UTILITY OF THE NEW GOLD CLASSIFICATION
FOR COPD IN ALPHA ONE ANTITRYPSIN
DEFICIENCY

BY

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Abstract

Background
The revised 2011 GOLD strategy presented a new classification and treatment of usual COPD based on symptom assessment by CAT or mMRC and risk assessment based on exacerbations estimated from the spirometric grade or number of exacerbations in previous year (1). This new strategy has not previously been applied to patients with AATD.

Aims
To apply new GOLD strategy/categories in AATD and assess comparable symptom thresholds and predictability of mortality, future exacerbations and lung function decline (FEV1, Kco) and the role of comorbidities.

Results
The results have validated the strategy/classification in AATD with a suggested threshold of 13 rather than 10 for CAT to match with mMRC 1. Mortality and Kco decline was worse in the more severe category D which also had patients with more comorbidity. Applying COTE index to patients with AATD did not help in predicting mortality.

Conclusion
The new GOLD classification helps identify AATD patients who are at risk of poorer outcome based on lung function decline, mortality and exacerbation risk with patients in group D being most at risk. Presence of comorbidities does not appear to influence outcomes in AATD although they do tend to indicate a poorer quality of life.
DEDICATION

This thesis is dedicated to my mother K. Sarojam

For your endless love, support and encouragement. And also for the myriad of ways in which, throughout my life, you have actively supported me in my determination to find and realise my potential.
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# Table of Contents

1 Introduction ................................................................................................................................. 1  
  
1.1 Definition of COPD .................................................................................................................... 1  
  
1.2 Pathogenesis of COPD ............................................................................................................. 3  
  
1.2.1 Cellular changes in COPD ................................................................................................... 6  
  
1.2.2 Proteases and Anti proteases ............................................................................................... 8  
  
1.2.3 Oxidants and Anti-oxidants ............................................................................................... 11  
  
1.2.4 Other mechanisms .............................................................................................................. 12  
  
1.3 Classification of COPD .......................................................................................................... 13  
  
1.3.1 Historical classifications relevant to modern day COPD ................................................. 14  
  
1.3.2 The FEV1 to classify COPD ............................................................................................... 15  
  
1.3.3 Predicting prognosis in COPD .......................................................................................... 16  
  
1.4 Symptom scores in COPD ..................................................................................................... 19  
  
1.4.1 The modified Medical Research Council (mMRC) scale ................................................. 19  
  
1.4.2 The CAT score ................................................................................................................... 21  
  
1.4.3 Other health status questionnaires in COPD ................................................................. 25  
  
1.5 Exacerbations in COPD ....................................................................................................... 27  
  
1.5.1 Causes of exacerbations ..................................................................................................... 28  
  
1.5.2 Clinical assessment of exacerbations ............................................................................... 29  
  
1.5.3 Treatment of an exacerbation ........................................................................................... 31  
  
1.5.4 Pathophysiological changes in an exacerbation .............................................................. 33  
  
1.6 GOLD 2011 classification of COPD ..................................................................................... 35
2.2 To validate the new GOLD strategy in AATD and the proposed thresholds for CAT and mMRC in AATD ................................................................. 61

2.2.1 Placing patients in GOLD groups ......................................................... 61

2.2.2 Establishing a CAT threshold ............................................................. 62

2.2.3 Data analysis .................................................................................. 63

2.3 To validate the new GOLD classification in predicting clinical outcomes ........ 63

2.3.1 Subjects ......................................................................................... 64

2.3.2 Outcomes ....................................................................................... 64

2.3.3 Statistical analysis ........................................................................ 66

2.4 To assess comorbidities in patients with AATD and their relation to GOLD categories ................................................................. 68

2.4.1 Data collection ................................................................................ 68

2.4.2 Data analysis .............................................................................. 72

3 Results – Part 1 ..................................................................................... 73

3.1 To validate the new GOLD classification in AATD ................................ 74

3.1.1 Aim ............................................................................................... 74

3.1.2 Methods ..................................................................................... 74

3.1.3 Results ........................................................................................ 75

3.2 To validate the proposed thresholds for CAT and mMRC in AATD ........ 88

4 Results - Part 2 ..................................................................................... 101

4.1 Aim ................................................................................................. 102

4.2 Methods .......................................................................................... 102
4.3 Results ...................................................................................................................... 103
4.3.1 Mortality ........................................................................................................... 104
4.3.2 FEV1 Decline ................................................................................................... 107
4.3.3 Kco Decline ...................................................................................................... 108
4.3.4 Exacerbation History ........................................................................................ 110
4.4 Results using Spirometry and Exacerbation history for risk assessment.......... 113

5 Comorbidities in AATD ....................................................................................... 118
5.1.1 Non-specific Comorbidity Indices and their application in COPD ............... 119
5.1.2 Comorbidity patterns in usual COPD ............................................................... 120
5.1.3 Relationship to prognosis ................................................................................. 120
5.1.4 Common comorbidities in COPD ................................................................. 121
5.2 Comorbidities in AATD ....................................................................................... 127
5.3 Aims ......................................................................................................................... 129
5.4 Methods ................................................................................................................... 130
5.4.1 Subjects ............................................................................................................. 130
5.4.2 Comorbidities studied in AATD ................................................................. 130
5.5 Results ...................................................................................................................... 131
5.5.1 Prevalence of comorbid disease in PiZZ AATD .............................................. 131
5.5.2 The role of smoking in comorbidity ............................................................... 133
5.5.3 The role of body mass index in comorbidity ............................................... 134
5.5.4 Impact of comorbid disease on outcome in AATD ......................................... 135
5.5.5 Decline in lung function ................................................................................. 137
5.5.6 Quality of life ................................................................................................... 139
6 Discussion

6.1 Validation of the new GOLD classification in AATD
   6.1.1 Proposed thresholds for CAT and mMRC in AATD
   6.1.2 Strengths and limitations

6.2 New GOLD strategy in predicting clinical outcomes in AATD
   6.2.1 Strengths and Limitations

6.3 Comorbidities in AATD
   6.3.1 Prevalence
   6.3.2 Relation to Smoking
   6.3.3 Relation to BMI
   6.3.4 Relation to Outcomes
   6.3.5 COTE index in AATD
   6.3.6 Multimorbidity

6.4 Comparison of GOLD 2011 with previous classification

6.5 Conclusions

6.6 Future studies

7 Appendix

Appendix 1: Ethics and Consent Form for AATD assessment
Appendix 2: Reference Equations
Appendix 3: Ethics, Consent Form and Questionnaire for COPD Study .........................175

Appendix 4: Publications resulting from this thesis ........................................................... 182

8 References .........................................................................................................................183
List of Tables

Table 1.1 Different historical classifications of COPD ........................................................... 14
Table 1.2 modified Medical Research Council Dyspnoea scale ...................................................... 20
Table 1.3 CAT questionnaire ........................................................................................................ 22
Table 1.4 CAT severity categories ............................................................................................... 23
Table 1.5 CAT ladder of severity .................................................................................................... 24
Table 1.6 Factors influencing Hospital management of an exacerbation .................................. 31
Table 1.7 Spirometric assessment of Risk categories in COPD ...................................................... 37
Table 1.8 GOLD 2011 treatment recommendations ...................................................................... 39
Table 1.9 Genotypes and their associated levels of AAT and risk of developing lung or liver disease ....................................................................................................................................... 47
Table 1.10 Effect of smoking on the rate of FEV1 decline among individuals with α 1-antitrypsin deficiency ........................................................................................................................................ 51
Table 2.1 AATD phenotypes derived from clinical data ............................................................... 60
Table 3.1 Patient distribution (number and per cent of cohort) for the four methods of assessment proposed by GOLD ......................................................................................................................... 76
Table 3.2 Patient demographics for the four groups defined by CAT and spirometry ........... 78
Table 3.3 Patient demographics for the four groups defined by CAT and exacerbation frequency ........................................................................................................................................ 81
Table 3.4 Patient demographics for the four groups defined by mMRC symptom score and spirometry ........................................................................................................................................ 84
Table 3.5 Patient demographics for the four groups defined by mMRC symptom score and exacerbation frequency ........................................................................................................................................ 87
Table 3.6  Patient distribution (number and per cent of cohort) for the four methods of assessment proposed by GOLD using CAT 13 as threshold .................................................... 90
Table 3.7  Patient demographics for the four groups defined by CAT 13 and spirometry ...... 92
Table 3.8  Patient demographics for the four groups defined by CAT 13 and exacerbation history ....................................................................................................................................... 95
Table 3.9  Distribution of patients taking into account highest risk according to GOLD or Exacerbation history using a CAT threshold of either 10 or 13 and mMRC 0-1 ................... 100
Table 4.1  Distribution of patients according to the GOLD 2011 combined risk assessment method and their baseline characteristics ................................................................. 103
Table 4.2  Multivariate analyses for mortality ........................................................................ 106
Table 4.3  Univariate analysis comparing the groups for decline in lung function .......... 107
Table 4.4  Multivariate analysis for decline in FEV1 and Kco .............................................. 110
Table 4.5  Exacerbation history of patients in Years 1 and 2 ................................................. 111
Table 4.6  Logistic regression analysis showing associations with frequent exacerbations .. 112
Table 4.7  Distribution of patients according to the symptom/risk assessment methods ...... 113
Table 4.8  Mortality distribution ............................................................................................. 114
Table 4.9  Causes of mortality in each group ........................................................................... 115
Table 4.10  Distribution of the mean decline in FEV1 in the four groups ............................. 116
Table 4.11  Distribution of the mean decline in Kco in the four groups ............................... 117
Table 5.1  List of co morbidities assessed in AATD ............................................................. 130
Table 5.2  Comorbidities observed in patients with AATD .................................................. 132
Table 5.3  Distribution of smokers in those with comorbidities ........................................... 134
Table 5.4  Mean BMI in the groups ....................................................................................... 135
Table 5.5  Mortality seen in patients with co morbidities and their distribution .................. 136
Table 5.6  Logistic regression analysis to determine the association between comorbidities and mortality

Table 5.7  Analysis of Comorbidities against lung function decline

Table 5.8  Mean CAT scores in patients with and without the comorbidities

Table 5.9  Significance of comorbidities

Table 5.10  COTE index stratified by GOLD grouping

Table 5.11  Patient distribution according to the COTE index
List of Figures

Figure 1.1 Pathogenesis of COPD ............................................................................................. 5
Figure 1.2 Diagram showing the pathways leading to smoking-induced protease-anti protease imbalance in the lung.................................................................................................................. 9
Figure 1.3 Mechanisms of reactive oxygen species (ROS)-mediated lung inflammation ...... 12
Figure 1.4 The GOLD 2011 assessment grid .......................................................................... 36
Figure 1.5 Comorbidities in COPD ......................................................................................... 42
Figure 3.1 Patient distribution according to CAT (10) and Spirometry .................................. 77
Figure 3.2 Patient distribution according to CAT (10) and Exacerbation ............................... 80
Figure 3.3 Patient distribution according to mMRC and Spirometry ...................................... 83
Figure 3.4 Patient distribution according to mMRC and Exacerbation ................................. 86
Figure 3.5 Average CAT scores for each mMRC score .......................................................... 89
Figure 3.6 Patient distribution according to CAT 13 and Spirometry .................................... 91
Figure 3.7 Patient distribution according to CAT (13) and Exacerbation ............................. 94
Figure 3.8 Proportion of patients (%) categorised into each of the four groups using CAT 10, mMRC and CAT 13 for symptom assessment respectively and spirometry as risk. ............ 96
Figure 3.9 Proportion of patients (%) categorised into each of the four groups using CAT 10, mMRC and CAT 13 for symptom assessment respectively and exacerbation history as risk. 97
Figure 3.10 Average FEV1% predicted (±SE bar) in each group classified by CAT 10, CAT 13 and mMRC with spirometry as risk............................................................................................................. 98
Figure 3.11 Average FEV1% predicted (±SE bar) in each group classified by CAT 10, CAT 13 and mMRC with Exacerbation as risk............................................................................................................. 99
Figure 4.1 Mortality distribution in the four groups.............................................................. 104
Figure 4.2  Kaplan-Meier all cause survival plot according to the symptom risk assessment groups. ................................................................. 105

Figure 4.3  Decline in FEV1 across the groups ................................................................................................................................. 108

Figure 4.4  Decline in Kco across the groups ................................................................................................................................. 109
ABBREVIATIONS

AATD- Alpha 1 antitrypsin deficiency
ADAPT- Antitrypsin Deficiency Assessment and Programme for Treatment
ATS – American Thoracic Society
BAL – Broncho alveolar lavage
BMI – Body Mass Index
BTS – British Thoracic Society
CAT- COPD Assessment Test
CD – cluster differentiation
COPD - Chronic Obstructive Pulmonary Disease
COTE – COPD specific comorbidity test
COTE index - COPD comorbidity index
CRP – C Reactive Protein
CT – Computed tomography
CXC - chemokine sub-family based upon the position of cysteine residues
DLco/TLco – diffusing capacity or transfer factor of the lung for carbon monoxide
ECG - Electrocardiogram
ECLIPSE – Evaluation of COPD longitudinally to identify predictive surrogate end-points
ERS – European Respiratory Society
FEV1- Forced expiratory volume in one second
FVC- Forced vital capacity
GOLD- Global Initiative for Chronic Obstructive Lung Disease
GORD – Gastro oesophageal reflux disease
HADS – Hospital Anxiety and Depression Scale
HRCT – High Resolution CT scan
HRQoL – Health Related Quality of Life
IFN - Interferon
IL - Interleukin
Kco- Transfer coefficient (the value of the transfer factor divided by the alveolar volume)
LTOT – Long term Oxygen Therapy
MMP – matrix metalloproteinase
mMRC - modified Medical Research Council
NF – Nuclear factor
NHLBI – National Heart, Lung and Blood Institute
PaCO₂ - Partial pressure of carbon dioxide in the arterial blood
PaO₂ – Partial pressure of oxygen in the arterial blood
QoL – Quality of Life
RV- Residual volume
SGRQ- St. George's Respiratory Questionnaire
TGF – Transforming growth factor
Th – T helper cell
TLC- Total lung capacity
TNF – Tumour Necrosis Factor
TORCH – Towards a Revolution in COPD Health
UPLIFT - Understanding the Potential Long-term Impacts on Function with Tiotropium
2p- Two tailed p value
1 Introduction

Chronic Obstructive Pulmonary disease (COPD) is one of the most prevalent respiratory diseases and is the fourth leading cause of death worldwide (2). It is an important cause of chronic morbidity and mortality and is a public health challenge that can be prevented and treated (2). The global COPD risk is expected to increase in the coming decades with an increase in the elderly population and continued exposure to risk factors. (3) The hallmark of COPD is a chronic inflammatory response of lungs to inhaled cigarette smoke and other noxious particles and gases which in turn may result in destruction of lung parenchyma leading to emphysema. Furthermore the disruption of the normal defence mechanisms may also lead to fibrosis of the small airways; the relative contribution of each of these processes varies in different individuals. These pathological changes eventually result in persistent and progressive airflow limitation and air trapping which manifests as breathlessness and other characteristic symptoms of this condition. The prevalence of COPD and its associated morbidity varies in different countries of the world and in different ethnic groups, in part due to genetic factors and in part due to differences in environmental exposures, such as biomass fuel.(2)

1.1 Definition of COPD

There have been many different definitions of COPD since the term was coined.

The American Thoracic Society (ATS) has defined COPD as “a disease state characterized by the presence of airflow limitation due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyper reactivity, and may be partially reversible.”(4)
The European Respiratory Society (ERS) defined COPD as “reduced maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive and mostly irreversible to present medical treatment.”(5)

The ATS (American Thoracic Society) / ERS (European Respiratory Society) consensus statement defines COPD as “A preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.” (6)

The Global initiative for chronic obstructive lung disease (GOLD) was launched in 1998 with the aim of increasing the awareness of the burden of COPD and to improve the prevention and management of this condition through concerted international effort. This also implied greater research in this field. The initial GOLD strategy paper on COPD provided state of the art information on COPD and the subsequent reports and updates have evaluated published research in COPD and its impact on the management of this very important condition.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classified COPD as “a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases”. (7)

Later in 2007, GOLD (Global Initiative for Chronic Obstructive Lung Disease) defined COPD as ‘a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually
progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases’ (8).

Subjects with COPD display heterogeneity in clinical, physiological and radiological characteristics which are thought to result from different pathophysiological mechanisms. Identifying and understanding specific phenotypes of COPD not only enables development of better prognostic markers, thus optimising patient management but also helps design better and robust studies in this field leading to the development of effective targeted therapies.

By 2011, it became evident that there was considerable new information in the field of COPD research, and that the time had come for a comprehensive major revision of the document. It has previously been shown that the FEV1 based staging system corresponds to important differences in health status (9), however it did not adequately explain difference in outcomes such as mortality. The new GOLD outcome strategy further stratifies patients on the basis of their CAT scores (a simple marker of health status), MRC stage (a symptom score for dyspnoea) and exacerbation rate, hypothesising that this would be a better predictor of future risk of adverse outcomes (1). The studies conducted as part of this thesis are based on this new GOLD strategy.

1.2 Pathogenesis of COPD

COPD is characterised by an abnormal inflammatory response to inhaled particles or gases in excess of the normal inflammatory response in the lungs potentially causing lung injury (10). Pathogenesis of COPD is complex and cannot be explained by a single unifying mechanism. The most likely explanation is an interaction between different mechanisms involving protease anti-protease balance, oxidative stress and apoptosis (Fig 1.1).
The pathological changes observed in COPD include inflammation and fibrosis of the small airways, ciliary damage, increased secretion of mucus and emphysema (11). Some of the risk factors that predispose to COPD include smoking, occupational exposures, biomass fuel, airway hyper responsiveness and certain genetic variations e.g. Alpha 1 Antitrypsin deficiency (AATD) (12). The airflow limitation in COPD is progressive and involves a combination of small airway inflammation and parenchymal destruction. The contribution of these processes varies in different individuals (13).
Figure 1.1 Pathogenesis of COPD

Cigarette smoke and other inhaled pro-inflammatory agents (such as ozone (14) or particulate matter (15)) activate macrophages (1), and neutrophils (2) leading to the direct release of proteases or neutrophil chemo attractants, together with the release of oxidants (3) resulting in subsequent breakdown of connective tissue in the lung (4), causing emphysema. Epithelial cell stimulation (5) by oxidants, such as oxygen free radicals, promotes fibroblast activity (6), eventually leading to fibrosis and small airways disease (7).
1.2.1 Cellular changes in COPD

Neutrophils play a key role in the pathogenesis of COPD, although not fully understood. Neutrophil numbers in bronchial biopsies and induced sputum have been shown to be related to the severity of disease (16) and the rate of lung function decline (17), the latter also being shown to associate with circulating neutrophil numbers and impaired function (18). Cigarette smoking has been shown to increase the number of circulating neutrophils and reduce their deformability, thereby leading to sequestration in lung capillaries (19). It also directly stimulates granulocyte production in the bone marrow (20). Sequestered neutrophils stick to endothelial cells and can then make their way to the respiratory tract. Chemotactic factors e.g. leukotriene B4, interleukin 8 (IL-8) and related CXC chemokines control this process (20).

Macrophages are also increased in the lungs and BAL fluid of patients with COPD and their numbers in the airways have been shown to correlate to COPD severity (21). They are activated by cigarette smoke and release many potent inflammatory mediators including tumour necrosis factor α, IL-8 and other CXC chemokines, leukotriene B4, monocyte chemotactic peptide -1 and reactive oxygen species (21). Macrophages also secrete variety of proteases including MMP-2, MMP-9 and MMP-12, cathepsins K, L, S and neutrophil elastase (21). Patients with COPD have more activated macrophages which have been shown to produce more inflammatory proteins and have more elastolytic activity. Exposure to cigarette smoke augments these further (22, 23).

Monocytes also play a role in the pathogenesis of COPD. Monocyte chemotactic chemokines recruit monocytes from the circulation. Monocyte chemotactic peptide -1 is one such chemokine whose levels have been shown to be elevated in sputum and bronchoalveolar
lavage fluid of patients with COPD (23). This may also recruit more macrophages in the lungs of patients with COPD.

Bronchial biopsies in patients with mild to moderate COPD show enhanced inflammatory cell infiltrates in the central airways (24). This infiltrate predominantly consist of T lymphocytes, chiefly CD8+ cells and macrophages. The precise role/s of T cells in the pathogenesis of COPD is continuing to be unravelled.

The presence of CD8+ cells distinguishes smokers who do and do not develop COPD and a correlation between T cell numbers, amount of alveolar destruction and severity of airflow limitation has also been demonstrated (25). However some smokers with normal lung function may also show increase in CD8+ cell numbers in comparison to non-smokers (25). CD8+ cells can release tumour necrosis factor α, perforins and granzymes and also activate the Fas – Fas ligand apoptotic pathways.

It has been suggested that dendritic cells may have a role in COPD although this has not been fully defined yet. They are seen in greater numbers in the airways and alveolar walls of smokers (26) and may have an important role to play in innate and adaptive immune responses in COPD.

Cigarette smoke also stimulates airway epithelial cells which then produce pro inflammatory mediators including TNF-α, IL-1β, granulocyte-macrophage colony stimulating factor and IL-8 and transforming growth factor β (TGF-β) which in the small airway epithelium can induce fibrosis (27). Another important molecular mechanism in the inflammation seen in COPD could be the activation of NF-κβ in the lung cells during exacerbations of COPD (28).
Increasing severity of disease in COPD manifests with an enhanced inflammatory response with increased expression of pro inflammatory proteins such as macrophage inflammatory protein 1α which is a chemokine that leads to the activation of mononuclear cells and granulocytes, increased numbers of neutrophils and macrophages, decrease in T lymphocytes (CD$^{3+}$ cells) and a shift towards cells that are phagocytic and proteolytic in the bronchial tissues (16). The fibrosis seen in the small airways of patients with moderate to severe COPD could result from the increased numbers of inflammatory cells in the peripheral airways which are also seen in patients with chronic bronchitis with normal lung function compared to smokers (24). Studies in patients with severe COPD have demonstrated an increase in both the CD4 and CD8 lymphocytes in the peripheral airways and the lung parenchyma (24), in those with mild to moderate COPD, only CD8 cells are increased in number and not the CD4 cells whereas smokers with normal lung function do not show changes in CD4 and CD8 cells (29, 30).

### 1.2.2 Proteases and Anti proteases

The pathogenesis of emphysema in smokers has been explained by an imbalance between proteases and anti-proteases leading to breakdown of connective tissue components especially elastin. This results in loss of elasticity in the parenchyma of the lung and originated from studies in AATD patients. Studies showed that the function of alpha one anti trypsin (AAT) was reduced in smokers by about 40% compared to non-smokers (31). This deficiency in function of AAT was believed to be due to inactivation of AAT by the oxidants in cigarette smoke (32). However Boudier et al did not get the same result (33). Afford et al showed that other inhibitors are present in normal lavage fluids (34) while Stone et al showed that increased neutrophil elastase was responsible for the development of emphysema in smokers
Studies on bronchoalveolar lavage fluid, one hour after smoking, have shown a little or only a transient fall in AAT activity. (36)

Key concepts in protease balance are illustrated in Figure 1.2.

![Diagram showing the pathways leading to smoking-induced protease-anti protease imbalance in the lung](image)

**Figure 1.2** Diagram showing the pathways leading to smoking-induced protease-anti protease imbalance in the lung

IL interleukin; LTB leukotriene B; NE neutrophil elastase; MMP matrix metalloproteases; TIMP tissue inhibitor of metalloproteases; TNFα - tumour necrosis factor alpha.

Smoking induces epithelial cells to produce cytokines that stimulate neutrophils and macrophages. Cigarette smoke also acts directly on neutrophils and macrophages to activate them. Cigarette smoke has oxidants that can inactivate anti proteases, in addition to anti protease inactivation by oxidants released by macrophages and neutrophils. The stimulated neutrophils and macrophages release proteolytic enzymes. Neutrophil elastase can activate MMPs, while MMPs can inactivate alpha 1-antitrypsin. Not shown in the diagram is the role of MMP-12 in releasing TNFα, which amplifies the inflammatory reaction. These processes lead to a protease-anti protease imbalance, which can degrade lung elastin and connective tissue; if sustained, this will lead to emphysema.
1.2.2.1 Elastin synthesis and repair

Intratracheal instillation of elastase in animal models leads to elastin depletion in hours to a few days (38) which is followed by an increase in the synthesis of elastin over a period of weeks. The emphysematous areas in these experimental models have an abnormal appearance of elastic fibres (39) resembling that found in human emphysema. Despite the fact that elastin content is restored by elastin synthesis after injury, normal lung architecture is, however, lost.

Cigarette smoke increases neutrophil degranulation and release of elastase (37) and the oxidants in the smoke potentially inactivate AAT leading to a functional deficiency of AAT (37). However this postulation could be an oversimplification and has not been supported in studies showing the fall in AAT activity in BAL fluid one hour after smoking to be transient and not significant (36) leading to the assumption that most of the AAT in smokers remains active and capable of providing protection against the increased protease burden.

Tropoelastin is the precursor of elastin and crosslinks to form insoluble elastin polymers. These crosslinks, called desmosines, are unique to elastin and have been used as marker of elastin degradation (38). However its utility as a marker of elastolysis has not been fully established with questions over its lung specificity.

1.2.2.2 Other proteases

MMPs may also have a role in COPD (40). Patients with COPD have higher concentrations of MMP-1 (collagenase) and MMP-9 (gelatinase B) in BAL fluid (41, 42) and those with emphysema have been shown to have increased activity of MMP-9 in the lung parenchyma (43, 44) and also increased expression of MMP-1 (45). MMPs are known to activate TGF-β and mice failing to activate TGF-β because of a lack of integrin α_5β_6 do not develop age related emphysema (46) suggesting that under normal conditions, MMP-12 could be
downregulated by TGF-β₁ and that the absence of TGF-β results in excessive MMP-12 production and emphysema. It has also been demonstrated that mice lacking MMP-9 are protected from small airway fibrosis (47). From the studies done so far it appears that MMP-9 is more important in humans compared to MMP-12. TGF-β is activated by MMP-9 and this mechanism could provide a link between increased elastin degradation activity by MMP-9 and the simultaneous production of fibrosis by activation of TGF-β.

Cathepsins may also have a role in COPD. IFN γ over expression induces cathepsin C which can lead to emphysema (48). In mouse lung models, cathepsin inhibitors have been shown to reduce emphysema induced by over expression of IL-13 (49). Cathepsin L has been detected in BAL fluid from patients with emphysema (50). Cathepsin secretion by alveolar macrophages is increased in patients with COPD compared to those from normal smokers or non-smokers (51).

1.2.3 Oxidants and Anti-oxidants

Oxidative stress occurs when there is an imbalance between the toxicity of oxidants and anti-oxidant defence mechanisms in favour of oxidants. There is evidence of increased oxidative stress in smokers and in patients with COPD (52).

Cigarette smoke has a high concentration of free radicals and other oxidants. These free radicals are in both the gas and tar phases (40). Some of these are immediately inactivated whereas others remain active for several days (40). The oxidant burden in the lung is further increased by the greater numbers of neutrophils and macrophages in the alveolar space. Oxidants in cigarette smoke can directly damage the connective tissue matrix components e.g. elastin and collagen (41) and also interfere with elastin synthesis and repair (42), thus contributing to the development of emphysema.
Oxidants in the cigarette smoke increase epithelial permeability (43) and also attack cell membranes producing lipid peroxidation. Lipid peroxidation products are significantly elevated in the plasma and BAL fluid of healthy smokers and patients with acute exacerbations of COPD compared to healthy non-smokers (43-45).

Key concepts in oxidative stress are shown in Figure 1.3.

**Figure 1.3  Mechanisms of reactive oxygen species (ROS)-mediated lung inflammation**

Inflammatory response is mediated by oxidants either inhaled and/or released by the activated neutrophils, alveolar macrophages (AMs), eosinophils (Eos) and epithelial cells leading to the further production of ROS and membrane lipid peroxidation. Activation of transcription of the pro-inflammatory cytokine and chemokine genes, up regulation of adhesion molecules and increased release of pro-inflammatory mediators are involved in the inflammatory responses in patients with COPD. EPO: eosinophil peroxidise; MPO: myeloperoxidase; PMNs: polymorphonuclear cells; H2O2: hydrogen peroxide; HOCl: hypochlorous acid; HOBr: hypobromus acid; O2•−: superoxide anion; •OH: hydroxyl radical; 4-HNE: 4-hydroxynonenal; MAP: mitogen-activated protein; TF: transcription factor.

### 1.2.4 Other mechanisms

#### 1.2.4.1 Mechanisms related to inflammation

Latent adenoviral infection has been implicated in susceptibility to COPD. Adenoviral E1A protein occurs more commonly in the lungs of smokers with COPD than in smokers who have
not developed the disease (53). In E1A animal models, it has been shown that exposure to cigarette smoke amplifies the inflammatory process (53), likely due to increased activation of NF-κB with consequent enhanced release of IL-8 in response to cell activation and increased production of TGF-β (54, 55).

Another mechanism that is thought to contribute to the perpetuation of inflammation in COPD may be the imbalance between histone acetylation and deacetylation leading to chromatin remodelling and enhanced expression of pro-inflammatory genes (56, 57).

1.2.4.2 Apoptosis and Emphysema

It has been proposed that apoptosis leading to loss of alveolar cells can also result in the development of emphysema (58). Studies have demonstrated apoptosis in emphysematous lungs of humans (58, 59). The process may involve the vascular endothelial growth factor pathway and oxidative stress. It has been hypothesised that in emphysematous lungs, cigarette smoke mediates the blockade of vascular endothelial growth factor receptor (VEGF) leading to loss of alveolar cells due to apoptosis (60, 61).

1.3 Classification of COPD

Classification of COPD has come a long way since the Ciba symposium in 1959 which proposed the definitions of emphysema, chronic bronchitis and introduced the concept of airflow obstruction (62). Two contrasting types of patients with chronic airway obstruction were recognised but there was disagreement over how they should be defined and characterised. Many attempts were made to distinguish the different clinical types of COPD (Dornhorst 1955, Simpson 1958, Ogilvie 1959, Richards 1960, Fletcher et al. 1963, Mitchell et al 1964, Briscoe and Nash 1965) (63-69) (see also table 1.1) a debate which continues even to this day.
1.3.1 Historical classifications relevant to modern day COPD

Using clinical and laboratory criteria, Richards (66) distinguished between one group of patients with marked dyspnoea and hyperinflation and another group with cough and cyanosis. Filley et al (70) defined two characteristic groups of patients based purely on clinical grounds: the ‘emphysematous’ type whom they referred to as ‘pink puffer’ (PP) patients and the ‘bronchial’ type whom they referred to as ‘blue bloater’ BB patients. Those who had emphysema were PP patients and had bigger lungs and clinically hyperventilated at rest and exercise. On the other hand BB patients had higher carbon dioxide levels and lower arterial oxygen levels. PP patients had below normal pulmonary blood flow while BB patients had normal cardiac output at rest and on exercise. This corresponded to the A and B types of patients described by Burrows et al (71) who also described an indeterminate type ‘X’ that did not fulfil the criteria for A or B groups. The differentiation into the groups was based on clinical, x-ray and physiological parameters. The emphysematous type was clinically described as ‘pink puffers’ and the bronchitis type came to be recognised as the ‘blue bloaters’. This basic classification of patients into the emphysematous and bronchitis groups has continued for many decades.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Classification of COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richards et al (66)</td>
<td>2 groups of patients – one with dyspnoea and hyperinflation and other with cough and cyanosis</td>
</tr>
<tr>
<td>Filley et al (70)</td>
<td>Emphysematous (pink puffer) and bronchial (blue bloater) types</td>
</tr>
<tr>
<td>Burrows et al (71)</td>
<td>A (corresponding to PP type), B (corresponding to BB type) and X (indeterminate)</td>
</tr>
</tbody>
</table>

Table 1.1 Different historical classifications of COPD
However over the last three decades there has been greater understanding of the pathophysiology underlying COPD and it is recognised that there are clinical phenotypes of COPD distinct from the ‘pink puffers’ and ‘blue bloaters’. The contribution of small airways in the development of airflow limitation was recognised (72-74); for instance, Hogg et al demonstrated the association between small airway inflammation and progression of COPD. This was thought to result from changes occurring at the microscopic level with remodelling and repair of the airway wall along with accumulation of inflammatory exudates in the lumen (72).

1.3.2 The FEV1 to classify COPD

The FEV1 (forced expiratory volume in one second) has been widely used for epidemiological purposes to detect airflow obstruction and as an end point in clinical trials in patients with COPD (75, 76). Since it is simple to measure and easy to use in a primary care setting, it has also been widely accepted for the assessment and monitoring of obstructive airway disease and to stratify patients into mild, moderate and severe disease categories. This was incorporated in the GOLD guidelines in 2006 where an ‘at risk’ category (FEV1>80% predicted) was also introduced. The GOLD classification of COPD at that time was based on the level of spirometric impairment as measured by the FEV1.(8)

The use of FEV1 to stratify patients with COPD led to studies based on spirometric severity, thus accumulating evidence about the utility of this in risk prediction and stratification of patients with COPD. It came to be recognized that COPD is a complex, multidimensional and heterogeneous condition where the clinical, functional and radiological manifestations varied greatly from patients despite having similar extent of airflow obstruction. The ECLIPSE study demonstrated that within each GOLD stage of disease severity, there was wide variation in the
patient population in symptoms, exercise tolerance, number of annual exacerbations and presence of comorbidities (77). The severity and extent of these manifestations did not correlate with the severity of airflow obstruction such that many individuals with severe airflow obstruction did not report severe symptoms or demonstrate impaired exercise capacity (77). Thus FEV1 alone therefore does not adequately describe the complex nature of COPD (especially symptoms) and other factors must be taken into account (78). A good multidimensional COPD classification would adequately categorise patients with COPD through all aspects of its physiology and impact thus enhancing patient care and management and also improving the quality of clinical trials. A suitable single alternative to FEV1 has however not emerged.

1.3.3 Predicting prognosis in COPD

Different approaches to classify disease severity and progression in COPD have been attempted as it became increasingly evident that other components besides lung function would have to be included; typically these have involved careful ‘phenotyping’ of patients. A phenotype is any ‘observable structural and functional characteristics of an organism determined by its genotype and modulated by its environment’ (79). In order to be of use in clinical practice, a clinical phenotype must be related to certain clinically meaningful outcomes such as symptoms, response to therapy, rate of disease progression or death (80). Low body mass index, increased dyspnoea, reduced exercise capacity and frequent exacerbators are some of the clinical phenotypes that have been shown to be associated with poorer outcome in COPD (1, 81-83). These factors have traditionally not been taken into account while classifying disease severity in COPD but have been used as components of several multidimensional indices which have been shown to predict prognosis in COPD.
The BODE Index is a well known multidimensional index in COPD and incorporates Body mass index, Airflow Obstruction as measured by FEV1, Dyspnoea and Exercise capacity as measured by 6 minute walking distance. There is evidence that it is more useful in predicting mortality in COPD than FEV1 alone. Modifications of the BODE index have been described including the mBODE (replacing 6 minute walk with vO2), e-BODE (BODE plus exacerbations) (86), BODE – x (exacerbations substituted by exercise capacity) and the ADO index (Age, Dyspnoea and Airflow Obstruction measured by FEV1) (87). These have also been found to be better in predicting mortality than FEV1 alone in patients with COPD (84, 87). They combine information from several clinically relevant predictors into a composite score which has better discriminative ability compared to lung function alone. These indices can be used in both in primary and secondary care settings, with varying degrees of ease, to improve the prognostic assessment of patients with COPD. Steuten et al proposed that a multidimensional grading system taking into account nutritional status i.e. fat free mass (FFM) is of more use in the primary care setting as many of the other indices used in these grading systems (e.g. exercise capacity) may be difficult to measure in primary care (88). Data on FFM is more commonly available and has been shown to have a strong association with exercise capacity (89),(90),(91). Studies have shown that low BMI and a low FFM are related to increased health care utilisation in the inpatient setting (91).

Some of the other indices described include the COPD Prognostic Index (Quality of Life, FEV1, age, sex, BMI, exacerbation history, cardiovascular disease history) which has been shown to predict mortality, hospitalization, and exacerbation frequency (92), the SAFE Index (QoL, FEV1, 6 Minute Walking Distance) which predicts exacerbation frequency (93), and the DOSE Index (dyspnoea, smoking status, FEV1, and previous exacerbation history), which also helps to predict exacerbations (94).
NICE recommendations suggested considering a diagnosis of COPD in patients aged over 35 years who have a risk factor (generally smoking) and present with exertional breathlessness, chronic cough, regular sputum production, frequent winter “bronchitis” or wheeze with confirmation by post bronchodilator spirometry (95). However it has been shown that patient reported symptoms are not reliable to arrive at a diagnosis. The Third National Health and Nutrition Examination survey in the US, demonstrated that 70% of those with undiagnosed early airway disease and up to 50% with undiagnosed stage 3 COPD did not report symptoms of cough or sputum and 40% denied having a wheeze (96). A multinational longitudinal study of more than 2000 patients with COPD also concluded that a substantial proportion of patients with severe airflow obstruction denied having symptoms of COPD. Among those with severe airflow obstruction as defined by GOLD, about 40% were not short of breath – mMRC 0 (10%) or 1 (30%) (97). Similar observations were reported in a Chinese population survey of 20000 people over the age of 40 where among the 8% of those shown to have COPD, 35% had no symptoms suggestive of COPD - they reported ‘no’ to the questions- ‘do you have cough, phlegm wheeze or breathlessness?’(98).

COPD progressively impacts the quality of life of those affected by it, although again with wide variability. The ability to predict the future risk of disease progression and its impact on health status of the individual is an important feature of any parameter used to stratify the condition. Various studies have demonstrated that FEV1 alone is inaccurate in predicting the health status in a patient with COPD and other factors also play a role (99). These could be physiological, clinical, radiological or a combination of these. It is being increasingly recognised that airflow obstruction is just one aspect of COPD. Other key aspects include hyperinflation, exercise capacity, nutrition and muscle mass and clinical manifestations like dyspnoea (100). Co morbidities in COPD have been described and accepted as part of the
systemic inflammatory process. In the case of a complex condition like COPD, presence of co-
morbidities also has a significant adverse impact on health status (9), (101).

The inability of FEV1 alone to describe outcomes in COPD adequately, inaccuracy of
symptoms alone to diagnose COPD, multiple prognostic indices and severity scores, and the
emerging knowledge regarding the multidimensional nature of COPD resulted in the
development of a new strategy based on assessment of symptoms and risk of exacerbations.
This is the cornerstone of the new GOLD strategy for COPD published in 2011 (1).

1.4 Symptom scores in COPD

There are several validated questionnaires to assess symptoms in patients with COPD. GOLD
recommendation is to use either the modified Medical Research Council (mMRC)
questionnaire or the COPD Assessment Test (CAT), hence these will be the main focus of this
thesis and others will be covered more briefly.

1.4.1 The modified Medical Research Council (mMRC) scale

The MRC questionnaire is well known and gives an assessment of disability arising from
breathlessness (102). The scores range from 0-4 (Table 1.2) and have been found to relate
well with other measures of health status (103) and also predicts future mortality risk (104).
The modified MRC scale (102) is used to grade the effect of dyspnoea on daily activities. It
can be self-administered and patients are able to indicate the extent to which breathlessness
affects their activities. It comprises five statements that encompass the entire spectrum from
no disability (Grade 0) to almost complete incapacity (Grade 4).
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description of Breathlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not troubled by breathlessness except on strenuous exercise</td>
</tr>
<tr>
<td>1</td>
<td>Short of breath when hurrying or walking up a slight hill</td>
</tr>
<tr>
<td>2</td>
<td>Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace</td>
</tr>
<tr>
<td>3</td>
<td>Stops for breath after walking about 100m or after a few minutes on level ground</td>
</tr>
<tr>
<td>4</td>
<td>Too breathless to leave the house, or breathless when dressing or undressing</td>
</tr>
</tbody>
</table>

Table 1.2 modified Medical Research Council Dyspnoea scale

(102)

The MRC dyspnoea scale was developed as a dyspnoea measurement tool. As such it is widely used as a general respiratory questionnaire and is a physician assessment of patient reported symptoms. Fletcher and colleagues developed a five point scale (102) based on patient volunteered information of dyspnoea developing on the flat and on inclines. Later the Medical Research Council developed a four point scale (105) that continues to be used to this day for diagnostic evaluation, epidemiologic studies and in clinical trials. However with the advancement in the knowledge that COPD is a heterogeneous condition, it became evident that the MRC scale is only able to express one aspect of this complex condition. It was not adequate to diagnose or characterise the severity of extra-pulmonary features of COPD (106). An inherent disadvantage is that it measures dyspnoea arising from the magnitude of the task but there is no provision for the associated effort (107). Functional impairment arising from the dyspnoea is also not considered. This led to different comprehensive questionnaires being developed, the CAT being one of them.
1.4.2 The CAT score

The CAT (Table 1.3) assesses the impact of COPD on the patient’s daily life and well-being and gives a broader indication of the overall impact on health. It is a brief and simple set of questions that is completed by the patient and forms an 8 item one-dimensional measure of health status impairment in COPD (108). The scores range from 0-40 (Table 1.3) and a higher score represents a worse health status. CAT was generated following interviews with COPD patients, community physicians and respiratory physicians. It is reliable and has also been found to correlate well with health status measured using the COPD specific version of the St George Respiratory Questionnaire (SGRQ) (108). Initial tests of reliability were based on data from six countries (Belgium, France, Netherlands, Spain, USA and Germany) and showed that it provided a reasonable estimate of the severity of COPD from the patient’s viewpoint irrespective of their language which made it useful for an international population. Initial tests of validation also demonstrated that patients with COPD used the entire scale range of the instrument (108). It has been validated in different countries and in different languages around the world. Despite the relatively smaller number of questions, it has a broad coverage of the impact of COPD on the day to day health of the patient. It is not a diagnostic tool but it is useful in the assessment and monitoring of patients with COPD, in particular the impact on their health status. It has also been found to be as valid and reliable as other health related quality of life scores e.g. CCQ (Clinical COPD Questionnaire) (109) and SGRQ. The CAT is however easier to administer compared to the SGRQ which has 50 questions and a computer based scoring system. It has been shown to be sensitive to both exacerbations and improvement following pulmonary rehabilitation in a general COPD population (110). Although at a group level it may be useful in determining the response to a specific treatment, it may not be so at an individual level (108).
<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I never cough</td>
<td>0 1 2 3 4 5</td>
<td>I cough all the time</td>
</tr>
<tr>
<td>I have no phlegm (mucus) in my chest at all</td>
<td>0 1 2 3 4 5</td>
<td>My chest is completely full of phlegm (mucus)</td>
</tr>
<tr>
<td>My chest does not feel tight at all</td>
<td>0 1 2 3 4 5</td>
<td>My chest feels very tight</td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am not breathless</td>
<td>0 1 2 3 4 5</td>
<td>When I walk up a hill or one flight of stairs I am very breathless</td>
</tr>
<tr>
<td>I am not limited doing any activities at home</td>
<td>0 1 2 3 4 5</td>
<td>I am very limited doing activities at home</td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition</td>
<td>0 1 2 3 4 5</td>
<td>I am not at all confident leaving my home because of my lung condition</td>
</tr>
<tr>
<td>I sleep soundly</td>
<td>0 1 2 3 4 5</td>
<td>I do not sleep soundly because of my lung condition</td>
</tr>
<tr>
<td>I have lots of energy</td>
<td>0 1 2 3 4 5</td>
<td>I have no energy at all</td>
</tr>
</tbody>
</table>

Table 1.3 CAT questionnaire

Adapted from www.catestonline.co.uk
CAT scores have been categorised into severity bands (Table 1.4); 0-10 representing low impact, 11-20 medium impact, 21-30 high impact and 31-40 very high impact. (111)

<table>
<thead>
<tr>
<th>CAT severity category</th>
<th>CAT scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Impact</td>
<td>0-10</td>
</tr>
<tr>
<td>Medium Impact</td>
<td>11-20</td>
</tr>
<tr>
<td>High Impact</td>
<td>21-30</td>
</tr>
<tr>
<td>Very High Impact</td>
<td>31-40</td>
</tr>
</tbody>
</table>

**Table 1.4 CAT severity categories**

Jones et al used an objective scientific method to create clinical scenarios that correlate to CAT scores (111). A COPD ladder of severity was constructed correlating the CAT scores with descriptions of poor health. This severity mapping was used in the GOLD strategy to select a score of 10 as the marker of distinction between low symptoms and high symptoms as it was felt that the symptom descriptions up to 10 were of low severity and those beyond 10 represented progressively worsening symptoms (Table 1.5).
<table>
<thead>
<tr>
<th>CAT score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>Cannot move far from bed or chair</td>
</tr>
<tr>
<td></td>
<td>Have become frail or an invalid</td>
</tr>
<tr>
<td></td>
<td>Cannot do housework</td>
</tr>
<tr>
<td>35</td>
<td>Cannot take bath/shower or takes a long time</td>
</tr>
<tr>
<td></td>
<td>Breathless walking around the home</td>
</tr>
<tr>
<td></td>
<td>Chest trouble has become a nuisance to friends/relatives</td>
</tr>
<tr>
<td>30</td>
<td>Everything seems too much of an effort</td>
</tr>
<tr>
<td></td>
<td>No good days in the week</td>
</tr>
<tr>
<td></td>
<td>Stops patient doing most of what they want to do</td>
</tr>
<tr>
<td>25</td>
<td>Feel that not in control of chest problem</td>
</tr>
<tr>
<td></td>
<td>Cough/breathing disturbs sleep</td>
</tr>
<tr>
<td></td>
<td>Get afraid or panic when cannot get breath</td>
</tr>
<tr>
<td>20</td>
<td>Wheeze worse in the morning</td>
</tr>
<tr>
<td></td>
<td>Breathless on bending over</td>
</tr>
<tr>
<td></td>
<td>Wheezing attacks on most days</td>
</tr>
<tr>
<td>15</td>
<td>Cough several days a week</td>
</tr>
<tr>
<td></td>
<td>Breathlessness on most days</td>
</tr>
<tr>
<td></td>
<td>Housework takes a long time or have to take rests</td>
</tr>
<tr>
<td>10</td>
<td>Usually cannot play sports or games</td>
</tr>
<tr>
<td></td>
<td>Gets exhausted easily</td>
</tr>
<tr>
<td></td>
<td>Walk slower than other people or stop for rests</td>
</tr>
<tr>
<td>5</td>
<td>Breathlessness stops patient doing one or two things</td>
</tr>
<tr>
<td></td>
<td>Chest condition causes a few problems</td>
</tr>
<tr>
<td></td>
<td>Breathless walking up hills</td>
</tr>
</tbody>
</table>

Table 1.5  CAT ladder of severity

(111)
1.4.3 Other health status questionnaires in COPD

Measurement of health status or health related quality of life has become a central feature for evaluation of patients with COPD. It is also a chief feature of most studies in COPD arising from the fact that incorporation of patient reported outcome measures is a crucial requirement in clinical trial of drugs in COPD (112). Various questionnaires have been in use both for clinical and research purposes and some of them are described below.

CRQ (Chronic Respiratory Questionnaire)
This is one of the most commonly used disease specific questionnaires designed specifically for chronic lung diseases. It’s sensitivity to change after pulmonary rehabilitation has been consistently reported (113). However it is time consuming as it is not self administered - it is operator led and takes up to 30 minutes to administer.

CCQ (Clinical COPD Questionnaire)
The need for a shorter and validated questionnaire to measure health status in order to assess control in clinical trials as well as in daily clinical practice is met by the CCQ (114). It is a 10 item self administered questionnaire and can be completed in less than 2 minutes. There are 3 domains – symptom, functional state and mental state. Each domain has a 7 point Likert scale and the final score is the mean of all the 10 items. It has been validated and has shown strong discriminative properties, test –retest reliability and responsiveness (114).

SF 36 (Short Form item 36 questionnaire)
In its original form it was the MOS-20 (Medical Outcomes Study 20) question survey to quantify general health status. It was later expanded to a 36 item short form survey (SF-36) to incorporate additional health concepts. There is strong evidence for validity of SF-36 to
measure HRQL in patients with symptomatic COPD (115). It is a generic questionnaire and has shown responsiveness in pulmonary rehabilitation (116, 117).

**SGRQ (St Georges Respiratory Questionnaire)**

*Jones et al* (118) developed the SGRQ, a 76 item instrument that incorporates the three domains of symptoms, activity and impact. Scores ranging from 0 to 100 are calculated for each domain (as well as a total score) based on weighting as an estimate of the distress for each item of the questionnaire. A COPD specific SGRQ – SGRQ-C has been developed by removing 10 weaker items without altering the performance of the instrument. It is shorter, no longer specifies a recall period and produces scores equivalent to the existing instrument (78).

**HADS – Hospital Anxiety and Depression Scale**

HADS is a self-reported questionnaire and has been used extensively to screen psychiatric morbidity(119). It has high validity when used as a screening instrument for psychiatric morbidity (120-122). It is comprised of two parts, the first with seven questions related to anxiety and the second with seven questions related to depression. A score of 8 or more on either part is used as a cut off point for diagnosing anxiety and depression respectively (119).

A study to investigate the use of HADS with recuperating COPD showed clinically relevant anxiety, indicated by higher HADS scores, was more common in patients with severe COPD. Anxiety and total mood improved during inpatient rehab (122). Another study to analyse the risk of rehospitalisation in patients with COPD concluded that anxiety is an important risk factor for rehospitalisation (123).

**MAUGERI study**

This study evaluated the effectiveness of a comprehensive individually tailored pulmonary rehabilitation programme in COPD patients with Chronic Respiratory Failure (CRF),
comparing its effects in this group with those in COPD patients not affected by CRF. CRF was defined as a condition in which patients had an arterial oxygen tension (PaO2) < 60mmHg requiring long term oxygen therapy and/or arterial carbon dioxide tension (PaCO2) > 45 mmHg (124),(125, 126). The study showed that pulmonary rehabilitation is also equally effective in end stage COPD, i.e. patients with CRF (126).

**Maugeri Foundation Respiratory item set (MRF – 28)**

This is a 28 item document that determines health status in CRF. It identifies a core set of items relevant to patients with CRF that are related to global impaired health. The 28 items were selected using classical test theory (127). The questionnaire was developed primarily for use in patients with respiratory failure secondary to pulmonary or chest wall diseases (127). It is the first instrument specifically developed for use with CRF patients. A reduced form of the questionnaire, MRF 26, has also been developed as a unidimensional measure of HRQoL impairment for CRF patients (128).

**1.5 Exacerbations in COPD**

Exacerbations play a very important role in COPD. They are a key cause of the increased morbidity, mortality and poor health status seen in COPD and also place a considerable burden on the healthcare system (129). The BTS Burden of lung disease report (2006) reckon that they account for nearly 16% of hospital admissions in the UK, are the commonest medical cause of hospitalisation in the UK and cost over £253 million a year. Some patients appear to suffer from frequent exacerbations while others do not. Those reporting two or more exacerbations of COPD per year are classified as ‘frequent exacerbators’, a phenotype that appears relatively stable over time (81). Exacerbations are important outcome measures in COPD and a reduction in exacerbation frequency is an important target to achieve for any
intervention. Although in about half of exacerbations treated in the community, patients recover to their baseline level in about 7 days it can be prolonged in some patients. In 14% of these events, patients do not reach their baseline levels even after 35 days of onset and never achieved baseline level in a small proportion of these events (130). About 10% of patients admitted with hypercapnoeic respiratory failure due to COPD die in hospital (131). In those requiring artificial ventilation, it may be as high as 40% within one year after discharge and the all-cause mortality 3 years after hospitalisation is again high at 49% (131-135). Thus it is important to recognise and treat exacerbations promptly and also institute preventative measures as early as possible.

An exacerbation is defined as an acute event characterised by a worsening of the patient’s respiratory symptoms that is beyond normal day to day variations and leads to a change in medication (136-138). It is an acute worsening of respiratory symptoms associated with a variable degree of physiological deterioration (130).

Exacerbations have an adverse effect on a patient’s quality of life (139, 140). It may take many weeks for the symptoms and lung function to recover and they have also been shown to lead to a rapid decline in lung function (130, 141, 142).

1.5.1 Causes of exacerbations

The most common causes are respiratory tract infections, either viral or bacterial although other factors including pollution (143-145) can precipitate them. During an exacerbation, bacteria can be found in the lower respiratory tract in at least 50% of patients, although a significant proportion of these patients also have bacteria in the lower respiratory tract in the stable state (146-148). It has also been demonstrated that the bacterial load increases during an exacerbation (149-151) and also that acquiring new strains of bacteria is associated with an
exacerbation (152). However in about one-third of the cases, a clear cause cannot be identified.

It is increasingly recognised that COPD exacerbations are heterogeneous. Exacerbations associated with viruses and with sputum eosinophilia apart from those associated with bacteria have been described (153). In their study, Bafadhel and co-workers concluded that the etiologic and inflammatory causes of exacerbation episodes in COPD were bacteria alone 37%, virus alone 10%, sputum eosinophilia alone 17%, bacteria plus virus 12%, bacteria plus sputum eosinophilia 6%, virus plus sputum eosinophilia 3%, bacteria plus virus plus sputum eosinophilia 1%, and none 14% (153).

1.5.2 Clinical assessment of exacerbations

Assessment of an exacerbation is based on a combination of the patient’s medical history, clinical signs and laboratory tests, if available. Some of the factors taken into account while deciding the severity of an exacerbation include the severity of the underlying COPD which is based on the degree of limitation of airflow, duration of symptoms, frequency of exacerbation episodes and previous use of non-invasive and/or invasive ventilation.

Clinical signs of severity include use of accessory muscles of respiration, paradoxical movements of the chest wall, central cyanosis, the development of ankle oedema, altered mental state and haemodynamic instability.

There are certain investigations which aid in establishing the severity of an exacerbation. Some of these can be performed at the bedside. Pulse oximetry is essential to adjust the flow rate of oxygen and also to track the clinical state. Arterial blood gas measurements are necessary to determine if the patient is in respiratory failure which is defined as $\text{PaO}_2 < 8.0$
kPa (60 mm Hg) with or without a PaCO$_2$ > 6.7 kPa (50 mm Hg) breathing room air. This is a prerequisite to guide decisions involving ventilatory support.

Chest x-ray gives information regarding presence of consolidation and other alternative diagnoses leading to deterioration in the same symptoms including pneumothorax and pulmonary oedema. An ECG helps in diagnosing coexisting cardiac problems. Full blood count gives an indication of polycythaemia (haematocrit > 55%), anaemia and leucocytosis. Other abnormalities in blood tests include electrolyte disturbances and sometimes hyperglycaemia which has been shown to be associated with an adverse outcome (154). However these could also reflect presence of comorbidities which are a common feature of COPD (155).

Sputum purulence during an exacerbation, especially if it is new or increases is a sufficient indication for starting empirical antibiotic therapy (156). Presence of green or purulent sputum at presentation has been shown to be 94.4% sensitive and 77.0% specific in identifying a group of patients likely to benefit most from treatment with antibiotics. Patients with white or mucoid sputum improved without antibiotics (156). The commonest bacterial pathogens seen during an exacerbation are *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis* (148). *Pseudomonas aeruginosa* becomes important in GOLD stage 3 and 4 patients (148). In patients not responding to the initial course of antibiotics it is imperative to perform a sputum culture and sensitivity test to determine antibiotic sensitivities and proceed appropriately (6).

During an exacerbation, spirometry or any other lung function test is not recommended as it is difficult to perform and the results are not accurate enough (1).
1.5.3 Treatment of an exacerbation

Goals of treatment for an exacerbation of COPD are to lessen the impact of the current episode and to prevent future exacerbations (157). Exacerbations can be managed either in the hospital or on an outpatient basis depending upon the severity of the exacerbation and the presence of certain associated factors. It is estimated that approximately 80% of the exacerbations can be managed in the community (81, 158, 159) with antibiotics, corticosteroids and bronchodilators. Presence of certain factors in a patient with an exacerbation that influence the decision for hospitalisation rather than domiciliary management are shown in Table 1.6.

| Marked increase in the intensity of symptoms, e.g. sudden development of resting dyspnoea |
| Severe underlying COPD |
| New physical signs (e.g. cyanosis, peripheral oedema) |
| Failure of an exacerbation to respond to initial medical management |
| Presence of serious co morbidities e.g. heart failure, newly occurring arrhythmias |
| Frequent exacerbations |
| Older age |
| Inadequate social situation |

Table 1.6 Factors influencing Hospital management of an exacerbation

1.5.3.1 Pharmacological management of an exacerbation of COPD

Corticosteroids, antibiotics and bronchodilators are the three classes of drugs that are used to treat an exacerbation of COPD.

Oral Prednisolone is the preferred corticosteroid in COPD exacerbations (160). There is no consensus on either the dosage or the duration although most international and national guidelines advocate a dose of 30-40 mg once a day for 10 to 14 days (1, 92). A recent study
concluded that a 5 day regimen is sufficient for most COPD exacerbations being non–inferior and did not show any significant difference compared to a 14 day course in terms of re exacerbation rate at 6 months, lung function, dyspnoea or quality of life (161). Nebulised budesonide has also been found to be effective although more expensive (162-164). Hospital based studies have shown that use of systemic corticosteroids in COPD exacerbations hasten recovery, improve FEV1 and arterial oxygen content (162, 165-167) and also reduce the risk of early relapse, treatment failure and length of hospital stay (165, 166, 168). It has also been suggested that directing corticosteroids to a subgroup of exacerbations based on the peripheral eosinophil count may lessen the inappropriate use of systemic corticosteroids (153).

Antibiotics are the mainstay in the treatment of infective exacerbations of COPD. It is particularly indicated when patients exhibit clinical signs of a bacterial infection i.e. new or increased purulence of sputum (156). There are very few placebo controlled antibiotic trials in COPD exacerbations but a systematic review of the literature has demonstrated that in an exacerbation, antibiotics reduce the risk of short term mortality by 77%, treatment failure rates by 53% and sputum purulence by 44%. It supports the use of antibiotics in those exacerbators who are moderately or severely ill with worsening cough and purulence of sputum (169, 170). It has also been shown in a group of COPD patients with exacerbations who required mechanical ventilation (invasive or non-invasive) that withholding antibiotics was associated with greater mortality and also a higher incidence of hospital acquired pneumonia (171). The decision regarding the preferred antibiotic is usually based on the pattern of local bacterial resistance (172).

Short acting beta 2 agonists (SABA) and short acting anti-muscarinic agents (SAMA) are the drugs used during an exacerbation, although there have been no controlled trials of these drugs in this setting (6, 173). They are delivered either via a nebuliser or a metered dose
inhaler and spacer. The nebuliser is more convenient for unwell patients as it requires no optimal coordination of technique although a systematic review of the route of delivery of short acting bronchodilators found no significant differences in FEV1 improvement between the modes of delivery (174).

In addition to the above, controlled oxygen therapy is required in most cases admitted to the hospital and non-invasive or invasive ventilation may be required in some instances. Appropriate fluid and electrolyte balance and stabilisation of co-existing co morbid conditions are also essential in most cases.

1.5.4 Pathophysiological changes in an exacerbation

An increase in airway and systemic inflammation is observed in general during an exacerbation. It is hard to define the exact nature of this inflammation in the airways as it is very difficult to obtain bronchial biopsies during an exacerbation. In one study, bronchial biopsies in patients with severe COPD who were intubated during an exacerbation revealed marked airway neutrophilia, neutrophil elastase expression and upregulation of neutrophil chemokine expression (175). Increase in the large airway interleukin – 8 (IL-8) levels and oxidative stress has been demonstrated in patients with severe exacerbations who were hospitalised or required ventilatory support (176). Markers of oxidative stress e.g. hydrogen peroxide and 8-isoprostane have been shown to be elevated in the airways of patients with an exacerbation and they take time to reach their baseline levels (177).

During an exacerbation, there is an increase in systemic inflammation. It is unclear as to what exactly triggers this response but it is thought that there is a spill-over of inflammation from the lungs. There seems to be a direct correlation between the degree of inflammation in the airways and the size of the systemic acute phase response (178) which is in contrast to that
seen in the stable state (179). Systemic inflammation has been shown to be greater when the exacerbation is due to bacteria or viruses (156, 180). There is also an increase in cardiovascular risk during an exacerbation, especially if caused by an infection (181, 182). Certain markers of inflammation e.g. plasma fibrinogen and CRP that have been shown to be associated with increased cardiovascular risk are also increased during an exacerbation (180). An association between respiratory infections and cardiac events has also been documented (183).

The inflammatory response in the airways during an exacerbation of COPD causes oedema of the airway wall and bronchospasm and sputum production is also increased. These lead to increase in airflow limitation and dynamic hyperinflation (184). Dynamic hyperinflation plays an important role in the development of dyspnoea which is the most common symptom of an exacerbation and also affects gas exchange and the cardiovascular system (184). With increasing severity of COPD, the physiological changes observed during an exacerbation are relatively greater leading to increased airflow limitation and potential to develop respiratory failure.

There are functional consequences that arise from exacerbations. Weakness of peripheral muscles has been observed during an exacerbation leading to reduction in functional capabilities and loss of fitness (185). Frequent exacerbators have a more rapid decline in their functional status than infrequent exacerbators as measured by the time spent outdoors (185). Systematic review of six randomized controlled trials has demonstrated that pulmonary rehabilitation, when introduced immediately after an acute exacerbation, reduces unexpected hospital admissions and mortality and improves HRQoL and exercise capacity (186). It has also been demonstrated that the risk of readmission is increased in those who do not improve their walking distance within one month of an exacerbation (187).
1.6 GOLD 2011 classification of COPD

The GOLD 2011 classification (1) is based on a system of symptom and risk assessment and not just FEV1 alone. The new strategy guide emphasises the importance of patient assessment and recommends management strategies for the individual patient incorporating symptoms, risk of future exacerbations and the degree of airflow limitation using spirometry. The assessment places emphasis on impact of the disease and the future risk of disease progression and highlights the importance of exacerbations and comorbidities in the management of COPD. In a departure from the previous version, a staging system for COPD based on FEV1 is no longer advocated; instead COPD is simply graded as mild, moderate, severe and very severe split at 80 per cent, 50 per cent and 30 per cent of the predicted value of FEV1. Exacerbation risk is determined through exacerbation history and spirometry: an individual who has had two or more exacerbations in a year and/or an FEV1 less than 50 per cent of the predicted value is considered to be at high risk of future exacerbations. Symptoms can be assessed through the COPD Assessment Test (CAT) or the Medical Research Council (MRC) Breathlessness scale. Based on this combined assessment, four patient types can be identified as shown in Figure 1.4.

There are specific treatment recommendations based on the category the patient fits, the objective being individualised treatment for each patient depending on where they are placed on the GOLD assessment grid. Importantly these are not recommendations based on primary clinical trial evidence, as no trials have yet used this grouping; instead it is a consensus of expert opinion.
Table 1.7 shows the assessment of risk based on spirometry.

Type A individual has low risk and few symptoms; type B is a low risk individual but with more symptoms, type C defines one who is at high risk but with less symptoms and type D is one who is at high risk and has many symptoms.

### 1.6.1 Assessment of Risk – Based on spirometry

Table 1.7 shows the assessment of risk based on spirometry.
In patients with FEV1/FVC < 0.7

<table>
<thead>
<tr>
<th>GOLD 1</th>
<th>Mild</th>
<th>FEV1 &gt; 80% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 2</td>
<td>Moderate</td>
<td>50% ≤ FEV1 &lt; 80%</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
<td>30% ≤ FEV1 &lt; 50%</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>Very severe</td>
<td>FEV1 &lt; 30% predicted</td>
</tr>
</tbody>
</table>

Table 1.7 Spirometric assessment of Risk categories in COPD

For purposes of this assessment, GOLD 1 and 2 categories are classified as lesser risk and those in categories 3 and 4 are at higher risk. However the relation between FEV1, symptoms and impact on quality of life is weak. It has been demonstrated that within any given category, there is a wide variation with people having well preserved to poor health status (81). As a result a formal symptomatic assessment is also required.

Data from 3 large prospective studies (TORCH, UPLIFT, and ECLIPSE) demonstrated that as the previous GOLD stage worsened, the exacerbation rate increased, hospitalisation rate increased and mortality increased. This was built into the current GOLD assessment taking a cut off point between GOLD 2 and GOLD 3. It has to be borne in mind that this is a population based estimate i.e. a probability estimate like blood pressure (BP); increased BP increases the risk of stroke and myocardial infarction, but knowing an individual patient’s BP does not tell you whether or when that patient is going to have a stroke. Similarly knowing an individual’s FEV1 helps in knowing the severity of airflow limitation but on its own it does not predict the severity of symptoms or whether the symptoms would progress or remain static.
1.6.2 Assessment of Risk – Based on Exacerbation History

Exacerbations are very important in the natural progression of COPD. They result in significant morbidity and mortality and have an adverse impact on lung function (141). Exacerbation rates vary widely among patients. The ECLIPSE study demonstrated that about 20% of patients in GOLD category 2 (Moderate airflow limitation) had > 2 exacerbations. It also showed that the rate of exacerbations per year does help to predict to a large extent the number of exacerbations in the subsequent years (81). Thus it was felt that exacerbation history had to be taken into account in addition to the risk estimated from spirometry to assess the risk more fully.

Exacerbations may accelerate decline in lung function and are directly responsible for hospitalisations, death and poor prognosis in COPD (188). Hence the risk estimate can be based on a combination of spirometric risk and risk arising from exacerbation history. Where it was felt that the risk from one of these parameters is higher it was decided that the patients should be assigned to the category with the higher risk. This was justified based on the purpose of the classification i.e. to identify patients with poorer prognosis.

This raises an interesting question- We have two risk estimates. Which do we use? The purpose is to identify patients who are at greatest risk and hence we should use the highest risk estimate. This would help identify patients with GOLD 1 or 2 but with >2 exacerbations – that would move them up from A to C and from B to D categories. It has been shown that about 22% with moderate COPD (GOLD stage 2) had frequent (≥ 2) exacerbations. It is important to recognise these patients for management options to lower exacerbations.
### 1.6.3 Treatment recommendations

The GOLD strategy also recommends treatment options based on these 4 categories shown in Fig 1.4 and are detailed in table 1.8 below.

<table>
<thead>
<tr>
<th>PATIENT GROUP</th>
<th>FIRST CHOICE</th>
<th>SECOND CHOICE</th>
<th>ALTERNATIVE CHOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SABA prn or SAMA prn</td>
<td>LAMA or LABA or SABA + SAMA</td>
<td>THEOPHYLLINE</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA+LABA</td>
<td>SABA ± SAMA</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA/LAMA</td>
<td>LAMA + LABA</td>
<td>PDE-4 inhibitor SABA ± SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA/LAMA</td>
<td>ICS + LAMA or ICS + LAMA + LAMA or LAMA + LABA or LAMA + PDE-4 inhibitor</td>
<td>Carbocysteine SABA ± SAMA Theophylline</td>
</tr>
</tbody>
</table>

**Table 1.8 GOLD 2011 treatment recommendations**

- **SABA** Short acting bronchodilator
- **SAMA** Short acting muscarinic antagonist
- **LABA** Long acting bronchodilator
- **LAMA** Long acting muscarinic antagonist
- **ICS** Inhaled corticosteroid
- **PDE** Phosphodiesterase 4

Therapy in COPD is mainly directed at airflow obstruction and inflammation, with additional effects on exacerbations, although it is not known if this influences infective or non-infective aetiology. Thus short and long acting bronchodilators, acting via beta adrenoceptors (β2 agonists) and anticholinergic pathways are recommended to be used in a stepwise manner, with the addition of inhaled steroids later in the disease. It has been suggested that they should be combined with a long acting β2 agonist when FEV1 is below 50% of the predicted
normal value, and when the patient is experiencing regular exacerbations (173). Many of the newer treatments for COPD have been directed at individual components of inflammation, given its’ importance in pathogenesis. However most, such as anti-TNFα, have been disappointing (189).

Peripheral blood eosinophilia has been shown to be a surrogate marker for eosinophilic inflammation in COPD (153) and a peripheral blood eosinophilia >2% has been shown to indicate response to corticosteroid therapy in outpatient management of exacerbations of COPD (190).

1.6.4 Controversies of the new strategy

The new classification system has not been without its controversies. The strategy assumed that an mMRC threshold of 1 equates to a CAT score of 10. There is a lack of convincing evidence to support this assumption; this threshold has not been independently validated yet nor has the utility in predicting clinical outcome. It has also not been validated in sub-groups of COPD patients, such as those with AATD. Despite this there is agreement that the new assessment system represents an important step forward towards personalised medicine in COPD and studies to validate its assumptions and predictive abilities are needed for future refinement.

1.7 Comorbidities in COPD

Comorbidities or co-morbid conditions are other chronic conditions seen in patients with COPD; those most commonly observed are summarised in Fig 1.5. FEV1 has traditionally been the outcome measure in COPD; hence the contribution of comorbidities to the health status and outcomes in COPD has been somewhat ignored until recently. Randomised clinical
trials of new treatments in COPD specifically exclude those with serious comorbidities. However there is increasing recognition that comorbidities are likely to affect outcomes in COPD and are an accurate indicator of poorer prognosis. It has been shown that for every smoker who succumbs to COPD (98,007), three others die of smoking-related cardiovascular disease (148,605), cancer (155,761), or some other non-respiratory related illness (40,025) (191). The presence of comorbidities has an adverse impact on healthcare cost utilisation which is as much or more than that of the respiratory effects of COPD (192). Also recognised is the fact that COPD patients are more likely to die of cardiovascular complications or cancer than from respiratory failure (192). The increased prevalence of comorbidities in COPD may provide an opportunity to identify persons at risk for undiagnosed COPD efficiently and to appropriately evaluate, diagnose and treat them (192).

In their analysis, Mannino et al (192) demonstrated that patients with COPD had a substantially higher prevalence of coronary artery disease, congestive cardiac failure, peptic ulcers and gastritis. However many conditions that were not specifically related to smoking such as depression and other psychiatric ailments, chronic pain syndromes, chronic liver disease and diabetes were also noted to be more frequent in individuals with COPD (193-195). This has an impact on health care costs such that the marginal cost increase for COPD, (the difference in the costs between COPD and their matched controls) averaged $1,333 per patient for respiratory-related hospitalisation, but the marginal cost for all non-respiratory related hospitalisations was greater ($1,740 per patient per year) (193, 196). These authors concluded that one-half of the increased healthcare utilisation and costs found in COPD patients are attributable to comorbid conditions and that comorbid conditions are at least as important as airflow obstruction in their effects on future prognosis. Thus comorbidities are one of the strongest predictors of increased future healthcare costs along with lung function.
impairment (192). The new GOLD strategy has stressed the importance of comorbidities in patients with COPD whilst recommending that they should be treated on their individual merit and should not alter the treatment of COPD.

Figure 1.5 Comorbidities in COPD

A disease specific comorbidities index, the COTE (COPD specific comorbidity test) index has been developed (197) and helps in assessment of the mortality risk in patients with COPD. 12 co morbidities that predicted mortality have been integrated into the COTE index. Increases in the index are associated with increased risk of mortality from COPD and non-
COPD specific causes. It has been suggested that the presence of these co morbidities are important indicators of mortality and patients with COPD should ideally be screened for them as effective interventions are available that can potentially reduce the mortality risk. For example lowering of LDL cholesterol levels have demonstrated a statistically significant reduction in death from coronary heart disease or nonfatal myocardial infarction (198). Similarly in COPD, early intervention in case of comorbidities has the potential to reduce the risk of mortality.

1.8 Survival in COPD

FEV1 has been used widely to predict survival in COPD. Fletcher and Peto reported a relationship between airflow obstruction and survival in COPD (199). Other studies have also confirmed this (200-203). However this relationship is weak and studies have established that several factors apart from airflow limitation influence survival in patients with COPD. Some of them include hyperinflation (204), reduced exercise capacity (205, 206), malnutrition (207), muscle wasting (82, 208), degree of dyspnoea (104), impaired health status (206), depression (209) and presence of low grade inflammation (210, 211). Multidimensional indices BODE (84) and ADO (87) have been shown to predict mortality better than their individual components.

Exacerbations influence survival in COPD. In a group of patients with COPD, it has been shown that outcomes including survival are related to the presence, frequency and intensity of exacerbations. Patients who have no exacerbations have lower mortality compared to those with frequent exacerbations (188).

Physical activity has been shown to be related to survival in healthy subjects (212) and those with chronic conditions (213-215). Waschki et al found that physical activity measured
objectively was the best predictor of all-cause mortality in COPD patients compared with an array of other prognostic factors (216). Levels of adiponectin and assessment of vascular status by a combination of echocardiography, serum levels of N-terminal pro-B-type natriuretic peptide and vascular sonography measured ankle-brachial index were also shown to be independent predictors of mortality in patients with COPD (216).

Extent of emphysema as assessed by CT scan has also been shown to predict respiratory mortality in outpatients with COPD (217).

1.9 Alpha 1 Antitrypsin Deficiency

Alpha 1 antitrypsin deficiency (AATD) is a genetic disorder that predisposes to COPD and chronic liver disease. It was described in 1963 by Laurell and Eriksson who, while working in a clinical laboratory in Malmo, Sweden, observed the absence of the alpha -1 band among the electrophoretic abnormalities of 5 patients, 3 of whom had lung disease (218). Serum electrophoresis separates serum proteins into five major bands: albumin, alpha-1-globulins, alpha-2-globulins, beta globulins and gamma globulins. Alpha 1 antitrypsin constitutes most of the alpha-1-globulin band and in AATD the band is not present. Clinically it manifests most commonly as emphysema (219).

AATD is associated with COPD, emphysema, chronic bronchitis, bronchiectasis, neonatal jaundice, liver cirrhosis, vasculitis and panniculitis (220). Not all individuals with AATD develop emphysema and this could be due to environmental factors, such as cigarette smoking, but could also be the result of other genetic factors. AATD is usually diagnosed while investigating lung or liver pathology but in countries where neonatal screening is offered, it is diagnosed at birth before symptoms develop. Individuals present with non-specific symptoms of cough, wheeze and frequent chest infections and thus the diagnosis may
be delayed. The delay has been estimated to be of approximately 5.6 years from the onset of symptoms (221).

Classically patients present with progressive breathlessness, similar to COPD, but at an earlier age or with less smoke exposure (220). Some UK individuals with AATD have been shown to demonstrate features of emphysema in late teenage years by regression modelling (222). This is in contrast to COPD which usually presents after the age of 45. Current UK national guidelines suggest testing for AATD only in people under the age of 45 or with a severity of disease that is out of proportion to their exposure to cigarette smoke (223). Cigarette smoke exposure is usually expressed in pack years smoked and one pack year is equivalent to one pack of cigarettes (i.e. 20 cigarettes) a day for a year. Most individuals with COPD have at least a ten pack year history of cigarette smoke, if not more, but this is generally much less in AATD (220).

Lung function tests usually show an obstructive airway disease pattern which is associated with COPD. Gas transfer may be normal or reduced and static lung volumes are increased. Reversibility after bronchodilators, which is characteristically seen in asthma, may also occur (224). A post bronchodilator reversibility of at least 12% from baseline FEV1 was observed in 28% of individuals with AATD in the NHLBI AATD registry (224). Lung function may be normal in asymptomatic subjects. Exposure to cigarette smoke is likely to be the most important determinant of lung function abnormalities. Differences between smokers and non-smokers are seen even as early as 18 years of age (225). A mean decline in FEV1 of 70 ml per year has been observed in current smokers compared to 47 ml per year in never smokers (219). Extent of upper zone emphysema, low body mass index, frequent exacerbations and male sex are some of the other factors implicated in an accelerated decline in lung function (226).
HRCT scan of the chest is being increasingly used in the early diagnosis of emphysema in symptomatic patients. It is now possible to describe the type, distribution and severity of emphysema and bronchiectasis as a result of recent developments in imaging (227, 228). It has been observed that distribution of emphysema in AATD relates to lung function (229). Most individuals with AATD have predominantly lower zone emphysema on HRCT as opposed to usual COPD where emphysema is predominantly in the upper zones. Bronchiectasis is also observed in many individuals along with emphysema but is the predominant pathology in a much smaller subgroup (228).

1.9.1 Definition and classification of AATD

AATD is one of the most common hereditary disorders in Caucasians and affects approximately 1 in 2500-5000 individuals (230). AATD is determined by detecting the phenotype by serum protein electrophoresis which detects the common disease associated variants, such as the Z allele. Measurement of serum AAT levels is specific for diagnosis of AATD and a level of less than 11µM is considered significant pathophysiologically (231). The minimum protective level is generally considered to be 11 µM as it has been observed that subjects above this concentration are usually protected from lung disease (231). Severity of AATD is generally defined by the genetic defect causing the altered level, and by the severity of the reduction in level; for example the Z allele causes very low plasma levels (<7 µM) (Table 1.9).
Recognising the challenges encountered in investigation of uncommon conditions, registries of patients with alpha one have been established in many countries to bring together progress in research in the pathophysiology of the condition and its application to clinical practice.

### 1.9.2 Pathogenesis of disease in AATD

Alpha one antitrypsin is an acute phase glycoprotein, synthesised in hepatocytes (233), and subsequently secreted into the plasma. It is also produced in small quantities by alveolar macrophages, circulating monocytes (234) and lung epithelial cells (235, 236). It is comprised of 394 amino acids with an active site residue of methionine at position 358, and a predominant target protease of neutrophil elastase (NE), though it can also bind irreversibly to proteinase 3 and cathepsin G. Point mutations in its mobile domain can lead to protein polymerisation within the liver (237), such that it is not secreted effectively into the plasma, resulting in low pulmonary levels and vulnerability to neutrophil elastase induced damage. These mutations underlie the most common forms of AATD.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>AAT serum level</th>
<th>Risk of lung disease</th>
<th>Risk of liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µmol/L</td>
<td>mg/dl</td>
<td></td>
</tr>
<tr>
<td>PiMM</td>
<td>20-48</td>
<td>150-350</td>
<td>No risk</td>
</tr>
<tr>
<td>PiMZ</td>
<td>17-33</td>
<td>90-210</td>
<td>Minimal risk</td>
</tr>
<tr>
<td>PiSS</td>
<td>15-33</td>
<td>100-200</td>
<td>Low risk</td>
</tr>
<tr>
<td>PiSZ</td>
<td>8-16</td>
<td>75-120</td>
<td>Low risk</td>
</tr>
<tr>
<td>PiZZ</td>
<td>2.5-7</td>
<td>20-45</td>
<td>High risk</td>
</tr>
<tr>
<td>Null</td>
<td>0</td>
<td>0</td>
<td>High risk</td>
</tr>
</tbody>
</table>

Table 1.9 Genotypes and their associated levels of AAT and risk of developing lung or liver disease

(232)
1.9.3 Exacerbations in AATD

In AATD, lung function declines at a faster rate (238) and it has been suggested that this is worsened by the frequency of exacerbations (239). Thus interventions that reduce the frequency of exacerbations may have an impact on lung function decline too. Wencker et al (240) have suggested that AAT augmentation therapy may alleviate the decline in lung function and it has been shown to be associated with slower decline in lung function in some patients. It has also been hypothesised that augmentation therapy may reduce the frequency and intensity of exacerbations in patients with AATD (241). The EXACTLE (EXAcerbations and Computed Tomography scan as Lung End-points) trial demonstrated that although frequency of exacerbations was unchanged by AAT augmentation there was a reduction in the severity of exacerbations and also a trend towards a slowing of emphysema progression for AAT augmentation therapy (242). Another clinical trial using inhaled AAT (KAMADA) is currently underway; although the initial results from phase 2/3 concede that they have not met either the primary or secondary exacerbation end points in the intent to treat population (www.kamada.com/product-development, April 2015).

Needham et al (243) have shown that the average frequency of exacerbations is similar in both AATD and non AATD related COPD (129). However the median length of symptoms in their patients with AATD was 14 days which is considerably longer than that of 7 days seen in usual COPD (130).

1.9.4 Management

Current treatment for AATD is targeted towards symptoms at presentation and for most this would mean management of the underlying COPD. Individuals with COPD due to AATD are managed with the usual therapy for COPD which includes bronchodilators, inhaled
corticosteroids, anti-muscarinic agents, smoking cessation, preventive vaccinations, supplemental oxygen when indicated and pulmonary rehabilitation (244, 245).

Treatment approaches directed towards the root cause (i.e. molecular basis of the disease) continue to be the subject of much research. Such approaches have the potential to treat all aspects of the condition and include AAT augmentation (246), blocking the polymerisation process within the hepatocyte (247, 248) and gene therapy (249). AAT replacement therapy has been shown to be beneficial in reducing emphysema progression as quantified by CT scanning (242). Gene therapy trials are progressing but are not yet of proven efficacy. Blocking the polymerisation process enhances secretion of AAT into the circulation in animal models. This is at an in vitro stage in the development process and raises the prospect of preventing both the cirrhosis and the emphysema associated with AATD (247).

Liver transplantation from an individual homozygous for the normal allele returns AAT levels to normal. If this is performed prior to the development of lung disease it offers likely protection. Due to the scarcity of suitable organs and the implications of subsequent life-long immunosuppression, this is used only in those with end stage liver disease.

Lung Volume Reduction Surgery (LVRS) has been shown to enhance survival in some subsets of individuals with usual COPD (250) but in a small series of patients with AATD, the benefits observed were generally short-lived (251). It offers only short term benefits in terms of functional effects in most patients with AATD compared to those with smoker’s emphysema where these improvements were sustained for a longer duration (252). In this study the functional status of those with AATD returned to baseline at 6 to 12 months post operation and showed further deterioration at 24 months. By contrast, the functional status of
the group with smoking related emphysema remained significantly improved over this period (252).

1.9.5 Novel treatments

Attempts have been made to facilitate secretion of the abnormal alpha one protein by administering low molecular weight medications called chemical ‘chaperones’. In Z phenotype mouse models of AATD, 4 - phenylbutyric acid (PBA) has been shown to increase serum levels of AAT protein. However, chaperones have so far not been successfully used in humans with AATD (253). Retinoid therapy to repair emphysema, although successful in animal models, has not been successful in human emphysema (254).

Gene therapy using intravenously transferred genes to liver cells which then synthesise AAT protein and excrete them into the serum (255) and the use of viral vectors (249, 256) for the same purpose have not been successfully adapted in humans.

1.10 Predicting Clinical outcomes in AATD

The estimated annual decline in FEV1 in Pi ZZ individuals varies from 41 ml to 109 ml in different studies (219, 257-262). Factors predicting an accelerated decline in FEV1 include smoking history (i.e. current vs. ex vs. never smokers) (Table 1.10), male sex, age group 30-44 years, FEV1 35-79% predicted, low levels of AAT in serum and response to bronchodilators (257).

Respiratory failure is the commonest cause of death in patients with AATD (accounting for 50–72% of deaths) followed by liver cirrhosis (10–13%) (257, 263, 264). Overall annual mortality rate ranges from 1·7% to 3·5% (257, 261, 263-265)
Data from different registries vary on the factors predisposing to mortality. While the US NHLBI data show that older age, lower education, more severe baseline FEV1 impairment, lung transplantation and not receiving augmentation therapy are all associated with higher rates of mortality (257), Dawkins et al reported that only age and CT assessment of proportion of emphysema predicted respiratory and all-cause mortality (264). Seersholm et al found an association between mortality and low FEV1 (266), smoking (266), low body mass index and patient acquisition (267) i.e. index cases have a poorer outcome than non-index cases identified by family screening.

<table>
<thead>
<tr>
<th>FEV1 slope ml/year</th>
<th>N</th>
<th>Never smokers</th>
<th>Ex-smokers</th>
<th>Current smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Janus 1985</strong></td>
<td>21</td>
<td>-80 (SE 38)</td>
<td>-61 (SE 43)</td>
<td>-316 (SE 43)</td>
</tr>
<tr>
<td><strong>Hutchison 1987</strong></td>
<td>82</td>
<td>-66 (SD 55)</td>
<td>-44 (SD 56)</td>
<td>-67 (SD 46)</td>
</tr>
<tr>
<td><strong>Wu 1988</strong></td>
<td>80</td>
<td>-61 (SD 100)</td>
<td>-81 (SD 70)</td>
<td>-61 (SD 170)</td>
</tr>
<tr>
<td><strong>Seersholm 1995</strong></td>
<td>161</td>
<td>-86 (SD 107)</td>
<td>-52 (SD 80)</td>
<td>-132 (SD 105)</td>
</tr>
<tr>
<td><strong>Seersholm 1997</strong></td>
<td>198</td>
<td></td>
<td>-53 (95% CI 48–58)</td>
<td></td>
</tr>
<tr>
<td><strong>Piitulainen 1999</strong></td>
<td>608</td>
<td>-47 (95% CI 41–53)</td>
<td>-41 (95% CI 36–48)</td>
<td>-70 (95% CI 58–82)</td>
</tr>
</tbody>
</table>

Table 1.10 Effect of smoking on the rate of FEV1 decline among individuals with α1-antitrypsin deficiency

(268)

*Germans on augmentation therapy. ! Danes not on augmentation therapy.
1.11 Applying GOLD 2011 to AATD

Some of the measures that correlate with progression of disease in COPD have been found to be sensitive to progression of disease in patients with COPD related to AATD (269). Individuals with AATD are an ideal model to study the effects of the disease on health status as they develop the disease when relatively young and progress with time so that health status is less affected by co-morbidities that become common at a later age. Although the GOLD 2011 strategy is chiefly aimed at patients with COPD, a substantial proportion of patients with AATD have COPD and the initial management is similar to that of individuals with COPD. The only difference being the role of augmentation therapy and the less effective response to LVRS (see section 1.9.4).

The GOLD 2011 recommendations emphasise the importance of symptom and risk assessment to arrive at a comprehensive evaluation of the individual with COPD. This is important not only for therapeutic considerations, as the recommended treatment is based on the category assigned to the individual, but also helps to predict risk of exacerbations, hospitalisations and mortality. Lange et al demonstrated that individuals in the high symptom high risk category (Group D) are at risk of poorer outcome compared to other categories. Individuals in group B, characterised by more dyspnoea, had significantly poorer survival than those in the next higher category C which they speculated could be attributed to presence of coexisting cardiovascular disease or cancer (270).

The GOLD strategy of risk assessment could be used in patients with AATD to evaluate clinical outcomes. Dawkins et al investigated the predictive potential of physiological and CT measures in relation to mortality in patients followed for up to four years (264). However no study so far has investigated the impact of this unique GOLD symptom risk assessment
system in predicting outcomes in AATD. The only published study to date has been in individuals with usual COPD where it has been demonstrated to have a better prognostic predictive ability than the previous classification based entirely on spirometry (270).

The UK AATD Registry has data on patients for close to sixteen years at the time of analysis; hence represents an ideal resource to study the clinical course in untreated AATD. The GOLD risk assessment system may also help to predict which group or subgroup of patients may be in greater need of augmentation therapy. A good prognostic scoring system could be useful in clinical management, if it were able to accurately identify patients at risk of subsequent decline, and hence with greater potential benefit from augmentation.

### 1.12 Comorbidities in AATD

Comorbidities in AATD have not been explored in detail. It is likely that the systemic inflammatory state seen in usual COPD could play a crucial role in the development of comorbidities in AATD. Other potential causative factors include physical inactivity and deconditioning as in usual COPD (271, 272) and protease - anti protease imbalance (273).

In COPD, the extent of emphysema has been related to cardiovascular and bone abnormalities (274, 275); whether this applies in AATD is yet to be fully explored. It has been suggested that low levels of AAT lead to unopposed neutrophil elastase activity which may result in the degradation of elastin in the blood vessels. This may lead to increased deposition of collagen and consequent arterial stiffness which is a risk factor for arteriosclerosis and subsequent cardiovascular risk (276, 277). *Duckers et al* (273) demonstrated that patients with COPD due to AATD have increased aortic stiffness, as determined by pulse wave velocity measurements indicating increased cardiovascular risk in this group of patients. They had lower bone mineral density compared to matched controls and a significant proportion of them had a new
diagnosis of osteoporosis despite not receiving oral corticosteroids. They also had lower body mass index and one third of the patients had features of skeletal muscle loss (271). However studies of cardiovascular risk in AATD have thrown up conflicting results which could be due to the small sample size of the studies or sub-analysis of the homozygous state in larger studies (278-280).

The COTE Index has been shown to relate to mortality risk in patients with usual COPD (197). This has not been assessed in AATD. Although many of the co morbidities seen in COPD are smoking related, the consequences of cigarette smoke are similar to that induced by AATD and hence it is likely that a similar set of co morbidities play an important role in AATD too. However patients with AATD are on an average younger and the incidence and spectrum of co morbidities is likely to be quite different to that seen in usual COPD. This determines if comorbidity is an age or smoking or COPD severity issue.

1.13 Aims of thesis

This is the first study of its kind applying the new GOLD strategy to patients with alpha 1 antitrypsin deficiency.

1. To validate the new GOLD classification in AATD
The symptom/risk assessment, as suggested in the 2011 GOLD algorithm will be explored, in a highly characterised group of patients with Alpha-1-antitrypsin deficiency (PiZZ) to ascertain if there are patients in the same categories as are seen in usual COPD and their characteristics.
2. To assess the proposed thresholds for CAT and mMRC in AATD
The proposed CAT threshold (≤ 10) will be compared with the proposed mMRC threshold (≤1) to see whether a different threshold would be more appropriate to generate comparable patient groups and also to determine if using either CAT or mMRC to assess symptoms would result in differences in classification of patients.

3. To validate the new GOLD classification in predicting clinical outcomes:

   Mortality
   Future exacerbations
   Lung function decline (FEV1, Kco)

These are the important factors predicting clinical outcomes in usual COPD and AATD. The decline in FEV1 and Kco will be calculated for patients in each of the GOLD groups. This will help to determine if the 2011 GOLD classification helps in predicting lung function decline. The association between CAT scores and lung function decline will also be explored in our cohort.

Mortality will also be ascertained in the four GOLD groups as well as the number of exacerbations in patients and the ability of frequency of exacerbations in one year to predict exacerbations in subsequent years in AATD as in usual COPD.

4. To assess comorbidities in patients with AATD and their relation to GOLD categories
Comorbidities are an important component of morbidity in COPD. The COTE index has been proposed as a means for quantifying this aspect.

The impact of comorbidities in AATD has not been fully ascertained. Using our comprehensive database of patients with AATD prevalence of co morbidities will be analysed and the COTE index applied. The association between CAT scores and co morbidities in this group of patients with AATD will also be explored.
2 Materials and Methods

2.1 Subject Selection

Subjects were recruited from the UK national registry for AATD, which is based in Birmingham, UK. This is part of ADAPT (Antitrypsin Deficiency Assessment and Programme for Treatment), a programme started in 1996 and funded mainly by a non-commercial grant from Grifols Therapeutics. More recently funding has included grants from the NIHR, Alpha 1 Foundation and EU FP7. Subjects were referred to the registry by health care professionals, including chest physicians and general practitioners, or identified through family screening of those related to someone with AATD. ADAPT has ethical approval to conduct clinical and genetic studies on registered participants (South Birmingham Local Ethics Committee 3359 and 3359a). Informed, written consent is obtained from all participants at registration (the consent forms are included in Appendix 1). All subjects registered with ADAPT have their diagnosis confirmed by genotyping (Heredilab, Salt Lake City, USA).

The procedures described in this section are those for all subjects attending ADAPT. Clinical data was collected by all research fellows in the department, including me, as well as research nurses. Extraction of data from the ADAPT records and calculation of specific phenotypes contained in this thesis particularly those delineated by the GOLD strategy were performed solely by me.

2.1.1 Demographic data collection

At the baseline assessment a full clinical history was taken, including the symptoms of chronic bronchitis (281) and frequency of exacerbations (282). All basic demographic details
(gender, date of birth, height, weight and home address) were recorded, alongside a full smoking history, including age started, age stopped (if relevant) and amount smoked per day, allowing calculation of pack year exposure (calculated by dividing the number cigarettes per day by 20 and multiplying by number of years smoked). Subjects were classified as index cases if they were diagnosed with AATD after investigation of their symptoms and non-index if they were diagnosed through family screening.

**Index and non-index cases**

Index case is the first diagnosed case in a family whereas non index cases are identified by family screening. Index cases have been symptomatic for many years before being diagnosed as AATD by which time lung damage is established (221). Holme et al have shown that Kco, health status and upper zone voxel index (in never smokers) deviate from normal up to 30 years prior to FEV1 in non index subjects with AATD (283). We have analysed the outcomes for index and non index cases.

**2.1.2 Questionnaires**

All patients attending for their baseline visit and subsequent annual visits completed questionnaires that assessed their symptoms and the impact these have on their day to day lives. These included the St George’s Respiratory Questionnaire (SGRQ) (118) and COPD Assessment Test (CAT) (108). Disability arising from dyspnoea was estimated by the physician through the modified Medical Research Council scale (mMRC). Permission for using SGRQ has been obtained for research purposes. CAT is available online (www.CATestonline.org.uk) and can be used for clinical or research purposes. SGRQ and CAT were not modified, adapted or translated in anyway.
2.1.3 Exacerbations

For each patient we used exacerbation history at year one of follow up at ADAPT to define the initial exacerbation frequency. The exacerbation history at year two of follow up at ADAPT was used to define the exacerbation frequency for the following year. Thus we defined a one year period of observation from the baseline assessment (hence year one) to calculate the initial exacerbation frequency. This was done using the criteria described by Anthonisen (282) and was obtained from patients on an annual questionnaire (retrospective recall) accompanied by diary card usage and clinical notes (prospective data collection by patients and research/clinical teams respectively). Episodes were then classified as Anthonisen Type 1 (all three symptoms i.e. dyspnoea, increase in sputum volume and change in sputum colour), Type 2 (two of three symptoms) and Type 3 (one symptom plus at least increased cough). At each annual visit details of occurrence and nature of exacerbations of respiratory symptoms as defined above over the previous year were obtained. They were noted from patient recall with support from diary cards. Symptoms were scored on an all or none (1 or 0 respectively) basis. Patients completed their diary cards recording any change in their everyday respiratory symptoms. An exacerbation of COPD was defined as a course of treatment with oral steroids alone or in combination with an antibiotic for acute episodes of worsening symptoms or one requiring a hospital admission for an exacerbation of COPD (136). Studies performed in the unit have obtained consistent results using this approach (284).

It has also been shown that using diary cards based on retrospective recall was a strong method to categorise patients into frequent or infrequent exacerbators classes for subsequent years (285). However there is potential for recall bias when patients were asked about details of their exacerbations during the previous year. The accuracy of exacerbation history could be
enhanced with additional information obtained from pharmacy prescription records of use of steroids and antibiotics along with centralised database of healthcare utilisation records.

2.1.4 Lung function

All tests were performed in the stable state by trained respiratory physiologists within the Lung Investigation Unit at University Hospitals Birmingham, UK, and compared to predicted values derived from standard reference equations for Caucasian adults (Appendix 2). Spirometry was measured using a wedge bellows (Vitalograph Ltd; Buckinghamshire, UK), after the administration of 5 mg nebulised salbutamol and 150 microgram of ipratropium bromide. Post bronchodilator lung volumes and gas transfer were measured (Benchmark TT501; Morgan Medical; Kent, UK) and predicted values were calculated using equations for normal subjects as defined by European Community for Steel and Coal (286).

At the baseline visit spirometry was performed pre and post nebulised short acting bronchodilators. At subsequent annual visits only post bronchodilator spirometry was performed, such that changes in lung function over time were derived from post-bronchodilator values. Annual follow up has been offered throughout the period that ADAPT has been established, such that those registered in the early years of the programme may have up to 16 years data available, with correspondingly fewer years for those registered later.

Static lung volume measurements including total lung capacity (TLC) and residual volume (RV) were assessed using helium dilution (287). Gas transfer measurements (DLco) were obtained by the single breath carbon monoxide method (288). Together these values were used to calculate the uptake of gas per unit of effective alveolar volume (Kco). The equation used to calculate this, and the reference equations for predicted values are in Appendix 2.
2.1.5 ADAPT databases

The ADAPT programme comprises 2 clinical databases, the older of the two was used to collect data from 1996, the newer one started in 2000 to improve both the quality and quantity of data collected. There is also a microbiological database and a laboratory database containing information on the location and type of stored samples. Data was extracted from the two clinical databases, and unified with a database specific to the study, set up in Excel 2011. Additional data that were not initially recorded e.g. details of co morbidities were extracted from medical notes. Clinical features and phenotypes available from the databases and lung function, and the degree to which the data was transformed are shown in table 2.1.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Data type</th>
<th>Derived from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Bronchitis</td>
<td>History</td>
<td>Raw ADAPT data and medical notes</td>
</tr>
<tr>
<td>Exacerbation frequency per year</td>
<td>History</td>
<td>Symptoms using Anthonisen criteria(282)</td>
</tr>
<tr>
<td>FEV1 %predicted</td>
<td>Lung function</td>
<td>Raw ADAPT data and reference equations</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>Lung function</td>
<td>*</td>
</tr>
<tr>
<td>KCO %predicted</td>
<td>Lung function</td>
<td>Raw ADAPT data and reference equations</td>
</tr>
<tr>
<td>FEV1 decline over at least 3 years</td>
<td>Lung function</td>
<td>Linear regression of raw ADAPT data</td>
</tr>
<tr>
<td>KCO decline over at least 3 years</td>
<td>Lung function</td>
<td>Linear regression of raw ADAPT data</td>
</tr>
<tr>
<td>Mortality</td>
<td>History</td>
<td>Medical notes</td>
</tr>
<tr>
<td>Co morbidities</td>
<td>History</td>
<td>Medical notes</td>
</tr>
</tbody>
</table>

Table 2.1  AATD phenotypes derived from clinical data

*Data regarding FEV1/FVC was extracted directly from ADAPT databases and did not require any calculation or transformation for the studies contained within this thesis.
2.2 To validate the new GOLD strategy in AATD and the proposed thresholds for CAT and mMRC in AATD

The first part of my study was to validate the new GOLD strategy in patients with AATD. For this part of the study, the UK Alpha-1-antitrypsin deficiency (AATD) registry database was reviewed to retrieve data on CAT, mMRC, exacerbation history, demographics, full lung function and health status. CAT has been in use only since 2009 when it was validated (108). For this reason I could only include the patients recruited or followed up after this time in the CAT analyses. All patients on whom the first CAT score had been recorded at their annual follow up visit were included, giving a total of 309 patients. Of these, 300 patients had a recorded mMRC score (in 9 patients there was no documented mMRC score) and 298 had an exacerbation history documented in the last year (11 patients did not have a documented exacerbation history). Subjects for the other parts of the study differed from this and are specified wherever indicated.

Permission was obtained for use of SGRQ. CAT was available online (www.CATestonline.org.uk) and could be used for clinical or research purposes. SGRQ and CAT were not modified, adapted or translated in anyway.

2.2.1 Placing patients in GOLD groups

Initially patients were categorised using their CAT scores (<10 and ≥ 10) and GOLD spirometric category or exacerbation history into the four proposed groups A, B, C and D. This gave rise to four different methods of classifying the study subjects:

CAT/Spirometry

mMRC/Spirometry
CAT/Exacerbations

mMRC/Exacerbations

Patient distribution and demographic features were then compared to determine any differences. Following this, the process was repeated using the mMRC threshold (0-1 and ≥ 2) and once again, comparisons of distribution and demographics were made.

2.2.2 Establishing a CAT threshold

As a second step, different CAT thresholds from 11 to 15 were assessed to determine whether this produced a comparable distribution of patients to that seen with the mMRC threshold. The objective was to ascertain the most accurate and comparable threshold between CAT and mMRC scores. With an ideal CAT threshold there should be no statistically different distribution when patients were assigned into the four GOLD groups A, B, C and D between CAT and mMRC symptom scores. In addition the correlation between the different mMRC scores and CAT scores was examined.

These 309 patients were then assigned into the four GOLD groups taking into account the new cut off CAT score and the demographic characteristics of patients in each category were studied. The GOLD strategy mentions that if there is discordance between risks estimated by spirometry and exacerbation history, one must use the highest risk (also called the combined risk). For example if a patient has a spirometric stage of 1 but an exacerbation history of 5, the patient would be assigned into the higher risk group based on the exacerbation history and not in the lower risk group as suggested by the spirometric staging. These patients were also assigned into the four GOLD categories based on their combined risk.
2.2.3 Data analysis

Statistical analysis was performed using a statistical software package (SPSS, version 20 for Windows and Graph Pad software 2012). The t test was used to compare categories for parametric data, and the Mann-Whitney U test was used for nonparametric data. Two tailed statistics were used in all univariate statistics to determine differences between groups and a 2p value of <0.05 was taken to be statistically significant. Chi Square analysis was used to determine differences in patient distribution between assessment methods and ANOVA was used to compare means between three or more groups.

2.3 To validate the new GOLD classification in predicting clinical outcomes

Mortality
Lung function decline (FEV1, Kco)
Future exacerbations

The aim of the second part of my study was to document the predictive potential of the new GOLD strategy with regard to mortality, exacerbations and lung function decline in a group of patients with AATD, prospectively followed for up to 16 years. Importantly almost all patients have never received augmentation therapy. As a result the UK registry of patients with AATD offers a unique opportunity to investigate the relationship of clinical and physiological features of untreated patients to outcomes. Crucially mMRC has been documented in all patients throughout the programme providing data for long term outcomes on GOLD categories assigned using mMRC, especially mortality.
2.3.1 Subjects

The details of patient assessment, questionnaires completed and the tests performed at each annual visit as part of the UK Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) programme have been previously described in sections 2.1.1 and 2.1.2.

The registry database was reviewed to retrieve data on all PiZZ patients with a physiological diagnosis of COPD (FEV1/FVC <0.7) (n=502 patients). Compliance with annual follow up exceeds 80% of those who attend baseline assessment; hence the dataset included here is a good reflection of the UK AATD population referred to the ADAPT programme. Elements extracted included CAT, mMRC, exacerbation history, demographics, full lung function, health status, index status, smoking status (ex, current or never) and mortality.

Index cases were defined as those patients who presented to the registry with a diagnosis of AATD, and non-index cases were those ascertained by screening the family of index cases.

All patients were categorised into the four GOLD groups based on their initial mMRC scores and spirometry or exacerbation history. The combined risk, defined as the highest group assigned by the various possible methods described in the GOLD outcome strategy, was used to assess natural history. Differences between spirometric and exacerbation based classifications are also shown.

2.3.2 Outcomes

Three clinically important outcomes were assessed: mortality, FEV1 decline and exacerbation risk. Whilst this is not an exclusive list of outcomes that could be used in AATD it was felt that they would be the most broadly applicable from the literature in usual COPD (289) and likely to alter AATD management in the future.
Mortality

At the time of analysis, all patients or relatives were contacted to determine those who had died, if this had not already been documented. Most cases were known to the registry. The cause of death for all patients was confirmed from death certificates or hospital records where available. Details of the cause of death written in the death certificates were obtained from the patient’s registered general physician.

Lung function decline (FEV1, Kco)

The details of the lung function tests performed have been described in section 2.1.4. The minimum dataset required for determination of decline was set at three years with three data points during this time because measuring true decline in FEV1 can be difficult due to variability in individual patients; longer follow up reduces the inter subject variation in the annual decline in FEV1 (290). 436 PiZZ patients on the registry met this criterion for FEV1 and 416 PiZZ patients for Kco. These data were used in summary statistics to determine an annual rate of decline in post-bronchodilator lung function.

Post bronchodilator FEV1 and Kco were estimated at each annual visit and for each subject an annual rate of decline in these parameters was calculated by using slope analysis. The subjects were assigned to groups according to their symptom risk assessment and a mean decline for each group was also calculated.

Exacerbation history

Data on 502 patients was assessed for exacerbation history as described previously in section 2.1.3.
A full clinical history was obtained from all patients with particular attention to the frequency of acute exacerbations, using the criteria described by Anthonisen (282). The exacerbation history was obtained from retrospective recall on an annual questionnaire accompanied by diary card usage and clinical notes. Episodes were then classified as Anthonisen Type 1 (all three symptoms i.e. worsening dyspnoea, increase in sputum volume and increase or new sputum purulence), Type 2 (two of three symptoms) and Type 3 (one symptom plus at least one minor symptom).

Those who had received any AAT augmentation or other active drug as part of a clinical trial, those currently involved in clinical trials and post-lung transplant patients were not included in the outcome analyses.

2.3.3 Statistical analysis

Statistical analysis was performed using a statistical software package (Graph Pad software 2012 and SPSS, version 20 for Windows).

Univariate and multivariate analyses were performed for mortality, FEV1 and Kco decline and exacerbations using combined risk groups (Tables 7-10 for univariate tests using the spirometric and exacerbations methods).

General statistical tests

For each outcome, it has been necessary to describe the cohort studied, and then compare subgroups. In each case data normality was assessed using the Kolmogorov-Smirnov test. The t test was used to compare categories for parametric data, and the Mann-Whitney U test was used for nonparametric data. Two tailed statistics were used to determine differences between groups and a 2p value of <0.05 was taken to be statistically significant. Chi Square analysis
was used to determine differences in patient distribution between assessment methods. ANOVA was used to compare means between three or more groups. Where correction for multiple statistical testing was appropriate, a Bonferroni correction was used.

Linear regression was used to calculate decline in lung function. Subjects were included for the decline analyses if they had at least four data points over at least 3 years in the regression: a baseline and 2 subsequent values. The slope of the resultant regression line was used to indicate decline in the given lung function parameter per year. Those variables that were non-normally distributed within the group were transformed appropriately prior to use in subsequent regression models assessing influences on this phenotype.

Cox analysis was used to assess mortality; follow up period was calculated from the date of baseline assessment to the date of death for those who had died, and from the date of baseline assessment to the present day for those who had survived.

For exacerbation analyses, significant variables in the stepwise analyses were included in further logistic regression analyses together with age, sex and smoking status in order to determine whether they remained significant following adjustment for these factors. All such variables were then entered into a linear regression analysis to identify independent factors that predicted overall decline. This compared FEV1 and Kco decline as continuous variables against the factors, adjusting for age, sex and smoking status.

Data has been displayed as mean with standard deviation (SD).
2.4 To assess comorbidities in patients with AATD and their relation to GOLD categories

The third part of my study was to analyse the presence of co morbidities in our cohort of AATD patients.

2.4.1 Data collection

I looked for the presence of co morbidities in the 502 PiZZ patients described in section 2.3.1. Elements extracted included comorbidities, CAT, mMRC, exacerbation history, demographics, full lung function, health status, index status, smoking status (ex, current or never) and mortality.

Co morbidities were analysed by analysis of individual case notes. As patients joined the registry over a period of 16 years, they were not recorded initially in the database. I went through individual case records to ascertain comorbidities for the following conditions:

1. Diseases included by Divo et al in their study to calculate the COTE index (197)
2. All comorbidities listed in the case records
3. Those expressed at the time of the baseline visit and follow up

The diagnosis of a comorbidity was confirmed either by reviewing the patient’s medication list or when available, by confirmatory tests available from the case records. This was performed to confirm the comorbidity and to ensure there was consistency of ascertainment of comorbidities over time.

Many of the patients were enrolled at a time when the idea of comorbidities in COPD were at a nascent stage and were not recorded in the ADAPT database. Hence I analysed the case notes of each of the 502 patients for details of comorbidities.
COTE index and weighting
Divo et al (197) studied the presence and impact of coexisting conditions in patients with COPD. They evaluated the strength of association between number and nature of the comorbidity with risk of mortality over time. They then developed a point scale index called the COPD specific comorbidity TEST (COTE). This was the most well validated co-morbidity score at the time of inception of studies contained in this thesis.

COTE index – development
Divo et al (197) studied comorbidities systematically in 1664 patients with COPD. 79 different comorbidities were noted in these patients. 15 of the 79 comorbidities were more prevalent in non survivors than survivors. Using multivariate analysis, they found that 12 of these comorbidities increased the risk of mortality over the period of the study and were chosen to build the COTE index. A graphical representation of the prevalence and strength of the association of each comorbidity to mortality was created in the form of an orbital bubble chart called the ‘comorbidome’. The size of the circle was proportional to the prevalence of the disease and the distance from the centre expressed the risk of mortality.

The 12 co morbidities were

**Oncologic** – lung cancer, pancreatic cancer, oesophageal cancer, breast cancer

**Pulmonary** – pulmonary fibrosis

**Cardiac** – atrial fibrillation/ flutter, congestive cardiac failure, coronary artery disease

**Gastrointestinal** – gastric/duodenal ulcers, liver cirrhosis

**Metabolic** – Diabetes with neuropathy

**Psychiatric** – depression and anxiety
COTE Index

In proportion to the hazard ratio of the comorbidity, scale value of points in the range of one to six were allotted to each chosen comorbidity (1.0 – 1.5 = 1, 1.5 – 2.0 = 2, > 2 = 6 points with the exception of other cancers which were allotted 2 points). Increases in COTE index were associated with an increased risk of death from COPD related (HR 1.13; 95% CI 1.08-1.18, p<0.001) and non-COPD related causes (HR 1.18; 95% CI 1.15-1.21, p<0.001).

To identify the level of the COTE index with the greatest predictive value for death in patients with COPD, receiver operating characteristic curves were used. A COTE index ≥ 4 resulted in the greatest area under the curve and was associated with a 2.3 times increased risk of death (HR 2.3; 95% CI 2.00-2.75; p<0.001).

The same weighting was used in our study population. Complete COTE information was captured in our patients and 12 comorbidities were chosen that were used to build the COTE index. Some of the comorbidities found in the study population used by Divo et al were not found in our cohort of AATD patients.

The COTE index was derived from the co-morbidity data and compared between the GOLD groups. We used the 12 comorbidities, used by Divo et al for the COTE index, in our patients with AATD to determine whether they would indicate increased risk of death in patients with AATD.

All patients were categorised into the four GOLD groups based on their initial mMRC scores and spirometry or exacerbation history. The combined risk, defined as the highest group assigned by the various possible methods described in the GOLD outcome strategy, was used to finalise groups. The cause of death for all patients was confirmed from death certificates or hospital records. The distribution of comorbidities in the four GOLD groups was analysed as
well as their association with mortality. The six most common co morbidities seen in patients with AATD were determined.

It is thought that systemic inflammation plays a key part in the development of comorbidities in COPD and my aim was to ascertain if the COTE index could be useful in patients with AATD. Identification of the comorbidities in patients is vital as many of the top 6 comorbidities can be easily screened for by healthcare professionals looking after these patients with availability of effective interventions for these which may substantially reduce the risk of death in these patients.

Body Mass Index (BMI) was also recorded for these patients and was taken as a marker of skeletal muscle dysfunction. Anthropometric measurements were obtained at each visit. Height was measured in metres using a clinical stadiometer in bare or stocking feet. Body weight was measured in kilograms with a calibrated precision scale. BMI, defined as weight (kilograms) divided by the square of height (meters), was then calculated. The distribution of BMI in the four GOLD groups by combined risk was also analysed.

The details of the lung function tests performed have been described previously in Chapter 3. Post bronchodilator FEV1 and Kco were estimated at each annual visit and for each subject an annual rate of decline in these parameters was calculated for each of the subjects by using the slope function in the excel spreadsheet. The subjects were assigned to groups according their symptom risk assessment and a mean decline for each group was also calculated.

The minimum dataset required for determination of decline was at least three years with four data points during this time. These data were used to determine an annual rate of decline in post-bronchodilator lung function.
Those who had received any AAT augmentation or other active drug as part of a clinical trial, those currently involved in clinical trials and post-lung transplant patients were excluded from analysis. In this study, patients with established liver cirrhosis on ultrasound scan and also those who went on to have a liver transplant were included as having liver disease.

2.4.2 Data analysis

Statistical analysis was performed using a statistical software package (SPSS, version 20 for Windows and Graph Pad software 2012). The t test was used to compare categories for parametric data, and the Mann-Whitney U test was used for nonparametric data. Two tailed statistics were used in all univariate statistics to determine differences between groups and a 2p value of <0.05 was taken to be statistically significant. Chi Square analysis was used to determine differences in patient distribution between assessment methods and ANOVA was used to compare means between three or more groups.

For comorbidity analyses, significant variables in the stepwise analyses were included in further logistic regression analyses together with age, sex and smoking status in order to determine whether they remained significant following adjustment for these factors. All correlates were then entered into a linear regression analysis to identify independent factors that predicted overall lung function decline. This compared FEV1 and KCO decline between those with a specified comorbidity to those in whom it was absent, adjusting for age, sex and smoking status.
3 Results – Part 1

The Global initiative for chronic obstructive lung disease (GOLD) was launched in 1998 with the aim of increasing the awareness of the burden of Chronic Obstructive Pulmonary Disease (COPD) and to improve the prevention and management of this condition through concerted international effort which also implied the need for further research. The initial GOLD strategy paper provided state of the art information on COPD and the subsequent reports and updates have evaluated published research in COPD and impact on management. With increasing data from COPD research it was necessary to undertake a major revision of the document which was published in 2011 (1). This revision built on existing understanding of COPD and incorporated the latest advances in COPD and its management and emphasised the need to focus on management strategies for both stable disease and exacerbations (1).

The GOLD strategy has always emphasised accurate grading of the severity of COPD and the FEV1 has been used as a marker for this purpose. However, the new strategy document emphasised the importance of individual patient assessment and recommended management strategies incorporating symptoms and the risk of future exacerbations based on past history and the degree of airflow limitation. It was suggested that symptoms assessed through the COPD Assessment Test (CAT) or the Medical Research Council (MRC) Breathlessness scale could be broadly divided into minimal or major categories with proposed cut off points of ≥10 and ≥2 respectively. Future risk of exacerbations could be determined in part by the level of FEV1 and more accurately by the past history of exacerbations and thereby categorised into those with high risk as predicted by GOLD FEV1 stage of 3 or 4 or previous exacerbation frequency of ≥ 2/year (81), (291, 292).
Based on this combined assessment, four patient groups would be identified - Group A with low risk of exacerbations and few symptoms, Group B with low risk but more symptoms, Group C with high risk of exacerbations but few symptoms and Group D with high risk and more symptoms. Specific initial treatment recommendations were evidence based and related to the individual patient group using this algorithm. The strategy placed importance on appropriate categorisation of patients into each of the groups but importantly, whatever the symptom scoring system it should generally result in comparable categorisation to reduce confusion on therapeutic management.

3.1 **To validate the new GOLD classification in AATD**

3.1.1 **Aim**

The 2011 GOLD strategy recommended the use of the symptom/risk assessment model for assessment of patients with usual COPD. The first part of this study attempted to explore if this symptom/risk assessment model could be used in a highly characterised group of patients with Alpha-1-antitrypsin deficiency (PiZZ) and ascertain if there are patients in the same categories as are seen in usual COPD. In particular the distribution of patients to the four proposed GOLD groups was determined.

The second part of this study attempted to determine how the proposed CAT threshold (≥ 10) compared with the proposed mMRC threshold (≥ 2) or whether a different threshold would be more appropriate to generate comparable patient groups.

3.1.2 **Methods**

Details of the examination and tests performed at each visit have been described in Chapter 2.
Patients were assigned into the four GOLD groups initially using CAT for symptom assessment and then mMRC for symptom assessment. Similarly risk assessment was performed initially with spirometry and later using frequency of exacerbations. This gave rise to four different methods of classifying the study subjects:

CAT/Spirometry

mMRC/Spirometry

CAT/Exacerbations

mMRC/Exacerbations

Patient distribution and demographic features were then compared to determine any differences.

As a second step, we assessed different CAT thresholds from 11 to 15 to determine whether this produced a comparable distribution of patients to that seen with the mMRC threshold.

Statistical analyses

Details of the statistical methods used for analyses have been described in Chapter 2.

3.1.3 Results

Patients were assigned to the four GOLD groups A, B, C and D according to either CAT or the mMRC symptom score and spirometry or exacerbation for risk assessment. Table 1 summarises the distribution of patient numbers and percentage of the cohort for the four methods of assessment proposed by GOLD (1).

The majority of patients fell into Group D with fewest in group C (Table 3.1). This was true irrespective of the symptom or risk assessment used to assign patients into groups.
However there were significant differences in distribution with fewer patients in Group A and more in group B (2p<0.002) when CAT was used as the symptom score compared to mMRC. The difference in distribution in groups C and D was not statistically significant (2p >0.05).

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>CAT 10/ SPIROMETRY</th>
<th>CAT 10/ EXACERBATIONS</th>
<th>mMRC 0-1 / SPIROMETRY</th>
<th>mMRC 0-1 / EXACERBATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NUMBER</td>
<td>PERCENT</td>
<td>NUMBER</td>
<td>PERCENT</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>6.14*</td>
<td>17</td>
<td>5.7*</td>
</tr>
<tr>
<td>B</td>
<td>121</td>
<td>39.15*</td>
<td>121</td>
<td>40.6*</td>
</tr>
<tr>
<td>C</td>
<td>07</td>
<td>2.27</td>
<td>08</td>
<td>2.7</td>
</tr>
<tr>
<td>D</td>
<td>162</td>
<td>52.43</td>
<td>152</td>
<td>51.0</td>
</tr>
<tr>
<td>MISSING</td>
<td>0</td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>309</td>
<td></td>
<td>309</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.1  Patient distribution (number and per cent of cohort) for the four methods of assessment proposed by GOLD

(Significance in bold)

*Indicates a significant difference in distribution between the two symptom assessment tools (2p <0.002).

3.1.3.1  Demographic data

CAT 10 SPIROMETRY

Fig 3.1 displays the patient distribution into the four groups and Table 3.2 summarises the demographic data using the proposed CAT threshold of 10 and risk determined by spirometry.
Figure 3.1  Patient distribution according to CAT (10) and Spirometry

(With number per group and % of total in parentheses)
Table 3.2 Patient demographics for the four groups defined by CAT and spirometry

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>A (n=19, 6.14%)</th>
<th>B (n=121, 39.15%)</th>
<th>C (n=7, 2.27%)</th>
<th>D (n=162, 52.43%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Male N (%)</td>
<td>15 (79%)</td>
<td>53 (44%)</td>
<td>5 (72%)</td>
<td>112 (70%) #</td>
</tr>
<tr>
<td>Female N (%)</td>
<td>04 (21%)</td>
<td>68 (56%)</td>
<td>2 (28%)</td>
<td>50 (30%)</td>
</tr>
<tr>
<td>Age (yrs.) (Mean ±SD)</td>
<td>58.21 (8.69)</td>
<td>60.39 (9.60)</td>
<td>51.14 (8.61)</td>
<td>56.38 (9.87)</td>
</tr>
<tr>
<td>mMRC ≤1 (Mean ±SD)</td>
<td>13</td>
<td>68</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>≥2</td>
<td>0.94 (0.78)</td>
<td>1.84 (1.11)</td>
<td>1.86 (0.99)</td>
<td>2.86 (0.94)$</td>
</tr>
<tr>
<td>EXACERBATIONS ≤1 (Mean ±SD)</td>
<td>14</td>
<td>62</td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td>≥2</td>
<td>0.78 (0.92)</td>
<td>1.75 (1.78)</td>
<td>2.14 (2.59)</td>
<td>2.33 (2.03)$</td>
</tr>
<tr>
<td>CAT (Mean ± SD)</td>
<td>7.00 (1.81)</td>
<td>19.19 (7.07)</td>
<td>6.14 (0.99)</td>
<td>23.67 (6.69)</td>
</tr>
<tr>
<td>SGRQ TOTAL (Mean ±SD)</td>
<td>17.16 (9.17)</td>
<td>45.36 (17.79)</td>
<td>29.71 (9.92)$</td>
<td>59.78 (15.58)#</td>
</tr>
<tr>
<td>SYMPTOMS (Mean ±SD)</td>
<td>26.42 (14.43)</td>
<td>54.50 (21.46)</td>
<td>29.43 (18.23)</td>
<td>69.06 (19.28)#</td>
</tr>
<tr>
<td>ACTIVITIES (Mean ±SD)</td>
<td>25.05 (17.57)</td>
<td>60.83 (22.98)</td>
<td>47.14 (10.53)$</td>
<td>78.24 (17.35)#</td>
</tr>
<tr>
<td>IMPACT (Mean ±SD)</td>
<td>11.16 (7.29)</td>
<td>33.73 (17.62)</td>
<td>20.43 (10.24)$</td>
<td>45.69 (17.70) #</td>
</tr>
<tr>
<td>FEV1 L/min (Mean ±SD)</td>
<td>2.79 (0.83)</td>
<td>1.97 (0.60)</td>
<td>1.41 (0.40)</td>
<td>1.08 (0.34)</td>
</tr>
<tr>
<td>FEV1 % predicted (Mean ±SD)</td>
<td>89.11 (22.77)</td>
<td>72.41 (19.78)</td>
<td>40.71 (6.94)</td>
<td>35.03 (8.84)</td>
</tr>
<tr>
<td>FEV1/FVC (Mean ±SD)</td>
<td>0.54 (0.10)</td>
<td>0.46 (0.11)</td>
<td>0.37 (0.17)</td>
<td>0.29 (0.07)</td>
</tr>
<tr>
<td>Kco % predicted (Mean ±SD)</td>
<td>71.05 (12.58)#</td>
<td>59.99 (16.59)</td>
<td>60.86 (15.90)</td>
<td>52.98 (15.66)#</td>
</tr>
<tr>
<td>RV % predicted (Mean ±SD)</td>
<td>96.21 (18.84)</td>
<td>100.98 (23.54)</td>
<td>111.29 (44.47)</td>
<td>127.28 (33.14)#</td>
</tr>
<tr>
<td>TLC % predicted (Mean ±SD)</td>
<td>114.32 (12.00)</td>
<td>113.54 (13.79)</td>
<td>108.86 (21.57)</td>
<td>107.91 (15.91)</td>
</tr>
<tr>
<td>RV/TLC% (Mean ±SD)</td>
<td>29.14 (5.10)</td>
<td>32.42 (5.99)</td>
<td>31.68 (7.24)</td>
<td>40.15 (8.52)#</td>
</tr>
</tbody>
</table>

Half of the patients were classified as group D with very few patients in Group C. There was also a difference in sex distribution in the two high symptom groups B and D with a greater proportion of males in Group D than Group B (2p<0.0001) where the ratio was reversed.

By classification, group C and D had the worst spirometry (FEV1 and FEV1/FVC ratio). However the same was not true for other lung physiology and although gas transfer was lowest in Group D (2p<0.0001) and highest (although still impaired) in Group A (2p<0.0001),
groups B and C had comparable values. Group D also had the most air trapping ($2p<0.0001$) compared to other groups determined by the residual volume and RV/TLC ratio although data from the other three groups were comparable. These physiological differences were reflected in the more comprehensive health status SGRQ scores for both the total and individual domain scores with the worst values seen in Group D ($2p<0.0001$) but also reflecting the high symptoms of Group B. Group C, although small, had a worse health status than Group A ($2p\leq0.016$ for total score, activities and impact domain scores) despite similar CAT scores. A similar pattern was also seen for the mMRC scores ($2p\leq0.006$) and exacerbation frequency ($2p\leq0.012$) with patients in Group D being the most affected and with an average history of nearly 3 exacerbations in the previous year.

**CAT 10 EXACERBATION**

Fig 3.2 displays the patient distribution using exacerbation history for risk assessment and CAT for symptom assessment. When the groups were defined by the proposed CAT threshold and exacerbation history, differences were observed compared to CAT spirometry classification (see Table 3.3).
Figure 3.2  Patient distribution according to CAT (10) and Exacerbation
(With number in each group and % of total in parentheses)
### Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>A (n=18, 5.7%)</th>
<th>B (n=121, 40.6%)</th>
<th>C (n=8, 2.7%)</th>
<th>D (n=151, 51%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Male N (%)</td>
<td>14 (78%)</td>
<td>83 (69%)</td>
<td>5 (63%)</td>
<td>76 (50%)</td>
</tr>
<tr>
<td>Female N (%)</td>
<td>4 (22%)</td>
<td>38 (31%)</td>
<td>3 (37%)</td>
<td>75 (50%)</td>
</tr>
<tr>
<td>Age (yrs.) (Mean ±SD)</td>
<td>58.39 (8.47)</td>
<td>59.28 (10.69)</td>
<td>53.50 (9.87)</td>
<td>56.85 (9.32)</td>
</tr>
<tr>
<td>mMRC</td>
<td>≤1</td>
<td>≥2</td>
<td>(Mean ±SD)</td>
<td>13</td>
</tr>
<tr>
<td>(Mean ±SD)</td>
<td>05</td>
<td>39</td>
<td>82</td>
<td>19</td>
</tr>
<tr>
<td>EXACERBATIONS</td>
<td>≤1</td>
<td>≥2</td>
<td>(Mean ±SD)</td>
<td>18</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td>0.39 (0.49)</td>
<td>0.61 (0.49)</td>
<td>3.00 (1.94)</td>
<td>3.26 (1.88)</td>
</tr>
<tr>
<td>CAT (Mean ±SD)</td>
<td>6.56 (1.74)</td>
<td>18.71 (5.90)</td>
<td>7.13 (1.62)</td>
<td>24.17 (7.01)</td>
</tr>
</tbody>
</table>

### SGRQ

- Total (Mean ±SD)
  - A: 17.17 (9.25)
  - B: 46.07 (16.27)
  - C: 28.63 (9.77)
  - D: 59.63 (16.59)
- Symptom (Mean ±SD)
  - A: 21.00 (12.80)
  - B: 51.63 (20.14)
  - C: 42.25 (11.01)
  - D: 71.44 (18.07)
- Activity (Mean ±SD)
  - A: 26.11 (16.81)
  - B: 63.26 (21.44)
  - C: 43.50 (15.48)
  - D: 76.93 (19.37)
- Impact (Mean ±SD)
  - A: 12.61 (7.83)
  - B: 34.82 (17.27)
  - C: 15.63 (11.58)
  - D: 45.20 (18.00)

### FEV1

- L/min (Mean ±SD)
  - A: 2.67 (0.83)
  - B: 1.61 (0.67)
  - C: 1.68 (0.78)
  - D: 1.33 (0.57)
- % predicted (Mean ±SD)
  - A: 84.44 (28.12)*
  - B: 53.75 (22.37)
  - C: 53.25 (16.79)
  - D: 48.13 (23.45)£

### FEV1/FVC

- Mean ±SD
  - A: 0.52 (0.13)
  - B: 0.37 (0.12)
  - C: 0.41 (0.14)
  - D: 0.36 (0.12)

### Kco

- % predicted (Mean ±SD)
  - A: 69.72 (12.78)
  - B: 56.91 (16.56)
  - C: 67.25 (16.73)
  - D: 55.15 (16.28)£

### RV

- % predicted (Mean ±SD)
  - A: 98.17 (23.39)
  - B: 111.91 (26.39)
  - C: 109.75 (37.97)
  - D: 119.52 (36.17)

### TLC

- % predicted (Mean ±SD)
  - A: 114.56 (14.75)
  - B: 111.97 (14.61)
  - C: 108.88 (15.96)
  - D: 109.35 (15.93)

### RV/TLC%

- (Mean ±SD)
  - A: 28.95 (3.86)
  - B: 35.02 (7.24)
  - C: 33.83 (8.10)
  - D: 38.14 (9.18)

### Table 3.3 Patient demographics for the four groups defined by CAT and exacerbation frequency

# 2p<0.0001 compared to groups B and A
£ 2p≤ 0.05 compared to the other groups
* 2p<0.0079 compared to the other groups

In general, the groups followed the same pattern as for the spirometric classification although by definition, the exacerbation frequency was highest in Groups C and D (2p<0.0001). Most of the patients were in Group D with very few patients in Group C.

The average FEV1 (% predicted) was significantly higher in group A (2p ≤ 0.0079) than the other three groups and Group D was lowest on average (2p≤0.046 compared to groups A and B). A similar distribution was seen for air trapping.
However gas transfer showed a different distribution with lowest average values in the highest symptom groups D (2p ≤ 0.05 compared to the other groups) and B (2p=0.0021 with group A) whilst being comparable in groups A and C. This was reflected in the results for total and individual domains for the SGRQ which were comparable to the values for these groups when classified by spirometry.

mMRC SPIROMETRY
Patient distribution according to mMRC and spirometry for symptom risk assessment are shown in Fig 3.3. Table 3.4 summarises the patient distribution and demographics into the four groups using the proposed mMRC symptom threshold and spirometric classification as risk. Half of the patients were classified as group D and only a minority (5%) as group C patients, all of whom were male and were on average, the youngest group, though only significantly younger than Group B (2p=0.0014).
Figure 3.3  Patient distribution according to mMRC and Spirometry

(With number in each group and % of total in parentheses)
<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>A (n=61, 20.33%)</th>
<th>B (n=74, 24.66%)</th>
<th>C (n=15, 5%)</th>
<th>D (n=150, 50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male N (%)</td>
<td>31 (51%)</td>
<td>36 (49%)</td>
<td>15 (100%)</td>
<td>98 (66%)</td>
</tr>
<tr>
<td>Female N (%)</td>
<td>30 (49%)</td>
<td>38 (51%)</td>
<td>0 (0%)</td>
<td>52 (34%)</td>
</tr>
<tr>
<td>Age (yrs.) (Mean ±SD)</td>
<td>58.67 (±10.20)</td>
<td>61.61 (±8.47)</td>
<td>5.27 (±11.00)#</td>
<td>56.55 (±9.78)</td>
</tr>
<tr>
<td>mMRC ≤1 (Mean ±SD)</td>
<td>61</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>mMRC ≥2 (Mean ±SD)</td>
<td>0.69 (±0.46)</td>
<td>2.57 (±0.70)</td>
<td>0.87 (±0.34)</td>
<td>3.01 (±0.77)</td>
</tr>
<tr>
<td>EXACERBATIONS ≤1 (Mean ± SD)</td>
<td>43</td>
<td>33</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>EXACERBATIONS ≥2 (Mean ±SD)</td>
<td>1.03 (±1.15)</td>
<td>1.92 (±1.70)</td>
<td>1.73 (±1.95)</td>
<td>2.41 (±2.05)</td>
</tr>
<tr>
<td>CAT (Mean ± SD)</td>
<td>13.08 (±5.18)</td>
<td>21.19 (±7.63)</td>
<td>15.53 (±6.55)</td>
<td>23.78 (±7.04)</td>
</tr>
<tr>
<td>SGRQ TOTAL (Mean ± SD)</td>
<td>29.11 (±14.13)#</td>
<td>52.05 (±16.34)#</td>
<td>39.64 (±16.79)</td>
<td>60.36 (±15.16)</td>
</tr>
<tr>
<td>SGRQ SYMPTOMS (Mean ± SD)</td>
<td>38.43 (±20.18)</td>
<td>60.66 (±20.04)</td>
<td>51.71 (±21.93)</td>
<td>69.19 (±19.77)</td>
</tr>
<tr>
<td>SGRQ ACTIVITIES (Mean ±SD)</td>
<td>41.36 (±22.85)</td>
<td>69.06 (±18.78)</td>
<td>55.50 (±16.77)</td>
<td>79.09 (±16.75)</td>
</tr>
<tr>
<td>SGRQ IMPACT (Mean ± SD)</td>
<td>19.41 (±11.50)</td>
<td>39.95 (±17.14)</td>
<td>27.57 (±18.26)</td>
<td>46.16 (±17.26)</td>
</tr>
<tr>
<td>FEV1 L/min (Mean ±SD)</td>
<td>2.33 (±0.73)</td>
<td>1.87 (±0.58)</td>
<td>1.52 (±0.31)</td>
<td>1.05 (±0.32)</td>
</tr>
<tr>
<td>FEV1 % predicted (Mean ±SD)</td>
<td>82.25 (±22.99)*</td>
<td>67.88 (±17.25)</td>
<td>42.07 (±5.93)</td>
<td>34.47 (±8.84)</td>
</tr>
<tr>
<td>FEV1/FVC (Mean ±SD)</td>
<td>0.51 (±0.11)</td>
<td>0.44 (±0.11)</td>
<td>0.31 (±0.06)</td>
<td>0.29 (±0.08)</td>
</tr>
<tr>
<td>Kco % predicted (Mean ± SD)</td>
<td>66.28 (±16.58)</td>
<td>57.07 (±15.30)</td>
<td>65.67 (±17.24)</td>
<td>51.82 (±14.96)</td>
</tr>
<tr>
<td>RV % predicted (Mean ±SD)</td>
<td>101.54 (±22.78)</td>
<td>99.47 (±23.89)</td>
<td>112.67 (±27.02)</td>
<td>128.36 (±34.18)</td>
</tr>
<tr>
<td>TLC % predicted (Mean ±SD)</td>
<td>115.56 (±12.84)</td>
<td>111.68 (±14.32)</td>
<td>110.80 (±16.08)</td>
<td>107.65 (±16.30)</td>
</tr>
<tr>
<td>RV/TLC% (Mean ±SD)</td>
<td>31.20 (±5.51)</td>
<td>32.67 (±6.01)</td>
<td>32.21 (±5.56)</td>
<td>40.76 (±8.46)</td>
</tr>
</tbody>
</table>

Table 3.4 Patient demographics for the four groups defined by mMRC symptom score and spirometry

# 2p = 0.0014 compared to Group B

* 2p<0.05 compared to respective groups characterised by CAT and spirometry

£ 2p≤0.0093 compared to respective groups characterised by CAT and spirometry

Although the proportion of patients categorised into Groups D or C using mMRC and spirometry were similar to that defined by CAT and spirometry, there were significant differences with more patients classified as groups A and B (2p <0.002) when defined by mMRC.
There were general similarities in the average physiological data compared to those seen using CAT for symptom assessment and spirometry. However, minor but significant differences were observed in the average values for FEV1 in group A which was higher using CAT (2p<0.05). Although the average values for gas transfer, which were higher in groups A and B using CAT, were not significantly different using mMRC, the average Total SGRQ scores were higher using the mMRC classification and significantly different in Groups A and B (2p ≤0.0093) but not Groups C and D.

mMRC EXACERBATION

Table 3.5 summarises the patient distribution and demographics into the four groups using the proposed mMRC symptom threshold and frequency of exacerbations as risk. The distribution of patients in the four groups (Fig 3.4) did not differ significantly from those using mMRC and spirometry for symptom risk assessment (2p>0.05).
Classification using mMRC and exacerbation history however also produced differences to that using spirometry with lower FEV1 and FEV1/FVC ratio in Group B (2p<0.0001) and higher values in Group D (2p<0.0001) although gas transfer and air trapping data were similar. Nevertheless there was still a difference in distribution compared to the CAT/exacerbation groupings and this was reflected in the SGRQ values for groups A and B (2p≤0.019 for total and individual domains in Group A and 2p ≤0.033 for total and activities domains in Group B) although comparable for groups C and D (see Table 3.5).
<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>A (n=52, 17.68%)</th>
<th>B (n=85, 28.91%)</th>
<th>C (n=22, 7.48%)</th>
<th>D (n=135, 45.91%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Male N (%)</td>
<td>35 (62%)</td>
<td>61 (72%)</td>
<td>10 (46%)</td>
<td>71 (53%)</td>
</tr>
<tr>
<td>Sex Female N (%)</td>
<td>17 (38%)</td>
<td>24 (28%)</td>
<td>12 (54%)</td>
<td>64 (47%)</td>
</tr>
<tr>
<td>Age (yrs. (Mean ±SD)</td>
<td>57.33 (±10.70)</td>
<td>60.62 (±9.95)</td>
<td>57.50 (±10.33)</td>
<td>56.66 (±9.22)</td>
</tr>
<tr>
<td>mMRC ≤1</td>
<td>52</td>
<td>0</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>mMRC ≥2</td>
<td>0.65 (0.48)</td>
<td>85</td>
<td>0.86 (0.34)</td>
<td>135</td>
</tr>
<tr>
<td>EXACERBATIONS ≤1</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>2.94 (0.80)</td>
</tr>
<tr>
<td>EXACERBATIONS ≥2</td>
<td>0.54 (0.50)</td>
<td>0.61 (0.49)</td>
<td>2.68 (1.61)</td>
<td>2.38 (1.83)#</td>
</tr>
<tr>
<td>CAT (Mean ± SD)</td>
<td>12.85 (4.81)</td>
<td>19.87 (6.63)</td>
<td>14.64 (6.36)</td>
<td>24.70 (±7.09)</td>
</tr>
<tr>
<td>SGRQ TOTAL (Mean ±SD)</td>
<td>29.02 (15.03)</td>
<td>50.84 (14.88)</td>
<td>35.77 (14.73)</td>
<td>61.58 (15.36)</td>
</tr>
<tr>
<td>SGRQ SYMPTOMS (Mean ±SD)</td>
<td>35.32 (18.84)</td>
<td>55.51 (20.22)</td>
<td>53.95 (20.43)</td>
<td>72.74 (17.32)</td>
</tr>
<tr>
<td>SGRQ ACTIVITIES (Mean ±SD)</td>
<td>41.37 (22.86)</td>
<td>69.62 (17.78)</td>
<td>50.00 (21.13)</td>
<td>79.23 (17.36)</td>
</tr>
<tr>
<td>SGRQ IMPACT (Mean ±SD)</td>
<td>20.49 (13.09)</td>
<td>39.15 (16.95)</td>
<td>21.82 (14.25)</td>
<td>47.06 (17.07)</td>
</tr>
<tr>
<td>FEV1 L/min ( Mean ±SD)</td>
<td>2.30 (0.75)</td>
<td>1.40 (0.58)*</td>
<td>1.80 (0.55)</td>
<td>1.27 (0.56)£</td>
</tr>
<tr>
<td>FEV1 % predicted (Mean ±SD)</td>
<td>76.19 (26.03)</td>
<td>46.42 (17.25)*</td>
<td>67.73 (25.74)$</td>
<td>44.79 (20.82)£</td>
</tr>
<tr>
<td>FEV1/FVC (Mean ±SD)</td>
<td>0.48 (0.13)</td>
<td>0.33 (0.11)</td>
<td>0.43 (0.12)</td>
<td>0.35 (0.12)</td>
</tr>
<tr>
<td>Kco % predicted (Mean ±SD)</td>
<td>65.73 (15.58)</td>
<td>53.82 (15.50)</td>
<td>67.50 (19.69)</td>
<td>53.69 (15.23)</td>
</tr>
<tr>
<td>RV % predicted (Mean ±SD)</td>
<td>106.94 (24.35)</td>
<td>112.00 (27.72)</td>
<td>96.95 (22.86)</td>
<td>123.34 (36.79)</td>
</tr>
<tr>
<td>TLC % predicted (Mean ±SD)</td>
<td>115.79 (13.71)</td>
<td>110.00 (14.96)</td>
<td>112.00 (13.82)</td>
<td>108.62 (16.23)</td>
</tr>
<tr>
<td>RV/TLC% ( Mean ±SD)</td>
<td>31.58 (5.42)</td>
<td>36.04 (7.66)</td>
<td>30.91 (5.82)</td>
<td>39.34 (8.97)</td>
</tr>
</tbody>
</table>

Table 3.5 Patient demographics for the four groups defined by mMRC symptom score and exacerbation frequency

* 2p<0.0001 compared to Group B characterised by mMRC and spirometry
£ 2p<0.0001 compared to Group D characterised by mMRC and spirometry
$ 2p<0.0001 between groups C and D
# 2p<0.0001 compared to groups A and B

With mMRC to define symptoms and exacerbation frequency to determine risk, groups C and D, as expected, had the highest exacerbation history and was greatest in Group D (2p<0.0001 compared to groups A and B). The spirometry showed a different pattern which although lower in the patients with greatest symptoms, was significantly different (2p<0.0001) between those patients in groups C and D indicating that spirometry alone is not
a major determinant of exacerbation frequency. Nevertheless the remaining physiology showed a similar distribution for gas transfer and air trapping compared to the mMRC group defined by spirometry.

Although similar patterns are seen for the demographics between CAT and mMRC, it is clear that differences occur. This suggests that the two scoring systems provide different information. Nevertheless health status assessed by SGRQ and symptoms assessed by CAT were similar in the four groups to those seen when risk was assessed by spirometry suggesting a closer relationship between these two methods of assessing symptoms.

3.2 To validate the proposed thresholds for CAT and mMRC in AATD

Although there is a significant correlation between the average CAT scores and mMRC values 1-5 (Figure 3.5), there is clearly a difference between mMRC 0 and 1. Tables 3.4 and 3.5 also show that the average CAT scores in the low symptom groups defined by mMRC scores 0 and 1 range from 12.8 to 15.5. This observation together with differences in demographic data using the CAT score of 10 to define low and high symptom groups, compared to mMRC ≥2, suggest that the cut-off point of 10 does not give comparable data and hence the initial patient management will differ in some patients depending on which symptom scoring system is used.
Figure 3.5 Average CAT scores for each mMRC score

(± SE)

*indicates a significant difference in CAT score for mMRC 1 compared to mMRC 0. (2p=0.006)

We therefore explored the use of different CAT thresholds to define symptoms and compared the data again to that obtained using mMRC 0-1 and ≥2 to define low and high symptoms (Table 3.6). Analysis demonstrated that the use of CAT thresholds between 12 and 15 reduced the demographic differences and the optimal threshold of 13 provided statistically similar distribution and demographic data to that obtained with the mMRC 0-1/≥2 threshold.
Using CAT 13 as symptom threshold and spirometry for risk resulted in a distribution of patients which was similar using CAT and/or mMRC and spirometry and/or exacerbation history for risk. The full demographic tables using CAT 13 as the symptom threshold are shown for spirometry (Table 3.7) and exacerbation history as the risk respectively (Table 3.8). There were no statistical differences in the demographic data for these tables compared to those for mMRC (Tables 3.4 and 3.5).

**CAT 13 SPIROMETRY**

Fig 3.6 shows the patient distribution and Table 3.7 summarises the demographics in the four groups using CAT 13 as symptom threshold and spirometric classification as risk. Maximum numbers of patients were still seen in Group D but more patients were distributed in the groups A, B and C compared to CAT 10 as the threshold for symptoms.
Figure 3.6 Patient distribution according to CAT 13 and Spirometry

(With number per group and % of total in parentheses)
Health status as measured by the SGRQ was worse in Groups B and D as expected. The mean FEV1 % predicted was lowest in Group D and highest in Group A. A similar pattern was observed for gas transfer. Highest proportion of air trapping was also observed in Group D.

Compared to CAT 10 spirometry, the mean FEV1 % predicted did not differ significantly between the groups (2p>0.05). Mean FEV1 % predicted in Group A was 89.11 using CAT 10 and 82.34 using CAT 13 and it was 35.03 and 34.83 in Group D using CAT 10 and CAT 13 respectively. However, using mMRC spirometry, it was 82.25 and 34.47 in Groups A and D, closer to CAT 13 than CAT 10 at least for Group A.
The mean Kco % predicted also did not differ significantly between the groups (2p>0.05). Mean Kco % predicted was 71.05 and 69.96 in Group A and 52.98 and 52.49 in Group D using CAT 10 and CAT 13 respectively. The values for Kco % predicted using mMRC spirometry were closer to CAT 13 (66.28 and 51.82 in Groups A and D respectively), once again in Group A than CAT 10.

The comparison of demographics and mean FEV1 % between the different assessment methods has been discussed later in this chapter. The graphical representation of these comparisons has also been performed in the same section (Fig 3.8, 3.9, 3.10, 3.11).

**CAT 13 EXACERBATION**

The patient distribution into the four groups using CAT 13 as symptom threshold and exacerbation frequency as risk is shown in Fig 3.7 and Table 3.8 summarises patient demographics in the four groups. Most patients were still in Group D with more number of patients in the other groups compared to CAT 10 as a threshold.
Figure 3.7 Patient distribution according to CAT (13) and Exacerbation
(With number per group and % of total in parentheses)
<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>A (n= 40, 13.42%)</th>
<th>B (n=99, 33.22%)</th>
<th>C (n= 19, 6.38%)</th>
<th>D (n= 140, 46.97%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (68%)</td>
<td>71 (71%)</td>
<td>09 (47%)</td>
<td>72 (51%)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (32%)</td>
<td>28 (29%)</td>
<td>10 (53%)</td>
<td>68 (49%)</td>
</tr>
<tr>
<td>Age (yrs.) (Mean ±SD)</td>
<td>57.03 (9.29)</td>
<td>59.68 (10.84)</td>
<td>55.74 (10.50)</td>
<td>56.81 (9.21)</td>
</tr>
<tr>
<td>mMRC ≤1</td>
<td>26 (1.08)</td>
<td>26 (1.11)</td>
<td>12 (0.64)</td>
<td>10 (0.93)</td>
</tr>
<tr>
<td>mMRC ≥2</td>
<td>13 (1.26)</td>
<td>72 (2.24)</td>
<td>07 (2.84)</td>
<td>128 (1.40)</td>
</tr>
<tr>
<td>EXACERBATIONS  ≤1</td>
<td>40 (0.44)</td>
<td>99 (0.63)</td>
<td>0 (2.84)</td>
<td>0 (3.31)</td>
</tr>
<tr>
<td>EXACERBATIONS  ≥2</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>19 (2.84)</td>
<td>140 (3.31)</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAT (Mean ± SD)</td>
<td>9.13 (2.81)</td>
<td>20.37 (5.21)</td>
<td>9.53 (2.41)</td>
<td>25.19 (6.23)</td>
</tr>
<tr>
<td>SGRQ TOTAL</td>
<td>24.25 (10.23)</td>
<td>50.25 (14.42)</td>
<td>28.21 (9.08)</td>
<td>62.14 (14.33)</td>
</tr>
<tr>
<td>SGRQ SYMPTOMS</td>
<td>28.03 (17.02)</td>
<td>55.34 (18.37)</td>
<td>43.21 (14.70)</td>
<td>73.62 (16.28)</td>
</tr>
<tr>
<td>SGRQ ACTIVITIES</td>
<td>40.41 (18.52)</td>
<td>67.24 (19.22)</td>
<td>40.00 (16.43)</td>
<td>80.06 (15.80)</td>
</tr>
<tr>
<td>SGRQ IMPACT</td>
<td>15.28 (7.06)</td>
<td>38.77 (16.26)</td>
<td>16.74 (9.12)</td>
<td>47.39 (16.76)</td>
</tr>
<tr>
<td>FEV1 L/min</td>
<td>2.19 (0.78)</td>
<td>1.52 (0.61)</td>
<td>1.83 (0.76)</td>
<td>1.29 (0.53)</td>
</tr>
<tr>
<td>FEV1 % predicted (Mean ±SD)</td>
<td>71.41 (24.35)</td>
<td>50.68 (21.00)</td>
<td>64.32 (24.32)</td>
<td>46.23 (22.16)</td>
</tr>
<tr>
<td>FEV1/FVC (Mean ±SD)</td>
<td>0.46 (0.13)</td>
<td>0.35 (0.11)</td>
<td>0.45 (0.14)</td>
<td>0.35 (0.11)</td>
</tr>
<tr>
<td>Kco % predicted (Mean ±SD)</td>
<td>65.84 (15.37)</td>
<td>55.20 (16.14)</td>
<td>70.95 (13.52)</td>
<td>53.60 (15.89)</td>
</tr>
<tr>
<td>RV % predicted (Mean ±SD)</td>
<td>99.09 (21.93)</td>
<td>114.62 (27.06)</td>
<td>99.37 (28.53)</td>
<td>121.83 (36.47)</td>
</tr>
<tr>
<td>TLC % predicted (Mean ±SD)</td>
<td>113.16 (13.31)</td>
<td>111.79 (14.94)</td>
<td>106.84 (913.46)</td>
<td>109.68 (16.23)</td>
</tr>
<tr>
<td>RV/TLC% ( Mean ±SD)</td>
<td>30.04 (4.77)</td>
<td>35.89 (7.28)</td>
<td>32.53 (6.94)</td>
<td>38.68 (9.20)</td>
</tr>
</tbody>
</table>

Table 3.8 Patient demographics for the four groups defined by CAT 13 and exacerbation history

Health status as measured by the SGRQ was worse in Groups B and D as expected. The mean FEV1 % predicted was low in Groups B and D compared to Groups A and C (2p<0.05). A similar pattern was observed for gas transfer and is related to the higher frequency of exacerbation seen in Groups B and D. This is different to the data seen using spirometry for risk assessment where the mean FEV1% predicted and the mean Kco % predicted got progressively worse from Groups A to D.
CAT 10 vs mMRC vs CAT 13

Figure 3.8 shows the proportion of patients distributed in the 4 classification groups using the mMRC 0-1 and CAT 10 or CAT 13 threshold for spirometric (Fig 3.8) and exacerbation risk (Fig 3.9). The differences in distribution are summarised in Figures 3.8 and 3.9.

Figure 3.8  Proportion of patients (%) categorised into each of the four groups using CAT 10, mMRC and CAT 13 for symptom assessment respectively and spirometry as risk.

* indicates significant difference compared to mMRC (2p<0.002)
Figure 3.9 Proportion of patients (%) categorised into each of the four groups using CAT 10, mMRC and CAT 13 for symptom assessment respectively and exacerbation history as risk.

* indicates significant difference compared to mMRC ($2p = 0.007$)
Figures 3.10 and 3.11 summarise the average FEV1 % predicted (± SE) for the three symptom thresholds using spirometry (Fig 3.10) and exacerbation history (Fig 3.11) as the risk. Whereas data for group D are similar using all methods, changing the CAT threshold to 13 produced more comparable values for patients to mMRC especially for groups A and B compared to CAT 10 and no significant differences in spirometry or other demographics remained (Tables 3.2 to 3.5, 3.7 and 3.8).

**Figure 3.10** Average FEV1% predicted (±SE bar) in each group classified by CAT 10, CAT 13 and mMRC with spirometry as risk.

* indicates a significant difference 2p<0.05 compared to respective group characterised by mMRC and spirometry.
Figure 3.11 Average FEV1% predicted (±SE bar) in each group classified by CAT 10, CAT 13 and mMRC with Exacerbation as risk.

* indicates a significant difference 2p<0.0001 compared to respective group characterised by mMRC and spirometry.
COMBINED RISK

The GOLD strategy advocates using the highest risk according to spirometry or exacerbation history to determine initial treatment. Patients were categorised according to the highest risk using CAT 10, CAT 13 and mMRC for symptom assessment.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>CAT 10</th>
<th>mMRC</th>
<th>CAT 13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>A</td>
<td>14</td>
<td>4.69</td>
<td>43**</td>
</tr>
<tr>
<td>B</td>
<td>62</td>
<td>20.80</td>
<td>33**</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>4.02</td>
<td>31**</td>
</tr>
<tr>
<td>D</td>
<td>210</td>
<td>70.46</td>
<td>187**</td>
</tr>
<tr>
<td>MISSING</td>
<td>11</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>TOTAL</td>
<td>309</td>
<td></td>
<td>309</td>
</tr>
</tbody>
</table>

Table 3.9  Distribution of patients taking into account highest risk according to GOLD or Exacerbation history using a CAT threshold of either 10 or 13 and mMRC 0-1

** 2p=0.0001 compared to CAT 10; *2p= 0.0014 compared to CAT 10; there was no significant difference between CAT 13 and mMRC.

Categorising the patients using the highest risk whether determined by spirometry or exacerbation history, resulted in more patients in Group D using both CAT and mMRC. However there remained a significant difference in the distribution using these symptom scores. This difference was no longer present when a CAT threshold of 13 was used. (Table 3.9)
4 Results - Part 2

The 2011 update of the GOLD document on COPD introduced the concept of categorising patients based on symptoms measured by CAT or mMRC scores and risk estimated by spirometry and/or exacerbation frequency (1). This practice has been validated in AATD comparing both the mMRC and CAT thresholds proposed (Chapter 3) (293). The risk group may change dependent on the method of categorisation chosen – for instance someone could be low risk based on lung function, but high risk based on their exacerbation frequency. The aim of stratifying patients is to initiate relevant treatment to reduce risk and/or symptoms and the strategy makes therapeutic recommendations based on this categorisation. However it remains to be determined if it has the ability to identify successfully subjects or groups of subjects who are at increased risk of worsening of lung function and mortality for whom more aggressive treatment regimen might be appropriate. A recent study in individuals with COPD showed that the GOLD stratification performed well in identifying individuals at risk of exacerbations and possibly death (270) although there has been insufficient time to use the proposed symptom parameters to quantify this accurately. Furthermore there are no data published currently regarding the ability of this strategy in predicting long term outcomes in usual COPD or COPD related to AATD.

Various clinical and physiologic factors including FEV1, Kco (carbon monoxide transfer progression in AATD is reflected in decline in FEV1 and gas transfer and also by the extent of emphysema on HRCT (269). Progression of emphysema occurs at a faster rate in AATD than in usual COPD (239) and the presence of emphysema has been associated with rapid decline in FEV1 in usual COPD (294). Frequency of exacerbations also influences decline in lung function in both usual COPD (129) and AATD (243). Identifying patients who are at risk of rapid progression of disease would help to target them for more aggressive therapeutic
options, early preventative interventions and help enrichment of patient phenotypes for relevant clinical trials. This is particularly important as some therapies have been shown overall to lessen the decline in FEV1 in COPD (159, 295) and AATD (296) although there have been few studies to identify patients most likely to respond.

The UK registry of patients with AATD offers a unique opportunity to investigate the relationship of clinical and physiological features to outcomes. Importantly mMRC has been documented in all patients throughout the duration of the programme providing data for long term outcomes, especially mortality.

4.1 Aim

The aim of the current study was to document the predictive potential of the new GOLD strategy with regard to mortality, lung function decline and exacerbation in a group of patients with AATD, prospectively followed for up to 15 years and, importantly, who have never received augmentation therapy.

4.2 Methods

Subjects
The details of patient assessment, questionnaires completed and the tests performed at each annual visit as part of ADAPT have been described in chapter 2.

Outcomes
The details of the lung function tests performed, collection of mortality data and exacerbation history have been described previously in Chapter 2.

Data analysis
Details of the statistical analysis of data have been described in Chapter 2.
### 4.3 Results

Table 4.1 summarises the patient distribution in the four categories using the highest risk and their general characteristics.

339 subjects were males and 193 were females. Mean age was 53.68 years. Most individuals were index cases (88.8%) and the largest proportion met the criteria for the more severe group D (n=280, 55.78%). 367 patients (73.11%) were ex-smokers while 40 (7.97%) were current smokers at the time of data collection. For the patients as a whole the mean mMRC score was 2.20; SD ± 1.14 with the mean annual exacerbations being 1.79; SD ± 2.07. Median follow up was 9 years, with a range of 3 to 15.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>502</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>53.68 ± 9.53</td>
</tr>
<tr>
<td>Sex Males</td>
<td>309 (61.55%)</td>
</tr>
<tr>
<td>Females</td>
<td>193 (38.45%)</td>
</tr>
<tr>
<td>mMRC</td>
<td>2.20 ± 1.14</td>
</tr>
<tr>
<td>Exacerbations/year</td>
<td>1.79 ± 2.07</td>
</tr>
<tr>
<td>BMI</td>
<td>25.56 ± 4.84</td>
</tr>
<tr>
<td>Status</td>
<td></td>
</tr>
<tr>
<td>Index</td>
<td>446 (88.84%)</td>
</tr>
<tr>
<td>Non Index</td>
<td>56 (11.16%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>95 (18.92%)</td>
</tr>
<tr>
<td>Ex</td>
<td>367 (73.11%)</td>
</tr>
<tr>
<td>Current</td>
<td>40 (7.97%)</td>
</tr>
<tr>
<td>Combined Risk Groups- GOLD 2011</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>(%)</td>
</tr>
<tr>
<td>A</td>
<td>81 (16.10%)</td>
</tr>
<tr>
<td>B</td>
<td>58 (11.53%)</td>
</tr>
<tr>
<td>C</td>
<td>83 (16.50%)</td>
</tr>
<tr>
<td>D</td>
<td>280 (55.78%)</td>
</tr>
</tbody>
</table>

**Table 4.1 Distribution of patients according to the GOLD 2011 combined risk assessment method and their baseline characteristics**

Data are presented as number (%) and mean ± SD
4.3.1 Mortality

There had been 118 deaths in the cohort by the time of analysis and the majority (94; 79.66%) occurred in patients in the high symptom high risk group D. Groups A, B and C had 6 (5.08%), 7 (5.93%) and 11 (9.32%) deaths respectively (Fig 4.1).

![Combined Risk - Mortality Distribution](image)

**Figure 4.1 Mortality distribution in the four groups**

The Kaplan Meier plot of the groups for all-cause mortality is shown in Fig 4.2. The survival in Group A (least symptoms and lowest risk) was significantly better than Group D (more symptoms and high risk) (2p=0.0001) as was the survival in groups B and C compared with group D (2p = 0.002 and 0.001 respectively). There was considerable overlap in the
confidence intervals in Groups A, B and C, with no overall difference in the survival time. The results are summarised in Table 4.2.

Figure 4.2 Kaplan-Meier all cause survival plot according to the symptom risk assessment groups.

2p=0.0001 between Groups A and D. See also Table 4.2
Hazard ratios (HR) with confidence intervals (CI) are shown for each of the variables used in mortality analysis, and are for each parameter in isolation rather than additively. Significant contributors are shown (p value) in bold. This shows a higher HR (i.e. risk of death) in older patients and lower HR in never smokers. Risk of death goes up with each increment added of combined risk, such that overall an increase in risk by 1 unit (from A to B, B to C and so on) results in a HR of 1.861. If each individual risk group is compared to the highest risk group (D) progressive reductions in risk of death are seen.

Cox Regression analysis revealed that age (2p=0.0001), FEV1 GOLD stage (2p=0.0001), Kco (2p=0.0001) and the GOLD group assignment (2p=0.0001) were significant factors related to mortality whereas sex and smoking status were not (2p>0.05) after adjusting for confounding variables (Table 4.2). Among FEV1 GOLD stages, those in stage 3 (2p= 0.007) and 4 (2p= 0.003) had worse survival compared to those in stage 1. Age and group assignment continued to remain significant even after adjusting for sex and smoking status (2p<0.05). After adjusting for age and Kco, patients in Group D still had a significantly poorer outcome (2p = 0.007).

Table 4.2  Multivariate analyses for mortality

<table>
<thead>
<tr>
<th>variable</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>2p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.050 (1.030-1.071)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex (males vs. females)</td>
<td>1.047 (0.719-1.524)</td>
<td>0.811</td>
</tr>
<tr>
<td>Combined risk Groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A vs. D</td>
<td>1.861 (1.465-2.364)</td>
<td>0.0001</td>
</tr>
<tr>
<td>B vs. D</td>
<td>0.202 (0.088-0.461)</td>
<td>0.0001</td>
</tr>
<tr>
<td>C vs. D</td>
<td>0.294 (0.136-0.635)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>0.346 (0.185-0.646)</td>
<td>0.001</td>
</tr>
<tr>
<td>Kco</td>
<td>0.263 (0.142-0.487)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEVER vs. EX</td>
<td>0.737 (0.503-1.080)</td>
<td>0.230</td>
</tr>
<tr>
<td></td>
<td>0.424 (0.525-1.420)</td>
<td>0.088</td>
</tr>
</tbody>
</table>
4.3.2 FEV1 Decline

For the patients as a whole, the mean decline in FEV1 was 50.04; SD ±58.76 ml/year. When categorised into the groups based on combined risk, the fastest mean decline in FEV1 occurred in Group A (Fig 4.3). These results are summarised in table 4.3. The table shows the demographics and degree of lung function decline in each of the GOLD groupings.

The decline in FEV1 was significantly different between groups A and D ($2p=0.002$) and between groups C and D ($2p=0.012$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>A n = 78</th>
<th>B n = 55</th>
<th>C n = 77</th>
<th>D n = 226</th>
<th>A n = 77</th>
<th>B n = 51</th>
<th>C n = 71</th>
<th>D n = 217</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, N (%)</td>
<td>50 (64.10%)</td>
<td>29 (52.72%)</td>
<td>58 (75.32%)</td>
<td>128 (56.64%)</td>
<td>50 (64.94%)</td>
<td>26 (50.98%)</td>
<td>54 (76.06%)</td>
<td>128 (58.99%)</td>
</tr>
<tr>
<td>Age in years</td>
<td>54.80 (10.20)</td>
<td>54.15 (10.45)</td>
<td>49.71 (9.26)</td>
<td>52.24 (8.80)</td>
<td>54.95 (10.27)</td>
<td>53.60 (10.20)</td>
<td>49.83 (9.03)</td>
<td>52.14 (8.87)</td>
</tr>
<tr>
<td>Smoking status, n</td>
<td>44</td>
<td>43</td>
<td>43</td>
<td>43</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Never</td>
<td>04</td>
<td>02</td>
<td>03</td>
<td>21</td>
<td>04</td>
<td>02</td>
<td>03</td>
<td>18</td>
</tr>
<tr>
<td>Ex</td>
<td>-66.59* (61.39)</td>
<td>-53.00 (47.09)</td>
<td>-56.96** (48.87)</td>
<td>-41.24 (62.09)</td>
<td>-0.021# (0.028)</td>
<td>-0.022 (0.030)</td>
<td>-0.032 (0.031)</td>
<td>-0.031 (0.031)</td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.3 Univariate analysis comparing the groups for decline in lung function

*$2p=0.002$ and  # $2p=0.012$ for differences between A and D

**$2p = 0.045$ for differences between C and D
Figure 4.3 Decline in FEV1 across the groups

Multiple linear regression of FEV1 decline as a continuous variable on the factors listed in Table 4.4 showed that age ($2p = 0.001$) and category assignment ($2p = 0.006$) were significantly associated with fast decline after adjusting for other variables with GOLD category assignment being most strongly associated ($2p = 0.006$). The difference in decline between groups A and D was significant ($2p = 0.002$), although smoking status and sex were not significantly associated ($2p \geq 0.05$) with rapid decline.

4.3.3 Kco Decline

The mean absolute Kco decline for the whole group was $0.028 \pm 0.031$ mmol/min/kPa/L/year. When categorised into the four GOLD groups based on combined risk, there was a faster decline in Groups C and D ($0.032 \pm 0.031$ mmol/min/kPa/L/year and $0.031 \pm 0.031$ mmol/min/kPa/L/year).
mmol/min/kPa/L/year respectively) than in groups A and B (2p = 0.012 between groups A and D) (Table 4.3). These are shown in Fig 4.4.

**Figure 4.4  Decline in Kco across the groups**

Multivariate analysis indicated that category assignment was independently predictive of a more rapid decline (2p=0.020) whereas age, sex and smoking status were not. Multiple linear regression of Kco decline as a continuous variable adjusting for age, sex and smoking status, showed that GOLD category assignment was still significantly associated with fast decline (2p=0.004) (Table 4.4).
Table 4.4 Multivariate analysis for decline in FEV1 and Kco

This table shows the regression coefficients (B) for analyses of lung function decline; 95% confidence intervals are given in parentheses; significant differences (p value) are shown in bold. For variables where there are more than 2 groups, a p value is shown for the overall contribution of the variable to the regression model, and then p values with HR (95% CI) for the specified sub-group comparisons. Thus, smoking status and gender did not contribute significantly to decline, whereas age and GOLD risk group did. For GOLD groupings patients in group A had significantly greater FEV1 decline than those in D, as shown by the negative B value, whereas the KCO decline was greater in group D, as shown by the positive B values.

4.3.4 Exacerbation History

Patients were grouped into the four GOLD categories on the basis of exacerbation history as a risk factor (Table 4.5). To assess the predictive ability of baseline exacerbation history in determining whether a patient would be a frequent exacerbator (≥ 2 per year) in AATD, 502 PiZZZ patients were analysed for the number of exacerbations in both year 1 and year 2 after recruitment to the database.
Table 4.5 shows the exacerbation history of patients in year 1 and the following year. Frequency of exacerbations in year 1 predicted frequency in the following year as in usual COPD. In the first year, 70.77% of patients were classified as having infrequent exacerbations. Nearly 71% of these patients had infrequent exacerbations in year 2. Of those who had frequent (≥2) exacerbations in year 1, 63% had ≥2 exacerbations in the following year suggesting that GOLD groupings based on exacerbation frequency are generally likely to predict future exacerbation risk.

<table>
<thead>
<tr>
<th>Exacerbations/year</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>exacerbations</td>
</tr>
<tr>
<td>0-1</td>
<td>284</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DNA</td>
</tr>
<tr>
<td>≥2</td>
<td>218</td>
<td>≥2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DNA</td>
</tr>
</tbody>
</table>

Table 4.5 Exacerbation history of patients in Years 1 and 2

DNA – did not attend follow up appointment in year 2
Table 4.6 Logistic regression analysis showing associations with frequent exacerbations

95% confidence intervals are given in parentheses; statistically significant relationships (p values) are shown in bold. In multivariate analysis the only significant predictors of frequent exacerbations were older age and lower baseline FEV1.

Univariate analysis showed that age, smoking status and baseline FEV1 were significantly predictive of frequent exacerbations (≥2). Logistic regression analysis showed that after adjusting for sex and Kco, smoking status was no longer significant but age and FEV1 remained independent predictive factors (Table 4.6).
4.4 Results using Spirometry and Exacerbation history for risk assessment

The above analyses were performed using combined risk as recommended in the GOLD strategy document. Analyses were also performed using spirometry and exacerbation history separately as risk assessment factors and the results are described here.

Table 4.7 summarises the patient numbers and percentage of the cohort using mMRC for symptom assessment and spirometry and exacerbation history respectively for risk assessment.

There was a significant difference in patient distribution in the four groups when exacerbation history was used for risk assessment compared to spirometry ($2p = 0.0094$). These data are shown in Table 4.7.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>mMRC/SPIROMETRY</th>
<th>*mMRC/EXACERBATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>A</td>
<td>105</td>
<td>20.87</td>
</tr>
<tr>
<td>B</td>
<td>98</td>
<td>19.48</td>
</tr>
<tr>
<td>C</td>
<td>59</td>
<td>11.73</td>
</tr>
<tr>
<td>D</td>
<td>240</td>
<td>47.81</td>
</tr>
<tr>
<td>TOTAL</td>
<td>502</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.7 Distribution of patients according to the symptom/risk assessment methods

*2p = 0.0094
Majority of the patients were in Group D by either risk assessment criteria. However using exacerbation history rather than spirometry for risk assessment assigned more patients in Group B (162/502, 32.21% vs. 98/502, 19.48%; 2p < 0.0002). Group C had the least number of patients by both risk assessment methods (2p = 0.0947).

Compared to the category assignment by the combined risk method (Table 4.1) most patients are in the high symptom risk group D by all the assessment methods. However the distribution in the other groups varied as per the symptom risk assessment method chosen (2p = 0.051 for category assignment by combined risk compared to mMRC/Spirometry and 2p < 0.0001 for category assignment by combined risk compared to mMRC/Exacerbation).

**Mortality**

Table 4.8 shows the distribution of mortality in the four GOLD groups using mMRC for symptoms assessment and spirometry and exacerbation history respectively for assessing risk.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>mMRC/SPIROMETRY</th>
<th>mMRC/EXACERBATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mortality (% of total deaths)</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>6.78</td>
</tr>
<tr>
<td>B</td>
<td>15</td>
<td>12.71</td>
</tr>
<tr>
<td>C</td>
<td>9</td>
<td>7.63</td>
</tr>
<tr>
<td>D</td>
<td>86</td>
<td>72.89</td>
</tr>
<tr>
<td>TOTAL</td>
<td>118</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.8 Mortality distribution**

*2p<0.0001

There were 118 (21.73%) deaths over the 17 year period and the largest proportion were in Group D defined by either method (n=86, 72.89% by mMRC/spirometry and n= 54, 45.76%
by mMRC/exacerbation). However the distribution in the groups differed significantly according to criteria used for risk assessment (2p<0.0001).

Compared to the combined risk method (Fig 4.1) most patients are in the high symptom risk group D by all the assessment methods. However the distribution in the other groups varied as per the symptom risk assessment method chosen (2p = 0.0184 for category assignment by combined risk compared to mMRC/Spirometry and 2p < 0.0001 for category assignment by combined risk compared to mMRC/Exacerbation).

Cause of death in each group has been shown in Table 4.9. Specific comorbidities do not seem to have contributed significantly to mortality in our cohort.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mortality (n)</th>
<th>Mortality – Cause (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respiratory Failure</td>
<td>Other causes</td>
</tr>
<tr>
<td>A</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>D</td>
<td>94</td>
<td>43</td>
</tr>
</tbody>
</table>

**Table 4.9  Causes of mortality in each group**

Most of the deaths were from respiratory failure (52/118, 44.07%). However 43 (36.44%) deaths were from other causes which included death from cirrhosis, cardiac causes and malignancy. Cause of death in 23 (19.49%) cases could not be ascertained from the medical records.
**FEV1 decline**

Table 4.10 shows the mean decline in FEV1 in the four GOLD groups using either spirometry or exacerbation history for risk assessment and mMRC for assessment of symptoms.

Compared to the combined risk method (Table 4.3) the distribution in the groups varied as per the symptom risk assessment method chosen ($2p = 0.0251$ for category assignment by combined risk compared to mMRC/Spirometry and $2p < 0.0001$ for category assignment by combined risk compared to mMRC/Exacerbation).

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>mMRC/SPIROMETRY</th>
<th>mMRC/EXACERBATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>FEV1 Decline (ml/year)</td>
</tr>
<tr>
<td>A</td>
<td>101</td>
<td>-67.57(60.17)</td>
</tr>
<tr>
<td>B</td>
<td>89</td>
<td>-58.73(58.72)*</td>
</tr>
<tr>
<td>C</td>
<td>54</td>
<td>-51.04(44.25)</td>
</tr>
<tr>
<td>D</td>
<td>192</td>
<td>-36.51(58.78)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>436</td>
<td>-36.51(58.78)</td>
</tr>
</tbody>
</table>

Table 4.10  Distribution of the mean decline in FEV1 in the four groups

*2p = 0.02 compared to Group B (mMRC/Exacerbations)

Data are presented as mean (SD)

Using mMRC/Spirometry, the greatest decline was observed in group A (67.566 ml ± 60.17) with progressively lesser decline in the other groups. However with mMRC/Exacerbations, greater decline was observed in groups A and C as opposed to B and D which were similar. There was a significant difference in the decline values in group B by the different assessment methods ($2p = 0.02$) which was not the case with the other groups ($2p > 0.05$).
Kco decline

Table 4.11 shows the mean decline in Kco in the four GOLD groups using either spirometry or exacerbation history for risk assessment and mMRC for assessment of symptoms.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>mMRC/SPIROMETRY</th>
<th>mMRC/EXACERBATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Kco Decline (mmol/min/kPa/L/year)</td>
</tr>
<tr>
<td>A</td>
<td>97</td>
<td>-0.024 (0.027)</td>
</tr>
<tr>
<td>B</td>
<td>83</td>
<td>-0.026 (0.034)</td>
</tr>
<tr>
<td>C</td>
<td>51</td>
<td>-0.032 (0.033)</td>
</tr>
<tr>
<td>D</td>
<td>185</td>
<td>-0.031 (0.029)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>416</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.11  Distribution of the mean decline in Kco in the four groups

Data are presented as mean (SD)

Compared to the combined risk method (Table 4.3) the distribution in the groups varied as per the symptom risk assessment method (2p = 0.0353 for category assignment by combined risk compared to mMRC/Spirometry and 2p < 0.0001 for category assignment by combined risk compared to mMRC/Exacerbation).

The mean decline in Kco across all groups was 0.028 (±0.031) mmol/min/kPa/L/year. The decline was least in Group A and greatest in groups C and D. The mean decline in Kco in the groups defined by the different risk assessment methods however, was not statistically significant (2p < 0.05).
5 Comorbidities in AATD

Usual COPD is associated with a number of comorbidities that place a significant burden on the individual and the healthcare system. Association of COPD with cardiovascular, psychiatric and musculoskeletal morbidity has been well documented (2, 297-301). Several mechanisms have been proposed to explain these associations including: a “spill over” of pulmonary inflammation into the systemic circulation to affect other organs; shared genetic predispositions between COPD and other diseases; and common environmental exposures, the most notable being cigarette smoking (302-304). Another view is that pulmonary manifestations of COPD are a form of expression of a ‘systemic’ inflammatory state with involvement of multiple organs (305, 306). TNFα appears to be a chief mediator in this process as shown both in animal models and in the COPD phenotype with low body mass index (307), (271). Factors affecting its production may lead to a chain of events leading to several other conditions. This process could be augmented by the release of reactive oxygen species (ROS) in patients with COPD (308, 309). Polymorphisms of the TNFα receptor are associated with more severe disease which may be due to the heightened effects of TNFα.(310, 311).

Assessing comorbidities in usual COPD has been recommended in the GOLD strategy document. Some of the comorbidities have been shown to adversely affect survival in usual COPD (197). A disease specific comorbidity index (COTE index) has been proposed (197) as a means to assess the mortality risk in patients with COPD.

A universally accepted definition of comorbidity is lacking. Traditionally the term ‘comorbidity’ has been used to include a disease coexisting with the primary disease under consideration, though there are many instances where this definition has not been strictly
adhered to. In case of COPD certain disease associations may be a consequence of the patients’ underlying COPD. Examples of some of these ‘comorbid’ conditions include cardiovascular diseases, lung cancer, diabetes and osteoporosis.

5.1.1 Non-specific Comorbidity Indices and their application in COPD

The Charlson Index was designed for analytical purposes to quantify the comorbid conditions that might modify the risk of mortality in hospitalised patients (312). In a prospective study of 171 patients admitted with acute exacerbation of COPD, comorbidities were analysed for their contribution to one year mortality (313). More than two-thirds had one comorbid illness and the mean Charlson index score was $1.55 \pm SD 0.90$. However a major limitation of this index was that the weighting used to calculate the scores was complex.

Since then, modified versions of this index using weighting that is more easy to use have been developed. The Deyo-modified Charlson index is one such index which is commonly used for research involving hospital administrative databases, International Classification of diseases (ICD)-9 diagnoses and procedural codes (314). The Deyo-Charlson Index scores were found to be significantly associated with mortality in a study using administrative databases to estimate the mortality in hospital in patients admitted with an acute exacerbation of COPD and also to identify predictors of mortality (315). Individuals with a score of 5 or more (indicating at least four comorbidities) were over five times as likely to die in hospital compared with COPD patients without comorbidities, adjusting for variables including age and sex.
5.1.2 Comorbidity patterns in usual COPD

In COPD, multidimensional indices, (e.g. BODE index) have been used to determine the risk of mortality; however the presence of coexisting diseases is not taken into account by these indices. Several attempts have been made to describe COPD co-morbidities. Vanfleteren et al (12) grouped 13 clinically important comorbidities and identified five comorbidity clusters. They concluded that multimorbidity is common in patients with COPD.

The comorbidities analysed were anaemia, myocardial infarction, low body weight, depression, anxiety, renal impairment, obesity, muscle wasting, osteoporosis, dyslipidaemia, hypertension, atherosclerosis and hyperglycaemia. The five comorbidity clusters were: 1) less comorbidity; 2) cardiovascular; 3) cachectic; 4) metabolic; 5) psychological.

In a multicentre study, Divo et al evaluated comorbidities in COPD and their relationship to mortality prospectively (197). They found that the commoner comorbidities were hypertension, hyperlipidaemia, Coronary artery Disease (CAD), Benign Prostatic Hypertrophy (BPH), Degenerative Joint Disease (DJD), Diabetes and Congestive Heart Failure (CHF) in non-survivors. Using multivariate analysis, Divo et al identified 12 comorbidities which increased the risk of death and used these to construct the COTE index. They demonstrated that COTE index improved the prognostic accuracy for mortality in COPD when used along with the BODE index.

5.1.3 Relationship to prognosis

The importance of comorbidity to prognosis in COPD has been explored in some studies (316-320) and some comorbidities have been shown to have an impact on pertinent outcomes such as HRQoL (316, 317), use of healthcare resources (319), response to intervention (316)
and mortality (318, 319). Some of these studies have had a small sample size (316, 318) and some have included patients admitted to the hospital after an acute exacerbation (318, 319) which are limitations of these studies.

5.1.4 Common comorbidities in COPD

Cardiovascular disease
There is a clear overlap between risk factors associated with the development of COPD and cardiovascular disease such as cigarette smoke. Right ventricular dysfunction and pulmonary hypertension resulting from lung disease can also affect cardiovascular system apart from coronary artery disease.

Risk factors common to COPD and CAD include cigarette smoke exposure, advancing age and an inactive life style. There is a significantly greater risk of mortality from myocardial infarction in those who also have airflow limitation and this is independent of age, sex and smoking history (321). The Lung Health Trial showed that FEV1 is able to independently predict mortality from myocardial infarction (322).

Low grade systemic inflammation seen in COPD and atherosclerotic cardiovascular disease could potentially be the common factor involved in both pathologies. In patients with COPD, this systemic inflammation has been linked to the pathogenesis of atherosclerotic cardiovascular disease (323). Lungs of patients with COPD and plaques seen in atherosclerotic disease both exhibit a low grade inflammation where the numbers of macrophages and IFN –γ secreting Th1 lymphocytes are greater (324, 325).

Increased arterial stiffness seen in patients with COPD (195, 272) may increase susceptibility to systemic hypertension and could also lead to a greater risk of cardiovascular disease (326).
Arterial stiffness could also result from the systemic inflammation seen in COPD or could reflect abnormalities in connective tissue or inflammation.

It has been observed that patients with stable COPD, who have no history of CAD, have higher levels of high sensitivity cardiac Troponin T (hs-cTnT) compared with randomly drawn subjects from general population (327). In these patients, higher hs-cTnT appears to be associated with immune activation and the severity of the disease. It has been suggested that these patients may be suitable for further cardiac investigations and could potentially benefit from cardiovascular interventions and medications (327).

Another observation from the study was that hs-cTnT levels increase with severity of airflow limitation. There was an association between higher hs-cTnT levels, higher IL-6 concentrations and pathological Q waves in ECG, suggesting that inflammation as well as unrecognised myocardial infarction may contribute to the higher hs-cTnT concentrations in stable COPD (327).

**Depression and Anxiety**
Symptoms of depression and anxiety are common in patients with COPD. Patients with COPD have a higher prevalence of depression and anxiety than the general population (328) and COPD patients have relative risk of 1.69 for developing depression (329).

The reported prevalence of each condition is quite varied, depending on the population analysed and the tools used to assess depression and anxiety. For patients with stable COPD in an outpatient setting, the prevalence of depression varies widely from 10% to 57 % (328, 330) and for anxiety, the prevalence ranges from 7% to 50% (328, 331).

Risk factors for increased rates of depression include living alone (332) and female sex (122, 333, 334) in whom rates of depression are more strongly correlated with severity of dyspnoea.
compared to males (333). End stage COPD patients (335) and those on LTOT (336) also have high rates of depression. The strongest predictors for depression among COPD patients appear to be the severity of symptoms and reported QoL (334).

The exact process leading to depression in patients with COPD has not been clarified and it is likely that there is more than one (337). There is considerable evidence that systemic inflammation may be a major factor predisposing to depression. It has been demonstrated that IL-6 plays a key role in humans and also animal models of depression (338). There is also a suggestion that systemic inflammation may have a role to play when depression is present in patients with COPD (339), but the exact nature of the role is uncertain.

Different factors have been considered to play a role in causing depression in patients with COPD, chief among them being cigarette smoking. Individuals with depression are more likely to smoke (340) and smokers are more likely to be depressed (341). Hypoxia may also play a role in the development of depression in COPD (334). This complex interaction between COPD and depression may result in a self-propagating cycle which severely impacts upon a patient’s well-being.

**Effect on mortality and COPD exacerbations**

Symptoms of depression have been found to be associated with increased mortality among inpatients (342, 343) and out patients (209, 344-346) with COPD. Some studies in patients with COPD have shown an association between anxiety and increased mortality (342, 343, 347) whereas others have failed to show any association (209). A meta-analysis in patients with COPD showed that the presence of depression and anxiety were associated with increased risk of mortality with relative risks of 2.29 and 1.27 respectively (329).
Depression and anxiety have been shown to increase the risk of hospitalisation for COPD patients (348), increase length of hospital stay for patients admitted with COPD exacerbations (342, 349, 350) and also to adversely impact QoL and functional status, independent of the severity of COPD or related comorbidities (351-357).

Symptoms of anxiety and depression have been shown to improve following completion of a course of pulmonary rehabilitation (358, 359). The BTS guideline on pulmonary rehabilitation in adults also recommends that individuals with symptoms of anxiety and depression should also be considered for pulmonary rehabilitation (360).

**Lung cancer**

Lung cancer is a common cause of mortality in patients with COPD and this is more so in those with severe COPD (295, 361). Compared to smokers with normal lung function, those who have COPD have a three to four fold greater risk of developing lung cancer (362, 363). Cigarette smoking appears to be a common aetiological factor in both these conditions.

Different factors are responsible for the increased prevalence of lung cancer seen in patients suffering from COPD. The enhanced inflammation and oxidative stress seen in COPD could be one of the factors predisposing to lung cancer in these patients (364). Other factors which contribute to this include activation of NF-κB (365), pro inflammatory cytokines, transcription factor nuclear factor erythroid 2 - related factor 2 (Nrf2) (366) and epidermal growth factor receptors (EGFR) (367).

**Diabetes mellitus**

An increased prevalence of diabetes has been observed among patients with COPD even in those with mild disease (368, 369). It is speculated that systemic inflammation may also play a role in this. Pro inflammatory cytokines including TNF-α and IL-6 have been shown to
increase risk of type 2 diabetes mellitus (370). Insulin resistance and cardiovascular disease are important components of the metabolic syndrome. These have also been shown to be more common in patients with COPD indicating a possible link between them (371). Elevated levels of plasma CRP, TNFα and IL-6 are also seen in the metabolic syndrome (372) implying the possible involvement of systemic inflammation.

**Osteoporosis**

An association between emphysema and osteoporosis may also be relevant to progression of both diseases. The osteoporosis related - protein triad osteoprotegerin (OPG)/ receptor activator of NF-κB (RANK)/RANK ligand (RANKL) plays an important part in regulating bone metabolism and remodelling. It is thought that this protein system may play a role in emphysema and bone loss in COPD (373).

_Sabit et al_ described increased aortic pulse wave velocity (PWV) in patients with osteoporosis and an association with systemic inflammation, suggesting that age-related bone and vascular changes occur prematurely in COPD (272). It has been shown that osteopenia is a feature of COPD (271). Low bone mineral density (BMD) and high fracture rates have been demonstrated in patients with COPD not receiving systemic glucocorticoids (374) and impaired FEV1 has been shown to be an independent predictor of osteoporosis in studies of patients with and without COPD (375). Furthermore, TNFα and IL-1 have been linked to the pathophysiology of osteoporosis (376) providing a possible direct link.

It has been suggested that radiographic emphysema is a strong, independent predictor of low BMD in current and ex-smokers (377). Although overlapping risk factors complicate the relationship between emphysema and osteoporosis, the increased prevalence of low BMD in the absence of steroid use and even in those with milder airflow limitation (271),(378)
suggests alternative pathogenic associations between the two processes that are different from traditional osteoporosis risk factors. Mechanisms underlying this relationship are not clearly defined and may relate to local inflammatory factors acting on lung and bone matrix or the effects of lung inflammation spilling over into the systemic circulation (377).

Lung volume reduction surgery (LVRS) has been shown to significantly improve BMD compared to pulmonary rehabilitation, even in patients requiring oral steroids. The increase in BMD was found to correlate with Residual volume (RV), Transfer factor for carbon monoxide (DLCO), and fat-free mass. This suggests that the improvement in respiratory mechanics, gas exchange, and nutritional status brings about improvement in bone metabolism and mineral content (379), perhaps lending credence to a specific relationship between emphysema and osteoporosis at a mechanistic level.

**Gastroesophageal reflux Disease (GORD)**

GORD is also common in patients with COPD and is associated with increased frequency of exacerbations (380). Patients with chronic bronchitis and emphysema develop peptic ulcer disease more frequently than controls (381) and are more likely to have positive serology for *Helicobacter pylori* (382). FEV1 has been observed to be lower in patients with peptic ulcer disease (383).

*Mokhlesi et al* reported an increased prevalence of reflux symptoms among patients with COPD compared with control subjects (384). They noted that reflux symptoms were more common in those with an FEV1< 50%.

It has been postulated that aspiration of *H pylori* or its exotoxins may enhance the airway inflammation (382) or that increased rates of COPD exacerbations are related to reflux symptoms. Studies using 24 hour oesophageal pH monitoring have shown increased reflux in
patients with severe COPD (385) and conversely an increased risk of COPD in those with gastroesophageal reflux (386).

5.2 Comorbidities in AATD

Different diseases have been associated with AATD; however whether these are different to the co morbidities of usual COPD and their impact on the individual has not been fully ascertained. Cigarette smoking is a vital factor in the comorbidities in COPD which may be less so in AATD where lung disease is also a feature of never smokers.

Cardiovascular comorbidity in AATD has been identified in some studies (273), (277, 387) but not in others (279). Increased aortic stiffness and thereby cardiovascular risk has been demonstrated in patients with AATD (273). Talmud et al studied the link between progression of atherosclerosis and common AAT variants in two clinical trials and concluded that disease progression is associated with variation in AAT with low levels of AAT enhancing atherogenesis (279). It has been demonstrated that patients with AATD also had lower BMD and an association with osteoporosis has also been proposed (271). However many of these studies are based on a small sample size which may explain the inconsistent results.

Liver disease in AATD

Clinical manifestations of liver disease in AATD vary widely among PiZZ patients from asymptomatic disease in some to fatal liver disease in others. Pathologically chronic protein polymerisation observed in PiZZ AATD leads to altered hepatocyte function and cirrhosis (388). Presentation is either in childhood or in those over the age of 50 (389). In addition to cirrhosis, a relatively high prevalence of hepatocellular carcinoma and cholangiocarcinoma has also been reported (390). It has been stated that just over a third of genetically susceptible adult patients with the most severe phenotype, PiZZ, develop clinically significant liver injury.
Factors that predispose some individuals to liver disease while sparing others are unknown (391). The mechanisms of liver and lung disease are distinct and unique (391).

Management of liver disease in AATD is as for any other form of liver cirrhosis. It is recommended that patients with liver cirrhosis should be monitored for liver failure and evaluated for liver transplant in the presence of end stage liver failure. Prognosis is generally poor with a mean survival of 2 years after diagnosis of cirrhosis is established; making it a clear indication for liver transplant (263).

**Bronchiectasis**

Bronchiectasis has been shown to co-exist in some patients with COPD (392). In some instances the use of the term ‘comorbidity’ has been broadened to include a reciprocal or causal relationship between two disease states (393). Bacterial infection has been suggested as a potential co morbid condition to the aetiology, pathogenesis and clinical course of COPD (393). Although bronchiectasis itself is not thought of as comorbidity in COPD, it is suggested that it could be a distinct phenotype (393). Presence of bronchiectasis in patients with COPD has been shown to increase the duration of intensive care unit and hospital stays but did not influence mortality (394).

Studies have shown a high prevalence of bronchiectasis in patients with moderate to severe COPD which was associated with severe airflow obstruction, isolation of a potentially pathogenic microorganism (PPM) from sputum, and at least one hospital admission for an exacerbation in the previous year (392). Some authors have observed an association between the two, reporting the presence of bronchiectasis in up to 50% of patients with moderate to severe COPD (395, 396). This suggests that there may be a causative relationship in which COPD is a risk factor for bronchiectasis.
Bronchiectasis is recognised in AATD but its prevalence is thought to be greater than previously recognised. Only a limited number of studies have assessed the association between AATD and bronchiectasis. These studies have been small case series (397-399). One study identified a high prevalence of bronchiectasis and bronchial wall thickening of 27% in their subjects with AATD and demonstrated that the morphologic features identified from HRCT images relate to clinical phenotype (228).

5.3 Aims

The aims of this part of the study were as follows:

- To analyse the prevalence of co-morbidities in our cohort of patients with AATD and describe the association between CAT scores and comorbidities, to give an indication of whether this QOL score, which is specific to COPD, was in fact picking up symptoms of comorbid disease. This might be the case particularly in GOLD group B patients, whose symptoms appear to exceed their spirometric impairment or exacerbations.

- To assess the relationship of smoking and BMI to prevalence of specified co-morbidities.

- To assess the impact of specified comorbidities on outcome in AATD including mortality and lung function decline. Our hypothesis being that certain comorbidities would contribute to these outcomes as has been shown in usual COPD with bronchiectasis and osteoporosis (141, 392, 395, 400, 401).

- To apply the COTE index to patients with AATD, comparing between GOLD groups. Our hypothesis was that comorbidity burden would be higher in the more symptomatic groups, thus COTE would also vary between GOLD groups. The COTE index was the most comprehensive index of comorbidity in usual COPD and a similar index for AATD is lacking.
The intention was to examine the value of this index for subjects with PiZZ AATD taking into consideration that many of the comorbidities in usual COPD have a strong association with smoking which may not be the case with AATD.

5.4 Methods

5.4.1 Subjects

The details of patient assessment, questionnaires completed and the tests performed at each annual visit as part of ADAPT have been described in chapter 2.

5.4.2 Comorbidities studied in AATD

The comorbidities assessed in COPD which were sought in AATD patients are listed in Table 5.1.

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Metabolic</th>
<th>Neoplastic</th>
<th>Psychological</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Hyperlipidaemia</td>
<td>Lung</td>
<td>Depression</td>
<td>BPH</td>
</tr>
<tr>
<td>CAD</td>
<td>Diabetes</td>
<td>Prostate</td>
<td>Substance abuse</td>
<td>DJD</td>
</tr>
<tr>
<td>PVD</td>
<td>Erectile dysfunction</td>
<td>Breast</td>
<td>Anxiety</td>
<td>GORD, Duodenal ulcer</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>Osteoporosis</td>
<td>Urinary tract</td>
<td>Psychiatric disorders</td>
<td>CKD</td>
</tr>
<tr>
<td>AF, Arrhythmia</td>
<td>Hypothyroidism</td>
<td>Oesophageal</td>
<td></td>
<td>OSA</td>
</tr>
<tr>
<td>CVA/Stroke/TIA</td>
<td>Gout</td>
<td>Pancreatic</td>
<td>Pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension/Cor pulmonale</td>
<td></td>
<td></td>
<td>Pulmonary fibrosis</td>
<td>Cataract</td>
</tr>
<tr>
<td>AAA, DVT</td>
<td></td>
<td></td>
<td></td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>

Table 5.1 List of co morbidities assessed in AATD

CAD coronary artery disease, PVD peripheral vascular disease, AF atrial fibrillation, CVA cerebrovascular accident, TIA transient ischaemic attack, AAA abdominal aortic aneurysm, DVT deep vein thrombosis, BPH benign prostatic hypertrophy, DJD degenerative joint disease, GORD gastroesophageal reflux disease, CKD chronic kidney disease, OSA obstructive sleep apnoea

Data analysis

Details of the statistical analysis of the data have been described in Chapter 2 section
5.5 Results

5.5.1 Prevalence of comorbid disease in PiZZ AATD

Table 5.2 summarises the comorbidities found in our patients with AATD and the relationship to GOLD stage. There were similarities in the frequently occurring comorbidities in our cohort of PiZZ patients with AATD to those reported in COPD (197) - hypertension, hyperlipidaemia, GORD, depression and osteoporosis along with coronary artery disease and diabetes were observed in our group of patients as with usual COPD. 76.1% of subjects studied had at least one comorbidity.

The top 6 co morbidities in AATD in our cohort were Bronchiectasis (156, 31.08%), Hypertension (118, 23.51%), GORD (90, 17.93%), Depression (73, 14.54%), Hypercholesterolaemia (59, 11.75%) and Osteoporosis (56, 11.16%). (Table 5.2)
Most patients with bronchiectasis belonged to group D (n=84) with fewer in group B compared to groups A and C. The distribution across the GOLD groups was not significant (2p= 0.745).

Hypertension was diagnosed in 118 patients (23.51%) and GORD in 90 (17.93%). 60 (50.85%) of those with hypertension and 42 (46.67%) of those with GORD belonged to Group D. There were more patients with hypertension and GORD in group A (n=25 and n=20 respectively) compared to groups B and C suggesting that these co morbidities developed early on in the disease in a proportion of the cohort. Osteoporosis (n = 56, 11.16%) and hypercholesterolemia (n = 59, 11.75%) were also observed with a majority of these patients being in high symptom high risk group D (n = 40 and 30) respectively. The

<table>
<thead>
<tr>
<th>COMORBIDITY</th>
<th>COMBINED RISK GROUPS</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>156</td>
<td>31.08</td>
</tr>
<tr>
<td>Hypertension</td>
<td>118</td>
<td>23.51</td>
</tr>
<tr>
<td>GORD</td>
<td>90</td>
<td>17.93</td>
</tr>
<tr>
<td>Depression</td>
<td>73</td>
<td>14.54</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>59</td>
<td>11.75</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>56</td>
<td>11.16</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>27</td>
<td>5.38</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21</td>
<td>4.18</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>19</td>
<td>3.78</td>
</tr>
<tr>
<td>Pulmonary Fibrosis</td>
<td>9</td>
<td>1.80</td>
</tr>
<tr>
<td>Thromboembolic disease</td>
<td>34</td>
<td>6.77</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>28</td>
<td>5.58</td>
</tr>
<tr>
<td>Colitis</td>
<td>8</td>
<td>1.60</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>23</td>
<td>4.58</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>14</td>
<td>2.79</td>
</tr>
</tbody>
</table>

Table 5.2  Comorbidities observed in patients with AATD

*n<5 in some of the groups
distribution of GORD, depression and osteoporosis varied across the GOLD groups ($2p = 0.015, 0.011$ and $0.027$ respectively).

Coronary artery disease and diabetes, which are significant co morbidities in usual COPD (197), were observed in 27 patients ($5.38\%$) and 21 patients ($4.18\%$) respectively. The majority of these patients (19 and 13 respectively) were in group D. Coronary artery disease was evenly distributed in groups A, B and C but Diabetes was present more in group B ($n = 5$) compared to groups A and C ($2$ and $1$ respectively).

Liver cirrhosis was seen in 28 ($5.58\%$) patients overall and $50\%$ of these patients were in group D ($n = 14$).

From our patient records, we found that some with AATD also had colitis and diverticulitis. These have not been reported as co morbidities in usual COPD. In our overall cohort, 8 patients had colitis ($1.60\%$) while 23 ($4.58\%$) had diverticulitis. The distribution of these patients was greater in group D ($4$ out of $8$, $50\%$ and $12$ out of $23$, $50\%$ respectively). However the numbers were too small to conclude a real association although group D had the highest number of any group.

### 5.5.2 The role of smoking in comorbidity

Cigarette smoking plays a crucial role in the development of comorbidities in usual COPD (305, 361, 402, 403). The pattern of co morbidities seen in AATD is somewhat different to that seen in usual COPD. However many patients with AATD also smoked ($81.08\%$) or were smokers at least up to diagnosis. The pathogenesis of these comorbidities in COPD has been linked to systemic inflammation to which cigarette smoking contributes and assessing the relationship of smoking to the most frequently occurring comorbidities in AATD was thought
to be important. The distribution of ex and current smokers is also reflected in those with comorbidities (Table 5.3).

<table>
<thead>
<tr>
<th>Co morbidity</th>
<th>Smoking status (N)</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
<td>ex</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>32</td>
<td>101</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27</td>
<td>79</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td>GORD</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>Depression</td>
<td>9</td>
<td>52</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>6</td>
<td>44</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 5.3 Distribution of smokers in those with comorbidities

The distribution of these comorbidities across the smoking categories was not different (2p > 0.05), although there were some strong trends for bronchiectasis, hypertension and GORD.

5.5.3 The role of body mass index in comorbidity

Body mass index (BMI) has been shown to be an independent predictor of risk of death in COPD (404, 405) with low BMI (particularly below 21) associated with an increased risk of death (84, 207).

We analysed the distribution of mean body mass index (BMI) in the four groups (Table 5.4). The mean BMI was highest in group B (27.68 ± 5.76) and not very different in the other groups (A, C and D). The difference in the mean BMI between group B and the other groups was statistically significant (2p ≤ 0.01). [Groups A (2p = 0.015), C (2p = 0.0002) and D (2p = 0.008)].
Table 5.4  Mean BMI in the groups

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>BMI</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>25.64 (±4.02)</td>
<td>0.0151</td>
</tr>
<tr>
<td>B</td>
<td>27.68 (±5.76)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>25.58 (±3.51)</td>
<td>0.0081</td>
</tr>
<tr>
<td>D</td>
<td>25.13 (±4.44)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

2p between group B and other groups. Data are presented as mean ± SD (n=502)

5.5.4 Impact of comorbid disease on outcome in AATD

Mortality
Table 5.5 shows the mortality distribution of those with co morbidities throughout the GOLD groups.

35 patients with bronchiectasis died (22.44%), of whom 26 were in the high symptom high risk group D. Of those with hypertension, 26 (22%) died during the period of observation with the majority (n = 18) being in group D.

The mortality figures for the other common co morbidities were 8 out of 90 (8.88%) for GORD, 21 out of 73 (28.76%) for depression and 11 out of 56 (19.64%) for osteoporosis. Importantly 48.15% of those with coronary artery disease died (n = 13) and 11 of the deaths were patients in group D.

Among those with liver cirrhosis, 11 (39.29%) died and again, the majority (9 out of 11) were in group D.

We have previously shown that group D is associated with overall higher mortality (Chapter 3) (406). The co morbidities were mostly associated with Group D where also the mortality is
highest. From the available data, the comorbidities were rarely mentioned as a cause of death in the death certificate.

<table>
<thead>
<tr>
<th>COMORBIDITY - MORTALITY</th>
<th>COMBINED RISK GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>35</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>11</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>GORD</td>
<td>8</td>
</tr>
<tr>
<td>Depression</td>
<td>21</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>11</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary Fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>Thromboembolic disease</td>
<td>13</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>11</td>
</tr>
<tr>
<td>Colitis</td>
<td>2</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>3</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 5.5 Mortality seen in patients with co morbidities and their distribution

To determine if comorbidity was associated with mortality after adjustment for GOLD group (combined risk), age and smoking status, logistic regression was performed with each plus
each of the top 6 comorbidities in turn (Table 5.6). With each of the comorbidities, age and group assigned i.e. Group D were associated with mortality ($p=0.0001$ for age and GOLD groups respectively). Addition of smoking status in the step wise regression analysis was not significant ($p > 0.05$). In multivariate analysis the only significant predictors of mortality were older age ($2p=0.0001$) and GOLD groups ($2p=0.0001$).

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>1.051 (1.023-1.079)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.052 (1.024-1.081)</td>
</tr>
<tr>
<td>GORD</td>
<td>1.052 (1.024-1.081)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.050 (1.022-1.078)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.051 (1.024-1.080)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1.053 (1.025-1.082)</td>
</tr>
</tbody>
</table>

Table 5.6 Logistic regression analysis to determine the association between comorbidities and mortality

Odds Ratios were generated after adjustment in the regression for age, smoking status and GOLD groups. 95% confidence intervals are given in parentheses.

### 5.5.5 Decline in lung function

It is recognised that frequent exacerbations play an important role in the long term decline in lung function in patients with moderate to severe COPD (141). The presence of bronchiectasis has also been found to be associated with increased risk of airway colonisation and hence airway inflammation, and more frequent and severe exacerbations in usual COPD (392, 395). Bronchiectasis therefore also potentially contributes to decline in lung function in patients with COPD.
It has also been demonstrated that BMD is low in COPD patients and decreases with increasing severity of the disease (400). Advanced COPD (GOLD stage 4) is one of the risk factors for presence of a low BMD which is seen in 75% of GOLD stage 4 patients (401).

On the basis of the above data, analysis was performed in our cohort of patients with AATD to address the following questions. (Table 5.7)

1) Does bronchiectasis and osteoporosis associate with more rapid FEV1 or Kco decline?

2) Does coexistent osteoporosis imply greater emphysema severity and progression?

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>FEV1 Decline</th>
<th>Kco Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>2p Beta</td>
<td>2p</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>0.779</td>
<td>0.015</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.868</td>
<td>-0.012</td>
</tr>
</tbody>
</table>

**Table 5.7 Analysis of Comorbidities against lung function decline**

In univariate analyses, there was no significant difference in either FEV1 or Kco decline between those with and without the two comorbidities. Multivariate analyses are not appropriate, as decline is not normally distributed, but show no impact of the comorbidity after adjustment for combined risk group and index status.
However we found that severity of emphysema as measured by percent predicted Kco was significantly related to the presence of osteoporosis (2p = 0.001), but not Kco decline.

### 5.5.6 Quality of life

CAT is designed as a COPD specific measure of quality of life; however others have proposed that high CAT scores can also occur in the presence of certain comorbidities - GORD, depression, arrhythmia, and anxiety (407). The frequency of comorbidities according to CAT defined GOLD groups and difference in average CAT score between those with specified comorbidities were analysed. The results are summarised in Table 5.8.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Mean CAT score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>not present</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>20.44 (±8.014)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20.40 (±8.196)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>20.40 (±8.051)</td>
</tr>
<tr>
<td>GORD</td>
<td>20.86 (±7.939)</td>
</tr>
<tr>
<td>Depression</td>
<td>20.09 (±8.021)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>20.07 (±8.091)</td>
</tr>
</tbody>
</table>

Table 5.8 Mean CAT scores in patients with and without the comorbidities

Data presented as Mean (±SD)

No difference in comorbidity frequency was observed among the CAT defined GOLD groups. However the differences in the mean CAT scores between those with and without depression and with and without osteoporosis were significant (2p < 0.05) (Tables 5.8 and 5.9).
### Table 5.9 Significance of comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>2p (frequency of comorbidities)</th>
<th>2p (CAT vs. comorbidities)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>0.877</td>
<td>0.920</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.610</td>
<td>0.756</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0.530</td>
<td>0.642</td>
</tr>
<tr>
<td>GORD</td>
<td>0.065</td>
<td>0.117</td>
</tr>
<tr>
<td>Depression</td>
<td>0.409</td>
<td>0.027</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.134</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Significant difference in mean CAT scores shown in bold (2p<0.05)

Column 2 shows significance of distribution of the comorbidities in the GOLD groups and Column 3 shows the significance difference in the mean CAT scores between the comorbidities.

#### 5.5.7 Validity of COTE index in PiZZ AATD

We applied the COTE index in our cohort of 502 patients. 110 patients had one or more comorbidities from those that constitute the COTE index (21.91%). The COTE scores ranged from 1 to 8 in Group D, 1 to 6 in Groups B and C and 1 to 7 in Group A (Table 5.10).

### Table 5.10 COTE index stratified by GOLD grouping

<table>
<thead>
<tr>
<th>GROUP</th>
<th>N</th>
<th>%</th>
<th>Mean COTE</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>16</td>
<td>19.75</td>
<td>3.13 (±2.06)</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>19</td>
<td>32.76</td>
<td>2.47(±1.50)</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>13.25</td>
<td>3.00 (±1.90)</td>
<td>3</td>
</tr>
<tr>
<td>D</td>
<td>64</td>
<td>22.86</td>
<td>2.53 (±1.69)</td>
<td>24</td>
</tr>
</tbody>
</table>

Data are presented as mean (±SD)
The mean COTE index was lower for Groups B and D (2.47 and 2.53 respectively) than for Groups A and C (3.13 and 3.00 respectively) (2p=0.282 between groups A and B and 0.405 between groups C and D) (Table 5.10).

Since COTE was a good predictor of mortality in usual COPD we also analysed the mortality distribution in each group among those who scored on the COTE index. Twenty nine patients out of 110 (26.36%) died during the study. Of these 24 (82.76%) were in Group D, 2 in Group B (6.90%), 3 in Group C (10.34%) and none in Group A.

5.5.8 Was COTE index higher in those who died?

Among the 118 non survivors, 29 scored on the COTE index (24.58%). The remaining 89 did not score on the COTE index as they did not have the requisite co morbidities. No predilection for a higher COTE index was observed among those who died. In fact only 4 of them had a score of 6 whereas 10 each had a score of either 2 or 1.

Using regression analysis, after adjusting for age, smoking and GOLD groups, the COTE index was not higher in non-survivors compared to survivors (2p = 0.305) in our AATD cohort.

5.5.9 COTE index in relation to CAT scores

Since comorbidity has been proposed as one of the drivers behind high symptom scores (407), and therefore movement from group A to B, or C to D, we analysed QoL in comparison to COTE. Applying the COTE index to these patients in whom we had a CAT score (n = 309), 49 patients scored on the COTE index (15.86%) with scores ranging from 1 to 6 and a mean COTE of 2.55 (Table 5.11). The distribution of these patients in the four GOLD groups by CAT 10, CAT 13 and mMRC criteria are shown in Table 5.11.
Using either of these symptom risk assessment methods, Group D had the greatest distribution of patients followed by Group B. Comparatively fewer patients were assigned to groups A and C. Group D had the highest distribution of patients by all the symptom risk assessment methods. Fewer patients in Groups A and C meant that we could not reasonably compare the means. However in this smaller subset of patients, those who scored by the COTE index criteria were mostly distributed in the higher symptom groups B and D (Table 5.11).
6 Discussion

Summary of results

This thesis concerns the application of the GOLD 2011 strategy to patients with AATD.

The results can be divided into those describing the validation of the new GOLD strategy in AATD, in predicting clinical outcomes such as mortality, lung function decline and exacerbation and analysing comorbidities in AATD. The interpretation of the results in the context of current knowledge of AATD is considered using this format.

The 2011 revision of the GOLD strategy document presented a new classification of COPD which intended to provide a better understanding of the impact and treatment of the disease on an individual patient than the previous classification based solely on spirometry (1).

This new strategy has not previously been applied to patients with AATD; thus this is the first such study. The detailed assessment of comorbidities in AATD has also not been performed previously.

The results from the studies carried out for this thesis have validated the new GOLD classification in AATD and also suggested a cut off of 13 rather than 10 for CAT to replicate that for a mMRC of 1. Mortality, decline in Kco and co-morbidity burden was worse in the most severe category (D). This is similar to usual COPD. However when the COTE index, which describes co-morbidity burden and relates to mortality in usual COPD, was applied to patients with AATD, it did not improve prediction of mortality.
6.1 Validation of the new GOLD classification in AATD

In general, the distribution of our patients showed relatively few in Group C which is similar to the COPDGene study in usual COPD (408) but at variance with the results reported by Soriano et al (409). These authors found nearly 15% of patients in Group C in usual COPD using CAT or SGRQ equivalent scores. The reasons for these differences may very well reflect patient acquisition or choice of symptom threshold.

When using CAT or mMRC for symptom assessment it was seen that it is not the same set of patients that move across when using exacerbation history or spirometry for risk assessment. The patients were different depending on where they were on the spirometry grading and history of exacerbations. Patients moving groups when using either spirometry or exacerbation history for risk assessment did not show any particular pattern. Some of the patients are the same depending on the risk assessment grading but differences are evident depending up on the individual patient’s CAT and mMRC scores.

Of greater importance, there were also differences in distribution between groups if either CAT 10 or mMRC ≥2 was used as the symptom threshold. This observation has significant implications for the management of patients as it is likely to lead to different therapeutic strategies for individual patients dependent on the symptom scoring system used. Whilst it is recognised that mMRC 0-1 indicates minimal breathlessness, the current study suggests this is equivalent to a CAT score between 12 and 15. Whereas it could still be argued that these differences do not influence initial therapy proposed by GOLD if highest risk is used, the data suggest this is not the case with more patients assigned to groups A and C and less to groups B and D using mMRC compared to CAT 10 (Table 3.9).
The differences in patient classification seen when using CAT 10 in place of mMRC 0-1 disappeared when a CAT threshold of 13 was used. Although individual patients may still be placed in different categories and hence assigned different initial treatment strategies, this accounted for just 34/309 using CAT 13 compared to mMRC (Table 3.9) but 100 using CAT 10. Thus with this modified CAT threshold, the same initial treatment would be implemented according to the GOLD strategy in nearly 90% of patients whichever of the symptom scoring systems was used.

6.1.1 Proposed thresholds for CAT and mMRC in AATD

Comparison of CAT and mMRC scores demonstrated that CAT 10 was on average equivalent to mMRC 0 and CAT 15 to mMRC 1 (Figure 3.5). This is supported by the average CAT scores of 12-15 for patients characterised by mMRC ≥2. It should be noted that CAT 10 is equivalent to mMRC 0 which reflects no breathlessness using the latter but still evidence of symptoms using the former. Thus it is debatable whether CAT 10 or CAT 13 should be used and this will depend on future evidence that supports or refutes mMRC ≥2. Assessing symptoms is subjective although various tools have been developed to provide some consistent and objective measures. Although the CAT includes a grading system for breathlessness it is a multidimensional tool that includes other relevant COPD symptoms. It is thus more difficult to define a low symptom threshold although a score of 10 has been suggested as a general indicator of few symptoms (111). Thus it is important to validate this threshold if either symptomatic or preventative treatment is to be implemented. Jones et al recently suggested that mMRC ≥1 rather than mMRC ≥2 as a symptom cut off will classify patients more closely to using the CAT 10 in patients with COPD although our data suggests mMRC 1 is equivalent to CAT 15 at least in AATD. The mMRC threshold of ≥ 1 reported by Jones et al identified more AATD patients with similar health status to those classified by
CAT although still not directly equivalent (410, 411). Clearly further studies are indicated to understand the implications of these findings both for COPD in general and individual patients in particular as the new GOLD strategy is implemented. It is also worth noting that the therapeutic recommendations suggested by this classification have not been evaluated in AATD related COPD. Augmentation therapy in AATD, although not mentioned in the strategy document, has been shown to be of varying benefit (242, 269, 296, 412-414).

6.1.2 Strengths and limitations

The current study is based on a unique data set of patients with alpha 1 antitrypsin deficiency and as far as we are aware, this is the only study of its kind to test the validity of the symptom thresholds suggested by GOLD 2011. It is a well characterised cohort of patients with a balanced proportion of male and female patients and allows extensive data to be compared between symptom grades. The data set is virtually complete and CAT data is available for all the patients to allow a comparison with mMRC to be undertaken. To date this has not been the case with other reported studies.

There are some limitations to the study. Firstly the cohort remains relatively small as CAT has been in use only recently and is collected only at annual visits. Nevertheless the numbers are sufficient for general conclusions to be drawn compared to mMRC. Secondly the cohort includes non-index cases that tend to have better or normal lung function and hence will not represent the same spectrum as usual COPD in secondary (or even primary) care. Thirdly, the majority of patients have predominant emphysema pathology at the lung bases, which is uncommon in usual COPD. Despite this, the results did not differ markedly from those reported in usual COPD (408). Finally robust conclusions on this data set regarding validity at
predicting outcomes was not possible as mortality was low in the three years since CAT was implemented. This was carried out in the next part of the study.

6.2 New GOLD strategy in predicting clinical outcomes in AATD

This is the first longitudinal study providing data exploring the utility of the new GOLD strategy to predict clinical outcomes in AATD patients. The strategy has been shown to perform well in usual COPD, using an alternative symptom assessment test (SGRQ) (270), in that it identifies more individuals at high risk of exacerbations and mortality than the earlier classification based on FEV1 alone. Our data supports this, and adds further information on lung function decline.

Demographics

There were some differences in demographics when compared to a usual COPD cohort. In a study involving a large database of primary care COPD patients across UK (415) involving 9219 subjects, mean age was 69.5 ±11.1 with 50.9% being male. Current smokers constituted 37.1% and mean BMI was 27.2 ±6.3. 55.8% had 0 exacerbations in the previous year and 22.4% had ≥2 exacerbations in the previous year. 37.0% had a mMRC score of 1 and 4% had a score of 4. 52.0% had FEV1 between 50 and 80%. 46% had cardiovascular comorbidity and 15.2% had depression.

In our cohort of AATD patients, mean age was younger at 53.68 ± 9.53 with 61.55% being male. Current smokers constituted only 7.97% and mean BMI was 25.56 ± 4.84.

Mortality

As part of the ADAPT data set, mMRC scores have been collected since 1997 and this was used to gain a longitudinal insight into mortality in the new GOLD groupings. The study
shows that the strategy is successful in identifying AATD subjects with greater risk of death. Mortality followed the risk stratification and was greatest in group D, which also had the greatest impairment of Kco. Lower Kco was predictive of mortality in both univariate and multivariate models indicating that emphysema severity assessed by this parameter is more likely to affect outcome than the degree of airflow obstruction. Rapid decline in gas transfer occurs late in disease progression (416), reflecting destruction of alveoli especially in the apical areas of the lung (229) unlike FEV1 which declines more rapidly earlier in the disease process and reflects airway pathology particularly in the lower part of the lung (229). In a study in usual COPD, Lange et al found that survival was also poorest in Group D but in addition was poorer in group B compared to group C which they concluded was likely due to co-morbidities, particularly heart disease (270). Co-morbidity in AATD may well differ from usual COPD as patients are usually younger and this may account for the difference with our results. Age was understandably associated with mortality in both univariate and multivariate analysis, and is a result consistent with prior published work (264). No difference in mortality was noted between males and females, in contrast with reports in usual COPD where females have a better prognosis (417, 418).

**Lung Function Decline**

More rapid decline in lung function is associated with frequent exacerbations, poorer health status (129), increased risk of future exacerbations and hospitalisation (141) and is therefore an important clinical outcome. An attempt to alleviate decline in FEV1 is a major focus of any new therapy and often a major outcome in clinical trials (159, 295). Lung function declines more slowly in those who have developed severe COPD and more rapidly in those with better lung function (239). Our data supports this since greatest FEV1 decline was seen in group A and slower FEV1 decline in group D (239, 416). Lower zone emphysema, as seen in AATD,
has been shown to affect FEV1 more than Kco and therefore it might be expected that Kco decline would be more pronounced in severe disease (Group D) as emphysema progresses from the bases to involve the upper zones (229, 419). The current data confirms this concept and is consistent with our previous data (416).

**Exacerbation risk**

Exacerbation frequency relates to a faster decline in lung function in AATD (243) and usual COPD (141). Predicting the future risk of exacerbations will enable prompt intervention and prevention in susceptible individuals using optimum combinations of pharmacological and non-pharmacological therapies. In our cohort, a history of frequent exacerbations was a good predictor of subsequent exacerbations; this is similar to usual COPD (81). GOLD risk is partly determined by exacerbation history; overall concordance in our patients indicates the classification is generally predictive for this outcome in AATD, as in usual COPD.

**6.2.1 Strengths and Limitations**

Key strengths include large sample size and long duration of follow up. The magnitude of the annual decline observed in this study compares favourably with those reported in our previous work (416). Measuring true decline in FEV1 can be difficult due to effort dependent variability in individual patients; longer follow up reduces the inter subject variation to assess the annual decline in FEV1 (290).

There were some limitations to the study. Exacerbation data relied mainly upon recall by the patient, as it would in routine clinical practice, although such recall has proven to be reasonably reliable when diary card identification and primary care records have been compared (243). This suggests that the associations found here are likely to be valid and
clinically applicable. Smoking status was included in our models only from baseline assessment; since no patients started smoking during follow up, the proportion of current smokers was <10% and although accumulated pack years in these patients was high even prior to baseline assessment this should not have impacted greatly on results.

The symptom scoring system based on CAT was not used as it has only been available for a short time and robust conclusions on mortality and lung function decline could not be drawn from the limited data available to date.

The cohort also includes some non-index cases. The proportion in our cohort was very low and index status did not influence mortality (2p = 0.163) or Kco decline (2p = 0.067) although it did have an impact on overall FEV1 decline (2p = 0.032), presumably because patients were less severely affected, and better lung function was a predictor of a more rapid FEV1 decline. Furthermore the physiological decline observed was consistent with the trends seen in analysis of different impairment ranges as described previously (416).

If we look at index cases alone it could lead to a selection bias as a representative cohort of patients with AATD includes index and non-index cases. As the number of non-index cases was relatively small, by the time this group was split into GOLD stages meaningful analysis would not have been possible for some factors (e.g. there would have been no patients in GOLD group D).

6.3 Co morbidities in AATD

Comorbidities are an important feature of usual COPD. They have been associated with increased morbidity and mortality (318, 319). In the case of COPD due to AATD, the issue of co-morbidities has not been fully addressed. Certain co-morbidities related to
autoimmunity including inflammatory bowel disease and hypothyroidism have been reported to be more common (420) and liver disease is a well-known association independent of the presence of COPD (388). The data presented herein has established that certain diseases are associated with AATD and although the associations may not be the same as in usual COPD, they appear to have less impact on outcomes or quality of life than in usual COPD.

6.3.1 Prevalence

In our cohort of patients with AATD, the commonest comorbidities seen were bronchiectasis, hypertension, GORD, depression, osteoporosis and hypercholesterolaemia which are also observed in usual COPD. In the AATD cohort however, the prevalence was lower for most of the 12 comorbidities described by Divo et al (197) in usual COPD, many of which were not present among the common comorbidities identified in our patients with AATD.

Bronchiectasis has been included as comorbidity in AATD, as it may be clinically important. In patients with moderate to severe COPD, frequency of exacerbations contribute to decline in lung function (141) and the presence of bronchiectasis has been found to enhance the frequency and severity of exacerbations (392, 395). Bronchiectasis occurred in 31.08% patients with AATD which is similar to that published in usual COPD UK cohorts where it has varied from to 29% in primary care in the UK (396) to 50% in the East London cohort (395). In other studies, however, the prevalence in usual COPD has varied from as little as 4% in a multinational ECLIPSE cohort (97) to 57.6% in one study from Spain (392) which may reflect both acquisition bias and/or the criteria used to diagnose bronchiectasis.

The prevalence of AATD specific co-morbidities, such as liver disease was less in our dataset than had been expected. We found evidence of clinical liver disease in only 5.58% (n=28) of
our patients and half of these (n=14) were assigned to GOLD group D. As a respiratory group, it is likely that our registry attracts referrals predominantly of those with lung disease.

### 6.3.2 Relation to Smoking

Smoking is a major factor for systemic inflammation predisposing to systemic effects in usual COPD. Systemic features including skeletal muscle dysfunction, cardiovascular disease, osteoporosis and diabetes have been identified in association with COPD even after controlling for common aetiological factors such as smoking and steroid use. The ECLIPSE study (421) concluded that a number of concomitant diseases was significantly higher in patients with COPD than in smokers and never smoking control subjects of similar age, implying that the cause was not solely smoking, and could relate to the pathophysiological processes underlying COPD. Moreover the prevalence of these comorbidities was similar in different GOLD stages. It has been hypothesised that inflammation in the lung results in ‘overspill’ into the circulation causing systemic inflammation, and thereafter drives development of some co-morbid diseases at distant sites. Whether such a situation exists in AATD is not clear at present. We explored the role of smoking in the comorbidities in our group of patients and found no significant association. Whilst this seems somewhat counterintuitive, particularly for diseases such as CAD where smoking is a major risk factor, it may be explained by a relatively lower smoke exposure in our AATD patients and a generally younger age. There were some relationships to GOLD stage, similar to that seen in the ECLIPSE data (421), and consistent with the ‘overspill’ hypothesis.

### 6.3.3 Relation to BMI

*Sapey et al* found that sputum level of IL-1β, TNFα and LTB4 (Leukotriene B4) related negatively to BMI, supporting the hypothesis that an increase in lung inflammation is
associated with lower body weight (422). Other studies have linked low BMI to systemic inflammation (423). We also explored the role of low BMI in comorbidities. In our patients with AATD, there was no clear relationship between low BMI and severity of disease and although, group D had a lower mean BMI compared to the other groups, this did not achieve statistical significance.

In our cohort of 502 patients, 47 (9.36%) had a low BMI (BMI <21 (424)). The proportion of patients with low BMI in our AATD cohort was lower than in a usual COPD cohort - 15% in the study by Divo et al (425). It was found that subjects in Group B had a higher BMI on average compared to those in other groups. This was an incidental finding and the objective was to analyse the association between BMI and comorbidities in AATD. It has been reported that in usual COPD, low BMI increases the risk of mortality (84), (207) but in our group of patients with AATD such an association was not observed.

### 6.3.4 Relation to Outcomes

This is the first study to explore the impact of comorbidities on outcomes in AATD in detail.

#### Mortality

Comorbidities and the relationship to mortality in AATD were observed more in the high symptom/risk GOLD group D, but most deaths were from respiratory causes, and not the co-morbid disease. We did not observe any major difference in group B patients, in whom we had hypothesised that the increased symptomatology might be co-morbid disease. In usual COPD, it has been shown that GOLD group B, characterised by higher FEV1 but more dyspnoea compared to Group C, had poorer survival which could reflect comorbidities, especially cardiovascular disease or cancer (270) . However in our cohort of patients, the
comorbid diseases were mostly distributed in the high symptom risk group D with a low prevalence in Group B unlike in usual COPD (270).

Mortality of 48.15% over the course of the study period was observed in our patients who had established coronary artery disease. Similarly mortality observed in those with liver cirrhosis was 39.29%, hypertension 22.03% and hyperlipidaemia 18.64% over the same period. In usual COPD, the prevalence and the mortality attributed to different comorbidities varies in different studies (197, 319). The direct risk of death conferred by hypertension and hyperlipidaemia in usual COPD is not considered significant (197) although the presence of liver cirrhosis does increase the risk of death (197). AATD patients are younger, on average, than those with usual COPD and thus it is likely that prevalence of comorbidities and hence their impact on mortality would differ from usual COPD. Furthermore in our patients, smoking status was not a significant contributor to mortality (2p>0.05), perhaps because exposure was typically lower than in usual COPD.

**Decline in lung function**

The impact of comorbidities on lung function decline has not been comprehensively analysed in usual COPD although the presence of bronchiectasis and osteoporosis has been associated with faster decline in lung function (392, 395) (375). Emphysema may also be a marker of more rapid decline (426), and the co-existence of emphysema with osteoporosis has been noted in smokers (377).

The current study therefore assessed whether bronchiectasis or osteoporosis was associated with more rapid decline in FEV1 and Kco. No difference in decline was found in either of these lung function parameters suggesting that neither bronchiectasis nor osteoporosis influence lung function decline in AATD. However coexistent osteoporosis was associated
with greater severity of emphysema as measured by Kco. The findings are consistent with the
observation that BMD decreases with increasing severity of usual COPD (400) and that severe COPD is one of the risk factors for presence of a low BMD (401). This is consistent with studies in usual COPD showing a mechanistic link between the two diseases with loss of extracellular matrix and a common association with inflammatory mediators such as tumour necrosis factor-α (307, 427-429). Gas transfer and the extent of emphysema seen on HRCT scans have been shown to be sensitive to disease progression in patients with COPD related to AATD and it has been established that rapid decline in gas transfer occurs late in disease progression (416). These observations therefore are consistent with the cross sectional observation of an association between osteoporosis and emphysema severity in AATD though not the progression of physiological impairment in AATD.

6.3.5 COTE index in AATD

Relation to CAT scores (QoL)
The association between comorbidities in AATD and quality of life in the 309 patients where we had baseline CAT scores was also explored. The majority of the patients were in the high symptom GOLD groups B and D using either CAT 10 or CAT 13 as the threshold (Chapter 3) which is expected as higher CAT scores imply more symptoms suggesting that presence of comorbidities is more likely to impact on symptoms in AATD.

When the COTE index was applied to these patients, the mean value was higher in patients assigned to GOLD group D by their CAT symptom score whatever the threshold and irrespective of the risk assessment used. The mean COTE index in groups B and D was not different. Patients in groups B and D have, by definition, more symptoms and some of which may be related to the presence of comorbidities as in usual COPD (430) especially in Group
D. Nevertheless it is important to be aware of comorbidities and investigate and manage appropriately as recommended by GOLD (1).

In our patients with AATD, it was observed that those with higher CAT scores (Group D) also had more comorbidity as evidenced by higher mean COTE indices. Thus it can be reasonably concluded that presence of these additional conditions does have an impact on the quality of life in patients with AATD. Studies with a larger sample size, or using non-COPD specific HRQoL scores would clarify this further.

Studies performed to assess the impact of comorbidities on the CAT score of patients with usual COPD have shown variable results. It has been reported that cardiovascular comorbidity did not alter the CAT score significantly (431) and neither did renal failure, obesity and sleep disorders (432). Alternatively it has been observed that metabolic and cardiovascular comorbidities in usual COPD may increase in prevalence in higher symptom risk GOLD groups (433). Miyazaki et al have observed that COPD specific measures such as FEV1 and CAT do not reliably suggest the presence of comorbidities and hence these should be sought and assessed irrespective of the score (407).

In patients with AATD, apart from CAT, other disease specific questionnaires should be used to identify the presence of comorbidities specifically. Some of these could be the Medical Outcomes Study Short-Form 36-item (SF-36) to assess the general health status (115), Frequency scale for symptoms of GORD (FSSG) questionnaire to evaluate symptoms of GORD (434) and evaluation of anxiety and depression using HADS (119). This would provide a more comprehensive clinical assessment and enable the identification of comorbidities that may benefit from specific interventions.
Significantly more AATD patients with depression, GORD and osteoporosis were distributed in the high symptom/risk group D compared to the other comorbidities indicating the impact of these comorbidities, in particular on HRQoL. This is consistent with observations in usual COPD where depression has been known to be a key contributor to poorer HRQoL (351-357). Osteoporosis can cause fragility fractures, both vertebral and non-vertebral, which can further impair mobility and increase morbidity and mortality leading to poorer HRQoL. Increasing episodes of GORD have been demonstrated to be associated with lower HRQoL (435) and the association between COPD exacerbations and GORD (380) might contribute to poor QoL as reported for exacerbations alone (436).

Using mMRC for symptom assessment in patients with AATD also resulted in a majority of patients being distributed to the high symptom GOLD groups B and D indicating that dyspnoea is one of the most important determinants of QoL. The mean COTE scores were higher in groups B and D also emphasising that dyspnoea whether from respiratory or cardiovascular causes or both should be identified and treated appropriately. The unexpectedly higher COTE scores in GOLD Group A using mMRC/spirometry for risk assessment could be dependent on the relatively few patients in this group lending to bias. Clearly further studies will be necessary to clarify this issue.

**Performance of COTE index with regard to mortality in AATD**

The adverse impact of comorbidities in COPD and their association with mortality has been recognised (197). The COTE index is derived from comorbidity data, and is a good predictor of mortality in usual COPD. We found that the COTE index in our group of patients with AATD was not different between survivors and non-survivors. Hence there was no direct
association between COTE index and mortality in our patients. This was supported by the cause of death which was predominantly respiratory.

Although the COTE index is a useful prognostic tool in COPD, our data shows it is much less useful in AATD. This result is consistent with the observation that co-morbidities do not seem to be significantly increased or add to the symptomatology in AATD especially with regards to outcome measures (section 5.5.4), and most deaths were attributed to respiratory causes. This is perhaps an example of how extrapolation from usual COPD to AATD (or vice versa) may not be entirely appropriate. Although it has been shown that GOLD groupings can be applied in AATD, and generally predict outcome similarly to usual COPD (chapters 3 and 4) there are notable differences between the two conditions, such as patient demographics (239) and neutrophil function (11), smoking history and age (220).

Table 5.6 shows that the odds ratios for each of the co-morbidities after adjustment for GOLD were very small, such that the value of making a specific COTE would likely be small. Furthermore, since only age and GOLD stages were significant in the multivariate analysis (and not co-morbidity), deriving a COTE would not be statistically appropriate. In contrast to usual COPD, there were no general prognostic scores in AATD and a comorbidity index provided no additional prognostic value.

### 6.3.6 Multimorbidity

Numerous studies have suggested that the term ‘multimorbidity’ is more appropriate as opposed to ‘comorbidity’. These studies assessed other chronic diseases associated with individual ones e.g. COPD, heart failure, obesity, osteoporosis (437, 438). It appears that various chronic diseases develop simultaneously, potentially in response to multiple common risk factors including smoking, alcohol, aging, pollution, inactivity and diet.
In the study by Vanfleteren et al, 97.7% COPD patients had at least one concomitant chronic disorder (12). In our group of patients with AATD, this was lower at 76.1 % (382 out of 502). It must however be emphasised that in the above study, they were able to carry out extensive investigations thus enabling the recording of comorbidities in detail. This is not always possible in our healthcare setting because of economic considerations precluding investigations unless absolutely indicated. Nevertheless this still emphasises the need to identify and manage these chronic conditions optimally for improved outcomes.

The data suggests that each patient presenting with COPD/AATD should be carefully and actively monitored for concomitant chronic disorders, particularly the most frequent and undiagnosed disorders as in usual COPD. Although symptoms and exacerbations of COPD/AATD can be treated by pharmacological means, they do not appear to alter the natural course of the disease (1). In contrast, the consequences of most of the associated metabolic and cardiovascular chronic diseases may be prevented and reversed by pharmacological means in usual COPD (439-441). Hence they should also be included to identify phenotypes, assess the severity and progress of the disease and be treated appropriately in AATD.

### 6.4 Comparison of GOLD 2011 with previous classification

The GOLD 2011 strategy has been applied to different cohorts and populations with COPD. Some of them are briefly discussed here.

The new GOLD recommendations were applied to four existing COPD cohorts – COPDGene (408), Copenhagen (430), Collaborative cohorts to assess Multicomponent Indices of COPD in Spain (409) and ECLIPSE (442) and were evaluated by Agusti et al (443).
Applying the GOLD 2011 recommendations to the COPD Gene cohort, Han et al (408) concluded that assigning patients to categories is influenced by the instrument used to measure symptoms something which even we have shown in our study. They had fewer patients in Group C and exacerbation rates appeared different depending on whether or not categorising as high risk was based on spirometry, exacerbation history or both.

In their pooled data analysis, Lange et al (430) found that majority of their patients belonged to Group A which could be due to the fact that this cohort was identified from the general population. They also observed that the proportion of patients experiencing an exacerbation of COPD during the first year of observation increased from groups A to B to C to D (2.2%, 5.8%, 25.1% and 28.6% respectively). At the three year follow up, mortality rates were 3.8%, 10.6%, 8.2% and 20.1% in groups A, B, C and D respectively. More patients died from cardiovascular disease and cancer in groups B and D (characterised by more dyspnoea) than in groups A and C.

In the COCOMICS study (409), a pooled analysis of individual data from 11 COPD cohorts recruited in 7 different cities in Spain, Soriano et al concluded that the ability of the GOLD 2011 strategy to predict mortality was no different from the previous classification based on spirometry only. It also resulted in an uneven split of the COPD population. It is however worth noting that the GOLD strategy aim was to provide a structured assessment of patients with COPD in order to guide treatment decisions and not in predicting outcomes.

When the GOLD 2011 recommendations were applied to the ECLIPSE cohort (442), there was significant heterogeneity across the four categories. Groups A and D were relatively stable over time but groups B and C showed greater temporal variability which is probably due to progression of disease and/or response to treatment. The strategy seemed to be valid in
assessing the risk of future exacerbations but does not differentiate the risk of future hospitalisations and all-cause mortality for groups B and C – underlining the importance of symptom (and comorbidity) assessment in clinical practice. However one study demonstrated that patients in Group D have highly variable clinical presentation even after taking into account gender differences (444).

Studies in general practice have also demonstrated that the prevalence of the four groups depends on the population studied with Group C being least prevalent (415, 445).

**Prediction of mortality**
Although the GOLD recommendations were not designed to predict mortality, the four categories do relate to mortality in ECLIPSE (442) and COCOMICS cohorts (409) – better for Group A, worse for Group D, intermediate and similar for Groups B and C.

**Prediction of exacerbations and hospitalisations**
All four studies demonstrated that the incidence of exacerbations increases progressively from groups A to B to C to D. the ability to predict hospitalisations was explored only in ECLIPSE (442) and were scant in group A, frequent in group D and intermediate (and similar) in groups B and C during follow-up. Patients in group B had more comorbidities and persistent inflammation.

In an Asian population it has been shown that the new strategy predicts mortality and exacerbation frequency moderately well (446).

**Lung function decline**
No significant differences were observed in the rate of decline in lung function in the four groups in the ECLIPSE (442) study.
When the new GOLD strategy was applied to the BODE cohort and compared with the BODE index and the addition of COTE index (447), the BODE index performed better in prediction of mortality than the ABCD GOLD groups. When the COTE index was added to the BODE index it was complementary and significantly improved prediction of outcome (all-cause mortality – both short term at 24 months and long term at 50 months).

In the COCOMICS study (409), the new GOLD categories did not improve prognostic capacity over the previous spirometry based classification. Results from a cohort of 912 patients followed in Norway over 9 years (448) observed no difference in the ability to predict mortality or exacerbations leading to hospitalisations between the new GOLD strategy and the earlier classification.

In the HUNT Study (The Nord-Trøndelag Health Study) (449), there were more patients with in group A (61%) compared to other studies. There were only minor differences in mortality between groups A and B and between C and D. the authors concluded that the new strategy was inferior to the previous spirometry based classification in predicting mortality.

In the Copenhagen City Heart study (430), Group B had worse prognosis compared to Group C but there was no difference between the new and previous classification in their ability to predict mortality.

### 6.5 Conclusions

Symptom risk assessment as proposed by the new GOLD strategy is a step towards personalised medicine in COPD. However it currently presumes equivalence between CAT score of 10 and mMRC score of ≥2. In our patients with AATD, a CAT symptom threshold of 13 resulted in a similar distribution of patients across the four GOLD groups to that obtained
using mMRC threshold of 2. Using either spirometry or exacerbation history to assess risk did not result in significant differences in distribution across the groups.

It is important to have the correct threshold for symptom assessments (whatever tool used) for consistency of characterisation, thus enabling either to be used for similar treatment and outcome. This would make the current options consistent. It is likely that due to the heterogeneous nature of COPD, different phenotypes may have somewhat different symptom thresholds and that a threshold range rather than a strict cut off may be appropriate especially with CAT. This would need to be investigated further along with the influence of co-morbidities on the thresholds.

The GOLD categorisation enables clinicians to identify those AATD patients most at risk of death, exacerbations and worsening lung function thereby enabling more aggressive therapy to be focussed on those with the highest risk. Kco has been shown to decline with increasing severity of the disease, thus highlighting the value of this measurement over and above the measures required for GOLD groupings.

Comorbidities in AATD associated COPD are different from those in usual COPD. The common comorbidities observed in our patient population increase symptom burden and also affect functional performance and health status but not mortality. Presence of multiple comorbidities was a notable feature in our group of patients as in usual COPD (438).

Although it has been suggested in usual COPD that the concept of comorbid diseases being a feature of severe COPD is probably not correct, in our patients with AATD, comorbidities were more frequent in the high symptom/risk GOLD group D implying an association with more severe disease. Nevertheless, comorbidities are also seen in Group A indicating the need to investigate patients thoroughly whatever their GOLD group and manage them
appropriately, even early in the disease development. It is essential to have further research in the area of multiple comorbidities to enable the development of clinical guidelines tailored towards management of multiple comorbidities rather than a single disease in isolation supporting the position taken by GOLD (1).

The new GOLD strategy works well in AATD. This novel method of assessment using either CAT or mMRC for symptom assessment and spirometry or exacerbation history for risk assessment provided useful information in AATD. It is important to establish a cut off for both CAT and mMRC that is equivalent to ensure the same patients are distributed in the four GOLD groups. This would ensure that patients with the same risk assessment characteristics are managed in the same manner as proposed by GOLD and hence reduce confusion. Using combined risk assessment appears to be the better strategy in assessment of patients at risk of deterioration. The results from the current study suggest that the new strategy helps identify AATD patients who are at risk of poorer outcome in the form of decline in lung function, mortality and exacerbation risk with patients in the high symptom high risk group D being most at risk. Presence of comorbidities does not appear to influence outcomes in AATD although they indicate a poorer QoL.

6.6 Future studies

The data generated here and the conclusions drawn from the current study suggest the need for further research to strengthen the evidence base for future guidelines.

To clarify the equivalent thresholds between CAT and mMRC

We have identified that a cut off of CAT 13 relates better with mMRC of 1 by classifying more AATD patients in the same GOLD groups.
The mMRC threshold of $\geq 1$ reported by Jones et al identified more AATD patients with similar health status to those classified by CAT although still not directly equivalent (410, 411). Further studies also using other putative symptom tools are indicated to understand the implications of these findings both for usual COPD and AATD related COPD.

The current data set was from a relatively smaller group of patients. This can be replicated in a larger cohort of patients as the ADAPT programme continues to recruit subjects. However it may prove beneficial to also replicate this data in a second cohort through the use of the various other International registries for AATD. Alternatively a protocol has been established to recruit a well characterised cohort of patients with usual COPD in Birmingham (REC ref 12/EM/0090, RRK 4348). The patient information leaflet and consent form are included in Appendix 3. Data collection is underway and this will also facilitate comparison between AATD and a usual COPD cohort in the same geographic location. Direct, reliable comparisons between usual COPD and the UK AATD cohorts will be facilitated by use of the same data collection techniques, and an identical database to that used throughout this project. This will help support an accurate symptom threshold for the GOLD classification and particularly if it is similar in both datasets.

The therapeutic recommendations suggested by this classification need to be evaluated alongside current practice in usual COPD and AATD. The GOLD classification recommends initial treatment based on the category assigned. Obviously this will be less practical if different symptom assessment methods assign patients to different groups. Hence accurate category assignment based on correct cut off points is likely to be important. However the GOLD classification is only suggested for initial therapy and continued symptoms and progression are reasons for reviewing and updating treatment. Therefore it will be a continuing update of evaluation and minor differences in classification may have little effect
on overall management in the longer term. The major concern would be whether patients become over treated despite few symptoms.

The ADAPT database has details of all treatments for each patients. A study on a small set of patients (n= 309) was undertaken and presented as an abstract at the BTS 2012 (450). Many patients in group A were on triple therapy. It would be of interest to determine why physicians adopted a more aggressive approach to this group of patients if it was concern about severity in the long run as they have few symptoms or reasons for triple therapy. A questionnaire could be designed to be sent to general physicians and consultants to see what their approach to GOLD group A patients would be if they had COPD or if they had AATD. These results should be replicated in the entire ADAPT dataset with a chronological record of therapies introduced. This will provide data on clinical practice and its’ concurrence with the GOLD strategy.

A similar study should be performed in our COPD dataset as well as other cohorts worldwide to determine if the GOLD approach is consistent with, or modifies current clinical practice. In particular it would be of interest to determine whether physician perception results in a more aggressive approach to treating COPD especially early in the disease as indicated by our preliminary data (450). If so this would appear inappropriate and should be addressed.

**Decline in lung function in AATD**

Identification of those whose lung function declines rapidly is an important goal as specific and more aggressive therapy should be especially targeted to this group of individuals. Identification of those who may benefit from augmentation therapy is important as the current evidence regarding its benefit based on lung function decline is somewhat equivocal. Individual lung function is influenced by sex, height, race and the normal ageing process. For
this reason results are expressed as a % of the predicted values which for a stable and/or healthy individual should remain constant. Decline in lung function in COPD is accepted as being greater than normal whilst the disease process remains active (the so called ‘rapid decliner’). Identification of rapid decliners is an essential process especially in alpha-1-antitrypsin deficiency (AATD) where it should be an indicator for considering expensive augmentation therapy.

We could assess the rate of decline in lung function in a never treated (augmentation therapy) cohort of AATD (PiZZ) subjects by categorising them into those with no decline (< -0.1 %predicted/year) and those with decline divided in a variety of ways such as (-0.1 to -0.5%; -0.5 to -1.0% and >1.0% predicted/year) for both FEV1 and Kco. The current study has calculated the overall decline in both FEV1 and Kco and analysis of individual decline would likely be highly informative. Indeed an initial report of such an approach has already been presented in abstract form (451). Data showed that once airflow obstruction is established, about 50% of subjects have a rapid annual decline in lung function including both FEV1 and Kco. However early in the disease process fewer subjects have a rapid decline in FEV1 (24.8%) compared to the COPD group whereas a similar proportion shows a rapid decline in Kco. Gas transfer is more specific for alveolar dysfunction and maybe a more sensitive indicator of emphysema progression especially useful early in the disease process. Thus it would make clinical sense to target augmentation therapy to this group of individuals. How these physiological studies fit with the recent controlled trial of augmentation therapy using CT densitometry (413) needs to be determined and the ADAPT data base includes many subjects with historical densitometry data and longer term physiological monitoring. Thus repeat CT densitometry studies should be undertaken to determine the relationship between density decline and more familiar physiological parameters.
The above studies have been performed in ZZ patients. It would be important to analyse the GOLD group distribution and lung function decline of patients with other “at risk” AATD phenotypes such as the SZ cohort to determine if it provides a more generalised approach.

**Comorbidities in AATD**

This study has shown that comorbidities are often present in patients with AATD and affect the quality of life in these individuals. The comorbidities were documented on the basis of the clinical information available for each patient. It is possible that some of these comorbidities could be better evaluated earlier on in the disease process by certain disease specific questionnaires. These include the Medical Outcomes Study Short-Form 36-item (SF-36) to assess the general health status (115), Frequency scale for symptoms of GORD (FSSG) questionnaire (434) and evaluation of anxiety and depression using HADS (119) in patients with AATD. This would provide a more comprehensive clinical assessment and enable the identification of comorbidities that may benefit from specific interventions. Given that these comorbidities affect quality of life it is important to identify them early and manage them appropriately. Patients who attend the ADAPT programme complete different questionnaires during their initial and subsequent annual visits. Patients should also complete these more specific questionnaires during their visits to give the information required for comprehensive management.

**Impact of comorbidities on the quality of life in patients with AATD**

We have used COPD specific scores to assess the impact of comorbidities in AATD. The current study has shown that those with higher CAT scores (Group D) also had more comorbidity. Studies with a larger sample size, or using non-COPD specific HRQoL scores
would clarify this further. These studies could be performed using non COPD specific questionnaires.

These disease specific questionnaires could also be applied to patients with usual COPD where there is evidence that these comorbidities affect quality of life (197, 320). The studies performed in AATD could then be replicated in usual COPD to determine whether they have more /less or similar impact in AATD.

The current study did not provide a reason for the high symptom load in group B patients and the reasons still remain unknown. It could be either cardiovascular, depression, or obesity. Or possible related to gas transfer. The reason why group C patients have so few symptoms could also be explored further to understand if it is related to gas transfer or activity or age. Comparing groups B and C might help.

The COTE study could be extended to patients with AATD and using similar methods i.e. comorbidities influencing mortality and calculating hazard ratio, a list of the most frequently occurring comorbidities could be constructed. Using similar weighting (which was similar to the one used for the Charlson index), an index could be developed for patients with AATD. However in our study, presence of comorbidities did not appear to influence survival and hence this approach was not considered. A more realistic approach would be to focus on the most frequently occurring comorbidities (top six as per our study) by healthcare professionals looking after these patients. Effective interventions that would reduce the morbidity burden and mortality risk from these are available and could be offered to patients.

Information obtained from the above studies would enable the development of clinical guidelines tailored towards appropriate management of multiple comorbidities supporting the position taken by GOLD (1) and thereby improving patient wellbeing and prognosis.
Appendix 1: Ethics and Consent Form for AATD assessment

What is the study about?
You or a member of your family has been identified as having alpha\textsubscript{1} antitrypsin deficiency. This is an inherited condition that is believed to increase the risk of development of lung health problems. However very little detailed information has been collected on the way this deficiency affects patients and some studies have suggested that lung disease may run in families even without the deficiency. It is likely however that the deficiency highlights the tendency to develop these diseases and when present will make them worse.

We wish to learn as much as possible about the deficiency and its relationship to lung disease and for this reason invite you to participate in our alpha\textsubscript{1} antitrypsin deficiency assessment programme.

What will I have to do?
In broad terms you will undergo all the routine questioning, examination and tests that we normally undertake when assessing somebody who presents with lung disease. However we hope to do this more carefully and in more detail than is routinely carried out by your own doctor or specialist.

We will ask many questions about your past and present symptoms, health and wellbeing. In addition you will be examined thoroughly to determine the presence of signs related to lung disease. After this screening programme you will be asked to perform some lung function testing which assesses how your lungs work and their ability to take oxygen in and out of your body. We may also perform a specialised CT scan of your lungs (if you have not had one) which is a very sensitive technique of detecting damage that has occurred. Finally we will ask you to provide one blood sample and if you have a cough productive of sputum we will arrange for you to collect this over several hours on one day before coming to see us.

Once all these tests have been performed we will be able to determine whether you have lung disease related to alpha\textsubscript{1} antitrypsin deficiency. This will be explained to you and any modifications in your treatment that are indicated will be communicated to both yourself and your own doctor.

It is our general clinical routine to follow patients with established lung disease on a long-term basis. Patients are usually seen once every 4-6 months to assess their wellbeing and follow any progress in the condition. If you have alpha\textsubscript{1} antitrypsin deficiency we would wish to see you once a year to assess your symptoms, clinical signs and repeat the extensive lung function tests and the CT scan to confirm the extent or any progression of your disease will be carried out every 2 years. After the first year the lung function may be repeated less frequently (2 or 3 yearly) depending on whether these are changing or are stable.

NOTE The CT scan exposes you to a small degree of radiation – about the equivalent of 6 months background radiation in the UK. Although this dose is safe (it is the same as a single
x-ray of the abdomen), it is important that you inform us if you are likely to be pregnant as we will not carry out the test in these circumstances.

What are the benefits?
The major purpose of the study is to find out as much as possible about the lung disease associated with alpha\textsubscript{1} antitrypsin deficiency. This will provide the background information that enables us to design studies to assess the role of alpha\textsubscript{1} antitrypsin replacement therapy in both the short and long term. The investigations that we undertake will allow us to advise upon the degree of lung disease that you have and simple measures that you can undertake with your current treatment in order to try and stabilize the lung disease. In addition the breathing tests that we will perform will help us to optimize your current treatment in order to improve your breathlessness where possible.

What are the risks?
All the investigations that are taking place are entirely routine, used in the assessment of patients with lung disease. As such they are repeated on many occasions in the same patient without any adverse effects. The only minor problem that is likely to occur is a slight degree of bruising in some patients when they have their blood taken.

What are the alternatives?
There are currently no alternatives to finding the information that is required other than the assessment programme outlined above.

What happens if I do not wish to take part?
If you do not wish to participate in the assessment programme or the short term follow up programme this will be fully understood. Your own general practitioner, or the consultant chest physician who normally looks after you, will be informed of the diagnosis and provided with advice on how to assess and manage your follow up along the lines outlined above. If for any reason they or you require further advice from us in the future we will be only too pleased to see you. It is important to emphasize that your overall management by your doctor will not be affected by your decision.

What happens to the information?
The important information that we collect over the next year or two will be written up as a report and submitted to medical journals so that other doctors may read about the problem. The research information obtained from the samples that we have collected will be the basis for future studies on the role of alpha\textsubscript{1} antitrypsin replacement therapy which we hope to start within the next 12-18 months. Neither your name or any details relating to you personally will be released to any other person outside the research programme.

Who is taking part?
All subjects that we identify with alpha\textsubscript{1} antitrypsin deficiency and in some cases members of their family will be asked to take part. At present we know of over 800 such patients as yourself and it is likely that there are several thousand similar people in the West Midlands alone. It is hoped over the next year or two to identify and assess all people with the deficiency in the Midlands.
What if something goes wrong?
The question largely relates to clinical trials and at present that is not part of the assessment programme. If you develop new symptoms for any reason during the assessment day this will be in the presence of a doctor who will take any steps that are necessary to help you. In between visits to the assessment centre your own doctor will be largely responsible for your care but (depending on where you live) we may collaborate with your doctor and help by seeing you if you become unwell.

What happens at the end of a study?
At the end of the study we will have learnt a lot about alpha\textsubscript{1} antitrypsin deficiency. If you remain part of the programme for assessment we will be having regular meetings for all patients to attend to discuss how the assessment programme is going and how our understanding is developing. If for any reason you are unable to attend we will be keeping in touch with you by letter and newsletter to inform you of the progress of the programme.

What if I have more questions or do not understand something?
The doctors, co-ordinator and nurse involved in the alpha\textsubscript{1} antitrypsin assessment programme will happily answer your questions on any occasion when you visit. If questions arise between visits you will be able to contact the centre and either speak to somebody at that time or arrange to do so if for any reason it is inconvenient.

What happens now if I decide to take part?
If you decide to take part in the programme now we will arrange an appointment in the not too distant future for you to come to the assessment centre for the investigations outlined above. This will be arranged to suit everybody’s convenience and all the assessment will be completed where possible on a single visit.

What happens if I change my mind during the study?
If you change your mind during the study, it is important that you notify the assessment centre. This will enable any investigations that have been organized or visits to be cancelled. Your decision will be passed on to both your own doctor and where appropriate your own specialist in order that they can arrange for appropriate appointments to monitor your progress. Providing you are agreeable we would like to contact your own doctor or specialist from time to time in order to find out how you are progressing. However if in the future you once again decide to join the programme, we would be only too pleased to see you.

Antitrypsin Deficiency Assessment and Programme for Treatment, Queen Elizabeth Hospital, Birmingham. B15 2TH
I …………………………………………………………………………………………………
voluntarily agree to participate in the alpha1 antitrypsin deficiency assessment programme.

I have been given a full explanation of the programme and read the patient information sheet and have had all my questions answered and agreed to cooperate where possible with this programme.

I understand that that if I suffer from any unexpected problems that it may be important to contact both my own doctor and the staff at the alpha-1-antitrypsin resource centre.

I understand fully that I am free to withdraw from the programme at any time without giving a reason and that this will not adversely affect my future management.

Signed (Patient)………………………………………………………………………………
Date ……………………………………………………………………………………………

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Appendix 2: Reference Equations

Pulmonary function tests
Reference equations that generate predicted lung function values are available from the Association for Respiratory Technology and Physiology in the UK (www.artp.org.uk). These were generated using regression models from a cohort of subjects aged 18-60, and include height, age and gender components. The equations are as follows:

<table>
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<tr>
<th>Unit</th>
<th>Regression equation</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>FEV1</td>
<td>l</td>
<td>4.30H - 0.029A - 2.49</td>
<td>3.95H - 0.025A - 2.60</td>
</tr>
<tr>
<td>FVC</td>
<td>l</td>
<td>5.76H - 0.026A - 4.34</td>
<td>4.43H - 0.026A - 2.89</td>
</tr>
<tr>
<td>TLC</td>
<td>l</td>
<td>7.99H - 7.08</td>
<td>6.60H - 5.79</td>
</tr>
<tr>
<td>RV</td>
<td>l</td>
<td>1.31H + 0.22A -1.23</td>
<td>1.81H + 0.016A - 2.00</td>
</tr>
<tr>
<td>TLCO</td>
<td>mmol.min⁻¹.kPa⁻¹</td>
<td>11.11H - 0.066A - 6.03</td>
<td>8.18H - 0.049A - 2.74</td>
</tr>
<tr>
<td>KCO</td>
<td>mmol.min⁻¹.kPa⁻¹.l⁻¹</td>
<td>Predicted TLCO/predicted Va</td>
<td></td>
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</tbody>
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174
Appendix 3: Ethics, Consent Form and Questionnaire for COPD Study

Title: A study of clinical phenotypes, disease progression and epigenetics in patients with chronic obstructive pulmonary disease and its associated co morbidities.

You have been asked to participate in a clinical study for research purposes. Before you decide to take part it is important that you understand why the study is being performed, what it involves, and any possible risks and benefits for you. Take your time reading the following information and discuss it with others if you wish.

Introduction to the research & invitation to take part

You have been diagnosed as having the symptoms or signs of chronic obstructive pulmonary disease (COPD) which is a chronic disease that usually progresses slowly. At present there is no specific therapy for COPD and it is also being appreciated that having COPD means it is more likely that you will develop other diseases such as heart disease and osteoporosis (thinning of the bones). The purpose of the study is to learn as much about COPD and how it affects you and your general health so that we can develop new understanding of the disease and hence develop new treatment strategies.

This study is being carried out by the research department in the Chronic Diseases Resource Centre, which is part of University Hospitals Birmingham NHS Foundation Trust, and is led by Professor RA Stockley. The department has a special interest in understanding and treating chronic lung disease, in particular COPD. You have been contacted because you already have evidence of COPD and we believe that you are suitable to take part in the study.

In summary

- The research aims to determine your symptoms and how they affect you. This includes a full general examination, and all the routine breathing tests, blood sputum tests (if you produce some) and scans (only if you have not had one before as part of your routine assessment and if clinically indicated) that we normally undertake when assessing patients with COPD as well as tests to detect other health problems known to be associated with COPD including but not limited to heart disease, diabetes, and osteoporosis.
- If you take part, you will be seen once a year in this special clinic (which will replace one of your routine appointments if you regularly attend outpatients) asked to provide blood, sputum and urine samples, undergo breathing tests and scans (if you have not already had them), a limited dental examination by a dentist and a hygienist with collection of plaque and saliva samples and answer questions about yourself, your quality of life, work experience and your chest problems
- All information will be stored in such a way that you cannot be identified by anyone without Professor Stockley’s permission
**What is the study about?**
The main purpose of the study is to learn as much as possible about your lung disease. We wish to study in detail how chest infections, smoking and various other factors influence your lung condition and how this progresses over time. Recent research suggests that COPD also has effects elsewhere in the body, chiefly but not limited to heart disease, diabetes, joint problems etc. and we wish to study this in more detail. This knowledge will help in developing newer forms of treatment. All the information obtained from you will be stored on a secure database and will be used in this study and in future research involving COPD.

**What will I have to do?**
In broad terms you will undergo all the routine questioning, examination and tests that we normally undertake when assessing somebody who presents with lung disease. However we hope to do this in more detail than is routinely carried out by your own doctor or specialist.

- We will ask many questions about your past and present symptoms, health and wellbeing.
- you will be examined thoroughly
  - to determine the presence of signs associated with lung disease.
  - for presence of other health problems known to be associated with COPD.
- you will be asked to perform routine lung function testing which assesses how your lungs work and their ability to take oxygen in and out of your body.
- we will ask you to provide blood samples and if you have a cough productive of sputum we will arrange for you to collect this over several hours on the day before coming to see us.
- You will undergo limited dental examination by a dentist and a hygienist and both plaque and saliva samples will be collected.
- A sample of urine for tests will be collected for tests.
- We may also perform a specialised CT scan of your lungs (only if it is clinically indicated and if you have not had one already as part of your routine assessment) which is a very sensitive technique of detecting lung damage that has occurred.
- We may perform a DEXA scan (only if it is clinically indicated and if you have not had one already) which is a technique to detect the extent of thinning of your bones.

We know that COPD is influenced by your genes which have made you susceptible to developing the disease. To determine the influence of genes, (if you agree), we will collect and store a sample of your blood from which we can extract your DNA. No information about the genetic data on you, can or will be released as we will not be able to link this with your name as the sample will be coded once it is processed and separated from any information that identifies it as yours. As medical science progresses new ideas and new genes related to lung disease are likely to become known and for this reason we will store the sample for such future studies. It is important to emphasise that the whole study will be confidential and specific procedures have been put in place to separate all confidential information that could help identify you from the results of genetic DNA analysis.

It is our general clinical routine to follow patients with established lung disease on a long-term basis. We would wish to see you at least once but thereafter we would also wish to review you once year in the CDRC, which will replace any routine clinic appointment, to
assess your symptoms, clinical signs and repeat the comprehensive tests and lung function
tests so that we can identify any factors that cause progression of the COPD. After the third
year the lung function may be repeated less frequently (2 or 3 yearly) depending on whether
these are changing or are stable. After 4 years we will also re assess the presence or
progression of any of the complicating conditions associated with COPD and ensure you are
on the right treatment.

NOTE The routine CT and DEXA scans expose you to a small amount of radiation. The total
dose will be equivalent to about 6 months (to 2 years) of background radiation in the UK.
Although this dose is safe, it is important that you inform us if you are likely to be pregnant as
we will not carry out the CT scan in these circumstances.

What are the benefits?
The major purpose of the study is to find out as much as possible about COPD. The
investigations that we undertake will allow us to advise upon the degree of lung disease that
you have and simple measures that you can undertake with your current treatment in order to
try and stabilise the lung disease. In addition the breathing tests that we will perform will
help us to optimise your current treatment in order to improve your breathlessness where
possible. Finally we will help you and your doctor to identify and manage any associated
health problems affecting other parts of your body that we detect.

What are the risks?
All the investigations that are taking place are entirely routine, used in the assessment of
patients with lung disease. As such they are repeated on many occasions in the patients
without any adverse effects. The only minor problem that is likely to occur is a slight degree
of bruising in some patients when they have their blood taken.

What are the alternatives?
There are currently no alternatives to finding the information that is required other than the
assessment programme outlined above.
There are many ways of looking at blood and sputum samples, but relating them to lung
scans, breathing tests, symptoms and genes has not been done together before. It is therefore
a new area of research, and there are no similar studies being done in the UK at present. Also
the association of COPD with heart disease, diabetes, osteoporosis and other health care
issues is a new area of research and there is a lot to be learnt from this study and how they
should be managed.

What happens if I do not wish to take part?
The study is entirely voluntary and if you do not wish to participate it will not affect your
current or future care. It is important to emphasize that your overall management by your
doctor will not be affected if you do not wish to take part.

What happens to the information?
If you decide to take part you will need to allow access to your medical records. They may be
looked at by the research team, by the hospital Research and Development department and by
regulatory authorities who check that the study is being carried out properly. By signing this
form you are giving permission for this to be done and all information will be kept
confidential. However the results of any tests we carry out will be provided to your own
doctors if it influences your health or management together with any suggestions about changing your treatment.

The information collected will be stored on a secure computer, but your name will not. This is known as linked anonymised data, meaning that only Professor Stockley or a delegated deputy will be able to link any of the information to your name. He or a delegated deputy will have sole access to a written record of your information, stored in a secure facility at University Hospitals Birmingham. All the data collected, samples you provide, and their results, including any information about your genes, will be coded with a number. The results of tests on your samples and about your genes will not be available to anyone outside of the research team and our collaborators. The link to your name will be destroyed 15 years after the study ends according to national guidelines.

Once the data is collected it will be the property of the research department. The data will be used for future research into COPD. Research undertaken will involve observational assessment, quantification of impact on health care and studies of factors that affect the outcome in COPD.

**Who will have access to the data?**
Members of the research team led by Prof Stockley will have full access to the database. Access will be built on a role based model, with registered users having graded levels of access to the data. They will have unique user names and passwords and there will be a record of anyone logging in to the database ensuring we have a record of users accessing the system.

The results of the study may be published in a medical journal, but your identity will not be revealed. The results may be used in statistical tests, in the development of new treatments and diagnostic tests.

**Who is taking part?**
About 1000 other patients with COPD will be asked to take part at the University Hospital Birmingham and Heart of England hospitals.

**What if something goes wrong?**
Since the study is not a clinical trial and involves only simple tests that could form part of your routine care, we do not expect any harm to come to you. Whatever part of the study you choose or decide not to take part in will not affect your future routine care.

**What happens at the end of a study?**
Throughout the study, and when it ends, your hospital doctor and general practitioner will continue to treat your chest problems and be kept informed of the results of our tests, so they will not need to repeat them unnecessarily.

**What if I have more questions or do not understand something?**
The doctors and nurses involved in the research study will happily answer your questions on any occasion when you visit. If questions arise between visits you will be able to contact the centre and either speak to somebody at that time or arrange to do so if for any reason if it is inconvenient.
What happens now if I decide to take part?
If you decide to take part in the programme now we will arrange an appointment in the not too distant future for you to come to the assessment centre for the investigations outlined above. This will be arranged to suit everybody’s convenience and all the assessment will be completed where possible on a single visit.

Will my General Practitioner (GP) be informed?
If you give your permission, your GP and usual hospital doctor will be informed of your participation in the study.

What happens if I change my mind during the study?
You are free to withdraw your participation at any time, and it will not affect your future care. If you withdraw your consent after your samples have been analysed it will be the responsibility of the research team to ensure that the samples are destroyed if you so wish.

Who can I contact about the study?
In the first instance any concerns or questions should be addressed to either your GP or hospital doctor. If you have further concerns you can contact

Thank you for taking time to read this information leaflet
CONSENT FORM

Title: A study of clinical phenotypes, disease progression and epigenetics in patients with chronic obstructive pulmonary disease and its associated co morbidities.

I………………………………………………………………… (Name in BLOCK CAPITALS)   Initials

Have read the attached information concerning my participation in this study and have had opportunity to discuss it and ask questions. All my questions have been answered in a satisfactory way.

I voluntarily consent to take part in this study.

I know that at any time, and without giving a reason, withdraw my participation in the study and that my future care and management will not be affected.

I understand that I will have a copy of this Patient Information Leaflet and Written Consent to keep.

I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

I hereby give permission for samples taken as part of this study to be stored for future use by the research team.

I understand that data collected during the study will be stored on the database for use in future studies.

I hereby give permission for my GP and hospital consultant to be informed about my participation in this research study.

........................................................................................................................................
Patient’s signature   Date

........................................................................................................................................
Name in BLOCK CAPITALS

Responsible investigator
I have explained the nature and purpose of this study for the person named above

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Responsible investigator/representative signature   Date

........................................................................................................................................
Name in BLOCK CAPITALS
COPD Questionnaire

Subject name: ………………………………………
Identification number: ……………………………
D.O.B: …………………………………………………

1. Have any members of your family been told they have any of the following:
   (if Yes please state which family member/s)
   COPD  □ Yes  □ No
   -----------------------------------------------
   Bronchitis  □ Yes  □ No
   -----------------------------------------------
   Emphysema  □ Yes  □ No

2. Have you been given a diagnosis of
   COPD  □ Yes  □ No
   Bronchitis  □ Yes  □ No
   Emphysema  □ Yes  □ No
   ---------------------------------------------------
   If you answered Yes who made the diagnosis
   □ GP  □ Hospital specialist
   □ Other (eg. nurse) ………………………………………

3. Have you smoked regularly?  □ Yes  □ No
   ---------------------------------------------------
   If you answered Yes
   How many cigarettes do / or did you smoke  ………… per day
   At what age did you start  …………. years of age
   Have you stopped smoking  □ Yes  □ No
   How old were you when you stopped  …………. years of age

4. Do you have a daily cough?  □ Yes  □ No
   ---------------------------------------------------
   If you answered Yes
   Do you produce sputum / phlegm  □ Yes  □ No
   Have you produced sputum / phlegm for more than 3 months in the past 2 years  □ Yes  □ No
   ---------------------------------------------------
   If you answered Yes
   Do you produce sputum / phlegm on a daily basis  □ Yes  □ No

4. Do you suffer from more breathlessness doing things than you would expect for people of your same age?
   □ Yes  □ No
Appendix 4: Publications resulting from this thesis

Original articles:


Abstracts:

- Rapid decliners in alpha one antitrypsin Deficiency. A Pillai, Turner AM, Stockley RA. Poster discussion at the American Thoracic Society Meeting, 2014

- Predicting the clinical course of AATD using the GOLD 2011 classification. A Pillai, Turner AM, Stockley RA. Poster discussion at the European Respiratory Society Annual Congress, 2013.


- Treatment of stable COPD in Alpha 1 Antitrypsin Deficiency (AATD) patients using the 2011 GOLD treatment algorithm. A Pillai, Stockley RA. Poster discussion at British Thoracic Society, 2012.
8 References


69. Briscoe WA, Nash ES. The slow space in Chronic Obstructive Pulmonary Disease.


200


201


McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-69.


