Diplomarbeit

The meaning of β-receptor antagonists in the treatment of chronic obstructive pulmonary disease (COPD)

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Graz, am 21.08.2017 *Sarah Likowetz eh.*

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Abbreviations

ACEI	Angiotensin-converting-enzyme inhibitor
ARB	Angiotensin receptor blocker
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAT	COPD Assessment Test
CCB	Calcium Channel Blocker
COPD	chronic obstructive pulmonary disease
ER	Emergency Room
ESC	European Society of Cardiology
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
HF	Heart Failure
HRLD	Heart rate limiting drugs
i.v.	intravenous
ICS	inhaled corticosteroids
ICU	Intensive Care Unit
ISA	Intrinsic sympathomimetic activity
LABA	long-acting beta-agonist
LAMA	long-acting muscarinergic antagonist
mmHg	Millimetre of mercury
mMRC	Modified British Medical Research Council
NRT	Nicotine replacement therapy
NYHA	New York Heart Association
p.o.	per os
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PDE4-inhibitor	phosphodiesterase type 4 inhibitor
SABA	short-acting beta-agonist
SAMA	short-acting muscarinergic antagonist
TNF-α	tumor necrosis factor α
VC	Vital Capacity

Abstract

Background Chronic obstructive pulmonary disease (COPD) is very common among elderly patients and often coexists with heart failure or other cardiovascular diseases. Those concomitant diseases often require treatment with beta-blockers, but traditionally they are contraindicated in patients with COPD, although they are proven to have beneficial effect on mortality and morbidity in patients with cardiovascular diseases. Since evidence is increasing that those drugs might be safe in those patients, this work aims to provide information about COPD and beta-blockers as well as the current perspective on this topic.

Methods and Results This work is a literature research paper. Literature about the disease and the drugs has been reviewed in order to provide well-grounded information about those central topics. Furthermore, several studies were reviewed to give an outlook on the current perspective and to analyze the meaning of beta-blocker in the treatment of COPD.

Conclusion Most of the studies are suggesting that the use of beta-blockers in patients with COPD and heart failure is safe and has beneficial effect on both conditions. Although many studies have several limitations, beta-blockers should be prescribed to those patients because of the consistency of evidence proving them to be safe and that they improve mortality and morbidity in those patients.

Aim of study

Chronic obstructive pulmonary disease (COPD) is a very common disease, especially among elderly patients, and patients with this condition are prone to cardiovascular diseases. (1) Patients with COPD are three times more likely to have concomitant heart failure, twice as likely to have coronary artery disease and have a higher prevalence of diabetes and arterial hypertension. (2) The high prevalence of patients with COPD developing heart failure and vice versa, could be due to shared risk factors. The most important risk factors are older age, cigarette smoking and systemic inflammation. (3) Whereas especially the two later risk factors are contributing to an accelerated progression of atherosclerosis, ischemic heart disease and COPD. (4) (2)

The coexistence of COPD and heart failure often leads to an underuse of beta-blocker, because of the possible pulmonary adverse effects that those drugs can produce. (5) This happens even though it is known that beta-blockers can reduce mortality of heart failure patients by 35%. (6) Thus, studies are increasing assessing this topic to examine the safety and efficacy of beta-blockers in patients with COPD and concomitant heart failure or other cardiovascular disease, especially since evidence is increasing that COPD is associated with worse clinical outcomes in heart failure patients. (7) Furthermore, either COPD or heart failure are underdiagnosed when the other condition is already present in a patient. (5) This can happen due to symptoms that are shared by both conditions, such as exertional breathlessness and nocturnal cough, as well as that COPD can obscure echocardiographic and radiological evidence of heart failure. (8)

With those entire controversial hypothesis this work is aimed to provide information on COPD and beta-blockers for a better understanding of these topics. Furthermore, several studies were reviewed, which examined the safety of beta-blockers and their potential beneficial effect on patients with COPD and concomitant heart failure or other cardiovascular diseases to show what the current perspective on this topic is.

1. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is characterized by airflow limitation that is not fully reversible and is progressive. The term COPD encompasses emphysema, chronic bronchitis and small airways disease. They can present together but they have different locations and pathophysiological mechanisms. (9)

In the United States COPD is the 4th leading cause of death. It is not only in the United States an important disease, but worldwide. According to the GOLD-Initiative it is estimated that COPD will rise from the 6th leading cause of death to the 3rd leading cause worldwide by the year 2020. (9)

One major problem with COPD is that it is often not diagnosed early enough because the patients think their respiratory problems are just related to normal aging or their smoking habits. (10) Thus, COPD is often underdiagnosed, despite the fact that it is a relatively easy diagnosis to make.

Initially the treatment of COPD was only considered at severe, end stage of the disease. Now it is known that an early diagnosis and treatment can significantly improve the well-being of the patients and reduce their symptoms. (10) However, it has to be said that the current therapies and treatments of the COPD are not able to cure this disease.

1.1 Definitions

As said before the term COPD is not a single disease but a group of diseases. The diseases it encompasses are chronic bronchitis, small airways disease and emphysema. (10)

Chronic bronchitis is clinically defined as existence of a productive, chronic cough on most days for 3 months during two successive years (11), although it has to be proven that there are no other causes of chronic cough, such as tuberculosis or bronchiectasis.

Small airways disease, or obstructive bronchiolitis, is associated with tobacco smoke and one of the first changes in patients, who are smokers. However, it is not easy to detect it. The obstructive bronchiolitis is a result from inflammation, squamous metaplasia and or fibrosis, which are limited to the small airways with a diameter less than 2 mm. (10)

Emphysema is an irreversible, permanent enlargement of the airspaces distal to the terminal bronchioles due to the destruction of the walls of these bronchioles. (12) This destruction is not accompanied by fibrosis, therefore the emphysema is not that solid and so it is rather common for those patients to develop a spontaneous pneumothorax.

1.2 Aetiology and Risk Factors

There are many factors that may have an important role in the development of COPD. In the industrialised world, the most important factor is tobacco smoking, but even in the developing world, smoking is gaining more and more importance. (9) Nevertheless, there are also other factors, which should not be neglected, like genetic factors, environment, air pollution and many more. Most of them will be explained in more detail in the further course of this chapter.

- Cigarette Smoking

One of the most important aetiological factors in COPD is cigarette smoking. The dose of cigarette smoke is essential to get to know how sever the consequences are going to be. This dose depends on different factors, like age of starting smoking, depth of inhalation and total number of cigarettes smoked (e.g. one 'pack year' is defined as smoking 20 cigarettes per day for one year). (10) However, about 15-20% of patients with COPD are lifelong non-smokers and on the other side there are about the same percentage heavy smokers who don not even have any loss of lung function. (12) There is also a higher risk in airflow limitation in non-smoking patients who were passive smoking, especially during their childhood. This is associated with an increased frequency of respiratory infections in the first three years of life, which can lead to airflow limitation in later life.

- Air pollution

Today it is still discussed how long term exposure to outdoor air pollution is correlated with the COPD, because the correlation with lower FEV_1 and airway limitation is not clear. (9) However, it is thought the air pollution may affect the growth of lung function in childhood, which may have an importance on the development of COPD in the later life. (10) A more important factor is the indoor air pollution deduced from burning of fuels in fires and stoves. This is particularly important in developing countries. (10)

- Gender

Until today the question, if gender is a risk for COPD, is unresolved. Historical studies showed that men had a higher risk of developing COPD and a higher mortality risk. (10) More recent studies show that now the risk is nearly equal for man and women, but this may be a result of the changing patterns in tobacco smokers. (10)

- Chronic Bronchopulmonary Infection

It is thought that chronic infections in the adulthood are a risk factor for the development and progression of COPD. (9) In the childhood such chronic infections are thought to predispose those children for a later development of COPD. But it has to be said that this assumption is not quite accepted due to the fact that there are not enough long-time studies on this subject. (9)

Although these are common thoughts it has to be discussed in which way the infections have an effect on the decline in forced expiratory volume in 1 second (FEV_1). Moreover, there have to be further studies so show how important the chronic infections really are for the development and progression of COPD.

- Genetic Factor

Smoking is the most important factor for developing a COPD, but it is not clear why there is such a great variability in the development of COPD among the tobacco smoking patients. (10) This leads to the assumption that there have to be genetic variations, which influence the development of COPD.

However, until today it is only safe to say that the alpha-1-antitrypsin is one of these genetic variations. (10) Although there have to be more variations, this is the only one that has been found and proven relevant for this disease.

1.3 Pathology

Since COPD is not a single disease but a combination of a few, it is clear that the pathologic changes are located in different sections of the lung. The main places where these changes take place are the central and peripheral airways, the pulmonary vasculature and the lung parenchyma. (13)

In the following text of this chapter the pathologic changes will be explained more detailed, but the pathogenesis will be discussed in a later chapter.

- Central Airways

The changes in these airways lead over a chronic hypersecretion of mucus to chronic bronchitis. (13) This mucus is produced by the mucus glands and the goblet cells. The mucus glands are seromucous glands that are located in the mucous membrane of the lamina propria throughout the central airways (e.g. bronchial, laryngeal, nasal and tracheal glands). (12) The goblet cells are endoepithelial, exocrine cells, which are scattered in the ciliated epithelium of the airways.

The amount of the goblet cells is increased within a chronic bronchitis and they are also expanding throughout the bronchial system. (10) These factors benefit the production of mucus in the central airways as well as in the peripheral airways and therefore lead to the hypersecretion of mucus. A great problem here is that the ciliated epithelium in the more peripheral airways is not present, so that the mucus cannot get out of the peripheral airways that easy. (14)

In smokers, the ciliated epithelium is transformed into a more resistant squamous epithelium. This metaplasia leads to a decreased function of the mucociliary escalator and it has to be seen as a pre-cancerosis. (9)

Additionally we have also a bronchial wall inflammation. Especially neutrophils are present in the mucus glands. There are also macrophages and the CD8 suppressor T-lymphocyte subset is predominant, which increases the CD8/4 ratio. (10) In the bronchial walls, an increased amount of eosinophils is found during a mild exacerbation, although they may not be this dominant during severe exacerbations.

In the clinical picture of the COPD hypertrophy of the non-striated muscles can be present as well as bronchial hyperactivity as it is seen in patients with asthma. (13)

- Peripheral airways

The first pathologic changes affect the small airways and they are the main reason for airflow obstruction in COPD. (10) Although these changes are the earliest, they are often not recognized for they can develop without any clinical relevant symptoms or changes in the spirometry. (9) In the clinical setting this specific inflammatory changes are described as chronic bronchiolitis.

The inflammatory change in the small airways, is similar to the changes in the central airways, for there is also an increase of the CD8/4 ratio and the CD8+ cells. (10) Within the small airways we have lot of change of cellular components. As it was described earlier there are now more mucus producing cells, a hypertrophy of the non-striated muscles and bronchial hyperactivity. Also, the surfactant producing Clara cells are replaced by mucus producing cells and infiltrating mononuclear cells. (10)

All these changes lead to an obstruction of the airways. The loss of surfactant leads to a decrease in the surface tension of the alveoli, which makes them more prone to collapse and leads to an obstruction of the airways. (10)

In the further progress of this disease, there is more and more structural remodelling due to all the pathologic changes, which were already described. This remodelling mostly contents of an increase of collagen tissue and scarring of the bronchioles. (12)

- Pulmonary vasculature

The changes that take place in the pulmonary vessels are also one of the earliest, like the changes in the small airways.

The first changes affect the intima of pulmonary arteries, which is becoming thicker. (12) The other changes that follow these thickening are similar to the changes, which take place in peripheral airways. Thus, there is also an increase of non-striated muscles and an infiltration with inflammatory cells. These are the same cells, which are also involved in the inflammatory changes of the peripheral airways. (12)

As the disease progresses the changes are getting worse and the thickening of the vessel walls is also increasing more and more. Furthermore, hypoxic vasoconstriction occurs due to the chronic alveolar hypoxia. (9)

When these changes are dominant enough it comes to more severe changes, which not only affect the lung and its vasculature but the cardiovascular system. Thus, the patients develop pulmonary hypertension, and a right ventricular hypertrophy and dilatation. (10)

- Lung parenchyma

Emphysema of the lung is defined as “irreversible enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls without obvious fibrosis”. (14) There are four types of emphysema: centriacinar, panacinar, paraseptal and irregular emphysema. (14) However, for the COPD only the centriacinar and the panacinar emphysema are relevant.

The centriacinar emphysema is the most common type of emphysema in patients with a tobacco related COPD. (14) This type of emphysema is characterized by an airspace enlargement in the proximal acinus, whereas the distal parts of the acinus are still normal. (14) The panacinar emphysema is not that often in patients with COPD as the centriacinar, but more common than the other two types. This emphysema is mainly associated with alpha1-antytrypsin deficiency, although it can also be found in patients with no genetically transformation of this gene. (14) This emphysema, like the prefix “pan” indicates, affects the whole acinus. Thus, there is an airspace enlargement throughout the whole acinus. However, not only is the difference between the expansions of the emphysemas a characteristic by which they get distinguished, they also get distinguished for their predominant locations in the lung. Thus, the centriacinar emphysema is mainly located in the upper lobes and the panacinar is located at the lung bases and the anterior margins. (14)

Both types can appear together or alone. Albeit the centriacinar emphysema is tobacco associated, smokers can have both types.

Although the other two forms may not be common in patients with COPD, they should also be explained.

The paraseptal emphysema is the contrary of the centriacinar emphysema, for it is characterized by an airspace enlargement in the distal acinus whereas the proximal acinus is not affected. (14) This emphysema is mainly located next to the pleura, pulmonary vessels, along the lobular connective tissue septa and at the margins of the lobes. (14) This type of emphysema has mostly no clinical relevance, except for one thing. It probably is the main reason for spontaneous pneumothorax in young patients. (14)

The last one is the irregular emphysema. This emphysema does not describe a specific location throughout the acinus like the other ones do, but it describes emphysematous

changes around the margins of a scar. (14) Therefore, it is far more common than the others are because such scars can develop from a previous inflammatory process. However, this emphysema is clinically asymptomatic and therefore insignificant. (14)

The inflammatory cells, which are involved here are the same as the ones, which were already discussed in the chapters about small airways and pulmonary vasculature.

1.4 Pathogenesis

The abnormal inflammatory response to inhaled gases or particles seems to be the central point of the pathogenesis. Thus, it is comprehensible that there are many pathogenic mechanism involved in these inflammatory processes, such as airway inflammation, proteinase/antiproteinase imbalance and oxidant/antioxidant imbalance.

- Airway inflammation

As it was said in the former passage, the inflammatory process is a response to inhaled particles and gases. Therefore, it is easy to understand that in tobacco smokers inflammation is present throughout the central and peripheral airways. Although an inflammatory response would seem normal due to their exposure to noxious particles these responses are abnormally amplified. (12) This amplified reaction is the reason for destruction of lung tissue and the diminution of the repair mechanisms.

These inflammatory processes are accompanied by inflammatory cells, such as macrophages and CD8 T-cells. (12) It seems that the CD8 cells may be part of apoptosis and destruction of the walls in the peripheral airways, for they release perforins and TNF-α. (10) The inflammatory cells are not alone, there also several inflammatory mediators involved. Some studies show that tobacco smokers who quit smoking have an improvement of pulmonary function. (10) On the other hand a few studies show that the inflammatory process persisted even after the patients had quit smoking (10). It is thought now that after these inflammatory responses are established they cannot be reversed by quitting tobacco smoke.

- Proteinase/antiproteinase imbalance

Due to some studies it is known that there is a correlation between the α1-antitrypsin deficiency and an early development of emphysema. (13) Thus, they developed a hypothesis. This hypothesis says that in a healthy person there is a balance between proteinase and antiproteinase. (12) So normally when inflammatory cells immigrate into

the lung to fight infection or toxic substances, as it appears after tobacco smoking, they release proteolytic enzymes, which would also damage the human tissue. (12) But this does not happen in a healthy human being due to inhibitors, which inactivate these proteolytic enzymes so they can't do any harm to the human. (12)

However, if there is an imbalance between the antiproteinase and the proteinase, because of an excessive activation of those proteolytic enzymes, as it happens during smoking a cigarette, or because there is an antiproteinase deficiency, the proteinase is predominant and therefore damages the connective tissue in alveolar walls. (12) This damage of the tissue leads then to an emphysema.

This is just a simplified theory for there are many more antiproteinases and proteinases that have an important role. One of the most important antiproteinase is α1-antitrypsin, which is synthesized in the liver. (12)

- Oxidant/Antioxidant Imbalance

Patients with COPD have an increased oxidative stress due to shift in the ratio of oxidants to antioxidants in favour of the oxidants. (9)

It is known that tobacco smoke increases the oxidative stress because it produces more oxidants than the antioxidants in the lung can handle. (13) This excess of oxidants is produced by the inflammatory processes, which are induced by tobacco smoke. Because of the imbalance between the oxidants and antioxidants the lung tissue gets damaged. (12) Furthermore, it is thought that the tobacco smoke does not only increase the oxidants but also have a negative effect on the antioxidants, thus the ratio shifts even more in favour of the oxidants. (12)

1.5 Pathophysiology

This chapter is mainly about the airflow limitation and hyperinflation; for the other topics have sufficiently been discussed in the former chapters.

Patients with COPD show a loss of lung elasticity and an increased resistance, which lead to a decrease in FEV_1.

In the beginning of this disease, when the patients are mostly asymptomatic, there is a change in closing volume. The closing volume is defined as the volume at which the small airways are collapsing during expiration (15). Normally this closing volume is not

significant and only increases in old age. However, in young adults, who are smoking, this closing volume is increased, as well as the closing capacity. (15) As soon as the closing capacity is greater than the functional residual capacity (FRC) the small airways are collapsing during expiration. (15) This collapsing of the small airways can increase the risk of hypoxemia and during exhalation, it can happen that there is air trapping and atelectasis, due to the collapsed airways. The air trapping leads to a dynamic hyperinflation of the lung. (15)

Dynamic hyperinflation especially causes hypercapnia during exercise and is also an important factor for the hypoventilation. (9) These clinical features do not only occur due to the dynamic hyperinflation, but in correlation with other changes that are typical for patients with COPD. Another thing is the involvement of dynamic hyperinflation in correlation with excessive recruitment of respiratory muscles in cardiac dysfunction. (10) Thus, the venous return is negatively affected and leads to a decrease in the right ventricular preload. (10) The impairment of venous return causes a congestion of the venous blood, which leads to peripheral oedema and congestive hepatopathy. Furthermore, the decrease of the preload causes tachycardia because the heart tries to pump the same blood volume as before. Not only the right heart is affected but also the left heart, because of the congestion of the venous blood the left-ventricular afterload increases, which causes hypertrophy of the left heart for it needs more force to pump the blood out against the increased pressure of the afterload. (10)

As the disease progresses the hyperinflation in correlations with emphysema and pathologic changes in the vasculature stresses the pulmonary circulation, which leads to pulmonary hypertension. (9) However, more often this pulmonary hypertension develops not only because of the COPD. It is more common that there are also cardiovascular diseases existing, which in correlation with COPD lead to pulmonary hypertension.

1.6 Systemic effects and comorbidities

Patients with COPD often show comorbidities, especially comorbid diseases of the heart and the cardiovascular system. Most of the patients do not only have one concomitant disease but multiple comorbidities, which have an important effect on morbidity and mortality of these patients. On the other side, COPD can lead to systemic effects, which have also an important relevance in morbidity and mortality of the patients.

The most common systemic effect of COPD is weight loss and loss of muscle mass, which seems to be a result of systemic inflammation. (9) Another important effect of COPD is osteoporosis. Risk factors for osteoporosis are common in those patients and include tobacco smoking, aging, vitamin D deficiency, systemic corticoid use, impaired physical activity and hypogonadism. (12) Osteoporosis in COPD patients increases the prevalence of vertebral fractures to 20-30%. (12) This consequence leads to increased kyphosis and impaired lung function.

Another important effect of COPD, is lung cancer. In patients with COPD lung cancer is three to four times more common than in patients without COPD. (12) Interestingly the smoking history has no important effect on the risk of developing lung cancer, but COPD itself is associated with small cell or squamous cell carcinoma and not with the adenocarcinoma of the lung. (10)

The most important comorbidities related to COPD are cardiovascular diseases, for COPD is a risk factor for ischemic heart disease, atherosclerosis, cerebrovascular happenings and sudden cardiac death. (10) COPD can also lead to pulmonary hypertension and cor pulmonale as it has been said before.

1.7 Clinical features

This chapter is about the clinical presentation and evaluation of COPD. Additionally the different methods of investigation and the severity classification will be discussed in this chapter.

- Clinical signs and anamnesis

The most characteristically symptoms are breathlessness and cough, although the cough does not have to be productive, for some patients just experience unproductive cough. (11) Cough is one of the first symptoms to appear in patients with COPD, but most of the patients ignore it and especially tobacco smokers do not think that there could be a correlation between their smoking habits and their cough. (12) The most common reason for patients with COPD to seek medical help is the breathlessness. In the beginning of the disease it occurs when patients climb stairs or hurry at ground level. (10) As the disease proceeds the breathlessness gets worse and patients experience dyspnoea in their everyday life, even when they are just dressing themselves. (10) Although the symptom of dyspnoea is a very common reason for patients to seek help, they mostly do this when the disease has

been progressing over months or even years. Therefore, it is very important to ask the patient exactly when the first symptoms of cough and breathlessness appeared, if there has been sputum and during which activities they experience the symptom of breathlessness. (9)

This information is an important part of the anamnesis. In order to collect a detailed medical history of the patient it has to include also the exposure history, such as occupations in the past and now and the possible exposure to noxious particles. There should also be an exact anamnesis about the smoking history, as for how long and how many cigarettes, the family history and former respiratory diseases. (13)

Then there are a lot more things that can be seen during an examination of the patient, and they may point out some things the patient may have forgotten to tell or even did not want to.

First, during the general examination tar stained fingers hint at a long-term smoking history. If the disease has progressed, it can be seen that the respiratory rate may be increased and the patient acquired a relieving posture, so he or she can breathe more easily. (11) Cyanosis may also be present, although it is not a distinct sign that indicates COPD, but it should be considered as sign of a severe respiratory problem. In advanced disease the patient can show weight loss or even signs of cachexia. (12) Furthermore, the chest gets more and more the typical barrel shape and the diaphragm flattens, which is the reason why the ribs get pulled in during inspiration, this is also called the Hoover's sign. (12)

- Investigations and Classifications

A very common and important test is the spirometry, although it may not show any abnormalities at an early stage of the diseases. (11) As the disease progresses the abnormalities start to show and thanks to the well-defined range of normal measurements it is an important diagnostic criterion. Thus, a low FEV_1 with an FEV_1/VC ratio are strong indicators for COPD. (12)

These spirometric measurements are also part of several classifications. The most common of these is the GOLD classification. This one uses not only the spirometric measurements but also the risk of exacerbations and symptoms to classify patients with COPD and to work out the best possible treatment. (16) To measure the symptoms objectively the patients are given standardised questionnaires, like the COPD Assessment Test (CAT) or

the Modified British Medical Research Council (mMRC) breathlessness scale. (16) After the evaluation of all these points, it has to be looked up which group the patient fits in. The different groups are shown in Table 1 and the spirometric classification in Table 2.

GOLD Stages	Severity	Symptoms	Spirometry
0	risk group	chronic cough, sputum production	normal spirometry
1	mild	with or without chronic cough and sputum production	$FEV_1 \geq 80\%$ predicted, $FEV_1/VC < 70\%$
2	moderate	with or without chronic cough and sputum production	$50\% \leq FEV_1 < 80\%$ predicted, $FEV_1/VC < 70\%$
3	severe	with or without chronic cough and sputum production	$30\% \leq FEV_1 < 50\%$ predicted, $FEV_1/VC < 70\%$
4	very severe	with or without chronic cough and sputum production	$FEV_1 < 30\%$ predicted, $FEV_1/VC < 70\%$ or $FEV_1 < 50\%$ and chronic respiratory failure or right-ventricular failure

Table 1: GOLD classification of COPD according to spirometry and symptoms (16)

Patient	Characteristics	Spirometric Classification	Exacerbations per year	mMRC	CAT
A	Low Risk, Less Symptoms	GOLD 1-2	≤ 1	0 - 1	< 10
B	Low Risk, More Symptoms	GOLD 1-2	≤ 1	≥ 2	≥ 10
C	High Risk, Less Symptoms	GOLD 3-4	≥ 2	0 - 1	< 10
D	High Risk, More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

Table 2: Patients classification according to GOLD guidelines (16)

Since the new GOLD classification and guidelines do not only include spirometric measurements but also symptoms, exacerbation and comorbidities, it is even more important for the clinical evaluation of patients with COPD. (16) Although there are other tests that can be used for diagnosing COPD, the evaluations according to GOLD are mostly enough so the other test can be used to get more detailed information about the severity of the disease. The most used other tests are arterial blood gases, reversibility testing and lung volumes. (12) The reversibility testing is important to get to know if the patient also suffers from an underlying asthma. The measurement of lung volumes is not always necessary, but it can help to estimate the degree of air trapping and hyperinflation. Arterial blood gases show the degree of hypoxemia and hypercapnia. In addition to the blood gases, a complete haemogram is important to trace a possible erythrocythemia, which shows a clinical important hypoxemia, or a polycythaemia. (13) Although before diagnosing a polycythaemia other reasons for the decrease of plasma volume, like dehydration, should be excluded.

At least imaging techniques can be used in the diagnosis of COPD. In order to do that a plain chest radiography has to be taken. (12) This may show existing emphysemas and changes of the anatomical structure of the chest, like flattening of the diaphragm. For a better assessment of the emphysemas, the patient can also undergo a computed tomography, although that is not necessary in every patient. (12)

1.8 Management of the chronic obstructive pulmonary disease

COPD is not a curable disease, but with the right treatment the health status and quality of life of patients with COPD can be improved. The treatment needs an interdisciplinary approach, which includes smoking cessation, medications, pulmonary rehabilitation and surgical interventions. (12) The main goals of the therapy according to the GOLD guidelines are a reducing of symptoms and a reducing of the risk of acute exacerbations and progressing of the disease. (16)

Smoking cessation can reduce the risk of disease progression and the decline in lung function, although it cannot undo the already inflicted damage. (9) It is not easy to encourage the patient to quit smoking, but direct inquiry and advice can lead to 10-20% cessation rate at 1 year. (10) The "five As" given from the GOLD guidelines can be very helpful to encourage the patient to give up smoking. The "five As" are: Ask, Advise, Assess, Assist and Arrange. (16)

If the patient is willing to quit smoking it can be helpful and even increase the chance of success by adding medications, such as bupropion, varenicline or nicotine replacement therapy (NRT). (10) In the United States it is recommended to use medication to assist the patient with smoking cessation. (10) Smoking cessation should be a goal for every patient with COPD regardless of the diseases severity.

Pharmacological interventions include bronchodilators, corticosteroids, oxygen therapy and other agents, such as mucolytics, antioxidants and α1-antitrypsin replacement therapy. Although these interventions can improve health status and reduce symptoms, they do not alter disease progression, like smoking cessation can.

The therapy of COPD starts with bronchodilators. They are the mainstay therapy and are given to every patient with COPD no matter how sever the disease already is. (10) Primarily bronchodilators are used for symptomatic treatment, but they also improve exercise capacity by reducing air trapping and hyperinflation. Furthermore, they can improve airflow and inspiratory capacity and reduce the frequency of acute exacerbations. (10) Although they show a lot improvement, the FEV_1 does not necessarily improve. Inhaled bronchodilators are preferred for they have far less adverse effects than the systemic administered ones.

Therapy starts with short-acting bronchodilators, such as short-acting β_2-agonists (SABA), short-acting muscarinic antagonists (SAMA) and theophylline, for symptomatic treatment. (10) These drugs can be given in combination to improve their positive effects or in patients with persistent symptomatic. There are a few factors that can influence the choice on which drugs are given to a patient. The main factors are the availability of the drug, the costs and patient preference.

Beta$_2$-agonist bronchodilators cause a smooth muscle relaxation, especially on the smooth airway muscles. (17) Although they are specific for β_2-receptors, they show a minimal binding to β_1-receptors, which explains the variety of adverse effects. The most common side effects are tachycardia, hypertension, electrocardiographic changes, palpitations, cardiac symptoms, gastro intestinal upset, hypokalaemia and tremor. (17) The toxicity of short-acting β_2-agonists is greater than with muscarinic antagonists, for they have more systemic effects.

Long-acting β_2-agonists (LABA) lead to an improved lung function and decrease in respiratory symptoms, if they are used regularly. (10) Although the regular use has a lot of benefits, there is the possibility of tachyphylaxis. In addition β_2-agonists lead to a down-regulation of β_2-receptors, which can be a serious problem in the treatment of an acute exacerbation. (10)

Muscarinic antagonists blockade, as the name indicates, the muscarinic-receptors of the bronchial muscles, which causes them to relax. (17) Although those agents bind with all muscarinic receptors and therefore would also have a variety of side effects, their binding with the receptors that are not on the bronchial muscles does not last long enough to produce severe side effects. (17) Adverse effects are very uncommon, but there can be hypertension, constipation, urinary retention, skin rashes and headache. The most common side effect is a dry mouth.

Ipratropium bromide is a short-acting muscarinic antagonist, which is similar to short-acting β_2-agonists. (10) It primarily leads to a decrease in symptoms, an increase in FEV_1 and improvement of health status. Tiotropium is a long-acting muscarinic antagonists (LAMA) with an once a day dosing, because its effect lasts more than 24 hours. (18) According to a few studies tiotropium is more effective than ipratropium bromide especially in reference of improving lung function, symptoms and quality of life and

reducing the risk of acute exacerbations. (10) Tiotropium is also a better bronchodilator and improves dyspnoea more effective than salmeterol, a long-acting β_2-agonist.

A combination of β_2-agonists and anticholinergics is proven to improve health status more effective and to provide a bronchodilation, which is more efficient than one of these drugs alone. (10) The use of this combination should be considered in patients with persistent symptoms and dyspnoea. They can be given simultaneously on a regular scheduled basis or on an as-needed basis. Advantage of the combination is that they are better tolerated than an increased dose of one of them and that their beneficial effects add up. (10)

Theophylline belongs to the group of methylxanthines. (17) It is only a modest bronchodilator, but it decreases respiratory symptoms and significantly improves FEV_1, forced vital capacity (FVC), PaO_2 and $PaCO_2$. (18) This agent has also some additional effects like mild diuretic properties, anti-inflammatory effects and a reducing of diaphragm fatigue. (10) Although all these benefits seem to make it a good bronchodilator, it is only used as a third line drug, because it's serum concentration has to be monitored closely for its toxic-therapeutic ratio is very low and there are many adverse effects. (10) The most common side effects are nausea, vomiting, abdominal pain, headache, muscle cramps, seizures, sleep disorder and arrhythmias. Therefore, the serum levels should be between 5 and 20 µg/ml at maximum. (17)

For the therapy of COPD corticosteroids can also be used, but they show less benefit than in the treatment of asthma. Although the benefit of inhaled corticosteroids (ICS) is very low, they can reduce the frequency of acute exacerbations, especially in patient with an FEV_1< 50% predicted and who have frequent exacerbations. (10) Long-term use of corticosteroids is not recommended, because of the many adverse effects, like candidiasis, osteoporosis and cataract. (17) Oral corticosteroids can be helpful when treating an exacerbation, because it increases the rate of recovery. (10) As mentioned before corticosteroids have few benefits, but they should not be used for long-term therapy, especially not the oral ones, because of the systemic adverse effects.

Another pharmaceutical treatment is the usage of oxygen. (10) The oxygen therapy should improve survival, reduce dyspnoea and allow more exercise by improving hypoxemia. This therapy should be considered in patients with persistent symptoms, which already have maximum pharmacological therapy. (10) The long-term oxygen therapy shows a survival benefit in patients, but the life expectancy is low. (10) That is not because of the

therapy itself, but of the patient's general health status. If a patient needs long-term oxygen therapy, he or she has severe COPD and therefore would already have a much lower life expectancy than with oxygen therapy. There are also other factors, which influence life expectation, such as old age, additional comorbidities, a BMI below 20 and cor pulmonale. (10) The oxygen saturation should be ≥ 90% and should be adjusted during exercise, rest at daytime and at night, especially in patients with nocturnal hypoxemia. (10)

Another pharmacological treatment is the prescription of a selective phosphodiesterase type 4 inhibitor such as roflumilast. (10) This PDE-4 inhibitor is an anti-inflammatory drug and should be given to patients with an FEV_1< 50% predicted and with a history of acute exacerbations. (18) The therapy guidelines in accordance to GOLD stage is displayed in Table 3: Therapy guideline according to GOLD patient classification

Group	First choice	Alternative choice	Other possible treatments
A	SAMA or SABA	LAMA or LABA or SABA and SAMA	Theophylline
B	LAMA or LABA	LAMA and LABA	SABA/SAMA Theophylline
C	ICS and LABA or LAMA	LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.	SABA/SAMA Theophylline
D	ICS and LABA and/or LAMA	ICS and LABA and LAMA or ICS and LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.	Carbocysteine SABA/SAMA Theophylline

Table 3: Therapy guideline according to GOLD patient classification (16)

Pulmonary rehabilitation is an interdisciplinary approach to help patients improving their exercise capacity and dyspnoea in combination with their medication. (10) This includes patient education in different disciplines and cardiovascular exercises. The training lasts for about 6 to 12 months, after this time the patient should do the exercises alone and use the things learned during patient education. (10) It is proven that pulmonary rehabilitation improves dyspnoea, exercise capacity and reduces hospitalizations. (10)

At least there are two surgical therapies. First, there is the lung volume reduction surgery. This surgery is performed in patients with emphysemas located in the upper lobe of the lung. (10) The national emphysema treatment trial demonstrated that this surgery is beneficial for patients with COPD. (9) But this surgery cannot be performed in patients with diffuse emphysemas all over the lung or if they have a FEV_1 < 20% predicted. (10) Other criteria that make surgery impossible are diseases of the pleura, pulmonary hypertension or severe co-morbidities.

The other surgical treatment is lung transplantation. COPD is the most common indication to perform lung transplantation as long as a patient does not have a substance addiction in the last 6 months before surgery, dysfunction of extra thoracic organs and is not hepatitis B positive, hepatitis C positive with proof of liver disease or HIV positive. (10) It is proven that the survival rates for patients with COPD are better than for those with other severe lung diseases. After the surgery the patients show significant improvement in pulmonary function, exercise capacity and quality of life. (10)

1.9 Management of acute exacerbations of COPD

Acute exacerbations are episodes during which patients experience greater dyspnoea, cough and a change in the volume and consistence of sputum. (13) There are many factors that can trigger an acute exacerbation, such as viral and bacterial infection or changes in the colonizing bacterial strain. (9) Although these are the most common factors, in about 20-35% of acute exacerbations no triggering factor can be found. (9)

There is no diagnostic test that verifies an acute exacerbation. First other causes, which can lead to respiratory symptoms, must be excluded. (10) It can also be helpful to make a culture of the sputum, especially to refine antibiotic treatment. After they have been excluded the specific treatment can start.

The mainstay of the therapy includes bronchodilators, systemic corticosteroids, theophylline, oxygen therapy, antibiotics when there is purulent sputum, ventilation and the treatment of comorbidities and complications. (13) An increase of inhaled bronchodilators is the beginning of therapy. The inhaled bronchodilators can be short-acting β_2-agonists, short-acting muscarinic antagonists or both drugs in combination. (19) Additionally methylxanthines, such as theophylline, can be given, although the benefit is not clearly documented. Furthermore, systemic corticosteroids are indicated for about two weeks with a dosage of 40mg per day. (19) Corticosteroids increase the recovery of these

patients and decrease the frequency of hospitalizations over the next 6 months. Antibiotic therapy should be considered if the patient experiences breathlessness, the sputum volume increases or purulent sputum is existent. (19) At least two of these three symptoms have to be present to start antibiotic treatment. (19) In addition there should be an antibiogram, so the antibiotic therapy becomes more specific and to prevent the developing of resistances.

Another important treatment is the oxygen therapy to correct the hypoxemia. Oxygen should be monitored either with arterial blood gas analysis or with saturation. If the PaO_2 is below 60 mmHg or the saturation is below 90%, oxygen should be given. (19)

If the patient suffers from hypercapnic respiratory failure, ventilator support is needed. (10) At the beginning, non-invasive ventilation should be tried, for it decreases mortality rates and complications. If the non-invasive ventilation does not work due to an incompliant patient or because of contraindications, such as a haemodynamic instability or life-threatening hypoxemia, invasive ventilation has to be performed. (19) Although the non-invasive ventilation is not a replacement of invasive ventilation it should always be tried in first place, because the mortality rate with invasive ventilation is higher than the other way.

2. β-adrenergic receptor antagonists

Beta-adrenergic receptor blockers are of clinical importance due to their efficacy in the treatment of various cardiovascular diseases, such as hypertension, certain arrhythmias, ischemic heart failure and congestive heart failure.

In 1958, the first β-adrenergic antagonist was discovered. It was called dichlorisoproterenol and had partial agonist properties, which showed fairly low potency. (20) However, it was not used in clinical routine. (21) The discovery of this drug confirmed the postulates of Ahlquist that β-adrenoceptors existed. (20)

In the late 1950s, Sir James Black and his colleagues commenced a program to develop more agents like dichlorisoproterenol. (22) The resulting agent was given the name propranolol. In comparison to the previous agent it is more potent, a pure antagonist and it blocks β_1 and β_2 receptors equally. (20) In 1965, propranolol was first put on the market.

Today there are a whole lot more β-adrenergic receptor antagonists with various pharmacological properties, which will be discussed later.

2.1 Chemistry

Beta-receptor antagonists have a similar structure as the agonists. These similarities are even closer than those between α-agonists and α-antagonists. (22)

The basic structure of beta-blockers is phenoxypropanolamine, except for carvedilol. (23) The phenoxypropanolamine has a stereogenic centre at the C_2 atom. This means that there are L- and D-enantiomers. Although the L-enantiomer is a thousand times more active than the other one, β-receptor antagonists are only available as a racemic mixture, which means that they contain the same amount of L- and D-enantiomers. (23)

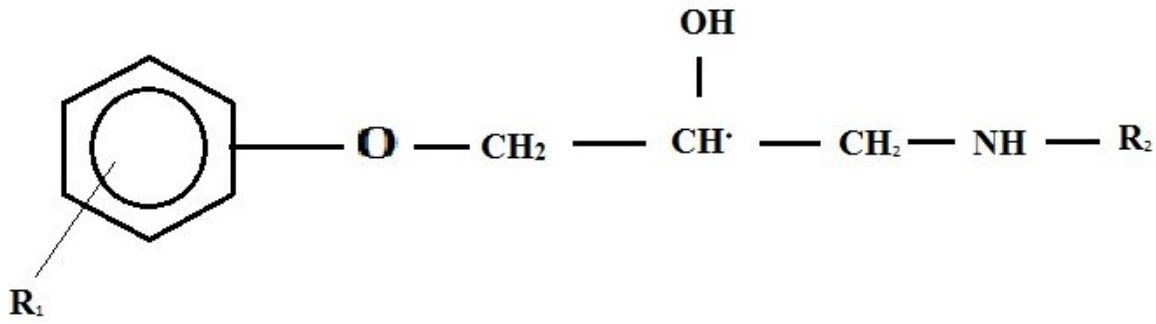

Figure 1: Phenoxypropanolamine; * marks stereogenic centre (23)

The affinity of the drug is determined by the aliphatic side chain and the substituent R_2 at the amino group. Furthermore, the aromatic substituent R_1 is responsible for the intrinsic sympathomimetic activity (ISA) of the drug, which influences the partial agonistic action of the drug. (23)

The agents also differ in their lipid solubility. This property is of importance because of their half-life. Thus, lipophilic agents have a shorter half-life than the lipophobic ones. (23) Besides, the lipid solubility determines the way of elimination for the drugs. Lipophobic beta-blockers are eliminated through the kidneys, but the lipophilic agents through the liver. (21) This is of great importance when treating patients suffering from kidney or liver failure.

2.2 Pharmacological properties

Beta-receptor antagonists are blocking the β-adrenergic receptors in the human body as the name already suggests. This effect is used to treat cardiovascular diseases to prevent adverse effects in patients, which will be discussed later on.

As said above β-receptor blockers are competitive inhibitors of adrenalin and noradrenalin. This inhibiting effect produced by the drugs depends on the sympathetic activity in the human body. Thus, they will not have much effect on a resting heart or on the bronchial or metabolic system of a healthy person. Although there is an exception: the β-adrenergic antagonists with ISA. (20) These drugs can increase the heart rate while resting, but decrease it during exercise or excitement. However, this partial agonistic activity is less than in sympathomimetic drugs, but they are considered to prevent bradycardia or negative inotropy in a resting heart. Furthermore, the agents decrease the coronary flow, but relatively less than myocardial O_2 consumption. (20) Therefore, the oxygenation of the heart is improved. This effect is especially of great use in the treatment of angina pectoris.

Another important characteristic is that there are β_1-selective agents, which are also known as cardio selective drugs. Those beta-blockers are of importance in the treatment of patients who not only suffer from a cardiovascular disease but also from diabetes, asthma or COPD. Due to their selectivity, they are less likely to cause severe side effects as bronchoconstriction or delayed recovery from hypoglycaemia.

There is another group, which has an additional function – the beta-blocker with membrane-stabilizing effect. Although these drugs form their own group, their additional

effect is of no importance to the patients. That is because this property only appears, if the dosage of the β-adrenergic antagonist is already in a toxic level. (24)

The last group of beta-blockers are those with additional vasodilating effects. (21) Normally these drugs have vasoconstricting function, which limits their use. However, the newer drugs have the before mentioned effect and so their usage is not as limited. Depending on the drug, there are various ways of how the vasodilating effect works. Carvedilol additionally blocks α-receptors and the calcium entry into the cells, which leads to vasodilatation. (22) Then there are drugs with β-agonistic function. At last, there is one agent, tilisolol, which opens the potassium-channels in order to lead to a vasodilating effect. (22)

Agent	Lipophilic Property	ISA	Oral Availability (%)	Additional Actions
Acebutolol	0	+	20-60	β1-selective, membrane-stabilizing
Atenolol	0	0	50-60	β1-selective
Carvedilol	0	0	25-35	non-selective, blocks α1-receptors, membrane-stabilizing, anti-oxidant and anti-inflammatory
Esmolol	+	0	NA, only parenteral application	β1-selective, short duration (15 min)
Metoprolol	+	0	65-70	β1-selective
Naldolol	0	0	30-40	non-selective, long acting
Nebivolol	0	0	>90	β-selective, anti-oxidant, endothelial NO-mediated vasodilatation
Pindolol	+	++	100	non-selective, slight membrane-stabilizing effect
Propranolol	+++	0	30	non-selective
Timolol	+	0	50	non-selective, potent

Table 4: Pharmacokinetic properties of beta-blockers (23) (22)

- Rebound phenomenon

When the beta-blockers are used for a long time, the body reacts to it with increasing the amount of β-receptors, which is called up-regulation. (23) If a patient abruptly stops taking his or her medication, the rebound phenomenon will appear. The patient will experience severe sweating, hypertension, tachycardia or even angina pectoris.

Therefore, patients should be thoroughly informed about the drugs including the adverse effects and the rebound phenomenon. Because sometimes patients tend to stop taking their medication, when they are feeling well and do not suffer from any symptoms of their disease.

2.3 Clinical use

The β-receptor antagonists are mainly used to treat various diseases of the cardiovascular system, but there are also other diseases that can effectively be treated with these drugs. In this chapter, the use of the beta-blockers will be shown according to the diseases.

- Treatment of hypertension

The β-receptor antagonists are often used in the treatment of hypertension, because they are greatly tolerated by most of the patients and because they can increase the life expectancy of those patients. (24)

The agents lead to a gradually fall in arterial pressure, although this can take several days or even weeks to happen.

The reason for the antihypertensive effect is complex and not entirely understood until today. (24) The mechanisms responsible involve a decrease in cardiac output as well as in the release of renin from the juxtaglomerular cells of the kidney and a central action that reduce the sympathetic impulses. (20) Furthermore, the pre-synaptic β-receptors are blocked, which causes a reduction in the release of noradrenalin.

Carvedilol and nebivolol are two agents, who are very effective in the treatment of hypertension due to their additional vasodilating property. (20)

- Angina pectoris and myocardial infarction

The β-receptor antagonists are used as an interval-therapy as well as prophylaxis for recurring angina pectoris attacks. These drugs are especially used because they positively affect the prognosis of the patients. (21)

Due to the negative inotropic and negative chronotropic effects of these drugs, they prolong the diastolic period and therefore decrease the oxygen consumption while at the same time increasing the amount of oxygen supply. (21) Furthermore, the beta-blockers protect the heart from excessive sympatho-adrenergic impulses, which also leads to a decrease in the myocardial oxygen consumption. (24)

For the treatment of patients, suffering from angina pectoris β-receptor antagonists with vasodilating properties should be preferably used. (24)

Patients, who suffered from a myocardial infarction, benefit from an early administration of these drugs. Some trials showed a significant decrease in mortality by 25%, if the drugs were administered in the early stages. (22) Furthermore, these drugs showed to be very effective in the prevention of a second myocardial infarction due to their cardio-protective properties. (24) However, these beneficial properties are only present, if the agents are administered as a long-term treatment and as above mentioned in the early stages.

- Anti-arrhythmic therapy

Beta-blockers also have an effect on the automaticity, rhythm and signal transduction of the heart. Therefore, they can be used as anti-arrhythmic agents and build their own class of anti-arrhythmic drugs – the Class-II-Anti-Arrhythmics. Apart from amiodaron, these were the only agents to show a decrease in patients' mortality. (24) Due to this fact and that, they are tolerated very well, they are considered as base line drugs in the treatment of arrhythmias.

Beta-receptor antagonists are used in this therapy because they decrease the stimulating effect of the catecholamines and therefore lead to a decrease in the hearts frequency and contractility, the AV conduction and the ventricular autonomy. The later one is due to an inhibition of intracellular calcium overload as well as an inhibition of spontaneous calcium excretion. (21)

It has to be said that in the case of acute ventricular arrhythmia the effect of the beta-blockers is not of any significance. Nevertheless, they are of importance in the long-term treatment, because of their anti-arrhythmic, anti-ischemic and energy saving effects.

The most important contraindication is the AV-block, since the drugs negatively affect the AV-conduction and therefore can lead to a complete block of this conduction.

- Heart failure

Although initially β-receptor antagonists can worsen an existing heart failure and even induce cardiac decompensation, they can significantly increase the long-term survival rate. They need to be administered in a very low dose at the beginning of the treatment. The starting dose should be about 1/10 of the final dose and should be increased to it over the course of two to four weeks, depending on the patient. (21)

If administered correctly the drugs are known to decrease the hospitalization rate along with decreases in sudden deaths and deaths caused by progressive heart failure in patients, who are suffering from all grades of heart failure. (22)

The positive factors leading to these benefits are the blockade of catecholamines, which are thought to be cardiotoxic. Thus, the apoptosis of myocardial cells can be prevented. (24) The previously mentioned anti-arrhythmic property as well as the decrease in heart rate and energy use are also contributing to these beneficial effects. The last factor that needs to be mentioned is the recovery of the ventricular function. This is caused by the resensitizing of the β-adrenergic cascade and the normalization of the calcium metabolism. (21)

In the long-term use the cardiac volume, the myocardial hypertrophy and the filling pressure are decreasing and the ejection fraction is increasing. Thus, if administered the right way β-receptor antagonists can be effectively used in the treatment of heart failure of any grade. They can also be combined with other drugs used in the heart failure therapy such as diuretics, angiotensin-converting-enzyme inhibitors (ACEI) and if needed with glycosides. (21)

- Glaucoma

Beta-adrenergic receptor blockers proved to be very useful in the treatment of the chronic open-angle glaucoma. Since they are only used topically as eye drops, they have no systemic effect. Furthermore, they do not affect the size of the pupils or the accommodation ability. Thus, they are not leading to blurred vision or night blindness. (22)

- Other uses

Apart from their use in the treatment of cardiovascular diseases, they have proved to be also useful in the therapy of various other diseases.

Beta- receptor antagonists are used in the migraine therapy, to ease acute panic symptoms and in patients suffering from essential tremor. (23)

Furthermore, they are used in the treatment of hyperthyroidism, for they can control the cardiovascular signs and symptoms of this disease. Propranolol can also inhibit the peripheral conversion of thyroxine to triiodthyronine, which also positively affects the treatment. (22)

β-adrenergic antagonist	Pharmacological Property	Clinical Use
Propranolol	non selective	Hypertension, angina pectoris, supraventricular and ventricular arrhythmias/tachycardias, migraine prophylaxis
Naldolol	non selective	Hypertension, angina pectoris; off-label use in migraine prophylaxis, parkinson tremors
Timolol	non selective	chronic open-angle glaucoma, intraocular hypertension, congestive heart failure, migraine prophylaxis
Pindolol	non selective	Angina pectoris, hypertension
Metoprolol	β1-selective	hypertension, angina pectoris, tachycardia, heart failure, vasovagal syncope, secondary prevention after myocardial infarction, hyperthyroidism
Atenolol	β1-selective	hypertension, coronary heart disease, arrhythmias, angina pectoris, reduce risk of complication after myocardial infarction
Esmolol	β1-selective	supraventricular tachycardia, if rapid onset and short duration is important
Acebutolol	β1-selective	hypertension, ventricular and atrial arrhythmia
Labetalol	with cardiovascular effect	chronic hypertension (p.o.), hypertensive crisis (i.v.), pregnancy-induced hypertensive crisis
Carvedilol	with cardiovascular effect	hypertension, heart failure, left ventricular dysfunction following myocardial infarction
Celiprolol	with cardiovascular effect	hypertension, angina pectoris
Nebivolol	with cardiovascular effect	hypertension

Table 5: Various beta-blockers and their clinical use (22)

2.4 Adverse effects

As beneficial as β-receptor antagonists are in the treatment of cardiovascular diseases, they have also systemic effects on the human body that can cause damage or even lead to life-threatening events.

If the effects of the beta-blockers are understood properly, it is easy to understand which and how the side effects can be caused. In this chapter, the main adverse effects in matter of the affected organ systems will be discussed.

- Pulmonary system

The blockade of β_2-receptors on bronchial smooth muscles leads to an increased airway resistance. Thus, bronchospasms and in the worst case bronchoconstriction will appear. In patients who do not suffer from a pulmonary disease, such as asthma or COPD, these effects are of little importance for they are not happening in this kind of patients. (23)

However, in patients suffering from one of the above mentioned pulmonary diseases, complications are likely to appear.

$Beta_1$-selective agents as well as those with intrinsic sympathomimetic activity are less likely to induce any of those adverse effects. Nevertheless, should they be used with caution. Although in patients suffering from COPD and a cardiovascular disease, which is a common combination, the benefits of the β-receptor antagonists outweigh the risks, especially if the β_1-selective agents or those with ISA are used. (22)

- Metabolism

The blockade of the adrenergic-induced glycogenolysis in the muscles and the liver leads to a decrease of glucose in the blood. Thus, the energy production is impaired and the exercise capacity is decreased. (21) Furthermore, the mobilization of glucose in response to hypoglycaemia is impaired. (22) Therefore, β-receptor antagonists delay the recovery from hypoglycaemia in diabetic patients, especially in those suffering from the insulin dependent type.

In addition, the drugs can mask the symptoms of hypoglycaemia, such as tachycardia and tremor. Only the sweating is increased. (21) Therefore, the β1-selective agents should be used in diabetic patients.

The non-selective drugs also have an effect on the lipid metabolism. They are increasing the LDL-cholesterol and triglyceride, while at the same time decreasing the HDL-cholesterol. However, β1-selective agents have been proven to have a positive effect on patients suffering from dyslipidemia, due to their lipid profile improving property. (22)

Furthermore, the vasodilating β-receptor antagonists can increase the insulin sensitivity in diabetic patients. (22) It seems that β1-selective agents as well as those with vasodilating properties may be of use in patients suffering from the metabolic syndrome.

- Cardiovascular system

As discussed in the previous chapter, β-adrenergic receptor antagonists can lead to a deterioration of a pre-existing heart failure and a life-threatening blockade of the AV-conduction and as well to bradyarrhythmias.

In patients with phaeochromozytoma, the administration of beta-blocker without the usage of α-receptor antagonists at the same time can induce major disturbances of the blood pressure. (24)

Although it is not very common, peripheral vascular diseases may worsen. A Reynaud's phenomenon may also develop. (22)

- Central nervous system

Beta-adrenergic receptor antagonists may cause headaches, sleep disturbances and fatigue. The later one might be caused because of the reduced cardiac output and muscle perfusion during exercise. Although some patients complain about experiencing depression while taking those agents, there is no clear association between this specific side effect and the drugs. (22)

- Miscellaneous

Men might be suffering from sexual dysfunction, which is an important adverse effect in reference to the patient's compliance.

Other unspecific side effects may occur, such as gastrointestinal symptoms and allergic reactions. (24)

2.5 Drug interaction

Like any other drugs, β-receptor antagonists also interact with various other agents. The knowledge of those interactions are important since many patients suffer from multiple diseases and therefore are administered many different drugs, which they take on a regular basis. In this part, a few of those drug interactions will be discussed.

Drugs decreasing the absorption and plasma concentration of β-receptor blockers include cholestyramine, colestipol, physostigmine and phenobarbital. Smoking can also lead to a lower plasma concentration of the beta-blockers. (22)

Administering cimetidine and propranolol at the same time increase the serum level of propranolol. (24) That also happens if hydralazine is administered together with propranolol or metoprolol.

Due to their effect on metabolism, the combination of β-receptor antagonists with insulin or sulfonylurea impairs the normalization of blood glucose, especially if hypoglycaemia is present. Thus, the occurring hypoglycaemia is intensified by this drug combination. (23)

The antihypertensive effect of the beta-blockers can be opposed by indomethacine as well as non-steroidal anti-inflammatory agents (NSAID). (24)

Bradycardia can be induced while narcotics are used and if verapamil or diltiazem are given at the same time as β-adrenergic receptor antagonists. (24) (23)

There are also drugs that can contribute to an additive effect. If β-receptor antagonists and calcium-channel blockers are used together their effects on the cardiac conducting system is increased. The additive effect can also be observed when β-adrenergic receptor antagonists are used in combination with other antihypertensive agents. This effect is an advantage in the treatment of hypertension and therefore used in this therapy. (22)

An increase of negative dromotropy can be seen when using methyl-dopa, clonidine or reserpine. Glycosides and beta-blockers lead to an increase of both negative chronotropy and negative dromotropy. (23)

Beta-receptor antagonists also happen to impair the clearance of lidocaine, which can be used as anti-arrhythmic agent or for local anaesthesia. (22)

2.6 Overdosage

Sometimes it can happen that patients suffer from an overdose if these drugs. The symptoms of this poisoning mainly depend on the pharmacological properties of the ingested drug.

Common symptoms are hypotension, bradycardia, prolonged AV-conduction and widened QRS-complexes. (22) Less common symptoms may occur such as seizure, hypoglycaemia and bronchospasms.

To increase the contractility of the heart β-agonists should be administered. If this drug alone is not enough, glucagon can be given additionally. (24) For severe bradycardia, the initial treatment should be with atropine, although often a cardiac pacemaker is required for a proper treatment.

In the end, the therapy of drug overdose is mainly a symptomatic treatment focused on preventing the patient from any long-term damage.

3. Review of studies

Comorbidities are common in elderly patients. COPD and heart failure (HF) are very common chronic diseases and often appear together. At least one third of the patients suffering from COPD also suffer from HF and vice versa. (25) The biggest issue with those two diseases is the pharmacological treatment. Beta-blockers are important for an optimised HF therapy, but are known to have potential adverse effects on the pulmonary system, especially in patients suffering from COPD or asthma. (26)

However, in the last few years various observational studies showed that the use of beta-blockers is safe and has beneficial effects in the treatment of HF and concomitant COPD. (27) Since the evidence is increasing, international guidelines also recommend the use of beta-blocker in the treatment of HF with co-morbid COPD, because the potential risk of adverse effects caused by these agents are outweighed by their beneficial effect. (28)

In this chapter, we will be reviewing the new guidelines regarding heart failure and concomitant COPD, as well as various studies in this field in order to provide information about the use of beta-blockers and their possible benefits as well as their adverse effects.

3.1 Guideline recommended treatment of heart failure and COPD

The aim of the pharmacological treatment is to improve the quality of life, clinical status and to reduce hospital admissions as well as mortality. (29)

The main pharmacological agents used in the therapy include neuro-hormonal antagonists (beta-blocker, angiotensin-converting enzyme inhibitors, and aldosterone receptor antagonists), diuretics, angiotensin receptor neprilysin inhibitor and If-channel inhibitor. (29) (30) There are also other drugs used but their benefits are not clear. (29) These drugs are given patients according to their NYHA (New York Heart Association) classification, which categorises the patients in classes I to IV according to their clinical presentation and symptoms. (31)

The neuro-hormonal antagonists have been proven to have a positive effect on the survival of HF patients and should be given to every HF patients. (29) However, these also include beta-blockers, which have the probability to cause pulmonary adverse effects in patients suffering from COPD or asthma. As mentioned before evidence, that supports the

administration of beta-blockers in those patients, is increasing and international guidelines are supporting this approach.

According to the ESC guidelines, beta-blockers are only relatively contraindicated in patients with asthma but with COPD and therefore they should not be withheld in these patients. (29) Furthermore, the National Institute for Health and Care Excellence as well as the ESC guidelines state that beta-blockers should be continued if mild deterioration of pulmonary function and symptoms occur. (32) Moreover, The Heart Failure Society of America's comprehensive practice guidelines for HF recommend the use of these agents in patients with HF and COPD. (33)

3.2 Studies with main focus on COPD

Beta-blockers are indicated in patients with various cardiovascular diseases such as congestive heart failure, myocardial infarction, cardiac arrhythmia, hypertension and angina pectoris. (34) Although it is widely acknowledged that COPD is a multisystem disease associated with various comorbidities including cardiovascular diseases, there are still concerns about the use of beta-blockers in patients suffering from both diseases because of the potential adverse effects on the lung. (35) However, former studies suggested that the use of beta-blocker is not associated with worsening of pulmonary function or symptoms (36) and may have beneficial effects such as reducing the morbidity and mortality in those patients and some even showed that the frequency of acute exacerbations is decreased. (35) Furthermore, beta-blockers seem to blunt the cardiotoxic effect of short-acting beta-agonists, which are frequently used in patients with COPD. (37)

Based on these suggestions and evidence further studies were made either to focus on other specific functions such as cardiopulmonary exercise function (36) or to prove that those findings can be reproduced.

In one meta-analysis of observational studies it was found that the majority of patients with COPD tolerated the treatment with beta-blocker well and that the use of these drugs was safe in this group of patients. (38) Furthermore, they described that these agents lead to a significant decrease in mortality and exacerbations of COPD, although the mortality benefit had more significance in the group of patients suffering from COPD and heart failure or coronary heart disease. (38) Beta-blockers also temper the sympathetic nervous system and thus lead to a reduction in heart rate, which is an independent factor for all-cause mortality in patients with and without cardiovascular diseases. (38) In addition,

experimental study showed that there is a reduction in inflammatory cells and the level of cytokines, a decrease in goblet cells and in the mucin content of the airway epithelium in mice treated with beta-blockers. (38) Other animal studies described an up-regulation of beta2-receptors in the lung of mice under chronic beta-blocker treatment, which improves the effectiveness of bronchodilators. (38)

The COPDGene study recruited 10.300 persons of whom 3.464 subjects suffered from COPD GOLD stage 2 to 4 and those were enrolled in another study with the aim to find out what impact beta-blockers have on COPD exacerbations. (35) They compared patients using different cardiac medications, such as beta-blockers, calcium-channel blockers (CCBs) and combined therapy with angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers (ARB). (35) They found that patients receiving beta-blockers had a lower heart rate and a better respiratory quality of life, but were more likely to have congestive heart failure or coronary artery disease. Furthermore, beta-blockers were associated with a significant decrease in the rate of total and severe exacerbations, especially in the group of GOLD stage B. (35) CCBs showed an increased risk of severe but not total exacerbations and the combined treatment with ACEI/ARB showed no association with exacerbations at all, which may be related to the beta-blocker as class effect. (35) They concluded that the use of beta-blockers in patients suffering from COPD had a beneficial effect on exacerbations in moderate and severe stages of this disease and they hypothesize that beta-blockers may be beneficial even in COPD patients without any concomitant cardiovascular disease. (35)

Another analytical cross-sectional study took interest in the relation between beta-blockers and COPD exacerbations. In this study, they included 256 patients with COPD and 101 without this disease and found that only 58% of the patients with COPD and an indication for beta-blocker received those, in contrast to 97% in the non-COPD group. (39) They showed that patients with COPD and a treatment with beta-blocker were less symptomatic, had fewer exacerbations and had fewer emergency room (ER) admissions due to an exacerbation although they received less respiratory medicine. (39) Furthermore, it seemed that the beta-blocker use reduced the mortality in those patients admitted to an ER due to an acute exacerbation. (39)

Since there is already a lot of evidence that beta-blockers do not lead to a worsening of pulmonary function or respiratory symptoms, there has been a case-control study based on a retrospective chart review to evaluate the effect of beta-blocker use on cardiopulmonary exercise testing. (36) Although the study cohort was rather small with 48 patients, it was found that the exercise capacity as well as the gas exchange was not significantly different between the groups of beta-blocker users and non-users, but the heart rate, systolic and diastolic blood pressure at peak exercise was significantly lower in those patients receiving beta-blockers. (36) A limited exercise capacity was observed, but this occurred due to ventilator limitations and breathing inefficiencies associated with ventilator abnormalities that lead to neuromechanical uncoupling and not due to the use beta-blockers. (36)

Another research took a closer look at the safety of beta-blockers in COPD patients suffering from respiratory failure in an intensive care unit (ICU) and their impact on mortality. (40) In elderly COPD patients, atrial fibrillation is a common comorbidity and during an acute exacerbation the risk for cardiac arrhythmia increases, which is a significant cause of mortality in this group of patients. (40) These conditions would require the treatment with a heart-rate-limiting drug (HRLD). Thus, they performed a case control study comparing two groups of patients – one treated with beta-blockers (bisoprolol, carvedilol and metoprolol) and the other one with other HRLDs (amiodaron, diltiazem, digoxin or any combination of these). (40) They included 188 patients from whom 74 received beta-blocker and 114 patients did not and most of them suffered from supraventricular tachycardia, which was the main reason for administering those drugs. (40) They found that there was no significant difference between those two groups in regard of mortality rates and length of their stay at the ICU, but the application rate of non-invasive ventilation was significantly higher in the beta-blocker group. (40) Thus, they concluded that beta-blocker use was not found to have significant impact on mortality and did not lead to a worsening of the patients' condition. (40)

One group performed a meta-analysis of randomized, placebo-controlled trials, which had to be single- or double-blinded, report FEV_1 and only included COPD patients. (41) They included 5 studies with 4 of them assessing cardio-selective and non-selective beta-blockers and one only approaching the use of cardio-selective beta-blockers. (41) It was found that non-selective and cardio-selective beta-blockers lead to a decrease in FEV_1, but only the non-selective ones showed a significant decrease in the responsiveness

of FEV_1 to beta-agonists while in three studies the cardio-selective drugs showed an improvement. (41)

In another study, they stated that although most of the COPD patients die due to respiratory failure cardiovascular diseases are also an important cause of death in those patients, since about 10-27% of the patients also suffer from a cardiovascular disease. (37) As already known the use of beta-blocker is denied to many COPD patients despite of existing evidence proving them to have a beneficial effect on mortality. Thus, they examined the use of beta-blockers in in-hospital patients and their effect on respiratory failure and mortality, which is about 32% in those patients. (37) They found out that the patients' age, an increased length of stay, respiratory failure and the number of prior acute exacerbations as well as congestive heart failure, cerebrovascular disease and liver disease are associated with an increased risk of in-hospital death, but that the use of beta-blockers and short-acting beta-agonists reduce mortality. (37) Furthermore, they found out that, spirometric data of the patients did not show any significant difference between beta-blocker users and non-users and that beta-blockers do not interfere with short-acting beta-agonists or alter their beneficial effect on the pulmonary system. (37)

In a retrospective observational cohort, study one group analyzed the effect of beta-blockers in patients with COPD regarding their survival and changes in the spirometry of those patients. (42) They included 5977 patients suffering from COPD and formed two groups depending on their use of beta-blockers. (42) Results of this study showed that there was no clinically significant deterioration of FEV_1 in any treatment group and that beta-blocker significantly improved the overall survival and decreased mortality by 22% independently from their selectivity. (42)

Since multiple studies showed that beta-blockers are safe in patients with COPD and in the long-term treatment are known to increase survival rates and decrease exacerbation rates without significantly changing the spirometry of those patients, one group performed a retrospective cohort study to assess the effect of beta-blockers on exacerbations. (43) They included 412 patients with diagnosed or medication implied COPD of whom 166 used either a non-selective or a cardio-selective beta-blocker. (43) They found that patients using a beta-blocker suffered fewer mild exacerbations, which shows in accordance with other studies that beta-blocker are not contraindicated in patients with COPD and cardiovascular disease. (43)

Another group performed a cohort study to investigate the effect of beta-blockers on mortality and exacerbation risk in COPD patients. (44) They included 2.230 patients of which 560 already had COPD and the other ones developed it during follow up and 44.9% had a concomitant cardiovascular disease. (44) It was found that patients who were prescribed a beta-blocker had higher survival rates and a lower risk of exacerbations independently of the drugs selectivity than those who were not using beta-blockers. (44)

It is known that COPD frequently occurs with cardiovascular diseases, which are responsible for at least 27% of all mortality in moderate to severe COPD patients, and that beta-blockers are associated with a reduced mortality and lesser acute exacerbations in those patients without a significant change in lung function. (45) However, most of the studies suggesting these beneficial effects had a short time frame, which lead a japanese group to assess the long-term effects of beta-blockers in COPD patients. (45) They recruited 103 patients with spirometrically diagnosed COPD, of whom 31 were taking beta-blockers and 72 were not, with an observational period of 4.1 years. (45) They mainly used cardio-selective beta-blockers and found no significant difference between the patients taking and those not taking a beta-blocker in reference to medication used to treat COPD, acute exacerbations requiring hospital admission and annual changes in FEV_1. (45)

Since there are more and more studies suggesting that beta-blockers are beneficial in COPD patients with comorbid cardiovascular disease and that the use of them is safe. A group from Australia assessed the safety of initiating those drugs during an acute exacerbation of COPD. (46) They recruited 36 patients with a spirometrically diagnosed COPD, who started beta-blocker therapy during their hospitalisation for acute exacerbation. (46) It was found that the initiation of a beta-blocker treatment in those patients, who mostly had severe or very severe COPD, was safe and well tolerated. (46)

One study group analyzed and compared patients participating in the STATCOPE trial, which mostly excluded cardiovascular diseases, and patients from the placebo arm of the MACRO, which had a high prevalence of cardiovascular diseases, in order to assess the effect of beta-blockers on lung function and exacerbation rates in COPD patients. (47) They divided the patients, who mostly suffered from COPD GOLD stage III or IV, into four groups according to which trial they belonged and if they were receiving beta-blocker therapy or not. (47) They found that there was no significant difference between patients with and without beta-blockers regarding airflow limitation. However, patients taking

beta-blocker were found to have a slightly increased FEV_1 and that the acute exacerbation rate was lower in the patients from the STATCOPE trial, especially in those who were prescribed a beta-blocker. (47) Thus, they concluded that beta-blocker use was safe within this patient group and supports the use of these, if needed.

At last, there was another meta-analysis of randomized, controlled and blinded clinical trials, which included only studies with reported FEV_1 at rest, baseline and follow up or symptoms for the study drug and placebo and only included patients with COPD. (34) The group found 19 articles that met the inclusion criteria and of which 11 were single dose studies and 8 longer duration studies. (34) The single dose studies showed that beta-blocker were not associated with a change in FEV_1, did not increase respiratory symptoms or had a significant change in the FEV_1 and the longer duration studies showed that the study drug did not significantly differ from the placebo. (34) Therefore, they concluded that beta-blocker might be given to COPD patients for their beneficial effect and the lack of severe adverse effects in respiratory symptoms and spirometry. (34)

3.3 Studies with main focus on heart failure and COPD

As already, known heart failure and COPD are common diseases in elderly patients and often occur together. Although patients with COPD were often excluded from studies on heart failure patients and beta-blocker treatment, the trend now is to include more patients with comorbid COPD because beta-blocker are necessary for an optimized heart failure treatment and international guidelines such as the European Society of Cardiology approve of beta-blockers in the treatment of heart failure with concomitant COPD. (26)

The aim of one study was based on the OPTIMIZE-HF study to find out if the patients outcome vary depending on the selectivity of the beta-blocker prescribed. (48) In both groups with and without COPD the distribution of selective (most common metoprolol succinate, metoprolol tartrate and atenolol) and non-selective (mainly carvedilol) beta-blockers were similar with 60% non-selective and 40% selective ones. (48) They found that the use of beta-blockers in patients with and without COPD had a lower mortality rate and fewer rehospitalisation rates, which had no significance in regard of the drugs selectivity. (48) Furthermore, there was no evidence that the selectivity of the beta-blockers was associated with different outcomes in neither patients with COPD nor those without, which together with the other findings supports the use of beta-blockers in the treatment of patients suffering from both heart failure and COPD. (48) Since there were no

significant differences between the selective and non-selective agents the authors of this study hypothesize that the potential adverse effects of the non-selective drugs may be balanced by an alternative set of beneficial cardiac, pulmonary and systemic effects, such as the attenuation of the dysrhythmogenesis, ischemia and inflammation induced by beta-agonists. (48)

One group stated that the prevalence of COPD in heart failure patients is 11-52% in North America and 9-41% in Europe and COPD management guidelines recommend the use of selective beta-blocker in patients with heart failure and COPD, because the benefits of these drugs outweigh the potential risk of adverse events even in patients with a sever stage of this disease. (28) Although these facts are known today, beta-blockers are still underprescribed in patients suffering from both diseases due to the fear of possible adverse effects. Therefore this group assessed the use of beta-blockers in patients with heart failure alone and patients with both heart failure and COPD. (28) They found that in the treatment of acute coronary syndrome only 16% of COPD patients were administered beta-blockers compared with 64% of those without COPD and that also in the treatment of myocardial infarction COPD patients were 62% less likely to receive beta-blockers, which shows that the use of those drugs need to be increased to improve survival rates, especially since the benefits outweigh the risks. (28)

An analysis of the SHIFT study was performed with the aim to evaluate clinical profile of COPD and heart failure and the comparative effect and safety of ivabradine in patients with heart failure only or concomitant COPD. (49) 65.050 patients, of which 730 patients had comorbid COPD, were included in this study and the treatment for chronic heart failure was similar in both COPD and non-COPD groups, except for the use of beta-blockers – only 69% of the COPD patients received those drugs in comparison to 92% of non-COPD patients. (49) The majority of the patients took cardio-selective beta-blockers though 40% of COPD and non-COPD patients were prescribed carvedilol and fewer patients with COPD than those without reached the drugs target dose. (49) All cause mortality, hospitalization and adverse events were more frequent in COPD patients independently from their beta-blocker use and it is thought that the poorer outcome in those patients is due to the underlying COPD and the underuse of beta-blocker. (49) Ivabradine was found to be safe and effective in regard of lowering the heart rate and furthermore showed fewer all cause mortality and cardiovascular mortality compared to

placebo and there was no significant difference in impact between COPD and non-COPD patients. (49)

In a randomized crossover trial one group evaluated how switching from cardio-selective beta-blocker to non-selective and vice versa affected patients with chronic heart failure and COPD. (50) 51 patients with optimal heart failure therapy were enrolled, 35 of them had concomitant COPD and all of the patients were treated with a beta-blocker (carvedilol, metoprolol succinate or bisoprolol). (50) The patients were switched randomly to another dose-matched beta-blocker, taking each drug for six weeks before switching again until they had been switched to every beta-blocker and back again to their originally prescribed agent. (50) During the study period they found that the FEV_1 was significantly higher with bisoprolol compared to carvedilol in both COPD and non-COPD patients, but the FVC was unchanged and there was no change in the responsiveness to bronchodilators between the different treatments. (50) Although most patients only suffered from mild lethargy and dyspnoea immediately after switching the drugs, 7 patients had to withdraw from the study, because of adverse effects such as dyspnoea, pancreatic cancer, angina or personal reasons. (50) These adverse effects occurred after switching from one selective agent to another selective on and from carvedilol to metoprolol as well as to bisoprolol, but after all the switching was well tolerated within both patient groups. (50)

Since most large-scale heart failure trials excluded patients with concomitant COPD, one group performed a randomized open-label study to explore the differences between bisoprolol and carvedilol in patients with heart failure and COPD, who were naive to beta-blocker and had no cardiovascular contraindication to these drugs and did not suffer from asthma. (27) They included 63 elderly patients with NYHA 2 (54%) and NYHA 3 (46%) and moderately to severe GOLD stage (76%; 24%) and assigned them randomly to either bisoprolol or carvedilol. (27) It was found that bisoprolol significantly increased FEV_1 and both agents significantly reduced the heart rate, but 24 adverse events occurred in 19 patients, of which most were mild and only transient. (27) However, eight patients had to withdraw from the study due to hypotension (both drugs), bradycardia (bisoprolol) and wheezing, dyspnoea and oedema (carvedilol), but they concluded that the use of beta-blockers is safe in this patient group and support the international guidelines recommendation of beta-blocker use in the treatment of heart failure and COPD. (27)

One retrospective cohort study's aim was to approach the use of different beta-blockers (carvedilol, bisoprolol and metoprolol) in patients with COPD and comorbid heart failure. (33) They had two cohorts consisting of patients with heart failure and patients with both heart failure and COPD, who were all taking a beta-blocker. (33) It was shown that the survival decreased with increasing severity of COPD or heart failure and that a significant better dose-dependent survival outcome was associated with bisoprolol in heart failure and COPD patients, but metoprolol and carvedilol did not show any significant survival difference. (33)

To analyse the impact of beta-blocker selectivity on long-term outcomes one group performed a retrospective, non-randomized, single centre trial based on data collected over 48 months. (32) 132 patients were enrolled and divided into two groups according to the agents used – patients with and without a beta-blocker (carvedilol and bisoprolol). (32) It was found that patients without a beta-blocker had a significant higher heart rate and that all-cause mortality was significantly reduced by the use of beta-blockers, probably due to their heart rate limiting effect. (32) Furthermore, they found that bisoprolol significantly reduced the risk of re-hospitalization and had a greater heart rate reducing effect than carvedilol, which supports the use of beta-blockers in patients with heart failure and concomitant COPD. (32)

3.4 Studies with focus on COPD and other cardiovascular diseases

Although most studies are focused on COPD and heart failure, there are other comorbidities present in patients suffering from COPD. Therefore, some groups approached the use of beta-blockers in patients suffering from myocardial infarction, post surgical treatments or other cardiovascular diseases apart from heart failure.

- Vascular surgery

COPD is a frequently observed comorbidity in patients undergoing a coronary artery bypass crafting (CABG), ranging from 4% to 27%, and are associated with an increased risk of post-operative mortality. (51) Since beta-blockers are recommended for patients undergoing this surgery, the aim of this study was to assess the effect of the drugs on those surgical patients, who also suffer from COPD. They included only patients with spirometry confirmed COPD and undergoing CABG for the first time and divided them into two groups, one with 104 patients receiving cardio-selective beta-blockers and 104 patients not receiving any of these drugs. (51) The post-operative mortality was not significantly

different between these groups, there was no significant increase in exacerbations in the beta-blocker group, but the overall-mortality during follow-up was 7.7% in the beta-blocker group compared to 18.3% in the one not receiving these drugs and the patients without them were more likely to have a new onset of atrial fibrillation. (51) Thus, they concluded that the treatment with cardio-selective beta-blockers is beneficial in this group of patients and should not be withheld from them. (51)

Another study also focused on patients with COPD undergoing CABG, but focused only on the long-term survival of these patients. They included 33.137 patients and divided them by their comorbidities, such as COPD alone, no comorbidities, COPD and another comorbidity and other comorbidities without COPD. (52) It was found that COPD had a significant effect on long-term survival for the incident of death occurred twice as often compared to patients not suffering from COPD. The 10 years survival was 64% for patients only suffering from COPD, but 37% if they had not only COPD but also another concomitant disease. (52) Thus, it is clear that there had to be other studies approaching a treatment that could improve those survival rates.

- Myocardial infarction

Beta-blockers are known to reduce risk of mortality and re-infarction after suffering from myocardial infarction and they reduce mortality in patients with COPD and acute coronary syndrome, but despite these evidences and a study by Gottlieb et. al. in 1998, suggesting survival improvement in patients with COPD and myocardial infarction, beta-blockers are underprescribed in those patients. (53) Thus, one group in the United Kingdom performed a study to quantify the association between COPD and mortality after myocardial infarction to investigate whether the use and timing of prescription of beta-blocker in patients with COPD after the first myocardial infarction was associated with improved survival rates. (53) They found that the survival of patients regarding cardiac and non-cardiac death was better, if they were prescribed a beta-blocker during hospital admission or prior to myocardial infarction, but that only 38.6% of the patients received a beta-blocker on admission and therefore they suggested that beta-blockers should not be withheld from those patients. (53)

In Sweden, a nationwide study aimed to investigate the association between prescription of beta-blocker at discharge after myocardial infarction and all-cause mortality for patients with COPD. (54) They included 4.858 patients with COPD of whom 84.1% (4.086) were discharged with a beta-blocker and had a median follow up of 1.033 days. (54) It was found that the COPD patients with a beta-blocker had a lower all-cause mortality rate compared to non-users and that this association was even stronger in patients who had also a history of congestive heart failure. (54)

- Other cardiovascular diseases

One study aimed to assess the effect of beta-blocker on the health-related quality of life in patients with COPD and peripheral artery disease, since this effect has not been evaluated before. (55) The study was based on an original cohort study of vascular surgery patients of which they had follow up on 326 eligible patients for a median time of 6.4 years. (55) Of these patients, 71% (232 patients) used a beta-blocker at the end of follow up and there were no significant differences found in the health-related quality of life between beta-blocker users and non-users, which supports the use of those drugs in patients with COPD and an indication for beta-blocker. (55)

A multinational study compared calcium channel blockers and cardio-selective beta-blockers in regard of their safety and effectiveness in patients with COPD and acute coronary syndrome. (56) They used cohorts from 5 databases in the United States, Italy and Taiwan, enrolling patients, who were admitted to hospital with acute coronary syndrome and a diagnose of COPD previously to their discharge. (56) They found that beta-blockers were initiated more often than CCBs. The mean duration of follow up was 1.9 to 3.5 years and they found no association between beta-blocker use and a reduced risk of mortality or reduced cardiovascular hospitalisation. (56) However, there was a strong inverse association between beta-blockers and COPD suggesting the presence of bias due to unmeasured confounding, which applies to other observational studies as well and questions their validity. (56)

Another group explored the association between cardio-selective beta-blocker and overall death in COPD patients, as well as cardiovascular deaths and events. (57) They compared patients with COPD using either a cardio-selective beta-blocker or non-dihydropyridine calcium channel blockers, because of a cardiovascular disease, such as hypertension, ischemic heart disease or congestive heart failure. (57) The mean follow up time was 2 years and it was found that were was only a marginally significant survival benefit for patients with beta-blocker, but there was no decrease in the risk of cardiovascular deaths or events in this group of patients. (57)

In one study, 1.062 elderly patients with COPD and a cardiovascular disease were enrolled to examine the effect of beta-blockers in regard of major cardiac events, major pulmonary events and all-cause mortality. (58) They found that beta-blockers did not adversely affect pulmonary outcomes, but a beneficial effect on cardiac outcomes or events was not observed compared to other studies, which described beneficial effects. (58)

It is already known that beta-blocker lead to a small, but mostly insignificant fall in FEV_1, but there is a lack of data about their effect on other lung functions in COPD patients. Therefore, a group assessed the effect of beta-blocker on lung function including body plethysmography and dynamic hyperinflation during exercise testing. (59) They recruited patients with or without COPD; from a cohort attending abdominal aortic aneurysm, who were either taking beta-blockers or not. (59) The patients had to undergo lung function measurements, including spirometry, lung volumes, gas transfer as well as airway resistance using body plethysmography, once while they were taking beta-blockers and once when they did not. (59) They found that beta-blockers lead to a small, but significant fall in FEV_1, independent of COPD, but there were no other significant changes in lung function or dynamic hyperinflation. (59) However, of the 38 patients enrolled in this trial, 6 patients were already diagnosed with COPD, but during the lung function measurements 9 patients were newly diagnosed with it. (59) Thus, they concurred that beta-blockers are safe and do not worsen lung function in COPD; but that there is a high prevalence of COPD in vascular surgery patients. (59)

3.5 Studies assessing the use of beta-blocker in asthmatic patients

Asthma is mostly known to affect children, but there are also many adults suffering from this disease. Evidence is suggesting that asthma, especially in women and patients receiving multiple medications, increases the risk of coronary heart disease, stroke and cardiovascular disease mortality. (60) Those are the same concomitant diseases found in patients with COPD and that diminished COPD as a contraindication to beta-blockers in cardiovascular patients if those drugs are needed, but asthma still remains a relative contraindication. (29) Thus, studies are increasing to explore the possible beneficial effect of beta-blockers in patients with asthma.

The main therapy of asthma, especially in the acute symptomatic treatment, are β2-receptor agonists and inhaled corticosteroids. (61) Beta-agonists can also relieve acute symptoms of heart failure, but in the long-term treatment, they increase mortality risk, which has also been found in asthmatic patients using isoprenaline in the 1960's. (61) On the other hand the acute use of beta-blockers lead to a worsening of symptoms in heart failure and asthma patients, but in patients with heart failure it is known that the chronic use of those drugs have beneficial effects and decreases the mortality rate. (61) This paradoxical effect may also be true for patients with asthma and a few studies suggested that the use of beta-blockers in patients with cardiovascular disease is safe and may have a protective effect on airway hyperresponsiveness, but further prospective studies are needed to verify those findings. (61)

Since beta-blocker are essential in the therapy of heart failure, one group assessed the use and tolerability of carvedilol in heart failure patients with concomitant COPD or asthma. (62) The study population was rather small with 31 COPD patients and 12 asthmatic patients of a total of 487 patients with heart failure. (62) The mean observation was 2,4 years with tolerability defined as continued use of carvedilol for at least 6 months and it was found that 26 (84%) of the COPD patients tolerated the drug well, whereas only 6 (50%) asthmatic patients tolerated carvedilol. (62) Thus, it appears that asthmatic patients should still be a contraindication to beta-blockers in the authors' opinion, although the cardiac function improved in all patients tolerating carvedilol. (62)

An asthma model study in mice challenged with ovalbumine was conducted to investigate the anti-inflammatory effect of beta-blocker in order to reduce the dosage of corticosteroids. (63) Asthma is a chronic inflammatory airway disease with reversible

airflow obstruction and poorly reversible airway remodelling and the most effective long-term treatment of this disease is the use glucocorticoids, which are proven to reduce inflammation, but have many adverse effects especially if chronically used and with high doses. (63) The drugs used in this study were naldolol and dexamethasone in various dosages and combinations, to investigate their individual and combined effect on inflammatory cells as well as epithel cell mucin content. (63) It was found that naldolol has the ability to reduce the dose of dexamethasone while still achieving the same anti-inflammatory effect and that the combination of both drugs lead to a greater reduction in inflammatory cells and epithel mucin content at an intermediate dosage, although further clinical trials are needed to confirm those findings. (63)

Evidence is increasing that the long-term use of long-acting beta-agonists is associated with a decrease in the number of β2-receptors and a desensitization of those as well as a paradoxical worsening of asthma control in regard of exacerbation and rare cases of death despite the use of inhaled corticosteroids. (64) In a mouse-model study, it was shown that the chronic use of naldolol and metoprolol have a bronchoprotective effect against metacholine challenge and that this effect occurs together with reduced inflammation and mucous metaplasia and an increase of beta-receptor cells. (64) Since there are not enough clinical trials the authors propose further human studies and proof-of-concept studies to investigate the possible beneficial effects of beta-blocker in asthmatic patients. (64)

Since asthma is associated with an increased risk for cardiovascular diseases, one study assessed the use of beta-blockers in patients with asthma and cardiovascular disease, who were actively treated for both conditions. (65) The cohort was given either a cardio-selective or a non-selective beta-blocker and it was shown that the cardio-selective agents were not associated with an increased risk of moderate or severe exacerbations independent of dose and duration. However, that the non-selective drugs showed a significantly increased rate of moderate and severe exacerbations at a high dosage but not at a low or moderate dose. (65) Thus, the authors suggest that cardio-selective agents should be considered more widely in this patient group, especially because the exacerbation risk is not significantly increased. (65)

4. Conclusion

COPD is the 6th leading cause of death worldwide and concomitant cardiovascular diseases are frequently observed in those patients. (9) Since COPD is not a curable disease the treatment focuses on relieving symptoms and preventing acute exacerbations, which can lead to a increased mortality rate, especially if the patients suffers from a cardiovascular disease as well.

The treatment of patients with COPD and cardiovascular disease holds many difficulties, because the mainstay drugs for either disease seem to be diametrically. Beta-agonists are important in the treatment of COPD to relieve respiratory symptoms and to reduce the rate of acute exacerbations. On the other hand, beta-blockers, which are the mainstay therapy in heart failure and other cardiovascular diseases, are effectively reducing mortality rates in patients with those diseases. However, both of these drugs have adverse effects that should not be overlooked, for they can have a negative impact on both diseases. The long-term use of beta-agonists in patients with heart failure leads to an increased morbidity and mortality, although the acute use of them lead to an increased cardiac index and stroke volume. (61) However, beta-agonists are chronically used by COPD patients, which diminishes the beneficial effect of those drugs in heart failure. The most important adverse effects of beta-blockers are a reduced FEV_1 and bronchoconstriction, especially in patients with obstructive lung diseases, such as COPD or asthma. However, there is growing evidence that the feared pulmonary adverse effects caused by beta-blockers do not occur as frequently as it was thought before and that beta-blockers may have beneficial effects in patients with COPD and cardiovascular disease, if administered chronically. These beneficial effects include a possible reduction of mortality and morbidity rate as well as lower acute exacerbation rates. (42) (47) (48) (53) (54)

The numbers of patients with COPD are increasing and they frequently have concomitant heart diseases or other cardiovascular diseases. Thus, many studies were conducted to assess the pharmacological management of COPD patients with comorbidities, in order to establish more refined therapies, which would improve the patients situation and would not lead to severe adverse reactions. These studies mainly focused on patients with heart failure, but some also assessed patients, who had other concomitant cardiovascular diseases, such as myocardial infarction and peripheral artery disease. The results of those studies stated that the use of beta-blockers in COPD patients is safe and did not lead to the feared pulmonary adverse effects. Furthermore, some studies even suggested a beneficial

effect in regard of mortality, morbidity and hospitalization rate due to acute exacerbation. However, other studies did not find any beneficial effects, which were described earlier, and also described a decline in FEV_1. (41) (45) (57) (58) Although the results of some studies differ in regard of the beneficial effects, international guidelines, such as the ESC, recommend the use of beta-blockers in patients suffering from heart failure and COPD to optimize the management of heart failure. (29)

However, many of these studies have several limitations, which can lead to potential bias and therefore, to a misinterpreting of the studies' results. A recurring limitation was the few numbers of participants enrolled in various studies, which affect the validity of those studies. In respect to the small numbers one group from New Zealand assessed the feasibility of a randomised controlled trial in COPD patients. (66) In their study they aimed to assess the effect of beta-blockers in COPD patients admitted to hospital due to an acute exacerbation and they found 527 eligible patients, but ended up with only enrolling 23 patients after matching them to inclusion criteria and only 16 of them completed the study. (66) Due to their small numbers of participants they stated that the feasibility is not given using their study design and that they could not determine the balance of risk and benefit in COPD patients receiving beta-blockers during hospital admission for acute exacerbation. (66) This study highlights the issue of many other studies with small patients numbers and the difficulty of starting a new treatment with beta-blockers, especially in a hospital setting. Furthermore, observational studies often did not specify the beta-blockers used or had an unclear diagnosis of COPD, which was often based on symptoms or prescribed medications instead of using spirometry according to GOLD classification. A state of the art review stated that not only these limitations contributed to a significant bias, but also the lack of long-term studies assessing cardiovascular prophylaxis with beta-blocker in patients with a history of angina or myocardial infarction and COPD, as well as the issue that specific causes of death were often missing. (67) Taking all these limitations in account, it is no surprise that many physicians are hesitant to prescribe beta-blockers to patients with COPD, even if international guidelines support the use of those drugs in patients with heart failure and concomitant COPD.

After reviewing literature about COPD and pharmacological properties of beta-blockers, as well as various studies about the use of these drugs in patients with COPD and concomitant cardiovascular diseases, I am confident that beta-blockers should be used in the treatment of heart failure and COPD, especially because of the many studies suggesting that the usage of the drugs is safe. However, due to the limitations affecting most of the studies, I think beta-blockers should be used with precaution and only if the patient requires them for treatment of heart failure, myocardial infarction or other cardiovascular diseases. In my opinion the studies, conducted so far, are a good base for further prospective studies using larger cohorts and longer duration of treatment in order to verify the beneficial effects of beta-blockers, prescribed earlier. However, as long as there are only experimental animal studies and limited observational studies, I would not take the beneficial effects of these drugs for granted and prescribe them to patients with COPD only, especially since there is no information about how the long-term treatment would affect those patients. However, I think it would be interesting to determine, if the beneficial effects are conducted because of the heart-rate limiting properties of beta-blockers, because if this is the case, then there are more drugs, such as ivabradine, available, which would not interfere with beta-adrenoceptors. (67)

The meaning of beta-blockers in the COPD treatment remains controversial and if there are no further studies, the difficulties and uncertainties in the treatment of those patients will persist. Therefore, I think it is very important to pursue more large scale, randomized placebo trials. However, one group proposed a different way to approach this difficult topic, by facilitate the further development and assessment of a truly β_1-selective beta-blocker, since the ones used nowadays are only poorly selective and loose this selectivity as the administered dose is increased. (67)

In the end I think, that if the patients requires treatment with a beta-blocker, it should not be denied to him or her. However, to solely use them in patients with COPD only, I would wait until studies with fewer limitations and more representative results have been conducted.

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