve the effects of nebulised salbutamol. Subsensitivity of beta-2-adrenoceptors occurs following treatment with long acting beta-agonists.[42,140] Previous work has shown that high dose systemic corticosteroids (200mg intravenous hydrocortisone with 50mg oral prednisolone) can re-establish the beta-2-adrenoceptor function following agonist promoted down-regulation.[47] These effects were seen in patients already taking inhaled corticosteroids with a median dose of 1000ug/day budesonide, thus suggesting that systemic corticosteroid has a dual action in acute asthma, with effects on beta-2-adrenoceptor response as well as established ant-inflammatory properties. It therefore seemed plausible in this instance that a similar response may occur with intravenous corticosteroid following acute beta-blockade (ie. reversal of beta-blockade whilst re-establishing beta-agonist sensitivity).

This study showed that intravenous hydrocortisone did not potentiate the effect of salbutamol on FEV_1 recovery post sequential beta-blockade and histamine challenge. It is worth pointing out though, that even in the placebo arm salbutamol reversed

histamine induced bronchoconstriction back to baseline, therefore there may have been no further room for improvement with intravenous corticosteroid. Moreover as LABAs were withdrawn for the duration of the study, there was no agonist promoted down-regulation, aside from the effects of on demand salbutamol in between study visits. However in a real life scenario of a patient having an asthma exacerbation whilst concurrently receiving beta-blockers, it would still be prudent to give acute systemic corticosteroid to treat any worsening airway inflammation, as well as reversing any down-regulation due to concomitant LABAs. This study did not address the potential influence of acute corticosteroids on airway inflammation, because histamine works directly on airway smooth muscle histamine receptors to produce bronchoconstriction.

This study evaluated the relative sensitivity of spirometry and impulse oscillometry at demonstrating the effects of beta-blocker induced bronchoconstriction. Due to safety concerns, and to mimic the proposed initial dose for a future chronic dosing study, low doses of propranolol were used in this study. Despite participants having relatively preserved spirometry, indicating mild-to-moderate disease, all participants received inhaled corticosteroids for asthma control. In the selected cases where the baseline histamine PC_{10} was greater than 8mg/ml, these patients all received at least 800ug/day BDP. It can be presumed that reducing inhaled corticosteroids would result in a worsening of response to histamine bronchial provocation, however the histamine PC_{10} threshold was irrelevant in this study, with the pertinent inclusion criteria being that each patient experienced a 10% fall in FEV1 post histamine challenge, thus allowing us to assess reversibility to salbutamol and ipratropium in the presence of acute beta-blockade.

In view of relatively preserved spirometry in the study subjects, IOS was used to assess airway resistance. IOS has been shown to be a more sensitive marker of bronchodilation than spirometry in mild asthmatics receiving salbutamol, and thus it was hypothesised that IOS would be more sensitive at identifying any evidence of beta-blocker induced bronchoconstriction.[141] This proved to be the case with FEV_1% predicted falling by 4.7% on the placebo visit at 2hours post-propranolol with R5% predicted, (a measure of total airway resistance) increasing by 31.3% post propranolol at the same time point and visit. R5% predicted also significantly increased 25.7% on the hydrocortisone visit at 2 hours post-propranolol whilst FEV_1% did not fall significantly 2 hours post-propranolol. The difference in change in FEV_1% 2 hours post-propranolol between the hydrocortisone and placebo visit, highlights that in patients with preserved lung function, IOS is a more sensitive method of assessing bronchoconstriction and the discordance in FEV_1 between visits may be partly due to daily FEV_1 variability. Furthermore airway resistance measured by R5, R20 and R5-R20 all showed persistent significant deterioration at 4hours post-propranolol, whilst spirometry measures no longer demonstrated any evidence of bronchoconstriction at the same time point (prior to histamine challenge).

Heart rate and serum potassium measurements provided surrogate markers of systemic beta-1 and beta-2 adrenoceptor blockade respectively.[142] Serum potassium remained significantly elevated following ingestion of propranolol and failed reverse back to baseline following high dose salbutamol. This provided evidence of sustained systemic beta-2-blockade throughout the study period and supports previous work showing a prevention of salbutamol-induced hypokaleamia in the presence of propranolol 40mg as a single dose.[143]

This study has therefore demonstrated an unexpected disconnect between the interaction of propranolol and salbutamol on airway smooth muscle and skeletal muscle beta-2-adrenoceptors. Whilst the local concentration of salbutamol used in the study was clearly enough to overcome airway beta-2-blockade conferred by propranolol, it was not enough to overcome antagonism of systemic skeletal muscle beta-2-adrenoceptors. Although this study did not have a control arm where placebo propranolol was given, it is already known that 5mg nebulised salbutamol on its own would be sufficient to induce significant hypokalaemia.[133]

Heart rate showed a significant fall at 2 hours post-propranolol but this fall was not sustained at 4 hours post-propranolol, whilst markers of beta-2-blockade persisted. Whilst peak blood levels following dosing with propranolol occur at approximately 2 hours, with an elimination half life of 4-6 hours this finding is unsurprising due to the relatively low dose of propranolol used and although non-selective, propranolol has a greater binding affinity to beta-2 than beta-1 adrenoceptors.[59] Indeed a similar finding has been reported with low dose nadolol in terms of preferential beta-2/beta-1 antagonism in man.[142] The beta-2-adrenoceptor binding affinity of propranolol is actually higher than that of nadolol, while its beta-1 binding affinity is lower, [59] thus making propranolol well suited for use in trials in asthma where a high degree of beta-2-adrenoceptor antagonism is required during the initial dose ramp. In this regard it has been shown that significant and near maximal up regulation of peripheral blood lymphocyte beta-2-adrenoceptors occurs after 2 days of oral propranolol at 160mg/day in healthy volunteers.[144]

Due to the known variability between subjects in the oral bioavailability of propranolol due to saturable first -pass kinetics, the study employed a stepwise dose regime. Whilst the starting dose of 10 or 20mg of propranolol is relatively low in comparison to the usual maintenance dose used in clinical practice for treatment of hypertension, angina and anxiety(usually 80-160mg/day), the study findings are clinically relevant since there was a clear demonstration of significantly sustained beta-2-blockade. As this study was the designed primarily as a safety study using a contraindicated medication in asthma it was unethical to use a higher dose for initial exposure.

This study has however shown through the measurements of IOS and serum potassium evidence of sustained beta-2-blockade at 4 hours following 10 or 20mg of propranolol. The limitations of this study are that it was pilot in design and thus a small sample size was used, however importantly there were no observed clinically relevant adverse effects with beta-blocker use in the study group. Within the study design well controlled asthmatics taking inhaled corticosteroids were deliberately chosen, as such the first dose effects of propranolol were minimised. Thus the degree of bronchoconstriction seen in this study was less than seen by McNeill prior to the introduction of inhaled corticosteroids.[61]

In conclusion, this study has demonstrated that a single low dose of oral propranolol caused a small but significant deterioration in airway calibre, which was more evident with impulse oscillometry rather than spirometry. Importantly nebulised salbutamol and ipratropium produced a full recovery of FEV_1 and airway resistance after acute histamine induced bronchoconstriction in the presence of acute beta-blockade. This was achievable due to the relatively low dose of propranolol used in comparison with

salbutamol. Furthermore the use of muscarinic antagonist, ipratropium provided a non beta-adrenergic mediated method of bronchodilatation. Intravenous hydrocortisone did not potentiate salbutamol recovery post-histamine challenge. However in a real-life scenario of an individual suffering an asthma exacerbation whilst receiving beta-blockers, intravenous corticosteroids remain vital due to their anti-inflammatory benefits. Since the greatest risk of beta-blockade is after first dose exposure, this study offers reassurance for proceeding to the evaluation of chronic dosing with propranolol as a potential treatment option for asthma.

5. CRITIQUE

This study was designed primarily due to safety concerns regarding acute beta-blocker dosing in asthma. Whilst it is already known that the greatest risk of bronchospasm with beta-blockers is after administration of the first dose, the study attempted to address what would happen in the "worst case scenario" where the patient suffered from a concurrent asthma attack. In order to simulate this scenario, the study visits were designed as a 6 hour study visit where the patient underwent concurrent beta-blockade and histamine challenge testing.

This study was incredibly challenging to perform and as with any clinical trial involving human subjects, ethical approval had to be approved prior to the study being commenced. There were major concerns as to whether this study could be justified due to the potential adverse effects of beta-blocker use in asthma. In view of the clear risk associated with this study, and as a pre-requisite for study approval, the potential risk of death was included in the participant information sheet.

In order to mitigate this risk, a relatively low dose of propranolol was used in a mild-to-moderate group of asthmatics. Whilst undoubtedly improving the safety of the study, it could be argued that the clinical implications of this study were biased as a result. Whilst I believe it is safe to conclude that this study showed no significant adverse effects of acute beta-blocker use in asthma, these findings are restricted to this study cohort and no conclusions can be drawn as to what would happen in a more severe group of asthmatics. Furthermore the dose of propranolol used in this study at 10 or 20mg was lower than any dose routinely used in clinical practice and therefore the results cannot be extrapolated to higher doses of propranolol or other beta-blocker

formulations. This relatively low dose of propranolol was used due to ethical issues with regards to the greater risk of bronchospasm with higher dosing. Importantly the clinical findings of salbutamol reversibility being preserved in the presence of oral beta-blockade could be simply due to the relatively low dose of propranolol being used.

Finally the primary outcome of this study was to assess the impact of intravenous hydrocortisone on salbutamol reversibility post histamine challenge in the presence of concurrent beta-blockade. The underlying hypothesis that hydrocortisone would improve salbutamol reversibility in comparison with placebo. This was based upon previous data from our department showing the potential for high dose systemic corticosteroids (200mg intravenous hydrocortisone with 50mg oral prednisolone) to re-establish beta-2-adrenoceptor function.[47] In the previous study by Tan, beta-2-adrenceptor down-regulation was achieved by 4 weeks of sustained long-acting beta-agonist use with formoterol. On reflection the same degree of beta-2-adrenoceptor down-regulation would not be achieved with a single oral dose of propranolol, and therefore this may account for why no beneficial effects on salbutamol reversibility were seen with hydrocortisone.

CHAPTER 4:

SENSITIVITY OF SPIROMETRY AND IMPULSE OSCILLOMETRY IN ACUTE BETA-BLOCKER INDUCED BRONCHOCONSTRICTION AND ACUTE BETA-AGONIST INDUCED BRONCHODILATATION IN ASTHMA

Study Aims

1. **To compare the various indices of impulse oscillometry with standardised spirometry in the assessment of bronchoconstriction and bronchodilatation.**
2. **To determine the "signal to noise" ratio of each test, allowing an analysis of both effect size and responsiveness of each test.**

1. INTRODUCTION

Spirometry and Impulse oscillometry (IOS) are two distinct methods of assessing lung function and provide means of measuring change to airway tone following either a bronchoconstricting or bronchodilating stimulus. Unlike conventional spirometry, which is an effort dependent test, IOS is performed at tidal volume during normal breathing that assesses several components of respiratory physiology, namely airway resistance and pulmonary reactance.[123]

Whilst the effects on spirometry and predominantly FEV_1 have been extensively studied following beta-blocker use,[61] the effects of beta-blocker induced bronchoconstriction on IOS are less well known.

IOS is known to be a sensitive marker of airway dysfunction, but is commonly associated with a wider variation than spirometry.[141] In the previous chapter IOS was shown to be more sensitive than spirometry at demonstrating beta-blocker induced bronchoconstriction, however the variability associated with IOS was not accounted for. When considering the relative sensitivities of spirometry and IOS it is important to determine the "signal to noise" ratio of each test thereby allowing an analysis of both the effect size and responsiveness of each test.

Accounting for the variability of each test, by calculating standardised response means, in this chapter, the relative sensitivities of IOS and spirometry in the assessment of bronchoconstriction to propranolol and bronchodilatation to salbutamol were compared.

2. METHODS

A post-hoc analysis of lung function data from the placebo limb of the randomised placebo-controlled double-blind crossover trial described within chapter 3 was performed. The methods within the reference study have been described previously however the key details and measurements specific to this study are reiterated here. Mild-to-moderate persistent stable asthmatics taking ≤1000μg day beclomethasone dipropionate equivalent (BDP) of inhaled corticosteroids (ICS), FEV_1 >80% predicted, aged 18-65yr who had AHR to histamine challenge were recruited. All participants were non-smokers.

On the study visit, each participant received a single dose of 10mg or 20mg of oral propranolol followed by histamine bronchial challenge testing (PC_{10}) 4 hours later, with recovery to nebulised salbutamol 5mg. Spirometry and IOS were measured pre and 2-hour post beta-blocker, post histamine and 20 min post salbutamol.

Spirometry and impulse oscillometry were performed in accordance with published guidelines.[122,123] IOS is an effort independent method of assessing lung function by the use of sound waves being superimposed on normal breathing cycles. A super Spiro spirometer (Micro Medical, UK) and IOS Jaeger Masterscreen (Germany) were used. Histamine Bronchial challenge testing was performed with the provocative dose of histamine required to cause a 10% fall in FEV_1 being calculated. A Mefar dosimeter was used with histamine concentrations of 0.3125 to 40mg/ml.

Data were analysed for normality with Shapiro-Wilk tests and Boxplots. Pre vs post percentage change (95%CI) values were calculated and compared with paired student t-tests for spirometry and IOS indices following bronchoconstriction to propranolol and bronchodilatation to salbutamol. Standardised response means (SRM) were also calculated. SRM is a relative measure of effect size and responsiveness. It allows the expression of the signal of change in an outcome relative to its variability.[145] SRMs therefore express the signal (ie mean) to noise (ie standard deviation) ratio and is calculated as mean change in an outcome divided by the standard deviation of the difference. Ideally a SRM would be greater than unity, however an SRM of approximately 0.20 is considered small, one of 0.50 indicates moderate responsiveness, and those of ≥ 0.80 are considered highly sensitive. As SRMs are standardised scores, the SRM for spirometry can be compared directly with the SRMs for impulse oscillometry. [145]All statistical analyses were performed using SPSS version 17.

3. RESULTS

A total of 13 participants (mean age, 34 years) completed the study (see table 5). Two participants withdrew as they could not complete the study visits for personal reasons. 11 participants received 20mg of oral propranolol, 2 received 10mg as this dose was sufficient to cause >10% fall in FEV_1 on the test-dose algorithm. There were no adverse events following beta-blocker ingestion.

All IOS indices showed a greater magnitude of response to propranolol (i.e. as %change) compared to spirometry. The greatest magnitudes of change were observed in R5-20 and AX, measurements of small airway resistance and pulmonary reactance. With regards to bronchodilator response, FEF_{25-75} demonstrated a greater magnitude of change to salbutamol compared to R5 and fres, however the greatest magnitude of change was again seen in R5-20 and AX (see figure 9).

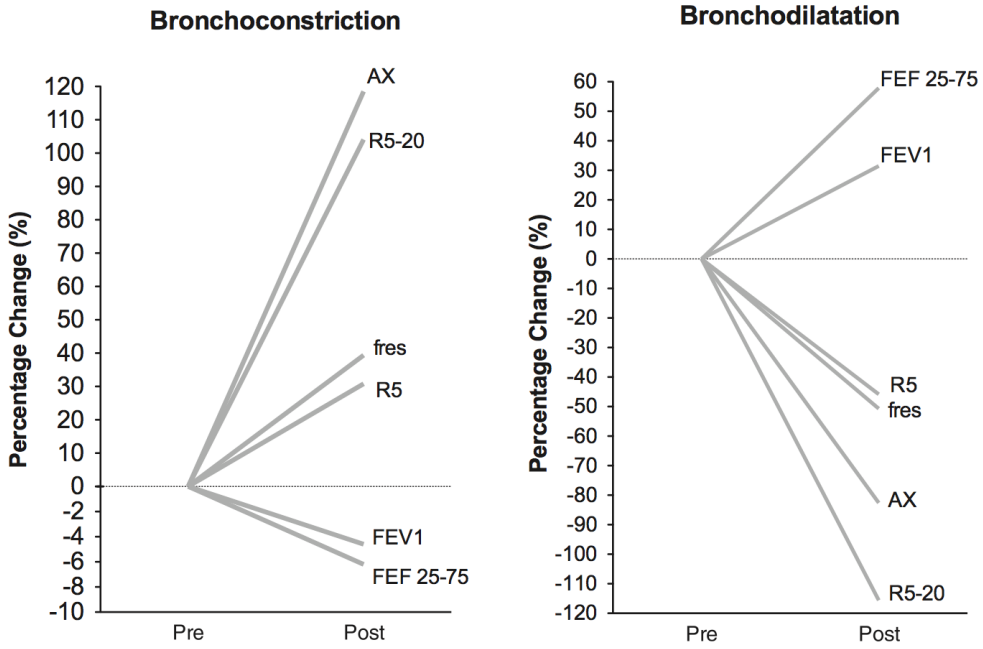


Figure 9. Percentage change for spirometry (FEV_1, FEF_{25-75}) and impulse oscillometry (AX, R5-20, R5, fres) for the bronchoconstrictor response to propranolol and the bronchodilator response to salbutamol.

All IOS indices (R5, R5-R20, AX, fres) showed significant worsening of airways resistance or reactance to propranolol. FEV_1 and not FEF_{25-75} showed significant deterioration post beta-blocker. Individual participant response post propranolol and salbutamol and their effects on FEV_1 and R5% predicted are shown in figure 10.

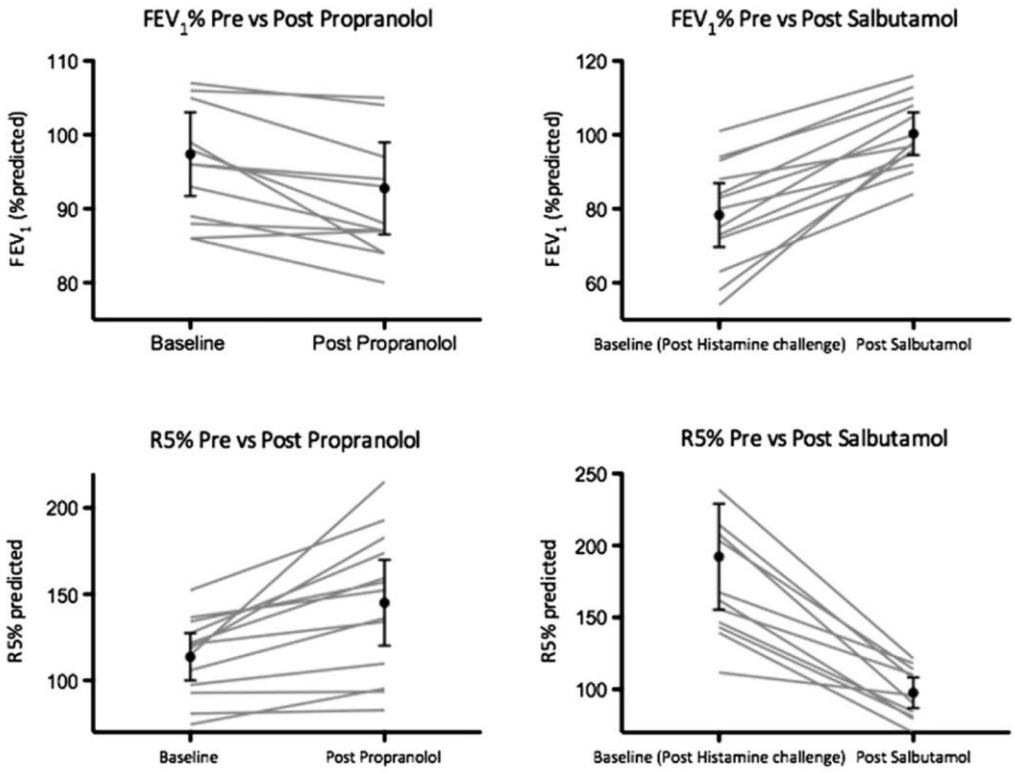


Figure 10. Individual participant percentage change for FEV1% and R5% bronchoconstrictor response to propranolol and the bronchodilator response to salbutamol. Data displayed with respective means and 95%CI.

After adjustment for test variability, by calculation of SRMs, IOS outcomes were better than spirometry post-bronchoconstriction with the highest SRM seen with R5. All measures of IOS and spirometry showed a significant bronchodilator response post salbutamol with the greatest SRMs seen in fres and R5 (see table 9).

Outcome	Bronchoconstriction			Bronchodilatation		
	Mean Difference (95% CI), P value	Mean Percentage Change (95% CI)	Standardised Response Mean	Mean Difference (95% CI), P value	Mean Percentage Change (95% CI)	Standardised Response Mean
Spirometry						
FEV_1 (L)	0.16 (0.05 to 0.27), p=0.009	4.6% (1.9 to 7.3)	0.86	0.77 (0.49 to 1.05), p<0.001	31.5% (18.2 to 44.7)	1.67
FEF_{25-75} (L)	0.21 (-0.06 to 0.46), p=0.116	6.2% (-0.2 to 12.6)	0.47	1.08 (0.63 to 1.55), p<0.001	57.9% (29.1 to 86.7)	1.42
Impulse Oscillometry						
R5 (Airway Resistance at 5Hz) (kPa L/s) *(Total airway resistance)*	0.099 (0.054 to 0.144), p<0.001	30.8% (14.01 to 47.6)	1.32	0.280 (0.189 to 0.37), p<0.001	45.8% (36.7 to 55)	1.87
R5-20 (difference) *(Small Airways resistance)*	0.052 (0.020 to 0.084), p=0.004	104.1% (22.6 to 185.6)	1.05	0.171 (0.095 to 0.246), p<0.001	115.6% (55.6 to 175.7)	1.43
AX (area) *(Respiratory reactance)*	0.496 (0.162 to 0.831), p=0.007	118.5% (37.2 to 200)	0.94	1.88 (0.933 to 2.827), p=0.001	82.6% (73.9 to 91.3)	1.26
fres (Resonant Frequency) (Hz) *(Respiratory reactance)*	4.81 (2.24 to 7.37) p=0.002	39.4% (16.6 to 54.3)	1.13	12.71 (9.1 to 16.31), p<0.001	50.7% (40.7 to 60.8)	2.13

Table 9. Relative sensitivities of spirometry and impulse oscillometry.

4. DISCUSSION

This is the first study, accounting for test variability to directly compare the sensitivities of impulse oscillometry and conventional spirometry when using beta-blockers as the bronchoconstricting stimulus. Beta-blockers are avoided in asthma due to the concerns regarding potential bronchospasm.[68] Subsequently trials involving beta-blocker use in asthmatics need to be performed with safety as the primary focus. Participants enrolled into studies using contraindicated medications in asthma subsequently have mild-to-moderate disease and thereby relatively preserved spirometry.[102] As a result of this spirometry may be regarded as an insensitive measurement to assess bronchoconstriction and conversely bronchodilatation in these patients.

In the previous chapter it was demonstrated that IOS is a more sensitive measurement for assessing beta-blocker induced bronchoconstriction, however the previous analysis did not account for the variability associated with IOS. Standardised response means are highly informative measures calculated by dividing the mean change in an outcome by the standard deviation of the difference (ie, it is a measure of effect size or responsiveness). As the denominator examines response variance, it provides a sensitive indication of signal-to-noise ratio. As SRMs are standardised scores, they are routinely used to compare differing health related outcomes, which in the case of this study, allows the comparison of spirometry and IOS.[145-148] Reflecting the greater magnitude of change seen with IOS outcomes, the highest standardised response means were also seen with IOS measurements.

Impulse oscillometry is an alternative technique to assess changes in airway tone, which has been shown to be sensitive to measuring bronchodilatation to salbutamol and

ipratropium within both asthma and COPD populations.[141,149,150] IOS is an effort independent test, using oscillation of differing sound waves to derive a variety of output measurements thus determining both the degree of total (R5) and peripheral airway resistance (R5-R20) and pulmonary reactance (AX, fres). IOS does not include the forced expiratory manoeuvres required when performing spirometry, as a result, IOS is routinely used to good effect in paediatric populations as an alternative or adjunct to spirometry.[151] Within this analysis the greatest magnitude of change to beta-blocker and beta-agonist use were seen within IOS measurements that are reflective of small airway dysfunction, namely R5-R20 and AX. IOS is routinely used when determining small airway dysfunction has also been used to good effect in assessing asthma control in children.[152] These findings reaffirm the importance of evaluating small airway disease in the asthmatic individual and demonstrating the ability of IOS to examine both small and large airway dysfunction independently in those with relatively preserved spirometry.

In conclusion, IOS has been shown to be a more sensitive marker of bronchoconstriction to oral propranolol than spirometry, even when adjusted for greater test variation. This is true for both small changes (propranolol induced bronchoconstriction) and large changes (salbutamol induced reversal of histamine).

CHAPTER 5:

RANDOMISED PLACEBO CONTROLLED TRIAL TO EVALUATE CHRONIC DOSING EFFECTS OF PROPRANOLOL IN ASTHMA

Study Aims

1. **To evaluate whether chronic dosing with propranolol in asthma results in an improvement in airway hyper-responsiveness to methacholine and histamine challenge testing.**
2. **To assess whether concurrent tiotropium prevents drug induced bronchoconstriction following chronic beta-blockade.**
3. **To assess the tolerability of chronic dosing with propranolol in asthma by utilising a gradual dose-ramp regime.**

1. INTRODUCTION

The evolution of the management of heart failure has shown the differing effects between acute and chronic beta-adrenoceptor antagonism. Despite the potentially acute deleterious effects on cardiac function in heart failure, chronic beta-blocker use results in beneficial effects on both ejection fraction and morbidity and mortality.[91] The ability to tolerate beta-blockers in heart failure was achieved by gradually increasing the dose, and as a result beta-blockers are now considered part of standard therapy. The observed effects of beta-blockers in heart failure prompted an examination of the putative therapeutic role of beta-blockade in asthma, questioning despite the potential acute deleterious effects, whether there were any benefits of chronic beta-blockade.[95] This hypothesis was also fuelled by emerging data suggesting chronic exposure to long acting beta-agonists may worsen asthma control due to beta-2-adrenoceptor down regulation and associated desensitisation of response, in turn pointing to the possibility that that antagonist of the agonist might be beneficial in causing the opposite effects.[137,153]

The first evidence in support of this hypothesis was derived from studies using the ovalbumin-sensitised mouse model of asthma. Chronic exposure to nadolol produced bronchoprotection against methacholine challenge (a direct acting cholinergic spasmogen which induces airway hyper-responsiveness), in conjunction with reduced airway inflammation and mucous metaplasia, and simultaneous up-regulation of airway beta-2-adrenoreceptors.[98-100] These initial studies led to two open label pilot studies in steroid naïve asthmatics, with chronic nadolol dosing achieving significant improvements in methacholine induced airway hyper-responsiveness compared to baseline. [102,104] These results might appear to be counterintuitive since anti-cholinergic

medication prevents beta-blocker induced bronchoconstriction.[10] Hence one would predict that beta-blockers would increase rather than decrease cholinergic tone, therefore resulting in augmented methacholine responsiveness. This in turn questions as to whether the previously observed reduction in methacholine response with beta-blockers is specific to the cholinergic pathway per se, or whether attenuated airway hyper-responsiveness (AHR) to other spasmogens not acting through the muscarinic receptor such as histamine would also be demonstrated.

In order to assess the putative effects of propranolol on AHR, within this study both methacholine and histamine challenge testing was used, in order to evaluate different signaling direct acting pathways on airway smooth muscle. Due to ethical concerns regarding the safety of propranolol especially on initial exposure, this study enrolled stable asthmatics controlled on inhaled corticosteroid (ICS), to mitigate the risk of potentially inducing acute bronchoconstriction in the presence of untreated asthmatic inflammation. To further reduce this risk of propranolol induced bronchoconstriction a mirror the dosing regime of beta-blockers in heart failure, a gradual dose titration regime was used. Furthermore based upon previous work by Ind et al, demonstrating the ability for the inhaled anti-cholinergic oxytropium in preventing propranolol induced bronchoconstriction,[10] study participants were administered with concomitant tiotropium in the dose up-titration phase.

The method by which anti-cholinergic medication prevents beta-blocker induced bronchoconstriction is poorly understood however is thought to involve crosstalk between muscarinic M2 autoreceptors and beta-2-adrenoceptors, which are both inhibitory to the release of acetylcholine, thereby preventing bronchoconstriction.[11] In

the presence of acute beta-blockade, the inhibition of acetylcholine is removed and subsequent bronchoconstriction by increases in airway hyper-responsiveness and airway tone occurs.

Within this study hypothesis, whilst is it postulated that chronic beta-blockade pre-synaptically may reduce airway hyper-responsiveness, post-synaptically muscarinic M3 autoreceptor induced bronchoconstriction would still occur with subsequent increases in airway tone. Thus the addition of tiotropium to chronic beta-blockade may result in a reduction of M3 induced bronchoconstriction in addition to the potential reduction in pre-synaptic AHR observed with chronic beta-blockade (see figure 11).

With these reassurances, this chapter examines the safety and effects of chronic propranolol use versus placebo, in the presence of concurrent inhaled tiotropium, in mild-to-moderate asthmatics taking inhaled corticosteroids.

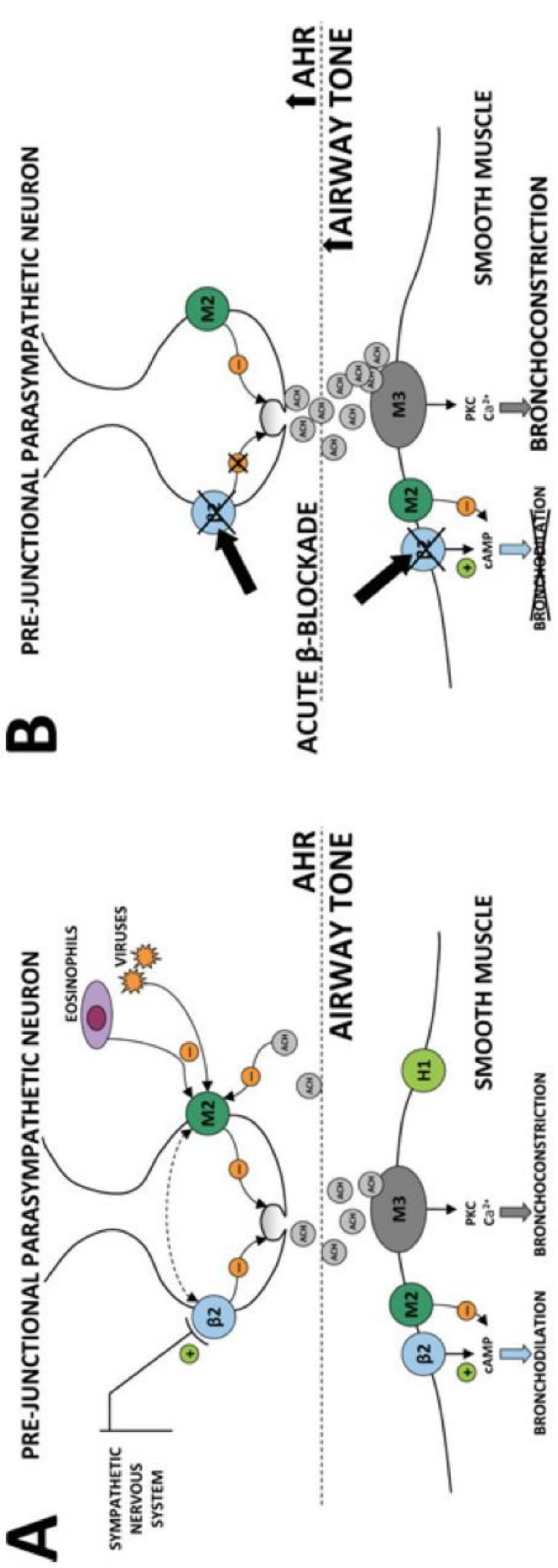
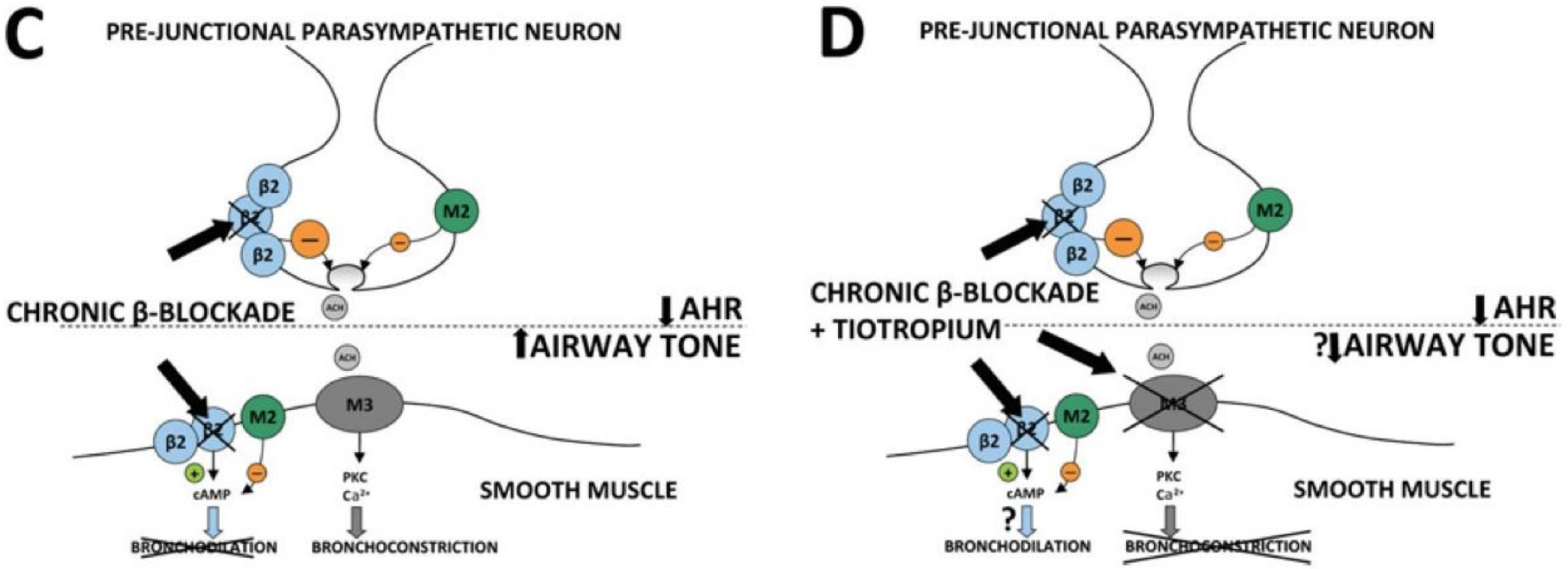


Figure 11. Neuronal control of airway smooth muscle and the effects of beta-blockade. (A) Normal airway function; (B) effects of acute beta-blockade; (C) proposed effects of chronic beta-blockade; (D) proposed effects of chronic beta-blockade with concurrent tiotropium. Reproduced with permission from Lipworth et al.[95]



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2. METHODS

Study Design

A double-blind randomised placebo controlled crossover trial was performed (see fig 12). The Tayside Medical Research Ethics Committee gave approval before commencement of the trial. The study was registered with http://www.clinicaltrials.gov (NCT01074853).

Study Design

Persistent mild-to-moderate asthmatics, aged between 18 to 65 years, with FEV_1 >80% predicted and diurnal FEV_1 variation <30% who were taking ICS ≤1000μg BDP per day or equivalent were recruited. Participants were required to demonstrate airway hyper-responsiveness to methacholine bronchial challenge with a PC_{20} <8mg/ml. Participants were all non-smokers. Exclusion criteria included: an asthma exacerbation within the last six months, resting systolic blood pressure <110mmHg, heart rate <60 bpm, history of arrhythmias, concurrent negative chronotropic medications.

Following a screening visit to assess eligibility, a one to two week run-in period to assess asthma disease stability was performed using electronic domiciliary FEV_1 measurements, prior to randomisation. Participants continued their normal dose of ICS throughout the study. Participants who usually took a combination inhaler of ICS and LABA were switched to the equivalent dose of ICS only for the duration of the study. For reliever use, participants were issued with both ipratropium bromide and salbutamol to be used in a staged fashion as required i.e. ipratropium as first line reliever, followed if necessary by salbutamol as second line.

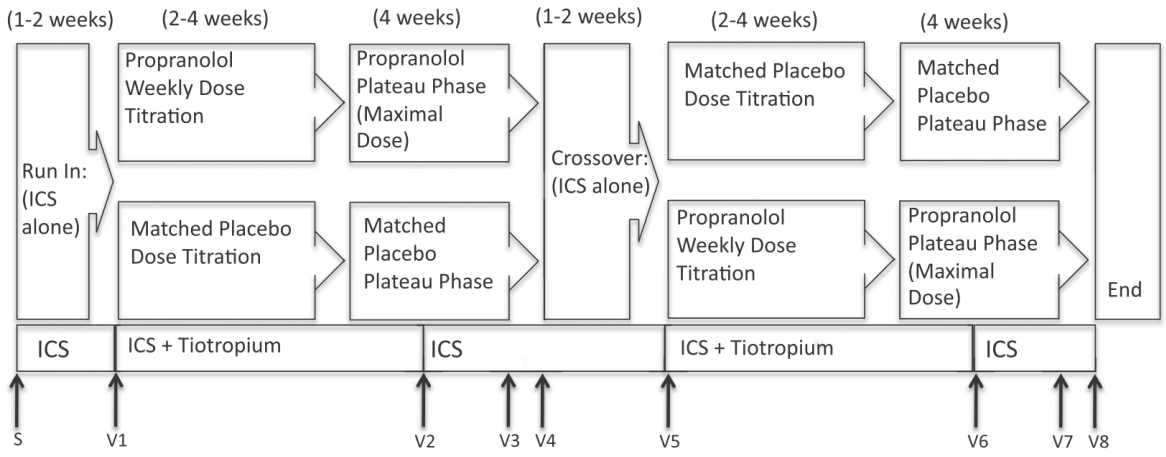

Figure 12. Study diagram. Shown are procedures performed at each study visit. S: screen visit. Spirometry, methacholine bronchial challenge, exhaled nitric oxide (FE_{NO}), heart rate (HR), and blood pressure (BP) were performed. V1: first observed dose of propranolol or placebo. Spirometry, HR, and BP were performed before and after dosing. V2: histamine bronchial challenge (with concomitant tiotropium) with staged salbutaomol and ipratropium recovery. Spirometry, HR, and BP performed before challenge and after recovery. V3: methacholine bronchial challenge with staged salbutamol and ipratropium recovery. Spirometry, HR, and BP were performed before challenge and after recovery. V4: histamine bronchial challenge (without concomitant tiotropium) with staged albuterol and ipratropium recovery. Spirometry, HR, and BP were performed before challenge and after recovery. FE_{NO} was performed before challenge. V5: crossover of treatment limbs. First observed dose of propranolol or placebo. Spirometry, HR, and BP were performed before and after dosing. V6: histamine bronchial challenge (with concomitant tiotropium) with staged salbutamol and ipratropium recovery. Spirometry, HR, and BP were performed before challenge and after recovery. V7: methacholine bronchial challenge with staged salbutamol and ipratropium recovery. Spirometry, HR, and BP were performed before challenge and after recovery. V8: histamine bronchial challenge (without concomitant tiotropium) with staged salbutamol and ipratropium recovery. Spirometry, HR, and BP were performed before challenge and after recovery. FE_{NO} was performed before challenge. ICS = inhaled corticosteroid.

Participants underwent initial dose titration with either propranolol or matched placebo at weekly intervals (10mg twice daily, 20mg twice daily, 80mg LA once daily) as tolerated over a two to four week period, based upon the dose titration algorithm (figure 13). Blinding and randomisation was performed by St May's Pharmaceutical Unit, Cardiff and Vale University LHB, Wales.

Following the first dose of propranolol or placebo, and at every subsequent up-titration visit participants were observed within the department for three hours with serial pulmonary function recorded. Once the maximal dose of propranolol or placebo was established the treatment was then continued for a further four weeks (plateau phase). Tiotropium was given concurrently throughout the dose titration period and for the first two weeks of the plateau phase. In total each treatment limb (including dose titration and plateau phase) continued for a minimum of six weeks and maximum of eight weeks of randomised treatments.

Participants were seen at weekly intervals, for assessment of FEV_1 domiciliary measurements, spirometry, impulse oscillometry (IOS), blood pressure (lying and standing) and heart rate. Participant's symptoms and physiological measurements were considered and randomised treatment was titrated up or down accordingly.

Methacholine challenge PC_{20} followed by sequential salbutamol and ipratropium bromide reversibility was performed at the end of each treatment period. Histamine challenge PC_{20} with reversibility was performed after two weeks of plateau phase with concurrent tiotropium and four weeks of plateau phase (i.e. with no concurrent tiotropium). Following completion of the first treatment limb participants received their

usual ICS alone, for a two week period prior to crossover. Participants were continued any anti-histamines and leukotriene receptor antagonists (LTRA) throughout the study with the exception of stopping for 5 days prior to any bronchial challenge test visit.

Measurements

Spirometry and IOS were performed in accordance with published guidelines.[122,123] A SuperSpiro spirometer (Micro Medical, UK) and IOS Jaeger Masterscreen (Germany) were used. A Mefar dosimeter was used for Methacholine and Histamine Bronchial Challenges. The provocative concentration required to cause a 20% fall in FEV_1 was calculated (PC_{20}).

Statistical Analysis

Data were assessed for normality with the Shapiro-Wilk test and Box-plots. The primary outcome was methacholine PC_{20}. The null hypothesis was that there was no significant difference in methacholine PC_{20} following propranolol compared to placebo. *An a priori* calculation predicted 16 patients would ensure 80% power, with an α-error of 0.05 (two tailed), in order to detect a minimal important difference of one doubling dilution shift in methacholine PC_{20}. For methacholine and histamine challenge, data were logarithmically transformed prior to analysis and then calculated as doubling dose/dilution change from placebo. For all outcomes, comparisons were made by a multi-factorial analysis of variance model, including sequence, visit, treatment and patient effects, with Bonferroni corrections for pairwise comparisons. For salbutamol and ipratropium bromide recovery post bronchial challenge testing, areas under the time response curve for percentage change from baseline were calculated. All analysis was performed using SPSS version 18.

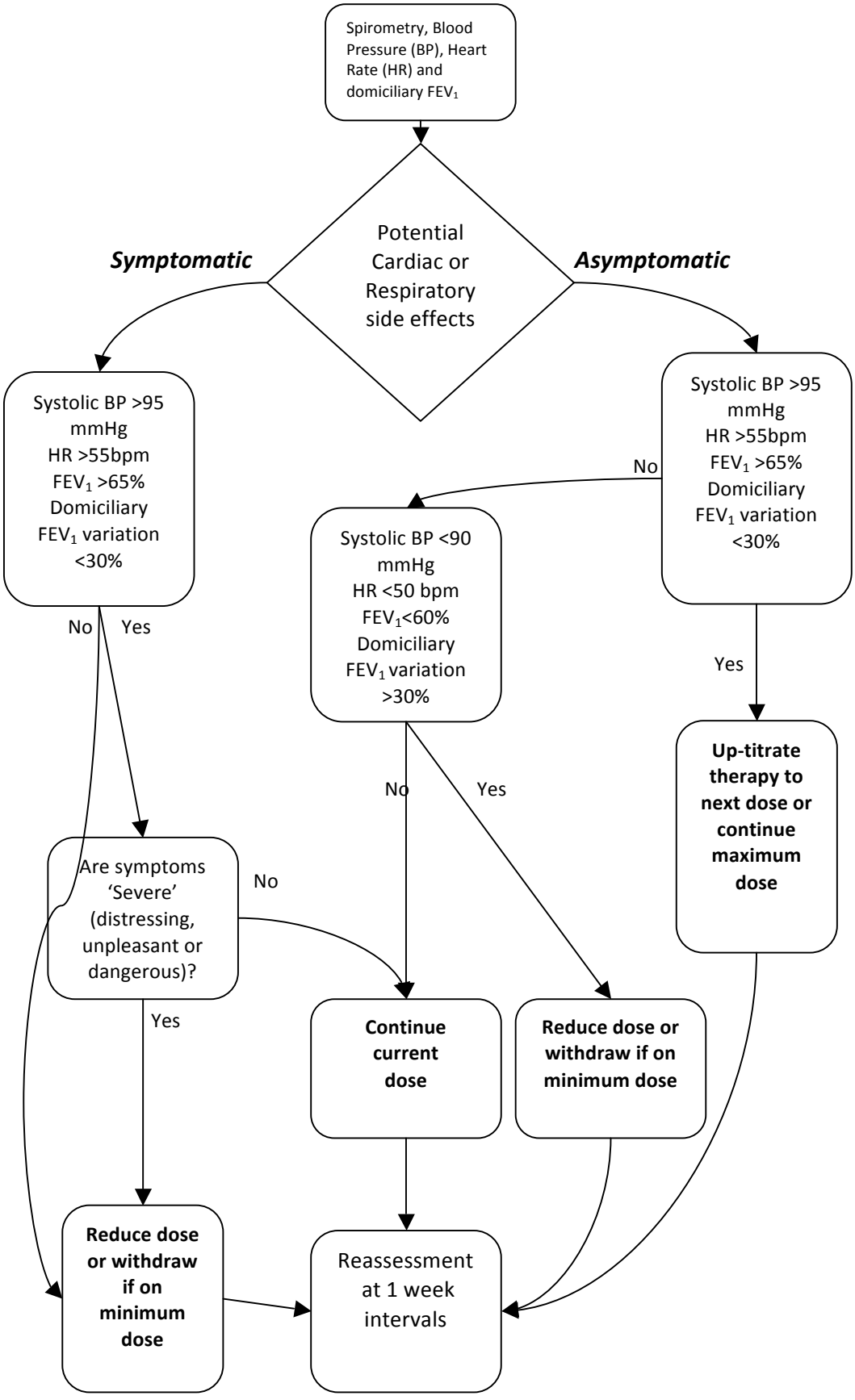

Figure 13. Dose Titration Algorithm

3. RESULTS

21 participants were randomised of which, 18 participants (10 female, 8 male) completed per protocol. Mean age (SEM) was 36 (4). 17 participants achieved dose titration to the maximal propranolol dose. Baseline characteristics are shown in table 10. Three participants withdrew during the study due to: practical difficulties in completing study visits; hypotension; lower respiratory tract infection (figure 14).

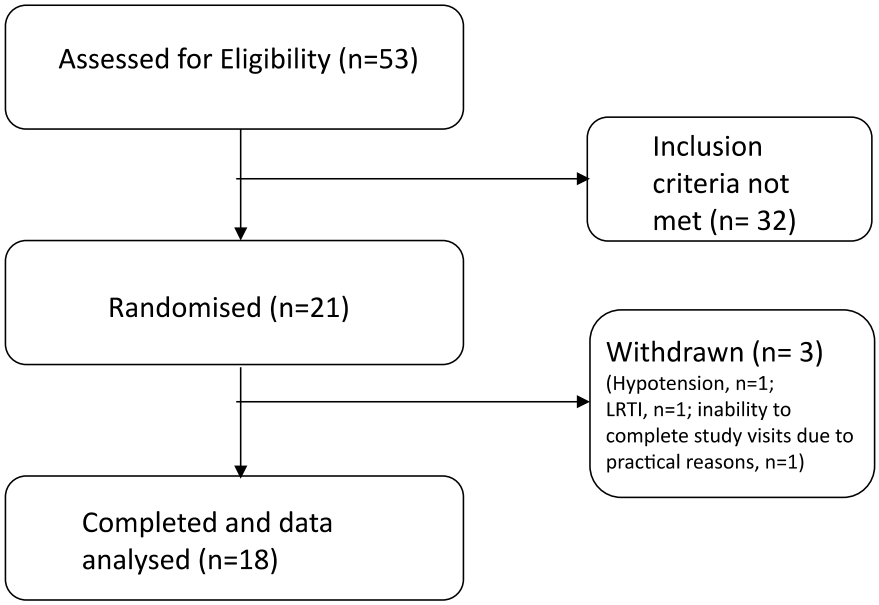

Figure 14. Study Consort diagram

Subject/Sex	Age (years)	FEV_1%	FEV_1/FVC Ratio	Methacholine PC_{20} (mg/ml)	BDP equivalent daily dose(μg)	Concurrent Medications:
1/F	21	92	0·78	0·92	400	L,A,NS
2/F	64	99	0·71	2·48	400	L,LT,NS
3/F	31	85	0·75	0·99	500	A,LT
4/M	48	85	0·68	2·0	500	L,LT
5/F	65	103	0·69	0·71	200	-
6/M	29	98	0·71	1·36	100	-
7/M	57	106	0·81	3·45	1000	
8/M	20	91	0·76	3·71	400	-
9/F	19	91	0·83	0·67	400	A
10/M	19	90	0·85	1·73	200	A
11/F	25	91	0·85	2·4	200	A
12/F	50	88	0·67	1·13	400	A,NS
13/M	57	88	0·76	2·19	200	A,NS
14/F	22	102	0·82	0·67	800	-
15/M	35	95	0·83	5·42	800	L,NS
16/F	46	91	0·72	0·31	1000	L
17/F	21	85	0·75	3·31	200	-
18/M	25	86	0·76	0·1	200	L,A
Mean (SEM)	36(4)	93(2)	0·76(0.01)	1·32 (0.81-2.15)*	440 (66)	

Table 10. Participant demographics

*Data displayed as geometric mean (95%CI). Data shown as % predicted for age, gender, race.
FEV_1, Forced Expiratory volume in 1 second; FVC, Forced Vital Capacity; BDP, Budesonide.
LABA(L), Antihistamine (A), LTRA (LT), Nasal Spray

Airway Hyper-responsiveness

No significant difference was observed in methacholine challenge PC_{20} following chronic propranolol exposure compared to placebo, geometric mean mg/ml: 2·57 (95%CI 1·13 to 5·85) versus 2·50 (95%CI 1·14 to 5·50), -i.e. a mean doubling dilution difference (DDD) of 0·04 (95%CI -0·56 to 0·63), p=0·89 (figure 15).

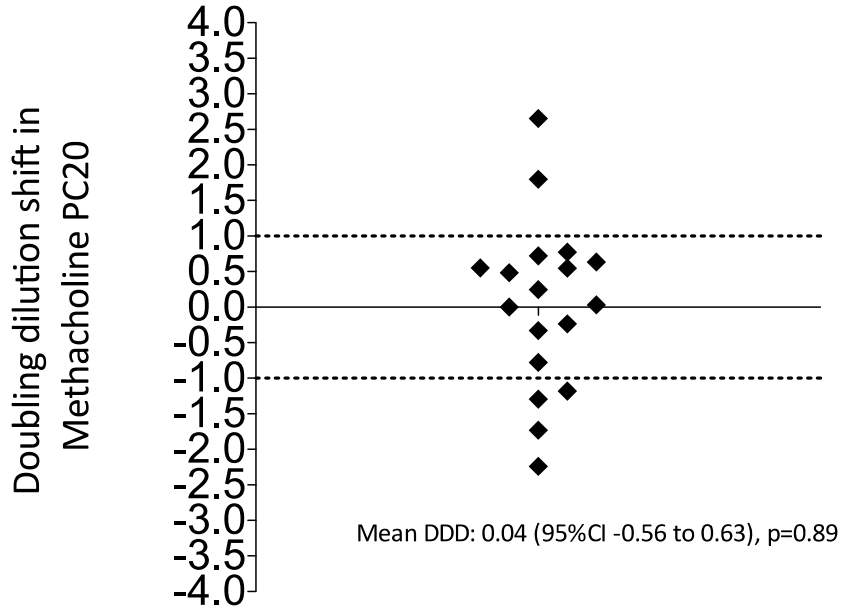

Figure 15. The effect of chronic treatment with propranolol on methacholine provocation concentration causing a 20% fall in FEV (PC_{20}). Data for each participant are displayed as the doubling dose in methacholine PC_{20} values between propranolol versus placebo.

After two weeks chronic dosing with propranolol, whilst receiving concurrent tiotropium, no significant difference was seen with histamine challenge PC_{20} for propranolol versus placebo as geometric mean mg/ml: 2·11 (95%CI 1·33 to 3·33) versus 2·52 (95%CI 1·64 t0 3·85) ,i.e. a DDD of 0·26 (95%CI -0·36 to 0·87), p=0·39 (figure 16).

Following the cessation of tiotropium for 14 days, after a further two weeks of chronic dosing with propranolol, no significant difference was seen with histamine challenge PC_{20} for propranolol versus placebo as geometric mean mg/ml: 1·73 (95%CI 1·10 to 2·73) versus 2·32 (95%CI 1·65 to 3·27), i.e. a DDD of 0·42 (95%CI -0·09 to 0·93), p=0·10 (figure 16).

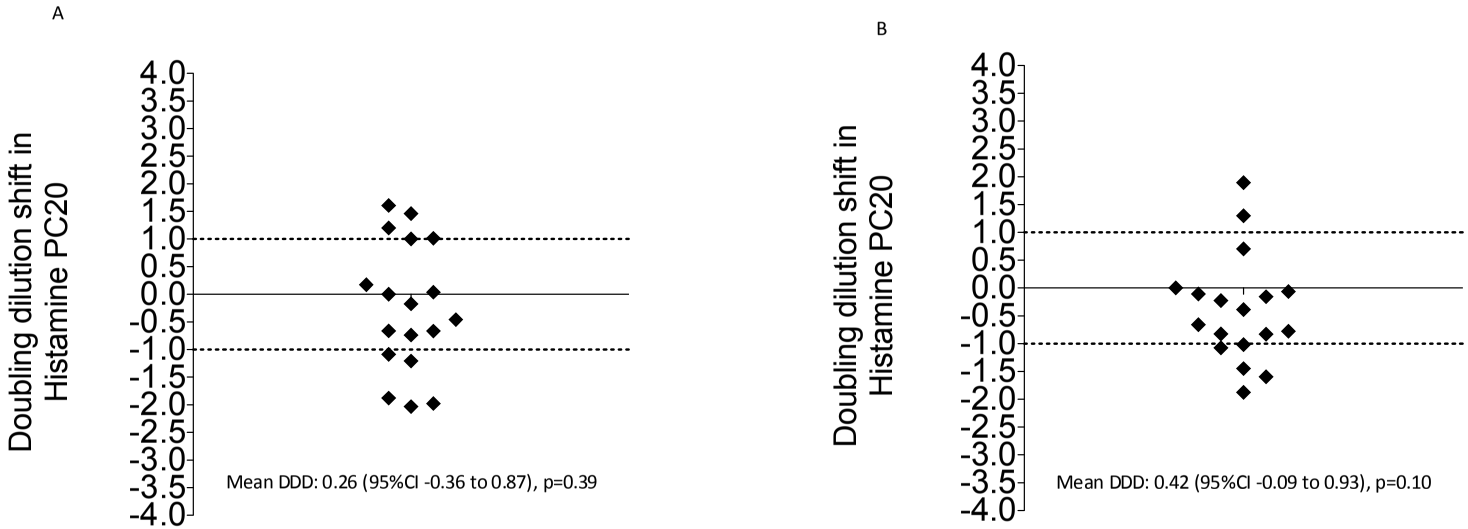

Figure 16. The effect of chronic treatment with propranolol on histamine provocation concentration causing a 20% fall in FEV (PC_{20}) with and without tiotropium. (A) Histamine challenge with concurrent tiotropium. B) Histamine challenge without concurrent tiotropium. Data for each participant are displayed as the doubling dose in histamine PC_{20} values be- tween propranolol versus placebo.

Systemic beta-blockade

Salbutamol induced chronotropic response, measured at the end of each study period, (i.e recovery post histamine challenge, study visit four or eight) was significantly blunted following propranolol in comparison with placebo: mean difference 25 bpm (95%CI 14 to 37), p<0·001. Resting heart rate was also significantly lower following chronic propranolol dosing: mean difference 5 bpm (95%CI 1 to 9), p<0·001 (figure 17). No differences were seen for supine systolic or diastolic blood pressure at the end of each study period (visit four or eight), for placebo versus propranolol: mean difference 3 mmHg (95%CI -1 to 7), p=0·11, and 2 mmHg (95%CI -2 to 5), p=0·26.

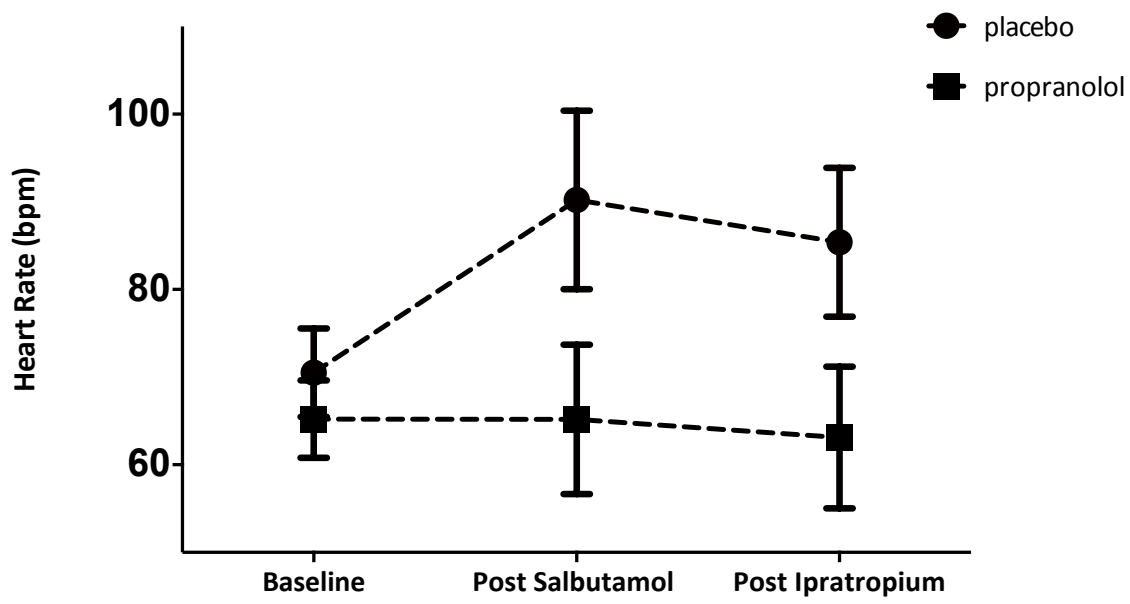

Figure 17. Salbutamol Response following Chronic Beta Blockade or Matched Placebo.
Data displayed as mean (95%CI).

Recovery to Salbutamol and Ipratropium post challenge

Following methacholine challenge, staged recovery to nebulised salbutamol and ipratropium showed a significant overall difference between propranolol and placebo as AUC %.min (SEM) : 4077·4 (102) versus 4362·5 (102), mean difference: 285·1 (95%CI 34·6 to 535·7), p=0·028. No significant difference was seen at 20 mins post salbutamol for propranolol versus placebo as FEV_1% predicted mean difference: 5·05 (95%CI -0·13 to 10·24), p= 0·055 (figure 18).

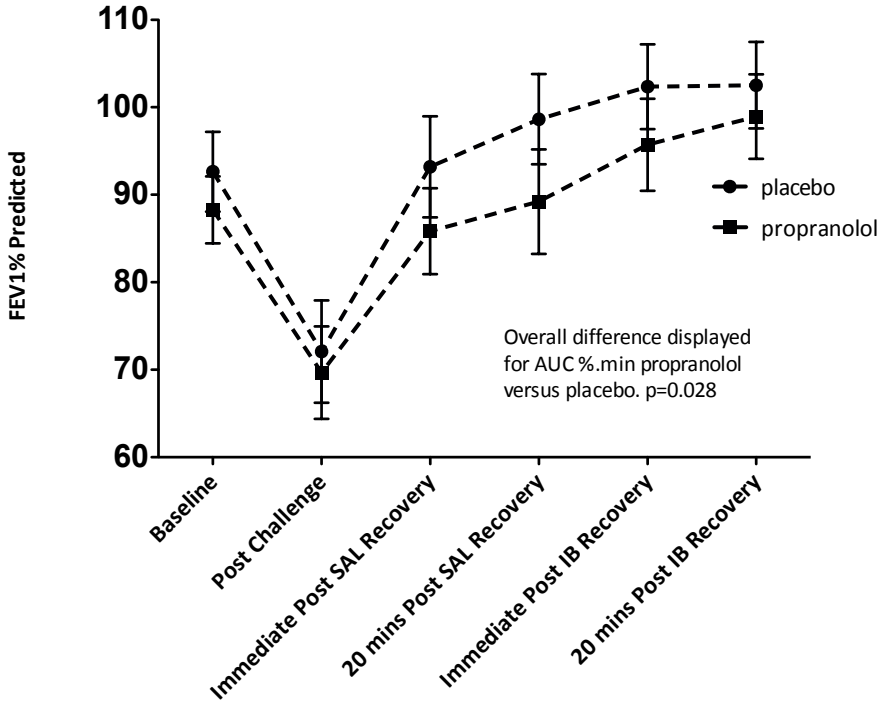

Figure 18. Salbutamol and ipratropium recovery after methacholine challenge.

Data are displayed as mean (95%CI). SAL: salbutamol, IB; ipratropium bromide.

Comparisons of recovery post histamine challenges whilst receiving concurrent tiotropium showed a significant difference in staged salbutamol and ipratropium recovery for propranolol versus placebo, as AUC %.min (SEM) : 4082·9 (94) versus 4413·6 (97), mean difference 330·8 (95%CI 208·8 to 452·8), p=0·01. Furthermore, at 20 minutes post salbutamol the response was significantly different for propranolol versus placebo as FEV_1% predicted mean difference 4·94 (95%CI 1·10 to 8·79), p=0·015. Following the cessation of tiotropium, after a further two weeks of chronic dosing with propranolol, there remained a significant difference versus placebo in staged salbutamol and ipratropium recovery, as AUC %.min (SEM) 4061·8 (94) versus 4363·7 (99), mean difference 301·8 (95%CI 190·5 to 413·1), p=0·016. A significant difference was present at 20 minutes post salbutamol for propranolol versus placebo as, FEV_1% predicted mean difference 5·28 (95%CI 2·54 to 8·01), p=0·001 (figure 19).

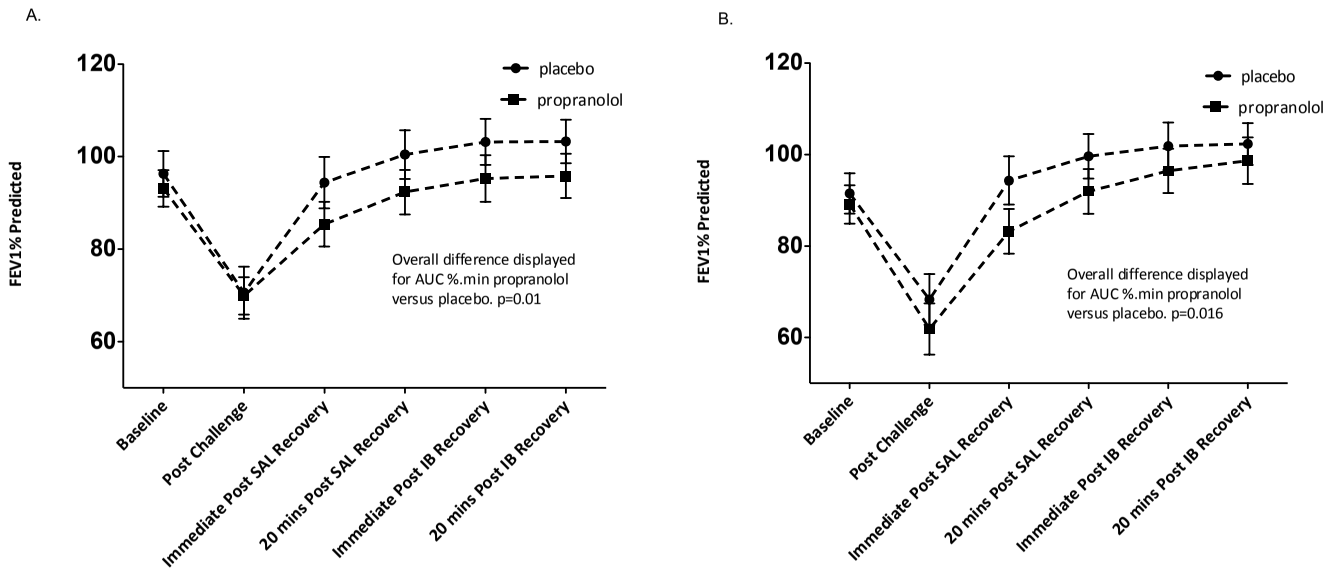

Figure 19. Salbutamol and ipratropium recovery after histamine challenge with and without concurrent tiotropium. (A) Histamine challenge with concurrent tiotropium. (B) Histamine challenge without concurrent tiotropium. The overall difference is displayed for area under the curve (%.min), propranolol versus placebo. Data displayed as mean (95% confidence interval).

Effects on Pulmonary Function and Airway Inflammation

FEV_1 % predicted prior to methacholine challenge, without concurrent tiotropium, (study visit three or seven) showed a fall with propranolol versus placebo amounting to a 4·3% (95%CI -0·6 to 9·2) p=0·08. Measured at the end of each study period, (i.e study visit four or eight) prior to histamine challenge, there was a difference in FEV_1 % predicted 2·4% (95%CI -0·1 to 4·8), p=0·055 without tiotropium, and a difference of 3·2% (95%CI 0·05 to 6·3), p=0.046 with concomitant tiotropium (at study visit two or six).

No significant difference was seen in R5% predicted measured prior to histamine challenge at the end of each study period, (study visit four or eight) following propranolol versus placebo: mean difference 3·65% (95%CI -14·7 to 22·0), p=0·68.

In terms of airway inflammation measured by FE_{NO}, there was no significant difference following propranolol versus placebo, as geometric mean (SEM) 28·0 ppb (10·1) versus 25·3 ppb (7·6), amounting to a geometric mean fold difference of 1·11 (95%CI 0·70 to 1·16), p=0·41.

Asthma Control and Quality of Life

At the end of the study period, no significant difference was found between propranolol versus placebo for ACQ, mean difference: 0·18 (95%CI -0.23 to 0·58), p=0·79. Furthermore no significant difference was seen in the mini-AQLQ, mean difference: 0·14 (95%CI -0·19 to 0·46), p=0·84.

4. DISCUSSION

The purpose of this study was to assess the effects of chronic propranolol in patients with stable persistent asthma as add on therapy to inhaled corticosteroids. Previous open-labeled studies have shown attenuation of methacholine AHR with nadolol compared to baseline in steroid–naïve asthamatics.[102] The results of this study showed no significant effect of propranolol compared to placebo on either methacholine or histamine AHR.

Airway remodelling describes structural changes in the human airway associated with asthmatic inflammation and is a complex process that involves all component tissues of the airway from the epithelium to the adventitia. Deemed irreversible, remodelling changes contribute to thickening of airway walls with subsequent airway narrowing, bronchial hyper-responsiveness, airway oedema and mucous hypersecretion. Airway remodelling is associated with poor clinical outcomes among asthmatic patients.[154] Although no effects were demonstrated on airway smooth muscle, the proposed benefits seen in murine models of asthma with chronic nadolol being able to reduce mucous metaplasia and mucin production was intriguing.[100]

Although using beta-blockers in asthma may at first sight seem counterintuitive, there is evidence to suggest that chronic long-acting beta-2-agonist therapy with inhaled corticosteroid use results in down-regulation and sub-sensitivity of the beta-2-adrenoceptor,[155,156] sometimes with worsening asthma control.[157,158] Therefore the paradox for beta-2-adrenoceptor up-regulation and increased sensitivity following chronic beta-blocker use in asthma is intriguing.[137] In the same way that LABAs are

only routinely given in conjunction with ICS, it could be argued that when examining the effects of chronic beta-blocker use in asthma, this should also be performed as add on therapy to pre-existing ICS, as was the case in the present study. Unlike previous open label chronic dosing studies with nadolol in steroid naïve patients, no attenuation of airway hyper-responsiveness to methacholine following chronic propranolol compared to placebo was seen when added to ICS. Pointedly even when using a spasmogen acting via a different pathway, namely histamine, there was still no difference in comparison to placebo, regardless of presence or absence of concurrent tiotropium use.

In the absence of any worsening of airway hyper-responsiveness it could be assumed that the presumed deleterious chronic effects of beta-2-blockade in asthma might conceivably result in increased airway tone. At the final visit prior to histamine challenge there was a small worsening in FEV_1% predicted following propranolol compared to placebo amounting to a 2.4% difference, this was despite systemic beta-2-blockade being evident as attenuation of salbutamol induced tachycardia. For post challenge recovery to salbutamol, the degree of reversibility remained mostly preserved following chronic propranolol, with or without the presence of concomitant tiotropium.

The rationale for long acting anticholinergic therapy was to obviate any initial worsening of airway calibre during the initial up titration with propranolol,[10] when patients would be most vulnerable before beta-2-adrenoceptor adaptation had occurred, which is thought to take at least two weeks with propranolol on peripheral blood mononuclear cell cAMP response to isoprenaline. [138,139] However data on beta-

2-adrenoceptor binding density on peripheral blood mononuclear cells with propranolol has shown near maximal up regulation after only two days reaching a peak after ten days.[144]

When reviewing historic case reports of beta-blocker use in asthmatics, the greatest concerns of bronchoconstriction have been with acute dosing. In chapter 3 it was demonstrated that nebulised salbutamol and ipratropium can achieve a full recovery of pulmonary function post histamine challenge testing despite the presence of 10 or 20mg of propranolol given as single acute dose, in steroid treated asthmatics. In the present study it has been shown that by means of slow dose titration, doses of propranolol up to 80mg can be well tolerated in patients with stable steroid treated persistent asthma, without any associated deleterious effects on ACQ or AQLQ. Indeed the mean differences in either ACQ or AQLQ were well within the accepted minimal important difference of 0.5 units for both outcomes. This finding alone would challenge current clinical equipoise that asthmatics should never be given a beta-blocker let alone a non-selective agent like propranolol.[95] This in turn may suggest that as in heart failure, chronic beta-blockade can be given relatively safely without deleterious effects when given by a gradual dose escalation regime, whilst allowing the beta-2-adrenoceptors to adapt.

Although this study did not demonstrate any significant deleterious effects of chronic propranolol dosing within carefully chosen asthmatic patients, the study also failed to show any beneficial effects in comparison to placebo control. Despite being non-selective beta-blockers, whether the use of propranolol in this study rather than nadolol has affected findings is unclear. In this regard both drugs exhibit inverse

agonist activity (i.e. an ability to effectively switch off the receptor), as well acting as conventional competitive receptor antagonists.[159]

In conclusion, this study has shown that by means of a placebo controlled design, that the non-selective beta-blocker propranolol may be safe to use without any worsening of AHR and only a small effect on pre-challenge pulmonary function, in carefully selected stable steroid treated asthmatics. These results cannot be extrapolated to more severe asthmatics or when propranolol is given for greater than 6-8 weeks duration.

5. CRITIQUE

This study was designed to assess the effects of chronic propranolol dosing on airway hyper-responsiveness. As previously discussed murine models and open label studies in humans have suggested putative benefits with chronic beta-blockade in asthma.

As with the acute dosing study, this study was restricted by ethical concerns. These concerns resulted in a maximum dose of 80mg being used and also relatively short study duration of 6-8 weeks. It therefore remains unknown as to whether an increase in maximum dose or study duration would have resulted in any therapeutic benefit being seen.

With regards to the primary outcome, methacholine challenge PC_{20} was chosen primarily because it was the study outcome used in the previous open label studies which suggested therapeutic benefits. Whilst the use of a PC_{20} is an accepted measurement of airway hyper-responsiveness, with hindsight the slope of the dose response curve could have been utilised to assess for subtle changes in airway hyper-responsiveness. In order to ensure that any potential benefit seen was not unique to methacholine challenge, histmaine challenge testing was used, both challenges are however direct bronchial challenges. Mannitol, as an example of an indirect challenge test that may have been better suited as an alternative challenge test. The basis for this is that indirect challenge tests stimulate inflammatory cells, epithelial cells and nerves to release mediators that act on specific receptors of the smooth muscle and induce its contraction with resultant airway narrowing, thus better mimicking the inflammatory cascade seen in asthma rather than a pure pharmacological challenge test such as methacholine.

CHAPTER 6:

EFFECTS OF INTRAVENOUS CARDIO-SELECTIVE BETA-BLOCKADE AND CHRONIC ORAL NON-SELECTIVE BETA-BLOCKADE IN ASTHMA

Study Aims

1. **To assess the pulmonary effects of acute intravenous esmolol dosing in mild-to-moderate asthmatics taking inhaled corticosteroids.**
2. **To assess the effects of first dose exposure to oral propranolol and the subsequent effects at dose up-titration.**

1. INTRODUCTION

Within the previous chapter, although a lack of therapeutic benefit was seen with chronic propranolol dosing, within the study participants it was demonstrated that non-selective beta blockade can be administered relatively safely in selected mild-to-moderate asthmatics.

Beta-blockers are integral in the treatment of cardiovascular disease. Despite their proven benefits, beta-blockers are avoided in asthmatics due to concerns of bronchoconstriction.[68] These concerns led to a consensus statement from the European Society of Cardiology stating that, a history of asthma should be considered a contra-indication to the use of any beta-blocker.[71]

In addition to data within this thesis showing a lack of any significant deleterious effects with non-selective beta-blocker use in asthma, as previously discussed the meta-analysis by Salpeter suggests that cardio-selective beta-blockers can be given relatively safely within patients with a history of obstructive airway disease.[77]

Several safety issues are likely to influence the prescription of beta-blockers in asthma. In addition to potential bronchoconstriction upon first exposure, subsequent up-titration of beta-blockers results in further exposure and potential risk. Up-titration is commonly performed in the community and without direct medical supervision. Moreover the presence of beta-2-adrenoceptor antagonism might conceivably attenuate the response to concomitant beta-agonist inhaled therapy.

The concern of beta-blocker use in asthma led partly to the development of ivabradine as an alternative negatively chronotropic medication, which does not results in any bronchoconstriction when used in asthma.[160]

Although there were no demonstrable beneficial effects on AHR with propranolol, the data generated allows an evaluation of the safety and tolerability of propranolol in asthma. Within the study described in the previous chapter, prior to randomisation a subgroup of participants were given a single intravenous injection of the cardio-selective beta-blocker esmolol with the effects on pulmonary function assessed. The results of this subgroup analysis are discussed in this chapter. In addition the observed pulmonary effects of first dose exposure to oral propranolol and the subsequent effects at dose up-titration, in the presence of concurrent tiotropium are discussed.

2. METHODS

A post-hoc analysis of a double-blind randomised placebo controlled trial of propranolol in mild-to-moderate asthmatics was performed. The study was registered with http://www.clinicaltrials.gov (NCT01074853).

Mild-to-moderate asthmatics, aged between 18-65 years, FEV_1 >80% predicted and diurnal FEV_1 variation <30%, taking inhaled corticosteroid ≤1000μg/day beclomethasone dipropionate equivalent dose were recruited. Participants were required to demonstrate airway hyper-responsiveness (AHR) to methacholine bronchial challenge PC_{20} <8mg/ml. Participants were all non-smokers. Exclusion criteria included: asthma exacerbation within the last six months, systolic blood pressure <110mmHg, heart rate <60 bpm, history of arrhythmias, concurrent negative chronotropic medications.

Prior to randomisation a subgroup of participants underwent a safety visit and received a single intravenous bolus dose of esmolol (0.5mg/kg). Spirometry, impulse oscillometry and heart rate and blood pressure were recorded pre and post acute esmolol dosing at 2, 8, 16 and 32 minutes.

As previously discussed, participants then underwent dose titration of propranolol or matched placebo at weekly intervals (10mg twice daily, 20mg twice daily, 80mg LA once daily) as tolerated over a two to four week period. Following the first dose of propranolol (or matched placebo) at 10mg, and at every subsequent up-titration visit (ie the first dose exposure to 20mg and 80mg) participants were observed within the

department for three hours with serial pulmonary function, heart rate and blood pressure recorded. Tiotropium was given concurrently during the dose titration period with propranolol (or matched placebo). The full methods of the main protocol have been described in detail in chapter 5. In this chapter only report the subgroup of participants who received an initial intravenous esmolol in addition to their propranolol up-titration data is discussed.

Outcome Measures

The main outcome measures were the effects on pulmonary function following acute esmolol and propranolol use. Spirometry and impulse oscillometry were recorded.

Measurements

Spirometry was performed in accordance with published guidelines.[122] Impulse oscillometry (IOS) was performed according to published guidelines.[123] A SuperSpiro Spirometer (Micro Medical, UK) and IOS Jaeger Masterscreen (Germany) were used. Bronchoconstriction was reflected as either a fall in forced expiratory lung volume as FEV_1 or an increase in airway resistance as R5. Asthma control questionnaires were performed.[161]

Statistical Analysis

Data were assessed for normality with the Shapiro-Wilk test and Box-plots. The primary outcome was change in FEV_1 post esmolol administration. For all outcomes, comparisons were made by a multi-factorial analysis of variance model with Bonferroni corrections for pairwise comparisons. All analysis were performed using SPSS version 21 (Chicago, IL).

3. RESULTS

12 participants (7 female, 5 male) underwent both esmolol and propranolol dosing and were used for the present analysis. No participant that received esmolol failed to be randomised and subsequently each participant received propranolol. Mean age (SEM) was 37(5). Baseline characteristics are shown in table 11.

Subject/Sex	Age (years)	FEV_1%	FEV_1/FVC Ratio	Methacholine PC_{20} (mg/ml)	BDP equivalent daily dose(μg)
1/F	21	92	0·78	0·92	400
2/F	64	99	0·71	2·48	400
3/F	31	85	0·75	0·99	500
4/M	48	85	0·68	2·0	500
5/F	65	103	0·69	0·71	200
6/M	29	98	0·71	1·36	100
7/M	57	106	0·81	3·45	1000
8/M	20	91	0·76	3·71	400
9/F	19	91	0·83	0·67	400
10/M	19	90	0·85	1·73	200
11/F	25	91	0·85	2·4	200
12/F	50	88	0·67	1·13	400
Mean (SEM)	37(3)	93(2)	0.76(0.02)	1.54 (1.06- 2.23)*	392 (67)

Table 11. Participant Demographics

*Data displayed as geometric mean (95%CI). Data shown as % predicted for age, gender, race.

FEV_1: Forced Expiratory volume in 1 second; FVC: Forced Vital Capacity; BDP:beclomethasone dipropionate.

Acute cardio-selective beta-blockade – effects on pulmonary function

Pulmonary function was assessed pre-esmolol dosing and post-esmolol dosing at (2 mins, 8 mins, 16 mins and 32 mins). No significant differences were seen in FEV_1% predicted following an intravenous esmolol bolus. Mean change in FEV_1% predicted (95% CI) were: 2 minutes post esmolol; -0.58% (-2.96 to 1.79), p=0.99, 8 minutes; 0.42% (-3.17 to 4.00), p=0.99, 16 minutes; 0.75% (-2.73 to 4.22), p=0.99, and 32 minutes; 0.67% (-3.51 to 4.85), p=0.99. (see figure 20).

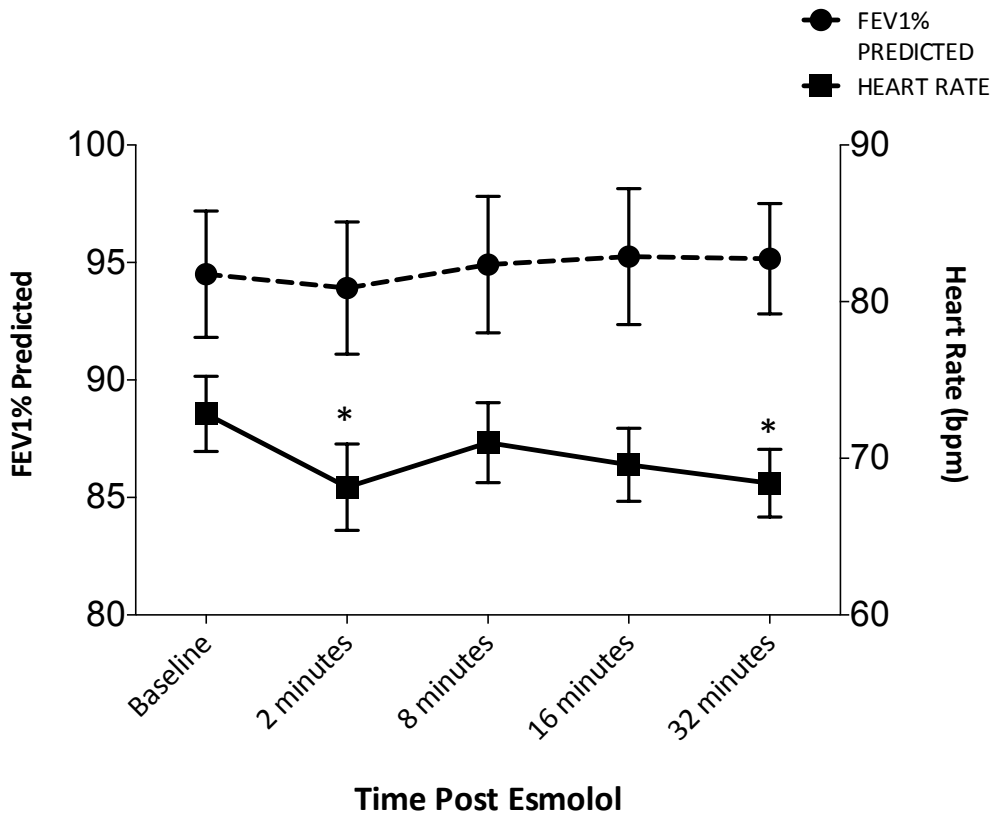

Figure 20. Effect of Esmolol on FEV_1% predicted and Heart Rate.

Data displayed as Mean (SEM). *significant difference from baseline p<0.05

No significant differences were seen in total airway resistance as R5% predicted post esmolol. Mean change in R5% predicted (95% CI) were: 2 minutes post esmolol; 1.6%

(-12.65 to 9.44), p=0.99, 8 minutes; 1.85% (-12.49 to 8.78), p=0.99, 16 minutes; -0.51% (-13.43 to 12.40), p=0.99 and 32 minutes; -1.1% (-11.64 to 9.44), p=0.99.

Acute cardio-selective beta-blockade – effects on blood pressure and heart rate

Significant reductions in heart rate were seen at 2 and 32 minutes post esmolol dosing. Mean fall (95%CI) in heart rate at 2 minutes post esmolol: -4.7 (-7.9 to -1.3), p=0.002 and 32 minutes; -4.4 bpm (95%CI -7.8 to -1.1), p=0.003 (figure 19). A significant small reduction was also seen in systolic blood pressure at 2 and 32 minutes post esmolol dosing. Mean fall (95%CI) in systolic blood pressure at 2 minutes post esmolol: -5.9mmHg (95%CI -11.4 to -0.41), p=0.03 and 32 minutes: -5.7mmHg (95%CI-11.2 to -0.17), p=0.04.

Acute non-selective beta-blockade with concurrent tiotropium. – effects on pulmonary function

A non-significant increase in FEV_1% predicted was seen 30minutes post 10mg propranolol (with tiotropium); mean difference 3.9% (95%CI -0.4 to 8.2), p=0.084, 1 hour post dose; 3.8% (95%CI -1.3 to 8.8), p=0.26, 2 hours post dose; 3.3% (95%CI -2.6 to 9.1), p =0.80, and 3 hours post dose; 3.3% (95%CI -3.6 to 10), p=1.0 (figure 21).

Falls in R5% predicted were seen at 30minutes post 10mg propranolol (and tiotropium); mean difference -39.3% (95%CI -69.9 to -8.8), p=0.009, 1 hour post dose; -32.8% (95%CI -58.8 to -6.8), p=0.01, 2 hours post dose; -31.3% (95%CI -58.2 to -4.3), p=0.01, and 3 hours post dose; -35.8% (95%CI-72.5 to 0.95), p =0.06.

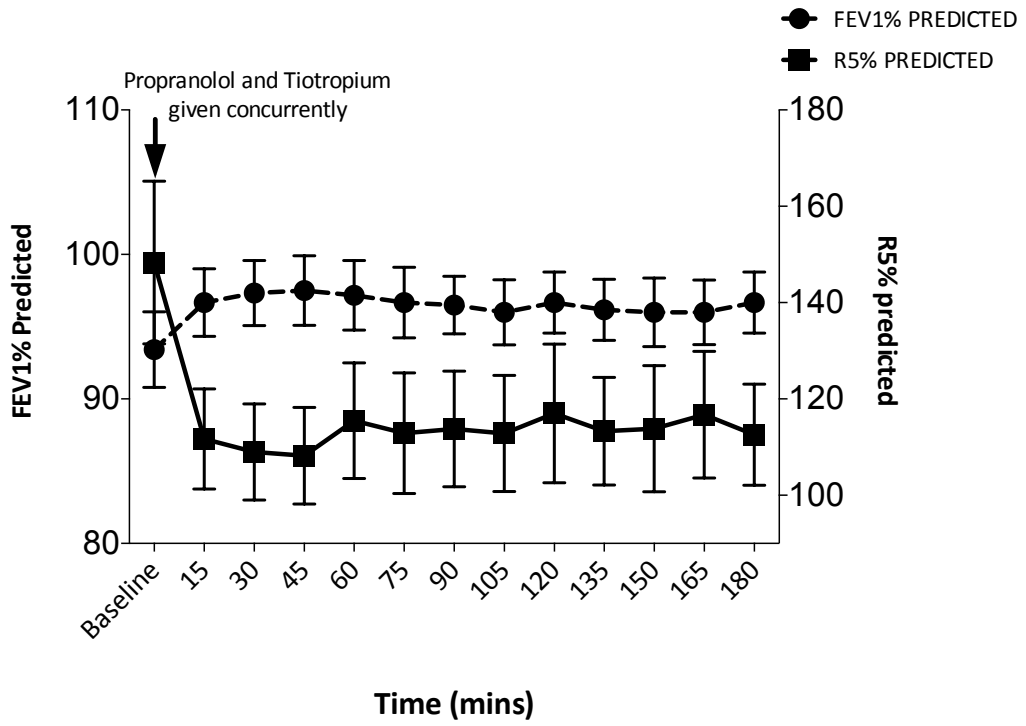

Figure 21. Protective Pulmonary Effects of Tiotropium post 10mg dose of propranolol.

Data displayed as mean (SEM).

Compared to matched placebo there were no significant differences observed in FEV1% and R5% predicted 3 hours post 10mg of propranolol in the presence of concurrent tiotropium (table 12).

	Propranolol (Mean, 95%CI)	Placebo (Mean, 95%CI)	P value		Propranolol (Mean, 95%CI)	Placebo (Mean, 95%CI)	P value
FEV1 % Predicted				***R5% Predicted***			
3 hours post 10mg dose	96.7 (92 – 101.3)	100.5 (94.1 – 106.9)	0.18	**3 hours post 10mg dose**	112.6 (89.5 – 135.7)	111.7 (84 – 139.4)	0.91
3 hours post 20mg dose	96.9 (91.8 – 102)	100.6 (93.5 – 107.6)	0.12	**3 hours post 20mg dose**	109.4 (91.6 -127.3)	102.3 (73.9 – 130.6)	0.32
3hours post 80mg dose	97.1 (91.4 -102.7)	99.7 (93.5 – 105.8)	0.09	**3hours post 80mg dose**	109.7 (87.9 – 131.5)	100.3 (76.4 - 124.1)	0.03

Table 12. Effects of acute dosing of propranolol vs. placebo on pulmonary function (with concurrent tiotropium).

Data shown as % predicted for age, gender, race. FEV_1: Forced Expiratory volume in 1 second.

R5: Total airway resistance at 5Hz.

Up-titration of non-selective beta-blockade with concurrent tiotropium

No evidence of bronchoconstriction was demonstrated in either FEV_1% or R5% predicted following 1st dose exposure to either the 20mg or 80mg dose of propranolol in the presence of concurrent tiotropium (figure 22).

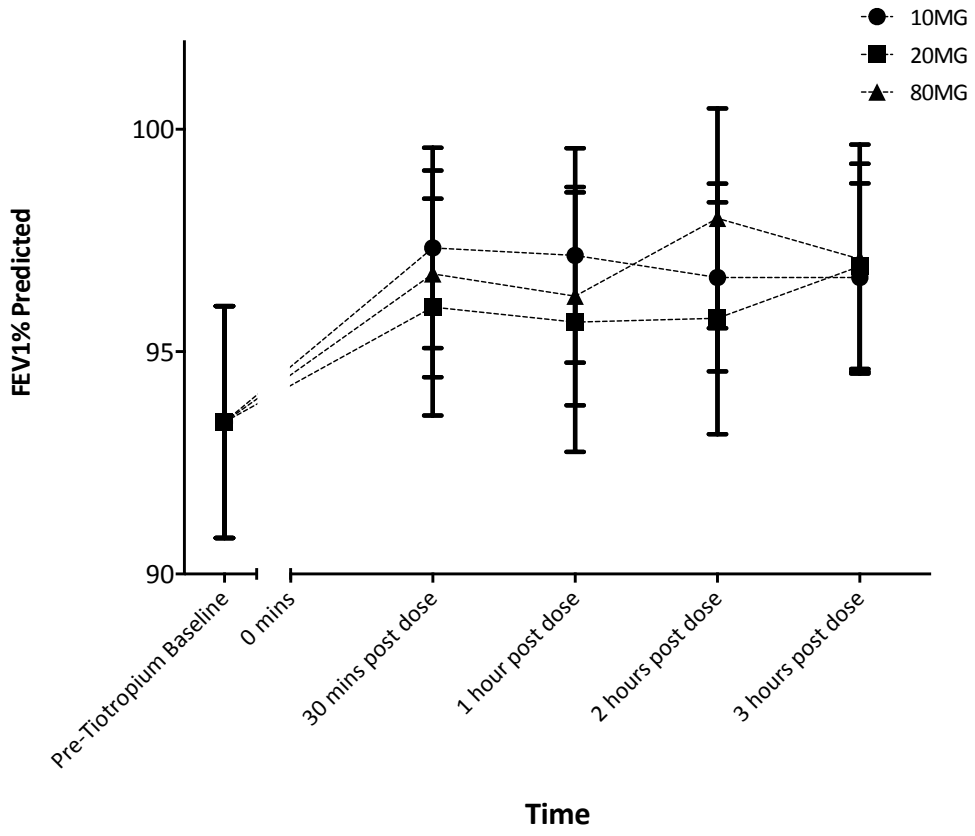

Figure 22. Protective Effects of Tiotropium on FEV_1% predicted at propranolol up-titration.

Mean increase in FEV_1% predicted 30 minutes post 20mg of propranolol (with tiotropium); 0.33% (95%CI -1.6 to 2.3), p=0.99, and 3 hours post dose; 1.3% (95%CI -1.6 to 4.1), p=0.99. Mean fall in R5% predicted 30 minutes post 20mg of propranolol (with tiotropium); -4.0% (95%CI -17.8 to 9.7), p=0.99, and 3 hours post dose, -7.7%(95%CI -21.7 to 6.2), p=0.80.

Mean increase in FEV_1% predicted 30 minutes post 80mg of propranolol (with tiotropium); 0.92% (95%CI -1.26 to 3.09), p = 0.99 and 3 hours post dose; 1.25% (95%CI -3.56 to 6.06), p=0.99. Mean fall in R5% predicted 30 minutes post 80mg of propranolol (with tiotropium); -5.5% (95%CI -20.3 to 9.2), p=0.99 and 3 hours post dose; -7.2% (95%CI -28.9 to 14.5), p=0.99.

Compared to matched placebo there were no significant differences observed in FEV1% and R5% predicted in the presence of tiotropium, except for after the 80mg dose of propranolol for R5% which amounted to a mean difference of 9.4%, p=0.03 (table 11).

Non-selective beta-blockade – effects on heart rate and blood pressure

Heart rate significantly fell 3 hours post 10mg of propranolol; -11bpm (95%CI -15 to -7), p<0.001, post 20mg of propranolol; -6bpm (95%CI -10 to -1), p=0.013, and post 80mg of propranolol; -7bpm (95%CI-15 to -1), p=0.049.

No significant change was seen in supine systolic blood pressure post 10mg of propranolol; mean difference 2mmHg (95%CI -3 to 7), p=0.40, post 20mg of propranolol 2mmHg (95%CI -4 to 7), p=0.53, and post 80mg of propranolol; 4mmHg (95%CI -2 to 9), p=0.19.

4. DISCUSSION

The aim of the present study was to assess the effects on pulmonary function of both cardio-selective and nonselective beta-blockade. Esmolol is highly cardio-selective in exhibiting a 34 fold higher affinity for beta-1 versus beta-2 adrenoceptors.[162] This along with the short-duration of action of esmolol (half-life of 9 minutes), made it ideally suited for assessing safety in asthma. As part of the initial study protocol, it was decided that if an individual demonstrated significant adverse pulmonary effects with intravenous esmolol, they would not proceed to oral propranolol.

This analysis has demonstrated that in a cohort of stable mild-to-moderate asthmatics, acute dosing with intravenous esmolol results in no significant adverse effects on pulmonary function, despite evidence of systemic beta-1-blockade with reduced heart rate and blood pressure. Given that intravenous esmolol avoids first pass inactivation, the lack of acute bronchoconstriction is reassuring.

Whilst the use of a forced expiratory manouevre with spirometry (as FEV_1) is considered the gold standard method for assessing airway calibre, impulse oscillometry provides a novel alternate effort independent technique.[123] In chapter 3 data demonstrates impulse oscillometry to be a more sensitive marker than spirometry for the assessment of beta-blocker induced bronchoconstriction, and thus it is reassuring to find no significant adverse effects on R5% predicted following acute esmolol dosing. The findings of this analysis support previous evidence that intravenous esmolol can be given safely in mild-to-moderate asthma. [163]

In chapter 3, acute propranolol dosing of 10 or 20mg in a cohort of mild-to-moderate controlled asthmatics resulted in a mean 4.7% reduction in FEV1% predicted and a mean 31.3% increase in R5% at 2 hours after propranolol dosing. Within the current analysis, by means of concurrent inhaled tiotropium administration, no significant worsening of FEV_1% predicted or R5% predicted following first dose exposure with 10mg of propranolol was seen. By means of significant reductions in supine heart rate 3 hours post propranolol there is clear evidence of systemic cardiac beta-1-adrenoceptor blockade.

It is well recognized that achieving optimal dosing of beta-blockers in clinical practice is challenging, with the tolerated doses of beta-blockers used in clinical practice often being substantially less than recommended.[164] Although lack of dose optimization is likely to be due to multi-factorial, it may be assumed that dose intolerance and contra-indications may have influenced beta-blocker dosing. In asthmatics prescribed beta-blockers, it is even more unlikely to achieve dose optimization due to clinical concerns of bronchospasm.

This analysis has shown that up-titration of propranolol can be achieved in asthma, without any significant deterioration in FEV_1% or R5% predicted at the time of first dose or up titration in the presence of concomitant tiotropium use.

This randomized controlled trial, was originally designed to investigate the proposed therapeutic benefits of nonselective beta-blockade in asthma.[165] Whilst the study did show any therapeutic benefits, the results allowed an evaluation of the safety of nonselective beta-blockade in asthma.

This results of this analysis should not be interpreted that on the basis of this data with oral propranolol that asthmatic patients should be given nonselective beta-blockers with tiotropium cover, when a cardio-selective oral agent such as bisoprolol is more likely to be tolerated, especially in the presence of inhaled tiotropium. Indeed recent data have indicated a role for regular tiotropium for use as long acting controller therapy in addition to inhaled corticosteroids.[166] However the results of this study do raise the possibility that if a nonselective beta-blocker such as propranolol can potentially be tolerated in asthma, then so may a cardio-selective beta-blocker, thus potentially offering reassurance to those wishing to utilize the cardiovascular benefits of beta-blockers in patients with asthma controlled on inhaled corticosteroids. This data cannot be applied to patients with more severe asthma.

When assessing the benefits of beta-blocker use in the treatment of cardiovascular disease, asthmatic patients have generally not been studied due to the reluctance to use beta-blockers in these patients. However when reviewing evidence of beta-blocker use within another contra-indicated group who have more severe impairment of pulmonary function, namely chronic obstructive pulmonary disease, reduced mortality rates have been associated with beta-blocker use.[116] It is unclear whether these benefits would be seen in an asthmatic population however limited evidence does suggest a reduction in two year mortality with beta-blocker use post-myocardial infarction.[84]

In conclusion this analysis has shown that acute esmolol did not cause any worsening of pulmonary function in controlled mild-to-moderate asthmatics. Furthermore first dose exposure and subsequent up-titration with propranolol up to 80mg was achieved without

any significant adverse impact on pulmonary function, due to concurrent administration of the long acting muscarinic antagonist tiotropium.

CHAPTER 7:

EFFECTS OF BETA-BLOCKERS IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A RETROSPECTIVE COHORT STUDY

Study Aims

1. **Examine the use of beta-blockers in COPD and their impact on mortality.**
2. **Examine the effects of beta-blocker use on hospital admissions and COPD exacerbations.**
3. **Assess the effects of co-prescription of beta-blockers and beta-agonists in COPD patients.**
4. **Assess the tolerability of beta-blocker use in COPD.**

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) and cardiovascular disease are intertwined due to the risk of smoking induced atherosclerosis.[106] Despite the proven benefits of beta-blockers in hypertension, ischaemic heart disease and heart failure, there remains a reluctance to prescribe beta-blockers in individuals with concurrent COPD.[118,167]

This thesis has evaluated the safety and tolerability of non-selective beta-blocker use in asthma and has demonstrated that non-selective beta-blockers may potentially be given relatively safely to selected individuals with mild-to-moderate asthma. Considering that theoretically the extent of airway reversibility is less within COPD, assumptions could be made that the degree of potential beta-blocker induced bronchoconstriction is also less than that seen in asthmatic patients.

COPD is a highly heterogeneous condition and recent evidence has shown that the degree of co-morbidities present appear to be independent of the degree of airway obstruction.[108] The treatment of co-morbid cardiovascular disease in COPD is especially relevant given cardiac failure has been shown to be a leading cause of death in these patients.[168]

In this regard the use of beta-blockers in individuals with COPD and cardiovascular disease has been shown to reduce rates of mortality in a series of observational studies.[84,117] Whether the improved survival seen with beta-blockers in COPD is purely due to cardiovascular effects has been questioned. Recent evidence suggests that beta-

blockers may improve survival and exacerbations in COPD patients without cardiovascular disease.[116]

Whilst cardio-selective beta-blockers are assumed to target beta-1-adrenceptors whilst avoiding beta-2-adrenoceptors in the lung, so called cardio-selective beta-blockers, for example atenolol and bisoprolol are only relatively beta-1-selective and have been shown to exert significant beta-2-antagonsim at therapeutic doses, albeit to a lesser extent than non-selective beta-blockers such as propranolol.[169-172]

Despite relative beta-adrenoceptor selectivity, it could be considered counterintuitive to co-prescribe both beta-blockers and beta-agonists in the same individual, even when they are targeting different organs. Current COPD management guidelines advocate a stepwise approach using long acting bronchodilators (including beta-agonists) and inhaled corticosteroids to reduce exacerbations, improve symptoms and lung function.[34] Furthermore combination treatments involving long acting bronchodilators and inhaled corticosteroids have failed to show any significant improvement in mortality.[173,174]

In this study the aim was to examine the use of beta-blockers in COPD, assessing their interrelationship with beta-agonists and other COPD medications and assess whether beta-blockers use improves mortality, hospital admissions and exacerbations when added to established stepwise inhaled therapy for COPD.

2. METHODS

This study utilised the NHS Tayside Respiratory Disease Information System (TARDIS) to identify patients since January 2001 to January 2010 who had a diagnosis of COPD. TARDIS is a disease specific database that was developed in 2001 to support primary care practitioners and secondary care respiratory physicians in managing patients with COPD in Tayside, Scotland. Entry into TARDIS requires a diagnosis of COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines,[175] comprising patient demographics, respiratory symptoms, lung function and smoking history. Data collected in the TARDIS database (including spirometry data) is performed at annual visits by specialist respiratory nurses.

Data provided by the Health Informatics Centre, at the University of Dundee (HIC) on behalf of the Information Services Division of NHS Scotland, using Scottish morbidity records (SMR) allowed patient within NHS Tayside Health Board, Scotland who had experienced a hospital admission due to COPD to be identified. Discharge summaries with a diagnosis of COPD were used to identify respiratory related hospital admissions. International Classification of Disease (ICD-9, ICD-10) codes were used.

Prescription data of respiratory and cardiovascular medications from the Tayside Community Prescription database was collected, as was history of death from the General Register Office for Scotland. Deprivation was calculated for each patient from their postcode and applying the Scottish Index of Multiple Deprivation (SIMD). A health board specific deprivation index (HBSIMD) was calculated in relation to the local population. A history of diabetes and admission to hospital due to cardiovascular

disease (including ischemic heart disease, heart failure and peripheral vascular disease) was identified using ICD-9 and ICD-10 codes. All datasets were subsequently merged into a single dataset for analysis.

Data provided to HIC by the Information Services Division of NHS Scotland undergoes data quality checks prior to release. The study was approved by the Tayside Medical Research Ethics Committee.

Data analysis

Patients were initially divided into two groups dependent on beta-blocker use. Kaplan Meier analysis with log-rank testing was performed to compare all-cause mortality dependent on beta-blocker use. Cox Proportional hazard regression analysis was used to calculate crude and adjusted hazard ratios and their 95% confidence intervals for all-cause mortality associated with beta-blocker use and for cardio-selective and non-selective beta-blockers. Adjusted hazard ratios were calculated after correction including the following covariates: cardiovascular and respiratory hospital admissions, diabetes, smoking, age, sex and cardiac drug use (aspirin, statins, calcium channel blockers, ACE inhibitors), FEV_1% predicted, resting Sa02 and deprivation index. A propensity score was calculated utilising covariates, influencing beta-blocker use and the Cox regression model was repeated in a subgroup of patients matched on propensity score. Time dependent analysis was also performed for the effects of beta-blocker use on all-cause mortality.

Patients were then divided into sub-groups based on their maximal stepwise inhaled therapy and beta blocker use: inhaled corticosteroids (ICS) (group 1); ICS and long-

acting beta-agonists (salmeterol or formoterol :LABA) (group 2); ICS and LABA and beta-blockers (BB) (group 3); ICS and LABA and long acting anti-muscarinic (Tiotropium :Tio) (group 4); ICS and LABA and Tio and BB (group 5); LABA/Tio (no ICS) (group 6); BB (no ICS) (group 7); ICS and BB (group 8); ICS and Tio (group 9) and LABA/Tio and BB (group 10). The control group comprised those who had only received inhaled therapy with either short acting beta-agonist (salbutamol, terbutaline) or short acting anti-muscarinic (ipratropium). Two or more sequential prescriptions were required for patients to be stratified into differing treatment groups.

Cox proportional hazard regression analyses were then used to calculate crude and adjusted hazard ratios for all-cause mortality, hospital admissions due to respiratory disease and emergency oral corticosteroid use dependent on treatment groups in reference to the control group. This was then repeated focusing upon death due to myocardial infarction and COPD as surrogate markers of cardiac and respiratory mortality respectively. Subgroup analyses were also performed for respiratory related hospital admissions specifically due to COPD exacerbation.

When calculating hazard ratios for all-cause mortality, patients were censored if they were lost to follow up or reached the end of the study period (January 2010). For hospital admissions and oral corticosteroid use, treatment groups were calculated using prescription data prior to the respective event occurring, with censoring as described.

Adjusted hazard ratios for mortality were calculated following correction after with the following covariates: cardiovascular and respiratory hospital admissions, diabetes, smoking, age at diagnosis, sex and cardiac drug use, FEV_1, resting Sa02 and deprivation

index. Additional models were developed to calculate adjusted hazard ratios, death due to COPD or myocardial infarction, hospital admissions due to respiratory disease, hospital admissions due to COPD and oral corticosteroid use. All hazard ratios were calculated from Cox regression models following forced entry of all available covariates to reduce residual confounding. For all tests, a two-sided P value of less than 0.05 was considered significant. Analyses were performed using SPSS version 17.0. Chicago, Illinois.

3. RESULTS

A total of 6,345 patients were identified through the TARDIS database. Within this cohort, 5,977 were over 50 years of age and used for analysis. Patients were excluded from the analysis if they had a history of malignancy prior to their entry into TARDIS. Stratified by GOLD spirometry classification: 897 (15%) of patients were GOLD stage 1 mean FEV_1% (SD) 90.8 (9.4); 3287 (55%) of patients were GOLD stage 2 mean FEV_1% (SD) 64.8 (8.3); 1494 (25%) of patients were GOLD stage 3 mean FEV_1% (SD) 40.9 (5.6); 299 (5%) of patients were GOLD stage 4 mean FEV_1% (SD) 24.8 (4.6). Mean (SD) follow up was 4.35 (2.28) years. In total 779 patients received beta-blockers. Stratified by GOLD stage, beta-blocker use was; 151 patients were GOLD stage 1; 462 were GOLD stage 2; 144 were GOLD stage 3 and 22 were GOLD stage 4. The mean (SD) age of patients at time of diagnosis of COPD (time of entry into TARDIS database) was 69.1 (9.4) years. 3048 (51%) of patients were male. 88% of beta-blockers (BB) were cardio selective. All patients were receiving SABA +/- ipratropium including the control group. Patient characteristics at study entry are illustrated in table 13.

Treatment Groups	Age (SD)	Male n, (%)	FEV1% (SD)	SaO2 (SD)	Smoking Pack Years (SD)	History of Cardiac Disease n,(%)	History of Diabetes n,(%)
ICS (n=464)	69.7 (9.8)	239 (51.5)	65.5 (19.5)	94.2 (10.9)	41 (16.5)	190 (40.9)	46 (9.9)
ICS+BB (n= 71)	71.7 (8.6)	36 (50.7)	64.2 (16.1)	93.3 (14.5)	39 (12.6)	51 (71.8)	18 (25.4)
ICS+LABA (n= 996)	68.9 (9.6)	547 (54.9)	62.7 (18.9)	92.5 (13.5)	41.2 (19.4)	429 (43.1)	148 (14.9)
ICS+LABA+ BB (n= 143)	68.8 (9.7)	70 (49)	65.7 (16.7)	94.2 (9.8)	41.5 (18.4)	96 (67.1)	25 (17.5)
ICS+LABA+ Tio (n= 1857)	68.3 (8.9)	972 52.3)	50.8 (17.1)	91.3 (11.6)	44.8 (16)	874 (47.1)	259 (13.9)
ICS+LABA+ Tio+BB (n= 187)	68.1 (8.4)	77 (41.2)	52.8 (16.4)	92.6 (9.5)	45.1(18.6)	146 (78.1)	33 (17.6)
LABA/Tio (no ICS) (n= 526)	69.9 (9.2)	263 (50)	60 (17.4)	93.5 (7.9)	45.7 (19.9)	220 (41.8)	67 (12.7)
BB (no ICS) (n= 276)	70.8 (8.8)	109 (39.5)	73.7 (16.3)	95.5 (7.1)	44.7 (16.4)	181 (65.6)	57 (20.7)
ICS + Tio (n= 158)	69.1 (9.2)	70 (44.3)	55 (16.6)	93.2 (9.5)	44.1 (19.7)	73 (46.2)	25 (15.8)
LABA/Tio +BB (n= 119)	70.1 (8.1)	48 (40.3)	63.5 (14.2)	95 (2.1)	48.6 (22.3)	84 (70.6)	32 (26.9)
Control group (n=1180)	70.5 (10.2)	617 (52.3)	69.1 (18.3)	94.7 (7.9)	43.5 (16.5)	534 (45.3)	145 (12.3)

Table 13. Patient demographics. Baseline characteristics at diagnosis of COPD -grouped according to final treatment group. Data unless otherwise stated presented as mean (SD) or mean (%).

Pulmonary function

A subgroup analysis of n= 2712 was analysed where 6639 serial FEV_1 and FVC measurements were available. Those patients being prescribed triple therapy with ICS+LABA +TIO had the lowest FEV_1% predicted in keeping with increased disease severity. The addition of a beta-blocker did not have any deleterious impact when added to a regimen that included a long acting bronchodilator or inhaled corticosteroid (tables 14 and 15) e.g. comparing ICS+LABA or ICS+LABA+TIO with and without beta-blocker. Moreover when comparing FEV_1 values at the beginning and end of the study period there was no clinically significant deterioration in any treatment group including a beta-blocker with a clinically significant difference regarded as a 30ml/year reduction in FEV_1 as found in the placebo limb of the UPLIFT study.[176]

Treatment Groups (n)	First FEV_1(L) (SD)	Last FEV_1 (L) (SD)	Mean Difference (95%CI)	p value
ICS (204)	1.64 (0.61)	1.63 (0.62)	-0.01 (-0.04 to 0.03)	0.658
ICS+BB (43)	1.55 (0.57)	1.58 (0.55)	0.03 (-0.05 to 0.10)	0.459
ICS+LABA (459)	1.52 (0.60)	1.54 (0.62)	0.02 (-0.01 to 0.05)	0.123
ICS+LABA+BB (89)	1.55 (0.54)	1.57 (0.55)	0.03 (-0.03 to 0.08)	0.355
ICS+LABA+Tio (753)	1.22 (0.51)	1.19 (0.51)	-0.03 (-0.06 to -0.01)	<0.001
ICS+LABA+Tio+BB (88)	1.27 (0.50)	1.28 (0.53)	0.01 (-0.06 to 0.08)	0.749
LABA/Tio (no ICS) (197)	1.48 (0.58)	1.44 (0.57)	-0.04 (-0.08 to -0.01)	0.016
BB (no ICS) (276)	1.83 (0.53)	1.74 (0.55)	-0.09 (-0.11 to -0.06)	<0.001
ICS+Tio (81)	1.37 (0.53)	1.40 (0.49)	0.03 (-0.03 to 0.09)	0.257
LABA/Tio +BB (47)	1.67 (0.56)	1.65 (0.57)	-0.02 (-0.09 to 0.04)	0.435
Control (SABA+/-SAMA) (475)	1.76 (0.62)	1.69 (0.59)	-0.07 (-0.09 to -0.05)	<0.001

Table 14. FEV_1 during study period.

Treatment Groups (n)	First FVC(L) (SD)	Last FVC (L) (SD)	Mean Difference (95%CI)	p value
ICS (204)	2.75 (0.94)	2.78 (0.97)	0.03 (-0.03 to 0.09)	0.369
ICS+BB (43)	2.58 (0.82)	2.71 (0.87)	0.13 (-0.02 to 0.28)	0.086
ICS+LABA (459)	2.61 (0.94)	2.71 (0.97)	0.10 (0.05 to 0.14)	<0.001
ICS+LABA+BB (89)	2.63 (0.89)	2.69 (0.87)	0.06 (-0.05 to 0.15)	0.287
ICS+LABA+Tio (753)	2.46 (0.89)	2.48 (0.84)	0.02 (-0.01 to 0.06)	0.241
ICS+LABA+Tio+BB (88)	2.40 (0.88)	2.50 (0.89)	0.10 (-0.01 to 0.20)	0.08
LABA/Tio (no ICS) (197)	2.67 (0.93)	2.66 (0.93)	0.01 (-0.07 to 0.05)	0.767
BB (no ICS) (276)	2.91 (0.84)	2.80 (0.89)	0.11 (0.05 to 0.16)	<0.001
ICS+Tio (81)	2.48 (0.81)	2.59 (0.75)	0.11 (0.01 to 0.20)	0.043
LABA/Tio +BB (47)	2.77 (0.93)	2.82 (0.95)	0.05 (-0.05 to 0.17)	0.297
Control (SABA+/-SAMA) (475)	2.90 (0.96)	2.86 (0.95)	-0.04 (-0.09 to -0.02)	0.041

Table 15. FVC during study period.

All-Cause Mortality

Evaluating the impact beta-blockers have on survival, Kaplan Meier analysis and log rank testing showed a significant improvement in overall survival for those that received beta-blockers (n=819) in comparison with those who did not (Chi-Square 18.97, $p<0.001$), (See figure 23). Following matched propensity scoring analysis, to balance associated covariates between groups, our study suggests that beta-blocker use is associated with a 22% reduction in mortality HR 0.78 (95%CI 0.67 to 0.92). Cox Regression with time dependent analysis comparing patients exposed to beta-blocker or no beta-blocker assessing effects on all-cause mortality, shows a significant overall effect; HR 0.92 (95%CI 0.85 to 0.96).

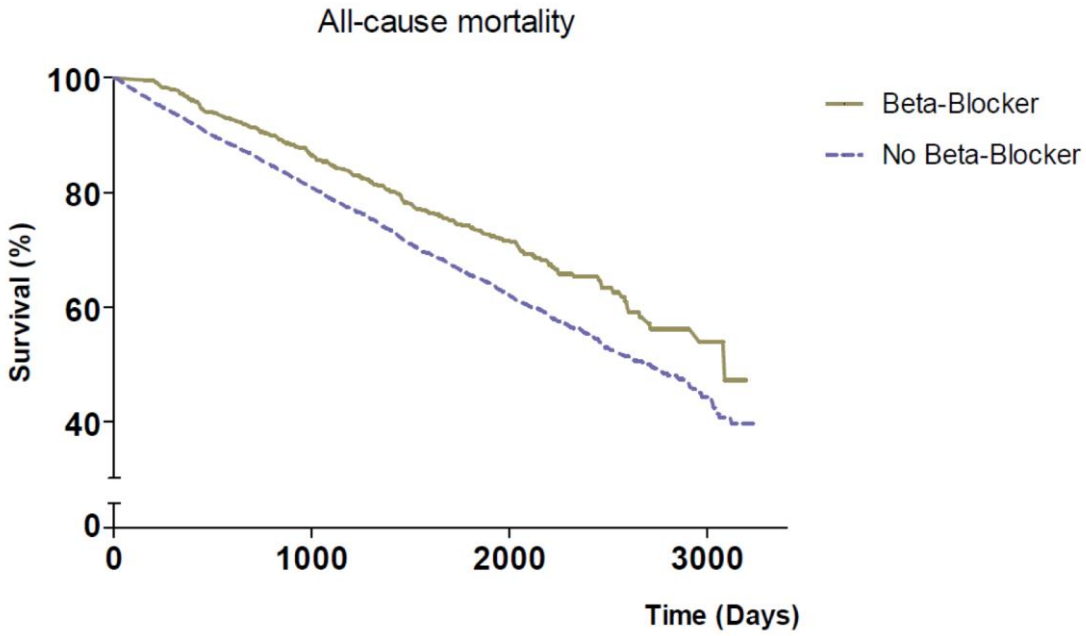

Figure 23. Kaplan-Meier estimate of probability of survival based upon beta-blocker use.

When comparing cardio-selective beta-blockers with non cardio-selective beta-blockers there was no significant difference between groups (Chi-Square 0.77, p=0.378). N=2005 patients died during the study period equating to an annual death rate of 34%. Cox Proportional hazards ratios were calculated for each treatment group based upon stepwise management for COPD. At each comparison the adjusted hazard ratio for treatment groups including a beta-blocker were lower than the respective treatment group without a beta-blocker. The crude hazard ratios for those patients on ICS+LABA+Tio with and without beta-blocker were 0.38 (95%CI 0.28 to 0.52) and 0.54 (95%CI 0.48 to 0.61), whilst the adjusted hazard ratios for those patients on ICS+LABA+Tio with and without beta-blocker were 0.28 (95%CI 0.21 to 0.39) and 0.43 (95%CI 0.38 to 0.48). The crude hazard ratios for treatment groups ICS+LABA

with and without beta-blocker were 0.43 (95%CI 0.31 to 0.60) and 0.67 (95%CI 0.59 to 0.78), whilst the adjusted hazard ratios for treatment groups ICS+LABA with and without beta-blocker were 0.44 (95%CI 0.31 to 0.62) and 0.64 (95%CI 0.57 to 0.74). Finally the crude hazard ratios for treatment groups ICS with and without beta-blocker were 0.51 (95%CI 0.33 to 0.79) and 0.66 (95%CI 0.55 to 0.79), whilst the adjusted hazard ratios for treatment groups ICS with and without beta-blocker were 0.48 (95%CI 0.31 to 0.74) and 0.69 (95%CI 0.58 to 0.83). Adjusted hazard ratios for all treatment groups and covariates used in the Cox regression model are illustrated in figure 24 and can also be found in table 16.

Cardiac and Respiratory Mortality

288 (14%) of patients who died had myocardial infarction whilst 625 (32%) had COPD recorded as their primary causes of death. Similar benefits in reducing death due to myocardial infarction and COPD were seen when these patients were stratified by treatment group. For example for those patients on ICS+LABA+Tio and beta-blocker the adjusted hazard ratios for death due to myocardial infarction and COPD were: 0.25 (95%CI 0.11 to 0.58) and 0.39 (95%CI 0.2 to 0.78) respectively, (see table 17).

Treatment Groups	Adjusted HR	95% CI
ICS+LABA+Tio+BB	0.28	0.21 to 0.39
ICS+LABA+Tio	0.43	0.38 to 0.48
ICS+LABA+BB	0.44	0.31 to 0.62
ICS+LABA	0.64	0.57 to 0.74
ICS+BB	0.48	0.31 to 0.74
ICS	0.69	0.58 to 0.83
ICS +Tio	0.61	0.47 to 0.80
LABA/Tio(no ICS) +BB	0.52	0.36 to 0.76
LABA/Tio(no ICS)	0.71	0.59 to 0.84
BB (no ICS)	0.65	0.51 to 0.83
Covariates used in Cox Regression Model		
History of hospital admission due to Cardiovascular Disease	2.04	1.84 to 2.27
History of hospital admission due to Respiratory Disease	2.38	2.16 to 2.62
Age at study entry	1.05	1.05 to 1.06
Sex (male)	1.19	1.09 to 1.31
Smoking (Pack Years)	1.01	1.00 to 1.01
History of Diabetes	0.91	0.80 to 1.03
FEV_1% Predicted	0.98	0.97 to 0.98
Sa02 at rest	0.99	0.99 to 1.00
Deprivation Index (HBSIMD) (1= most deprived)		
HBSIMD 1	0.99	0.89 to 1.11
HBSIMD 2	1.02	0.88 to 1.19
HBSIMD 3	0.88	0.76 to 1.02
HBSIMD 4	0.85	0.73 to 1.00
Cardiovascular Medications		
Aspirin	0.80	0.73 to 0.88
Statins	0.89	0.81 to 0.97
ACE Inhibitors	0.79	0.72 to 0.88
Calcium Channel Blockers	0.71	0.64 to 0.78

Table 16. Adjusted hazard ratios for all-cause mortality.

Treatment Groups	Mortality due to Myocardial Infarction N= 288		Mortality due to COPD N= 625	
	Adjusted Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
ICS+LABA+Tio+BB	0.25	0.11 to 0.58	0.39	0.20 to 0.78
ICS+LABA+Tio	0.44	0.31 to 0.62	0.30	0.24 to 0.38
ICS+LABA+BB	0.49	0.27 to 0.90	0.23	0.09 to 0.64
ICS+LABA	0.53	0.37 to 0.76	0.52	0.40 to 0.68
ICS+BB	0.46	0.19 to 1.13	0.25	0.06 to 0.99
ICS	0.80	0.51 to 1.27	0.45	0.32 to 0.65
ICS +Tio	0.63	0.29 to 1.37	0.39	0.25 to 0.61
LABA/Tio(no ICS) +BB	0.54	0.25 to 1.16	0.38	0.12 to 1.20
LABA/Tio(no ICS)	1.09	0.66 to 1.81	0.42	0.30 to 0.60
BB (no ICS)	0.67	0.41 to 1.10	0.88	0.32 to 2.38

Table 17. Adjusted hazard ratios for mortality due to myocardial infarction and COPD.

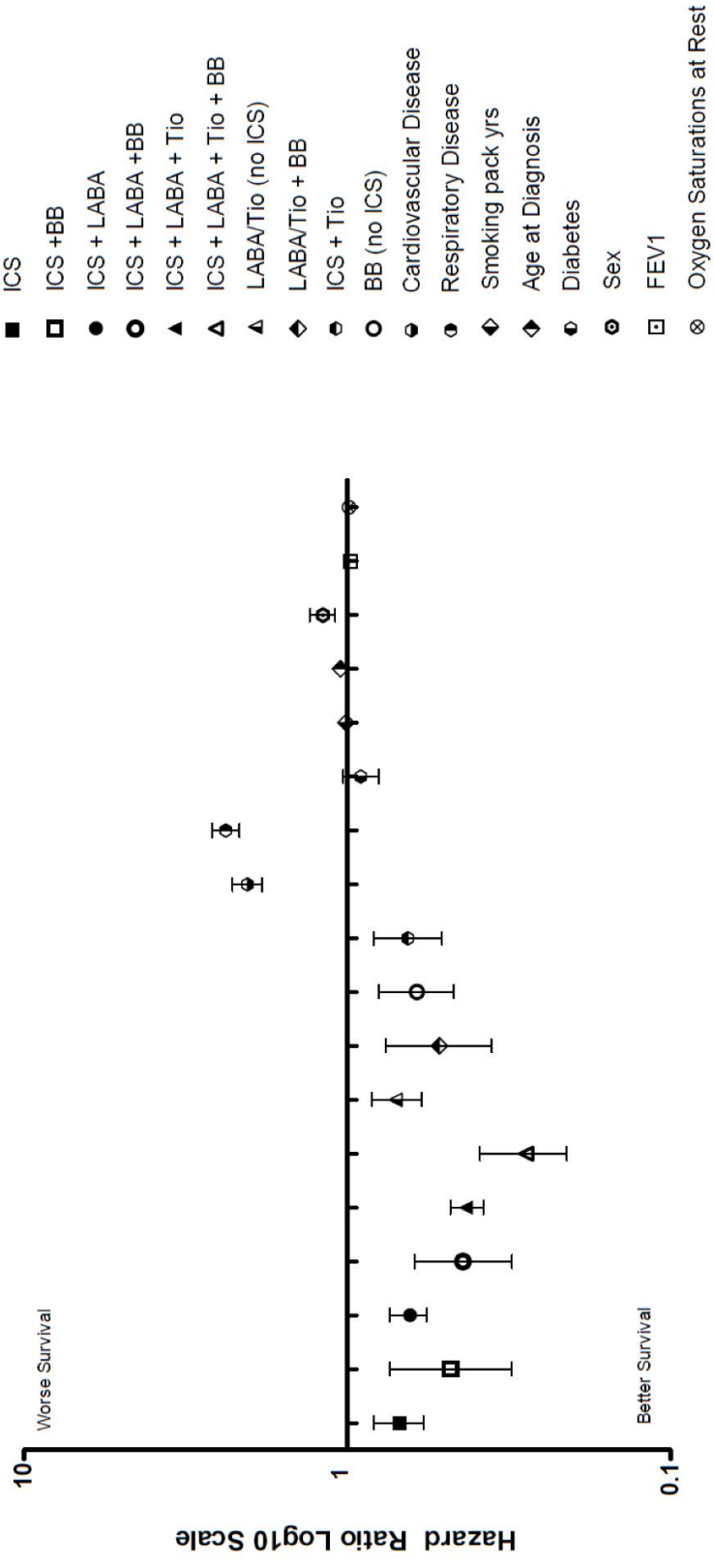

Figure 24. Adjusted Hazard Ratios (95% CI) for all-cause mortality.

Emergency Oral Steroid Prescription

3415 patients (57.1%) had at least one prescription of oral steroids during the study period. The adjusted hazard ratio for oral steroid prescription for those patients on ICS+LABA+Tio with and without beta-blocker were 0.31 (95%CI 0.22 to 0.43) and 0.68 (95%CI 0.61 to 0.75). The adjusted hazard ratios for treatment group ICS+LABA with and without beta-blocker were 0.46 (95%CI 0.34 to 0.63) and 0.93 (95%CI 0.85 to 1.03). The adjusted hazard ratios for ICS with and without beta-blocker were 0.51 (95%CI 0.39 to 0.69) and 0.77 (95%CI 0.69 to 0.87). Adjusted hazard ratios for covariates used in the Cox regression model are illustrated in figure 25 and can also be found in table 18.

Respiratory Hospital Admissions

1608 patients (26.9%) had at least one hospital admission due to respiratory disease during the study period. The adjusted hazard ratio for hospital admission due to respiratory disease for those patients on ICS+LABA+Tio with and without beta- blocker were 0.32 (95%CI 0.22 to 0.44) and 0.70 (95%CI 0.61 to 0.80). The adjusted hazard ratios for treatment group ICS+LABA with and without beta-blocker were 0.39 (95%CI 0.26 to 0.60) and 0.82 (95%CI 0.7to 0.96). The adjusted hazard ratios for ICS with and without beta-blocker were 0.36 (95%CI 0.22 to 0.58) and 0.79 (95%CI 0.66 to 0.95). Adjusted hazard ratios for covariates used in the Cox regression model are illustrated in figure 26 and can also be found in table 19.

Treatment Groups	Adjusted HR	95% CI
ICS+LABA+Tio+BB	0.31	0.22 to 0.43
ICS+LABA+Tio	0.68	0.61 to 0.75
ICS+LABA+BB	0.46	0.34 to 0.63
ICS+LABA	0.93	0.85 to 1.03
ICS+BB	0.51	0.39 to 0.69
ICS	0.77	0.69 to 0.87
ICS +Tio	0.81	0.68 to 0.96
LABA/Tio(no ICS) +BB	0.44	0.33 to 0.59
LABA/Tio(no ICS)	0.67	0.59 to 0.76
BB (no ICS)	0.39	0.32 to 0.48
Covariates used in Cox Regression Model		
History of hospital admission due to Cardiovascular Disease	1.14	1.06 to 1.22
History of hospital admission due to Respiratory Disease	2.01	1.87 to 2.16
History of Diabetes	0.99	0.90 to 1.10
Smoking (Pack Years)	1.00	0.99 to 1.01
Age at study entry	1.01	1.00 to 1.02
Sex (male)	0.95	0.89 to1.02
FEV1% Predicted	1.00	0.99 to 1.01
Sa02 at rest	1.01	1.01 to 1.02
Deprivation Index (HBSIMD) (1= most deprived)		
HBSIMD 1	1.01	0.93 to 1.10
HBSIMD 2	1.03	0.91 to 1.15
HBSIMD 3	0.94	0.84 to 1.06
HBSIMD 4	0.92	0.82 to 1.04

Table 18. Adjusted hazard ratios for emergency oral steroid prescription.

Treatment Groups	Adjusted HR	95% CI
ICS+LABA+Tio+BB	0.32	0.22 to 0.44
ICS+LABA+Tio	0.70	0.61 to 0.80
ICS+LABA+BB	0.39	0.26 to 0.60
ICS+LABA	0.82	0.70 to 0.96
ICS+BB	0.36	0.22 to 0.58
ICS	0.79	0.66 to 0.95
ICS +Tio	0.71	0.53 to 0.96
LABA/Tio(no ICS) +BB	0.31	0.19 to 0.51
LABA/Tio(no ICS)	0.70	0.58 to 0.85
BB (no ICS)	0.31	0.22 to 0.44
Covariates used in Cox Regression Model		
History of hospital admission due to Cardiovascular Disease	1.87	1.69 to 2.09
History of Diabetes	0.99	0.87 to 1.14
Smoking (Pack Years)	1.00	0.99 to 1.01
Age at study entry	1.01	1.01 to 1.02
Sex (male)	0.84	0.76 to 0.93
FEV_1% Predicted	0.98	0.97 to 0.99
Sa02 at rest	0.99	0.98 to 1.01
Deprivation Index (HBSIMD) (1= most deprived)		
HBSIMD 1	1.07	0.95 to 1.21
HBSIMD 2	1.26	1.07 to 1.48
HBSIMD 3	1.04	0.88 to 1.23
HBSIMD 4	0.92	0.77 to 1.11

Table 19. Adjusted hazard ratios for hospital admissions due to respiratory disease.

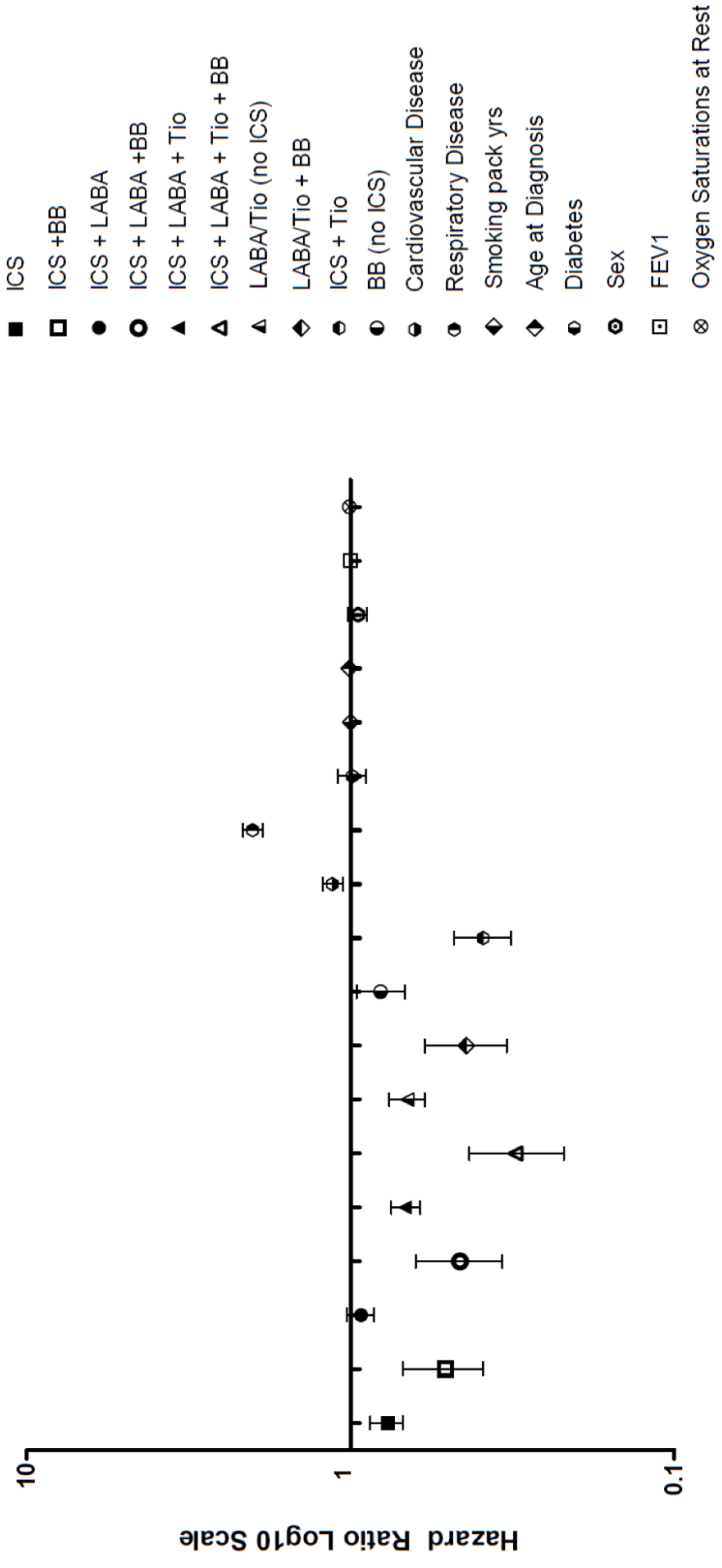

Figure 25. Adjusted hazard ratios (95% CI) for emergency oral corticosteroid prescription.

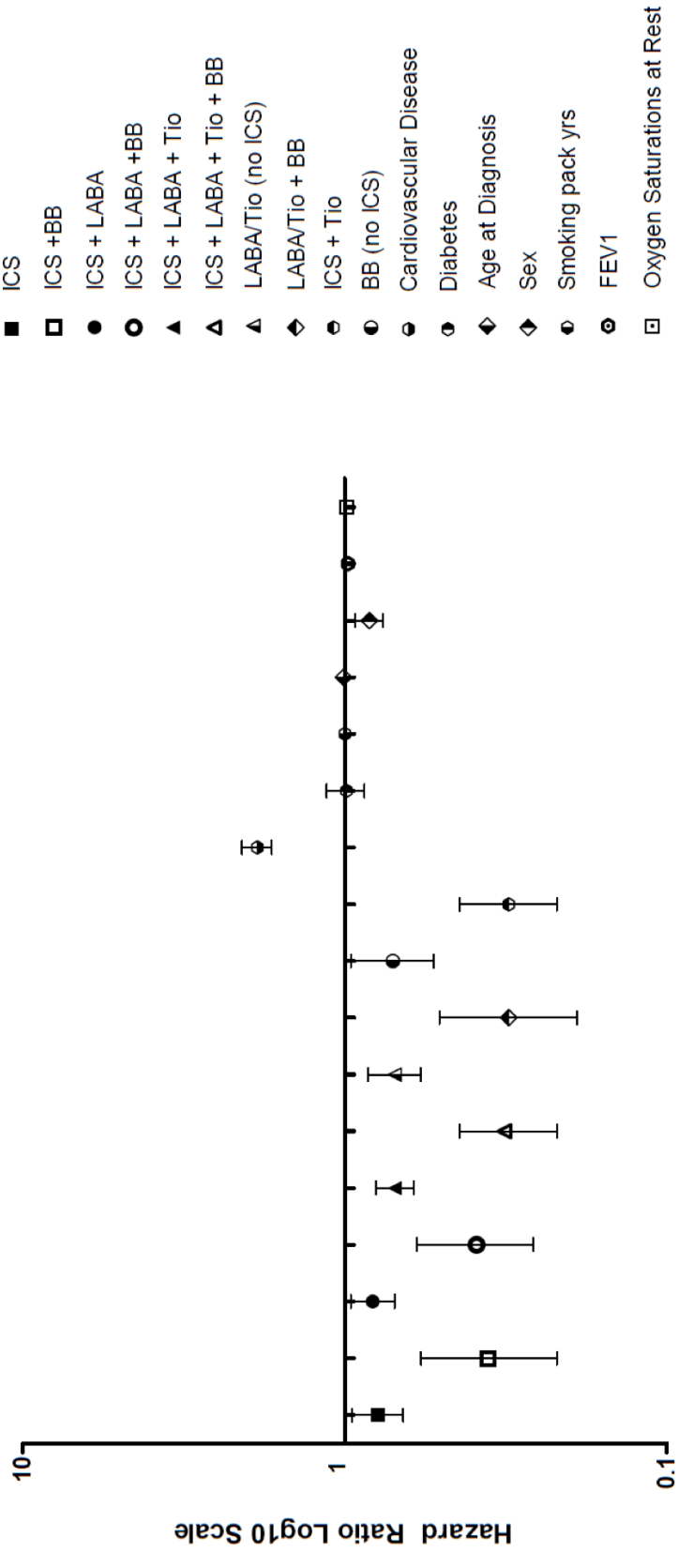

Figure 26. Adjusted hazard ratios (95% CI) for hospital admissions due to respiratory disease.

COPD Hospital Admissions

1094 (68%) of those who had a hospital admission due to respiratory disease, had a primary coded diagnosis of COPD exacerbation. Similar trends of improvement were seen as with all hospital admissions due to respiratory disease. The adjusted hazard ratio for hospital admission due to respiratory disease for those patients on ICS+LABA+Tio with and without beta-blocker were 0.25 (95%CI 0.14 to 0.42) and 0.77 (95%CI 0.65 to 0.91). The adjusted hazard ratios for treatment group ICS+LABA with and without beta-blocker were 0.37 (95%CI 0.22 to 0.64) and 0.81 (95%CI 0.67 to 0.97). The adjusted hazard ratios for ICS with and without beta-blocker were 0.24 (95%CI 0.20 to 0.49) and 0.69 (95%CI 0.54 to 0.87).

4. DISCUSSION

Through matched propensity scoring analysis, a 22% overall reduction in all-cause mortality with beta-blocker use was demonstrated in this study. Importantly this study also suggests there may be benefits when beta-blockers are added to established stepwise inhaled treatment regimes for COPD in reducing all-cause mortality. Through, Cox proportional hazard regression, the additive benefits of beta-blockers was demonstrated independent of other cardiovascular medications and history of overt cardiovascular disease (ischaemic heart disease, heart failure, peripheral vascular disease). These findings suggest that beta-blockers may add benefits to reducing mortality in COPD in addition to the benefits gained by addressing cardiovascular risk.

The baseline demographics of the treatment groups demonstrated similar levels of social deprivation. Deprivation is known to influence mortality rates and when considering beta-blocker use in heart failure, those individuals of worse deprivation are less likely to be treated.[177] The Scottish Index of Multiple Deprivation was used to calculate the deprivation score used in our cohort. 6.9% of the most deprived areas in Scotland are located within Tayside Health Board.[178]

Previous studies have focused upon the presence or absence of beta-blockers and their influence on mortality and hospitalisations.[116,179] In the study by Rutten et al. they found that the benefit on mortality seen with beta-blockers was preserved in those individuals who were concurrently prescribed two or more pulmonary drugs or who were using inhaled beta-2 agonists or anti-muscarinics. However their analysis did not stratify according to stepwise treatment regimens and in particular for LABA use. This issue is

pertinent given the potential for co-prescription of agonists and antagonists medications with theoretical interactions.

FEV_1 has previously been shown to decline over time.[180] Using a 30ml per year reduction as observed in the placebo limb of the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study for reference, in this study there was no clinically significant decline in mean FEV_1 over time in each treatment group.[176] Within treatment groups, decline in FEV_1 was observed in individuals, however the percentage of patients where decline was observed were consistent when comparing treatment groups.

In line with previous studies a benefit on all-cause mortality in COPD patients taking statins and ACE inhibitors was found.[113,181] As expected this study showed significant mortality reductions as evidenced by hazard ratios with aspirin 0.8 (95%CI 0.73 to 0.88), statins 0.89 (95%CI 0.81 to 0.97), ACE inhibitors 0.79 (95%CI 0.72 to 0.88) and calcium channel blockers 0.71 (95%CI 0.64 to 0.78). These findings demonstrate the importance of recognising COPD patients as having a high risk of developing cardiovascular disease.

This data showed the same trends in terms of additive benefits with beta-blockers to stepwise inhaled therapy, for all-cause mortality, oral steroid prescriptions and admissions, which may add support to the value of using beta-blockers in COPD. Although it could be suggested that the reduction observed in all-cause mortality seen with beta-blocker use is attributable to their cardiovascular effects, similar benefits were seen in reducing mortality due to COPD and myocardial infarction, although some

hazard ratios within groups failed to reach statistical significance. These observations along with the reductions in hospital admissions and emergency oral steroid use are by definition more difficult to be explained by improving cardiovascular risk.

This begs the key question as to whether beta-blockers confer independent beneficial pulmonary effects in COPD. With this in mind one possibility is that up-regulation of beta-2-adrenoceptors by chronic beta-blockade may improve the effectiveness of beta-2-agonists. Despite the majority of beta-blockers in this study being relatively cardio-selective, drugs such as atenolol and bisoprolol even at therapeutic doses have been shown to exert a significant degree of beta-2-adrenoceptor antagonism, which in turn may result in beta-2-adrenoceptor up-regulation. Thus from a pharmacological point of view up-regulation of beta-2-adrenoceptors by cardio-selective beta-blockers seems plausible. In this regard there was no worsening of FEV_1 or FVC seen when for example comparing groups receiving ICS+LABA vs. ICS+LABA +BB and ICS+LABA+Tio vs. ICS+LABA+Tio+BB. Ind et al, has demonstrated that anti-muscarinic therapy prevents beta-blocker induced bronchoconstriction in asthmatics .[10] This in turn would suggest a rationale for using tiotropium when adding a beta-blocker to a patient with COPD, aside from the known benefits of tiotropium on exacerbations and symptoms.[176]

TARDIS is an example of a NHS COPD database, routinely used to guide COPD management in Tayside. The strength of this disease specific database lies within all patients having a diagnosis of COPD made by a primary or secondary care physician on the basis of GOLD guidelines. Since 2001, patients with COPD have been invited to be included in the database, TARDIS has been used as the basis for previous published

COPD research thereby providing us with an unselected community population of COPD patients for analysis.[135]

Confounding by indication is a limitation when performing observational studies of this nature. As a COPD disease specific database was used for patient identification unfortunately the specific indication for beta-blocker prescription was unknown. In order to address this, a Cox proportional hazard regression model that corrected for all available influential covariates was used. Pointedly the study evaluated the effects of beta-blockers on all-cause mortality independently of cardiovascular outcomes including cardiac drug prescription and overt cardiovascular disease measured by hospital admissions due to ischemic heart disease, heart failure and peripheral vascular disease, although a history of hypertension was unavailable for analysis from the database.

Furthermore when assessing the impact of beta-blocker use on all-cause mortality, matched propensity scoring analysis suggested a beneficial effect with beta-blocker use. Propensity score matched analysis is designed to minimize the effects of confounding by indication.[182] Time dependent analysis also confirmed the beneficial effects of beta-blockade in this analysis.

An age cut-off of 50 years and above was used, in order to alleviate any concerns that younger patients than 50 years may be regarded as asthmatics. An age cut off of 45 years and above has been use in previous COPD observational studies.[116] Furthermore when analysing all patients in the dataset regardless of age (n=6345), similar trends in survival as with the study cohort (n=5977) were seen. For example in the

ICS+LABA+Tio and beta-blocker group the adjusted hazard ratio for all-cause mortality was 0.33 (95%CI 0.24 to 0.44) in the extended dataset compared with 0.28 (95%CI 0.21 to 0.39) in the study population.

In summary this study has shown that beta-blockers (predominantly cardio-selective) may confer reductions in mortality, exacerbations and hospital admissions in patients with COPD, in addition to the benefits attributable to addressing cardiovascular risk. These additive benefits were seen across a spectrum of inhaled step wise therapy, including inhaled corticosteroids, long acting beta-agonists and long acting anti-muscarinics, and did not result in any worsening of pulmonary function in the study cohort.

5. CRITIQUE

This study attempted to examine the potential beneficial effects of beta-blocker use on survival in COPD utilising a NHS disease specific database, namely TARDIS. Whilst TARDIS is used as a clinical tool for the management of COPD, diagnostic accuracy has to be considered when using this dataset for observational studies with potential clinical implications. In order to be included within TARDIS, patients had to be diagnosed with COPD by either a primary or secondary care physician. As a result there could potentially be diagnostic error as patients considered to have COPD, by a general practitioner could for example have an alternative respiratory disease such asthma with a history of smoking which may have been identified by the secondary care physician with the support of extensive pulmonary function tests available in a hospital setting. However despite the possibility for misdiagnosis, this large NHS dataset provides means of examining mortality benefits which otherwise could not be performed due to the lack of randomised controlled trial data.

This study suggested survival benefits with beta-blocker use in COPD. These results however must be interpreted with caution. Although a disease specific dataset was used, this study was retrospective and observational in design and therefore the risk of bias exists. Although statistical methods attempted to reduce this risk, bias remains and observational studies of this nature should not be used to change clinical practice, but rather act as a stimulus to performing randomised controlled trials.

CHAPTER 8:

DISCUSSION

DISCUSSION

The aim of this thesis was to evaluate the use of beta-blockers in the treatment of asthma and COPD. To address this topic this thesis was divided into two distinct sections. Firstly proofs of concept, randomised controlled trials, evaluating both non-selective and cardio-selective beta-blockade in asthma were performed. In addition to this health informatics datasets were utilised to perform a large observational study of beta-blocker use in COPD.

Within this thesis two distinct proof of concept studies were performed assessing beta-blocker use in asthma. The first study was designed primarily with patient safety as its major focus. The primary aim of this study was to assess the degree of beta-blocker induced bronchoconstriction following acute dosing with relatively low doses of oral propranolol in mild-to-moderate asthmatics. The results of this study were fundamental in helping to develop a research protocol by which the subsequent chronic dosing of beta-blockers could be evaluated safely.

By establishing whether acute propranolol dosing would prevent subsequent salbutamol and ipratropium recovery, following histamine challenge. The serious concerns of whether concurrent non-selective beta-blockade would result in a suboptimal bronchodilator response during an asthma exacerbation with potentially dangerous consequences were addressed. Reassuringly this study showed that staged salbutamol and ipratropium produced a full recovery after histamine induced bronchoconstriction following acute beta-blockade with either 10 or 20mg of oral propranolol. Since the greatest risk of beta-blockade is after first dose, these findings offered reassurances with

regards to evaluating chronic beta-blockade as a potential treatment for mild-to-moderate asthma.

In addition to assessing the effects of acute beta-blockade on subsequent salbutamol reversibility, the primary outcome of this study was whether concurrent intravenous hydrocortisone would result in augmented bronchodilator reversibility. It was hypothesised that hydrocortisone may partially reduce the effects of acute beta-blockade and improve the effects of nebulised salbutamol due its acute facilitatory effects on beta-2-receptors within 3 hours of administration.[47] The study however failed to show any beneficial effects of hydrocortisone versus placebo. However it is noted that in the scenario of patient having an asthma exacerbation whilst concurrently receiving beta-blockers, it would still be prudent to give acute systemic corticosteroid to treat any associated worsening of airway inflammation.

Performing studies of beta-blocker use in asthma contradicts established dogma that beta-blockers should never be given to asthmatics. Therefore performing any study of beta-blocker use is ethically challenging. Adopting first principles of "*Primum non nocere"* substantial ethical review was applied by the local ethics board to these study protocols prior to approval. When devising each research protocol, every available safety measure was adopted in order to reduce the risk to the individual participant. Within each study protocol, only asthmatics with mild-to-moderate disease were recruited. Individuals had to have preserved lung function by means of an FEV_1 greater than 80% predicted and be free of any exacerbation within the preceding 6 months. Furthermore participants had to be taking inhaled corticosteroids. Despite these safety measures, following ethical review, although it was accepted that the likelihood of

adverse events from beta-blocker use were small, there was potential for serious adverse events including severe asthma exacerbation and death, subsequently these risks were included within study participant information sheets.

Spirometry has historically been used to assess the degree of bronchoconstriction of associated with beta-blocker use in asthma.[61] In this thesis, relatively low doses of propranolol were used. Whilst this approach increased the safety of the research protocols, there were concerns that standard spirometry may prove to be too insensitive in identifying bronchoconstriction. In view of this, the novel technique of impulse oscillometry (IOS) was used. As IOS is effort independent method of assessing resistance, it is commonly used in children thereby avoiding the forced expiratory maneuvers required by spirometry.[151,152] In this thesis the relative sensitivities of IOS in comparison with spirometry showed that following acute propranolol dosing, airway resistance at 5HZ (R5) showed a greater magnitude of change in comparison with FEV_1 (4.7% versus 31.3%) post propranolol at the same time point and visit. Furthermore when accounting for the variability of each test the standardised response mean for R5 versus FEV_1 was greater, thereby demonstrating the better "signal to noise ratio". These findings demonstrated the usefulness of IOS when assessing beta-blocker induced bronchoconstriction, in addition to standardised spirometry.

The second study within this thesis was the first placebo-controlled trial of beta-blocker use in asthma to be recorded within the literature. The study was designed to assess the effects of chronic non-selective beta-blockade with oral propranolol as add on to inhaled corticosteroids in stable persistent asthmatics.

Once again the safety of participants was a fundamental concern. Similar inclusion criteria were applied to the acute dosing study based upon the lack of adverse events seen following acute propranolol dosing. Given the greatest theoretical risk of beta-blocker induced bronchoconstriction being after first dose exposure, a gradual dose titration regime was used. As previously described, anti-cholinergic blockade with tiotropium was given concurrently during the dose titration phase to reduce the associated risks of bronchospasm.[10] As part of the dose titration regime, this involved participants attending the department on a weekly basis for an observed dose up-titration. Study medication was also dispensed on a weekly basis, in order to reduce the possibility of dosing errors.

Originally based upon the previous open label studies it was planned to investigate the effects of the non-selective beta-blocker nadolol versus placebo on airway hyper-responsiveness in mild-to-moderate asthmatics.[102] However it transpired that the lowest dose of nadolol available in the UK is 80mg compared to 10mg for propranolol, which made initial dose titration possible with nadolol difficult, costly and time consuming for pharmaceutical reformulation. Furthermore nadolol is not routinely used in the UK and therefore the effects of propranolol were deemed to be of greater clinical relevance. Therefore following approval by the funding body Chief Scientist Office, nadolol was changed to propranolol.

Propranolol and nadolol are both non-selective beta-blockers with similar pharmacological properties. Both drugs exhibit in-vitro inverse agonist activity (i.e. an ability to effectively switch off the receptor), as well acting as conventional competitive

receptor antagonists. Indeed propranolol exhibits a slightly higher beta-2 receptor binding affinity compared to nadolol.[59]

In order to further enhance the safety of the chronic dosing study, an unblinded esmolol challenge visit was performed prior to randomisation to oral propranolol or placebo. This visit was performed on the pre-requisite of the Chief Scientist Office following review of the study proposal. The addition of this visit was designed in order to identify potential asthmatic participants highly susceptible to beta-blocker induced bronchoconstriction. Esmolol is a highly cardio-selective beta-blocker. Therefore following acute esmolol dosing, any individual that demonstrated evidence of significant bronchoconstriction, with a fall in FEV_1 by 20% would not proceed to non-selective beta-blockade. Reassuringly no individual that underwent esmolol challenge demonstrated significant bronchoconstriction as measured by either spirometry or impulse oscillometry thereby inferring that esmolol could potentially be safely administered as clinically indicated to controlled ICS treated asthmatics.

Due to unexpected national supply shortages of esmolol, following approval, the esmolol challenge visit was removed from the chronic dosing study protocol. This resulted in only 12 of the 18 participants receiving an esmolol challenge prior to chronic dosing with oral propranolol. Whilst it would have undoubtedly been preferable for each participant to undergo esmolol challenge testing, due to the lack of any significant beta-blocker induced bronchoconstriction being seen in the 12 completed participants it is unlikely that any bronchospasm would have been seen in the remaining participants. Furthermore due to the significantly different beta-adrenoceptors affinities displayed by both propranolol (beta1:beta2 selectivity ratio = 1:8) and esmolol (beta1:beta2

selectivity ratio =34:1), it is unlikely that the effects of esmolol challenge would fairly predict what may happen with propranolol.

This thesis failed to demonstrate any therapeutic benefits with non-selective beta-blocker use on airway hyper-responsiveness in asthma. Based upon previous work by Hanania et al, the study was designed to evaluate the potential beneficial effects on airway hyper-responsiveness demonstrated in previous open label studies.[102,104] The lack of observed beneficial effects with propranolol in comparison to the proposed benefits demonstrated with nadolol is intriguing and could be attributable to several factors.

Firstly the significance of randomised placebo controlled trials in comparison to open label studies should not be underestimated. However the effects of nadolol were reproduced in two distinct open label studies both showing an improvement in airway hyper-responsiveness to methacholine in comparison with baseline.[102,104] In this thesis in addition to demonstrating no improvement in AHR versus placebo, propranolol also failed to show any improvement in AHR in comparison with baseline measurements.

Whilst nadolol and propranolol have similar pharmacological profiles, it is conceivable that an improvement in AHR would have been seen in this current study if nadolol had been used. Originally the concept of putative beneficial effects of chronic beta-blocker use in asthma was based upon the concept of inverse-agonism. Both propranolol and nadolol both display inverse agonist properties and therefore are able to decrease beta-2-adrenoceptor activity below basal level and essentially “switches off” the receptor, thus displaying negative efficacy.[32] Prolonged treatment with inverse agonists, by reducing

constitutive receptor activity, would permit the system to resensitize and up-regulate receptors.[96] It was proposed that up-regulation of the beta-2-adrenoceptors would result in reductions in acetylcholine release and an improvement in airway hyper-responsiveness. The lack of therapeutic benefit with propranolol in this thesis suggests that inverse agonism is not the only concept potentially responsible for the benefits previously seen with nadolol.

As previously discussed beta-2-adrenoceptor signals via several pathways including the release of cAMP pathway with subsequent airway smooth muscle relaxation and the activation of beta-arrestin at the epithelial cells which in asthma has been shown to be pro-inflammatory.[15,27]

Whilst endogenous ligands such as noradrenaline stimulate both cAMP release and beta-arrestin, it has been proposed that other ligands may preferentially activate one pathway over another, such is the case with salmeterol.[183] The term 'biased agonism' has been proposed to describe preferential activation of differing pathways via the same receptor.[184] In addition to beta-agonists, certain beta-blockers have been shown to display beta-2-adrenoceptor ligand bias.

Carvedilol has previously been shown to activate beta-arrestin signaling while shutting down the cAMP pathway.[159] Furthermore propranolol has also been suggested to have similar signaling properties to carvedilol, which would result in worsening airway inflammation due to the inflammatory effects on airway epithelial cells. This is in comparison with nadolol with evidence supporting an inactivation of the beta-arrestin pathway with nadolol.[159] Evidence does however exist that propranol may reduce beta-

arrestin activation. In a study by Carter et al. isoprenaline-stimluated beta-arrestin activation was antagonised by propranolol.[185] The suggestion therefore that the putative benefits seen on airway hyper-responsiveness with nadolol and not propranolol may be due to beta-arrestin signaling is uncertain.

When comparing the differential effects displayed on airway hyper-responsiveness observed with chronic nadolol and propranolol dosing, the major difference between each study was the demographics of each respective study cohort. Whilst the previous benefits of nadolol were displayed in steroid naïve asthmatics, the study discussed in this thesis assessed the chronic dosing effects of propranolol in asthmatics controlled on inhaled corticosteroids. It is therefore plausible that the lack of benefit seen with propranolol was due to the study design. Whether the presence of concurrent ICS has masked any potential benefits on AHR is uncertain, and thus the logical next step is to examine the possibility of steroid sparing effects of non selective beta-blockade,[186] examining whether adding propranolol to a lower dose of ICS would be as effective as increasing the dose of ICS alone. This study is now underway.

The clinical decision to include steroid treated asthmatics was based primarily upon safety grounds. Furthermore one could argue that investigating the effects of non-selective beta-blockers in steroid naive asthmatics is clinically irrelevant, as it is unlikely that clinicians would ever consider giving a beta-blocker as monotherapy in asthma. There is however a clinical trial currently investigating the effects on AHR with nadolol versus placebo in mild ICS naïve asthmatics (NCT01804218).

What is arguably more clinically relevant is that in the presence of concomitant tiotropium during dose titration, carefully selected controlled asthmatic patients are able to tolerate non-selective beta-blockade. This in turn might infer that cardio-selective agents might also be safely administered to controlled ICS treated asthmatics, thereby providing the means for potentially improving treatment of cardiovascular disease in an otherwise contra-indicated cohort.

Addressing comorbidities in the overall management of the COPD patient is of great significance given the high rates extra-pulmonary complications, including myocardial infarction, stroke, lung cancer, depression, and osteoporosis that can occur. COPD and cardiovascular disease are undoubtedly linked due to the risk of smoking related atherosclerosis.[106] However studies have also shown that the presence of COPD, independent of cigarette smoking substantially increases the risk of hospitalisation and death.[107,187] Furthermore cardiovascular disease is the most common comorbidity and leading cause of hospitalisation in patients with mild to moderate COPD.[187]

As previously discussed, beta-blockers are integral in the management of hypertension, ischaemic heart disease and heart failure. Furthermore previous observational studies have shown the potential benefits of beta-blocker use in COPD.[84,116,119] The primary purpose of the study included in this thesis was to evaluate whether the proposed beneficial effects of beta-blockade in COPD could be reproduced. In addition, the interaction between beta-blockers and concurrent inhaled COPD medication including long–acting beta-agonists was assessed. This study showed that following matched propensity scoring a 22% overall risk reduction in mortality was seen with beta-blocker

use in COPD. When stratified by concurrent inhaled therapy, there was an increasing survival benefit throughout treatment groups, with the greatest benefit seen in the most severe patients treated with combination, inhaled corticosteroids, long-acting beta-agonists and long-acting muscarinic antagonists.

With regards to the management of heart failure beta-blocker use reduces mortality and morbidity by their impact on sympathetic and neurohumoral activation.[188] Neurohumoral activation refers to increased activity of the sympathetic nervous system, renin-angiotensin system, vasopressin and atrial natriuretic peptide, and has been proposed as a potential cause of systemic inflammation in COPD patients.[189] In a study by Heindl et al, using microneurography of the peroneal nerve, sympathetic nerve activity was twice as high in COPD patients in comparison with matched healthy controls.[190] Volterrani et al. have also described reduced heart rate variability in normoxaemic COPD patients versus healthy controls.[191] Reduced heart rate variability may reflect excessive sympathetic activity and is a strong predictor of mortality post-myocardial infarction.[192] It could therefore be speculated that the proposed benefits of beta-blocker use in COPD are due to a reduction in sympathetic activity.

Although the study included in this thesis, like other similar observational studies suggests a proposed benefit of beta-blocker use in COPD, results from a retrospective analysis should not be used in order to recommend changes to clinical practice, but to act as a stimulus to further research. Within this current analysis, Cox proportional hazard regression with matched propensity was used with all available co-variates, thought to influence the potential outcome included with the regression model.

Despite these measures the potential for bias within the study results remains. Immortal time bias is a common criticism of observational studies,[193] and has been suggested as a contributing factor to the proposed beneficial effects of beta-blockers in COPD.[194] Immortal time bias is suggested when an individual has to survive the period from their inclusion in a study until they receive a second prescription to be considered exposed to the study drug.[193] Time-dependent analysis attempts to correct for this potential bias. When the corresponding manuscript for this study was published, time-dependent analysis was not included. Since publication, the importance of considering immortal time bias was acknowledged and subsequently time-dependent analysis been included within this thesis. Importantly time-dependent analysis continues to show a survival benefit with beta-blocker use in COPD, HR 0.92 (95%CI 0.85 to 0.96). In addition to this a further analysis by Rutten et al in acute bronchitis, (including COPD patients) including time-dependent analysis has continued to show a survival benefit with beta-blocker use.[195]

Given the potential benefits of beta-blocker use in COPD, other studies have examined differing aspects of their use that is relevant to clinical practice. Co-prescription of both beta-agonist inhalers and beta-blockers may seem counterintuitive to the clinician in the management of COPD. This thesis has already demonstrated that beta-blockers treatment does not prevent salbutamol reversibility in asthma. Also co-prescription of both beta-blockers and beta-agonists appear to have increased survival benefit in COPD in comparison with beta-agonists alone. Stefan et al. examined the effects of continuing beta-blockers in those admitted with an exacerbation of COPD, showing that cardio-selective beta-blockers could be safely continued at the time of a COPD exacerbation.[196] No association between beta-blocker therapy and in-hospital mortality OR 0.88 (95%CI

0.71 to 1.09) or 30-day readmission OR 0.96 (95%CI 0.89 to 1.03) was seen. However, when compared with cardio-selective beta-blockers, non-selective beta-blockers use was associated with an increased risk of 30-day readmission (OR 1.25, 95% CI 1.08 to 1.44).[196]

Despite being integral to the treatment of ischaemic heart disease, beta-blockers remain under used in COPD patients who suffer a myocardial infarction. In a 10 year retrospective study of 6290 patients admitted with an acute myocardial infarction, patients with COPD were less likely to be treated with beta-blockers than patients without COPD. Patients with COPD were at higher risk for dying during hospitalization (13.5% vs 10.1%) and at 30 days after discharge (18.7% vs 13.2%).[197]

The potential role of beta-blockers in acute myocardial infarction in COPD patients is further highlighted by a recent study from Quint et al.[198] In 1063 patient with COPD, with a median follow up of 2.9 years, beta-blocker use either prior to, or at the time of hospital admission, for myocardial infarction was associated with significantly improved survival, HR 0.59 (95%CI 0.44 to 0.79) and HR 0.50 (95%CI 0.36 to 0.69) respectively.[198]

The degree of evidence suggesting a potential benefit of beta-blocker use in COPD is encouraging. Due to the size of study cohort required to prospectively examine the effects of beta-blocker use on mortality in COPD by means of a randomised controlled trial, it is entirely possible that a study of this nature may be ever performed. However in the first instance if the safety and tolerability of beta-blocker use can be demonstrated within COPD patients, this may act as supporting evidence for the treatment of cardiovascular co-morbidities with beta-blockers in COPD patients.

CONCLUSIONS

1. Acute dosing of either 10 or 20mg of oral propranolol caused a small but significant deterioration in airway calibre in mild-to-moderate asthmatics, which was more evident with impulse oscillometry rather than spirometry. Bronchodilator reversibility with nebulised salbutamol and ipratropium produced a full recovery of FEV_1 and airway resistance after acute histamine induced bronchoconstriction in the presence of acute beta-blockade. Intravenous hydrocortisone did not potentiate salbutamol recovery post-histamine challenge.
2. Acute cardio-selective beta-blockade with intravenous esmolol (0.5mg/kg) did not cause any worsening of pulmonary function measured by spirometry and impulse oscillometry and may therefore be safe to use in mild-to-moderate asthmatics controlled on inhaled corticosteroids.
3. Chronic dosing of 6 to 8 weeks of oral propranolol with a maximum dose of 80mg daily did not show any improvements in airway hyper-responsiveness to bronchial challenge testing. No worsening of asthma control or quality of life was observed with only a small effect on pre-challenge pulmonary function. This thesis has shown that by means of a placebo controlled design, that the non-selective beta-blocker propranolol may potentially be safe to use in mild-to-moderate asthmatics controlled on inhaled corticosteroids receiving concomitant inhaled tiotropium.
4. This thesis has shown that the use of beta-blockers in COPD patients may potentially confer reductions in mortality, exacerbations and hospital admissions, in addition to the benefits attributable to addressing cardiovascular risk. These additive benefits were seen across a spectrum of COPD severity.

PUBLICATIONS ARISING FROM THIS THESIS

SHORT PM, ANDERSON WJ, WILLIAMSON PA, LIPWORTH BJ. Effects of intravenous and oral beta-blockade in persistent asthmatics controlled on inhaled corticosteroids. **Heart.** 2013: Nov 7 (Epub ahead of print).

SHORT PM, WILLIAMSON PA, ANDERSON WJ, LIPWORTH BJ. Randomised placebo controlled trial to evaluate chronic dosing effects of propranolol in asthma. **American Journal of Respiratory and Critical Care Medicine.** 2013; 187(12):1308-14.

SHORT PM, WILLIAMSON PA, LIPWORTH BJ. Sensitivity of impulse oscillometry and spirometry in beta-blocker induced bronchoconstriction and beta-agonist bronchodilatation in asthma. **Annals of Allergy Asthma and Immunology.** 2012;109(6). 412-5.

SHORT PM, WILLIAMSON PA, LIPWORTH BJ. Effects of hydrocortisone on acute beta-blocker and histamine induced bronchoconstriction. **British Journal of Clinical Pharmacology.** 2012; 73(5) 717-26.

SHORT PM, LIPWORTH SI, ELDER DH, SCHEMBRI S, LIPWORTH BJ. Effect of beta-blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. **British Medical Journal.** 2011;342:d2549.

PRESENTATIONS ARISING FROM THIS THESIS

British Thoracic Society

Randomised placebo controlled trial to evaluate chronic dosing effects of propranolol in steroid treated persistent asthmatics. **Thorax** 2012;67 (suppl 2) A68 (Poster Presentation)

Sensitivity of impulse oscillometry and spirometry in the assessment of beta-blocker induced bronchoconstriction and beta-agonist bronchodilatation in mild-to-moderate asthmatics. **Thorax** 2011;66: (Suppl 4) A7 (Spoken Presentation)

Reduced mortality with beta-blockers when added to stepwise therapy for COPD. December 2010. **Thorax** 2010;65 (Suppl 4):P151(Poster Presentation)

American Thoracic Society

Beta- blockers reduce mortality and exacerbations when added to stepwise inhaled therapy for COPD without adverse effects on lung function. **Am. J. Respir. Crit. Care Med.** 2011; 183: A2630 (Poster Presentation and Discussion)

Reversal of acute sequential beta-blocker and histamine induced bronchoconstriction. **Am. J. Respir. Crit. Care Med.** 2011; 183: A1378 (Poster Presentation)

European Respiratory Society

Safety and tolerability of acute dosing of beta-blockers in asthma. **Eur Respir J**. 2013 Suppl 753s (Poster Discussion)

Chronic dosing of propranolol in asthma. **Eur Respir J.** 2013 Suppl 753s (Poster Discussion)

Beta-Blockers in COPD. A retrospective cohort study. **Eur Respir J.** 2011; 38: Suppl. 55, 607s(Spoken Presentation)

Effects of hydrocortisone on acute beta-blocker and histamine induced bronchoconstriction. **Eur Respir J** 2011; 38: Suppl. 55, 723s (Poster Presentation)

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