Anti-inflammatory effect of Statins in reducing the exacerbation and mortality rates of COPD patients: A review study

A project submitted

by

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This work is dedicated to my parents, my sibling and my husband to whom I got the outermost support.

Certification statement

This is to certify that, the project titled ‘Anti-inflammatory effect of Statins in reducing the exacerbation and mortality rates of COPD patients’ submitted for the completion of the precondition for the degree of Bachelor of Pharmacy from the department of pharmacy, BRAC university, this contain my personal work under the supervision of Fabliha Ahmed Chowdhury, Lecturer, Department of Pharmacy, BRAC University and proper acknowledgement goes to those from whom I got the ideas.

Signed,

_____

Counter signed by the supervisor

_____

Acknowledgement

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Abstract

Statins are cholesterol lowering drugs used against obesity in relation to hypertension and cardiovascular diseases, across the world, in an extensive scale. It reduces the synthesis of cholesterol by inhibiting the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) used in the mevalonate pathway. However recent studies have reflected their pleiotropic effect on victims of chronic obstructive pulmonary disease (COPD). In addition, to provide the cholesterol lowering action they have also shown an anti –inflammatory effect on the affected patients. Since the most commonly used treatment procedures are not successful in limiting the increasing cases of exacerbation and mortality rates of COPDs, use of statins will offer a new way out for the physicians. Different authentic papers, journals regarding this issue have been searched and their results have been compiled. Majority papers showed positive result which provides a positive effect of statin in COPD patient.

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Abbreviations

COPD	Chronic obstructive pulmonary disease
LTB4	Leukoterine B4
TNF-alpha	Tumornecrosis factor
IL-8	Interleukin-8
FEV_1	Forced expiratory volume
FVC	Forced vital capacity
PaO_2	Partial pressure of oxygen
WHO	World health organization
NCHS	National centre for health statistics
CDC	Centers for disease control and prevention
GBD	Global burden of disease
NHLBI	National heart, lung and blood institute
ISOLDE	Inhaled steroid in obstructive lung disease in Europe
ISEEC	Inhaled Steroid Effects Evaluation in COPD
HMG-CoA	3-hydrooxy-3methylglutaryl-coenzyme
LDL	Low density lipoprotin
FPP	Fernasylepyrophosphate
GGPP	Geranylgeranylpyrophosphate
BMP-2	Bone morphogenetic protein-2;
eNOS	Endothelial nitric oxide synthase;
t-PA	Tissue-type plasminogen activator;
ET-1	Endothelin-1;
PAI-1	Plasminogen activator inhibitor-1.
BMP-2	Bone morphogenetic protein-2;
eNOS	Endothelial nitric oxide synthase;
GEF	Guanine nucleotide exchange factors
GAP	GTPase-activating proteins
GDI	Guanine nucleotide dissociation inhibitors

ICAM-1	Intracellular adhesion molecule-1
MCH-II	Major histocompatibility complex Class-II
INF-γ	Interferon necrosis factor gama
hsCRP	High sensitivity C-reactive protein
HR	Hazard ratio
CI	Confidence Interval
RCT	Randomized control trial
RR	Risk ratio
PP	Primary prevention
SP	Secondary prevention
TC	Total cholesterol

Chapter one: Introduction to COPD

COPD (chronic obstructive pulmonary disease) is responsible for the increasing rate of mortality over the world. This is a condition by which the airways become obstructed and air flow become limited. COPD population is increasing day by day since there has been a transition from communicable to non-communicable diseases worldwide. COPD population is increasing day by day since there has been a transition from communicable to non-communicable diseases worldwide. (Black et al, 2008)

Globally, it is estimated that about 3 million deaths were caused by the disease in 2015 (that is, 5% of all deaths globally in that year). (Mathers et al, November 2006)

1.1 Pathogenesis:

Chronic inflammation in the pulmonary vasculature, airways and parenchyma is the major feature of COPD. Inflammatory cell like macrophages, neutrophills and T-lymphocytes become increased in this condition. Numerous mediators released from these cells including LTB4 (leukoterine B4), IL-8 (Interleukin-8), TNF-alpha (tumornecrosis factor) have the ability to damage lung structure. (keatings et al, 1996) Besides the inflammation there is two other process which are responsible for the progression of COPD. They are imbalance of two endopeptidse like proteinases and antiproteinases in the lung. Exposure to gases and noxious particles are also responsible for the occurrence of COPD. Smoking may induce inflammation and may cause direct damage to the lung. (Tamamoto et al, 1997) (Salvi et al, 1999)

1.2 Signs and symptoms:

Characteristic physiologic changes in the lung of COPD patient include a) Abnormality in gas exchange b) Airflow limitation c) Ciliary dysfunction d) Pulmonary hypertension e) Mucus hyper secretion.

The development of these conditions is observed over the course of the disease. Ciliary dysfunction and hyper secretion of mucus often gives rise to sputum production and excessive cough. These symptoms may appear before any other physiologic changes or

symptoms. The primary cause of those conditions is gradual increase of airway resistance and permanent airway obstruction.

Characteristic feature of Advanced COPD are:

- Parenchymal destruction
- Peripheral airways obstruction
- Pulmonary vascular abnormalities
- Reduction in lung capacity
- Hypoxemia

The major cardiovascular complication in COPD patient is the pulmonary hypertension which may develop in severe condition. (Macnee et al, 1994)

1.3 Risk factors:

Host factor and environmental factor are two risk factors that influence COPD. The interaction between these two factors gives rise to the disease. (Buist et al, 1994) The mostly seen host factor is hereditary deficiency of Alpha-1 antitrypsin. The prominent environmental factors are tobacco smoking, air pollutants, occupational dusts and chemicals. Many of the recent studies stated that the frequency of the disease in man and woman is almost same. (Anthonisen et al, 1994)

1.3.1 Host factors:

- **Genes:**

There are many genetic factors influencing COPD. Among them the mostly documented factor is the Alpha-1 antitrypsin deficiency. The premature and increased development of emphysema and decreased lung function are seen in many smokers and non-smokers due to the deficiency of Alpha-1 antitrypsin. (McElvaney et al, 1997)

- **Airway hyper responsiveness:**

Airway hyper responsiveness and asthma are the complex disorders that cause the development of COPD. These are induced by smoking and continuous exposure to the toxins. (Orie et al, 1961)

- **Lung growth:**

Lung growth causes reduction in lung function which may lead to increase the risk of COPD. This disorder occurs during gestation and also during childhood due to birth weight and exposures. (Tager et al, 1988)

1.3.2 Environmental factors:

- **Tobacco smoke:**

Cigarette smokers are at risk of lung function abnormalities, respiratory symptoms, decline in FEV1 and higher rate of morbidity and mortality. Not all the smokers develop COPD because genetic factor is related to this condition. Passive exposure to tobacco is also responsible for COPD. As it cause respiratory symptoms and increase lung burden. (Morgan et al, 1998)

- **Occupational dusts and chemicals:**

Prolonged and intense exposure of occupational dusts and chemicals may contribute to COPD. Other than that exposure to irritants, particulate matter, and organic dust may arise airway responsiveness.

- **Outdoor and indoor air pollution:**

People with existing heart or lung disorder if exposed to high levels of urban air pollution become more vulnerable to COPD. Indoor air pollution such as biomass fuel which is released during cooking may contribute to the development of COPD. (Chen et al, 1999)

1.4 Classification of COPD:

COPD is associated with two types of disease. One is emphysema and another one is chronic bronchitis. Two have different pathology, factors influencing the disease, diagnosis process, treatment procedure etc.

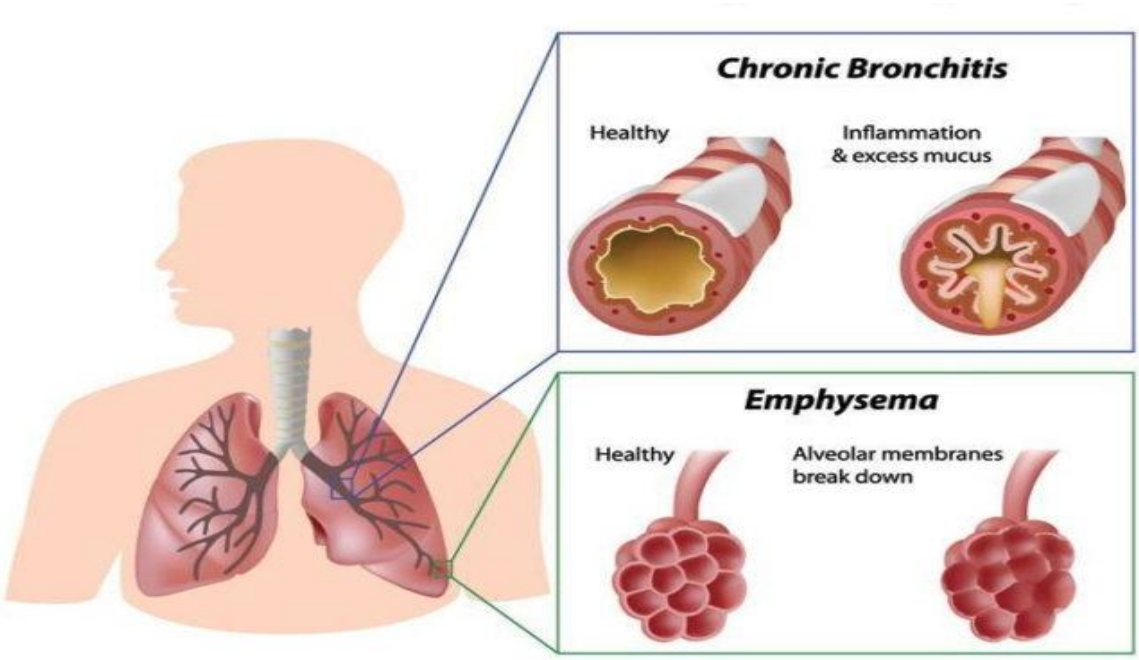


Figure1.1: Classification of COPD

1.4.1 Emphysema:

Pathophysiology:

Emphysema can be defined as damage of air sacs and they become large in size and ultimately burst. This damaged condition causes difficulties for people to breathe out properly and may increase the level of carbon dioxide in our body and gives rise to numerous signs and symptoms.

Sign and symptoms of Emphysema:

- **Breathlessness:** The most common symptoms of emphysema are breathlessness. Patient feels shortness of breath during their routine activity. Shortness of breath occurs due to the change in the structure of lung. These structural changes may give rise to the formation of pocket in lungs trap air causing difficulty to breathe. Due to this condition lungs get enlarged and breathing needs more effort.

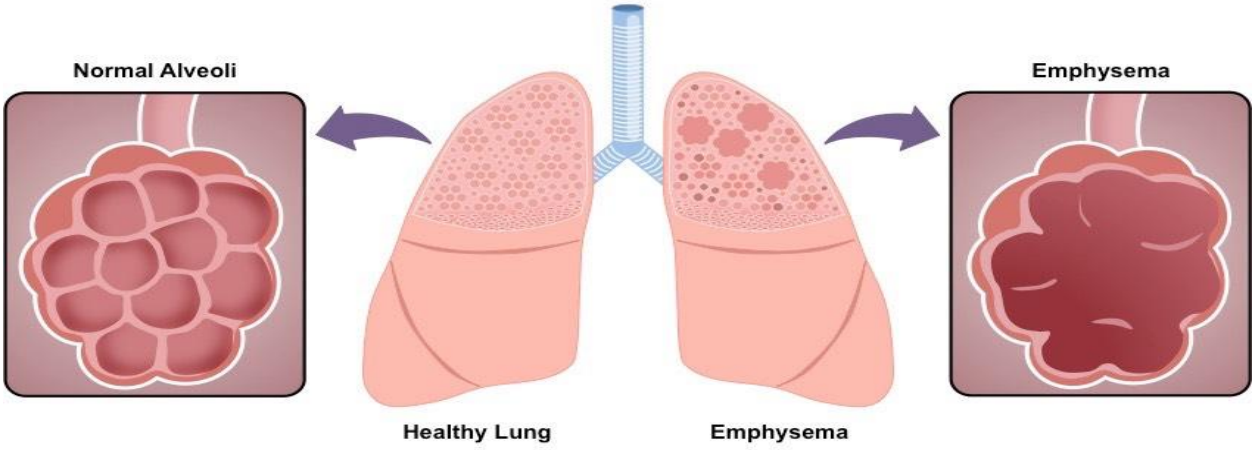


Figure 1.2: Pathophysiology of Emphysema

- **Wheezing:** Other symptoms are wheezing which is also common in asthma and also seen during use of inhaled medicine like bronchodilator.
- **Cough:** It is experienced by almost all the emphysema patient. It is also related to smoking which may continue symptoms of emphysema even after quitting smoking.
- **Chest tightness or pain:** Another symptom of emphysema, also seen in heart disease.
- **Less common symptoms:** Some other less common symptoms are anorexia, weight loss, insomnia, decreased sexual function.

Factors that accelerate the risk of emphysema:

- **Smoking:** Almost all types of smokers are in high risk of emphysema and the risk increases depending on the quantity of tobacco smoked and number of years of smoking.
- **Age:** Lung function deteriorates with age. Smokers are more likely to experience emphysema at the age of 40 and 60.

- **Secondary smoking:** Other name of this factor is environmental smoke. When a person smokes, the other person that lives beside or surround him get affected by the fume. This is known as secondary smoking.
- **Exposure to dust or fume (occupational):** Inhalation of fume from chemicals or dust from wood, cotton may increase risk of having emphysema.
- **Exposure to indoor or outdoor pollution:** Breathing indoor pollutants (fumes from heating fuel) and outdoor pollutants (car exhaust) both elevate the risk of emphysema.

Complications associated with emphysema:

- **Pneumothorax:** a collapsed lung can be life threatening for those people who is already suffering from severe emphysema. It is less common but when it appears it causes serious problem.
- **Heart problem:** Emphysema may increase arterial pressure which gives rise to a condition named corpulmonel. In this condition a section of a heart started to expand and weaken.
- **Giant bullae:** It is the empty space which takes place in the lung of people who are suffering from emphysema. It may increase the risk of Pneumothorax.

Diagnosis of emphysema:

Following symptoms helps a doctor to find out whether a patient suffering from emphysema or not-

- **Clubbing:** In advanced emphysema the oxygen level become lower which causes the finger tips to be rounded.
- **Cyanosis:** It is characterized by Blue-tinged lips in the case of severe emphysema due to low oxygen level in the blood.
- **Pursed-lip breathing:** As the people are suffering from breathing problem in emphysema, they tried to breathe rapidly in the course of pursed lips.
- **Hypoxemia (hypoxia):** A pulseoximetry or arterial blood gas testing is used to detect the low oxygen level in the blood of emphysema patient.

- **Hypercarbia:** Due to incapabilityof a patient to properly exhale carbon dioxide in emphysema increase the carbon dioxide level in the blood.
- **Malnutrition:** It is another condition often seen in emphysema patient.

Most of the above signs of emphysema grow in the advanced stage of the disease.

Possible treatments of emphysema:

The treatment pattern of a doctor is a step-wise approach which depends on the seriousness of condition.

- **Quitting smoking:** This is one of the recommendations that a doctor suggest to an emphysema patient. This help to stop theaggregation of the disease. Doctors also suggest some medications as well as some behavioral therapies which can assist a patient in quitting smoking.
- **Bronchodilator medications:** To treat the breathing problem in emphysema patient doctor often prescribe these medications which helps the air passages to be exposed more entirely and also permit better air exchange. The following bronchodilators are most commonly used.In case of mild emphysemaalbuterol is used which gives quick action in one dose by giving relief for 4-6 hours. It is available as metered dose inhaler and also known as rescue inhaler to the patient because it rescues them from severe condition of shortness of breath. To treat the shortness of breath at rest they suggest this medication to be administered at regularly scheduled interval. Another way of providing this is the nebulization.
- **Steroid medication:** They are often used to treat the inflammation. They are provided orally and also available as MDI or as other inhaler form.
- **Antibiotics:** In emphysema patient infection may play an important role in acute attack of emphysema. So to treat the infections antibiotics are suggested. It is suggested to the people who are coughing and are suffering from increased shortness of breath.
- **Oxygen:** In emergency cases the patient are supplied with oxygen to reduce their shortness of breath. In most severe cases, it is necessary to place windpipe which help in breathing.

1.4.2 Chronic Bronchitis:

Pathophysiology:

In bronchitis the bronchial tubes become inflamed. This causes accumulation of mucuswhich carry air into lungs and that blocks the air tube and causes cough. It also lead to wheezing, chest pain, discomfort and many more complications. The main two categories of bronchitis are acute and chronic. Chronic bronchitis is the one which gives rise to bronchitis. It is a dangerous and long term condition which occurs when lining of the bronchial tubules are continuously inflamed and irritated. This gives rise to ongoing cough with mucus. Irritated bronchial tubules easily get infected by bacteria and virus. In case of chronic bronchitis, it cannot be cured completely but proper medication and well maintained lifestyle can reduce signs and symptoms of bronchitis.

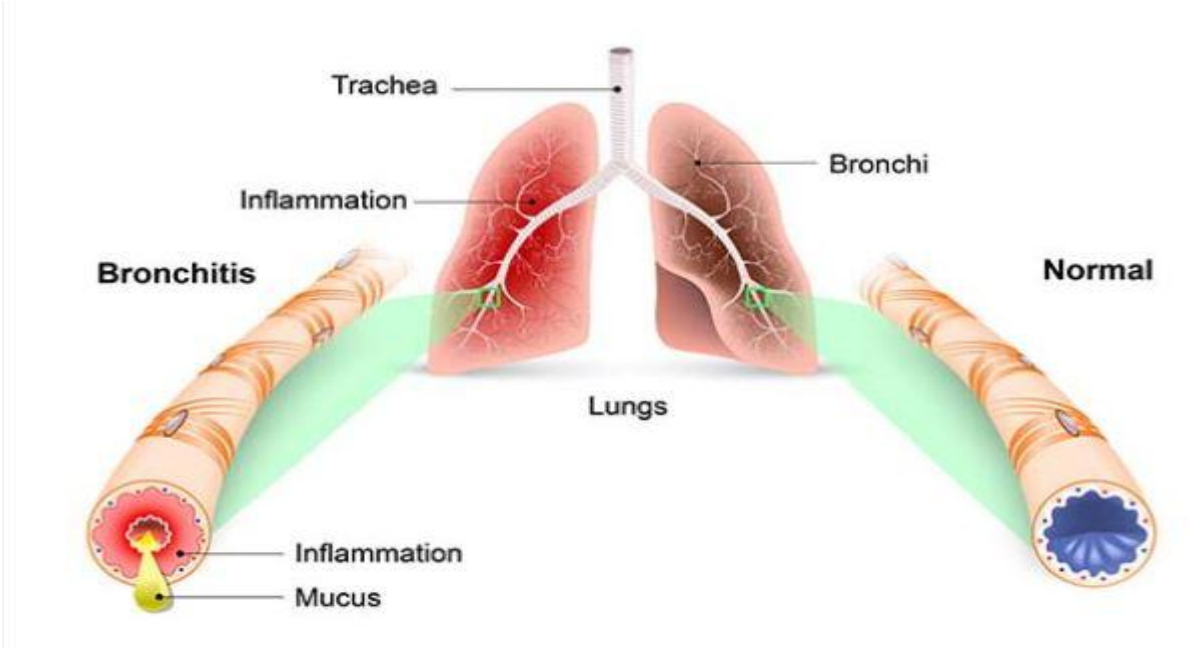


Figure 1.3: Pathophysiology of bronchitis

Signs and symptoms of bronchitis:

Persistent cough and infection are the most common symptoms of bronchitis. Infection occurs due to having cold or flu. Persistent cough stays for about 10 to 20 days with clear

mucus which causes difficulty in breathing. Other symptoms are wheezing, discomfort, low fever, chest tightness.

Factors causing bronchitis:

- **Bacterial or viral infections:** It gives rise to mucus and blocks the air pipe.
- **Long term smoking:** It irritates the bronchial pipe by causing excessive mucus.
- **Exposure to dust or fumes:** It gets worsen due to excessive presence of sulfur dioxide and other pollutants in the atmosphere.

Diagnosis of bronchitis:

Doctors generally diagnose it by observing common signs and symptoms. Other diagnosis processes are oxygen level in blood, chest x-rays, blood test etc.

- **Treatment:**

Bronchitis is mainly associated with fever, cold and flu. So the first medications given in this case are aspirin, acetaminophen etc. As most of the infections in case of bronchitis are viral, antibiotics are not the best treatment for curing bronchitis. Patients who are suffering from breathing problems are often prescribed to take humidifier or stream, bronchodilators, steroids etc. They are highly recommended to quit smoking to reduce the symptoms associated to it.

1.5 Another classification of COPD:

COPD are further classified into four stages according to their severity for the proper and easy management of this disease. This Classification is given in the following table:

Table 1.1: Classification of COPD according to its severity.

Class	Characteristics	Lung function by spirometry
Stage 0: At Risk	• Chronic cough • Sputum production	Normal

Stage I : Mild COPD	• Usually, but not always, by chronic cough and sputum production.	FEV1/FVC < 70% but FEV1 >80% predicted
Stage II: Moderate COPD	• Progression of symptoms, with shortness of breath typically, developing on excretion	30%<FEV_1 < 80% predicted
Stage III: Severe COPD	• Presence of respiratory failure or clinical signs of right heart failure. • Quality of life is appreciably impaired and exacerbations may be life-threatening.	FEV1 <30% predicted

Chapter two: Management of COPD and the interviewing loopholes:

According to GOLD workshop Report, an effective management of COPD mainly focuses on four components: (Pauwels RA. Et al., 2001)

- Assessing and Monitoring Disease
- Reducing Risk Factors
- Management of Stable COPD
- Management of Exacerbations

The main goals of this management's are-

- Prevention of diseases development
- Relief from symptoms
- Improvement of health status
- Prevention and treatment of exacerbation
- Decreasing mortality

These goals must be achieved with minimum occurrence of side effects due to management. The extent of this achievement varies from patient to patient. Some considerations must be kept in mind like the benefits or risk of the treatment and the cost of the treatment. It is an ongoing treatment process. Here, symptoms can be controlled but complete reduction is not possible. Both pharmacologic and non-pharmacologic treatment is required to control the further exacerbation. (Rice KL, 2010)

2.1 Assessment and monitoring of disease:

- **Diagnosis:**

A diagnosis of COPD is must for a patient, who is coughing, has sputum production and dyspenea, or who is exposure to risk factor for COPD. Diagnosis is performed by following assessment.

I. Symptoms Assessment:

The first symptom of COPD is chronic cough which may develop initially become intermittent and may also be present every day. In some cases development of air flow

limitation may take place without presence of any cough. Patient may often seek medical attention due to dyspenea and it is also the major cause of anxiety and disability regarding this disease. With lung function deterioration, breathlessness becomes worst. (Georgopoulas D, 1991)

II. Medical history Assessment:

A thorough medical history of a new patient who is suspected to have COPD must be assessed by taking following information-

a) Patients are exposure to any risk factors or not.
b) Checking all precedent medical history, such as, asthma, respiratory infections in childhood, allergy and additional respiratory diseases.
c) There is any family history of chronic respiratory disease.
d) Looking after the symptoms whether they are developing.
e) Checking the suitability of present medical treatments.
f) Checking the influence of the disease in patient's life as well as the restraint of activity; effect on family routines; and feelings of anxiety.
g) Checking the availability of having support from family to the patient.
(Loveridge et al, 1986) (Kesten et al, 1993)

- **Physical examination:**

It is very rare in case of COPD diagnosis. Without significant lung function deterioration physical sign of airflow limitation is absent and their detection is not sensitive and specific.

- **Measurement of airflow limitation:**

Spirometry helps to identify the level of the disease earlier and more easily. For that reason it is required to perform for patient who is coughing or has sputum production or has history of risk factor. It generally measure two important volume, one is the maximal volume of air forcibly exhaled from the point of maximal inhalation (FVC) and another one is volume of air exhaled during first second maneuver (FEV_1). The ratio of this two measurement gives the ultimate result which help to diagnosis of COPD. Patient who is suffering from COPD has low level of both FEV_1 and FVC. If the combination value is <70% then indicates the presence of airflow limitation.

In case of moderate COPD some additional investigation is required. Such as-

- **Bronchodilator reversibility testing:** It helps to diagnosis asthma and also provides treatment guidelines. It is also beneficial where spirometry does not give significant result.
- **Glucocorticosteroid reversibility testing:** It identifies the patient's response towards glucocorticosteroid
- **Chest X-ray:** High resolution of CT is performed when there is a doubt in the diagnosis.
- **Arterial blood gas measurement:** It is performed in case of advanced COPD. It is also applicable to those patient who have FEV_1 value < 40%. (Reis et al, 1982)

Table 2.1 Differential diagnosis (Prescott et al, 1999)

Diagnosis	Suggestive Features*
COPD	Onset in mid-life Symptoms slowly progressive Long smoking history Dyspnea during exercise Largely irreversible airflow limitation
Asthma	Onset early in life (often childhood) Symptoms vary from day to day Symptoms at night/early morning Allergy, rhinitis, or eczema also present Family history of asthma Largely reversible airflow limitation
Congestive heart failure	Fine basilar crackles on auscultation Chest X-ray shows dilated heart, pulmonary edema Pulmonary function tests indicate volume restriction, not airflow limitation

Bronchiectasis	Large volume of purulent sputum Commonly associated with bacterial infection Chest X-ray/CT shows bronchial dilation, bronchial wall thickening
Obliterative bronchiolitis	Onset in younger age, nonsmokers May have history of rheumatoid arthritis or fume exposure CT on expiration shows hypodense areas
Diffuse panbronchiolitis	Most patients are male and nonsmokers Almost all have chronic sinusitis Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

2.2 Reduce risk Factor:

Smoking cessation:

One of the most important therapeutic interventions for COPD is smoking cessation. Almost all COPD patients have smoking addiction. So it is an essential part in the management of COPD. It is the most effective and cost effective procedure to reduce the development of COPD.

Table-2.2 Following Strategies help the patients to give up Smoking (American Medical Association, 1994)

1. ASK: Systematically identify all tobacco users at every visit. Implement an office-wide system that ensures that, for every patient at every clinic visit, tobacco-use status is queried and documented. In a clear, strong, and personalized manner, urge every tobacco user to quit.
2. ADVICE: Strongly urge all tobacco users to quit.

3. ASSESS: Determine willingness to make a quit attempt. Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 d).
4. ASSIST: Aid the patient in quitting. Help the patient with a quit plan; provide practical counseling; provide intratreatment social support; help the patient obtain extra treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials
5. ARRANGE: Schedule follow-up contact. Schedule follow-up contact, either in person or via telephone.

Smoking cessation process:

a) Counseling:

Following tools are used for successful cessation:

a) Patient education
b) A target date to quit
c) Follow up support
d) Relapse prevention
e) Advice for healthy life style changes
f) Social support
g) Adherence to treatment

Physicians or health care providers may help the patient in fixing the quit date and should give follow up support to maintain the smoking cessation. Beside that individual counseling and telephone counseling also give beneficial effect in quitting smoking. (Mottillo et al, march 2009)

- Use of replacement therapy:

Different pharmacologic agents are available which provide self-help in smoking cessation. Such as:

a) Nicotine polacrilex

b) Transdermal nicotine patches
c) Antidepressant (bupropion)
d) Varnecline (chantix)

However, cessation program is not that much effective in the management of COPD because of the high addiction towards nicotine. It also has some negative impact such as poor education, psychological problem, forceful campaigns etc. This process include both pharmacologic and non-pharmacologic and also require different attempts to maintain the treatment. (Wilson et al, 1990)

2.3 Manage stable COPD and management of Exacerbation:

The treatment approach depends on the severity of the disease. The management requires the assessment of severity and how patient respond to therapies. Determination of severity depends on the severity of symptoms, air flow limitations, complications, comorbidities, health status of patient and many more. Positive outcome of the treatment depends on the patient's willingness towards recommended treatment, educational level and also on the availability of drug. (Ries et al, 1995)

Pharmacologic therapy is used to achieve many purposes-

- To control and prevent symptoms
- To decrease severity and frequency of exacerbation
- To improve health status
- To improve exercise tolerance

2.3.1 Management of bronchial muscle:

- **Bronchodilator:**

They are applicable for both as-needed basis and for relief symptoms. In case of bronchodilators dose-response relationship is very poor. Treatment given by inhaled route requires effective and trained drug delivery technique. (Maclay et al, 2011)

Table-2.3 Commonly used bronchodilator drugs (The Lung Health Study Research Group, 2000)

Drug (B2 agonist and anticholenergic)	Metered-Dose Inhaler (mg)	Nebulizer (mg)	Oral (mg)	Duration of Action (h)
Fenoterol	100–200	0.5-2		4-6
Salbutamol	100-200	2.5-5	4	4-6
Terbutaline	250-500	5-10	5	4-6
Formoterol	12-34			1-2
Salmeterol	50-100			1-2
Ipratopium Bromide	40-80	0.25-0.5		6-8
Oxitropium Bromide	200			7-9
Methylxanthine				
Aminophylline			225-450	
Theophylline			100-400	

Beta 2 agonist bronchodilator activates the beta 2 adrenergic receptor on the smooth muscle cell surface. Thus gives rise to the intracellular cAMP (cyclic adenosine monophosphate) and relax the smooth muscle. It is beneficial for the patient who has decreased post-bronchodilator expiratory airflow. (Celli, 2008)

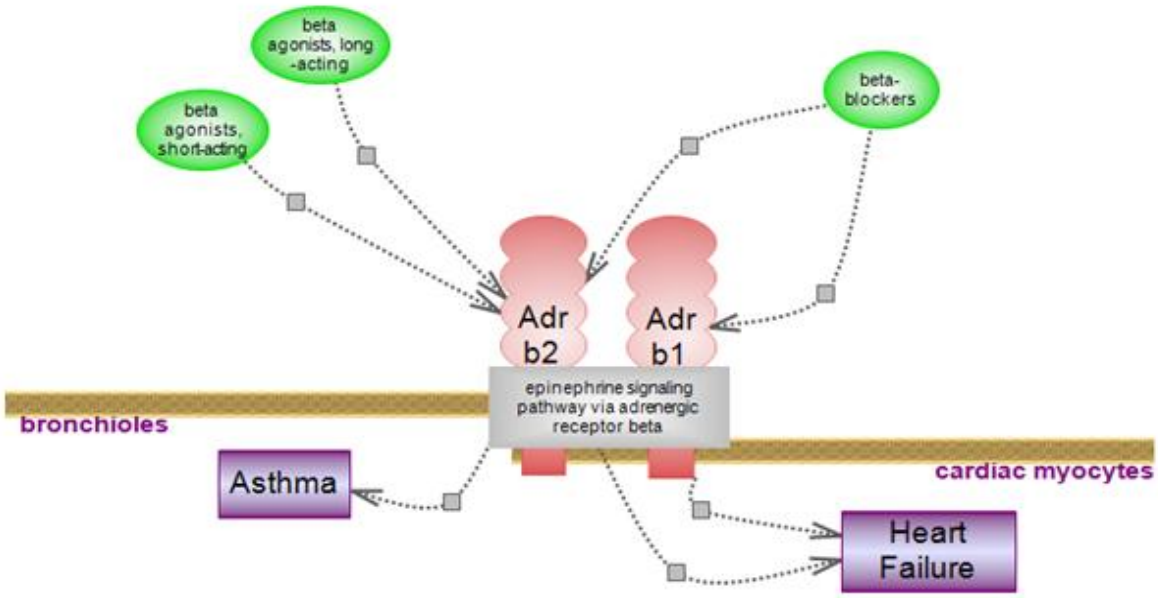


Figure- 2.1 Mechanism of action of beta blockers.

Anticholinergic Drug:

Anticholinergic drugs fight with acetylcholine for the receptor (postganglionic muscarinic receptor) thereby inhibits the Broncho motor tone and thus initiates the bronchodilation. They also cause bronchoconstriction by blocking reflex arcs.

2.3.2 Management of inflammation:

- Glucocorticosteroids:

Inflammation plays an important role in the pathogenesis of COPD. Systemic and inhaled steroids have significant effect on this inflammation. Regular treatment of inhaled glucocorticoids is appropriate for the patient who has spirometric response towards this medication or for those who has repeated exacerbations requiring medication with oral glucocorticoids. Long term treatment with inhaled glucocorticoids requires a trial of 6 weeks to 3 months with inhaled glucocorticoids or 2 weeks with oral glucocorticoids to identify the benefits and safety of the medication. (Carverley et al, 2007)

In the treatment of acute exacerbation the systemic steroids are highly recommended and accepted. Some Meta-analysis showed that these treatments bring possible reduction in the

need of additional treatment, treatment failure and also increase the improvement in lung function. However, long term treatment of oral glucocorticoids is not highly preferable due to its side effects. The serious side effect of this treatment is steroid myopathy (insidious disease) which leads to decrease functionality, muscle weakness, respiratory failure in patient who has advanced COPD. Beside that they are more effective in treating bronchial asthma then the COPD.

Inhaled corticosteroids are more beneficial than oral corticosteroid. Because it provides more direct route for administration and like other inhaled agents they are minimally absorbed. They are more effective in reducing exacerbation thus improving the quality of life in the patient with FEV<50% then bringing decline in FEV. In combination with long acting bronchodilators (beta agonist), the inhaled corticosteroids are more beneficial. So they are not given as monotherapy. (Sin et al, 2009)

Increased rate of pneumonia is common in patient taking inhaled corticosteroids.

Patients who are intolerable to oral intake are suggested for intravenous steroids which are reserved only for inpatient settings.

2.3.3 Management of infection:

- **Antibiotic**

COPD patient with exacerbation which can be characterized by sputum purulence and production or has increased dyspnea can be actively benefitted by the antibiotic medication. To prevent the colonization or chronic infection of lower airway from H influenza, S pneumoniae, M satarrhalis antibiotics are highly used. For the treatment of acute exacerbation in COPD patient antimicrobial therapy is used. It is also recommended to the patient having evidence of infectious process like leukocytes or fever. There are comprehensive antibiotic choice which should cover all pathogen in the basis of resistance pattern and clinical settings. In combination with corticosteroids, doxycycline shows significant result in the treatment of acute exacerbation. (Adams et al, 2007)

- **Reduction of infection by vaccines:**

Studies performed in elder patient with chronic heart disease showed that annual influenza vaccination has important health benefit including less hospitalization, and decreased mortality. A database review of four studies found that injectable antineumococcal vaccines have little effect. This vaccine recommended to the entire patient older than 65 years or to the patient have the FEV_1 level <40%. (Mosenifar, 2016)

2.3.4 Management of sputum secretion:

Mucolytic agents are effective in reducing sputum viscosity and can improve the secretionclearance. The oral agent, for example N-acetylceine, carry both antioxidant and mucokinetic properties which are beneficial in the treatment of COPD patient. But in case of inhalation therapy they are used in combination with bronchodilator to reduce incidence of bronchospasm.

2.4 Treatment of Hypoxemia:

- **Oxygen therapy:**

Progressive hypoxemia is very common in COPD patient. In advanced COPD oxygen therapy decrease mortality rates because it provides partial effects on pulmonary hemodynamics. Hypoxemia is the mother of partial pressure of oxygen in arterial blood (PaO_2 of > 55mm Hg. oxygen are supplied for about 15-19 hours per day. (Crockett et al, 2000)

Generally oxygen therapy is safe but high concentration more than of 60% may cause oxygen toxicity. Special observation and trained personnel is required for the treatment. Physical hazards like fires or explosions are rarely seen. To avoid these caregivers of family, patients are warned to avoid smoking. (Sandland et al, October 2008)

- **NIPPV (Noninvasive positive-pressure ventilation):**

They are used to reduce the respiratory failure. They can be administered without using the endotracheal tube. They help patients by increasing pH, reducing the severity of breathlessness, reducing PaO_2 in first four hours of the treatment. This intervention also

reduces mortality rates. However, it is not preferable for all patients. Following table shows us the selection criteria. (Lightowler et al, 2003)

Table- 2.4 Assortment and leaving out criteria for NIPPV (Kramer et al, 1995)

Selection criteria (at least two should be present)	Exclusion criteria (any may be present)
Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion Respiratory arrest Moderate to severe acidosis (pH 7.30–7.35) and hypercapnia (Pa CO 2 6.0–8.0 kPa, 45–60 mm Hg) Respiratory frequency. 25 breaths/min	Respiratory arrest Cardiovascular instability (hypotension, arrhythmias, myocardial infarction) Somnolence, impaired mental status, uncooperative patient High aspiration risk; viscous or copious secretions

2.5 Treatment of Alpha-1 antitrypsin deficiency:

The main treatment strategies are the reduction of neutrophil elastase burden. But primary treatment is smoking cessation and increased level of Alpha-1 antitrypsin (AAT). Available augmentation treatments are either increasing the endogenous production of AAT or administration of purified AAT by inhalation or intravenous infusion. Tamoxifen is a well-known medicine use to increase the AAT production. (Hubbard et al, march 990)

2.6 Inpatient care (Treatment of acute exacerbation):

In the United States hospital admission is common for acute exacerbation of COPD. There are some indications for hospital admission. Such as,

- Failure of outpatient treatment
- Marked increase in dyspnea

- Increase in hypoxemia
- Inability to tolerate oral medication

Acute exacerbation of COPD can be defined as chronic cough, elevated sputum production, and increase in dyspnea. It also gives rise to many abnormalities that are responsible for acute deterioration. Physicians recommend stepwise approach to drug therapy to reduce the complications and causes regarding exacerbation. To provide patient comfort pain management and sedation are required. (Hurst et al, march 2009)

2.7 Assisted ventilation:

In case of progressive airflow obstruction patient may require assisted ventilation. Following two points indicate ideal time to provide ventilation support.

1. During progressive respiratory acidosis

2. During significant hypoxemia despite of having supplementary oxygen

2.8 Bullectomy:

Patient with emphysema has the bullae of about 1-4 cm in diameter but sometimes the bullae can cover about 30% of the hemithorax and this is known as giant bullae. This giant bullae may squeeze nearby lung tissues and thus decreasing blood flow to healthier tissues. For this type patient removal of bullae is a standard treatment. (Fishman et al, 2003)

2.9 Lung volume reduction surgery:

Around 40 years ago, Brantigan et al reported for the very first time the resectional surgery for emphysema patient in about 33 patients. They resected 20-30 % of each lung that has been affected due to the disease. This investigation shows that removal of infected lung would elevate radial traction in the airways, thus reducing the symptoms. (Titman et al, 2009)

2.10 Lung transplantation:

The survival rate after lung transplantation is 5 years. 80-90 % survival has been seen at 1st year. The main purpose of this treatment is to improve quality of life and symptoms.

2.11 Long term Monitoring:

Further deterioration in acute exacerbation of COPD requires close follow up. (Burton et al, 2005). Follow up recommendation are given bellow-

- Monthly follow up for patient with severe disease
- In stable condition, biannual follow up is required
- Routine check up for theophylline level in case of dose adjustment
- In case of oxygen therapy arterial blood gases must be checked yearly

2.12 Safety and tolerability of COPD management:

- **Tolerability**

One of the trial known as TORCH trial (Carverley et al, 2007) gives that the discontinuation level of long term beta agonist (LABA) and inhaled corticosteroid combination (ICS) is 34% at three years even in highly monitored and motivated clinical trial. This rate was better than placebo. Withdrawal of single component is higher than the combination.

Table- 2.5 premature discontinuation value of tiotropium from an optimal study (Carverley et al, 2007)

Tiotropium	Discontinuation rate
placebo	47%
salmetarol	43%
SFC	26%

The reason behind discontinuation is apparent lack of medication effectiveness or decline in health status.

Table- 2.6 Withdrawal rate of ICS-LABA combination from same study (Carverley et al, 2007)

ICS-LABA combination	Discontinuation rate
Placebo	74%
Salmetarol	70%
SFC	54%

One of the retrospective study shows that 37% users continued the treatment with tiotropium for about one year, compared with 13%for LABA 17% for ICS-LABA and 14% for ipratropium. But compliance becomes better after hospitalization in about all groups. From above discussion it can be said that tolerability or patient preference are mostly seen with the ICS-LABA.

- **Safety:**

The TORCH data implied that inhaled corticosteroids may have elevated risk of complexity called pneeumonia. But the radiological confirmation for pneumonia was not acquired. That's why pneumonia episodes were not accurately characterized. This result is further supported by INSPIRE data which stated that pneumonias have been found 8% in SFC arm and 4% in tiotropium arm. (Wedzicha et al, 2008)

TORCH data did not show that ICS containing drug cause increased development of cataract or decrease in bone mineral density. Similarly, they also stated LABA containing medicines did not have cardiovascular events.

A meta analysis of nine randomized trial showed the safety of tiotopium. They suggested that there is no significant effect of tiotropium on all cause mortality. Dry mouth was the common side effects but compared with other drugs like salmeterol or ipratropium some risk were reported against tiotropium like urinary tract infection. Some major tiotropium study concluded that patient with myocardial infection or cardiac arrrythmia must not take tiotropium.The main concern of COPD is cardiovascular risk especially trachyarrythmias. Cardiovascular safety of Salmeterol has been assured by a small study of less than 1 year duration in COPD.

Chapter three: Mortality and exacerbation

3.1 The exacerbation rate of COPD:

Different studies had been performed on the prevalence of COPD in both developed and developing countries. In the year 1990 about 2.2 million deaths were estimated due to COPD and it became the leading reason of death. (AïtKhaled N et al, 2007) It is by conservative guess that in 2020 the number of death will be 3.5 million and COPD will become third leading reason of death. During the year of 2000, in US ten million adults reported physician-diagnosed COPD and COPD was responsible for eight million hospital outpatient visits, one and half million emergency department visits, seven lakh twenty six thousand hospitalization, and eleven lakh nine thousand deaths in USA. Tobacco smoke is the greatest risk factor for the development of COPD in developed countries. But in developing countries biomass fuels have been occupied in women. 9.8% men and 5.6% women are affected by COPD. A report from UK showed that the prevalence rate of COPD emerged to have peak in men but continuing to go up in women. However, report from Austria confirmed that both gender have same prevalence rate. (Mannino DM et al., 2007)

The exacerbation of COPD became important within past 10 years to the natural history and disease burden of COPD. Following table shows 9 studies regarding COPD patient in the past 40 years. A lot of factors cause difficulty to make comparison between the studies and also affect the ability to bring conclusion about the exacerbation of COPD. Contradictory variables are The method that is used to find out the exacerbation genetic makeup of the subject in the study, geography which includes weather, air, pollution etc and frequency of follow-up. Several studies estimated an annual rate of exacerbation regarding COPD which shows that it is as low as 0.5 to as high as 3.5 exacerbation/ patient. Hospitalization rates vary depending on the type of study but the range is in between 0.09 to 2.4% per year. (Johnston AK et al., 2008) So the more patients are followed up in studies the higher will be the detection of exacerbation rate. (Seemungal TAR et al., 2000)

National Health Interview Service

It is known as multipurpose health service and it is conducted by NCHS and CDC. It is considered as a main source of information on the health of household, non-institutionalized and civilian population of United State.

For survey population were questioned to separate following questions:

- In the past 12 months have you been suffer from chronic bronchitis?
- Have you ever been suffer from emphysema?

After dual diagnoses the survey concluded that 12.5 million US adults were diagnosed COPD. They also included that, COPD remain under-diagnosed for about up to 24 million Americans and they have abnormal lung function (figure 3.1). (Centers for Disease Control and Prevention, 2002)

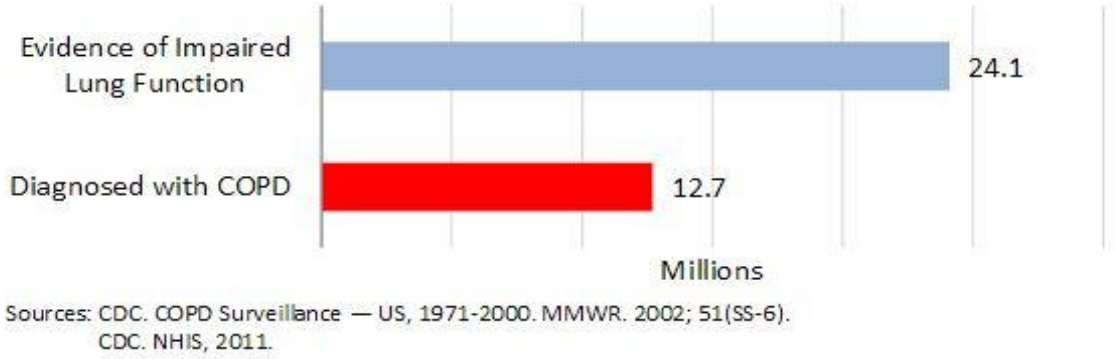


Figure: 3.1 COPD – Diagnosed Cases and Evidence of Impaired Lung Function (Centers for Disease Control and Prevention, 2002)

Chronic bronchitis

Following table 3.1 shows the exacerbation rates of chronic bronchitis patient. This table estimate and rate for chronic bronchitis based on ethnic origin and sex from 1999 to 2011. In the year of 2011 the diagnosis rates of chronic bronchitis among non Hispanic whites, non Hispanic blacks and Hispanics where respectively 7.5million (47.3 per 1000), 1.3 million (48.6 per 1000), and 943, 000 (28.8 per 1000) persons. The rate is higher in non Hispanic

white than the non Hispanic black.Women are more diagnosed with chronic bronchitis than men. In the year 2011 in comparison with 3.3 million men were diagnosed.

Table 3.1 Chronic Bronchitis - Number of Conditions and Prevalence Rate per 1,000 Populations by Ethnic Origin, Sex and Age, 1999-2011

Source: Centers for Disease Control and Prevention. National Center for Health Statistics. National Health Interview Survey, 1999-2011. Analysis by the American Lung Assocation Research and Program Services Division using SPSS software.

	Total [2]		Non-Hispanic						Hispanic	
			White		Black		Other			
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
1999	8,847,646	44.3	7,272,319	48.8	805,128	35.8	238,877	31.2	531,322	25.9
2000	9,354,982	46.4	7,680,117	51.4	922,045	40.4	186,426	22.4	566,394	26.7
2001	11,198,602	54.9	9,066,921	60.5	1,193,632	51.6	258,092	29.0	679,957	31.0
2002	9,113,581	44.3	7,177,946	47.7	1,081,002	46.1	225,054	24.7	629,579	27.7
2003	8,560,342	40.2	6,847,649	44.5	924,572	38.6	184,526	20.6	603,595	23.0
2004	9,047,481	42.0	7,302,106	47.3	899,836	37.1	184,526	18.1	603,595	25.0
2005	8,912,375	40.9	6,953,547	44.8	1,074,702	43.6	218,340	21.9	665,786	24.0
2006	9,463,082	43.0	7,315,058	47.4	1,145,153	44.6	358,802	30.6	644,069	22.5
2007	7,604,098	34.1	6,008,449	38.8	843,346	32.3	249,254	20.1	503,049	16.8
2008	9,832,089	43.7	7,905,680	50.8	1,023,702	38.6	272,056	21.9	630,651	20.6
2009	9,901,580	43.6	7,723,276	49.4	1,073,307	39.8	291,369	23.1	819,628	26.2
2010	9,883,229	43.1	7,635,860	48.5	1,127,051	41.1	242,232	19.2	878,086	27.4
2011	10,070,851	43.6	7,471,900	47.3	1,332,164	48.6	324,065	24.4	942,722	28.8

	Male		Female		18-44		45-64		65+	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
1999	2,661,435	27.8	6,186,211	59.4	3,978,344	36.7	2,962,010	50.5	1,907,292	58.7
2000	3,013,616	31.2	6,341,366	60.4	3,876,505	35.7	3,353,176	55.4	2,125,301	65.0
2001	3,718,647	38.0	7,479,955	70.5	4,913,277	45.3	4,073,615	65.1	2,211,710	67.3
2002	2,891,596	29.3	6,221,985	58.1	3,761,235	34.8	3,563,498	55.1	1,788,848	54.1
2003	2,740,594	26.8	5,819,748	52.6	3,253,728	29.4	3,310,933	48.5	1,995,681	58.3
2004	2,756,777	26.6	6,290,704	56.3	3,483,038	31.5	3,412,969	48.6	2,151,474	62.2
2005	2,886,344	27.5	6,026,031	53.4	3,504,174	31.7	3,543,899	49.0	1,864,302	53.2
2006	2,912,124	27.4	6,550,958	57.5	3,182,026	28.8	4,107,558	55.4	2,173,498	60.9
2007	2,558,623	23.7	5,045,475	43.7	2,515,141	22.7	3,225,607	42.4	1,863,350	51.5
2008	3,120,941	28.7	6,711,148	57.6	3,486,419	31.5	4,251,214	54.9	2,094,456	56.3
2009	3,189,161	29.0	6,718,419	57.2	3,092,989	28.0	4,411,101	55.7	2,403,490	63.5
2010	3,399,111	30.6	6,484,118	54.7	3,265,484	29.5	4,246,593	52.9	2,371,152	61.3
2011	3,316,488	29.6	6,754,363	56.7	3,170,362	28.6	4,355,878	53.9	2,544,611	64.2

Figure 3.2 shows exacerbation rate of chronic bronchitis based on age. More than 10 million American reported diagnosis of bronchitis in the year of 2011. Among them 70% cases took place in those patients with the age over 45. With increasing age the exacerbation rate increases such as the lowest rate were among those with 18 to 44 (28.6 per 1000) and highest among those with above 65 years (64.2 per 1000). (Centers for Disease Control and Prevention, 19997-2007)

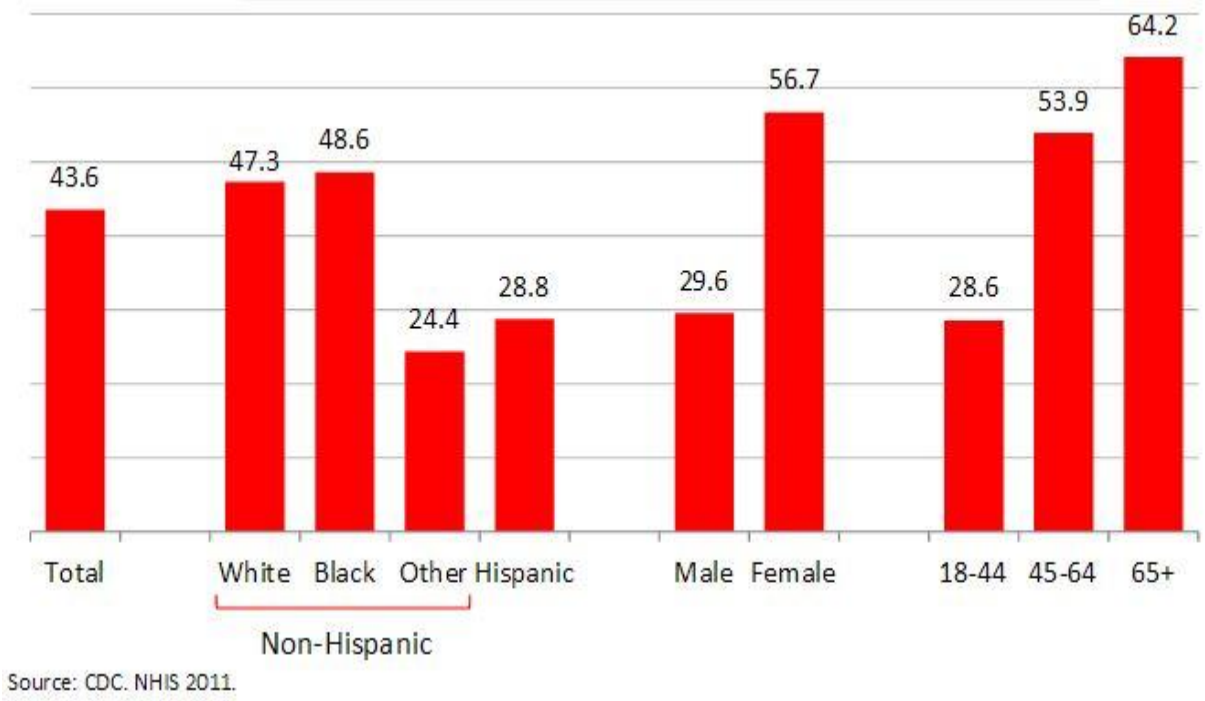


Figure 3.2 Chronic Bronchitis – Prevalence Rates per 1,000, 2011 (Centers for Disease Control and Prevention, 19997-2007)

Emphysema

Table 3.2 shows that exacerbation rate for emphysema for based on the age and ethnic origin. In the year of 2011, 4.7 million American were recognized with emphysema so the prevalence rate is 20.2 per 1000. More than 90% of emphysema cases were the individual over the age of 45. From the very beginning emphysema was seen more in non Hispanic whites than the non Hispanic blacks. But in 2011 there was a significant elevation in emphysema in the exacerbation which stopped up the racial gap. In 2011 it was concluded that in comparison with apparently 489,000 non Hispanic blacks have been ever diagnosed with emphysema than the 3.8 million non Hispanic whites. This rate was the highest rate ever recorded for non Hispanic blacks. The exacerbation rate is generally lower in the non Hispanic blacks than the non Hispanic others and much lesser than that of in non Hispanic white.

Table 3.2 Emphysema - Number of Conditions and Prevalence Rate per 1,000 Population by Ethnic Origin, Sex and Age, 1999-2011

Source: Centers for Disease Control and Prevention. National Center for Health Statistics. National Health Interview Survey, 1999-2011. Analysis by the American Lung Assocation Research and Program Services Division using SPSS software

			Non-Hispanic							
	Total [2]		White		Black		Other		Hispanic	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
1999	2,798,963	14.0	2,539,202	17.0	117,378	5.2	52,932	6.9	89,451	4.4
2000	3,124,699	15.5	2,792,954	18.7	208,025	9.1	32,847	4.0	90,873	4.3
2001	2,983,598	14.6	2,632,331	17.6	164,628	7.1	55,941	6.3	130,698	6.0
2002	3,131,410	15.2	2,809,643	18.7	197,404	8.4	45,193	5.0	79,170	3.5
2003	3,114,666	14.6	2,798,537	18.2	193,157	8.1	43,126	4.8	79,846	3.0
2004	3,575,684	16.6	3,086,086	20.0	238,734	9.8	95,553	9.8	155,311	5.8
2005	3,791,006	17.4	3,412,355	22.0	192,838	7.8	54,026	5.4	131,787	4.7
2006	4,068,667	18.5	3,619,091	23.5	190,398	7.4	147,078	12.5	112,100	3.9
2007	3,736,000	16.7	3,131,359	20.2	217,083	8.3	125,740	10.1	261,818	8.8
2008	3,789,224	16.8	3,286,507	21.1	214,072	8.1	97,161	7.8	191,484	6.3
2009	4,895,246	21.5	4,232,303	27.0	357,281	13.3	106,044	8.4	199,618	6.4
2010	4,313,991	19.8	3,644,268	23.2	290,143	10.6	148,228	11.7	231,352	7.2
2011	4,680,381	20.2	3,780,946	23.9	489,434	17.9	178,285	13.4	231,716	7.1

	Male		Female		18-44		45-64		65+	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
1999	1,637,536	17.1	1,161,367	11.2	224,033	2.1 *	936,939	16.0	1,637,991	50.4
2000	1,690,500	17.5	1,434,199	13.7	256,030	2.4 *	1,141,600	18.9	1,727,069	52.8
2001	1,678,868	17.2	1,304,730	12.3	200,259	1.8 *	1,099,638	17.6	1,683,701	51.2
2002	1,821,630	18.4	1,309,780	12.2	287,302	2.7 *	1,271,992	19.7	1,572,116	47.6
2003	1,701,065	16.6	1,413,601	12.8	154,649	1.4 *	1,261,139	18.5	1,698,878	49.6
2004	1,871,241	18.1	1,704,443	15.3	309,071	2.8 *	1,393,431	19.9	1,873,182	54.2
2005	2,060,742	19.6	1,730,264	15.3	340,694	3.1	1,429,606	19.8	2,020,706	57.7
2006	2,481,386	23.4	1,587,281	13.9	290,075	2.6	1,764,620	23.8	2,013,972	56.5
2007	2,017,689	18.7	1,718,311	14.9	226,384	2.0	1,765,325	23.2	1,744,291	48.2
2008	1,769,048	16.3	2,020,176	17.3	222,120	2.0	1,572,766	20.3	1,994,338	53.6
2009	2,578,428	23.5	2,316,818	19.7	369,226	3.3	2,064,627	26.1	2,461,393	65.0
2010	2,247,665	20.3	2,066,326	17.4	360,739	3.3	1,703,187	21.2	2,250,065	58.2
2011	2,128,540	19.0	2,551,841	21.4	365,033	3.3	2,146,121	26.6	2,169,227	54.8

Figure 3.3 denotes that the exacerbation rate for emphysema based on gender. The prevalence rate is lower in women than the men. But the trend a continuously changing similar likes that shown in the death rates. In the last 5 years the exacerbation rate decrease for about 6% in man and increased for about more than 63% in women. So women beat man in 2011 and the rate became 21.4 per 1000 women compared with 19per 1000 men.

Various events were performed to find out the exacerbation rate. Such as this events focused on the continuous increase in cough, onset of cough, sputum change and wheeze. On the other way the London COPD study and anthonisen introduced different definition which

includes increase in dyspnea or new onset of dyspnea, sputum volume or one of the them or any of the following wheeze, cold, sore throat etc. Except the heterogeneity in the COPD exacerbation, these all type of studies have one same feature that is they all used symptom based definition.

Besides that, the ISOLDE study utilized the treatment based definition and the preliminary result of London COPD study raised a debate about the occurrence of COPD exacerbation. This raised question has been answered by another study that is INSPIRE study. This study is the primary long term study of COPD exacerbation that shows a comparison between two types of exacerbation including both symptoms based and treatment based. It predicts that if symptom based definition is utilized to define exacerbation entirely then the detection of exacerbation will be 3 per year. But if treatment based study is used then the rate will become 1.5 per year. (Centers for Disease Control and Prevention, 19997-2007)

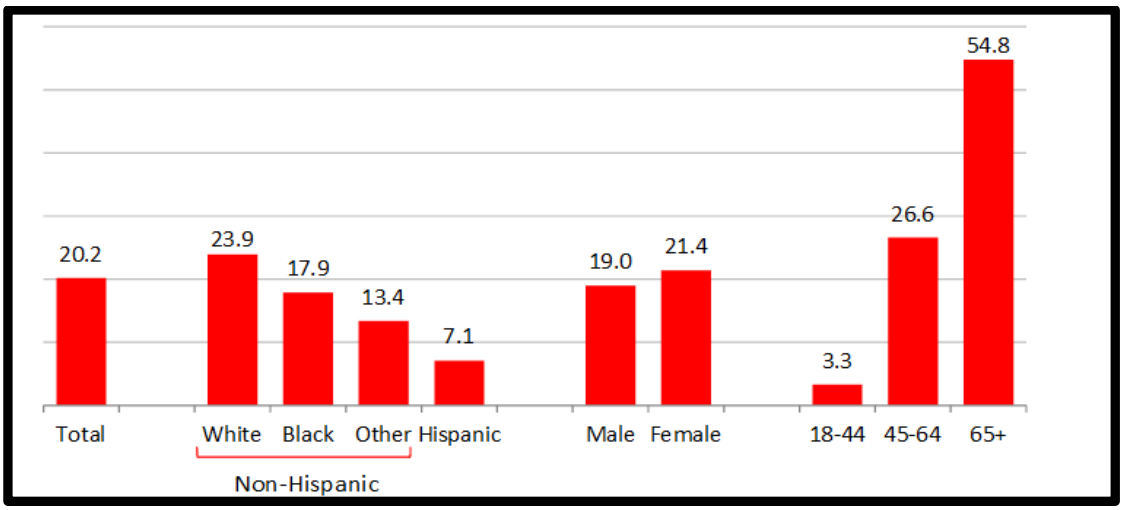


Figure 3.3: Emphysema – Prevalence Rates per 1,000, 2011 (Centers for Disease Control and Prevention, 19997-2007)

3.2 COPD mortality rate

Table 3.3 shows the number of death by sex and ethnic origin between the year of 1999 and 2009.due to COPD, 133,965 people died in 2009 in which more than half (52.3%) were women.

Table 3.3: COPD- number of deaths by ethnic, origin and sex, 1999-2009

Sources: Centers for Disease Control and Prevention. National Center for Health Statistics. CDC WonderOn-line Database, compiled from Compressed Mortality File 1999-2009 Series 20 No. 2O, 2012

							Non-Hispanic								
	Total			Hispanic			White			Black			Other		
Year	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female
1999	119,524	60,795	58,729	2,539	1,428	1,111	108,609	54,384	54,225	6,706	3,978	2,728	1,329	812	517
2000	117,522	58,372	59,510	2,397	1,322	1,075	107,065	52,311	54,754	6,383	3,712	2,671	1,351	840	511
2001	118,744	58,218	60,526	2,558	1,379	1,179	108,036	52,118	55,918	6,412	3,693	2,719	1,415	852	563
2002	120,555	59,133	61,422	2,771	1,511	1,260	109,408	52,767	56,641	6,647	3,794	3,853	1,419	887	532
2003	122,283	59,321	63,062	2,875	1,566	1,309	110,952	52,762	58,190	6,613	3,763	2,850	1,545	967	578
2004	118,171	57,260	60,911	2,826	1,520	1,306	107,293	51,166	56,127	6,330	3,558	2,772	1,503	888	615
2005	127,049	61,120	65,929	3,209	1,733	1,476	114,862	54,272	60,590	7,134	4,003	3,131	1,631	982	649
2006	120,970	57,964	63,006	3,053	1,614	1,439	109,313	51,555	57,758	6,714	3,677	3,037	1,665	992	673
2007	124,477	59,961	64,516	3,292	1,785	1,507	112,329	53,303	59,026	6,937	3,765	3,172	1,744	1,002	742
2008	137,693	65,936	71,757	3,678	1,903	1,775	124,076	58,643	65,433	7,787	4,127	3,660	1,917	1,122	795
2009	133,965	63,899	70,066	3,724	1,895	1,829	120,593	56,737	63,856	7,539	4,060	3,479	1,887	1,069	818

Figure 3.4 show that it is the tenth consecutive year where the number of death number because of COPD was more in the women than male. Non Hispanic whites constitute 80% of the COPD deaths. The least number of deaths was the Hispanics with 3714. In 2009 it was seen that the death rate in male was greater than the females by 1.3 times despite the fact that there were more death of women by COPD in 2009. This occurred due the fact that size of population are scaled by the rates and male are less in the general U.S than female.

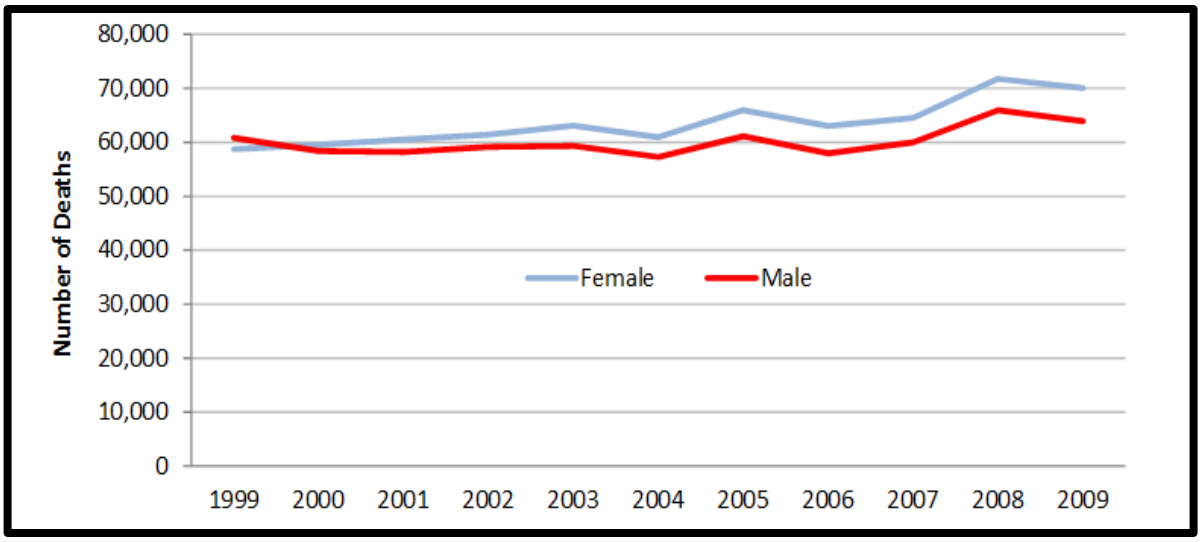


Figure 3.4: COPD- number of death by sex, 1999-2009 (Centers for Disease Control and Prevention, 19997-2007)

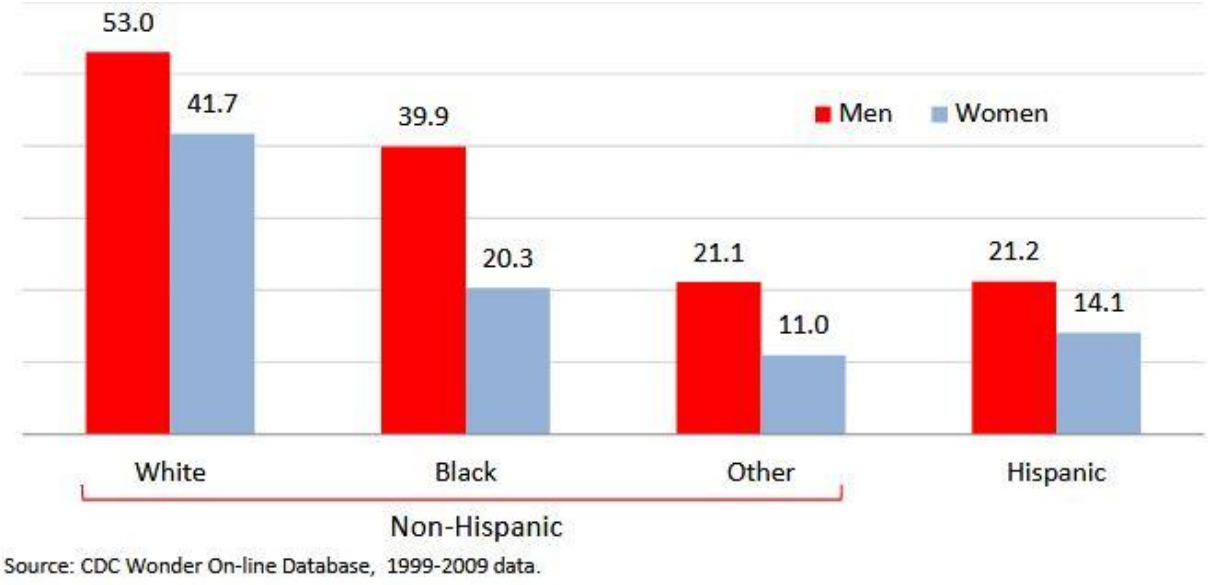
Table 3.4 and figure 3.5 shows the age-based deaths per rate 1000,000 population by ethnic origin and sex. For healthcare planning and defining magnitude of diseases, number of deaths or disease are usually important though they do not execute the necessary information to differentiate health status and diseases between groups (like male versus female), statisticians build up rates to make such comparisons. If the rate is a fraction then numerator is the number of people in which an event occurred during a certain period of time or death. Denominator is the total population at risk for the same period of time.

COPD adjusted 41.2 death rates per 1000,000 populations. It denotes that in the year 2009 41 people out of 1000,000 populations died from COPD. the age attuned death rate of non Hispanic whites (46.0 out of 1000,000) was 1.7, 2.6, and 3.1 times greater than the rate of non Hispanic blacks, Hispanics, non Hispanic others respectively. Therefore, non Hispanic white males had the highest age adjusted death rates (53 per 1000,000) than the non Hispanic other women who had the lowest age adjusted death rates(11.0 per 1000,000) (Centers for Disease Control and Prevention, 1999-2009)

Table 3.4 COPD - Age-Adjusted Death Rate per 100,000 Population by Ethnic Origin and Sex, 1999-2009

Sources: Centers for Disease Control and Prevention. National Center for Health Statistics. CDC WonderOn-line Database, compiled from Compressed Mortality File 1999-2009 Series 20 No. 2O, 2012.

							Non-Hispanic								
	Total			Hispanic			White			Black			Other		
Year	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female
1999	44.0	56.8	36.2	18.2	26.1	13.3	47.5	60.3	39.8	30.4	47.7	20.2	19.8	29.1	13.2
2000	42.7	53.6	36.1	16.2	22.3	12.2	46.4	57.1	40.0	28.4	43.5	19.5	19.2	29.0	12.4
2001	42.2	52.8	35.9	19.3	26.6	14.8	45.8	56	39.7	27.7	43.7	18.7	18.3	26.9	12.4
2002	42.0	52.3	35.7	19.3	26.2	14.7	45.7	55.6	39.8	28	43.4	19.4	16.9	25.8	10.7
2003	41.9	51.2	36.2	18.9	26.0	14.4	45.9	54.5	40.5	27.3	42.1	18.9	17.2	26.5	10.9
2004	39.9	48.4	34.5	17.3	22.9	13.5	43.8	52.0	38.8	25.5	38.5	18.1	15.8	23.1	10.9
2005	42.0	50.3	36.6	18.3	24.2	14.3	46.2	54.0	41.2	28.0	42.0	19.8	16.0	23.7	10.8
2006	39.3	46.7	34.6	16.4	21.2	13.1	43.5	50.5	39.1	25.8	37.7	18.9	15.3	22.5	10.5
2007	39.7	47.2	34.8	16.7	22.0	13.0	44.1	51.2	39.4	26.1	37.9	19.2	15.1	21.2	10.9
2008	42.9	50.6	37.9	17.3	21.8	14.2	47.8	55.2	43.0	28.5	40.1	21.6	15.6	22.3	11.0
2009	41.2	48.6	36.6	17.0	21.2	14.1	46.0	53.0	41.7	27.2	39.9	20.3	15.0	21.1	11.0



Source: CDC Wonder On-line Database, 1999-2009 data.

Figure: 3.5 COPD – Age-Adjusted Death Rates by Ethnic Origin and Sex, 2009 (Centers for Disease Control and Prevention, 19997-2007)

3.3 The Burden of COPD Mortality

There is a considerable amount of data regarding the number of death by COPD in this developed world, especially in the U.S.A, there is a scarcity of data in the developing regions. The accessibility of accuracy of data for COPD mortality is hindered due to the expense involved in gathering information and collaborating. The miscalculation of the cause of death, under-diagnosis etc underestimates the burden of mortality.

Another source of COPD death underestimation has been by asthma mortality reports. it includes data of death by asthma to patients over 65 years. It happened because of the miscalculation of breathing problems like asthma. A study based on the death certificate conducted by Reid and colleagues in the northern England, told that COPD was the true reason of 28 of the 55 deaths. Whereas, asthma was considered as direct reason.

In relative, COPD was less diagnosed in developing regions. Published information underestimates COPD mortality because of miscalculation of deaths by COPD and other causes. The WHO in the past issued death rates for categories of “ashthma, emphysema,bronchitis" which eliminates the most large category of COPD death. For which there may be acceptable underestimation on the rate of COPD mortality.

Despite these obstacles, several of international and national surveys describing COPD death rates have been issued. (European Respiratory Society and European Lung Foundation, 2003)

- **Gender Difference in COPD Mortality**

Evidences support that there is relation between gender and COPD death rates. like, WHO issued global mortality rate that shows that the death rate of COPD is more in males all regions. The one exception is situated in the Western Pacific region where the death rate in women was approximated at 90/1000000 population differentiate with 70/1000000 in men.

A noteworthy trend in US COPD death rate is elevated death in women in relative. Number of female death from COPD is increasing especially in white female. An issue from US centers for disease control published that, all death rate4s are lowering by 32% and for men 14% from 1968 to 1999. The COPD death rate in this time has enlarged by 382% for female

to 41/1000000 population. (Kazerouni N et al., 2004) The ALA report claimed that 51% of people dying occurred due to COPD were women in 2002. (ALA, 2004)This rate was more than in males. This was also seen in Canada, Spain, and Australia among women. This increased rate reflects more smoking among other factors.

In other European countries, rate for COPD was more in men than female including regions like Denmark, UK, etc. decreased rate have been noticed in Hungary, Bulgaria, and Romania. (Crockett AJ et al., 1994)

- **Societal burden of COPD morbidity and mortality**

The newest information from GBD study shows that in world in 2000, COPD resulted 16.5 million tears lost life and 10 million life with abnormality and 26.5 million abnormality based life years.

With regard of financial expense, the NHLBI chart book issued total cost of 37.2 billion US dollars in 2004 in which medical expenses were 20.9 billion dollars. Indirect expenses were 7.4 billion dollars was recognized to morbidity and 8.9 billion dollars. This analysis did not consider COPD as a secondary reason for mortality.

The European lung white book in 2003 issued total cost of 38.7 billion dollars in Europe with 4.7 billion for drugs, 2.7billion for patient care. Thus total 28.5 million was lost for COPD. As these data eliminates mortality costs, actual expense of COPD is much higher.

Another data suggests that COPD published a large and underestimated death rate related healthcare facilities to society. (NHLBI, 2004)

3.4 Impact of therapeutic interventions on COPD exacerbation and mortality

Undoubtedly, COPD burden can be decreased by prevention of risk of individuals from rising the diseases. It can be gained by scanning for COPD in a person and taking thorough medical history and to reduce risk factors like genetic and morbid conditions. Early prevention and diagnosis can reduce COPD. Different studies reported that management and therapies of COPD and the primary endpoint of those studies is survival.

3.4.1 Non-pharmacological interventions:

- **Smoking cessation**

It is one of the most efficient ways to decrease the risk of increasing COPD and also helpful in reduce the accelerated turn down in lung function. Though there are some few data which indicate the consequence of smoking cessation on the COPD mortality. Lung health cohort study found that 6000 smokers got benefitted by 10 week smoking cessation program and significant reduction in mortality was seen. Anthonisen et al in 2005 showed that the mortality rates in smoking cessation interference group was 8.83/1000 person per year. The rate was less than the usual group which was 10.38/1000 person per year. (Anthonisen et al., 2005)

- **Oxygen therapy and NIPPV:**

In 1980 two landmark studies was conducted with 290 patient with the disease COPD and they have the resting mean PaO_2 <60. In this study these patients were 40% improved with supplemental oxygen. This study also mentioned that continuous oxygen therapy give significant result (mortality rate 22.4%) compared to nocturnal oxygen therapy (mortality rate 40.8%). This treatment is beneficial in case of high degree of hypoxemia and severe disease. In additional trial with 211 patients having resting mean PaO_2 >60 mmHg, survival rate was low with supplemental oxygen therapy. (NOTTG, 1980)

- **Lung transplantation and lung volume reduction surgery (LVRS):**

Prolong survival has been shown with LVRS in a very short group of patient having severe COPD. A study conducted with patient having ruthless emphysema gone through liver transplantation or lung volume reduction surgery presented that the mortality rate was 0.11 per person per year. Besides that, mortality rate was lower in surgery group than in patient with medical treatment. (Fishman A et al., 2003)

3.4.2 Pharmacologic intervention

- **Short-acting and long acting bronchodilators**

Various studies shows that short acting bronchodilators especially short acting beta agonist and anticholinergic therapies did not give significant effect in reducing mortality rates.

A meta-analysis with 9 randomized trial including 4198 patients having moderate to severe COPD showed that treatment with long acting bronchodilators give little effect in reducing all cause mortality.

- **Inhaled corticosteroids**

A large randomizes and well controlled trials were designed to find out the effect of ICS on mortality. However, another randomized placebo controlled trial known as pooled analysis shows positive result of ICS on reducing the mortality rate. A different Meta analysis assessed data from five randomized trial that was performed with patient suffering from COPD and it involve all cause mortality rate. Here again no significant result in favor of ICS to improve endurance had not found. In addition two trials compared the combination therapy of ICS and LABA and significant positive effect towards this therapy was found but here again statistical data could not be found. Using those two studies pooled data presented relative risk for mortality of 0.52 using treatment with Inhaled corticosteroids plus salmeterol.

The ISOLDE trial was performed which found better survival in COPD patient when treated with Flutcasone proprinoate. First analysis of this trial includes 751 patient having moderate to severe COPD were treated with fluticasone proprinoate or placebo for 3 years, the result showed no improved treatment for steroid. But when it was reviewed non-significant result had been seen which showed that patient treated with Flutcasone proprinoate survive more than patient taking placebo.

ISEEC study performed recent analysis on the effect of ICS in reducing COPD mortality. This is done with individual patient and data was collected from 7 randomized controlled data which was continued for about at least 12 months in COPD patient. All cause mortality was decreased for about 27% by using ICS treatment compared to placebo. Women, patient

with FEV1 <60% and ex-smoker got more beneficial effect than other. (Waterhouse JC et al., 1999)

Table 3.5: Summary of different data which represent investigation of the effect of pharmacotherapy on mortality in COPD patients from. (Waterhouse JC et al., 1999)

Sources of data	Comparison	RR (95% Cl) of mortality	Statistical significance
Clinical trials for ICS			
(Burge et al 2000)	FP vs placebo	0.77 (0.54, 1.11)	NS
(Van Der Valk et al 2002)	FP vs placebo	0.98 (0.06, 15.55)	NS
(Lung Health Study Research Group 2000)	Triamcinolone vs placebo	0.79 (0.40, 1.53)	NS
(Vestbo et al 1999)	Budesonide vs placebo	0.80 (0.22, 2.92)	NS
(Pauwels et al 1999)	Budesonide vs placebo	0.81 (0.22, 2.04)	NS
Pooled summary (n=3678) (Sin et al 2003)	ICS vs placebo	0.78 (0.58, 1.05)	NS
Pooled summary (n=5085)(Sin et al 2005)	ICS vs placebo	0.73 (0.55, 0.96)	Significant
Clinical trials for LABA + ICS			
(Szafranski et al 2003)	Budesonide+formoterol vs placebo	0.66 (0.24, 1.81)	NS
(Mahler et al 2002)	FP+salmeterol vs placebo	0.16 (0.01, 3.01)	NS
Pooled summary (n=1486) (Sin et al 2003)	ICS+LABA vs placebo	0.52 (0.20, 1.34)	NS

Chapter 4: Statin and its correlation with COPD

4.1 Statin:

Statin is the class of drug that is the most effective and efficient in decreasing plasma cholesterol. They are prescribed to treat the hypercholesterolemia for their inhibiting action towards 3-hydrooxy-3methylglutaryl-coenzyme. Angiographic studies showed that they have the ability to reduce the development and may provoke the failure of atherosclerosis. (Hunninghake D.B. et al., 2000) Thus, these effects become beneficial for the reduction of mortality of patient suffering from cardiovascular disease. Thus as a HMG CoA reductase inhibitor provides the capacity to decrease cholesterol synthesis. As mevalonate (product of HMG CoA reductase reaction) is the precursor as well as key product of cholesterol and for various other non-steroidal isoprenoidic compounds. (Bellosta S.et al., 2000)Thus activity on mevalonate pathway enables statin to give the pleiotropic effect. The pleiotropic effect of statin can be categorized into two parts. They involve directly lipid signaling pathway and intracellular signaling pathway. The first part involves-

- Inhibition of cholesterol biosynthesis
- Inhibition of the secretion of lipoprotein
- Increasing the uptake and degradation of LDL (low density lipoprotein)
- Inhibition of LDL oxidation
- Inhibition of scavenger receptors expression

Secondly, Statin carries on a progression of processes that involve the following-

- Reduction of the accumulation of esterified cholesterol into macrophages
- Reducing inflammatory reaction
- Increasing the stability of the atherosclerotic plaques and platelet activity
- Increasing of endothelial synthetase

The invention of statin brought essential improvement in the prevention of primary and secondary coronary heart disease. Various clinical studies linked between reduction of coronary heart disease and reduction of blood cholesterol and also included reduction in mortality of coronary patient. (Vaughan C.J et al., 2000)

4.1.1 Classification of statin:

Classification criteria for statin may involve-

1. How they are achieved
2. Liver metabolism
3. Physicochemical properties
4. Specific activity

a) How they are achieved

Subsequent to fungal fermentation some of the statins are achieved, such as Simvastatin, lovastatin, pravastatin. Other statin was obtained by synthesis, such as Atrovastatin, Cerivastatin, Fluvastatin. Cerivastatin were banned from the pharmaceutical market by Bare AG voluntarily on 2001. Due to this agent many patient died by acute renal failure. So for this reason five statins are available as medications nowadays-

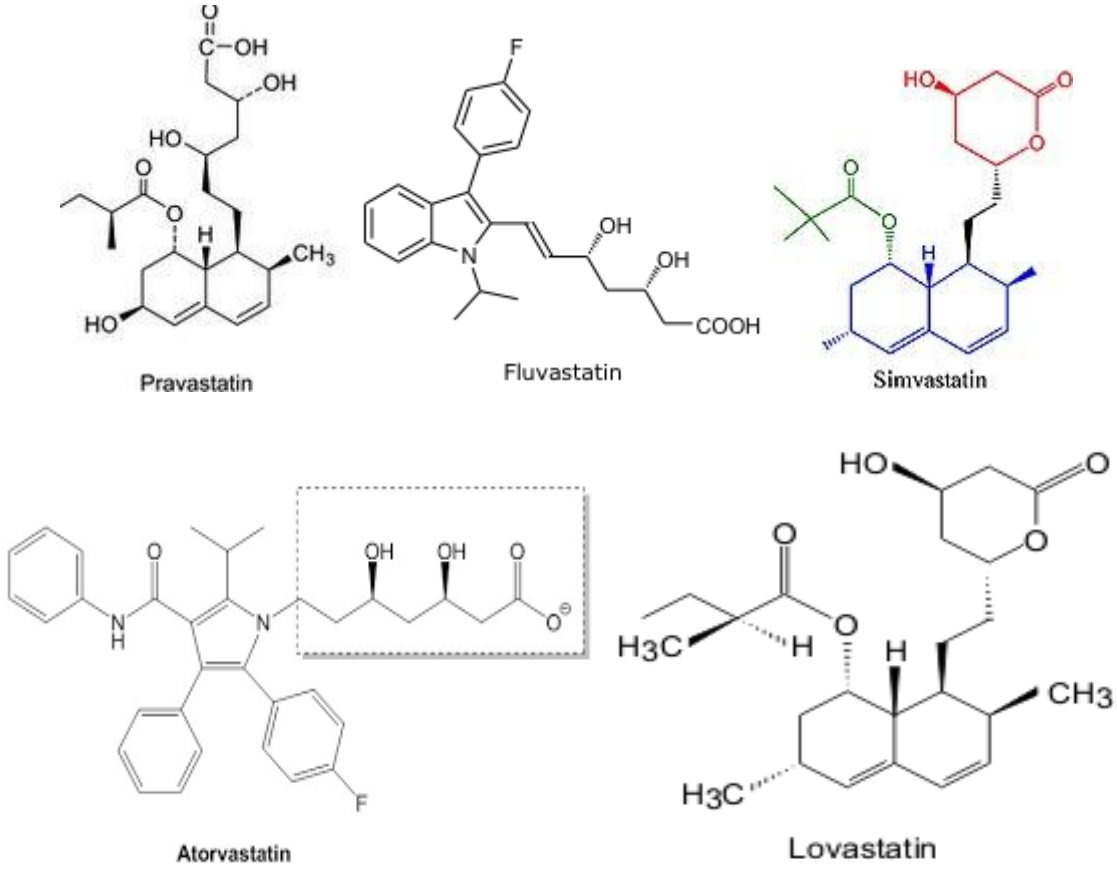


Figure 4.1: Structure of different Statin

b) Liver metabolism

The target organ of all statin is liver. Liver may retain the following percentage of dose of statins-

Table 4.1 percentage of dose of statins retained by liver (Vaughan C.J et al., 1994)

Statin	**Percentage of dose**
Fluvastatin and Lovastatin	>70%
Simvastatin	>80%
Pravastatin	46%

Cytochrome P450 pathway is followed by Lovstatin, Simvastatin, Atrovastatin and Cerivastatin for liver metabolism. CYP 2C9 is followed by Fluvastatin. Low circulation concentration was seen in many statins-

Table 4.2 Low circulation concentration of statins (Vaughan C.J et al., 1994)

Statin	**Percentage of circulatory concentration**
Atrovastatin	12%
Fluvastatin	20-30%
Pravastatin	17%
Simvastatin and lovastatin	5%

c) Physicochemical properties

Depending on physiochemical properties we can classify Statin as follows: (Lennernas H et al., 1997)

Table 4.3 Physicochemical properties of Statins (Vaughan C.J et al., 1994)

Statin	**Physicochemical properties**
Pravastatin	Extremely hydrophilic
Fluvastatin	Intermediate characteristics
Lovastatin and simvastatin	Hydrophobic

d) Specific activity

Administration processes of Atrovastatin, Cerivastatin, Pravastatin, Fluvastatin is active form whereas for Lovastatin and Simvastatin is inactive form. Thus they get hydrolyzed first to become active form. (Blumenthal RS, 2000)

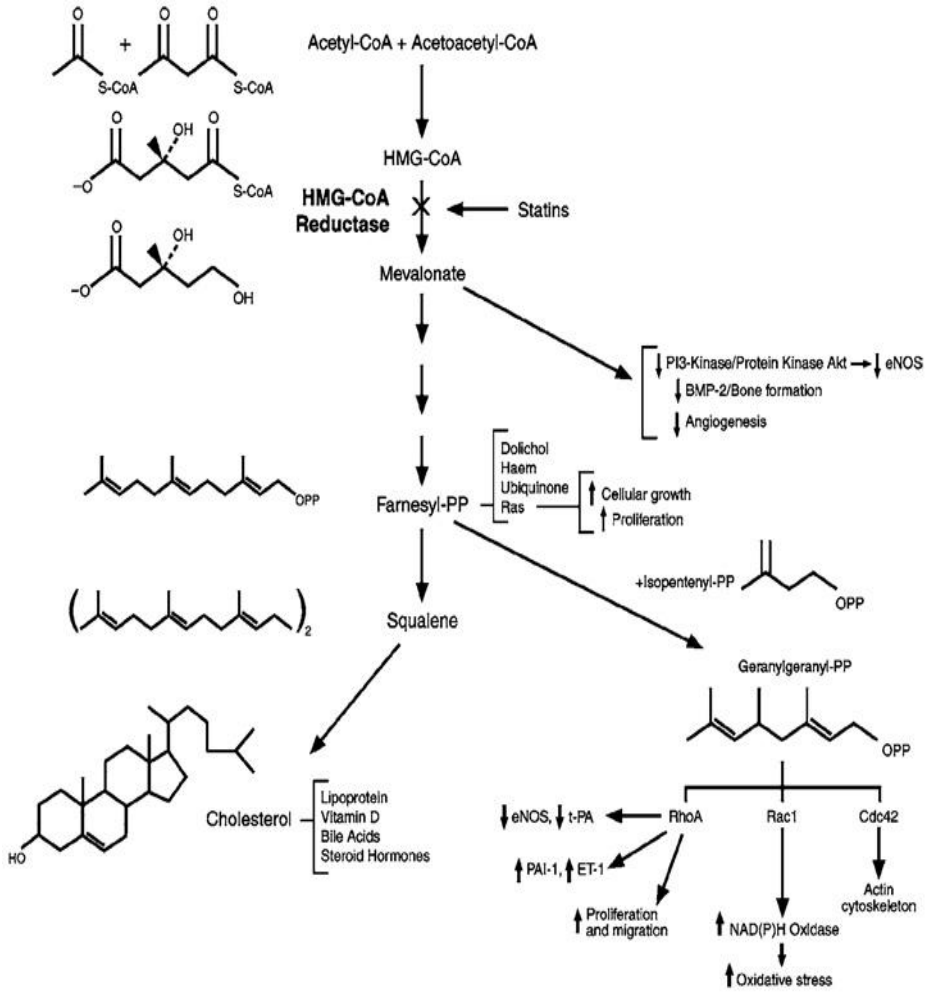
4.1.2 Mechanism of action of statin:

Statin perform their mechanism of action in two ways-

- Lipid signaling
- Intracellular signaling

Lipid signaling

Statin may inhibit synthesis of L-mevalonic acid as well as many other essential isoprenoid intermediates which took part in cholesterol biosynthesis pathway, for example FPP (Fernasylepyrophosphate), and GGPP (geranylgeranylpyrophosphate). From FPP Squalene intermediate are formed and which gave rise to cholesterol. The whole process is mediated by HMG-CoA reductase. This catalyst is inhibited by Statin which doesnot allow the reaction to go further. In this way Statin become beneficial in lowering cholesterol. (Kimura M. et al., 1997)



BMP-2- bone morphogenetic protein-2;

eNOS- endothelial nitric oxide synthase;

t-PA-tissue-type plasminogen activator;

ET-1- endothelin-1;

PAI-1- plasminogen activator inhibitor-1.

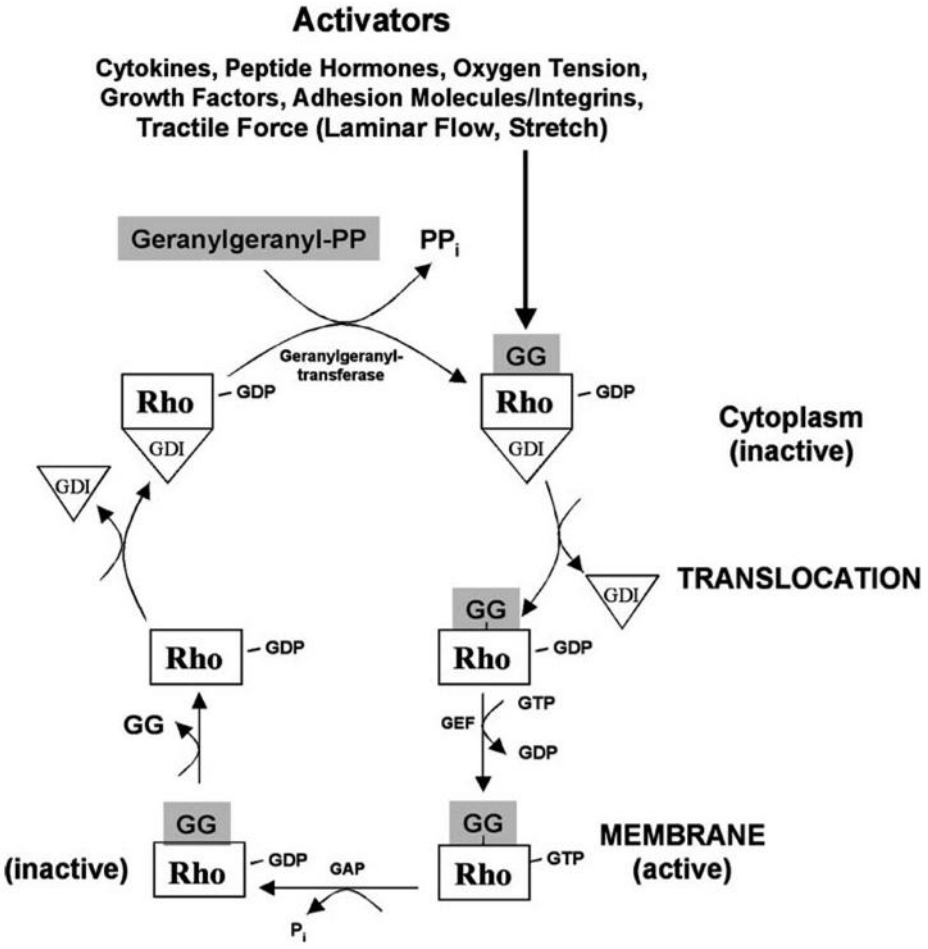
Figure 4.2: Cholesterol synthesis pathway and statin effect on the inhibition of HMG-CoA redutase. (Baetta R et al., 1997)

Intracellular signaling

FPP and GGPP intermediates are significant for lipid attachment which serve posttranslational modification of different protein, such as gama subunit of G=protein, GTP-binding protein RAS and other RAS like protein, such as Rab, Rac, Rho, Ral or Rap. (Baetta R et al., 1997) In this way, isoprenylation of protein allows the covalent attachment, membrane associated protein trafficking and sub cellular localization. By prenylation, main substrates for post translational modifications are the member of Rho and Ras GTPase family. Both Rho and Ras known as GTPase binding protein turn in between inactive GDP bound state and active GTP bound state. (Falk E et al., 1994) Translocation of Ras and Rho

from cytoplasm to plasma membrane depends on farnesylation and geranylgeranylation respectively. Here by inhibiting both isoprenylation of Rho and Ras, statin leads to the gathering of inactive Rho and Ras in cytoplasm. (Nofer J-R. et al., 1997)

Inhibition of Rho kinase in geranylgeranylation is the mechanism mediator of statin's pleiotropic effect on the vascular wall. Specific member of GTPase family has specific fuctions, such as motility, cell shape, proliferation and secretion, though the members may have overlapping function which could be experiential in over expressed system.



GEF-guanine nucleotide exchange factors

GAP-GTPase-activating proteins

GDI-guanine nucleotide dissociation inhibitors

Figure 4.3: Regulation of Rho GTPase by isoprenylation. (Nofer J-R. et al., 1997)

Rho family member has distinct and complementary functions which allow giving effect on cell signaling. When in response to signals cells recognize their actin cytoskeleton, they change intracellular protein;s three dimensional colocalization. This change have an effect on intracellular transport, mRNA stability, gene transcription and membrane trafficking. In

fact, experimental data proposes that many cholesterol independent outcome of statin are mediated by the inhibition of isoprenylation of Rho. (Laufs U. et al., 1999)

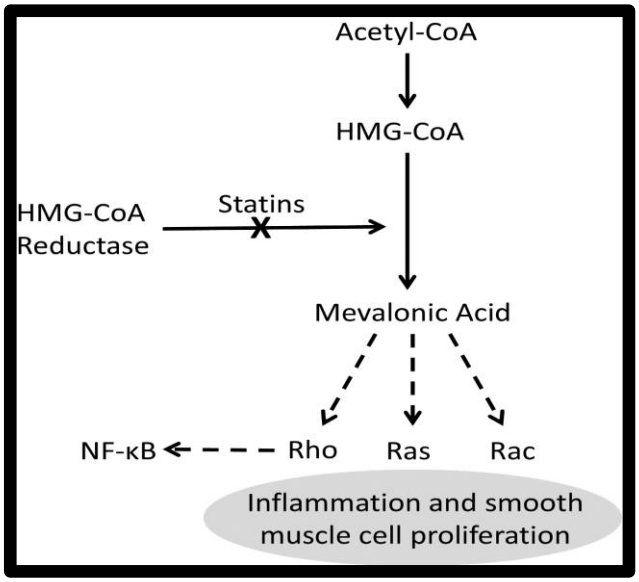


Figure 4.4: Inflammatory effects of Statin (Nofer J-R. et al., 1997)

Inflammatory process can be characterized by the presence of inflammatory cell, such as macrophages, T-lymphocytes and many more. These T-lymphocytes and macrophages release inflammatory cytokines that can change smooth muscle cell proliferation, endothelial function, thrombosis and collagen degradation. Current studies suggested that anti-inflammatory effects of statin provide the ability to decrease the amount of inflammatory cell. This mechanism is so far to be completely elucidated but may inhibit the adhesion molecule, for example ICAM-1 (Intracellular adhesion molecule-1) which allows the staffing of inflammatory cell.

The controlled immune system and activated T-lymphocytes are arbitrated by MCH-II (Major histocompatibility complex Class-II), CD450/CD40L. (Bhakdi S. et al., 1999) Antigen presenting cell provide MHC-II constitutively. In the other, induction of INF-γ (Interferon necrosis factor gama) increase the expression of MHC-II in various cell. Transactivator CIITA is the essential promoter of this pathway. Here, the statin inhibits expression of MHC-II on macrophages and endothelial cell. By inhibiting the promoter called transactivator CIITA. In this way they repress MHC-II mediated T-cell activation. High sensitivity C-reactive protein (hsCRP) is the clinical marker of inflammation which in

response to inflammatory cytokine, for example interleukin-6 is being produced by liver. (Zhang YX. Et al., 1999) High level of hsCRP is the predictor of coronary artery disease. Statin therapy may decrease the hs-CRP level in the patient suffering from hypercholesterolemia. CARE trial indicated that, a significant reduction in plasma hs-CRP levels can be experienced by patient by using statin over 5 years period. (Musial J. et al., 2001)

4.1.3 Adverse effect of Statin:

Statins are considered as well tolerated. But it has some important side effects. Among them most common are liver and muscle toxicity. If along with statin, cytochrome P450 inhibitor or further inhibitors of statin metabolisms are administered than it may cause myopathy. For example, administration of azole antifungal may increase the risk of myopathy. Other than that niacin and fibrate may increase the occurrence of myopathy. Other side effects can be hepatic dysfunction, hypothyroidism, serious infection, renal insufficiency etc.

The suspension cerivastatin has already been banned from pharmaceutical market because of their muscle toxicity which causes fatal rhabdomyolysis in many patients.

4.2 Co-relation between statin and COPD:

Recently COPD become a greatest trouble to society on a worldwide level. Just long term oxygen therapy and smoking cessation change scenario for survival. The lack of effective management option for COPD is an obstacle for the improvement of new management. There has been increased rate of exacerbation and mortality. Thus here we can consider Statin as an option since they also give anti-inflammatory action.

- **Pathophysiology of COPD:**

It involves the activation of WBC and inflammatory cells.

- **Activation of WBC:**

In COPD many etiologic factors gives rise to activation of WBC. The etiologic factors are smoke, noxious gases etc. These factors activate various inflammatory cells, such as neutrophils, macrophages and CD8 lymphocytes. These causes release of different chemical

mediators, like TNF, IL-8, LTB-4. This brings many destructive changes in lung, such as airways pulmonary vasculature and lung parenchyma.

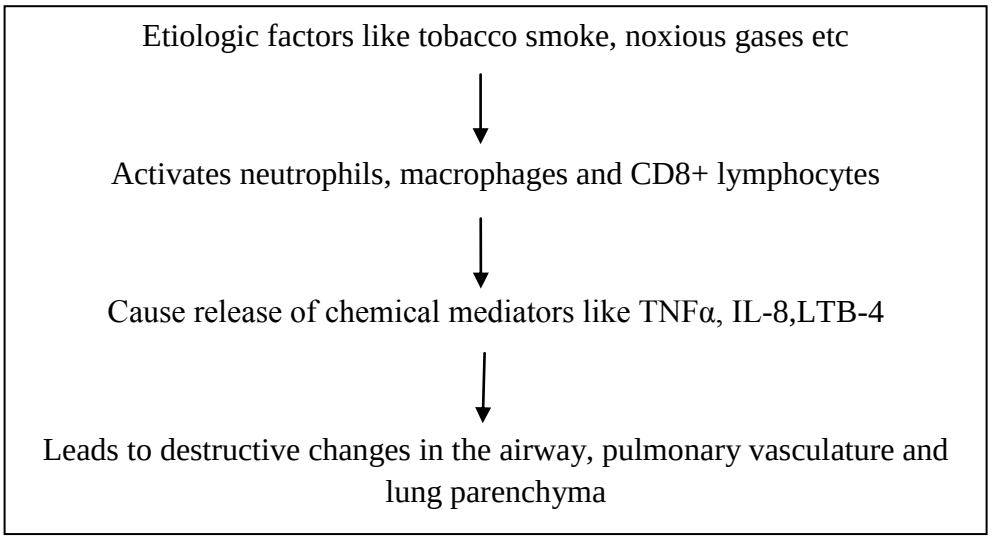


Figure 4.5: Activation of WBC

Correlation:

Pathology of COPD showed that inflammation is the main reason for the reduction on of lung function in COPD patient. The before mentioned mechanism of action of Statin explained that the pleiotropic effect can reduce the accumulation of inflammatory cell. Thus it can reduce effect of inflammation. Statin can reduce accumulation of IL-8, TNFα, CD8 and other inflammatory cells which may bring beneficial effect to the patient suffering from COPD.

By using the concept many physicians, researchers performed many analyses regarding this issue and trying to find out whether the statin can be used for the treatment of COPD.

Chapter five: Methodology

1. Method:

1.1 Identification and search strategy:

To identify desired articles I searched English-language literature which mainly focused on consequence of Statin on COPD patient. Searching options are BMC, MEDLINE, England articles and European articles through PUBMED. Searching terms that were used to find the articles are given below-

- COPD patient
- Management of COPD
- Pathophysiology of COPD patient
- Current mortality and exacerbation rate of COPD patient
- Statin
- Mechanism of action of statin
- Pleiotropic effects of Statin
- Anti-inflammatory effects of Statin
- Effect of Statin on exacerbation and mortality rates of COPD

In addition, some articles were taken from the reference lists of selected publications related to the topic. All types of studies including cohort studies, meta analysis, review papers were taken for study selection.

1.2 Study selection:

Those studies were selected that included above terms. All the duplicate citations were removed by using EndNote. After that full text of the selected papers were reviewed to verify eligibility. Only the original articles with proper article's name, author's name, year of publication, country were included and rest of them were excluded. Studies that involved data were selected if those reports had at least one outcome of interest such as mortality, episodes of exacerbation, statin use in reducing mortality or exacerbation and had to connect a minimum number of 100 participants.

1.3 Data extraction:

For data extraction all the papers were separated according to the following types:

- Management of COPD
- Present mortality rates of COPD
- Mechanism of action of Statin as an Anti-inflammatory drug
- Statin effects on exacerbation and mortality rates of COPD

Then information from each type were collected according to the study design, study characteristics, characteristics of participants, exposure's characteristics and information of the reported outcomes.

Chapter six: Result

In the result part different studies which are performed to analyze the effect of Statin on COPD and other related disease has been summarized. Among them 20 are cohort study, 5 are randomized controlled trial and rest of the one is ecological analysis. Most of the result shows positive effect of Statin in COPD patient accepts one.

6.1 Compilation of several studies which evaluated the effect of Statin on COPD patients:

1.Author , place, date of publication: Sheng et al, UK, 2012 (Sheng x et al, 2012)

Study design: Population based prospective cohort study

Study purpose: To evaluate statin-associated TC-concentration reduction and subsequent risk for cardiovascular (CV) morbidity and mortality in COPD.

Participants: Total 1,274. COPD patients in statin-exposed according to whether or not they were taking statin treatment during follow-up

Result: Statin-associated TC concentrations decreased by 0.86 mmol/L (16%) in patients treated for primary prevention (PP) (n = 1274) and 0.52 mmol/L (11%) in patients treated for secondary prevention (SP) (n = 443), from 5.30 mmol/L and 4.68 mmol/L at baseline, respectively. TC concentrations also declined by 2% in patients free from established CV disease and by 5% in patients with established CV disease in the statin-unexposed groups. A risk reduction of recurrent CV events with statins was observed (adjusted hazard ratio [HR] = 0.35; 95% CI, 0.15-0.87), but not for PP (adjusted HR = 0.84; 95% CI, 0.37-1.89). Statins reduced CV mortality (adjusted HR = 0.32; 95% CI, 0.13-0.77) in SP but not PP. There were statistically significant reductions in all-cause mortality in both PP (adjusted HR = 0.61; 95% CI, 0.43-0.85) and SP (adjusted HR = 0.58; 95% CI, 0.35-0.97).

Outcome measurement: In patients with COPD, statins were protective from CV events and CV mortality in SP but not PP, and statins improved all-cause mortality in both PP and SP.

2. Author , place, date of publication: Lee T-M, et al., Taiwan, 2008 (Lee TM et al., 2008)

Study design: Randomized, double-blinded, placebo-controlled trial

Study purpose: To investigate whether pravastatin administration is effective in improving exercise capacity in patients with COPD, and whether baseline or serial changes in hs-CRP over time are associated with corresponding changes in exercise capacity.

Participants: n = 62 patients with clinically stable COPD, received pravastatin (40 mg/day) over a period of 6 months (randomly assigned, double blind). n = 63 patients with clinically stable COPD, received placebo over a period of 6 months (randomly assigned, double blind).

Result: Exercise time increased by 54% from 599 +/- 323 seconds at baseline to 922 +/- 328 seconds at the end ($p < 0.0001$) in pravastatin-treated patients. A decrease in hs-CRP over baseline values was observed in 79% of patients (42 of 53) treated with pravastatin. Pravastatin-treated patients with a greater percent decrease in hs-CRP had a significant improvement in exercise time compared with those without hs-CRP decrease.

Outcome measurement: These data reinforce hs-CRP as a significant surrogate marker in COPD and underscore an important guide to the efficacy of treatment in COPD trials.

3. Author , place, date of publication: Wang et al, Chaina, 2013 (Wang M. T. et al., 2013)

Study design: Nationwide retrospective nested case-control

Study purpose: To examine the association between statin use and risk of hospitalized COPD exacerbation, and to assess whether the association varied by statin initiation, dose, or duration of use.

Participants: The study cohort comprised 14,316 COPD patients, from which 1584 cases with COPD exacerbations and 5950 matched controls were identified.

Result: Any use of statins was associated with a 30% decreased risk of COPD exacerbation (95% confidence interval [CI], 0.56-0.88), and current use of statins was related to a greater reduced risk (adjusted odds ratio [OR] 0.60; 95% CI, 0.44-0.81). A dose-dependent reduced risk of COPD exacerbation by statins was observed (medium average daily dose: adjusted OR 0.60; 95% CI, 0.41-0.89; high daily dose: adjusted OR 0.33; 95% CI, 0.14-0.73). The reduced risk remained significant for either short or long duration of statin use.

Outcome measurement: Statin use was associated with a reduced risk of COPD exacerbation, with a further risk reduction for statins prescribed more recently or at high doses.

4. Author , place, date of publication: Ingebrigtsen T et al., Denmark, 2014 (Ingebrigtsen T et al., 2014)

Study design: Case control study

Study purpose: statin use in individuals with COPD is associated with a reduced risk of exacerbations.

Participants: 5794 individuals with COPD and a measurement of C reactive protein (CRP) in the Copenhagen General Population Study (2003–2008).

Result: Statin use was associated with reduced odds of exacerbations in crude analysis, OR=0.68 (95% CI 0.51 to 0.91, p=0.01), as well as in multivariable conditional logistic regression analysis, OR=0.67 (0.48 to 0.92, p=0.01). However, in the subgroup with the most severe COPD and without cardiovascular comorbidity, we observed a null association between statin use and exacerbations, OR=1.1 (0.5 to 2.1, p=0.83). Furthermore, statin use was associated with reduced odds of a high CRP, OR=0.69 (0.56 to 0.85, p<0.001), and a high CRP was associated with an increased risk of exacerbations, HR=1.62 (1.35 to 1.94, p<0.001). We estimated the percentage of excess risk of the association of statin use with exacerbations possibly mediated through a reduction of CRP to be 14% (4–51%).

Outcome measurement: Statin use was associated with reduced odds of exacerbations in individuals with COPD from the general population, although this was not apparent in those

with the most severe COPD without cardiovascular comorbidity. Statins may thus only associate with reduced risk of exacerbations in patients with COPD with coexisting cardiovascular disease.

5. Author , place, date of publication: Van Gestel et al, Netherland, 2008

Study design: Retrospective national cohort

Study purpose: The purpose of the study was to examine the association of prior outpatient use of statins and angiotensin converting enzyme (ACE) inhibitors on mortality for subjects ≥ 65 years of age hospitalized with acute COPD exacerbations.

Participants: Among 11,212 subjects with a mean age of 74.0 years, 98% were male, and 12.4% of subjects died within 90-days of hospital presentation. In this cohort, 20.3% of subjects were using statins, 32.0% were using ACE inhibitors or angiotensin II receptor blockers (ARB).

Result: After adjusting for potential confounders, current statin use (odds ratio 0.51, 95% confidence interval 0.40–0.64) and ACE inhibitor/ARB use (0.55, 0.46–0.66) were significantly associated with decreased 90-day mortality.

Outcome measurement: Use of statins and ACE inhibitors prior to admission is associated with decreased mortality in subjects hospitalized with a COPD exacerbation. Randomized controlled trials are needed to examine whether the use of these medications are protective for those patients with COPD exacerbations.

6. Author , place, date of publication: Ishida W, et al., Japan, 2007 (Ishida W. et al., 2007)

Study design: Ecological analysis

Study purpose: To assess effects of statin use on mortality from major causes of death (cardiovascular diseases, COPD, pneumonia etc.)

Participants: COPD deaths in the >65 yrs old population in each of the 47 prefectures of Japan. No control

Result: There were significant negative correlations between statin sales per capita and mortality from cardiovascular diseases ($p < 0.05$). In addition, we found that there was a correlation between statin sales and the decrease in mortality from chronic obstructive pulmonary disease (COPD) ($p < 0.0001$), senility ($p < 0.01$), pneumonia ($p < 0.05$), accidents ($p < 0.05$), or all death causes ($p < 0.05$).

Outcome measurement: These results suggest a broad spectrum of beneficial effects of statins, including reduction of mortality rate of COPD as well as cardiovascular diseases.

7. Author , place, date of publication: Ozyilmaz et al, 2013 (Ozyilmaz E. et al., 2013)

Study design: Prospective cohort

Study purpose: The primary aim of this study was to evaluate the potentially modifiable precipitating factors of frequent severe exacerbations requiring hospital admission in COPD. The secondary aim was to investigate the risk factors of readmission within 2 months following an exacerbation requiring hospitalisation.

Participants: We included 107 COPD patients (85% men). The mean number of severe exacerbations was 1.3 ± 1.7 (per patient/per year), and 37.4% of the patients had frequent severe exacerbations (≥ 2/year).

Result: Multivariate analysis indicated that haematocrit < 41%, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, positive gastro-oesophageal reflux disease symptoms, poor adherence to inhaled therapy/regular outpatient follow-up visits and FEV1 < 50% were independent predictors of frequent severe exacerbations. Readmission rate within 2 months after hospital discharge was 39.3%. The independent risk factors of readmission were poor adherence to inhaled therapy/regular outpatient follow-up visits, serum haematocrit < 41%, and FEV1 < 50%.

Outcome measurement: Chronic obstructive pulmonary disease patients with frequent exacerbations should be carefully assessed for modifiable confounding risk factors regardless of poor lung function to decrease exacerbation frequency and related poor prognosis.

8. Author , place, date of publication: Søyseth et al, Norway, 2007
(Soyeseth V. et al., 2007)

Study design: Retrospective cohort study

Study purpose: To assess the effects of statin on mortality and morbidity with IHD in COPD patient.

Participants: 854 consecutive patients (mean age 70.8 yrs; 51.5% female) with a diagnosis of COPD exacerbation were included in the study

Result: The hazard ratio (HR) for statin users versus statin nonusers was 0.57 (95% confidence interval 0.38-0.87). When subdividing statin users and statin nonusers into groups according to concomitant treatment with inhaled corticosteroids (ICS) the following HRs were found: 0.75 (0.58-0.98) for ICS only; 0.69 (0.36-1.3) for statins only; and 0.39 (0.22-0.67) for the combined treatment with statin and ICS compared with no such treatment.

Outcome measurement: Treatment with statins was associated with improved survival after chronic obstructive pulmonary disease exacerbation, while inhaled corticosteroids appeared to increase the survival benefit associated with statin use.

9. Author , place, date of publication: Rutten, Netherland, 2010 (Rutten F.H. et al. 2010)

Study design: Retrospective cohort study
Study purpose: To assess the long-term effect of beta-blocker use on survival and exacerbations in patients with COPD.
Participants: In total, the study included 2230 patients 45 years and older with an incident or prevalent diagnosis of COPD between 1996 and 2006. The mean (SD) age of the patients

with COPD was 64.8 (11.2) years at the start of the study, and 53% of the patients were male.

Result: The crude and adjusted hazard ratios with Cox regression analysis of beta-blocker use for mortality were 0.70 (95% confidence interval [CI], 0.59-0.84) and 0.68 (95% CI, 0.56-0.83), respectively. The crude and adjusted hazard ratios for exacerbation of COPD were 0.73 (95% CI, 0.63-0.83) and 0.71 (95% CI, 0.60-0.83), respectively. The adjusted hazard ratios with the propensity score methods were even lower. Subgroup analyses revealed that patients with COPD but without overt cardiovascular disease had similar results.

Outcome measurement: Treatment with beta-blockers may reduce the risk of exacerbations and improve survival in patients with COPD, possibly as a result of dual cardiopulmonary protective properties.

10. Author , place, date of publication: Huang C, Taiwan, 2011 (Huang C. et al., 2011)

Study design: Cohort study

Study purpose: The aim of this study was to determine the association between statins and COPD by using the Taiwan National Health Insurance database.

Participants: A total of 6252 newly diagnosed COPD patients (median age, 64 years; 50.3% male) who received statins. Another 12,469 newly diagnosed COPD patients were enrolled as the control group.

Result: During an average of 4.58 (2.36) years' follow-up period, there were 1832 patients who experienced hospitalization for COPD exacerbation (statin vs control = 508 [8.1%] vs 1324 [10.6%]; P = 0.001). Statin use was independently associated with the decreased risk of COPD hospitalization (hazard ratio, 0.66; 95% CI, 0.60–0.74; P < 0.001).

Outcome measurement: Statins were associated with reduced hospitalization due to COPD in patients newly diagnosed with COPD, suggesting a potential beneficial effect of statins in patients with COPD.

11. Author, place, date of publication: Frost et al, USA, 2007 (Frost F. J. et al., 2007)

Study design: A matched cohort and two separate case-control

Study purpose: To assess whether statin users had reduced mortality risks from unchecked immune response to selected infections, including influenza and COPD.

Participants: This study conducted a matched cohort study (n = 76,232) and two separate case-control studies (397 influenza and 207 COPD deaths)

Result: For moderate-dose (>/= 4 mg/d) statin users, this cohort study found statistically significant reduced odds ratios (ORs) of influenza/pneumonia death (OR, 0.60; 95% confidence interval [CI], 0.44 to 0.81) and COPD death (OR, 0.17; 95% CI, 0.07 to 0.42) and similarly reduced survival hazard ratios. Findings were confirmed with the case-control studies. Confounding factors not considered may explain some of the effects observed.

Outcome measurement: This study found a dramatically reduced risk of COPD death and significantly reduced risks of influenza death among moderate-dose statin users.

12. Author, place, date of publication: Short, UK, 2011(Short PM. Et al., 2011)

Study design: Retrospective cohort study

Study purpose: To examine the effect of β blockers in the management of chronic obstructive pulmonary disease (COPD), assessing their effect on mortality, hospital admissions, and exacerbations of COPD when added to established treatment for COPD.

Participants: Population 5977 patients aged >50 years with a diagnosis of COPD.

Result: Compared with controls (given only inhaled therapy with either short acting β agonists or short acting antimuscarinics), the adjusted hazard ratio for all cause mortality was 0.28 (95% CI 0.21 to 0.39) for treatment with inhaled corticosteroid, long acting β agonist, and long acting antimuscarinic plus β blocker versus 0.43 (0.38 to 0.48) without β blocker.

Outcome measurement: β blockers may reduce mortality and COPD exacerbations when added to established inhaled stepwise therapy for COPD, independently of overt cardiovascular disease and cardiac drugs, and without adverse effects on pulmonary function.

13. Author, place, date of publication: Lahousse et al, The Netherland, 2013 (Lahousse L. et al, 2013)

Study design: Prospective population-based cohort

Study purpose: To investigated whether statins were associated with reduced mortality in COPD patients and whether effects differed according to baseline high-sensitivity C-reactive protein (hsCRP) concentration, a marker of systemic inflammation.

Participants: Total 2,708. COPD patients had received at leastone prescription for statins between start and index date

Result: Compared to never use, long-term statin use (>2 years) was associated with a 39% decreased risk of death in COPD patients. Stratified according to the level of systemic inflammation, long-term statin use was associated with a 78% reduced mortality if hsCRP level > 3 mg/L, versus a non significant 21% reduced mortality if hsCRP level ≤ 3 mg/L.

Outcome measurement: Statin use is associated with a beneficial effect on all-cause mortality in COPD, depending on the baseline level of systemic inflammation.

14. Author, place, date of publication: Lawes C, New Zealand, 2012 (Lawes C et al., 2012)

Study design: A national Cohort study

Study purpose: To assess whether statin use is associated with reduced mortality in patients with chronic obstructive pulmonary disease (COPD).

Participants: A total of 1,687 patients (mean age 70.6 years) were followed, including 596 statin users and 1,091 non-users.

Result: There were more men in the statin user group (58.4% vs. 48.5%), and statin users were more likely to have a history of cardiovascular disease (58.6% vs. 25.1%), prescription for frusemide as a proxy for heart failure (47.7% vs. 24.5%) or diabetes (35.4% vs.11.6%) than statin non-users ($p<0.001$). A total of 671 deaths occurred during the follow-up period. After adjustment for age, sex, ethnic group, history of cardiovascular disease, diabetes, and prescription for frusemide, the hazard ratio for statin users vs. statin non-users for all-cause mortality was 0.69 (95% CI 0.58 to 0.84).

Outcome measurement: Statin use is associated with a 30% reduction in all-cause mortality at 3–4 years after first admission for COPD, irrespective of a past history of cardiovascular disease and diabetes.

15. Author, place, date of publication: Bartziokas et al, Greece, 2011 (Bartziokas K. et al., 2011)

Study design: Prospective cohort study

Study purpose: To assess use of statins this is associated with reduced mortality and decreased hospitalizations from COPD.

Participants: These study followed-up prospectively 245 patients admitted to hospital for exacerbations of COPD (ECOPD) with monthly evaluations for one year.

Result: Patients receiving statins presented a lower total number of ECOPD during the 1-year follow up (2.1 ± 2.7 vs. 2.8 ± 3.2 ECOPD/patient respectively, $p = 0.037$). After proper adjustments, the use of statins was associated with a lower risk for ECOPD [HR: 0.656 (95% CI: 0.454-0.946)] and severe ECOPD [HR: 0.608 (95%CI: 0.381-0.972)]. The group of statins presented better improvement in HRQoL at 2, 6 and 12 months ($p < 0.001$).

Outcome measurement: The use of statins in patients hospitalized for ECOPD was associated with a lower risk for subsequent ECOPD and severe ECOPD and improved HRQoL. These data support a possible beneficial role for these agents in COPD.

16. Author, place, date of publication: Huang et al, Chaina, 2011 (Huang C. C. et al., 2011)

Study design: Nationwide population-based prospective cohort

Study purpose: The aim of this study was to determine the association between statins and COPD by using the Taiwan National Health Insurance database.

Participants: A total of 6252 newly diagnosed COPD patients (median age, 64 years; 50.3% male) who received statins for hyperlipidemia treatment were identified from the 1 million sampling cohort dataset. Another 12,469 newly diagnosed COPD patients (median age, 64 years; 50.3% male) who were matched for age, gender, and medication for COPD treatment, except for statin use, were enrolled as the control group.

Result: COPD exacerbation (statin vs control = 508 [8.1%] vs 1324 [10.6%]; P = 0.001). Statin use was independently associated with the decreased risk of COPD hospitalization (hazard rato-0.66, CI-95%, P< 0,001)

Outcome measurement: Taiwanese population, Statin were associated with reduced hospitalization of patients newly diagnosed with COPD.

17. Author, place, date of publication: Ekstrom, Sweeden, 2013 (Ekström M. P. et al., 2013)

Study design: Prospective cohort study

Study purpose: To estimate the time-dependent effects of cardiovascular drugs on survival in oxygen-dependent COPD, accounting for immortal and immeasurable time bias.

Participants: Total participants 2249. Time-dependent effects of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, antiplatelet drugs, β-blockers, and statins on all-cause mortality were measured. Of the 2,249 included patients.

Result: The adjusted time-dependent model was compatible with reduced mortality for antiplatelet drugs (hazard ratio [HR], 0.86; 95% CI, 0.75-0.99; P = 0.030) and trends for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (HR, 0.90; 95% CI, 0.79-1.04; P = 0.166) and statins (HR, 0.86; 95% CI, 0.72-1.03; P = 0.105), whereas β-blockers increased mortality (HR, 1.19; 95% CI, 1.04-1.37; P = 0.010).

Outcome measurement: This study supports that antiplatelet drugs improve survival and β-blockers decrease survival in oxygen-dependent COPD.

18. Author, place, date of publication: Blamoun et al, USA, 2008 (Blamoun A. I. et a., 2008l)

Study design: Retrospective cohort

Study purpose: This study assesses the rate of chronic obstructive pulmonary disease (COPD) exacerbation and intubations in patients taking statins.

Participants: Total 185. New patients admitted with a diagnosis of COPD who had been treated with statins

Result: The statin group had fewer episodes of exacerbation and required intubation fewer times than the subjects not receiving statins ($p < 0.0001$ for both outcomes). Unadjusted odds ratios (OR) for no statin use vs. statin use were 9.54 (95% CI: 4.54-20.02) for exacerbation and 10.47 (CI: 4.56-24.01) for intubation. The OR, adjusted for the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ORa), were 2.35 (CI: 1.01-5.50) for non-statin users exhibiting an exacerbation and 10.36 (CI: 2.77-38.76) for this group requiring intubation, compared with statin users. Similarly, ORa for long-acting beta(2) agonists as a covariate were 3.01 (CI: 1.46-6.10) for exacerbation and 8.89 (CI: 3.67-21.32) for intubation. Time to outcome during the observation period was reduced by statins with the hazard ratio (HR) for exacerbation of 0.19 (CI: 0.06-0.14); HR for statins reducing intubation was 0.14 (95% CI: 0.10-0.30).

Outcome measurement: These data suggest that the use of statins may be associated with lower incidence of both exacerbations and intubations in patients with COPD.

19. Author, place, date of publication: Keddissi JI, et al., USA, 2007 (Keddissi JI et al., 2007)

Study design: Cohort study

Study purpose: To assess the ability of statins to preserve lung function in current and former smokers and to reduce the incidence of respiratory-related urgent care

Participants: n = 215; statin users who were smokers or ex-smokers and had abnormal baseline spirometry (majority with obstructive spirometry findings, but restrictive findings also included). n = 203; non-statin users who were smokers or ex-smokers and had abnormal baseline spirometry (obstruction or restriction)

Result: Statin users had a lower decline in FEV(1) (- 0.005 +/- 0.20 L/yr vs 0.085 +/- 0.17 L/yr, $p < 0.0001$) and FVC (- 0.046 +/- 0.45 L/yr vs 0.135 +/- 0.32 L/yr, $p < 0.0001$) [mean +/- SD]. This difference remained significant irrespective of whether the patient had obstructive (n = 319), or restrictive (n = 99) disease, and regardless of whether the patient continued or stopped smoking. In patients with an obstructive spirometry finding, we found a lower incidence of respiratory-related urgent care in favor of the statin group (0.12 +/- 0.29 patient-years vs 0.19 +/- 0.32/patient-years; $p = 0.02$).

Outcome measurement: In smokers and former smokers, statins are associated with a slower decline in pulmonary function, independent of the underlying lung disease.

20. Author, place, date of publication: van Gestel et al, The Netherland, 2009 (van Gestel YR et al., 2009)

Study design: Prospective cohort

Study purpose: To investigate the association between COPD and total cancer mortality and to determine whether the use of statins, which have been associated with cancer risk in other settings, modified this relationship.

Participants: The study included 3371 patients with peripheral arterial disease who underwent vascular surgery; 1310 (39%) had COPD and the rest did not.

Result: COPD was associated with an increased risk of both lung cancer mortality (hazard ratio (HR) 2.06; 95% CI 1.32 to 3.20) and extrapulmonary cancer mortality (HR 1.43; 95% CI 1.06 to 1.94). The excess risk was mostly driven by patients with moderate and severe

COPD. There was a trend towards a lower risk of cancer mortality among patients with COPD who used statins compared with patients with COPD who did not use statins (HR 0.57; 95% CI 0.32 to 1.01). Interestingly, the risk of extrapulmonary cancer mortality was lower among statin users with COPD (HR 0.49; 95% CI 0.24 to 0.99).

Outcome measurement: Statins were associated with a reduced risk of extrapulmonary cancer mortality in patients with COPD.

21. Author, place, date of publication: G.J. Criner, England, 2014 (G.J. Criner et al., 2014)

Study design: Retrospective study

Study purpose: To assess the efficacy of Simvastatin in preventing exacerbation in moderate to severe COPD.

Participants: A total of 885 participants with COPD were enrolled.

Result: The mean number of exacerbations per person-year was similar in the simvastatin and placebo groups: 1.36±1.61 exacerbations and 1.39±1.73 exacerbations, respectively (P=0.54). The median number of days to the first exacerbation was also similar: 223 days (95% confidence interval [CI], 195 to 275) and 231 days (95% CI, 193 to 303), respectively (P=0.34). The number of nonfatal serious adverse events per person-year was similar, as well: 0.63 events with simvastatin and 0.62 events with placebo. There were 30 deaths in the placebo group and 28 in the simvastatin group (P=0.89).

Outcome measurement: Simvastatin at a daily dose of 40 mg did not affect exacerbation rates or the time to a first exacerbation in patients with COPD who were at high risk for exacerbations.

22. Author, place, date of publication: Lawes et al, Newzeland, 2012 (Lawes CM et al., 2012)

Study design: National prospective cohort study

Study purpose: To assess whether statin use is associated with reduced mortality in patients with chronic obstructive pulmonary disease (COPD).

Participants: A total of 1,687 patients (mean age 70.6 years) were followed, including 596 statin users and 1,091 non-users. There were more men in the statin user group (58.4% vs.

48.5%), and statin users were more likely to have a history of cardiovascular disease (58.6% vs. 25.1%),

Result: A total of 671 deaths occurred during the follow-up period. After adjustment for age, sex, ethnic group, history of cardiovascular disease, diabetes, and prescription for frusemide, the hazard ratio for statin users vs. statin non-users for all-cause mortality was 0.69 (95% CI 0.58 to 0.84).

Outcome measurement: Statin use is associated with a 30% reduction in all-cause mortality at 3-4 years after first admission for COPD, irrespective of a past history of cardiovascular disease and diabetes.

23. Author, place, date of publication: Mancini et al, Cnada, 2006 (Mancini G. B. et al., 2006)

Study design: Population-based retrospective time-matched nested case-control

Study purpose: The purpose of this study was to determine if statins, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) reduce cardiovascular (CV) events and pulmonary morbidity in chronic obstructive pulmonary disease (COPD) patients.

Participants: Total 103,004. Patients were drawn from the Quebec Linked Databases: two distinct COPD cohort.

Result: These drugs reduced both CV and pulmonary outcomes, with the largest benefits occurring with the combination of statins and either ACE inhibitors or ARBs. This combination was associated with a reduction in COPD hospitalization (risk ratio [RR] 0.66, 95% confidence interval [CI] 0.51 to 0.85) and total mortality (RR 0.42, 95% CI 0.33 to 0.52) not only in the high CV risk cohort but also in the low CV risk cohort (RR 0.77, 95% CI 0.67 to 0.87, and RR 0.36, 95% CI 0.28 to 0.45, respectively). The combination also reduced MI in the high CV risk cohort (RR 0.39, 95% CI 0.31 to 0.49). Benefits were similar when steroid users were included.

Outcome measurement: These agents may have dual cardiopulmonary protective properties, thereby substantially altering prognosis of patients with COPD. These findings need confirmation in randomized clinical trials.

Chapter seven: Discussion

Discussion:

The aim of this study is to analyze the effect of statin in the mortality and exacerbation of COPD to define the consequences for future studies. For this purpose different studies were selected which include beneficial effect of Statin on different clinical endpoint such as, decline in lung function, several respiratory problem and cardiovascular comorbidities , benefit of statin with inhaled steroid, COPD exacerbation intubation, exacerbation of COPD, All-cause mortality, mortality due to COPD and also included exercise capacity.

The study was designed according to the following concept. They were introduction to COPD, management of COPD, current mortality and exacerbation rate due to COPD, mechanism of action of Statin, association between statin and COPD. In introduction part the definition, pathogenesis, sign and symptoms, risk factors, classification of COPD had been included. In the management part this study showed the current diagnosis and treatment procedure of COPD. In third part, death rate and prevalence rate was included based on ethnic origin, sex, and age. In Statin part the definition, classification, mechanism of action, adverse effects of Statin were involved and co-relation was brought by associating pathologic condition with the pleotropic effects of Statin. The most common characteristic features of COPD are reduction in lung capacity, parenchymal destruction, and peripheral airway obstruction. Cardiovascular comorbidities are also mostly seen in COPD patients. In a large cohort study, a significant higher rate of coronary artery disease in COPD patient then non-COPD one (33.6% vs 27.1%) had been seen. In case of mild to moderate airways obstruction, 28% elevation in cardiovascular mortality was associated with 10% reduction of FEV1 (forced expiratory volume) in one second. Anti-inflammatory, immunomodulatory and antothrombotic effects gives Statin their protective and pleotropic effect. Inflammation is the most common problem in COPD patient. Here statin plays an important role by its anti-inflammatory effect by decreasing the inflammation marker for example CRP (C-reactive protein and IL-6 (interleukin-6)) in COPD patient. In addition statin also beneficial in regulating the balance of TH1/TH2 which are responsible in producing inflammation marker. Statin had also protective effect on the improvement of pulmonary hypertension as

it can lower the PAWP (pulmonary arterial wedge pressure) and mPAP (mean pulmonary arterial pressure). Thus they were able to reduce risk of exacerbation and increase survival.

In the included study, the outcome of most of the studies showed positive effect of statin on reducing mortality and exacerbation. Among them Soyeth et al. observed that Statin may reduce all-cause mortality by decreasing the inflammation. Because most of the COPD patient had unrecognized ischemic heart disease which is associated with pulmonary inflammation. In another study Keddissi et al. find that statin use may improve in declined lung function and also lower incidence of hospitalization showed that statin had exact disease modifying effect on COPD patient but only one article observed that statin mainly simvastatin had no significant effect in the reduction of COPD exacerbations which was inconsistent with the findings.

This systemic comprehensive study evaluated whether statin use is associated in the treatment of COPD by the following ways. First of all, this study mainly focused on the use of statin in COPD patient and its beneficial effect in reducing mortality and exacerbation due to COPD. Secondly, it only includes large scale studies for evaluation which involved minimum of 100 participants. Most of them included more than 1,000 participants. Finally, to make the review more effective, it took information from not only case control studies but also from some data based review articles. This review article conducted that the statin use may provide beneficial effect in reducing COPD mortality and all-cause mortality by its pleotropic effects. Besides that it also showed that statin use may decrease the risk of COPD exacerbations.

Chapter eight: Conclusion

In precise, this review represents an alternative treatment for COPD patients which are Statins. The compilation of different papers show positive effect of Statins in reducing the lung function decline, exacerbation, and all cause mortality rates and also improves the exercise capacity. Statins ani-inflammatory effect allows it to target airway inflammation directly which is the leading problem in COPD patients. Thus it can be concluded that, treatment with Statins may bring beneficial effect in COPD patent. The dose, dosage form and types of Statins for its pharmacologic effect have not been confirmed yet. Further investigations regarding this issue are required.

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