ADHERENCE TO GOLD GUIDELINES IN COPD PATIENTS AT A TERTIARY HOSPITAL

Steven Kaftel

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine.

February 2020

DECLARATION

I, Dr Steven Kaftel declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

…….. (signature)

The 9th day of February 2020

SUPERVISOR

Dr Ismail Sikander Kalla

MBBCH (WITS), PhD (WITS), FCP (SA), FCCP (USA), Cert. Pulm (SA), Cert. Crit Care (SA)

ABSTRACT

Background: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, updated in 2019, provide a framework to classify chronic obstructive pulmonary disease (COPD) severity. In so doing, it guides practitioner's choice of therapy for the individualized patient. The GOLD guidelines classify patients into one of four groups: A, B, C, or D. This is based on symptoms, as well as exacerbations or hospitalizations. Inhaled corticosteroids (ICS) should be reserved for GOLD C and D patients who have frequent exacerbations (≥2/year).

Aims: The primary objective of this research is to document adherence to GOLD treatment guidelines in COPD patients at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) respiratory clinic. The secondary objective of the study is to investigate whether a statistically significant association exists between GOLD category and lack of adherence to guidelines, as well as GOLD category and inappropriate use of ICS.

Methods: A retrospective record review of patients with COPD attending respiratory clinic over a three month period at CMJAH was conducted. Descriptive analysis of the data was carried out as follows: categorical variables were summarized by frequency and percentage tabulation and illustrated by means of bar charts. Continuous variables were summarized by the mean, standard deviation, and their distribution illustrated by means of histograms. The Chi Square test was used to assess the relationships between categorical variables and the Fisher's exact test when the sample size was small.

Results: A total of 146 patients were included in the study. In 54.1% of cases the modified Medical Research Council (mMRC) classification of breathlessness was not recorded in the notes. The majority of the patients (72.6%) were classified as Group B. Furthermore, 87.7% of the total patient cohort were using ICS or ICS/long acting beta 2 agonist (LABA) combination therapy, and 61.0% of patients were using triple therapy: long acting muscarinic antagonist (LAMA), LABA,

and ICS. Only 24.7% of patients were found to be receiving treatment adherent to GOLD guidelines with respect to appropriate use of ICS. There was a significant association between GOLD category and a lack of adherence to GOLD treatment guidelines ($p<0.0001$) with non-adherence to guidelines being much higher in group B with a significant percentage of patients (87%) on inappropriate ICS therapy.

Conclusions: Adherence to GOLD guidelines and therapeutic algorithms was lacking in this cohort of patients studied. The mMRC classification of breathlessness was poorly recorded in the patients' notes despite the fact that it forms a core part of the GOLD classification. In addition, the majority of patients are treated with ICS therapy. This may be as a result of the lack of the appropriate patient classification according to the GOLD criteria. This limitation has probably resulted in the injudicious use of ICS therapy with the potential for an increased risk of side effects such as pneumonia. In order to prevent this, we should be implementing strategies to ensure that the GOLD classification is correctly recorded at each clinic visit by means of a standard data collection sheet. This will prevent over treatment of patients, reduce the use of unnecessary inhalers and the cost thereof in a resource constrained setting, as well as potentially reduce the complications and side effects of ICS therapy. The use of serum eosinophil counts as a validated biomarker may help to guide practitioners to decide which patients to attempt withdrawal of ICS therapy.

ACKNOWLEDGEMENTS

I would like to thank Dr Ismail Kalla for all the time and effort he has afforded to me and to the completion of this research report. It has truly been a privilege to have him as my supervisor for this project. His wisdom and guidance have been invaluable to me throughout my career as a doctor and I consider him a mentor and role model.

I would like to acknowledge and thank Mr Duke Mokotedi, the clerk in the respiratory department at CMJAH who assisted in separating out the files of the COPD patients attending the respiratory clinic. This was extremely helpful in collecting data.

I would like to pay tribute to Mrs Petra Gaylard for her invaluable assistance with the statistical analysis of my data.

I would like to also thank my wife Dr Sara Glatt for all her support and love throughout my journey as a doctor and for encouraging me and assisting me in finalizing this research report. I love you very much. Thank you also for bringing our beautiful daughter Emma into the world. My darling Emma, you are the light of my life and your smile and laughter are my biggest blessings.

TABLE OF CONTENTS

DECLARATION ..... **II**

ABSTRACT ..... **III**

ACKNOWLEDGEMENTS ..... **V**

TABLE OF CONTENTS ..... **VI**

LIST OF TABLES & FIGURES ..... **X**

ABBREVIATIONS AND STUDY NAMES ..... **XI**

CHAPTER 1: INTRODUCTION **1**

1.1 GOLD guidelines 1

1.2 Definition 1

1.3 Risk Factors 1

1.4 Morbidity and Mortality 1

1.5 Diagnosis 2

1.6 Symptoms 2

1.7 Spirometry 2

1.8 Exacerbations/Hospitalizations 3

1.9 GOLD Classification 3

1.10 Therapy 4

1.10.1 Smoking cessation 4

1.10.2 Pharmacological agents: inhaler therapy and oral therapy 4

1.10.3 Other 6

1.11 GOLD guideline directed therapy 6

1.12 Monitoring and Follow Up 7

CHAPTER 2: LITERATURE REVIEW **8**

2.1 The UPLIFT study 8

2.2 The TORCH study 9

2.3 The WISDOM trial 10

2.4. The FLAME study 10
2.5. The INSPIRE trial 11
2.6. The INVIGORATE study 11
2.7. The TRILOGY trial 11
2.8 The IMPACT trial 12
2.9. The NOTT study 12

CHAPTER 3: RATIONALE, AIM AND OBJECTIVES 16

3.1 Rationale 16
3.2 Aim 16
3.3 Objectives 16
3.3.1 Primary objective 16
3.3.2 Secondary objective 17

CHAPTER 4: DESIGN, METHODOLOGY AND DATA ANALYSIS 18

4.1 Study Design 19
4.2 Study Population 19
4.2.1 Inclusion Criteria 19
4.2.2 Exclusion Criteria 19
4.3 Sample Size 19
4.4 Data Entry 20
4.5 Data Collection (Appendix 7) 20
4.6 Data Analysis 21

CHAPTER 5: RESULTS, DISCUSSION AND CONCLUSION 23

5.1 Results 23
Table 1: Baseline demographic characteristics of study sample 23/24
Descriptive Data: 25
Figure 1: Age distribution 25
Figure 2: FEV1 % category distribution 25
Figure 3: Number of hospitalizations in last year 26
Figure 4: Number of exacerbations in last year 26
Figure 5: GOLD category 27
Figure 6: GOLD stage and grade 27
Figure 7: Inhaler usage 28

Determination of the association between selected study variables 28
Figure 8: FEV1 % vs hospitalizations 29
Figure 9: FEV1 % vs exacerbations 29
Figure 10: GOLD category vs treatment adherence 30
Figure 11: GOLD category vs appropriate use of ICS 30
Figure 12: GOLD category vs home oxygen usage 31
5.2 Discussion 31
5.3 Limitations 33
5.4 Conclusion 33
5.5 Future Recommendations 34

CHAPTER 6: REFERENCES 35

CHAPTER 7: SUBMISSABLE ARTICLE 39

ABSTRACT 39

INTRODUCTION 41

METHODS 43
Study Design 43
Study Population 43
Sample Size 43
Data Analysis 43

RESULTS 44
Descriptive Data. 46
Determination of the association between selected study variables 49

DISCUSSION 52

LIMITATIONS 54

CONCLUSION 55

FUTURE RECOMMENDATIONS 55

CHAPTER 8: REFERENCES 57

CHAPTER 9: APPENDICES 59

Appendix 1: mMRC dyspnea scale 59

Appendix 2: COPD assessment test..... 60

Appendix 3: Severity of airflow limitation in COPD..... 61

Appendix 4: 2011 GOLD ABCD classification 62

Appendix 5: 2018 GOLD ABCD classification 63

Appendix 6: Pharmacological treatment algorithms by GOLD grade 2018 guidelines..... 64

Appendix 7: Data collection sheet 65

Appendix 8: Ethics clearance……..**66**

Appendix 9: Turn it in report……**67**

LIST OF TABLES & FIGURES (extended literature review & submissable article)

Table 1: Baseline demographic characteristics of study sample	23,24 & 44,45
Figure 1: Age distribution	25 & 46
Figure 2: FEV1 % category distribution	25 & 46
Figure 3: Number of hospitalizations in last year	26 & 47
Figure 4: Number of exacerbations in last year	26 & 47
Figure 5: GOLD category	27 & 48
Figure 6: GOLD stage and grade	27 & 48
Figure 7: Inhaler usage	28 & 49
Figure 8: FEV1 % vs hospitalizations	29 & 50
Figure 9: FEV1 % vs exacerbations	29 & 50
Figure 10: GOLD category vs treatment adherence	30 & 51
Figure 11: GOLD category vs appropriate use of ICS	30 & 51
Figure 12: GOLD category vs home oxygen usage	31 & 52

ABBREVIATIONS AND STUDY NAMES

BD: twice a day

CAT: COPD assessment test

CI: confidence interval

CCQ: COPD control questionnaire

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

COPD: chronic obstructive pulmonary disease

DPI: dry powder inhaler

E-Cigarettes: electronic cigarettes

FEV1: forced expiratory volume in 1 second

FF: fluticasone furoate

FLAME: indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD

FVC: forced vital capacity

GP: general practitioner

HIV: human immunodeficiency virus

HR: hazard ratio

ICS: inhaled corticosteroid

IMPACT: once-daily single-inhaler triple versus dual therapy in patients with COPD trial

INSPIRE: prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide

INVIGORATE: once daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease

LABA: long acting beta 2 agonist

LAMA: long acting muscarinic antagonist

LTDOT: long term domiciliary oxygen therapy

LVR: long volume reduction

mMRC: modified Medical Research Council

NOTT: nocturnal oxygen therapy trial group

NNT: numbers needed to treat

NRT: nicotine replacement therapy

OR: odds ratio

PaO2: partial pressure of oxygen in arterial blood

pMDI: pressurized metred dose inhaler

PRN: when necessary

SA: South African

SABA: short acting beta 2 agonist

SAMA: short acting muscarinic antagonist

SD: standard deviation

SFC: salmeterol/fluticasone

SMI: soft mist inhaler

SUMMIT: Study to Understand Mortality and Morbidity in COPD

TB: tuberculosis

TORCH: Towards a Revolution in COPD Health

TRILOGY: single inhaler triple therapy versus inhaled corticosteroid plus long acting B2 agonist therapy for chronic obstructive pulmonary disease

UMEC: umeclidinium

UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium

VI: vilanterol

VS: versus

WISDOM: Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

CHAPTER 1: INTRODUCTION

1.1 GOLD guidelines

The Global initiative for chronic obstructive lung disease (GOLD) guidelines is a consensus report which was released in 2011 and updated annually (1). It focuses on a global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (COPD). The GOLD guidelines are recommended to be used as a tool or "strategy document" in guiding health care professionals in implementing management algorithms for COPD patients within available resources.

1.2 Definition

COPD is defined by the GOLD 2019 guidelines as : "*a common preventable and treatable disease, that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases"* (1).

1.3 Risk Factors

The major risk factors for the development of COPD are cigarette smoking, tobacco smoking, marijuana smoking and exposure to biomass fuels, the burning of wood (2), and infectious agents like human immunodeficiency virus (HIV) (3) and tuberculosis (TB) (4). Air pollution is now also recognized as a major risk factor for the development of COPD (5).

1.4 Morbidity and Mortality

The morbidity and mortality due to COPD are significant. Contributors to morbidity include baseline levels of dyspnoea, visits to physicians, emergency room visits, infective and non-infective exacerbations, as well as hospitalizations.

COPD is not only often a primary cause of death, but also a contributory one. Cardiovascular and neoplastic diseases in patients with concomitant COPD are frequently the cause of mortality. In addition, COPD is currently the 4th leading cause of death worldwide and is estimated to become the 3rd leading cause of death by 2020 (6).

1.5 Diagnosis

COPD diagnosis requires the use of spirometry in the clinical context. The presence of post-bronchodilator forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) of <0.70 confirms the diagnosis of COPD. The most recent GOLD guidelines describe a "grey zone" of an FEV1/FVC between 0.6 and 0.8 and recommend repeat measurement on a separate occasion to account for patient variability. Any FEV1/FVC of < 0.6 confirms obstruction (7, 8).

1.6 Symptoms

Symptoms of COPD include dyspnoea, cough, sputum production, wheezing or chest tightness, fatigue, weight loss and anorexia. There are a variety of objective scoring systems available to assess the severity of COPD patients' symptoms. Examples include the modified Medical Research Council (mMRC) dyspnoea scale (9) (Appendix 1) and the COPD assessment test (CAT) (10) **(**Appendix 2). An mMRC of ≥2 is often used in distinguishing "less breathlessness" from "more breathlessness".

1.7 Spirometry

Spirometry is used to classify the severity of airflow limitation **(**Appendix 3**)**. The post bronchodilator FEV1 is used to define these four stages of COPD. There is, however, only a weak correlation between spirometry (FEV1) and the patient's symptoms as well as impairment of health status (11). This has been the major reason for the change in the GOLD severity assessment tool.

1.8 Exacerbations/Hospitalizations

GOLD defines an acute exacerbation as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day to day variation and leads to a change in medication" (1). It has been shown in studies that the best predictor of having frequent exacerbations (≥2/year) is a history of having previously treated exacerbations or events (12).

1.9 GOLD Classification

The 2011 GOLD guidelines initially proposed a combined COPD assessment strategy incorporating spirometry, symptoms, and/or risk of exacerbations, as well as hospitalizations. Patients are classified into A, B, C, or D groups according to this approach (Appendix 4). A higher GOLD classification indicates increased disease severity, worse symptoms, higher risk of exacerbations, and it also serves to guide treatment options. The 2011 GOLD guidelines clearly documented that assessment of FEV1 % predicted alone was insufficient in understanding the impact of the disease on the patient, assessing exacerbation risk, and guiding further treatment. With subsequent studies published (13-15), the 2018 GOLD guidelines **(**Appendix 5**)** have been revised to highlight these various limitations of the 2011 guidelines. The 2011 GOLD ABCD tool performed no better than simple spirometric evaluation in terms of mortality prediction as well as other important health outcomes in patients with COPD (16). The revised GOLD-ABCD assessment tool proposes that both airflow limitation as well as patient symptoms and exacerbations should be considered when classifying a patient with COPD. However, they should be considered as separate entities to better risk stratify patients and institute therapy. In other words, the numbers one to four would indicate the stage of airflow limitation determined spirometrically and the letter A-D would indicate the group as per symptoms and exacerbation risk. Treatment should then be guided by both parameters.

1.10 Therapy

There are several therapeutic interventions recommended by the latest GOLD guidelines and include: smoking cessation and pharmacological agents such as inhalers and oral therapy.

1.10.1 Smoking cessation

This is an intervention which has the greatest capacity to impact on the long-term history of COPD. Nicotine replacement therapy (NRT) in the form of chewing gum, patches, and sprays reliably increase long term smoking cessation and abstinence from cigarettes (17).

The efficacy of electronic cigarettes (E-cigarettes) in the setting of NRT remains controversial (18). GOLD guidelines in 2018 suggest exercising caution before widespread use of E-cigarettes is advocated. Further data needs to be collected.

1.10.2 Pharmacological agents: inhaler therapy and oral therapy

Inhaler options include short acting beta 2 agonists (SABA), short acting muscarinic antagonists (SAMA), long acting beta 2 agonists (LABAs), long acting muscarinic antagonists (LAMAs), as well as inhaled corticosteroids (ICS). Inhaler therapy can be metered dose inhaler (MDI), dry powder inhaler (DPI), soft mist inhaler (SMI), or nebulizers. There are a variety of inhalers on the market which have combinations of the above drugs. LABAs have been shown to improve FEV1 as well as lung volumes, dyspnoea, health status, exacerbation rates and number of hospitalizations. They however, have not been shown to affect mortality or the rate of decline of lung function (19). LAMAs such as tiotropium have been shown to improve symptoms and health status. In addition, tiotropium has been shown to reduce exacerbations as well as subsequent hospitalizations (20). Clinical data published to date have documented a greater reduction in exacerbation rates with the use of LAMAs preferentially over LABAs as monotherapy (21, 22), but if indicated, the combination of LAMA/LABA is superior to either alone (23).

There is significant heterogeneity and discordant data with regards to the use of ICS in patients with COPD. As per GOLD guidelines the following recommendations have been formulated based on the strength of the existing data published on ICS therapy:

- ICS therapy alone does not change the decline in FEV1 nor the mortality rate in patients with COPD (24).
- The Towards a Revolution in COPD Health (TORCH) trial documented a trend towards higher mortality in patients using fluticasone propionate (ICS) alone vs placebo or salmeterol (LABA) plus fluticasone propionate combination (25). However, this increase in mortality was not observed with the use of fluticasone fuorate in the Study to Understand Mortality and Morbidity in COPD (SUMMIT) which looked at the survival of patients with COPD with heightened cardiovascular risk (26).
- Studies have shown that in patients with moderate to severe COPD and frequent exacerbations, combination ICS/LABA is more effective than either alone (27), or when compared to LAMA/LABA combination in improving lung function, health status, and reducing exacerbations (28, 29).
- The above evidence must be balanced against the fact that use of ICS is associated with increased risk of oral candidiasis, hoarse voice, easy skin bruising, and pneumonia (24, 30).

With the recent introduction of triple inhaled therapy (LAMA/LABA/ICS) in a single device this debate has become even more complicated. Further clinical evidence is required to comment on the comparison of triple therapy to LAMA/LABA combination. However, various clinical trials have shown benefits of triple therapy in terms of improving lung function as well as patient symptoms (31).

Oral agents including methylxanthines such as aminophylline and theophylline have been shown to have a modest bronchodilator effect. When combined with salmeterol they have been shown to produce a greater improvement in breathlessness and FEV1 than the salmeterol alone (32, 33). Systemic corticosteroids such as prednisone have been shown to be useful in treating acute exacerbations (34). Phosphodiesterase 4 inhibitors such as roflumilast have been shown to reduce moderate to severe exacerbations in specific COPD patient phenotypes that include the frequent exacerbator phenotypes (35).

1.10.3 Other

Vaccinations such as the yearly influenza vaccination as well as the pneumococcal vaccination are both recommended for COPD patients (36). This is one of the key interventions recommended for risk reduction by the GOLD guidelines. Other treatment which may be of benefit includes: long term antibiotics such as azithromycin (37), and mucolytics such as n-acetylcysteine (38). Non-pharmacological therapies that have shown to be of benefit include pulmonary rehabilitation programs and exercise training (39). Long term domiciliary oxygen therapy (LTDOT) (>15 hours/day) has been shown to increase survival in patients with resting hypoxaemia and who fulfil the following criteria: partial pressure of arterial oxygen (PaO2) <55mmHg or oxygen saturation <88% confirmed twice over a 3-week period; or PaO2 between 55mmHg-60mmHg or oxygen saturation <88% if there is evidence of pulmonary hypertension, peripheral oedema suggesting congestive cardiac failure or polycythaemia (haematocrit >55%) (40). Lung volume reduction (LVR) surgery has been successfully used in patients with severe upper lobe emphysema and low post-rehabilitation exercise capacity. It has been shown to improve expiratory flow rates and reduce exacerbations (41). Medical LVR in the form of bronchoscopically inserted bronchial coils have also been shown to be beneficial (42).

1.11 GOLD guideline directed therapy

The goals of therapy are twofold:

A) Reduce symptoms – relief of symptoms, improving exercise tolerance, as well as improving health status.

B) Reduce risk – of disease progression, prevent and treat exacerbations, and reduce mortality.

Both pharmacological and non-pharmacological interventions should be used for these patients. The most important non-pharmacological intervention is smoking cessation. The proposed specific pharmacological management of COPD is based on the ABCD assessment of the disease severity. **(**Appendix 6**).** This new treatment algorithm is based on the revised COPD severity grades that incorporate patient symptoms as well as exacerbation risk. The GOLD guidelines advocate that treatment should be escalated or de-escalated based on patients' symptoms and response to treatment.

1.12 Monitoring and Follow Up

Patients with COPD should be followed up as outpatients regularly. Doctors should ask about symptoms such as dyspnoea, wheezing, cough, sputum production and sputum purulence. Spirometry should be performed to assess decline, stability, or improvement of lung function. The grade of dyspnoea should be documented: mMRC or CAT score. Exacerbations and hospitalizations should be documented. Smoking status and inhaler technique should be checked. Pharmacological therapy as well as non-pharmacological therapy should be introduced in all patients. Treatment should be escalated or de-escalated appropriately. With the latest GOLD guidelines placing a significant emphasis on addressing both symptom reduction as well as future risk reduction, this study was undertaken to assess adherence to these latest guidelines at the respiratory clinic at CMJAH.

CHAPTER 2: LITERATURE REVIEW

There are numerous landmark papers which have guided COPD management and have been instrumental in forming the GOLD treatment guidelines namely:

2.1 The Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study (43).
2.2 The Towards a Revolution in COPD Health (TORCH) survival study (25).
2.3 The Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD (WISDOM) trial (14).
2.4 The Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD (FLAME) study (13).
2.5 The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide (INSPIRE) study (44).
2.6 The once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE) study (22).
2.7 The single inhaler triple therapy versus inhaled corticosteroid plus long acting B2 agonist therapy for chronic obstructive pulmonary disease (TRILOGY) trial (31).
2.8 The once-daily single-inhaler triple versus dual therapy in patients with COPD (IMPACT) trial (45).
2.9 The nocturnal oxygen therapy trial group (NOTT) study (46).

This chapter will focus on these studies and their impact on the classification and management of patients with COPD.

2.1 The UPLIFT study

This was a multicentre, double blinded, parallel group, randomized placebo-controlled trial where 5993 patients were randomly assigned to tiotropium and placebo. This was done across 37 countries in 487 centres between January 2003-March 2004. Patients were followed up for a median period of 3.9 years. Within the patient population 75% were males and 30% were current smokers. Spirometry was measured at baseline and at regular follow ups as well as mean pre-and

post-bronchodilator FEV1. There was no statistically significant change in spirometry measurements. The UPLIFT study investigated whether the LAMA tiotropium would decrease the rate of decline of FEV1 among patients with COPD. Although the study did not show an improvement in this primary endpoint, it did show that tiotropium was associated with a reduced risk of exacerbations and a trend towards decreased 4-year mortality. This finding has led to many pulmonologists adding tiotropium to COPD patient management especially those with unacceptably high levels of exacerbations. This has been met with some scepticism due to the high cost of the drug**.** There was a statistically significant decrease in the median time to 1st exacerbation – 16.7 vs 12.5 months ($p<0.001$) and number of exacerbations of COPD – 0.73 vs 0.85 events/patient-year (RR 0.86 95% CI 0.81-0.91; $p<0.001$) in the tiotropium arm compared to placebo.

2.2 The TORCH study

This was is a multicentre, double blinded, parallel group, randomized placebo-controlled trial including 6112 patients with COPD and published in 2007. Follow up was for 3 years. It randomly assigned COPD patients to receive salmeterol/fluticasone combination (LABA/ICS) or salmeterol (LABA) or fluticasone (ICS) or placebo. The study documented that combination therapy with salmeterol/fluticasone (LABA/ICS) was associated with a reduction in the rate of exacerbations and hospitalizations; but there was only a trend towards improved survival at 3 years. Combination LABA/ICS was, however, associated with a 25% reduction in exacerbations corresponding to a number needed to treat (NNT) of 4 to prevent 1 exacerbation in 1 year. In addition, it also led to a 17% reduction in COPD related hospitalizations. The annual rate of moderate or severe exacerbation in the intervention group was:

- LABA/ICS vs placebo: 0.85 vs 1.13 (RR 0.75; 95% CI 0.69-0.81, $p <0.001$).
- LABA/ICS vs salmeterol: 0.85 vs 0.97 (RR 0.88; 95% CI 0.91-0.95 $p=0.002$).

This significant change was however counterbalanced by a 49% increased risk of pneumonia associated with ICS therapy:

- LABA/ICS vs placebo: 19.6% vs 12.3% ($p<0.001$).
- Fluticasone (ICS) vs placebo 18.3% vs 12.3% ($p<0.001$).

2.3 The WISDOM trial

This study was a multicentre, randomized, double blind, non-inferiority control trial where patients were randomized to continue or to slowly withdraw the ICS over a 12-week period. It included 2485 stable patients with severe or very severe COPD receiving triple therapy: tiotropium (LAMA), salmeterol (LABA), and fluticasone (ICS).

The study demonstrated that ICS withdrawal was non-inferior to ICS continuation. There was no difference in the time to first moderate/severe COPD exacerbation in the first 12 months (HR 1.06, 95% CI 0.94-1.19, p=0.35) or in the rate of moderate or severe COPD exacerbations 0.95 per patient year (95% CI, 0.87-1.04) in the glucocorticoid withdrawal group vs 0.91/patient-year (95% CI, 0.83-0.99) in the glucocorticoid continuation group. However, the FEV1 reduction was greater in the ICS withdrawal group - between group difference of 38mls and 43mls at 18 and 52 weeks respectively. The clinical significance of this change in FEV1 is unknown, but importantly, this trial demonstrated the safety of withdrawing an ICS from a patient with stable severe COPD. The advantage of the ICS withdrawal is that it may decrease the risk of pneumonia, as well as other opportunistic infections such as oral candidiasis. Nonetheless, the decision to do so, should be made on a patient to patient basis by weighing up risks and benefits.

2.4. The FLAME study

This study evaluated patients with COPD who had mMRC dyspnoea grade of ≥2. It compared the LAMA/LABA combination inhaler – indacaterol and glycopyrronium to the LABA/ICS combination - salmeterol and fluticasone. The primary end point of the study was the annual rate of all COPD exacerbations. There were 3362 patients from 43 countries with COPD and an mMRC of ≥2 that were randomized to 1 of the 2 groups. At 52 weeks indacaterol and glycopyrronium was associated with a significant reduction in the annual rate of exacerbation when compared to salmeterol and fluticasone (RR 0.88; 95% CI 0.82-0.94; p<0.001).

2.5. The INSPIRE trial

This was a multicentre, randomized, double blind, double dummy-controlled trial. It compared the effect of the combination LABA/ICS (salmeterol/fluticasone - SFC) to LAMA (tiotropium) on the rate of moderate and/or severe exacerbations during a 2-year period. The overall rates of exacerbations were 1.28 per year for SFC and 1.32 per year for tiotropium – Ratio of Rates 0.97 (95% CI 0.84-1.12) indicating no difference between the two groups. Exacerbations requiring antibiotics occurred more frequently in patients treated with SFC – 0.97 vs 0.82/year (p=0.028). Exacerbations requiring hospitalizations were 3% higher for SFC treated patients (p=0.032).

2.6. The INVIGORATE study

This was a multicentre, randomized, double dummy, parallel group study where 3444 patients were randomly assigned to receive either the LABA indacaterol (150ucg) or the LAMA tiotropium (18ucg) once daily for 52 weeks. This study demonstrated that indacaterol is non-inferior to tiotropium for trough FEV1 at 12 weeks. However, it did not show non-inferiority in terms of annual exacerbation rates with a higher exacerbation rate in the indacaterol arm: 0.79 vs 0.61 ratio 1·29 (one-sided 97.5% CI upper limit 1.44). This indicated that tiotropium may afford greater protection from COPD exacerbations when compared to indacaterol.

2.7. The TRILOGY trial

This trial compared the use of triple therapy (ICS/LABA/LAMA) in the form of a single inhaler formulation: beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide to ICS/LABA combination in the form of beclometasone dipropionate and formoterol fumarate. TRILOGY was a randomized, parallel group, double-blind, active-controlled study done in 159 sites across 14 countries. Patients included in the study were those with COPD stage 3 or 4 as per spirometry, those that had at least one moderate to severe exacerbation in the last year, CAT score of 10 or more, and a Baseline Dyspnoea Index focal score of 10 or less. Patients were followed up for 52 weeks after being randomly assigned to one of the two treatment groups. At week 26, halfway through the study, triple therapy improved pre-dose FEV1 by 0.081 L (95% CI 0.052-

0.109; p<0.001) and 2-h post-dose FEV1 by 0.117 L (0.086-0.147; p<0.001) compared with ICS/LABA. Adjusted annual moderate-to-severe exacerbation frequencies were 0.41 for triple therapy and 0.53 for ICS/LABA (rate ratio 0.77 [95% CI 0.65-0.92]; p=0.005). This corresponded to a 23% reduction in exacerbations with triple therapy compared with ICS/LABA. This study provides evidence for escalating patients with severe COPD to triple therapy in the form of a single inhaler.

2.8 The IMPACT trial

This study was a phase III, randomized, double-blind, three-arm, parallel-group, global multicenter study comparing the rate of moderate and severe exacerbations between the single inhaler (ICS/LAMA/LABA) fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) compared to dual therapy with FF/VI (ICS/LABA) or UMEC/VI (LAMA/LABA) over a 52-week treatment period. It looked particularly at severely symptomatic patients with advanced COPD and recurrent exacerbations as it is these patients that are high risk for complications and poor outcomes. The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the FF/VI group (rate ratio with triple therapy, 0.85; 95% CI, 0.80 to 0.90; p<0.001) and 1.21 per year in the UMEC/VI group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; p<0.001). The IMPACT trial clearly documented that the use of triple therapy in the form of a single inhaler with FF/UMEC/VI reduced the rate of moderate or severe exacerbations as compared to dual therapy with ICS/LABA combination FF/VI by 15% and LAMA/LABA combination UMEC/VI by 25% in patients with severe symptoms and recurrent exacerbations.

2.9. The NOTT study

Published in 1980, this trial documented that in patients with COPD and hypoxaemia, continuous oxygen therapy significantly reduces mortality as compared to nocturnal oxygen therapy. Mortality was higher for the nocturnal therapy group (RR 1.94; 95% CI 1.17-3.24). In addition, at 12 months, mortality was 20.6% vs 11.9% (p=0.01) in the nocturnal group. As a result of this study, oxygen therapy for more than 15 hours/day is recommended for patients with:

- PaO2≤55mmhg or oxygen saturation ≤88% confirmed twice in 3 weeks.

- PaO2 55-60mmhg or oxygen saturation of 88% if pulmonary hypertension, heart failure suggested by peripheral oedema, or haematocrit >55% are present.

The 2011 South African COPD guidelines (47) recommend the use of long term oxygen therapy in stable COPD patients with persistent hypoxaemia as it has been shown to reduce the complications of respiratory and right heart failure and improve survival. Indications for long term domiciliary oxygen include PaO2 <55mmHg at rest, or oxygen saturation of <90% at rest as well as smoking cessation for at least 3 months.

A recent randomized trial evaluated the use of long term oxygen therapy in patients with moderate desaturation (48). This was defined as resting oxygen saturation of 89-93% and also incorporated patients with moderate exercise induced desaturation (during the 6-minute walk test, oxygen saturation ≥80% for ≥5 minutes and <90% for ≥10 seconds). Time to death and time to first hospitalization were the two primary outcomes investigated. Patients were randomized to supplemental oxygen or no supplemental oxygen groups. The study found no significant difference between the supplemental oxygen group and the no supplemental oxygen group in the time to death or first hospitalization (hazard ratio, 0.94; 95% CI, 0.79 to 1.12; p = 0.52), nor in the rates of all hospitalizations (rate ratio, 1.01; 95% CI, 0.91 to 1.13), COPD exacerbations (rate ratio, 1.08; 95% CI, 0.98 to 1.19), and COPD-related hospitalizations (rate ratio, 0.99; 95% CI, 0.83 to 1.17). This study highlights the importance of strictly using a cut off of resting oxygen saturation of <88% to obtain the benefits of long-term oxygen therapy.

With these landmark papers as evidence, the GOLD treatment guidelines have been revised.
There have also been a variety of studies looking at adherence to GOLD treatment guidelines.

A study in Texas in 2013 (49) examined the frequency of and factors related to adherence to treatment guidelines at an academic facility. GOLD guidelines from 2007 were used as standard treatment guidelines. The study found that only 54.7% of patients received guideline concordant

therapy. In the study, 7.6% of patients with GOLD stage 1 as defined by spirometry were over-treated. The study also found that patients managed by both a primary care physician as well as a pulmonologist were more likely to receive guideline concordant therapy than those patients managed by primary care physicians only – Odds Ratio 4.59 (95% CI 2.92-7.22); ($p< 0.001$). In addition, patients managed according to 2007 GOLD guidelines (guideline concordant) had significantly fewer exacerbations per year compared to those who were not – 1.10 vs 1.56 ($p = 0.0012$).

A study in Nigeria was conducted to look at adherence to GOLD guidelines in a resource limited setting (50). A self-administered questionnaire to 156 physicians was provided and patient records were reviewed across the internal and family medicine departments in different hospitals. Approximately 60% of patients with COPD were on oral aminophylline. The combination of ICS/LABA was used to treat 72% of patients. No patients were vaccinated. Self-reported adherence to the COPD guidelines was 23.7%. Lack of familiarity (39.8%) to GOLD treatment guidelines was observed to be the most common barrier to the adherence thereof.

A multi-centre, cross-sectional, observational study was conducted in Turkey and published in 2015 (51). It was carried out in 11 outpatient pulmonology clinics in Turkey- a total of 719 patients with COPD were included. According to GOLD treatment guidelines only 59.5% of patients received appropriate treatment as per the GOLD staging system. Causes of inappropriate therapies were overtreatment, undertreatment and lack of treatment. In total 43.4% of patients received triple therapy, LAMA/LABA/ICS, regardless of the GOLD staging and 89% of patients received ICS.

In 2015, a study from the UK was published in the International Journal of Chronic Obstructive Pulmonary Disease (52). It looked at the prescription of triple therapy (LAMA/LABA/ICS) for patients with COPD. The severity of COPD was classified according to 2013 GOLD guidelines and 32% of all patients received triple therapy. Of these 19%, 28%, 37%, and 46% of patients classified as GOLD A, B, C, and D, respectively progressed to triple therapy within 1 year of

diagnosis ($p<0.001$). The most common prescription pathway to triple therapy was LABA/ICS. It was observed that exacerbation history influenced the pathway of this change in prescription.

An Italian Study in 2016 (53) looked at the nature of COPD treatment prescription in both general practitioners (GP) and pulmonologists. Using the GOLD guidelines, ICS is recommended to be reserved for use in GOLD C or D patients – i.e. the more severe, with more frequent exacerbation risk. The study found that approximately 50% of GP's patients with mild or moderate COPD were inappropriately prescribed ICS therapy. Pulmonologists had fewer patients with mild/moderate COPD and ICS were inappropriately prescribed in 19-30% of the time.

A study published in 2017, looked at the inverse relationship between adherence to original GOLD treatment guidelines, and exacerbations of COPD (54). In this study 878 patients with COPD confirmed on spirometry were followed up from 2005-2010. Only 19% of patients were appropriately treated according to guidelines, 14% were overtreated, 44% were undertreated, and in 23% of patients, treatment did not follow any guideline. Logistic regression analysis revealed a strong inverse relationship between adherence to treatment guidelines and exacerbation rates.

CHAPTER 3: RATIONALE, AIM, AND OBJECTIVES

3.1 Rationale

The South African (SA) COPD guidelines as well as the latest GOLD guidelines emphasize a significant paradigm shift in the assessment and management of patients with COPD. Increasingly in patients with COPD, the focus has shifted from one of just symptom control to one of risk reduction as well. Published literature suggests that there is a poor compliance to the current GOLD COPD guidelines especially in resource poor settings.

3.2 Aim

To assess the adherence to GOLD treatment guidelines at a dedicated respiratory clinic in a tertiary teaching academic hospital.

3.3 Objectives

3.3.1 Primary objective

The primary objective of this research project is to document the adherence to GOLD treatment guidelines in COPD patients at Charlotte Maxeke Johannesburg Academic Hospital respiratory clinic.

The focus was on the following:

1. Diagnosis and staging of COPD.
2. Classification of severity according to GOLD guidelines- using spirometry, mMRC classification of breathlessness, and exacerbations/ hospitalizations per year.
3. Smoking status.
4. Inhaled therapy usage.
5. Home oxygen usage.
6. Treating doctor: consultant pulmonologist, respiratory fellow and medical registrar.
7. Adherence to GOLD guidelines.

8. Use of triple therapy.
9. Appropriate use of ICS.

3.3.2 Secondary objective

The secondary objective of the study is to investigate whether a statistically significant association exists between GOLD category and lack of adherence to guidelines, as well as GOLD category and inappropriate use of ICS. Furthermore, associations between patient demographic data and spirometric parameters measured, as well as associations between the treating doctor and therapy prescribed were analysed.

These associations analysed included:

- Gender and all other study variables.
- GOLD FEV1% category and number of exacerbations or hospitalizations.
- Number of exacerbations or hospitalizations and smoking status, triple therapy, use of ICS.
- GOLD category and home oxygen usage.
- Doctor's qualification and use of triple therapy, ICS, SABA.

CHAPTER 4: DESIGN, METHODOLOGY, AND DATA ANALYSIS

The respiratory clinic at CMJAH is held twice a week on a Monday and Wednesday. Patients with a variety of respiratory disease profiles are seen by respiratory consultants, respiratory fellows, as well as medical registrars and medical officers rotating through the respiratory unit. A significant proportion of the patients seen at respiratory clinic have been diagnosed with COPD and have been referred for refractory symptoms, further investigations and institution of appropriate therapy.

There are a variety of different inhaler options to choose from depending on availability from the hospital pharmacy:

- Spiriva (tiotropium) 18ucg, a LAMA, dry powder inhaler (DPI) device.
- Foratec (formoterol) 12ucg, LABA, pressurized metered dose inhaler (pMDI).
- Budeflam (budesonide), an ICS, available in 50ucg/100ucg/200ucg but usually prescribed as 200ucg pMDI.
- Sereflo (salmeterol/fluticasone propionate combination), a LABA/ICS combination, available in 25ucg/125ucg or 25ucg/250ucg pMDI.
- Asthavent (salbutamol), a SABA, available in 100ucg pMDI.
- Ipvent (ipratropium bromide), a SAMA, available in 40ucg pMDI.

In addition, respiratory doctors have access to prescribing long term domiciliary oxygen therapy for specific patients who fulfil the clinical criteria discussed earlier. Vaccinations are available sporadically and often patients need to get them privately. Patients can be referred to physiotherapy for pulmonary rehabilitation as well as to cardiothoracic surgery for lung volume reduction surgery, although this is quite rare.

4.1 Study Design

A retrospective record review of patients with COPD attending respiratory clinic at CMJAH was conducted.

4.2 Study Population

The files of all adult patients seen at respiratory clinic at CMJAH over a 3-month period (1 June-31 August 2016) were included in the study. The sample size is 146 patients – approximately 48 patients per month.

4.2.1 Inclusion Criteria:

All adult patients > 18 years of age with a COPD diagnosis as defined by GOLD guidelines on spirometry: FEV1/FVC <0.70.

4.2.2 Exclusion Criteria:

Patients with the following diagnoses were excluded: asthma, asthma COPD overlap syndrome, bronchiectasis, previous tuberculosis, previous lung surgery, interstitial lung disease, and lung neoplasms. Patients' HIV status was not included in the data set.

If the patient attended the clinic more than once in the three-month study period, data was only collected from the first appointment.

4.3 Sample Size

Sample size estimation is based on the key research question to be answered, in this case the estimation of proportions. Based on worst-case (for sample size) estimates of 50%, 5% precision and the 95% confidence level, a sample size of 385 would be required. Relaxing the precision requirement to 8%, a sample size of 146 is required. This was approximately the number of COPD patients who attended respiratory clinic over a 3 month period and therefore deemed more feasible given the practical constraints of the study.

Sample size for prevalence was determined using the formula: (55)

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where n = sample size,

Z = Z-statistic for the chosen level of confidence,

P = expected prevalence or proportion

d = precision

4.4 Data Entry

Data was collected from patients' files and the doctors' notes therein. Data collection was completely anonymous and strict patient confidentiality was exercised: no patient names, identities, or hospital numbers were included in the study. Data was entered into an excel spreadsheet.

4.5 Data Collection (Appendix 7)

- Demographic data included was age and gender only.
- FEV1 % predicted post bronchodilator and the stage of COPD (Appendix 3).
- mMRC classification of breathlessness 0-4, or unknown (Appendix 1).

If the mMRC classification of breathlessness was not documented in the notes for that visit, then for the purposes of the study an mMRC of ≥2 was assumed in order to calculate the GOLD classification. This assumption was based on the fact that the respiratory clinic at CMJAH is a specialist referral clinic and almost all of the patients are referred for management of refractory symptoms. CAT scores are not utilized at the respiratory clinic.

- Exacerbations in the last year as documented in the clinical notes. An exacerbation was defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-day variation and leads to a change in medication"(1).

- Hospitalizations over the last year as documented in the clinical notes. Any admission to any hospital for any deterioration in patients' clinical status will be considered a hospitalization.
- GOLD classification of severity based on stage and grade i.e. 1-4 and A, B, C, or D **(**Appendix 5).
- Smoking status: total smoking cessation, and still currently smoking regardless of amount.
- Inhaler therapy used by the patients: LAMA and/or LABA and/or ICS and/or ICS/LABA combination and/or SABA.
- Long term domiciliary oxygen therapy: yes or no.
- Patient seen by a registrar in training or a consultant pulmonologist (consultants include respiratory fellows).
- Adherence to GOLD guidelines will be assessed as per Appendix 6.
    - Group A: any bronchodilator – LAMA or LABA.
    - Group B: LAMA or LABA or LAMA + LABA.
    - Group C: LAMA or LAMA + LABA or LABA + ICS.
    - Group D: Any combination – LAMA or LAMA + LABA or LAMA + ICS or LABA+ ICS or LAMA+LABA+ICS.
    - If any Group A or B patient received ICS it would be considered guideline non-adherent.
- Triple therapy – LAMA/LABA/ICS- can be 3 separate inhalers or 2 inhalers: LAMA plus ICS/LABA combination.
- Appropriateness of ICS therapy i.e. Group C or D.

4.6 Data Analysis

Descriptive analysis of the data was carried out as follows: categorical variables were summarized by frequency and percentage tabulation and illustrated by means of bar charts. Continuous variables were summarized by the mean, standard deviation, and their distribution illustrated by means of histograms.

The Chi Square test was used to assess the relationships between categorical variables and the Fisher's exact test when the sample size was small. The strength of the associations was measured by Cramer's V and the phi coefficient respectively. The following scale of interpretation was used:

0.50 and above	high/strong association
0.30 to 0.49	moderate association
0.10 to 0.29	weak association
below 0.10	little if any association

Data analysis was carried out using the Statistical Analysis Software programme (SAS – Cary North Carolina, USA) - the 5% significance level was used.

CHAPTER 5 RESULTS, DISCUSSION AND CONCLUSION

5.1 Results

Table 1: Baseline demographic characteristics of study sample.

Study Variable	Category	Number	Percentage (%)
Gender	Female	59	40.4
	Male	87	59.6
FEV1%	>80%	16	11
	50-80%	46	31.5
	30-50%	52	35.6
	<30%	32	21.9
mMRC	0	2	1.4
	1	14	9.6
	2	27	18.5
	3	13	8.9
	4	11	7.5
	unknown	**79**	**54.1**
mMRC (grouped)	0-1	16	11
	≥2	130	89
Number of hospitalizations in last year	0	126	86.3
	1	19	13
	2	1	0.7
Number of hospitalizations in last year (grouped)	0	126	86.3
	1-2	20	13.7
Number of exacerbations in last year	0	**106**	**72.6**
	1	**34**	**23.3**
	2	**5**	**3.4**
	>2	**1**	**0.7**
Number of exacerbations in last year (grouped)	0	106	72.6
	≥1	40	27.4
GOLD category	A	16	11
	B	106	72.6
	C	0	0
	D	24	16.4
GOLD category (including FEV1)	1A	3	2.1

	2A	8	5.5
	3A	3	2.1
	4A	2	1.4
	1B	9	6.2
	2B	37	25.3
	3B	39	26.7
	4B	21	14.4
	1D	4	2.7
	2D	1	0.7
	3D	10	6.9
	4D	9	6.2
Smoking status	No	120	82.2
	Yes	26	17.8
Home oxygen use	No	97	66.4
	Yes	49	33.6
Doctor type	Consultant	110	75.3
	Registrar	36	24.7
Treatment	SABA	126	86.3
	LAMA	98	67.1
	LABA	90	61.6
	ICS	**86**	**58.9**
	ICS/LABA	**42**	**28.8**
ICS	No	18	12.3
	Yes	**128**	**87.7**
Adherence to treatment guidelines	No	110	75.3
	Yes	**36**	**24.7**
Triple therapy	No	57	39
	Yes	**89**	**61**
Appropriate use of ICS	No	106	72.6
	Yes	**40**	**27.4**

FEV1: forced expiratory volume in 1 second; mMRC: modified Medical Research Council dyspnoea score; GOLD: Global Initiative for Chronic Obstructive Lung Disease guidelines; Triple Therapy: LAMA/LABA/ICS; LAMA: long acting muscarinic antagonist; LABA: long acting beta 2 agonist; ICS: inhaled corticosteroids

Descriptive Data:

The mean age of the patients was 68.0y (Standard deviation [SD] 9.4y; range 41-95y) (Figure 1). The majority (59.6%) of the patients were male. The majority of patients had FEV1 in the range 50-80% (31.5%) or 30-50% (35.6%) (Figure 2).

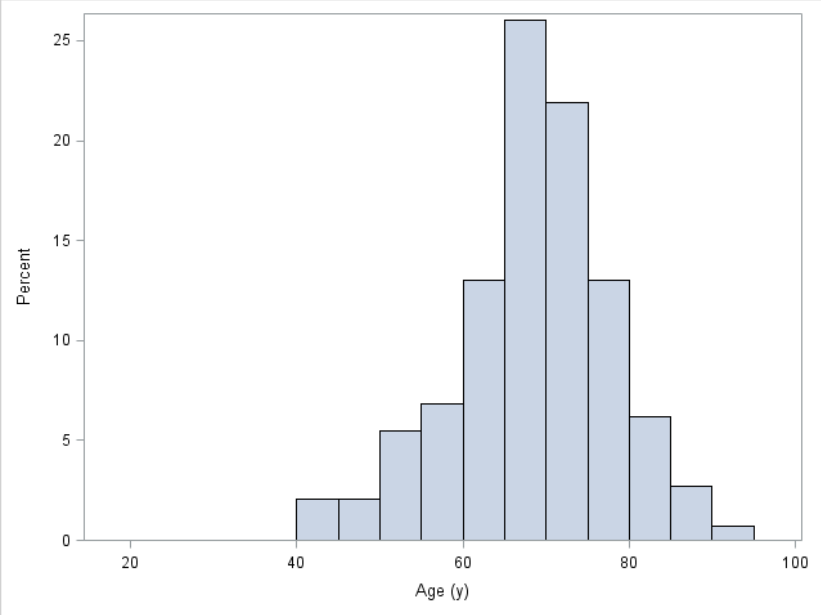

Figure 1: Age distribution.

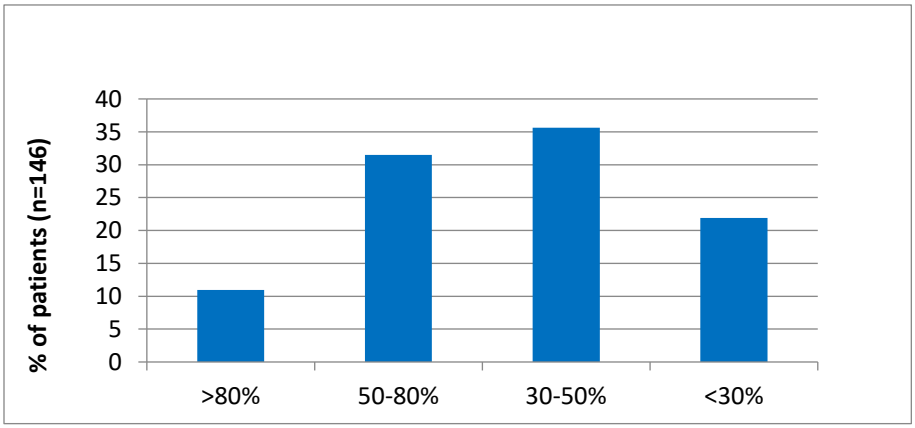

Figure 2: FEV1 % category distribution.

In 54.1% of cases the mMRC class of breathlessness was not recorded or documented. It was therefore collected as unknown. For the purposes of the study this mMRC was interpreted as ≥2. This assumption was based on the fact that the respiratory clinic at CMJAH is a specialist referral

clinic and almost all of the patients are referred for management of refractory symptoms. As such, 89.0% of the patients fell into the ≥2 mMRC category, while the remaining 11.0% fall into the 0-1 mMRC category.

The majority of patients (86.3%) had no hospitalisations in the last year (Figure 3).

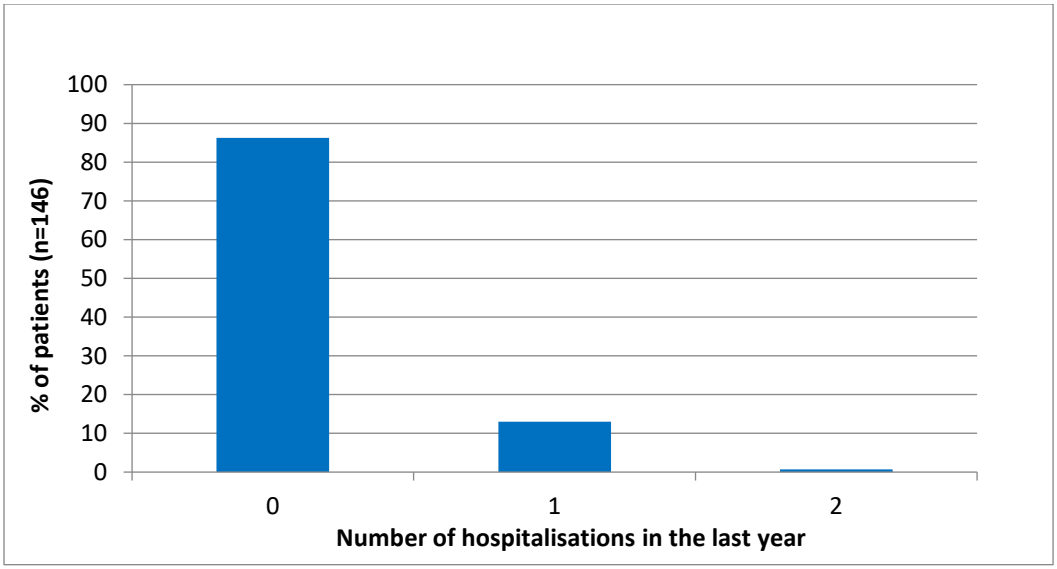

Figure 3: Number of hospitalizations in last year.

The majority of patients (72.6%) had no exacerbations in the last year (Figure 4).

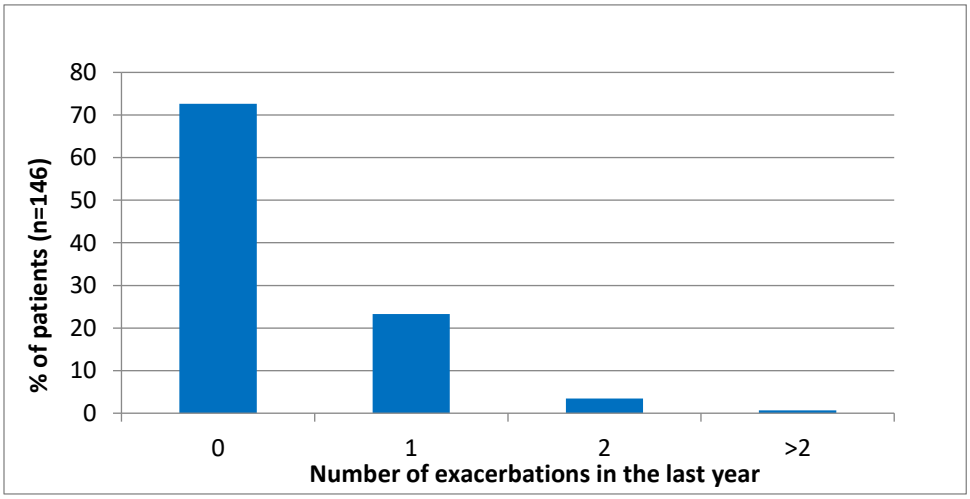

Figure 4: Number of exacerbations in last year.

The majority of patients were in GOLD category B (72.6%) (Figure 5).

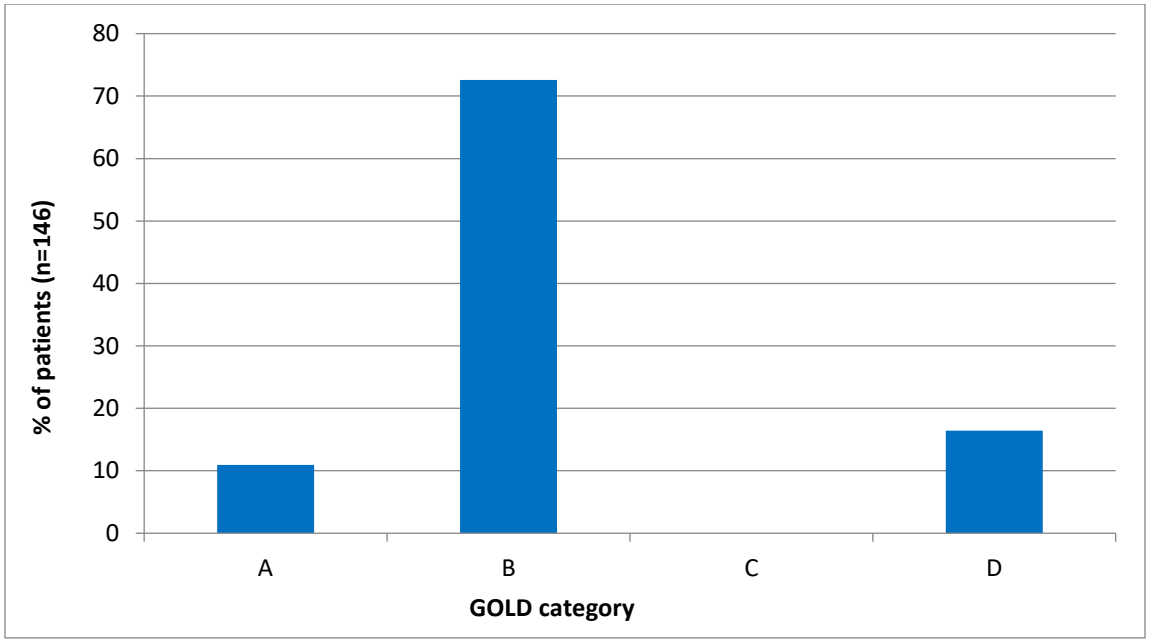

Figure 5: GOLD category.

Breaking this down further into FEV1 % categories, we find that patients in the 2B and 3B categories predominated (Figure 6).

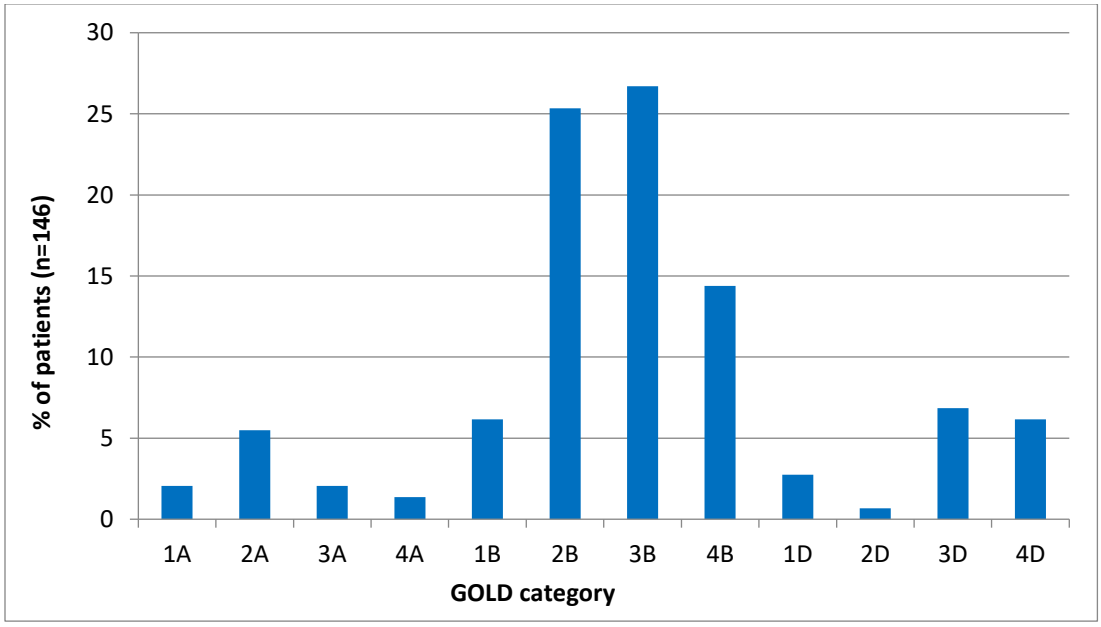

Figure 6: GOLD stage and grade.

In total, 17.8% of the patients were current smokers and 33.6% of patients were using LTDOT. In addition, 75.3% of the patients were treated by consultants, the rest by registrars.

The majority of patients were on a SABA (86.3%) (Figure 7). The majority (87.7%) of the patients were on ICS or ICS/LABA combination and 61.0% of the patients were on triple therapy. Only 24.7% of the patients were found to be treated in accordance with the GOLD guidelines, with 27.4% of the patients found to be treated appropriately with ICS therapy (Figure 7).

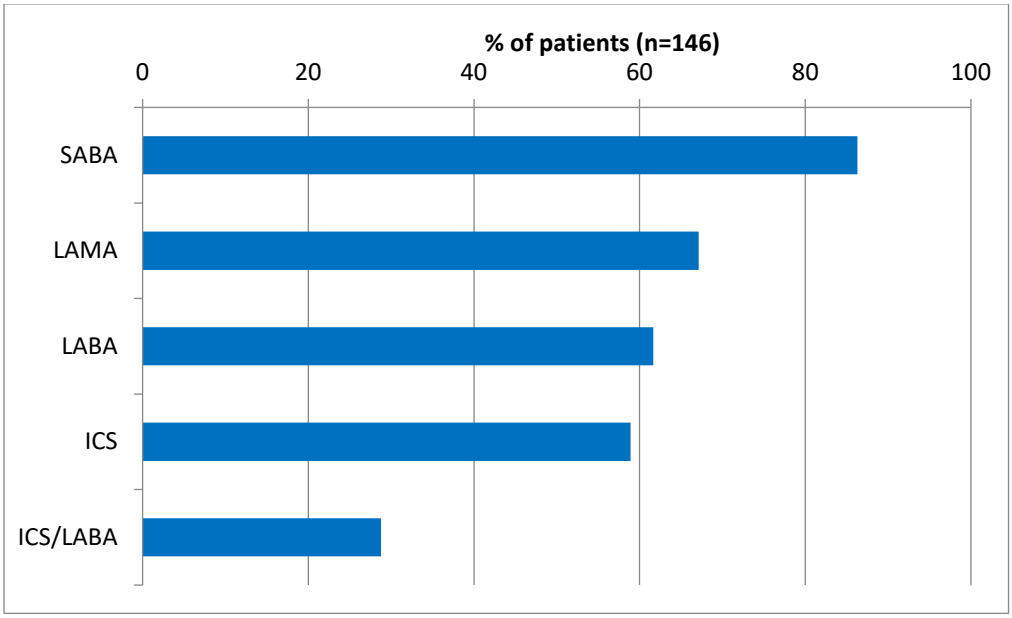

Figure 7: Inhaler usage.

Determination of the association between selected study variables:

There was a significant association between gender and LTDOT use with a higher percentage of female patients (46%) using LTDOT, compared to male patients (25%) (p=0.013).

There was a significant association between GOLD FEV1 categories and number of hospitalizations with a significantly lower percentage of hospitalizations occurring in the FEV1 50-80% category when compared to other categories (p=0.016) (Figure 8).

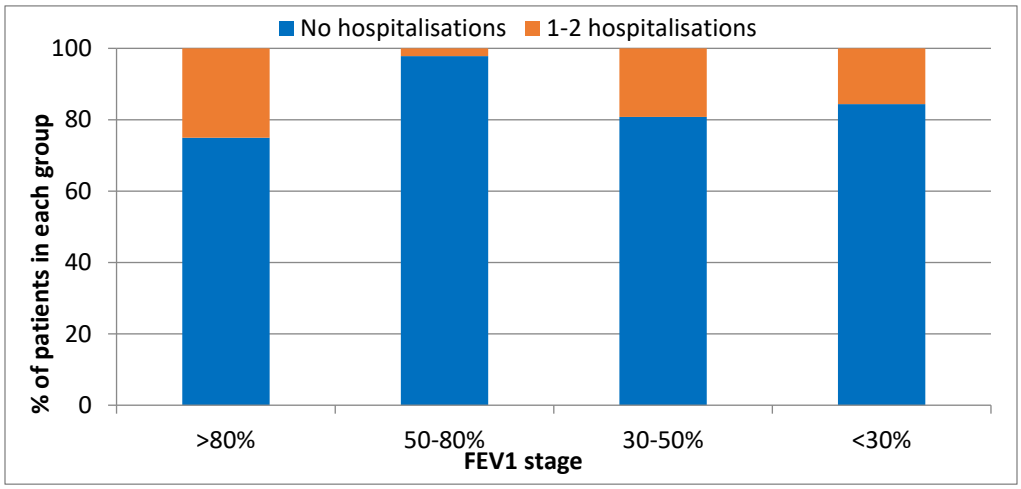

Figure 8: FEV1 % versus (vs) hospitalizations.

Furthermore, as documented with the hospitalizations, there was a significant association between FEV1 category and number of exacerbations, with a significantly lower percentage of exacerbations occurring in the FEV1 50-80% category compared to the other categories (p=0.046) (Figure 9).

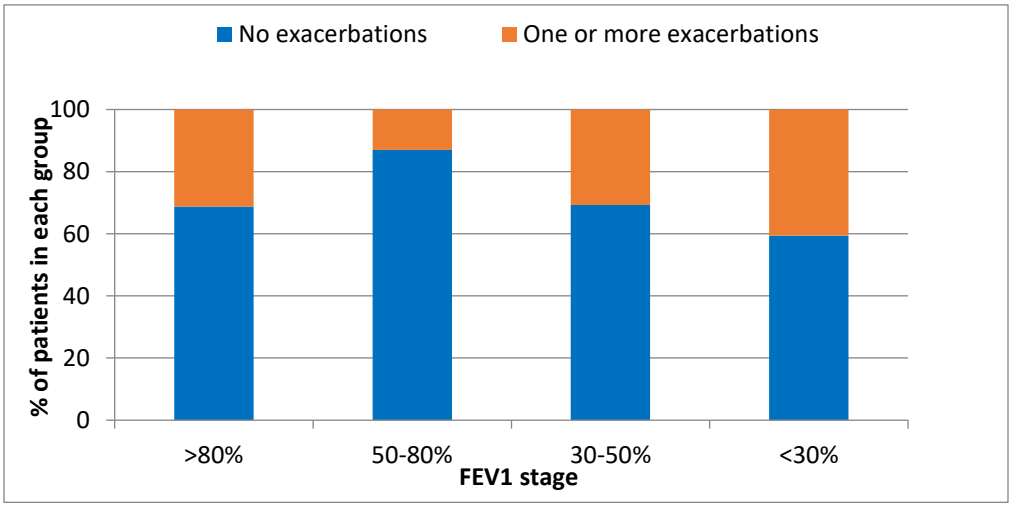

Figure 9: FEV1 % vs exacerbations.

There were no associations when the number of hospitalizations were compared to smoking status, use of triple therapy, or use of ICS. This finding was replicated with there being no associations when the number of exacerbations were compared to smoking status, use of triple therapy and the use of ICS. There was a significant association between GOLD category and a lack of adherence to GOLD treatment guidelines ($p<0.0001$). Non-adherence to guidelines was much higher in group B with a significant percentage of patients (87%) on inappropriate ICS therapy. Inappropriate use of ICS therapy was more prevalent in groups A and B than in group D (Figures 10 & 11).

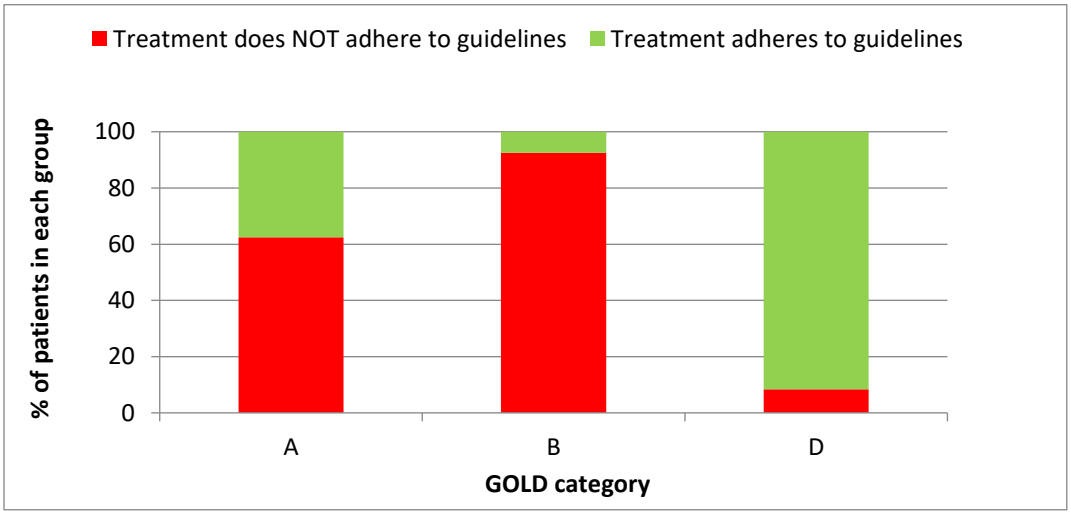

Figure 10: GOLD category vs treatment adherence.

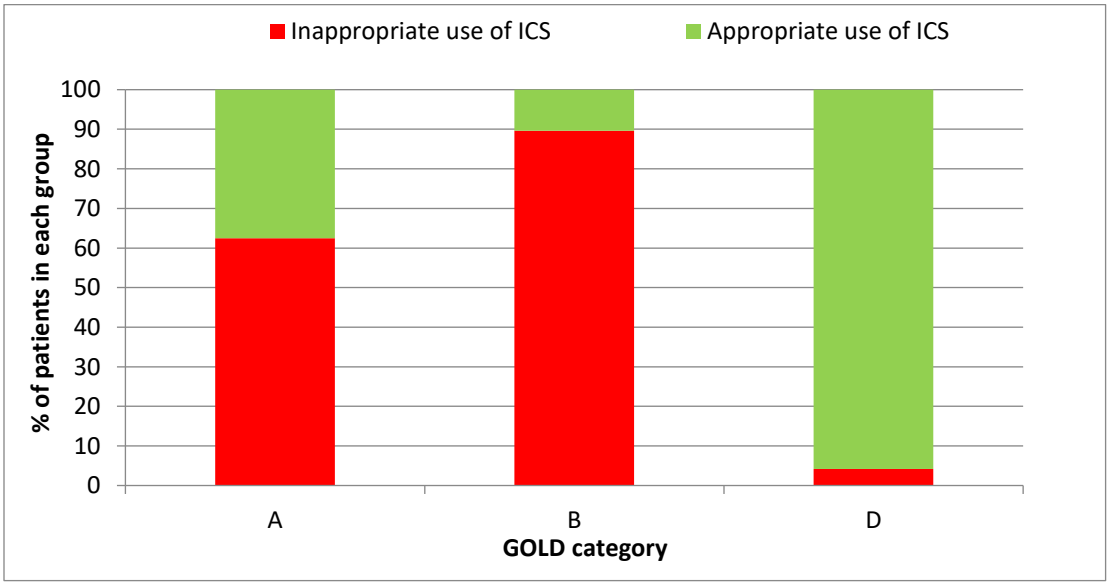

Figure 11: GOLD category vs appropriate use of ICS.

There was a significant association between GOLD category and LTDOT (p=0.0096) with a higher prevalence of domiciliary oxygen usage in patients categorized as GOLD B and D than in GOLD A (Figure 12).

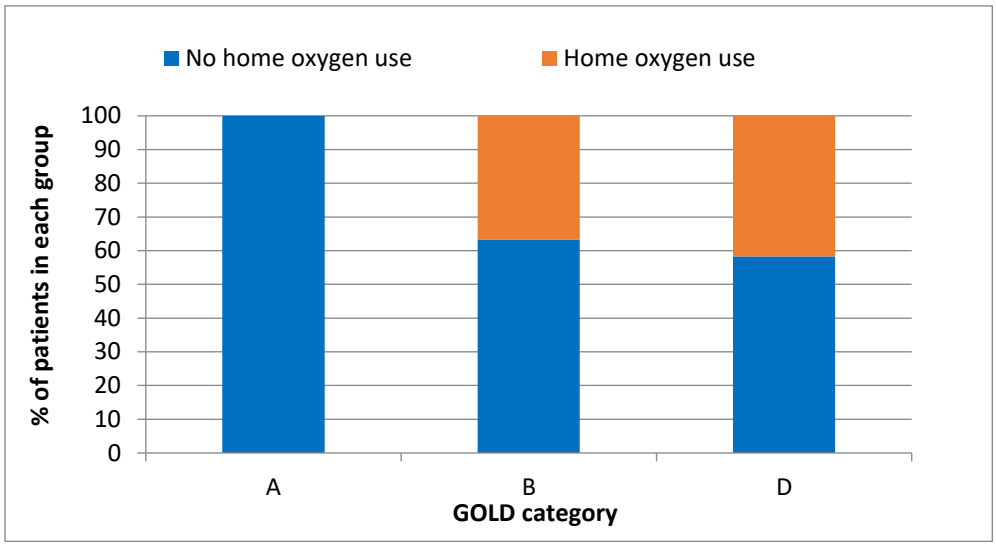

Figure 12: GOLD category vs home oxygen usage.

There was a significant association between the doctor's qualification and SABA prescription (p=0.0038) with a higher percentage of patients assessed by medical registrars prescribing SABA (100%) as compared to patients assessed by qualified physicians (82%) including consultant pulmonologists and pulmonology fellows.

5.2 Discussion

The recent amendments to the GOLD classification guidelines may have created a lot of confusion for those treating COPD. Doctors are often faced with the dilemma of which inhaler therapy to choose that will best treat the patient. In addition, often in the South African public health care setting, resources are limited and various inhalers may not be available for use. The most recent GOLD guidelines focus on symptom control and exacerbation risk. The GOLD recommendation is that patients with frequent exacerbations (≥2/year) – GOLD C or D should be offered ICS in addition to long acting bronchodilators. Bronchodilators (LAMA and LABA) should form the basis of therapy for all symptomatic COPD patients.

When comparing the results of this study to other similar studies with resource limitations in the African context, our results are similar. This study revealed adherence to GOLD guidelines in 27.4% of patients, while in a Nigerian study adherence to guidelines was 23.7% (50). However, studies from Texas and Turkey suggest that adherence to GOLD guidelines is better in America and Europe. The study from Texas documented that 54.7% of patients received guideline concordant therapy (49) and the study from Turkey documented that 59.5% of patients received appropriate treatment as per GOLD guidelines (51). When comparing triple therapy (LAMA/LABA/ICS) usage to other studies, this study documented 61% of patients received triple therapy whereas the study in Turkey documented 43.4% (51) and a UK study documented 32% of patients received triple therapy (52). In terms of ICS usage, this study documented that ICS was prescribed appropriately in 27.4% of patients (inappropriately in 72.6%) as compared to an Italian study which documented that ICS were inappropriately prescribed in 19-30% of cases (53). These comparisons highlight the over prescription of ICS in our patient cohort. However, with regards to this research, the mMRC classification of breathlessness was poorly documented in the notes despite the fact that it forms a key part of understanding the impact that COPD has on the patient's life as well as GOLD classification. This highlights a major deficiency in COPD assessment and subsequent management in our patient cohort.

Nonetheless, the current GOLD guidelines recommend the use of ICS to treat patients who have frequent exacerbations (≥2/year) and within this cohort 72.6 % had no documented exacerbations, 23.3% had 1 exacerbation and only 4,1% had ≥2 exacerbations documented. A large proportion of these patients are treated with ICS which is non-adherent to guidelines. However, this may be due to the fact that these patients were previously classified as GOLD C or D and have now improved on ICS therapy in combination with LAMA or LABA and therefore their exacerbations risk has declined with ICS therapy. This raises the question of whether or not we should be withdrawing ICS therapy from this patient group, and potentially putting these patients at risk for future exacerbations. The Wisdom trial (14) which included severe COPD patients who had stabilized on triple therapy, demonstrated non-inferiority with regards to time to first moderate or severe exacerbation when comparing ICS continuation vs withdrawal. So perhaps we should be attempting a withdrawal of ICS from certain stable COPD patients who have improved to GOLD

A or B. It remains uncertain how to select which patients should continue ICS and which patients should attempt a withdrawal. Studies (29) have shown that patients with high serum eosinophil counts (>300 cells/ul) are more likely to have frequent exacerbations and it is these patients that should remain on ICS therapy. Therefore, it would be prudent to introduce the use of a validated biomarker in the form of a serum eosinophil count when choosing in which patients to withdraw ICS therapy. We should be moving from the era of guideline based therapy into an era of personalized therapy and tailoring therapy to COPD phenotypes to achieve the best outcomes for patients (56, 57).

5.3 Limitations

All data collected is reliant on documentation in the clinical notes. This may have had an impact on the results if mMRC, exacerbations, and hospitalizations are not properly documented in the notes. The mMRC was not documented in the patients' files in 54.1% of cases. Therefore, an mMRC of ≥2 was used to calculate the GOLD classification based on the assumption that the respiratory clinic at CMJAH is a specialist referral clinic and almost all of the patients are referred for refractory symptoms.

GOLD classification is dynamic and can change over time with response to treatment, so a patient who was previously a GOLD D may now be reclassified as GOLD A or B. Therefore, treatment may seem non-adherent currently at this point in time but may previously have been adherent to guidelines. In addition, doctors and patients alike may be reluctant to de-escalate treatment especially if there has been a good response to it.

5.4 Conclusion

Adherence to GOLD guidelines and therapeutic algorithms was lacking in this cohort of patients studied. The mMRC classification of breathlessness was poorly recorded in the patient's notes despite the fact that it forms a core part of the GOLD classification. In addition, the majority of patients are treated with ICS therapy. This may be as a result of the lack of the appropriate patient

classification according to the GOLD criteria. This limitation has probably resulted in the injudicious use of ICS therapy with the potential for an increased risk of side effects such as pneumonia (1).

5.5 Future Recommendations

We should be implementing strategies to ensure that the GOLD classification is correctly recorded at each clinic visit by means of a standard data collection sheet. By classifying patients correctly, it will encourage guideline adherence, appropriate management and introduce a strategy of risk reduction assessment**.** By improving adherence to guidelines, patients with more severe uncontrolled COPD (GOLD C and D) can be escalated to appropriate therapy to ensure improved symptoms, decreased morbidity, decreased COPD exacerbation rates and hospital admissions, as well as decreased mortality. Patients who have achieved better control or have less severe COPD (GOLD A and B) can potentially have their treatment regimens de-escalated. This will prevent over treatment of patients, reduce the use of unnecessary inhalers and the cost thereof in a resource constrained setting, as well as potentially reduce the complications and side effects of ICS therapy (30).

In addition, measuring of serum eosinophil counts should be implemented at the clinic. Recent data have shown that patients with a history of exacerbations have higher serum eosinophil counts, specifically in patients treated with LABA but without ICS (58). The effect of treatment with combined ICS and LABA in comparison to LABA alone was greater in patients with high serum eosinophil counts (>300 cells/ul). In other words, serum eosinophil counts can be used as a validated biomarker to predict the risk of exacerbations in patients with a history of previous exacerbations, and can also predict the protective effect that ICS may have on preventing exacerbations in this group of patients (29, 59). Future studies at CMJAH could look at patients with COPD on ICS therapy with no recent documented exacerbations and measure serum eosinophil counts as a biomarker in deciding which patients are good candidates to attempt a trial of withdrawal of ICS therapy.

CHAPTER 6: REFERENCES

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. American Journal of Respiratory and Critical Care Medicine. 2017;195(5):557-82.
2. Kurmi OP, Semple S, Simkhada P, Smith WC, Ayres JG. COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis. Thorax. 2010;65(3):221-8.
3. Crothers K, Butt AA, Gibert CL, Rodriguez-Barradas MC, Crystal S, Justice AC. Increased COPD Among HIV-Positive Compared to HIV-Negative Veterans. Chest. 2006;130(5):1326-33.
4. Byrne AL, Marais BJ, Mitnick CD, Lecca L, Marks GB. Tuberculosis and chronic respiratory disease: a systematic review. International Journal of Infectious Diseases. 2015;32(March):138-46.
5. Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, et al. Passive smoking exposure and risk of COPD among adults in china: the Guangzhou Biobank Cohort Study. Lancet. 2007;370(9589):751-7.
6. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
7. Aaron SD, Tan WC, Bourbeau J, Sin DD, Loves RH, MacNeil J, et al. Diagnostic Instability and Reversals of Chronic Obstructive Pulmonary Disease Diagnosis in Individuals with Mild to Moderate Airflow Obstruction. American Journal of Respiratory and Critical Care Medicine. 2017;196(3):306-14.
8. Schermer TR, Roberts B, Crockett AJ, Thoonen BP, Lucas A, Grootens J, et al. Should the diagnosis of COPD be based on a single spirometry test? Primary Care Respiratory Medicine. 2016;26(16059).
9. Fletcher CM. Standardized questionnaire on respiratory symptoms: a statement prepared and approved by the MRC committee on the Aetiology of Chronic Bronchitis (MRC Breathlessness Score). British Medical Journal. 1960;2:1665.
10. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. European Respiratory Journal. 2009;34(3):648-54.
11. Han MK, Muellerova H, Curran-Everett D, Dransfield MT, Washko GR, Regan EA, et al. GOLD 2011 disease severity classification in COPDGene: a prospective cohort study. Lancet Respiratory Medicine. 2013;1(1):43-50.
12. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. The New England Journal of Medicine. 2010;363(12):1128-38.
13. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. The New England Journal of Medicine. 2016;374(23):2222-34.
14. Magnussen H, Disse B, Rodriguez-Roisin R, Kirsten A, Watz H, Tetzlaff K, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. The New England Journal of Medicine. 2014;371(14):1285-94.

15. Chapman KR, Hurst JR, Frent SM, Larbig M, Fogel R, Guerin T, et al. Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial. American Journal of Respiratory and Critical Care Medicine. 2018;198(3):329-39.
16. Soriano JB, Lamprecht B, Ramirez AS, Martinez-Camblor P, Kaiser B, Alfageme I, et al. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. Lancet Respiratory Medicine. 2015;3(6):443-50.
17. van der Meer RM, Wagena EJ, Ostelo RW, Jacobs JE, van Schayck CP. Smoking cessation for chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2003(2):CD002999.
18. Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, et al. Electronic Cigarettes for Smoking Cessation: A Systematic Review. Nicotine & Tobacco Research. 2016;18(10):1926-36.
19. Kew KM, Mavergames C, Walters JA. Long-acting beta2-agonists for chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2013;10(10):CD010177.
20. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2014(7):CD009285.
21. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MP, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. The New England Journal of Medicine. 2011;364(12):1093-103.
22. Decramer ML, Chapman KR, Dahl R, Frith P, Devouassoux G, Fritscher C, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respiratory Medicine. 2013;1(7):524-33.
23. Calzetta L, Rogliani P, Matera MG, Cazzola M. A Systematic Review With Meta-Analysis of Dual Bronchodilation With LAMA/LABA for the Treatment of Stable COPD. Chest. 2016;149(5):1181-96.
24. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2012(7):CD002991.
25. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. The New England Journal of Medicine. 2007;356(8):775-89.
26. Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet. 2016;387(10030):1817-26.
27. Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2013(11):CD003794.
28. Pascoe SJ, Lipson DA, Locantore N, Barnacle H, Brealey N, Mohindra R, et al. A phase 3 randomized controlled trial of single-dose triple therapy in COPD: the IMPACT protocol. European Respiratory Journal. 2016;48:320-30.
29. Pascoe SJ, Locantore L, Dransfield MT, Barnes NC, Pavord ID. Blood Eosinophil Counts, exacerbations, and response to the addition of inhaled Fluticasone Furoate to Vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomized controlled trials. Lancet Respiratory Medicine. 2015;3(6):435-42.
30. Janson C, Larsson K, Lisspers KH, Stallberg B, Stratelis G, Goike H, et al. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled

corticosteroid and long acting B2 agonist: observational matched cohort study (PATHOS). British Medical Journal. 2013;346(3306):1-11.
31. Singh D, Papi A, Corradi M, Pavlisova I, Montagna I, Francisco C, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet. 2016;388(10048):963-73.
32. ZuWallack RL, Mahler DA, Reilly D, Church N, Emmett A, Rickard K, et al. Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest. 2001;119(6):1661-70.
33. Price DB, Cotton S, Fielding S, McMeekin N, Barnes P, Briggs A, et al. Use of 'Low Dose' Theophylline to reduce exacerbations of COPD: A Pragmatic Multicentre randomised Placbeo Controlled Trial. American Journal of Respiratory and Critical Care Medicine. 2018;197(A7709).
34. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2014(9):CD001288.
35. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet. 2009;374(9691):685-94.
36. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2006(1):CD002733.
37. Uzun S, Djamin RS, Kluytmans JA, Mulder PG, van't Veer NE, Ermens AA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. Lancet Respiratory Medicine. 2014;2(5):361-8.
38. Cazzola M, Calzetta L, Page C, Jardim J, Chuchalin AG, Rogliani P, et al. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. European Respiratory Review. 2015;24(137):451-61.
39. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2015(2):CD003793.
40. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2005(4):CD001744.
41. Washko GR, Fan VS, Ramsey SD, Mohsenifar Z, Martinez F, Make BJ, et al. The effect of lung volume reduction surgery on chronic obstructive pulmonary disease exacerbations. American Journal of Respiratory and Critical Care Medicine. 2008;177(2):164-9.
42. Deslee G, Mal H, Dutau H, Bourdin A, Vergnon JM, Pison C, et al. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. Journal of American Medical Association. 2016;315(2):175-84.
43. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. The New England Journal of Medicine. 2008;359(15):1543-54.
44. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. American Journal of Respiratory and Critical Care Medicine. 2008;177(1):19-26.
45. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. The New England Journal of Medicine. 2018;378(18):1671-80.

46. Nocturnal Oxygen Therapy Trial Group.Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Annals of Internal Medicine. 1980;93(3):391-8.
47. Abdool-Gaffar MS, Ambaram A, Ainslie GM, Bolliger CT, Feldman C, Geffen L, et al. Guideline for the management of chronic obstructive pulmonary disease--2011 update. South African Medical Journal. 2011;101(5):61-73.
48. The Long-Term Oxygen Treatment Trial Research Group. A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation. The New England Journal of Medicine. 2016;375(17):1617-27.
49. Sharif R, Cuevas CR, Wang Y, Arora M, Sharma G. Guideline adherence in management of stable chronic obstructive pulmonary disease. Respiratory Medicine. 2013;107(7):1046-52.
50. Desalu OO, Onyedum CC, Adeoti AO, Gundiri LB, Fadare JO, Adekeye KA, et al. Guideline-based COPD management in a resource-limited setting - physicians' understanding, adherence and barriers: a cross-sectional survey of internal and family medicine hospital-based physicians in Nigeria. Primary Care Respiratory Journal. 2013;22(1):79-85.
51. Sen E, Guclu SZ, Kibar I, Ocal U, Yilmaz V, Celik O, et al. Adherence to GOLD guideline treatment recommendations among pulmonologists in Turkey. International Journal of Chronic Obstructive Pulmonary Disease. 2015;10:2657-63.
52. Brusselle G, Price D, Gruffydd-Jones K, Miravitlles M, Keininger DL, Stewart R, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. International Journal of Chronic Obstructive Pulmonary Disease. 2015;10:2207-17.
53. Visentin E, Nieri D, Vagaggini B, Peruzzi E, Paggiaro P. An observation of prescription behaviors and adherence to guidelines in patients with COPD: real world data from October 2012 to September 2014. Current Medical Research and Opinion. 2016;32(9):1493-502.
54. Foda HD, Brehm A, Goldsteen K, Edelman NH. Inverse relationship between nonadherence to original GOLD treatment guidelines and exacerbations of COPD. International Journal of Chronic Obstructive Pulmonary Disease. 2017;12:209-14.
55. Daniel W. Biostatistics: A Foundation for Analysis in the Health Sciences. New York: John Wiley & Sons. 2013;10th edition(chapter 6):191.
56. Lange P, Halpin DM, O'Donnell DE, MacNee W. Diagnosis, assessment, and phenotyping of COPD: beyond FEV1. International Journal of Chronic Obstructive Pulmonary Disease. 2016;19(11):3-12.
57. Woodruff PG, Agusti A, Roche N, Singh D, Martinez FJ. Current concepts in targeting chronic obstructive pulmonary disease pharmacotherapy: making progress towards personalized management. Lancet. 2015;385(9979):1789-98.
58. Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respiratory Medicine. 2016;4(5):390-8.
59. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, et al. Blood Eosinophils: A biomarker of response to extrafine Beclomethasone/ Formoterol in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2015;192(4):523-5.