

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

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TABLE OF CONTENTS

TABLE OF CONTENTS	2
PREFACE	6
PUBLICATIONS	8
ACKNOWLEDGEMENTS	10
THESIS ABSTRACT.....	13
CHAPTER 1: LITERATURE REVIEW	16
1.1 The Beta-Adrenergic Receptor.....	17
1.2 Beta-Blocker Medications.....	19
1.2.1 Therapeutic Uses	21
1.2.1.1 Heart Failure.....	22
1.2.1.2 Ischaemic Heart Disease.....	26
1.2.2 Perceived Beta-Blocker Contraindications.....	28
1.2.3 Potential Adverse Respiratory Effects.....	29
1.3 Areas of Knowledge Deficiency	42
1.3.1 Extent of Coexistence of Cardiac Disease and Obstructive Airways Disease.....	42
1.3.2 Beta-Blocker Prescription Practice Amongst Patients with Obstructive Airways Diseases.....	44
1.3.3 Cardiac Benefit of Beta-Blocker Medications in Patients with Obstructive Airways Disease	46
1.3.4 Adverse Respiratory Outcomes Related to Beta-Blocker Use.....	55
1.4 Objectives.....	57
1.4.1 The Prevalence of Obstructive Airways Disease	57

1.4.2	Investigate Beta-Blocker Prescription.....	58
1.4.3	Investigate Adverse Respiratory Effects	58
1.5	Summary.....	59
CHAPTER 2: THE STUDY PROTOCOL		62
2.1	Recruitment	62
2.2	Statistical Power	63
2.3	Abbreviations	64
2.4	Methods	66
2.5	Definitions	70
2.6	Statistical Analysis	71
CHAPTER 3: THE STUDY POPULATION		74
3.1	Recruitment	74
3.2.1	Demographics.....	75
3.2.2	Cardiac Pathology	77
3.2.3	Comorbid Disease	80
3.2.4	Use of Beta-Receptor Active Medication.....	80
3.3	Discussion.....	82
3.4	Conclusions	84
CHAPTER 4: THE PREVALENCE OF COEXISTENT AIRWAYS OBSTRUCTION IN PATIENTS WITH CARDIAC DISEASE		86
4.1	Aims	86
4.2	Methods	86
4.3	Results	86
4.4	Discussion.....	91
4.5	Conclusions	98

CHAPTER 5: BETA-BLOCKER PRESCRIPTION IN PATIENTS WITH COEXISTING CARDIAC AND OBSTRUCTIVE AIRWAYS DISEASE.....	100
5.1 Aims	100
5.2 Methods	100
5.3 Results	100
5.4 Discussion.....	104
5.5 Conclusions	108
CHAPTER 6: THE LONGER TERM EFFECTS OF BETA-BLOCKER MEDICATIONS ON LUNG FUNCTION, RESPIRATORY EXACERBATIONS AND SURVIVAL IN PATIENTS WITH CARDIAC DISEASE	110
6.1 Aims	110
6.2 Methods	110
6.3 Statistics.....	111
6.4 Results	111
6.4.1 Spirometry	111
6.4.2 Respiratory Symptoms	115
6.4.3 Longer Term Adverse Outcomes	116
6.4.3.1 Beta-Blocker Discontinuation	117
6.4.3.2 Respiratory Exacerbations.....	117
6.4.3.3 Acute Cardiac Events	118
6.4.3.4 Respiratory Exacerbations – Supplementary Analyses.....	120
6.4.3.5 Death.....	122
6.5 Discussion.....	128
6.6 Conclusions	138
CHAPTER 7: CLINICAL APPLICATIONS AND IMPLICATIONS.....	140

7.1	The Status Quo	140
7.2	Contribution to Existing Knowledge.....	141
7.3	Screening and Monitoring	143
CHAPTER 8: DIRECTIONS FOR FUTURE RESEARCH.....		148
8.1	Safety and Efficacy.....	150
8.2	A Potential Therapeutic Role for Beta-Blockers in the Obstructive Airways Diseases.....	151
BIBLIOGRAPHY		157
APPENDICES		169
Appendix 1		169
Appendix 2		175
Appendix 3		177
Appendix 4		179
Appendix 5		185
Appendix 6		190
Appendix 7		192
Appendix 8		210

PREFACE

Statement of Ethical Conduct

The research contained within this thesis was conducted initially in the wards of the Royal Prince Alfred Hospital. The study protocol was approved and periodically reviewed by the Central Sydney Area Health Service Ethics Committee. The research associated with this thesis abides by the international and Australian codes on human experimentation and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

Declaration of Originality

I am responsible for the work represented in this thesis, although many have provided assistance, enabling its completion. The extent to which others have contributed is detailed in the acknowledgements. This work has not previously been presented in application for any other degree or diploma, by the University or any other institution. To the best of my knowledge no material previously published or written by another person is included, except where due acknowledgement has been made in the text, nor does the thesis contain any material that infringes copyright.

Authority of Access

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Belinda Cochrane

Date: 4 October 2010

PUBLICATIONS

This thesis contains five chapters presenting original research, Chapters 2 - 6.

Research abstracts have been presented at the annual congresses of national and international scientific meetings, as follows:

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

Annual Congress of the Thoracic Society of Australia and New Zealand (oral presentation)

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

Annual Congress of the European Respiratory Society (poster presentation)

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

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

Annual Congress of the European Respiratory Society (poster presentation)

3. Cochrane B, Cochrane JA, Walters HE, Phipps P, Harris P, Young IH (2007)

Prolonged Beta-Blocker Treatment in Subjects with Comorbid Cardiac and Obstructive Airways Disease

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

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

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

ACKNOWLEDGEMENTS

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

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

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

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

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

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

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

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

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

THESIS ABSTRACT

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

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

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

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

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