REPUBLIC OF TURKEY
YEDITEPE UNIVERSITY
GRADUATE SCHOOL OF HEALTH SCIENCES

PHYSICIANS OPINIONS ON ICS/LABA (INHALED CORTICOSTEROID/LONG ACTING BETA 2 AGONIST) FIXED COMBINATIONS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) TREATMENT:

A PRELIMINARY SURVEY

PHARMACIST
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ISTANBUL – 2014

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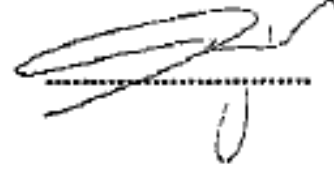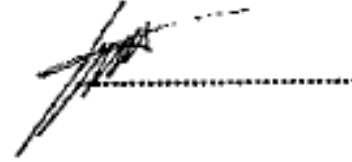
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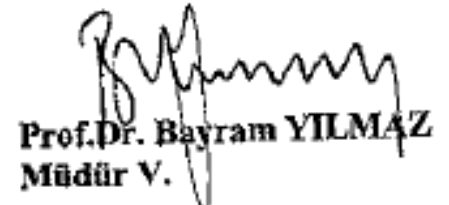
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ONAY

Yukarıdaki jüri kararı Sağlık Bilimleri Enstitüsü Yönetim Kurulu'nun ....../....../.......... ve ....4.8....sayılı kararı ile onaylanmıştır.

Prof.Dr. Bayram YILMAZ
Müdür V.

DEDICATION

To my precious family and friends...

ACKNOWLEDGEMENT

ABSTRACT

Purpose: Chronic Obstructive Pulmonary Disease (COPD), is a common, preventable and treatable disease. COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing.

Inhaled corticosteroid/ long acting beta$_2$ agonist (ICS/LABA) fixed combinations are commonly used drugs in COPD treatment. Inhaled Corticosteroids reduce the inflammation in lungs and beta$_2$-agonists relax airway smooth muscle by stimulating beta$_2$-adrenergic receptors.

The aim of this thesis is to gather physicians' opinions on ICS/LABA fixed combinations for COPD.

Materials & Method: In order to determine the impact of ICS/LABA fixed combinations on treatment, an expert opinion was investigated. Survey method was selected for data collection. Physicians' opinions and experiments for ICS/LABA fixed combinations on COPD treatment and their observations on disease treatment outcomes were gathered by the survey. The study was conducted at TÜSAD (Turkish Respiratory Society/Türkiye Solunum Araştırmaları Derneği) Congress in Çeşme/İzmir in October 2012.

Result and Conclusion: 91.5% of the respondents were pulmonary physician who were the target group of the survey. Most of physicians responded as the frequency and severity of exacerbations and the number of hospitalizations was decreased at patients which have been treated with inhale corticosteroid plus long acting beta$_2$ agonist fixed combinations (ICS/LABA) in their daily practice. Similarly, most of physicians responded as Health Quality of Life, spirometer results and exercise capacity of patients were improved at patients who have been treated with inhale corticosteroid and long acting beta2 agonist fixed combinations (ICS/LABA) in their daily practice. According to the recent studies,

the use of LABA/ICS fixed combinations in the severe stages of the disease is effective in reducing the long-term clinical impact of COPD and in optimizing the cost-effectiveness and the socio-economic convenience of therapeutic strategies by decreasing the number of exacerbations and hospitalizations. Our survey results showed that, most of Turkish physicians state that the number of exacerbations and hospitalizations were decreased at patients who have been treated with inhale corticosteroid and long acting beta$_2$ agonist fix combinations (IKS/LABA). These results can give rise to thought that the use of LABA/ICS fix combinations may have a positive impact on cost of COPD treatment in Turkey by decreasing the number of exacerbations and hospitalization according to the Turkish physicians survey results.

Key words: COPD, ICS, LABA, treatment cost, exacerbation, hospitalization.

ÖZET

Amaç: Kronik Obstriktif Akciğer Hastalığı (KOAH), zararlı partiküller ve gazların akciğer ve havayollarında artmış kronik inflamatuvar yanıtı ile ilişkili, genellikle progresif (ilerleyici) kalıcı hava akımı kısıtlanması ile karakterize, önlenebilir ve tedavi edilebilir bir hastalıktır. KOAH dünya genelinde mortalite ve morbiditeye etki ederek, ekonomik ve sosyal yükünün gün geçtikçe arttığı bir hastalıktır.

İnhale kortikosteroid/Uzun etkili beta2 agonist (İKS/UEBA) fiks kombinasyonları KOAH tedavisinde sık olarak kullanılan ilaçlardır. İnhale kortikosteroidler akciğerdeki inflamasyonu azaltır. ß2 agonistler ise, ß2 adrenerjik reseptörlerini stimüle ederek, havayolu düz kaslarını gevşetirler.

Bu tez çalışmasının amacı, KOAH tedavisinde kullanılan İKS/UEBA fiks kombinasyonları ile ilgili hekim görüşü araştırmaktır.

Materyal ve Metot: İnhale kortikosteroid, uzun etkili ß2 agonist fiks kombinasyonlarının Kronik Obstrüktif Akciğer Hastalığı (KOAH) tedavisine etkisini araştırmak amacıyla uzman görüşü alındı. Metot olarak KOAH hastalarında İKS/UEBA fiks kombinasyonlarını tercih eden hekimlere tedavi sonuçlarına ilişkin görüşlerini almayı hedefleyen sorulardan oluşan anket uygulandı. Anket Çeşme/İzmir'de gerçekleşen TÜSAD (Türkiye Solunum Araştırmaları Derneği) kongresinde hekimlere uygulandı.

Bulgular ve Sonuç: Anketi dolduran hekimlerin %91,5'ini araştırmanın hedef grubu olan göğüs hastalıkları uzmanları oluşturduğu görülmüştür. Anketi cevaplayan hekimlerin büyük çoğunluğu İKS/LABA fiks kombinasyonları ile tedavi ettikleri hastalarında alevlenmelerin şiddetinde ve sıklığında ve hastaneye yatış oranlarında azalma olduğunu belirtmişlerdir. Benzer şekilde, hastaların yaşam kalitelerinde, spirometrik değerlerinde ve egzersiz kapasitelerinde düzelme olduğunu belirtmişlerdir. Son dönem uluslararası çalışmalar ağır vakalarda İKS/LABA kombinasyonlarının kullanımının KOAH tedavisindeki etkinlik, maliyet etkililik ve sosyo-ekonomik uygunluk açısından alevlenmeleri ve hastaneye yatışları önemli derecede azaltması sayesinde fayda sağladığını

göstermektedir. Anket sonuçlarına göre, ankete cevap veren hekimlerin büyük bir kısmı İKS/LABA kombinasyonları ile tedavi ettikleri hastalarının alevlenme ve hastaneye yatış oranlarının azaldığını belirtmişlerdir. Bu sonuçlar bize, İKS/LABA fiks kombinasyonlarının KOAH tedavi maliyetine alevlenme ve hastaneye yatış oranlarını azaltarak pozitif etki sağladığını düşündürtmektedir.

Anahtar kelimeler: KOAH, İKS, UEBA, tedavi maliyeti, alevlenme, hastaneye yatış.

CONTENT

ABBREVIATIONS

COPD: Chronic Obstructive Pulmonary Disease

WHO: World Health Organization

GOLD: The Global Initiative for Chronic Obstructive Lung Disease

ICS: Inhaled corticosteroid

LABA: Long Acting Beta$_2$ Agonist

CVD: Cardiovascular Disease

ICU: Intensive Care Unit

DALY: Disability-Adjusted Life Year

FEV1: Forced expiratory volume in one second

FVC: Forced Vital Capacity

TÜSAD: Türkiye Solunum Araştırmaları Derneği

TORAKS: Türk Toraks Derneği

BOLD: The Burden of Obstructive Lung Diseases

ATS: American Thoracic Society

ERS: European Respiratory Society

TTD: Türk Toraks Derneği

NIMV: Non-invasive mechanical ventilation

MIV: Invasive mechanical ventilation

CAT: COPD Assessment Test

mMRC: Modified Medical Research Council

MDI: Metered Dose Inhaler

DPI: Dry Powder Inhaler

SMI: Smart Mist Inhaler

FIGURES

TABLES

1. INTRODUCTION

Owing to its increasing prevalence, morbidity and mortality, Chronic Obstructive Pulmonary Disease (COPD) represents a dramatic public health problem within all industrialized countries. COPD is usually caused by smoking. Symptoms include cough and breathlessness. The most important treatment is to stop smoking. Air pollution and polluted work conditions may cause some cases of COPD, or make the disease worse. The combination effect of occupational exposure to air pollutants and smoking increases the chances of developing COPD. However, people who have never smoked rarely develop COPD. (Passive smoking remains, however, a potential cause.)

Because awareness of COPD is low, most people are diagnosed only when the disease has reached later stages – with severe symptoms and extensive irreversible lung damage. As every COPD exacerbation decreases quality of life and reduces lung function, it is of critical importance that COPD is diagnosed as early as possible.

The goal of COPD treatment is to ease symptoms, slow the progress of COPD, prevent or treat any complications, and improve overall quality of life.

1.1. DEFINITION

According to the "Global Initiative for Chronic Obstructive Lung Disease (2011) Global strategy for the diagnosis, management and prevention of chronic pulmonary disease NHLBI/WHO Workshop Report" (1) COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

The chronic airflow limitation characteristic of COPD is caused by a mixture of a small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person (Figure 1). Chronic inflammation causes structural changes and narrowing of the small airways. Destruction of the lung parenchyma, also by inflammatory processes, leads to the loss of alveolar attachments to the small airways and decreases elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration. Airflow limitation is best measured by spirometry, as this is the most widely available, reproducible test of lung function (1).

Figure 1. Mechanisms underlying airflow limitation in COPD (1)
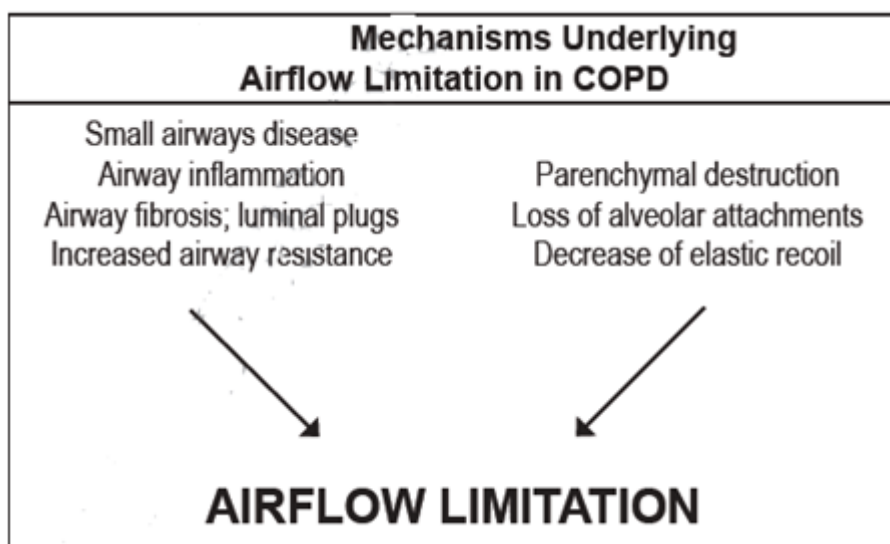
1.2. BURDEN OF COPD

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing (2, 3) (figure 2). COPD prevalence, morbidity and mortality vary across countries and across different groups within countries. COPD is the result of cumulative exposures over decades. Often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries, outdoor, occupational and

indoor air pollution are major COPD risk factors (10). The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population (with more people living longer and therefore expressing the long-term effects of exposure to COPD risks factors) (3). Owing to its increasing prevalence, morbidity and mortality, COPD represents a dramatic public health problem within all industrialized countries (4).

Figure 2. Change in mortality rates distributed by years (2).
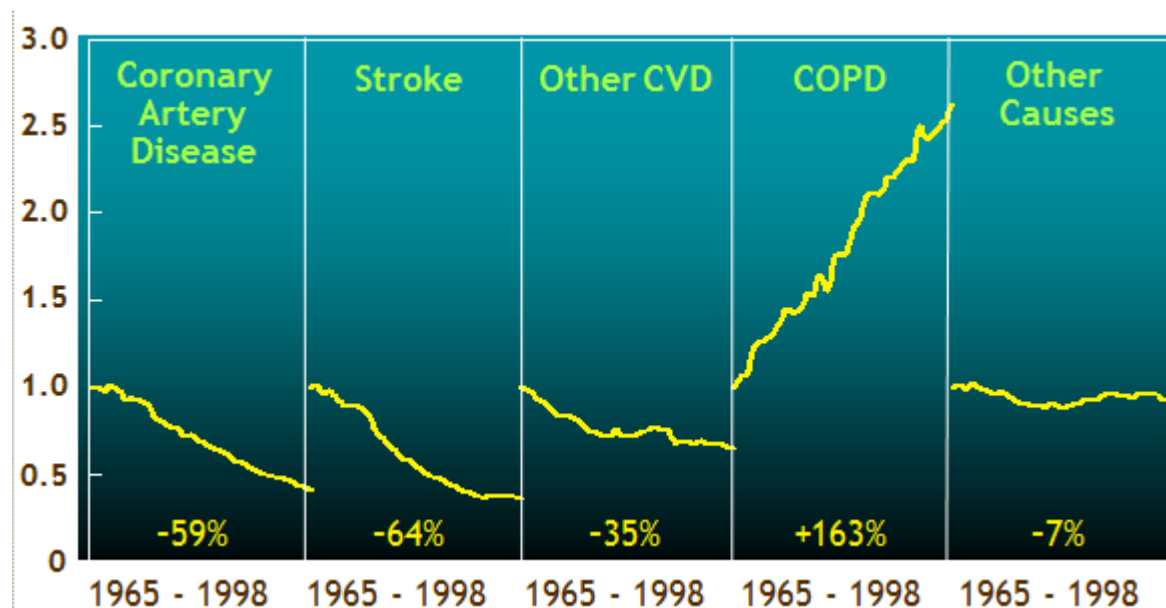
1.3. PREVALENCE

A systematic review and meta-analysis of studies carried out in 28 countries between 1990 and 2004, provide evidence that the prevalence of COPD is appreciably higher in smoker and in ex-smoker than non-smokers, in those over 40 years of age than those under 40, and in men than in women (11). The Burden of Obstructive Lung Diseases program (BOLD) has carried out surveys in several parts of the world in 2007 (12) and has documented more severe disease than previously found and a substantial prevalence (3-11 %) of COPD among never-smokers. At least 1 in 10 adults is identified with COPD in population surveys (13).

COPD prevalence was reported between %6,9 and 19,6 in Turkey referring to the study conducted in 2004 (14).

One of the centers of BOLD study was Adana, a city in Turkey. Total COPD prevalence was reported as %19.2 among the population over 40. It was considered %29.3 in men while %9.9 in women (12).

According to Eurostat statistics database, COPD Prevalence in Turkey is quite higher than other countries as shown in figure 3.

Figure 3. COPD prevalence distributed by countries (15)

Self-reported COPD, 2008 (or nearest year)

Country	%
Hungary	4.7
France	4.3
Belgium	4.0
Austria	3.7
Spain	3.5
Bulgaria	3.3
Latvia	3.3
Slovak Republic	3.3
Slovenia	3.1
EU16	3.1
Poland	3.0
Greece	2.9
Czech Republic	2.7
Cyprus	2.4
Estonia	2.1
Romania	1.7
Malta	1.2
Turkey	6.2

% of population aged 15 and over

1.4. MORBIDITY

Morbidity measures traditionally include, physician visits, emergency department visits and hospitalizations.

Although COPD databases for these outcome parameters are less readily available and usually less reliable than mortality databases, the limited data available indicate that morbidity due to COPD increases with age (17-19). Morbidity of COPD may be affected by other comorbid chronic conditions (such as, cardiovascular disease, musculoskeletal impairment and diabetes mellitus) that are related to COPD and may have an impact on the patient's health status, as well as interfere with COPD management (17). Especially, exacerbations of COPD are a major cause of morbidity. In particular, they greatly contribute to decline of health-related quality of life, increase in symptoms and breathlessness, progression of the disease, and increased risk of mortality (7).

1.5. MORTALITY

It is clear that COPD is one of the most important causes of death in many countries (Figure 4). The Global Burden of Disease (GBD) Study projected that COPD, which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2020; a newer projection estimated COPD supposed to be the fourth leading cause of death in 2030 (3). COPD accounts for 4.8% of global deaths and WHO predicts its mortality burden will increase to 7.9% by 2030 (13). This increased mortality is driven by the expanding epidemic of smoking, reduced mortality from other common causes of death (e.g. ischemic heart disease, infectious disease), and aging of the word population (1).

T.C. Ministry of Health National Disease Burden and Cost Effectiveness Study Turkey 2004 was reported that, COPD is the third leading cause of death which accounts for %5.8 of all deaths in Turkey. When analyzed as male and female; COPD is the third leading cause of death in males which accounts for %7.8 of all

deaths and it is the fifth leading cause of death in males which accounts for %3.5 of all deaths (14).

Exacerbations greatly contribute to decline of health-related quality of life, increase in symptoms and breathlessness, progression of disease and increased risk of mortality (5).

More than 15 million Americans are estimated to suffer from COPD. COPD is the fourth-leading cause of death in the United States, accounting for more than 95.000 deaths in 1993 (16, 20).

1.6. ECONOMIC BURDEN

COPD is a major cause of mortality and morbidity. Relatively few pharmacoeconomic studies have been conducted on this disease. However, according to the data published, COPD is associated with significant economic burden. In the European Union, the total direct costs of respiratory disease are estimated to be about 6% of the total health care budget, with COPD accounting for 56% (38.6 billion Euros) of this cost of respiratory disease (21). In the United States the estimated direct costs of COPD are $29.5 billion and the indirect costs $20.4 billion (22). In addition, because COPD is a systemic disease, the presence of COPD-related comorbidities increase as the disease progresses, adding significantly to the disease burden (23).

COPD exacerbations account for the greatest proportion of the total COPD burden on the health care system (22). Exacerbations increase health care utilization, including inpatient admissions, emergency department visits, and the use of rescue medications (5).

Burden-of-illness data in USA indicate that hospital care, medications and oxygen therapy are the major cost drivers. Costs are associated with health status, age, physician specialty, geographic location and type of insurance coverage (24).

In developing countries, direct medical costs may be less important than the impact of COPD on workplace and home productivity. Because the health care sector might not provide long-term supportive care services for severely disabled individuals, COPD may force individuals to leave the workplace – the affected individual and a family member who must stay home to care for the disabled relative. Since human capital is often the most important national asset for developing countries, the indirect costs of COPD may represent a serious threat to developing countries' economies (1).

Grasso et al. reported that 1992 Medicare per capita expenditures for patients with COPD were 2.4 times that of all Medicare beneficiaries in US – $8482 vs $US3511 ($US11 841 vs $US4901; 2000 values). Hospital expenditures, 64% of the total, were 2.7 times higher: $US5409 vs $US2001; ($US7551 vs $US2793) while physician care was 2.2 times higher: $US2604 vs $US1198 ($US3365 vs $US1672) (25).

Using data from a health maintenance organization (HMO), Mapel et al. reported that patients with COPD were 2.3 times more likely to be admitted to the hospital at least once during the year compared with age- and gender-matched patients with other conditions, and those admitted had longer average lengths of stay (4.7 vs 3.9 days, p < 0.001) (26).

COPD costs varies greatly by countries. Using the American Thoracic Society staging system, treatment costs were highly correlated with disease severity. Annual median treatment costs (1993/1994) by stage were: stage I = $US1681, stage II = $US5037 and stage III = $US10 812 (p < 0.01) [$US2177, $US6523 and $US14 002; 2000 values]. [Stage criteria: stage I = forced expiratory volume in 1 second (FEV1) ≥50% to ≤65% of predicted; stage II = FEV1 ≥35% to 49% of predicted; stage III = <35% of predicted] (20).

Crockett et al., in a study conducted in Australia, also noted a positive relationship between the number of comorbid conditions and hospital stay. Mean length of stay for patients with <3 comorbid conditions was 5.36 days; for patients with more than 5 comorbid conditions it was 7.64 days (28). This study showed that, comorbid conditions also contributed the economic burden of COPD. Comorbid

disease should be treated in order to maintain the disease control and decrease the total treatment costs.

In an Italian bottom-up study carried out on a representative sample of 5 million individuals from the general population that aimed to calculate the COPD cost of illness, the mean annual cost/ patient was €2100, ranging from €1500 for mild (65% of cases) to €3000 for moderate and €3900 for the most severe cases of the disease (5%) (29).

One study performed in Singapore has determined that the mean cost of a COPD patient hospitalized in the standard ward within a period of 5 years was $7184 (30). Mean cost of COPD has been calculated as $2008 in a cost-analysis study performed by Dalal et al. in the USA on 37089 patients with COPD (31). Cost has been reported as $305 in out-patients, $327 in emergency ward patients, $9745 in standard ward patients and $33440 in intensive care unit patients.

Figure 5. COPD hospitalizations distributed by years (32).
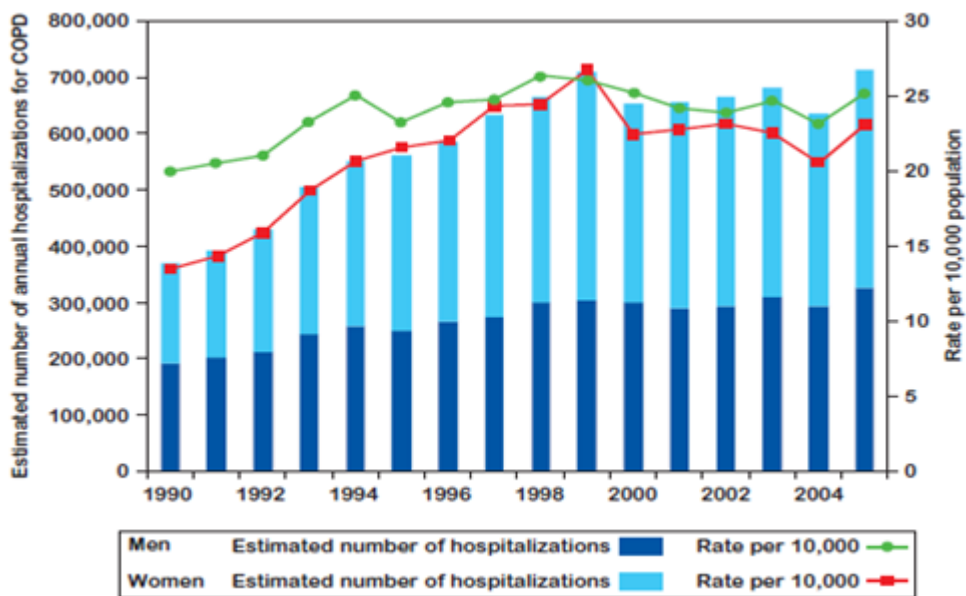
1.7. ECONOMIC BURDEN OF COPD IN TURKEY

According to the study of Köksal N et al. at TTD (Türk Toraks Derneği) Congress, 2007, the cost of COPD according to GOLD stages were reported as; Stage I: 51-110 TL/year, Stage II: 820-890 TL/year, Stage III: 1110-1830 TL / year, Stage IV: 2500-3310 TL / year and hospitalization treatment costs for service: 136 TL / day and for Intensive Care Unit : 360 TL / day (33).

Table 1. COPD treatment and hospitalization cost (33)

COPD treatment cost according to GOLD stages		
Stage I	51-110 TL/year	
Stage II	820-890 TL/year	
Stage III	1110-1830 TL / year	
Stage IV	2500-3310 TL	
Hospitalization treatment cost		
Service	136 TL / day	
ICU	360 TL / day	

In the study of Ozkaya et al. performed in 2011 in Samsun/Turkey, mean duration has been found as 718 ± 364 per admission among patients hospitalized for acute exacerbation of COPD (AECOPD) (34). However, costs of patients admitted due to AECOPD are expected to be greater since Intensive Care Unit patients who constitute the majority of costs have not been included. Another study from Turkey has demonstrated that patients with AECOPD were responsible from the great majority of total costs of patients admitted to the clinic of chest diseases and that mean cost was $997 (35).

Another study of Ornek T et al. 2012 investigated 284 patients hospitalized in Zonguldak because of acute COPD exacerbation. Data were examined retrospectively using the electronic hospital charts. Mean duration of hospitalization was 11.38 ± 6.94 days among study patients. Rates of admission to the intensive care unit, initiation of non-invasive mechanical ventilation (NIMV) and invasive mechanical ventilation (IMV) were 37.3% (n=106), 44.4% (n=126) and 18.3% (n=52) respectively. The rate of mortality was 14.8% (n=42). Mean cost of a single patient hospitalized for an acute exacerbation was calculated as 1765 ± 2139. Mean cost of admission was 889 ± 533 in standard ward, and 2508 ± 2857 in intensive care unit (ICU). The duration of hospitalization, a FEV1% predicted value below 30%, having smoked 40 package-years or more, the number of co-morbidities, NIMV, IMV, ICU, exitus and the number of hospitalizations in the past year were among the factors that increased costs significantly. Hospital acquired pneumonia, chronic renal failure and anemia also increased the costs of COPD significantly and the study concluded that the costs of treatment increase with the severity of COPD or with progression to a higher stage. Efforts and expenditures aimed at preventing COPD exacerbations might decrease the costs in COPD (36).

It can be concluded that majority of COPD costs result of acute exacerbations, treatment cost of exacerbations and hospitalization costs (22, 37, 38). Hospitalization costs of COPD exacerbations are two times higher than the other causes of hospitalizations (36, 37). More than half of the COPD patients, are hospitalized again because of acute exacerbation in six months after discharge (39). Patients who are hospitalized from COPD exacerbation have to stay longer time at hospital than the patients hospitalized from other reasons and the quality of life are affected negatively (40, 41).

According to recent literatures, majority of the COPD related costs are hospitalizations and emergency service visits as 72,8 %. Outpatient and doctor visits are 15 % of total cost and prescribed medicines are only 12,2% of total treatment cost (42).

1.8. SOCIAL BURDEN

Since mortality offers a limited perspective on the human burden of disease, it is desirable to find other measures of disease burden that are consistent and measurable across nations. The authors of Global Burden of Disease Study designed a method to estimate the fraction of mortality and disability attributable to major diseases and injuries using a composite measure of the burden of each health problem, the Disability-Adjusted Life Year (DALY) (2, 43, 44). The DALYs for a specific condition are the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability. In 1990, COPD was the twelf leading cause of DALYs lost in the word, responsible for 2.1% of the total. According to projections COPD will be the seventh leading cause of DALYs lost wordwide in 2030 (3).

1.9. FACTORS THAT INFLUENCE DISEASE DEVELOPMENT AND PROGRESSION

Cigarette smoking is the best studied COPD risk factor, it is not the only one reason and there is consistent evidence from epidemiologic studies that non-smokers may also develop chronic airflow limitation (45, 46 ,47, 48).

COPD results from a gene-environment interaction too, among people with the same smoking history, not all will develop COPD due to differences in genetic predisposition to the disease, or how long they live. Risk factors for COPD may also be related to more complex ways. For example, gender may influence whether a person takes up smoking or experiences certain occupational or environmental exposures; socioeconomic status may be linked to a child's birth (as it impacts on lung growth and development and in turn of susceptibility to develop the disease); and longer life expectancy will allow greater lifetime exposure to risk factors.

1.10. PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY

Inhaled cigarette smoke and other noxious particles such as smoke from biomass fuels cause lung inflammation, a normal response that appears to be modified in patients who develop COPD. This chronic inflammatory response may induce parenchymal tissue destruction (resulting in emphysema), and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis). These pathological changes lead to air trapping and progressive airflow limitation (49).

1.10.1. PATHOLOGY

Pathological changes characteristic of COPD are found in the airways, lung parenchyma and pulmonary vasculature. The pathological changes include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repaired injury and repair. In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation (49).

Figure 6. Pathological findings in patients with COPD (50).

Pathological Findings in Patients with COPD.
Panel A shows a collection of bronchial lymphoid tissue with a lymphoid follicle containing a germinal center (GC) surrounded by a rim of darker-staining lymphocytes that extend to the epithelium of both the small airway and alveolar surface (Movat's stain, ×6). Panel B shows another follicle, in which the germinal center stains strongly for B cells (×6), and Panel C shows a serial section of the same airway stained for CD4 cells, which are scattered around the edge of the follicle and in the airway wall (×6.5). Panel D shows an airway that has been extensively remodeled by connective-tissue deposition in the subepithelial and adventitial compartments of the airway wall. The arrow points to the smooth muscle that separates the subepithelial from the adventitial compartments (Movat's stain, ×6).

1.10.2. PATHOGENESIS

The inflammation in the respiratory tract of COPD patients appears to be a modification of the inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke. The mechanisms for this amplified inflammation are not yet understood but may be generally determined. Patients can clearly develop COPD without smoking, but the nature of the inflammatory response in these patients is unknown. Oxidative stress and an excess proteinases in the lung further modify lung inflammation. Together these mechanisms lead to the characteristic pathological changes in COPD. Lung inflammation persists after smoking cessation through unknown mechanisms, although autoantigens and persistent microorganisms may play a role (51).

1.10.3. PATHOPHYSIOLOGY

1.10.3.1. Airflow Limitation and Air Trapping;

The extend of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV1 and FEV1/FVC ratio, and probably with the accelerated decline in FEV1 characteristic of COPD (50). This peripheral airway obstruction progressively traps air during expiration, resulting in hyperinflation. Although emphysema is more associated with gas exchange abnormalities than with reduced FEV1, it does contribute to gas trapping during expiration. This is especially so as alveolar attachments to small airways are destroyed when the disease becomes more severe. Hyperinflation reduces inspiratory capacity such that functional residual capacity increases, particularly during exercise, resulting in increased dyspnea and limitation of exercise capacity (52, 53).

1.10.3.2. Gas Exchange Abnormalities;

Gas exchange abnormalities result in hypoxemia and hypercapnia, and hace several mechanisms in COPD. In general gas transfer for oxygen and carbon dioxide worsens as the disease progresses (54).

1.10.3.3. Mucus Hypersecretion;

Mucus hypersecretion, resulting in a chronic productive cough, is a feature of chronic bronchitis and is not necessarily associated with airflow limitation (55).

1.10.3.4. Pulmonary Hypertension;

Pulmonary hypertension may develop late in the course of COPD and is due mainly to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia (56).

1.10.3.5. Exacerbations;

Exacerbations of respiratory symptoms often occur in patients with COPD, triggered by infection with bacteria and viruses, environmental pollutants, or unknown factors. Patients with bacterial and viral episodes have a characteristic response with increased inflammation. During respiratory exacerbations there is increased hyperinflation and gas trapping, with reduced expiratory flow, thus accounting for the increased dyspnea (57).

COPD is a more costly disease than asthma and, depending on country, 50–75% of the costs are for services associated with exacerbations (16).

1.10.4. Systemic Features;

It is increasingly recognized that many patients with COPD have comorbidities that have a major impact on quality of life and survival (57). Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange. Inflammatory mediators in the circulation may contribute to skeletal muscle wasting and may initiate or worsen comorbidities such as ischemic heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, metabolic syndrome and depression (59).

1.11. DIAGNOSIS

Diagnosis of COPD should be considered in any patient who has the following:

- symptoms of cough

- sputum production or

- dyspnoea or

- history of exposure to risk factors for the disease.

1.11.1. Spirometric Classification

Spirometry is the most reproducible and objective measurement of airflow limitation available. Spirometry generally can be found in most of health care settings in Turkey. Table 3 summarizes stages of COPD according to the spirometric values.

Table 3. Spirometric classification (1)

Severity	Postbronchodilator FEV1/FVC	FEV1 % predicted

At risk
Patient who:
  smoke or have exposure to pollutants
  have cough, sputum or dyspnea
  have family history of respiratory disease
	> 0.7	≥80

Mild COPD	≤0.7	≥80
Moderate COPD	≤0.7	50-80
Severe COPD	≤0.7	30-50
Very severe COPD	≤0.7	<30
FEV1: forced expiratory volume in one second; FVC: forced vital capacity.		

Spirometric classification has proved useful in predicting health status (60), utilisation of healthcare resources (61), development of exacerbation (62, 63) and mortality (64) in COPD. It is intended to be applicable to populations (65) and not to substitute clinical judgment in the evaluation of the severity of disease in individual patients. Spirometric classification is one part of COPD staging. Staging system will be explained in detail in the following sections (in Figure 7).

The diagnosis requires spirometry; post-bronchodilator FEV1/forced vital capacity <0.7 confirms the presence of airflow limitation that is not fully reversible.

Spirometry should be obtained in all persons with the following history:

• exposure to cigarettes and/or environmental or occupational pollutants

• family history of chronic respiratory illness

• presence of cough, sputum production or dyspnea (16).

The goals of COPD assessment are to determine the severity of the disease, including the severity of airflow limitation, the impact of the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), in order to guide therapy. Comorbidities occur frequently in COPD

patients including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression and lung cancer. Given that they can occur in patients with mild, moderate and severe airflow limitation and influence mortality and hospitalizations independently, comorbidities should be actively looked for, and treated appropriately if present (1).

Table 2. Key indicators for considering a diagnosis of COPD (1).

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD.

Dyspnea that is: Progressive (worsens over time).
Characteristically worse with exercise.
Persistent.

Chronic cough: May be intermittent and may be unproductive.

Chronic sputum production:
Any pattern of chronic sputum production may indicate COPD.

History of exposure to risk factors:
Tobacco smoke (including popular local preparations).
Smoke from home cooking and heating fuels.
Occupational dusts and chemicals.

Family history of COPD

Modified Medical Research Council Questionnaire: This questionnaire relates well to other measures of health status (66) and predicts future mortality risk (67).

Table 4. Modified Medical Research Council Questionnaire for assessing the severity of breathlessness (1).

PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY)	
mMRC Grade 0. I only get breathless with strenuous exercise.	☐
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

1.11.2. The COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a new questionnaire for people with COPD (Table 5). It is designed to measure the impact of COPD on a person's life, and how this changes over time. The CAT is very simple to administer, and aims to help clinicians manage a patient's COPD better (http://www.catestonline.org/). It was developed to be applicable worldwide and validated translations are available in a wide range of languages. The score ranges from 0-40 (68).

Table 5. The COPD Assessment Test (CAT)

Example: I am very happy   0 ☒ 2 3 4 5   I am sad

SCORE

I never cough	0 1 2 3 4 5	I cough all the time
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is full of phlegm (mucus)
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	0 1 2 3 4 5	I have no energy at all

CLICK TO GET YOUR TOTAL SCORE!

1.11.3. Combined COPD Assesment

An understanding of the impact of COPD on an individual patient combines the symptomatic assessment with the patient spirometric classification and/or risk of exacerbations. This approach to combined assessment is illustrated in figure 7.

As seen in table 4 and 5, MRC and CAT scale is recommended for assessing symptoms, with mMRC grade ≥ 2 or a CAT score ≥ 10 indicating a high level of symptoms.

First assess symptoms with the mMRC and CAT scale and determine if the patient belongs to the left side of the box – Less symptoms (mMRC grade 0-1 or CAT < 10) – or the right side – More symptoms mMRC grade ≥ 2 or CAT ≥ 10).

Next assess the risk of exacerbations to determine if the patient belongs to the lower part of the box – Low risk – or the upper part of the box – High risk. This can be done by either of two methods: (1) use spirometry to determine the GOLD grade of airflow limitation (GOLD 1 and GOLD 2 categories indicate low risk, while GOLD 3 and GOLD 4 categories indicate high risk) (1).

Patient Group A - Low Risk, Less Symptoms

Typically GOLD 1 or GOLD 2 (Mild or Moderate airflow limitation) and/or 0-1 exacerbation per year and mMRC grade 0-1 or CAT score < 10 (1).

Patient Group B - Low Risk, More Symptoms

Typically GOLD 1 or GOLD 2 (Mild or Moderate airflow limitation) and/or 0-1 exacerbation per year and mMRC grade ≥ 2 or CAT score ≥ 10 (1)

Patient Group C - High Risk, Less Symptoms

Typically GOLD 3 or GOLD 4 (Severe or very severe airflow limitation) and/or
≥ 2 exacerbations per year and mMRC grade 0-1 or CAT score < 10 (1).

Patient Group D - High Risk, More Symptoms

Typically GOLD 3 or GOLD 4 (Severe or very severe airflow limitation) and/or
≥ 2 exacerbations per year and mMRC grade ≥ 2 or CAT score ≥ 10 (1).

Figure 7. COPD Classification (1).

Figure   Association Between Symptoms,
Spirometric Classification,
and Future Risk of Exacerbations
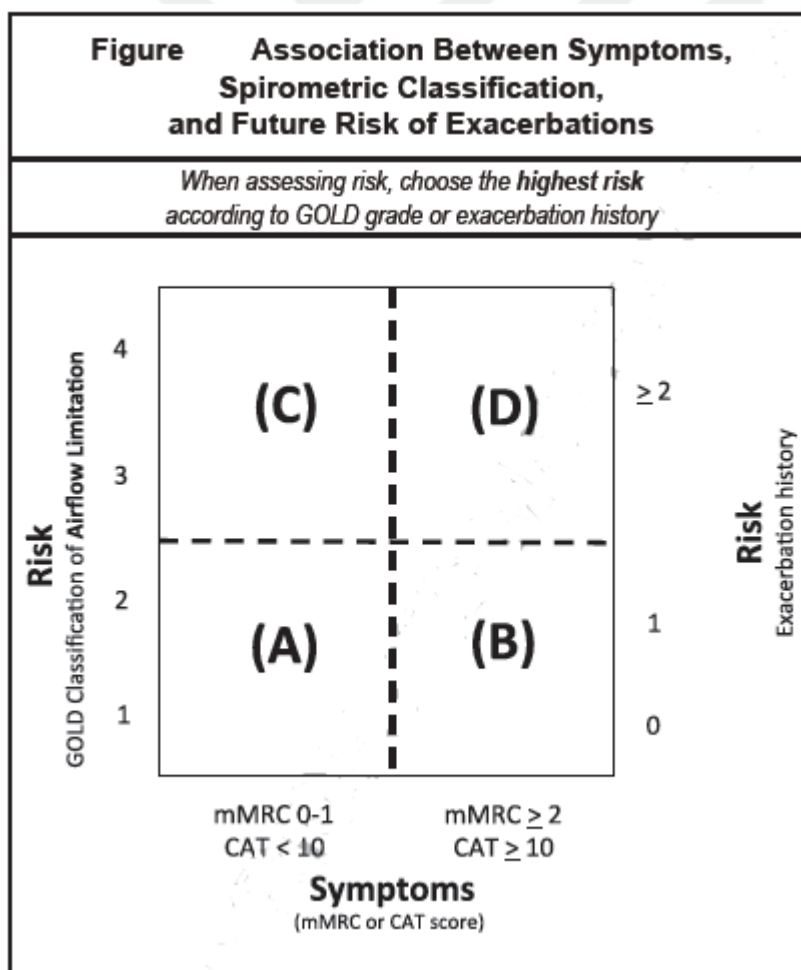
1.12. TREATMENT

Once COPD has been diagnosed, effective management should be based on an individualized assessment of disease order to reduce both current symptoms and future risks (1).

Identification and reduction of exposure to risk factors are important in the treatment and prevention of COPD. Since cigarette smoking is the most commonly encountered and easily identifiable risk factor, smoking cessation should be encouraged for all individuals who smoke. Reduction of all total personal exposure to occupational dusts, fumes and gasses and to indoor and outdoor air pollutants may be difficult but should be attempted (1).

Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations and improve health status and exercise tolerance.

The level of FEV1 is an inadequate descriptor of the impact of the disease on patients and for this reason individualized assessment of symptoms and future risk of exacerbation should also be incorporated into the management strategy for stable COPD.

1.12.1. Smoking Cessation

Smokers experience an accelerated rate of decline in lung function (69). Individual susceptibility, however, varies greatly and depends on a complex interaction of many genetic and environmental factors.

It is often stated that 15% of smokers will develop COPD. This dramatically underestimates the impact of smoking because the majority of smokers will develop loss of lung function (69, 70), and reduced lung function, at any level, is predictive of increased mortality (71).

Quitting smoking can slow the progressive loss of lung function (72) and can reduce symptoms (73) at any point in time. Yet, the beneficial impact of smoking

cessation on the natural history of COPD is greatest the earlier cessation is achieved. Adolescents who quit smoking will have increased lung growth.

1.12.2. Pharmacologic Therapy

The classes of medicaations commonly used in treating COPD are shown in table 6. The choice within each class depends on the availability and cost of medication and the patient's response. Each treatment regimen needs to be patient-specific as the realtionship between severity of symptoms, airflow limitation and severity of exacerbations will differ between patients (1).

Table 6. Formulations and typical doses of COPD medications (1).

Drug	Inhaler (mcg)	Solution for Nebulizer (mg/ml)	Oral	Vials for Injection	Duration of Action (hours)
Beta2-agonists					
Short-acting					
Fenoterol	100-200 (MDI)	1	0.05 % (Syrup)		4--6
Levalbuterol	45-90 (MDI)	0.21, 0.42			6--8
Salbutamol (Albuterol)	100, 200 (MDI & DPI)	5	5 mg (Pill) 0.024 % (Syrup)	0.1, 0.5	4--6
Terbutaline	400, 500 (DPI)		2.5, 5 mg (Pill)		4--6
Long-acting					
Formoterol	4.5-12 (MDI & DPI)	0.01			12
Arformoterol		0.0075			12
Indacaterol	75-300 (DPI)				24
Salmeterol	25-50 (MDI & DPI)				12
Tulobuterol			2 mg (Transdermal)		24
Anticholinergics					
Short-acting					
Ipratropium bromide	20, 40 (MDI)	0.25-0.5			6--8
Oxitropium bromide	100 (MDI)	01.May			7--9
Long-acting					
Tiotropium	18 (DPI), 5 (SMI)				24
Combination short-acting beta2-agonists plus anticholinergics in one inhaler					
Fenoterol/Ipratropium	200/80 (MDI)	1.25/0.5			6--8
Salbutamol/Ipratropium	75/15 (MDI)	0.75/0.5			6--8
Methylxanthines					
Aminophylline			200-600 mg (Pill)	240	Variable up to 24
Theophylline (SR)			100-600 mg (Pill)		Variable up to 25
Inhaled Corticosteroids					
Beclomethasone	50-400 (MDI & DPI)	0.2-0.4			
Budesonide	100,200,400 (DPI)	0.20,0.25,0.5			
Fluticasone	50-500 (MDI & DPI)				
Combination long-acting beta2-agonists plus corticosteroids in one inhaler					
Formoterol/Budesonide	4.5/160 (MDI) 9/320 (DPI)				
Salmeterol/Fluticasone	50/100,250,500 (DPI) 25/50,125,250 (MDI)				
Systemic corticosteroids					
Prednisone			5-60 mg (Pill)		
Methyl-prednisolone			4, 8, 16 (Pill)		
Phosphodiesterase-4 inhibitors					
Roflumilast			500 mcg (Pill)		24

1.12.2.1. Bronchodilators

Medications that increase the FEV1 or change other spirometric variables, usually by altering air way smooth muscle tone, are termed bronchodilators (74).

Three types of bronchodilator are in common clinical use: β-agonists, anticholinergic drugs and methylxanthines.

Despite substantial differences in their site of action within the cell and some evidence for nonbronchodilator activity with some classes of drug, the most important consequence of bronchodilator therapy appears to be airway smooth muscle relaxation and improved lung emptying during tidal breathing (16).

Bronchodilator medications are given on either an as needed basis or a regular basis to prevent or reduce symptoms (75-78).

1.12.2.1.1. Beta$_2$-Agonists

The principle action of beta$_2$-agonists is to relax airway smooth muscle by stimulating beta$_2$-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction (72).

Bronchodilator medications are central to symptom management in COPD. Inhaled therapy is preferred. Bronchodilators are prescribed on an as-needed or regular basis to prevent or reduce symptoms (72).

The bronchodilators effects of short acting beta$_2$-agonists usually wear off within 4 to 6 hours (78, 79). Regular and as-needed use of short acting beta-agonists improve FEV1 and symptoms (81).

Long-acting inhaled beta2-agonists show duration of action of 12 or more hours. Formoterol and salmeterol significantly improve FEV1 and lung volumes, dyspnea, health related quality of life and exacerbation rate (6).

Long- acting inhaled bronchodilators are convenient and more effective at producing maintained symptom relief than short-acting bronchodilators. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of single bronchodilator (1).

Stimulation of beta$_2$-adrenergic receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in susceptible patients, although these seem to have remarkably few clinical implications (1).

1.12.2.1.2. Anticholinergics

Anticholinergics are only available by the inhaled route, although a number of preparations are available, the commonest are:

• ipratropium

• oxitropium

• tiotropium (16).

These drugs act by blocking muscarinic receptors that are known to be functional in COPD (81). The long-acting anticholinergic tiotropium has a pharmacokinetic selectivity for the M3 and M1 receptors (83).

The bronchodilating effect of short-acting inhaled anticholinergics lasts longer than that of short-acting inhaled anticholinergics lasts longer than that of short-acting beta2-agonists, with some bronchodilator effect generally apparent up to 8 hours after administration (79) Tiotropium has duration of action of more than 24 hours (84).

1.12.2.1.3. Methylxanthines

Methylxanthines can only be taken by orally and include theophylline, aminophylline and its derivatives. These drugs are nonspecific phosphodiesterase inhibitors that increase intracellular cyclic AMP within airway smooth muscle. The bronchodilator effects of these drugs are best seen at high doses where there is also a higher risk of toxicity (85).

The narrow therapeutic margin and complex pharmacokinetics make their use difficult but modern slow-release preparations have greatly improved this problem and lead to a stable plasma level throughout the day. Generally, therapeutic levels should be measured and patients should be kept on the lowest effective dose (recommended serum level 8–14 μg·dl-1).

These drugs are commonly taken in the morning and the evening but 24-h formulations are available. The slow onset of action makes these agents suitable for maintenance but not rescue therapy. There is some evidence of a dose-response effect (86), which is limited by toxicity.

1.12.2.2. Corticosteroids

1.12.2.2.1. Inhaled Corticosteroids

Inhaled corticosteroids in regular treatment improves symptoms, lung function and quality of life and reduces the frequency of exacerbations (87) in COPD patients with an FEV1< 60 % predicted (6).

Preparations by inhalation:

• beclomethasone

• budesonide

• triamcinolone

• fluticasone

• flunisolide

Oral corticosteroids are not indicated in stable COPD due to the multiple side-effects and skeletal muscle myopathy in particular. They are also important during exacerbations (16).

Inhaled corticosteroid use is associated with higher prevalence of oral candidiasis, hoarse voice, and skin bruising. Treatment with inhaled corticosteroids is associated with an increased risk of pneumonia (1).

1.12.2.2.2. Combination Inhaled Corticosteroid/Bronchodilator (ICS/LABA)

An inhaled corticosteroid combined with a long-acting beta$_2$-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to severe COPD. These combination inhaler have a synergistic effect. Inhaled corticosteroids enhance the effectiveness of beta$_2$ receptors. In the same manner, beta$_2$-agonist enhance the potential of corticosteroid receptors.

Combination therapy is associated with an increased risk of pneumonia but no other significant side effect (6, 8, 88, 89, 90).

1.12.2.2.3. Oral Corticosteroids

Oral corticosteroids are not indicated in stable COPD due to the multiple side-effects and skeletal muscle myopathy in particular. They are also important during exacerbations (16).

1.12.2.3. Other Agents

There are no data to support the use of leukotriene receptor antagonists/cromones and maintenance antibiotic therapy in COPD (72).

1.12.2.3.1. Immunoregulators

One study has shown that an immunostimulator can reduce the severity, but not the frequency, of exacerbations in stable COPD. (91).

1.12.2.3.2. Vasodilators

Many drugs, including inhaled nitric oxide and oral calcium antagonists, have been given to COPD patients to reduce pulmonary artery pressure and/or prevent progression of pulmonary hypertension. In all cases this has resulted in a deterioration of ventilation-perfusion matching and a reduction in arterial oxygen tension, which has offset any beneficial effect (16).

1.12.2.3.3. α-Trypsin augmentation therapy

Patients identified with α1-antitrypsin deficiency are eligible for treatment with this agent (75).

1.12.2.3.4. Vaccination

Vaccination against influenza, using an appropriate recommended vaccine, can reduce serious illness and death in COPD by ~50%. Vaccines containing cold or live inactivated viruses are recommended, as they are more effective in elderly patients with COPD (92).

Vaccination against pneumococcal disease reduces bacteraemia in vaccinated patients with pneumonia (93). The vaccination is indicated for all elderly patients depending on national recommendations.

1.13. MANAGEMENT OF STABLE COPD

Identification and reduction of exposure to risk factors are important steps in the prevention and treatment of COPD (1).

Once COPD has been diagnosed, effective management should be based on an individualized assessment of disease order to reduce both current symptoms and future figure 7 (1).

1.14. PHARMACOLOGIC TREATMENT

Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance (1).

A proposed model for initial pharmacological management of COPD according to individualized assessment of symptoms and exacerbation risk is shown in Table 8.

Table 8. Initial pharmacological management of COPD (1)

Patient Group	Recommended First Choice	Alternative Choice	Other Possible Treatments
A	Short-acting anticholinergic prn or Short-acting beta2-agonists prn	Long-acting anticholinergic or Long-acting beta2-agonists or Short-acting anticholinergic and short-acting beta2-agonists	Theophylline
B	Long-acting anticholinergic or Long-acting beta2-agonists	Long-acting anticholinergic and Long-acting beta2-agonists	Short-acting beta2-agonists and/or Short-acting anticholinergic Theophylline
C	Inhaled corticosteroid+ Long-acting beta2-agonists (ICS/LABA) or Long-acting anticholinergic	Long-acting anticholinergic and Long-acting beta2-agonists or Long-acting anticholinergic and phosphodiesterase-4 inhibitor or Long-acting beta2-agonists and phosphodiesterase-4 inhibitor	Short-acting beta2-agonists and/or Short-acting anticholinergic Theophylline
D	Inhaled corticosteroid+ Long-acting beta2-agonists (ICS/LABA) and/or Long-acting anticholinergic	Inhaled corticosteroid+ Long-acting beta2-agonists (ICS/LABA) and Long-acting anticholinergic or Inhaled corticosteroid+ Long-acting beta2-agonists and phosphodiesterase-4 inhibitor or Long-acting anticholinergic and Long-acting beta2-agonists or Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine Short-acting anticholinergic and/or Short-acting beta2-agonists

A, B, C, and D classification and treatment choices for this classification were recently added the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guideline. Different staging system which highly depended on only FEV1 value, and treatment options were included in guidelines before 2011. In GOLD 2011 update, it was showed that, only FEV1 value is not enough for diagnose and decide a proper treatment. Symptoms, health status, exercise limitations, exacerbations, dyspnea of patients are also important parameters for a right diagnose and treatment. In order to take into account all patient factors, GOLD scientific team, built A, B, C, D classification (figure 7) and recommended treatment alternatives for each group. In table 8, treatment choices were displayed for each class. As GOLD is a global guideline, all physicians should follow and apply these recommendations. However in Turkey, although this staging system was written in theory, many physicians do not arrange treatments in practice with hundred percent alignment with GOLD guideline. Treatment approaches of Turkish physicians were also questioned in the survey and results will be discussed in the "Discussion" part.

1.15. NON-PHARMACOLOGIC TREATMENT OF COPD

- **Smoking Cessation**

Smoking cessation should be considered the most important intervention for all COPD patients who smoke regardless of the level of disease severity (1).

- **Physical Activity**

Physical activity is recommended for all patients with COPD (1).

- **Rehabilitation**

Although more information is needed on criteria for patient selection for pulmonary rehabilitation programs, all COPD patients appear to benefit from rehabilitation and maintenance of physical activity, improving their exercise tolerance and experiencing decreased dyspnea and fatigue (94).

Table 7. Non-pharmacologic management of COPD (1)

Patient Group	Essential	Recommended	Depending on Local Guidelines
A	Smoking cessation (can include pharmacologic treatment	Physical activity	Flu vaccination Pneumococcal vaccination
B-D	Smoking cessation (can include pharmacologic treatment Pulmonary rehabilitation	Physical activity	Flu vaccination Pneumococcal vaccination

2. METHODOLOGY

2.1. Aim of the Study

Inhaled Corticosteroid/ Long Acting Beta$_2$ Agonist (ICS/LABA) fixed combinations are commonly used drugs in COPD treatment. Inhaled Corticosteroids reduce the inflammation in lungs and beta$_2$-agonists relaxe airway smooth muscle by stimulating beta$_2$-adrenergic receptors. ICS/LABA fixed combinations are more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to severe COPD. There are international guidelines which recommends treatment alternatives to different COPD patient profiles. However in Turkey, there is a limitation of data available which can figure out physicians' prescription behavior in reality. There is no broad study or market research conducted including many cities in Turkey.

The aim of this thesis is to gather physicians' opinions on ICS/LABA (Inhaled corticosteroid/long acting beta$_2$ agonist) fixed combinations for Chronic Obstructive Pulmonary Disease (COPD).

Survey method was selected for data collection. Physicians' opinions and experiments for ICS/LABA fixed combinations on COPD treatment and their observations on disease treatment outcomes were questioned in the survey.

2.2. Survey Method

The term survey describes a type of study that consists of asking people to respond to questions. Surveys are an excellent research tool because they are relatively inexpensive and allow quick data acquisition. Generally, surveys are ideal for collecting data about people's attitudes, behaviors, knowledge, and personal history (95).

2.3. Organizing a Survey Study

Organizing a survey research involves several separate but important steps. Proper attention to the early steps of study design will save much time and trouble. The process starts with clearly identifying the question researchers want to be answered. This question should be very clear to the investigators and be summarized in a short sentence. Although a couple of secondary questions are acceptable, questions should be minimized. Questions are readable and understandable.

2.4. Modes of Survey Administration

2.4.1. Personal Interviews (face to face)

Personal interviews generally yield the highest cooperation and lowest refusal rates. They allow for longer, more complex interviews. They have high response quality. Also, this method takes advantage of interviewer presence. Personal interview is the most costly mode of administration. Data collection period is longer and interviewer concerns may interfere with the results (96).

2.4.2. Telephone Interviews

Telephone interviews are less expensive than personal interviews. This method allows randomized samples of general population to be analyzed. Short data collection may save time for studies. Control and supervision of interviewer is also an advantage of this method. The study can be generalized because of the samples of general population. The response rates are high but there is the risk of unservicable telephone numbers and nonresponsive calls. Questionnaire use may be constrainted. In addition to these points, as a disadvantage, it is difficult to administer questionnaires on sensitive or complex topics (96).

2.4.3. Mail Survey

Generally, mail survey method is the lowest cost mode of survey. Mail survey can be administered by a smaller team of people. Accessing otherwise difficult to locate, busy populations is possible. Respondents can look up information or consult with others. Nonetheless, using mail survey, it is difficult to obtain cooperation with interviewer. No interviewer can be involved in collection of data. For a substantive study, there is a need for good sampling. Slow data collection period is one of the down sides of this method. Mail survey is also more likely to need an incentive for respondents (96).

2.4.4. Web Survey

Web surveys have low cost like other web based survey types. Web survey can reach international populations. Less time is required for implementation. Complex skip patterns can be programmed. Sample size can be greater. However, it cannot generate random samples of general population. Differences in capabilities of people's computers and software for accessing web surveys can be a risk factor (96).

2.5. Selecting the Survey Method

Possible formats include personal interviews, telephone interviews, mailed questionnaires, etc. Among these different methods, paper questionnaires are the most common and generally are familiar to both potential subjects and scientific readers. Beside these reasons, because of the convenience of the place (TÜSAD congress) and sample size, paper questionnaire is the most suitable method for this thesis. Moreover, paper surveys are easier tools to collect data from physicians. Not being many survey questions provided an advantage.

2.6. Place of Study

The study was conducted at TÜSAD (Turkish Respiratory Society/Türkiye Solunum Araştırmaları Derneği) Congress in Çeşme/İzmir in October 2012.

TÜSAD congress is one if the biggest Chest congress which is organized every year in Turkey. TÜSAD congress gathers physicians from different territories of the country. For this reasons it was an ideal location to sample the physicians as respondents.

Participation of all physicians regardless of the speciality, was requested voluntarily during congress.

2.7. Population and sample

The population studied was the pyhsicians who participated to the TÜSAD congress. 1.500 physicians participated the congress.

Physicians who participated in the congress, regardless of the speciality were asked to join and complete the questionnaire.

2.8. Questionnaire Design

A survey method was used to assess determine the impact of ICS/LABA fixed combinations on treatment of the participants. The questionnaire was designed by researcher of the thesis (Appendix-1).

2.9. Content of Questionnaire

Mostly closed and a few open response questions were used.

The first seven questions were sociodemographic (age, gender, the city they work, speciality, academic title, hospital they work).

The 8th question aimed to find out how many patients physicians treat in one working day, the percentage of COPD patients among total patients and percentage of patients in different stages of COPD (mild/moderate/severe/very severe).

The 9th question explored that, how often do physicians prescribe inhale corticosteroid plus long acting beta2 agonist fix combinations (ICS/LABA) at moderate COPD patients?

The 10th question investigated that, how often do physicians prescribe inhale corticosteroid plus long acting beta2 agonist fix combinations (ICS/LABA) at severe and very severe COPD patients?

The 11th question aimed to find out, difference related to the below parameters at patients who have been treated with inhale corticosteroid plus long acting beta2 agonist fix combinations (ICS/LABA) in physicians' daily practice.

"Frequency of exacerbations, severity of exacerbations, hospitalizations, comorbid disease, Health Quality of Life, spirometry results, exercise capacity, dispnea".

For instance, our desire would be to explore frequency of exacerbations decreased or not at patients who have been treated with ICS/LABA fixed combinations or Health Quality of Life improved or did not change.

2.10. Pilot Survey

Content validity are reviewed and evaluated Pilot survey was conducted with several physicians in İstanbul, August 2012. Feedbacks from physicians were collected and revisions were made on survey questions according to the comments of physicians.

2.11. Ethical Committee Approval

This study and survey was approved by Yeditepe University Ethical Committee on 24.07.2012. (Approval number: 214).

2.12. Data Analysis Technique

Questionnaire results were recorded by the researcher to Excel documentation programme. For analysis, SPSS Version 17 Statistics Software was used. Descriptive statistics, cross-tabs, Fisher's exact test, Chi square test, Mann-Whitney U test were used for statistical analysis. $p < 0.05$ was accepted as significant. Validity test was applied.

2.13. Limitations of The Study

- Total numbers of surveys were limited to 57. Researcher could not reach high number of physicians.

- The other limitation of this study is the low number of internists. High number of pulmonary physicians responded the survey but very low number of internists agreed to answer questions. This may be because of the place of the study. Mainly pulmonary physicians attend this type of chest congress.

- Another limitation of this study is that, no physician responded to our survey from pulmonary hospital.

- Irregular distribution of academic degree. There is a huge difference between the number of specialists and the number of professors.

- Unbalanced distribution of hospital type

3. RESULTS

In this chapter the results of frequency distribution of all variables, cross tabulation and statistical tests analyses were tabulated and summarized. This section is mainly composed of two parts.

Totally 57 questionnaires were used for analysis. Unanswered questions were set apart from the tables.

3.1. Frequency Distribution

3.1.1. Demographic Characteristics

In the section of demographic characteristics; gender, age, city, profession, academic degree and hospital type distribution were displayed.

3.1.1.1. Gender

59,6 % of respondents were female and 40.4 % of respondents were male. Majority (n=34) of participants were female. There was no respondent who did not answer this question (Figure 8).

Figure 8: Gender Distribution of Physicians
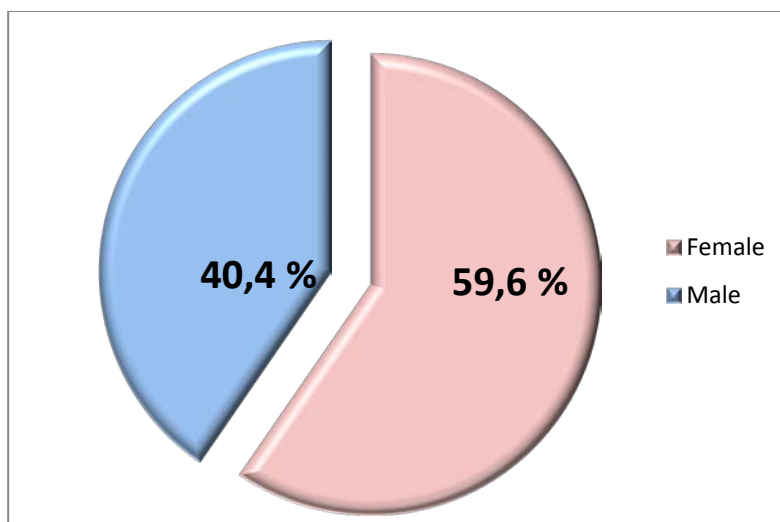
3.1.1.2. City

Majority of respondents were from Ankara (31.6%). Physicians from Istanbul constitute 19.3 % of respondents. Physicians from Zonguldak and Antalya were 5.3% of total. Rest of the physicians were from 18 different cities in Turkey.

3.1.1.3. Age

Youngest physician who respond the survey was 26 years old and the oldest respondent was 57 years old. The mean age among all respondents was $36.5 \pm 7,107$.

3.1.1.4. Profession

As seen in Figure 9, 91.5% of the respondents were pulmonary physician who were the target group of the survey. 5.3% of physicians were internists and 3.5% of physicians were thoracic surgeon.

Figure 9. Proffesion Distribution of Physicians
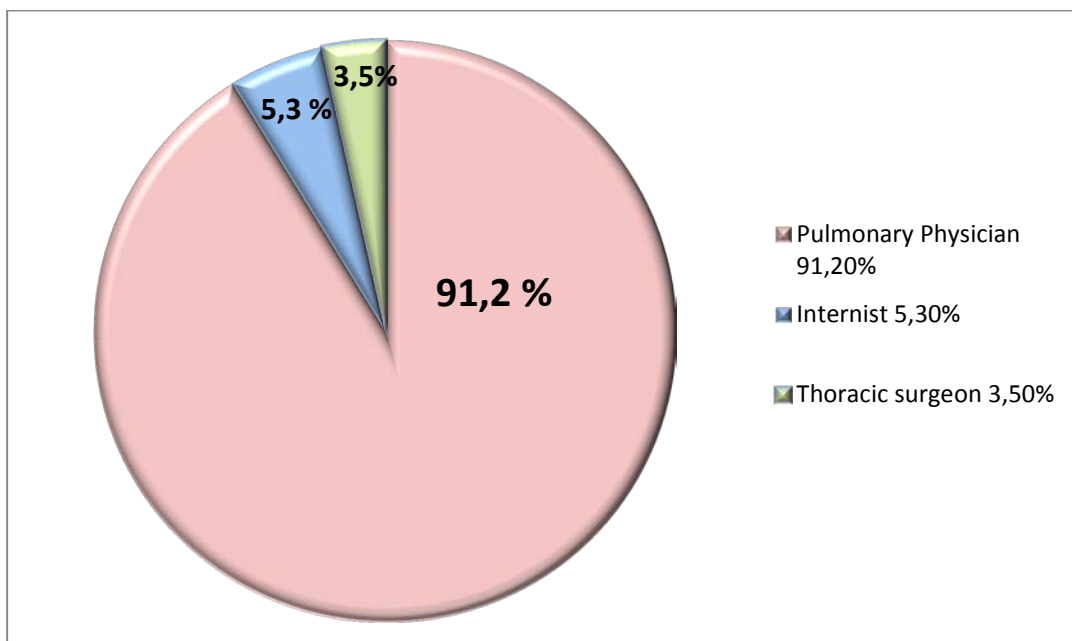
3.1.1.5. Academic degree

Majority of the respondents were specialists (66.7%). 21% of the respondents were assistant physician. The percentage of professors was found as 5.3%. Assistant professor and associate professor percentages were same and constituted 3.5% of respondents (Table 9).

Table 9. Academic Degree Distribution of Physicians

Academic Degree	Frequency (n)	Percent (%)
Professor	3	5.3
Associate Professor	2	3.5
Assistant Professor	2	3.5
Specialist	38	66.7
Assistant	12	21
Total	57	100

3.1.1.6. Working Area

Majority of the respondents were from State Hospital (36,8%). 29,8% of the respondents were from University Hospital. There were no respondent who was working at Pulmonary Hospital. 26,3% of the respondents were from Training and Research Hospital. Physicians who was working at Private Hospital was 7,1% of the respondents (Figure 10).

Figure 10. Working Area Distribution of Physicians

Pie chart legend:
- State Hospital 36,80%
- Training and Research Hospital 26,30%
- University Hospital 29,80%
- Private Hospital 7,10%

Chart segments: 36,8 %, 26,3 %, 29,8 %
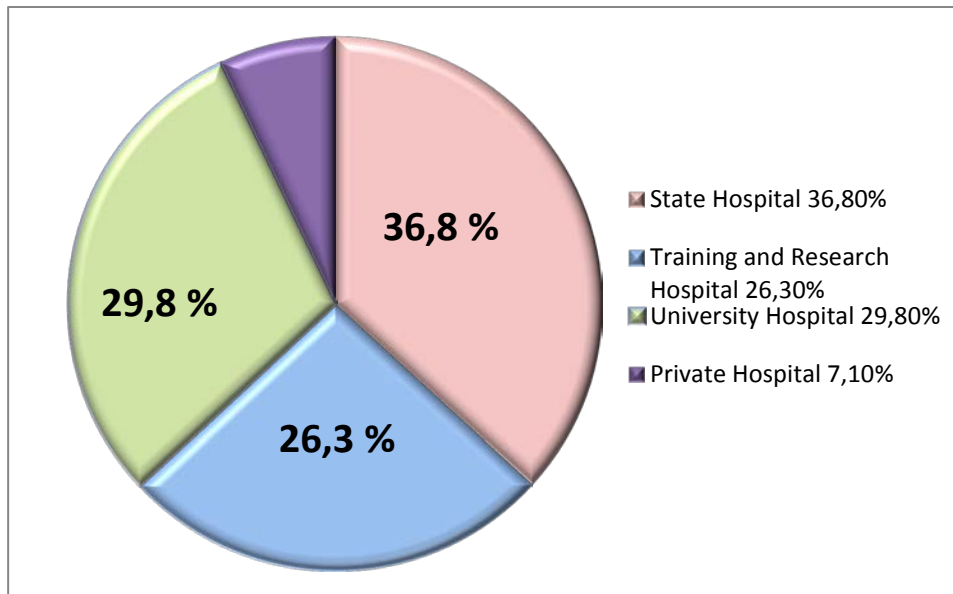
3.1.2. Total Number of Patients Treated in One Day

The least number of patients the physicians examine in one day were ten. The highest number of patients the physicians examine in one day were hundred and the average number of patients the physicians examine in one day were 43.51 ± 21.32.

3.1.3. The number of COPD Patients Treated in One Day

56 physicians responded this question. The minimum number of COPD patients, physicians examine in one day were five. The maximum number of COPD patients, physicians examine in one day were eighty and the mean number of COPD patients the physicians examine in one day were 31.88 ± 15.94.

3.1.4. Disease Severity of COPD Patients

Spirometric classification of COPD patients can be summarized as below.

The average number of mild COPD patients who physicians examine in one day were 13.35 ± 11.4.

The average number of moderate COPD patients who physicians examine in one day were 34.51 ± 17.8.

The average number of severe COPD patients who physicians examine in one day were 32.04 ± 16.2.

The average percentage of very severe COPD patients who physicians examine in one day were 17.82 ± 12.9.

3.1.5. ICS/LABA Prescription Frequency of Physicians at Moderate COPD Patients

The frequency of ICS/LABA prescriptions were questioned at moderate stage of COPD patients.

The percentage of physicians who responded as "always" prescribe ICS/LABA combinations at moderate stage COPD patients were 24.6 %.

The percentage of physicians who responded as "mostly" prescribe ICS/LABA combinations at moderate stage COPD patients were 59.6 %.

The percentage of physicians who responded as "sometimes" prescribe ICS/LABA combinations at moderate stage COPD patients were 15.8 %.

There was no respondent who did not answer this question

Table 10. ICS/LABA Prescription Frequency of Physicians at Moderate COPD Patients

ICS/LABA Prescriptions	Frequency (n)	Percent (%)
Always	14	24.6
Mostly	34	59.6
Sometimes	9	15.8
Rarely	0	0
Never	0	0
Total	57	100

3.1.6. ICS/LABA Prescription Frequency of Physicians at Severe/Very Severe COPD Patients

The frequency of ICS/LABA prescriptions were questioned at severe/very severe stage of COPD patients as seen in Table 11.

The percentage of physicians who responded as "always" prescribe ICS/LABA combinations at severe/very severe stage COPD patients were 73.7 %.

The percentage of physicians who responded as "mostly" prescribe ICS/LABA combinations at severe/very severe stage COPD patients were 24.6 %.

The percentage of physicians who responded as "sometimes" prescribe ICS/LABA combinations at severe/very severe stage COPD patients were 1.7 %.

There was no respondent who did not answer this question.

Table 11. ICS/LABA Prescription Frequency of Physicians at Severe/Very Severe COPD Patients

ICS/LABA Prescriptions	Frequency (n)	Percent (%)
Always	42	73.7
Mostly	14	24.6
Sometimes	1	1.7
Rarely	0	0
Never	0	0
Total	57	100

3.1.7. Physicians' Opinions on Frequency of Exacerbations

89.5% of physicians responded as frequency of exacerbations were decreased at patients which have been treated with inhale corticosteroid plus long acting beta$_2$ agonist fix combinations (ICS/LABA) in their daily practice.

10.5% of physicians responded as frequency of exacerbations were not changed at patients which have been treated with inhale corticosteroid plus long acting beta$_2$ agonist fix combinations (ICS/LABA) in their daily practice.

Table 12. Physicians' Opinions on Frequency of Exacerbations

Frequency of Exacerbations	Frequency (n)	Percent (%)
Increased	0	0
Decreased	51	89.5
No change	6	10.5
Total	57	100

Figure 11. Physicians' Opinions on Frequency of Exacerbations
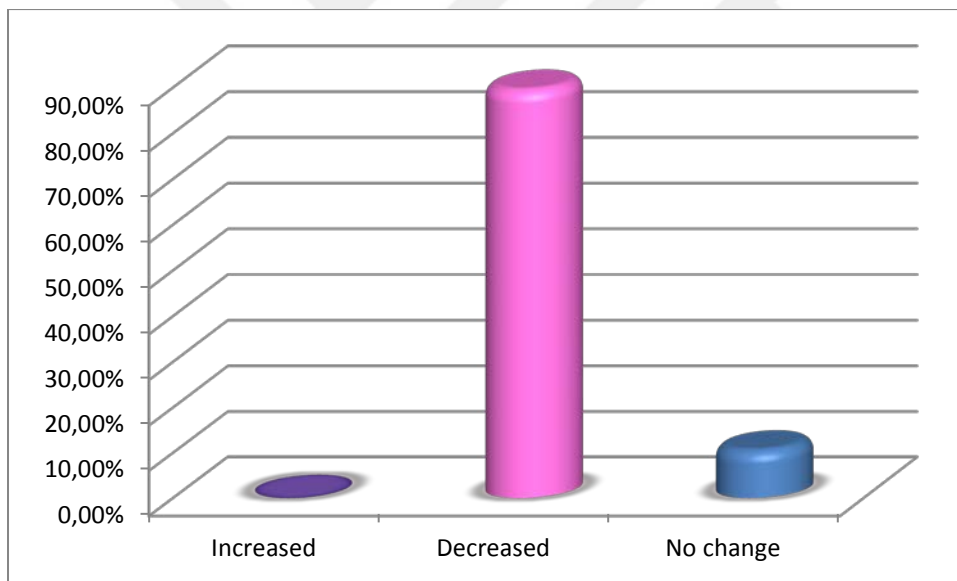
3.1.8. Physicians' Opinions on Severity of Exacerbations

86 % of physicians responded as severity of exacerbations were decreased at patients which have been treated with inhale corticosteroid plus long acting beta$_2$ agonist fix combinations (ICS/LABA) in their daily practice.

14 % of physicians responded as frequency of exacerbations were not changed at patients which have been treated with inhale corticosteroid plus long acting beta$_2$ agonist fix combinations (IKS/LABA) in their daily practice.

Table 13. Physicians' Opinions on Severity of Exacerbations

Severity of exacerbations	Frequency (n)	Percent (%)
Increased	0	0
Decreased	49	86
No change	8	14
Total	57	100

Figure 12. Physicians' Opinions on Severity of Exacerbations
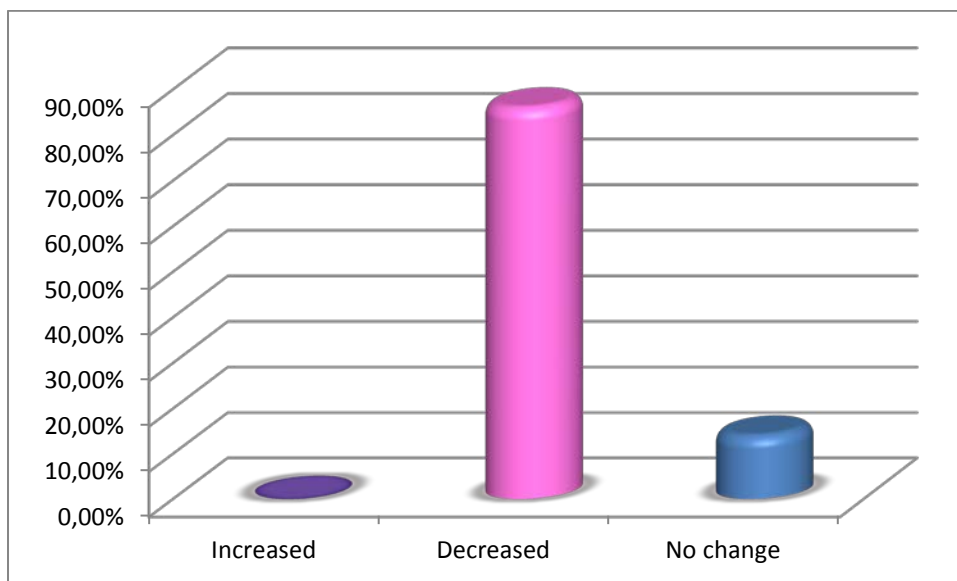
3.1.9. Physicians' Opinions on The Number of Hospitalizations

82.5 % of physicians responded as the number of hospitalizations were decreased at patients which have been treated with inhale corticosteroid plus long acting $beta_2$ agonist fix combinations (IKS/LABA) in their daily practice.

17.5 % of physicians responded as the number of hospitalizations were not changed at patients which have been treated with inhale corticosteroid plus long acting $beta_2$ agonist fix combinations (IKS/LABA) in their daily practice.

Table 14. Physicians' Opinions on The Number of Hospitalizations

Hospitalizations	Frequency (n)	Percent (%)
Increased	0	0
Decreased	47	82.5
No change	10	17.5
Total	57	100

Figure 13. Physicians' Opinions on The Number of Hospitalizations
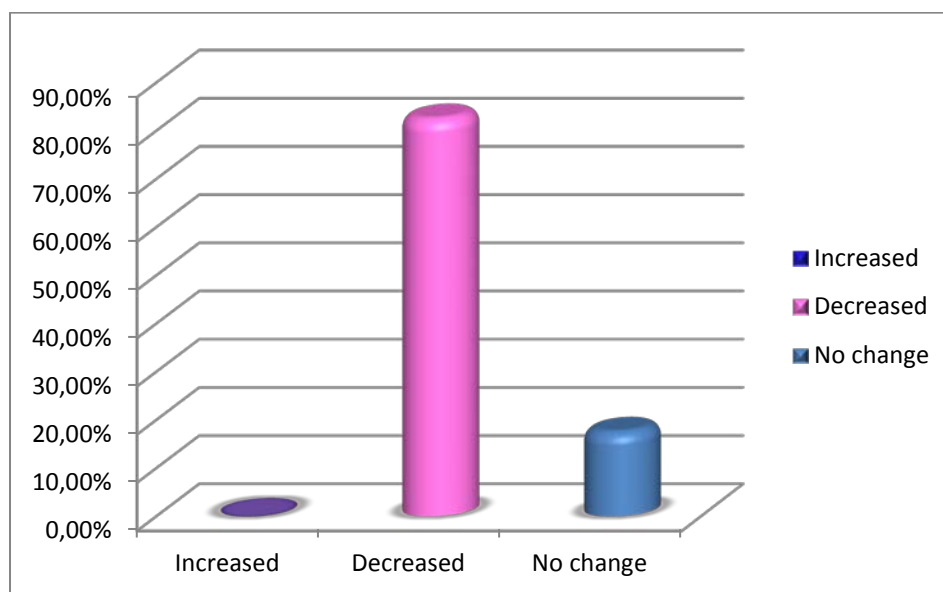
3.1.10. Physicians' Opinions on Comorbid Disease

1.7 % of physicians responded as the comorbid diseases were increased at patients which have been treated with ICS/LABA in their daily practice.

82.5 % of physicians responded as the comorbid diseases were decreased at patients which have been treated with ICS/LABA in their daily practice.

15.8 % of physicians responded as the comorbid diseases were not changed at patients which have been treated with ICS/LABA in their daily practice (Table 15).

Table 15. Physicians' Opinions on Comorbid Disease

Comorbid Disease	Frequency (n)	Percent (%)
Increased	1	1.7
Decreased	47	82.5
No change	9	15.8
Total	56	100

Figure 14. Physicians' Opinions on Comorbid Disease

3.1.11. Physicians' Opinions on Health Quality of Life

91.2 % of physicians responded as Health Quality of Life was increased at patients which have been treated with ICS/LABA in their daily practice according to physicians' point of view.

8.8 % of physicians responded as Health Quality of Life was not changed at patients which have been treated with ICS/LABA in their daily practice according to physicians' point of view.

Table 16. Physicians' Opinions on Health Quality of Life

Health Quality of Life	Frequency (n)	Percent (%)
Increased	52	91.2
Decreased	0	0
No change	5	8.8
Total	57	100

Figure 15. Physicians' Opinions on Health Quality of Life

3.1.12. Physicians' Opinions on Spirometry Results

73.7 % of physicians responded as the spirometry results were improved at patients which have been treated with ICS/LABA in their daily practice.

1.8 % of physicians responded as spirometry results were deteriorated at patients which have been treated with ICS/LABA in their daily practice.

24.6 % of physicians responded as spirometry results were not changed at patients which have been treated with ICS/LABA in their daily practice.

Figure 16. Physicians' Opinions on Spirometry Results
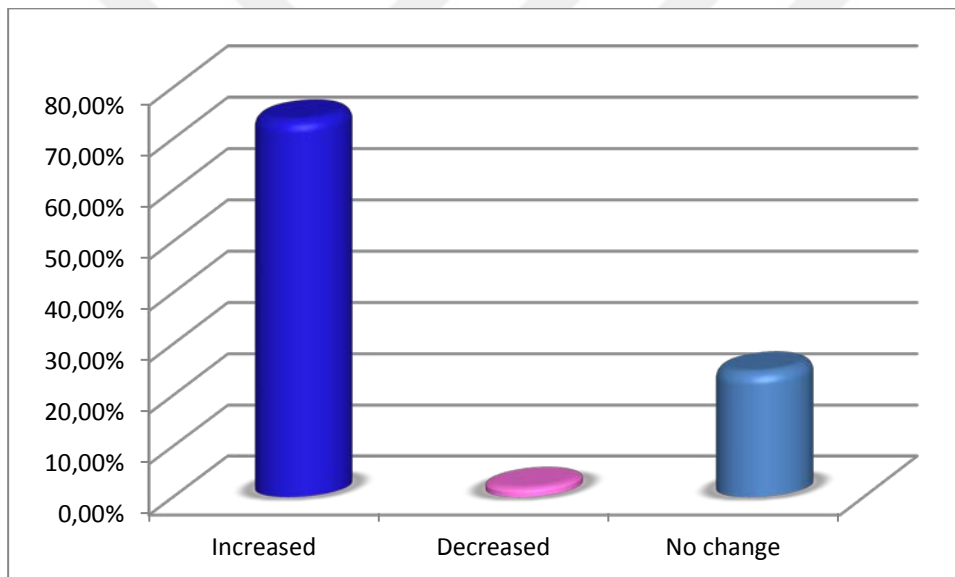
3.1.13. Physicians' Experience of Exercise Capacity after IKS/LABA Treatment.

94.7 % of physicians indicated as exercise capacity of patients was increased at patients which have been treated with ICS/LABA in their daily practice (Table 17).

5.3 % of physicians indicated as exercise capacity of patients was not changed at patients which have been treated with ICS/LABA in their daily practice.

Table 17. Physicians' Experience of Exercise Capacity after IKS/LABA Treatment.

Exercise capacity	Frequency (n)	Percent (%)
Increased	54	94.7
Decreased	0	0
No change	3	5.3
Total	57	100

Figure 17. Physicians' Experience of Exercise Capacity after IKS/LABA Treatment.

3.1.14. ICS/LABA Effect to Dispnea of Patients

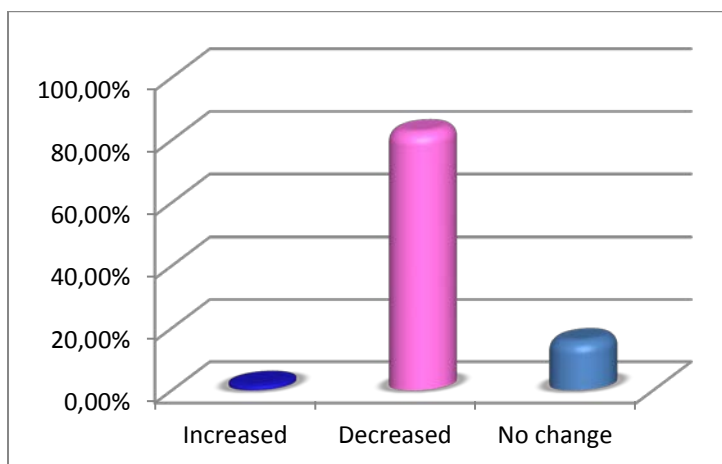98.2 % of physicians responded as the dispnea of patients was decreased at patients which have been treated with ICS/LABA in their daily practice (Table 18).

18 % of physicians responded as the dispnea of patients was not changed at patients which have been treated with ICS/LABA in their daily practice.

Table 18. ICS/LABA Effect to Dispnea of Patients

Dispnea	Frequency (n)	Percent (%)
Increased	0	0
Decreased	56	98.2
No change	1	1.8

Figure 18. ICS/LABA Effect to Dispnea of Patients

3.1.15. Professors' Opinions on Frequency of Exacerbations after ICS/LABA treatment

The number of professors who responded our survey was only three. Two of physicians responded as the frequency of exacerbations was decreased at patients which have been treated with ICS/LABA in their daily practice.

One of professors responded as the frequency of exacerbations was not changed at patients which have been treated with ICS/LABA in their daily practice.

3.1.16. Professors' Opinions on Severity of Exacerbations after ICS/LABA treatment

All professors responded as the severity of exacerbations was decreased at patients which have been treated with ICS/LABA in their daily practice.

3.1.17. Professors' Opinions on Hospitalizations after ICS/LABA treatment

All professors responded as the hospitalizations were decreased at patients which have been treated with ICS/LABA in their daily practice.

3.1.18. Professors' Opinions on Comorbid Disease after ICS/LABA treatment

One of professors responded as the comorbid disease was decreased at patients which have been treated with ICS/LABA in their daily practice.

Two of professors responded as the comorbid disease was not changed at patients which have been treated with ICS/LABA in their daily practice.

3.1.19. Professors' Opinions on Health Quality of Life after ICS/LABA treatment

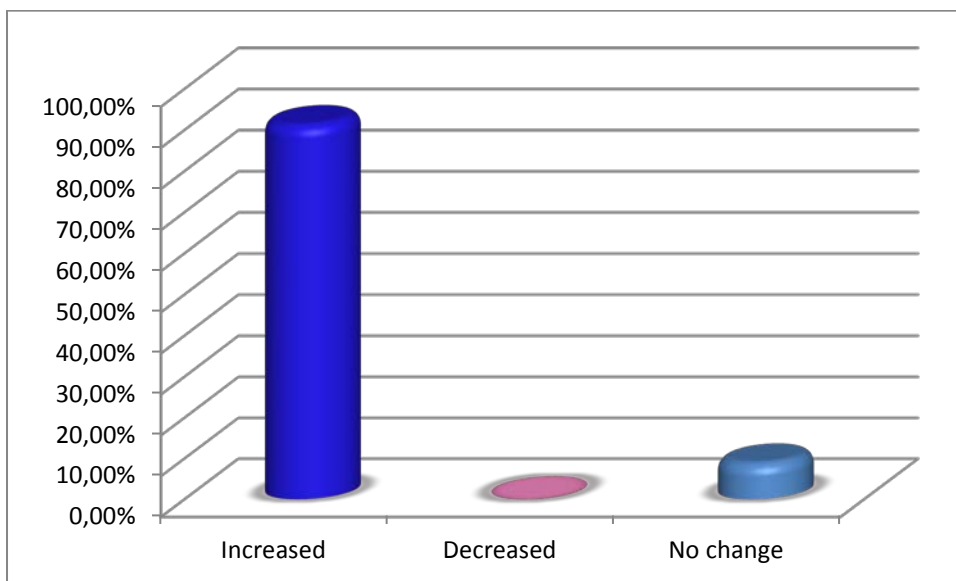All professors responded as the Health Quality of Life was increased at patients which have been treated with ICS/LABA in their daily practice.

3.1.20. Professors' Opinions on Spirometry Results after ICS/LABA treatment

Two of professors responded as the spirometry results was increased at patients which have been treated with ICS/LABA in their daily practice.

One of professors responded as the spirometry results was not changed at patients which have been treated with ICS/LABA in their daily practice.

3.1.21. Professors' Opinions on to Exercise Capacity after ICS/LABA treatment

Two of professors responded as the exercise capacity was increased at patients which have been treated with ICS/LABA in their daily practice.
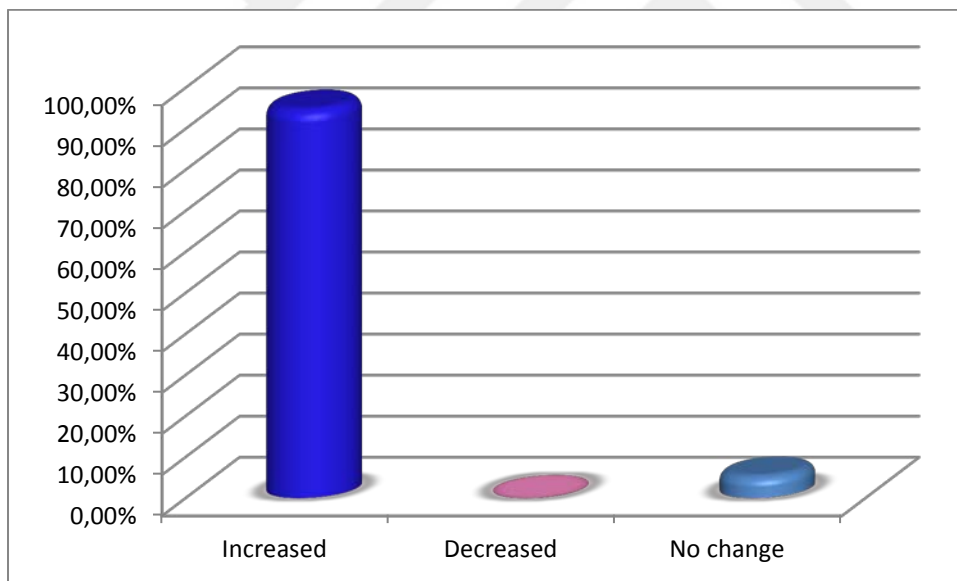
One of professors responded as the exercise capacity was not changed at patients which have been treated with ICS/LABA in their daily practice.

3.1.22. Professors' Opinions on to Dispnea after ICS/LABA treatment

All professors responded as the dispnea was decreased at patients which have been treated with ICS/LABA in their daily practice.

3.1.23. Specialists' Opinions on Frequency of Exacerbations after ICS/LABA treatment
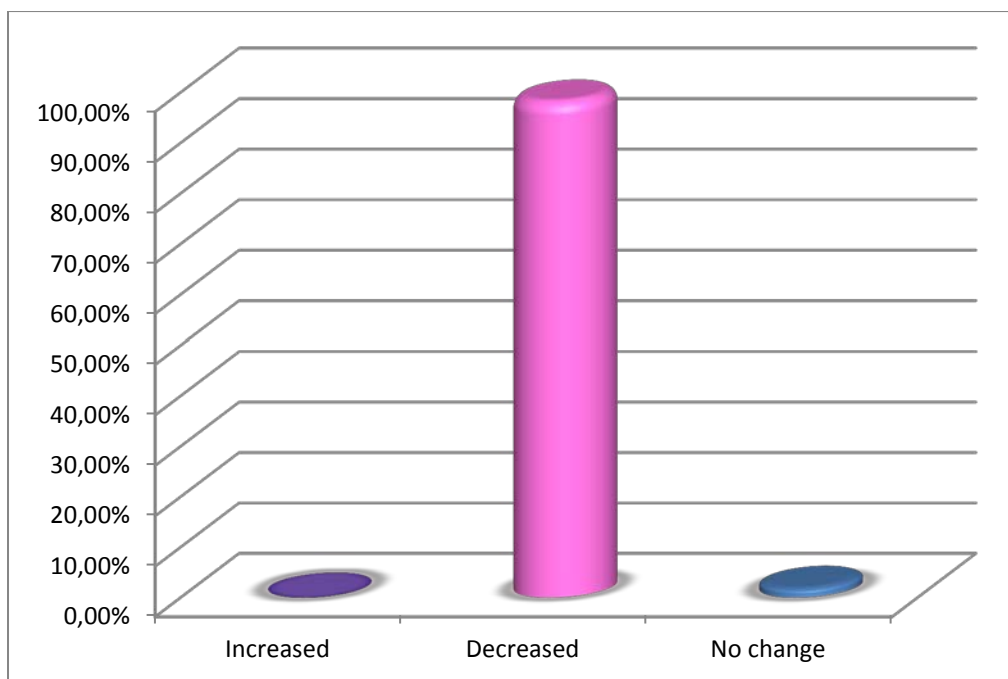
38 specialists responded our survey. 92.1 % of specialists responded as the frequency of exacerbations was decreased at patients which have been treated with ICS/LABA in their daily practice (Figure 19).

7.9 % of specialists responded as the frequency of exacerbations was not changed at patients which have been treated with ICS/LABA in their daily practice.

Figure 19. Specialists' Opinions on Frequency of Exacerbations after ICS/LABA treatment
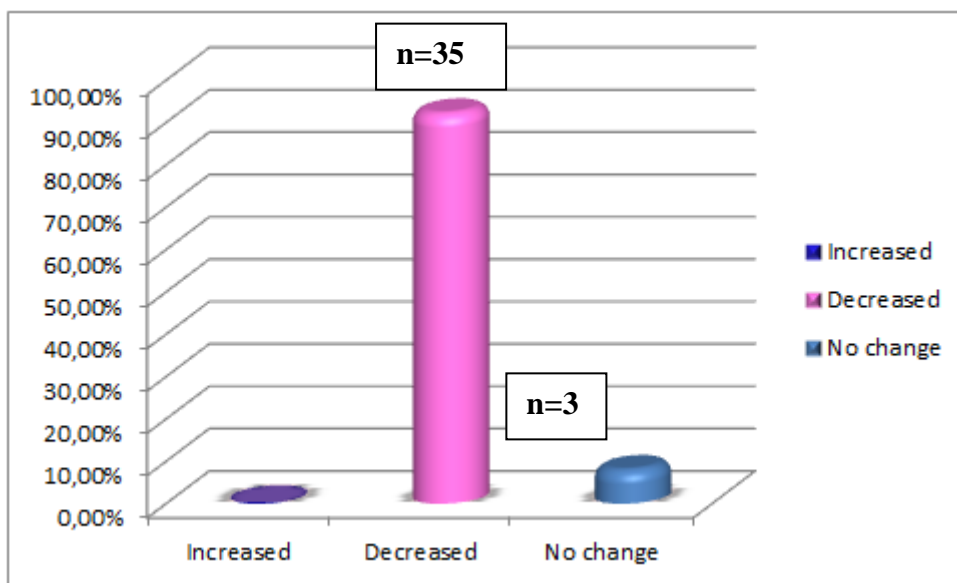
3.1.24. Specialists' Opinions on Severity of Exacerbations after ICS/LABA treatment

84,2 % of specialists responded as the severity of exacerbations was decreased at patients which have been treated with ICS/LABA in their daily practice (Figure 20).

15,8 % of specialists responded as the severity of exacerbations was not changed at patients which have been treated with ICS/LABA in their daily practice.

Figure 20. Specialists' Opinions on Severity of Exacerbations after ICS/LABA treatment
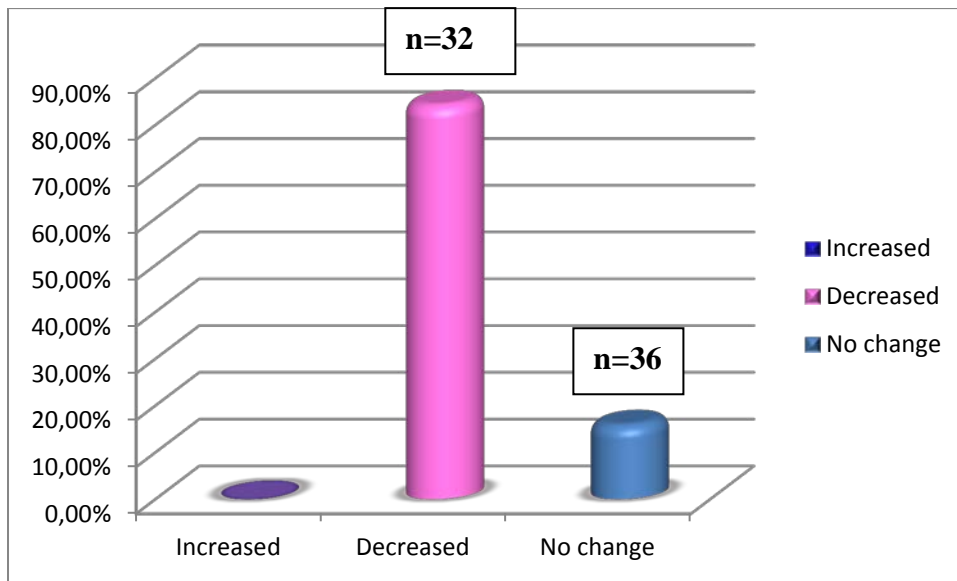
3.1.25. Specialists' Opinions on Number of Hospitalizations after ICS/LABA treatment

78,9 % of specialists responded as the hospitalizations were decreased at patients which have been treated with ICS/LABA in their daily practice (Figure 21).

21,1 % of specialists responded as the hospitalizations were not changed at patients which have been treated with ICS/LABA in their daily practice.

Figure 21. Specialists' Opinions on Number of Hospitalizations after ICS/LABA treatment
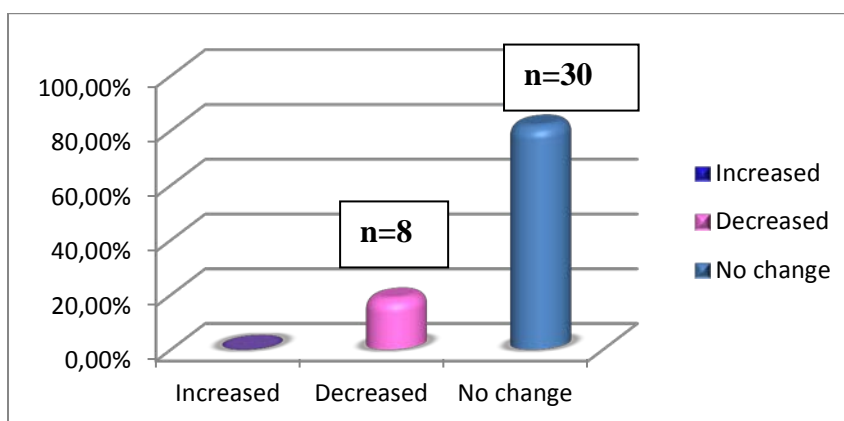
3.1.26. Specialists' Opinions on The Effect of ICS/LABA Treatment on Comorbid Disease

18,4 % of specialists responded as comorbid disease were decreased at patients which have been treated with ICS/LABA in their daily practice (Figure 22).

81,6 % of specialists responded as comorbid disease were not changed at patients which have been treated with ICS/LABA in their daily practice.

Figure 22. Specialists' Opinions on The Effect of ICS/LABA Treatment on Comorbid Disease
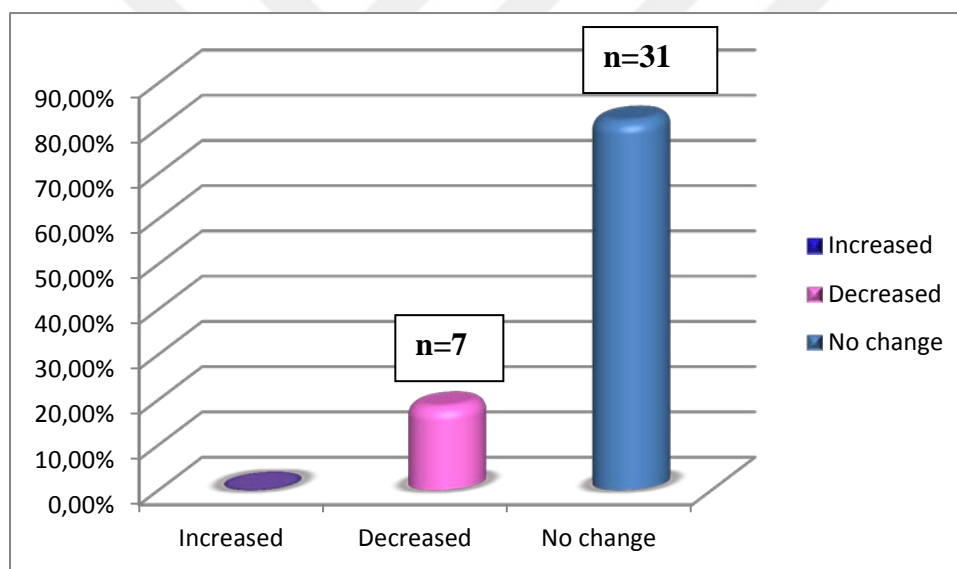
3.1.27. Specialists' Opinions on The Effect of ICS/LABA Treatment on Health Quality of Life

86,8 % of specialists responded as the Health Quality of Life was increased at patients which have been treated with ICS/LABA in their daily practice (Figure 23).

13,2 % of specialists responded as the Health Quality of Life was not changed at patients which have been treated with ICS/LABA in their daily practice.

Figure 23. Specialists' Opinions on The Effect of ICS/LABA Treatment on Health Quality of Life
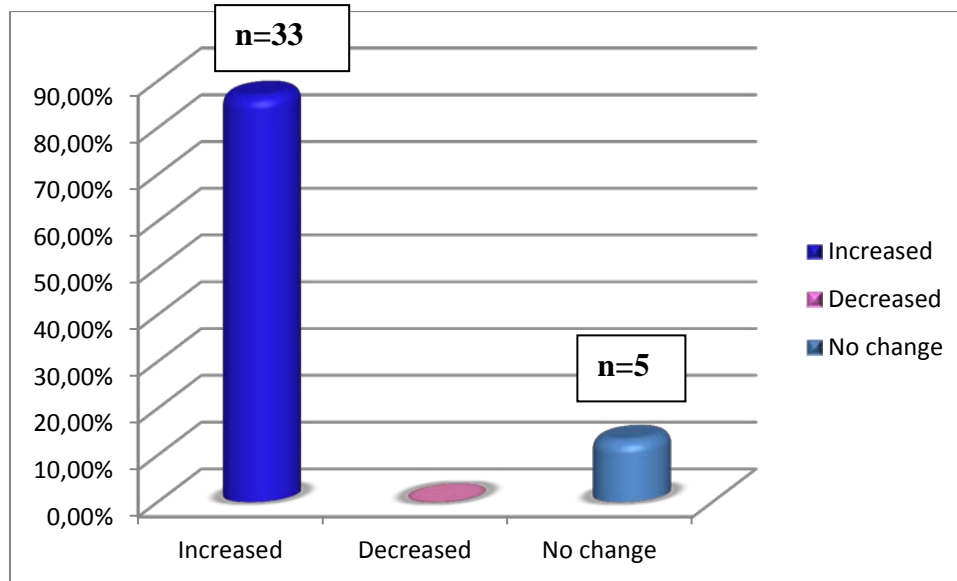
3.1.28. Specialists' Opinions on The Effect of ICS/LABA Treatment on Spirometry Results

68,4 % of specialists responded as spirometry results increased at patients which have been treated with ICS/LABA in their daily practice.

2,6 % of specialists responded as spirometry results decreased at patients which have been treated with ICS/LABA in their daily practice.

29 % of specialists responded as spirometry results was not change at patients which have been treated with ICS/LABA in their daily practice (Figure 24).

Figure 24. Specialists' Opinions on The Effect of ICS/LABA Treatment on Spirometry Results
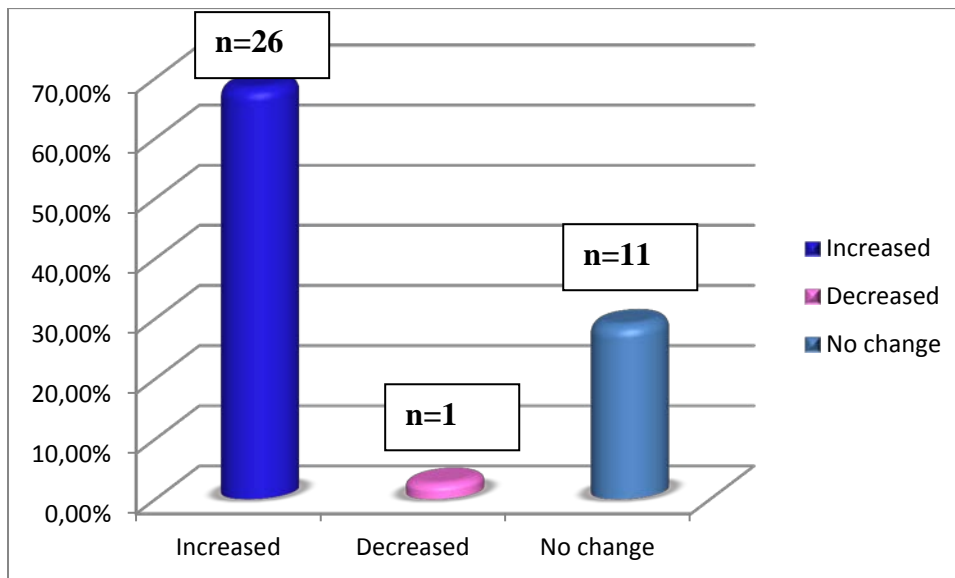
3.1.29. Specialists' Opinions on Exercise Capacity of Patients after ICS/LABA treatment

94,7 % of specialists responded as exercise capacity of patients increased at patients which have been treated with ICS/LABA in their daily practice (Figure 25).

5,3 % of specialists responded as exercise capacity was not change at patients which have been treated with ICS/LABA in their daily practice.

Figure 25. Specialists' Opinions on Exercise Capacity of Patients after ICS/LABA treatment
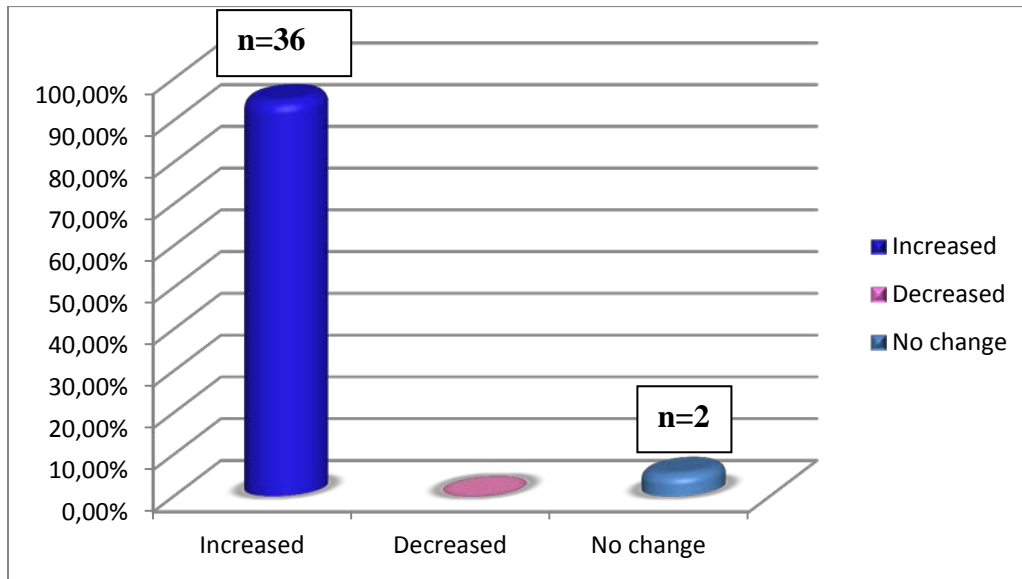
3.1.30. Specialists' Opinions on Dispnea of Patients after ICS/LABA treatment

All of the specialists responded as dyspnea of patients decreased which have been treated with ICS/LABA in their daily practice (Figure 26).

Figure 26. Specialists' Opinions on Dispnea of Patients after ICS/LABA treatment
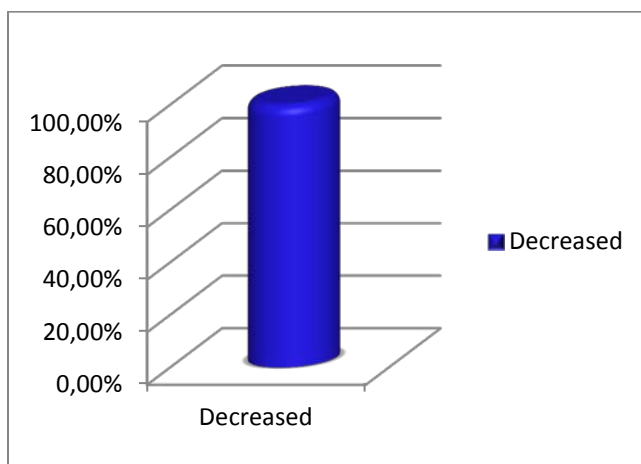
3.2. Cross-Tabulation

Relationship between demographic characteristics and treatment parameters were investigated.

3.2.1. Academic Degree of Physicians and Frequency of Exacerbations After ICS/LABA Treatment Cross-Tabulation

There were no difference found statistically significant between professions and frequency of exacerbations due to the number of participants.

Table 19. Academic Degree of Physicians and Frequency of Exacerbations After ICS/LABA Treatment Cross-Tabulation

Frequency of exacerbations		Profession					Total
		Professor	Associate Professor	Assistant Professor	Specialist	Assistant	
Decreased	Count	2	2	2	35	10	51
	Percent (%)	66,7%	100,0%	100,0%	92,1%	83,3%	89,5%
No change	Count	1	0	0	3	2	6
	Percent (%)	33,3%	0,0%	0,0%	7,9%	16,7%	10,5%
Total	Count	3	2	2	38	12	57
	Percent (%)	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

p=0,93

3.2.2. Academic Degree of Physicians and Severity of Exacerbations After ICS/LABA Treatment Cross-Tabulation

There were no difference found statistically significant between professions and severity of exacerbations (Table 20).

Table 20. Academic Degree of Physicians and Severity of Exacerbations After ICS/LABA Treatment Cross-Tabulation

Severity of exacerbations		Profession					Total
		Professor	Associate Professor	Assistant Professor	Specialist	Assistant	
Decreased	Count	3	2	1	32	11	49
	Percent (%)	100,0%	100,0%	50,0%	84,2%	91,7%	86,0%
No change	Count	0	0	1	6	1	8
	Percent (%)	0,0%	0,0%	50,0%	15,8%	8,3%	14,0%
Total	Count	3	2	2	38	12	57
	Percent (%)	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

p=0.18

3.2.3. Academic Degree of Physicians and Number of Hospitalizations After ICS/LABA Treatment Cross-Tabulation

There were no difference found statistically significant between professions and hospitalizations (Table 21).

Table 21. Academic Degree of Physicians and Number of Hospitalizations After ICS/LABA Treatment Cross-Tabulation

Hospitalizations		Profession					Total
		Professor	Associate Professor	Assistant Professor	Specialist	Assistant	
Decreased	Count	3	2	1	30	11	47
	Percent (%)	100,0%	100,0%	50,0%	78,9%	91,7%	82,5%
No change	Count	0	0	1	8	1	10
	Percent (%)	0,0%	0,0%	50,0%	21,1%	8,3%	17,5%
Total	Count	3	2	2	38	12	57
	Percent (%)	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

p=0.98

3.2.4. Hospital Type and Treatment Parameters Cross-Tabulation

There were no difference found statistically significant between hospital type and treatment parameters.

3.2.5. Profession and Treatment Parameters Cross-Tabulation

There were no difference found statistically significant between academic degree of physicians and treatment parameters.

3.2.6. Profession and ICS/LABA Prescription Frequency Cross-Tabulation

There were no difference found statistically significant between profession of physicians and ICS/LABA Prescription frequency.

3.2.7. Academic Degree and ICS/LABA Prescription Frequency Cross-Tabulation

There were no difference found statistically significant between academic degree of physicians and ICS/LABA Prescription frequency.

3.2.8. Hospital Type and ICS/LABA Prescription Frequency Cross-Tabulation

There were no difference found statistically significant between hospital type and ICS/LABA Prescription frequency.

3.2.9. Physicians who prefer "always/mostly" ICS/LABA fix combinations at moderate COPD patients and Treatment Parameters Cross-Tabulation

There were no difference found statistically significant between physicians who prefer "always/mostly" ICS/LABA fix combinations at moderate COPD patients and treatment parameters

3.2.10. Physicians who prefer "always/mostly" ICS/LABA fix combinations at severe/very severe COPD patients and Treatment Parameters Cross-Tabulation

There were no difference found statistically significant between physicians who prefer "always/mostly" ICS/LABA fix combinations at severe/very severe COPD patients and treatment parameters.

Results of frequency distribution of all variables, cross tabulation and statistical tests analyses were tabulated and summarized in this chapter. Significance of this data will be discussed in the following section.

4. DISCUSSION AND CONCLUSION

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing (2, 3). COPD prevalence was reported between %6,9 and 19,6 in Turkey (14).

It is clear that COPD is one of the most important causes of death in most countries. The Global Burden of Disease Study projected that COPD, which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2020; a newer projection estimated COPD will be the fourth leading cause of death in 2030 (3). COPD accounts for 4.8% of global deaths and the WHO predicts its mortality burden will increase to 7.9% by 2030 (13).

It was reported that, COPD is the third leading cause of death which accounts for %5.8 of all deaths in Turkey. When analyzed as men and women; COPD is the third leading cause of death in men which accounts for %7.8 of all deaths and it is the fifth leading cause of death in men which accounts for %3.5 of all deaths (14). It is obvious that, COPD is one of the major health problems in worldwide. Different treatment strategies and drugs were used in different countries for COPD treatment. In this thesis, in order to learn the physicians approach and experiments on ICS/LABA fixed combinations on COPD treatment, survey method was selected. Physicians' opinions and experiments for ICS/LABA fixed combinations on COPD treatment and their observations on disease treatment outcomes were questioned in the survey. The study was conducted at TÜSAD (Turkish Respiratory Society/Türkiye Solunum Araştırmaları Derneği) Congress in Çeşme/İzmir. TÜSAD congress is one of the biggest Chest congress which is organized every year in Turkey. This congress gathers physicians from different territories of the country. For this reasons it was an ideal location to sample the physicians as respondents. 1.500 physicians participated to the congress. Physicians who participated in the congress, regardless of the specialty were asked to complete the questionnaire and 57 physicians agreed to answer.

If the answers of physicians are analyzed in detail, firstly we can start from demographic characteristics under frequencies. 59,6 % of respondents were

female and 40,4 % of respondents were male. This distribution is compatible with the total gender distribution of physician population in congress. Approximately, 55 % of physicians were female in the congress. In this respect, survey gender distribution reflects the total physician gender population in congress but there is no statistically significant difference between gender and treatment approaches which is expected.

Majority of physicians who accepted to respond our survey were from Ankara (32,6). Physicians from İstanbul constitute 19;3% of respondents. Physicians from Zonguldak and Antalya were 5.3% of total. Rest of the physicians were from 18 different cities in Turkey. Because, total numbers of surveys were limited to 57, city distribution may not reflect the real population. As Ankara and İstanbul are the largest cities which have the biggest population, surveys from Ankara and İstanbul are higher than the other cities. When the treatment approaches were analyzed according to different cities in Turkey, no statistically significance found. The reason of this might be the low number of participants.

Youngest physician who respond the survey was 26 years old and the oldest respondent was 57 years old. The mean age among all respondents was 36.5 ± 7,107. Professors and assistant professors are older than specialists and assistants as expected, but the number of professors and assistant professors are limited therefore, the mean age was around 36,5.

When we look at the profession distribution, 91.5% of the respondents were pulmonary physician who were the target group of the survey. 5.3% of physicians were internists and 3.5% of physicians were thoracic surgeon. High number of pulmonary physicians is quite positive for data analysis as they are prescribing the drugs to patients for COPD treatment but one of the limitations of this study is the low number of internists. If the number of pulmonary physician and internists were nearly same, statistical analysis could be significant. Relationship between pulmonary physician and internists and treatment parameters as number of exacerbations and hospitalizations were investigated. According to the cross-tabulation, there were no difference found statistically significant between professions and hospitalizations and the number of exacerbations. There is no also

statistically significance between the professions and ICS/LABA prescription frequencies between pulmonary physicians and internists.

Majority of the respondents were specialists (66.7%). 21% of the respondents were assistant physician. The percentage of professors was found as 5.3%. Assistant professor and associate professor percentages were same and constituted 3.5% of respondents. High number of physicians who attended TÜSAD congress was specialists therefore, majority of the survey respondents were specialists but on the other hand, the irregular distribution of academic degree caused weak statistical results. There is a huge difference between the number of specialists and the number of professors (66.7% vs 5.3% respectively). Therefore, there is no statistically significance found between treatment approaches of specialists and professors. In practice, some difference may be expected in treatment approaches between specialists and professors. Professors may organize treatments according to clinical evidence more than specialists or may follow the treatment guidelines more than specialists.

Majority of the respondents were from State Hospital (36,8%). 29,8% of the respondents were from University Hospital. There were no respondent who was working at Pulmonary Hospital. 26,3% of the respondents were from Training and Research Hospital. Physicians who was working at Private Hospital was 7,1% of the respondents. Although the number of physicians who are working in State Hospital, University Hospital and Training and Research Hospital are not so different form each other, there is no also statistically significance between the type of hospitals and treatment approaches of physicians. There is no difference found statistically significant between hospital type and ICS/LABA prescription frequency either. Another limitation of this study is that, no physician responded to our survey from pulmonary hospital because pulmonary hospitals are one of the major hospitals in respect to high number of COPD patients.

The frequency of ICS/LABA prescription behaviour also questioned in the survey both for moderate and severe stage of COPD patients. According to the answers of physicians for ICS/LABA prescription behavior, ICS/LABA fixed combinations were mainly preferred as "mostly" at moderate stage and preferred as "always" at severe/very severe stage COPD patients (59,6 % vs 73,7 % respectively). This

data shows us, in line with the multi-national studies and guidelines, ICS/LABA fixed combinations were preferred mainly at severe/very severe COPD patients as a first choice in Turkey. On the other hand, this survey also showed that, ICS/LABA fixed combinations have been prescribed considerable percentage to moderate COPD patients. Physicians prefer ICS/LABA fixed combinations totally as "always and mostly" 84,2% at moderate COPD patients and similarly, physicians prefer ICS/LABA fixed combinations totally as "always and mostly" 98,3% at severe/very severe COPD patients. According to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guideline, ICS/LABA fixed combinations should be prescribed to "C" and "D" group patients (figure 7) who have higher number of exacerbations and lower FEV1 values, in a word more severe patients but our survey results showed that, considerably high percent of physicians prefer to treat most of patients with ICS/LABA combination although it is not compliant with the guideline.

At the last question of the survey, the changes of treatment parameters were questioned. First three parameters (frequency of exacerbations, severity of exacerbations and hospitalizations) are the most significant parameters as they give us the best clue for the treatment costs.

First treatment parameter is frequency of exacerbations. 89,5% of physicians responded as frequency of exacerbations were decreased at patients which have been treated with ICS/LABA in their daily practice.

10,5% of physicians responded as frequency of exacerbations were not changed at patients which have been treated with ICS/LABA in their daily practice.

Second treatment parameter is severity exacerbations. 86 % of physicians responded as severity of exacerbations were decreased at patients which have been treated with ICS/LABA in their daily practice.

14 % of physicians responded as frequency of exacerbations were not changed at patients which have been treated with ICS/LABA in their daily practice.

Third treatment parameter is number of hospitalizations. 82,5 % of physicians responded as the number of hospitalizations were decreased at patients which have been treated with ICS/LABA in their daily practice.

17,5 % of physicians responded as the number of hospitalizations were not changed at patients which have been treated with ICS/LABA in their daily practice.

As we can analyse above, majority of physicians regardless of profession, academic degree and other parameters, responded as frequency and severity of exacerbations and the number of hospitalizations were decreased at patients which have been treated with inhale corticosteroid plus long acting beta$_2$ agonist fixed combinations. This is very significant information for this thesis. According to the recent international studies, the use of LABA/ICS fixed combinations in the severe stages of the disease is effective in reducing the long-term clinical impact of COPD and in optimizing the cost-effectiveness and the socio-economic convenience of therapeutic strategies by decreasing the number of exacerbations and hospitalizations (1, 4, 5, 6, 7, 8, 9).

According to the study of Mapel et al, patients with COPD were 2.3 times more likely to be admitted to the hospital at least once during the year compared with age- and gender-matched patients with other conditions, and those admitted had longer average lengths of stay (4.7 vs 3.9 days, $p < 0.001$) (25) and Kardos et al reported that exacerbations greatly contribute to decline of health-related quality of life, increase in symptoms and breathlessness, progression of disease and increased risk of mortality. Therefore exacerbations incur significant direct and indirect health care costs. The prevention of exacerbations should be an important treatment goal (7). According to results of these studies, exacerbations and hospitalizations due to exacerbations are major treatment costs. Reducing exacerbations may therefore have a positive impact on patients' symptoms, progression of the disease, and health care expenditure. In this randomized study, ICS/LABA combination therapy (salmeterol/fluticasone) compared with LABA (salmeterol) monotherapy. ICS/LABA combination significantly reduced the frequency of moderate/severe exacerbations in patients with severe COPD (7). Our survey results were in line with the results of these studies. Majority of physicians stated that, frequency, severity of exacerbation and number of hospitalizations decreased with ICS/LABA fixed combination therapies.

There are also many other studies which showed that, the number of exacerbations and hospitalizations decreased with ICS/LABA fixed combinations. Calverley at al and Szafranski et al investigated the effects of different ICS/LABA combinations on COPD patients.

Calverley et al, conducted a randomized, double-blind trial comparing salmeterol (LABA) at a dose of 50 μg plus fluticasone propionate (ICS) at a dose of 500 μg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol (LABA) alone, or fluticasone propionate (ICS) alone for a period of 3 years. Of 6112 patients in the efficacy population, as compared with placebo, the combination regimen reduced the annual rate of exacerbations from 1.13 to 0.85 and improved health status and spirometric values (P<0.001 for all comparisons with placebo) (6).

Szafranski et al, investigated the efficacy and safety of budesonide/formoterol (another fixed ICS/LABA combination) in a single inhaler compared with placebo, budesonide (ICS) and formoterol (LABA) were evaluated in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). Budesonide/formoterol reduced the mean number of severe exacerbations per patient per year by 24% versus placebo and 23% versus formoterol. FEV1 increased by 15% versus placebo and 9% versus budesonide. Budesonide/formoterol decreased all symptom scores and use of reliever beta$_2$-agonists significantly versus placebo and budesonide, and improved HRQL versus placebo (8). These study results were compatible with our survey results as majority of physicians stated that number of exacerbations decreased at patients who were treated with ICS/LABA fixed combinations. Long acting beta$_2$ agonists underlie the COPD treatment but, at the same time adding inhaled corticosteroids to the treatment, may have a positive effect on exacerbations.

Many pharmacoeconomic studies also showed that, exacerbations and hospitalizations incur significant direct and indirect health care costs. Akawaza et al, investigated the costs, effectiveness, and cost-effectiveness of inhaled corticosteroids (ICS) augmenting bronchodilator treatment for chronic obstructive pulmonary disease (COPD). Study results showed that, ICS treatment reduced monthly risk of severe exacerbation by 25 percent. Total costs with ICS increased

for 16 months, but declined thereafter. ICS use was cost saving 46 percent of the time, with an incremental cost-effectiveness ratio of $2,973 per exacerbation avoided; for patients 50 years old, ICS was cost saving 57 percent of time. As conclusion, ICS treatment reduces exacerbations, with an increase in total costs initially for the full sample. Compared with younger patients with COPD, patients aged 50 or older have reduced costs and improved outcomes. The estimated cost per severe exacerbation avoided (5).

Dal Negro et al, also investigated the impact of LABA/ICS fixed combinations on morbidity and economic burden of COPD in Italy which is a six-year observational study. In 2004, Italian national health authorities stated the appropriateness of long-acting b_2 agonists (LABA) and inhaled corticosteroids (ICS) fixed combinations for treating COPD, even though this pharmaceutical option was limited to the severe and very severe stages of the disease (forced expiratory volume in one second [FEV1] <50% predicted). The effectiveness in primary care of this official recommendation has been investigated in 1125 COPD patients together with the appropriateness of the therapeutic approach to the disease. Clinical and economic outcomes were monitored over the 3 years before (2001 and 2003) and the 3 years following this recommendation (2004 and 2006). In general, the overall impact of COPD changed progressively after the pronunciation of the public health authorities. In particular, since the point when LABA/ICS fixed combinations were officially recommended, both morbidity of COPD and the corresponding consumption of healthcare resources have progressively lowered. Moreover, the appropriateness of the pharmaceutical approach increased in the same period, thus emphasizing the importance of the optimization of therapeutic strategies in reducing the long-term impact of the disease (4). According to the recent studies, the use of LABA/ICS fixed combinations in the severe stages of the disease is effective in reducing the long-term clinical impact of COPD and in optimizing the cost-effectiveness and the socio-economic convenience of therapeutic strategies by decreasing the number of exacerbations and hospitalizations (1, 4, 5, 6, 7, 8, 9). Our survey results showed that, most of Turkish physicians stated that the number of exacerbations and hospitalizations were decreased at patients who have been treated with inhale corticosteroid plus long acting beta$_2$ agonist fix combinations (IKS/LABA). These

results may give rise to thought that the use of LABA/ICS fix combinations may have a positive impact on cost of COPD treatment in Turkey by decreasing the number of exacerbations and hospitalization according to the Turkish physicians survey results.

Furthermore, 82,5 % of physicians responded as the comorbid diseases were decreased and 15,8 % of physicians responded as the comorbid diseases were not changed at patients which have been treated with ICS/LABA in their daily practice. Comorbid diseases also contribute the treatment cost. Decreasing the number or severity of comorbid disease with the use of ICS/LABA fixed combinations, may be a good sign for the treatment costs.

Other questioned treatment parameters are, Health Quality of Life, spirometer results, exercise capacity and dyspnea of the patients. Most of physicians responded as Health Quality of Life, spirometer results, exercise capacity of patients were improved at patients which have been treated with ICS/LABA in their daily practice and majority of physicians reported that, dyspnea of the patients were decreased. These answers, shows, the treatment success of ICS/LABA fixed combinations. This also may affect the treatment costs and decrease hospital visits and additional drug cost.

These treatment parameters were analyzed in the breakdown of academic degree, professions, age and prescription behaviors. Appropriate statistical tests were applied in order to find a statistical significant difference but, the limitation of the number of participants and unbalanced distribution of academic degree, profession, hospital type, and no significant difference was found among participants. For instance, the numbers of professors are too small so, there were no difference found statistically significant between professors and specialists. Because of this limitation, other statistical analysis gave us very limited information.

As a conclusion, this thesis was designed to collect an opinion regarding on the impact of ICS/LABA fixed combinations on COPD treatment in the view of Turkish physicians. According to the answers of physicians for ICS/LABA prescription behavior, ICS/LABA fixed combinations were mainly preferred as "mostly" at moderate stage and preferred as "always" at severe/very severe stage

COPD patients. This result may show us, ICS/LABA fixed combinations were preferred by majority of physicians as a treatment choice and furthermore most of physicians have a positive experience on these fixed combinations. Furthermore most of physicians responded as frequency and severity of exacerbations and the number of hospitalizations was decreased at patients who have been treated with inhale corticosteroid plus long acting beta$_2$ agonist fixed combinations (ICS/LABA) in their daily practice. Similarly, most of physicians responded as Health Quality of Life, spirometer results and exercise capacity of patients were improved at patients who have been treated with inhale corticosteroid and long acting beta$_2$ agonist fixed combinations (ICS/LABA) in their daily practice. According to the recent international studies, the use of LABA/ICS fixed combinations in the severe stages of the disease is effective in reducing the long-term clinical impact of COPD and in optimizing the cost-effectiveness and the socio-economic convenience of therapeutic strategies by decreasing the number of exacerbations and hospitalizations. These preliminary research shows, most of Turkish physicians state that the number of exacerbations and hospitalizations were decreased at patients who have been treated with inhale corticosteroid and long acting beta$_2$ agonist fix combinations (IKS/LABA). These results can give rise to thought that the use of LABA/ICS fix combinations may have a positive impact on cost of COPD treatment in Turkey by decreasing the number of exacerbations and hospitalization according to the Turkish physicians survey results.

5. SUGGESTION

Future studies are needed in COPD area with high number of participants. Also, balanced number of distribution according to specialty, profession and academic degree can give more detailed and accurate results. More detailed questionnaire may be applied in different congresses in order to diversify the participant group in terms of academic degree, profession and hospital type. One of the internal medicine congress may be added in order to increase the number of internists.

Suggestion of the research may be the application of this survey to broad number of physicians as a continuation of the study. Additionally, calculation of COPD treatment costs may be effective including drug costs, exacerbation cost, hospital cost, hospital treatment cost, adverse event cost and indirect costs comparing COPD treatment with ICS/LABA fixed combination and without fixed combination.

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Appendix 1

To whom it may concern,

This questionnaire is prepared in order to collect data for Yeditepe University Faculty of Pharmacy, Pharmacoeconomy and Pharmacoepidemiology Master Programme Thesis. Your outputs will guide our study. Thank you in advance for your kind support.

Regards,

Ecz. Pınar Akış   **Yrd.Doç.Dr. N. Şencan**   **Prof. Dr.Wertheimer**

1.   Gender?   2. City: ………………..

☐ Woman   3. Age:……………….
☐ Man   4. Detailed name of your hospital?................

5.Could you please indicate your profession?

☐   Pulmonary Physician

☐   Internist   ☐ Other (please indicate) …………

6.   Could you please indicate your academic degree?

☐ Professor   ☐ Specialist

☐   Associate Professor   ☐ Other (please indicate) …………

☐ Assistant Professor

7. Could you please indicate the hospital that you have been working?

☐   State Hospital

☐   Training and Research Hospital

☐ Pulmonary Hospital

☐ Training Hospital

☐ Private Hospital

☐ Other (please indicate) …………

8. a. Approximately how many patients do you examine in one day? ……………………

b. Could you please indicate the percentage of COPD patients among total: ………………..

c. Could you please indicate the percentage of severity?

% ……………. patients mild COPD

% ……………. patients moderate COPD

% …………… patients severe COPD

% ……………..patients very severe COPD

d. Could you please indicate the total number of patients that you have examine in one month?......

9. How often do you prescribe inhale corticosteroid plus long acting beta2 agonist fix combinations (ICS/LABA) at **moderate COPD patients**?

☐ Always

☐ Mostly

☐ Sometimes

☐ Rarely

☐ Never

10. How often do you prescribe inhale corticosteroid plus long acting beta2 agonist fix combinations (ICS/LABA) at **severe and very severe COPD patients**?

☐ Always

☐ Mostly

☐ Sometimes

☐ Rarely

☐ Never

11. Could you please indicate, have you experienced difference related to the below parameters at patients who have been treated with inhale corticosteroid plus long acting beta2 agonist fix combinations (IKS/LABA) in your daily practice?

Frequency of exacerbations	☐	Increased	☐	Decreased	☐ No change
Severity of exacerbations	☐	Increased	☐	Decreased	☐ No change
Hospitalizations	☐	Increased	☐	Decreased	☐ No change
Comorbid disease	☐	Increased	☐	Decreased	☐ No change
Health Quality of Life	☐	Increased	☐	Decreased	☐ No change
Spirometry results	☐	Increased	☐	Decreased	☐ No change
Exercise capacity	☐	Increased	☐	Decreased	☐ No change
Dispnea	☐	Increased	☐	Decreased	☐ No change

THANK YOU VERY MUCH FOR HELPING US… If you want to add something, please indicate?.. ☺