Chronic Obstructive Pulmonary Disease and Ischemic Heart Disease Comorbidity: A systematic review of mechanisms and clinical management.

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Abbreviation list.

IHD: ischemic heart disease

CVD: cardiovascular disease

COPD: chronic obstructive pulmonary disease

FEV_1: forced expiratory volume in one second

CAD: coronary artery disease

ACS: acute coronary syndrome

PCI: percutaneous coronary intervention

STEMI: ST elevation myocardial infarction

NT-proBNP: N-terminal pro-brain natriuretic peptide

AECOPD: acute exacerbation of chronic obstructive pulmonary disease

CRP: C reactive protein

PPI: proton-pump inhibitor

Abstract.

In last years, many studies focused their attention on the complex relationship between chronic obstructive pulmonary disease (COPD) and ischemic heart disease (IHD), showing that these diseases are mutually influenced. Many different biological processes as hypoxia, systemic inflammation, endothelial dysfunction, heightened platelet reactivity, arterial stiffness and right ventricle modification interact in determining the COPD-IHD comorbidity development. The presence of the COPD-IHD comorbidity requires more attention in diagnosis and treatment. Patients with COPD-IHD comorbidity have a worst outcome, as compared to patients with only COPD or only IHD. These patients showed a significant increase on risk of adverse events and of hospital readmissions for recurrent myocardial infarction, heart failure, coronary revascularization, and acute exacerbation of COPD. All these complications determine a significant increase in mortality. In most of cases death occurs for cardiovascular cause and recently after an acute exacerbation of COPD or a cardiovascular adverse event. The development of recent data, drugs and interventional approach may improve the long-term management and outcome of COPD-IHD comorbidity. The aim of this review is to describe the current knowledge on COPD-IHD comorbidity. Particularly we focused our attention on currently available treatments and strategies that may improve and optimize the clinical management of COPD-IHD patients.

Introduction.

Chronic obstructive pulmonary disease (COPD) is characterized by persistent and progressive airflow limitation, associated with an enhanced chronic inflammatory response to noxious particles in airways and lungs [1]. COPD prevalence, morbidity and mortality vary across countries [2]. Current data suggest that by 2030, COPD will be the third-leading cause of death worldwide [3]. These data are alarming because it is not only a disease with high prevalence worldwide but it is frequently under-diagnosed. Ischemic heart disease (IHD) is a chronic condition, result of coronary atherosclerosis, in which coronary arteries become narrow and inadequate to supply a proper oxygenated-blood flow to the heart. Coronary atherosclerosis develops over long time and may remain asymptomatic for many years before clinical manifestations. In most of cases, the first presentation of IHD is an acute coronary syndrome (ACS), due to erosion/fissuration of the atherosclerotic plaque endothelium leading to coronary flow limiting thrombus generation. Although the clinical/epidemiological association between COPD and IHD is well known and widely described, COPD resulted undiagnosed frequently in patients admitted to hospital for IHD. Soriano et al. found that in patients with coronary artery disease (CAD) airway limitation was undiagnosed and, therefore, untreated from 60% to 87% of cases [4]. Inflammation and hypoxia associated with COPD contribute to accelerate the course of IHD that remains the first cause of mortality and morbidity worldwide [5-6]. It is observed a significant negative synergy between COPD and IHD, by accelerating the disease progression, impairing the quality of life and worsening the long-term outcome. Concomitant COPD is an independent risk factor in patients with IHD. Contemporaneously, IHD is one of the principal causes of death in patients with COPD. Nevertheless, further studies are needed to better understand the complexity of the patho-physiological mechanisms underlying to the COPD-IHD comorbidity. The aim of this review is to evaluate current available data about the relationship between COPD and IHD. Particularly, we will

focus on all possible drugs, strategies and approaches to improve the clinical management of IHD-COPD patients, and so their prognosis.

Methods

We searched in *pubmed* following words "chronic obstructive pulmonary disease AND ischemic heart failure"; "chronic obstructive pulmonary disease AND myocardial infarction"; " COPD and betablockers"; "COPD and statins"; "COPD and ACE-inhibitors"; "COPD and bleeding"; "COPD and heart failure"; "COPD and corticosteroids"; "COPD and beta2 agonists". We looked for randomized control trial...

Chronic obstructive pulmonary disease

World health organization defines chronic obstructive pulmonary disease (COPD) as a "persistent and progressive airflow limitation, associated with an enhanced chronic inflammatory response to noxious particles or gases in airways and lungs" [1]. Spirometry is considered the gold standard for the diagnosis and assessment of COPD: it is the most reproducible, standardized, and objective way of measuring airflow limitation. A post-bronchodilator ratio between forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) < 0.70 confirms the presence of a not completely reversible airflow limitation [1]. The main risk factor for COPD is tobacco smoking and in and outdoor pollution. COPD prevalence, morbidity and mortality vary across countries and across different groups within countries [2-3]. Frequently is observed an under-diagnosis of COPD, as showed in several studies, in which known COPD varies from a percentage of 9.4% to 34% and new spirometry-defined COPD from 66% to 90.6% [7-11]. In particular, COPD resulted undiagnosed in individuals with ischemic heart disease (IHD) attended in the hospital: Soriano et al. found that in patient with coronary artery disease (CAD) airway limitation was undiagnosed and, therefore, untreated from 60% to 87% of cases [12]. This under-diagnosis of COPD is still affecting

also the accuracy of mortality data. COPD is one of the principal diseases impacting on costs of health care system, moreover, defining disability adjusting life year (DALY) as sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability, COPD will be the seventh leading cause of DALYs lost worldwide and third leading cause of death in 2030.

Ischemic heart disease

Ischemic heart disease (IHD), or coronary artery disease (CAD), is a chronic condition in which, as a result of atherosclerosis, coronary arteries become narrow and inadequate to supply a proper oxygenated-blood flow to the heart. Coronary atherosclerosis develops over long time and may remain asymptomatic for many years before clinical manifestations. Stable coronary artery disease is characterized by episodes of reversible mismatch between myocardial demand and coronary supply, leading to ischemia or hypoxia; the clinical manifestation of this mechanism is stable angina. Over time, atherosclerotic plaques can rupture, ulcerate or fissurate; if that occurs a blood clot forms on plaque surface and partially or completely obstructs the coronary lumen; that imply the clinical manifestations of acute coronary syndromes (ACS), that are unstable angina and myocardial infarction (MI). There is no need to point out that IHD is the leading cause of death and mass disability in industrialized and developing countries.

Ischemic heart disease is the leading cause of death worldwide, with an increasing economic burden, being one of the major cause of DALYs. Above all acute coronary syndromes are

COPD-IHD comorbidity: the prevalence.

In last years, properly designed prospective studies have been performed to assess the incidence, prevalence and role of IHD in COPD patients. These studies showed that IHD represents the most frequent comorbidity in COPD patients [4,7]. The risk to develop IHD, and particularly ACS, is significantly higher in COPD patients as compared to general population [8]. Contemporaneously, COPD is frequently present in IHD patients. Its prevalence showed a wide variability, ranging from 4% to 18% [9-13]. Probably this discrepancy is due to different criteria used to define COPD (spirometry vs. medical records vs. patients' reported diagnosis) and/or intrinsic limitation of studies in which patients with cardiovascular/respiratory comorbidity were *a priori* excluded [14]. Nevertheless, the diagnosis of COPD-IHD comorbidity is increasing over time. Implementation of COPD diagnostic test, ageing of the population and a better COPD awareness may help to explain this trend. Indeed there is consistent evidence that this trend over time likely reflects a true increase in COPD prevalence, underscoring that COPD is a major comorbidity among patients with IHD [15].

COPD-IHD comorbidity: long-term prognosis.

COPD-IHD comorbidity exerts significantly negative impact over long-term outcome. COPD patients after ACS have decreased short- and long-term survival as compared to patients without COPD [16-17] (Table 1). Up to a third of deaths in patients with COPD are attributable to IHD and for every 10% decrease in forced expiratory volume in one second (FEV_1), cardiovascular mortality increases by 28% [18-19]. Misdiagnosis or the delay in treatment of IHD also influences the worst outcome; it has been estimated that 4% of over 700000 patients admitted to hospital with AECOPD each year have unrecognized myocardial injury [20]. This lack of diagnosis/misdiagnosis is possibly related to the overlap in the clinical manifestation of IHD and AECOPD. Indeed, a study showed that a third of patient with COPD discharged with a primary diagnosis of myocardial infarction presented to hospital with dyspnea (suggesting AECOPD) and not with chest pain (suggesting IHD) [21]. COPD patients are at higher risk of recurrent myocardial infarction (MI), heart failure (HF), and bleeding complications. Particularly, patients with COPD undergoing PCI represent a very high-risk group [13]. Survival curve of COPD patients after MI diverges early from that one of patients without COPD, and this difference increases throughout the follow-up [10]. The negative impact of COPD is particularly evident on the acute phase of patients with ST segment elevation myocardial infarction (STEMI): COPD is a very strong predictor of hemodynamic compromise resulting in death or cardiogenic shock [17]. Also COPD patients who undergo surgical coronary revascularization are at higher risk of complications, including death, atrial fibrillation and pneumonia [22].

Cardiovascular risk and prognosis after acute exacerbations of COPD.

The natural history of COPD is punctuated by recurrent episodes of exacerbation. The risk of acute cardiovascular events appears to be particularly high during acute exacerbation of COPD. Respiratory tract infections and in particular viral infections are the most frequent cause of AECOPD, and may be involved in the increased cardiovascular risk. It has been showed that rhinovirus infection, i.e. the most frequently identified virus during exacerbation of COPD, is able to induce procoagulant changes in airways of infected patients [23]. Although future studies and demonstrations are clearly on demand, these procoagulant changes could be present also in the coronary blood flow triggering acute coronary events. Retrospective studies showed that concentrations of serum cardiac troponin (the most important and sensible marker of myocardial damage) are frequently raised during AECOPD [24]. Troponin increase seems to reflect the severity of exacerbations (even in the absence of a diagnosis of MI) and is related with a significantly higher risk of death after hospital discharge (Table 2) [24-35]. These data have been recently confirmed by Chang et al., who reported that elevated serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T, in patients hospitalized for AECOPD, are independently associated with increased early mortality. Particularly, they showed that increased troponin levels are related with a poor prognosis at 30 days from the discharge for AECOPD and with an increased risk of readmission at 6 month [28]. Interestingly, none of patients enrolled in this study died for ACS; thus the real meaning of the troponin increase during AECOPD is unclear. There are several causes that can explain the increase of this specific blood marker of cardiac injury during AECOPD (Figure 1). Myocardial infarction type 1 is often not recognized during AECOPD. This is demonstrated from analyses of pre-mortem ECG of people died during AECOPD and it is strongly related to hypoxia occurring during AECOPD [36-37]. Acute left ventricular dysfunction is

secondary to higher left afterload for tachycardia, increased work of respiratory muscles during dynamic hyperinflation, increased arterial stiffness with secondary increased systolic and diastolic blood pressure [29]. Acute right ventricular dysfunction is associated with the increase in right ventricular afterload in condition of increased pulmonary hypertension (hypoxic vasoconstriction or concomitant pulmonary embolism).

COPD-IHD comorbidity: underlying pathological mechanisms.

Despite the evidence of frequent clinical association, the underlying common biological and pathological mechanisms are still largely unexplored (Figure 2).

- *Smoking habit.*

It is well known that cigarette smoke plays a leading role for the development of both COPD and IHD. Smoke and other inhaled noxious particles such as biomass fuels or gases are the key factors determining lung and arterial wall inflammatory response. This persistent inflammatory response induces chronic airways obstruction, promotes atherosclerosis and favors coronary plaque instability [1].

- *Hypoxia, inflammation and endothelial dysfunction.*

Local (airways and vessels) and systemic inflammation and hypoxia are common and simultaneously present in COIPD and IHD. Hypoxia is responsible of the activation of renin-angiotensin system, inducing peripheral vasoconstriction and reducing renal blood flow, and may lead to oxidative stress and myocardial infarction [38-39]. COPD patients showed persistent systemic inflammation and increased levels of acute phase proteins as IL-6, C-reactive protein (CRP) and fibrinogen. Fibrinogen is involved in the atherosclerotic process, inducing plaque growing, stimulating the adhesion of platelets and white blood cells to the vessels wall, promoting muscle cell proliferation and migration. Higher plasmatic levels of fibrinogen are directly related to a higher risk of ACS [40]. CRP is an acute phase protein released after vascular damage, it

stimulates the production of IL-6 and endothelin-1 and it is well related to cardiovascular outcome in patients with and without IHD [41]. IL-6 may facilitate atherosclerotic plaque formation [42].

- *Platelet reactivity.*

Systemic inflammatory status of COPD may affect significantly also platelet reactivity and responsiveness to antiplatelet drugs. Indeed, it has been documented that, as a result of inflammation, COPD patients have decreased platelet volume and increased platelet count [43]. High on-treatment platelet reactivity is a strong predictor of poor prognosis in patients undergoing percutaneous coronary intervention (PCI) and stent implantation [44]. Recently, we showed that the platelet reactivity is effectively and significantly higher in COPD patients. This is independent to age, sex, cardiovascular risk factor and clinical presentation of IHD [45]. All COPD patients were treated with aspirin and clopidogrel (dual antiplatelet therapy) and it has been observed lower drug responsiveness, as compared to patients without COPD. Moreover, platelet aggregation is accelerated by hypoxia [46]. All together this data documents a significant increased pro-thrombotic risk in COPD patients. The recently reported improvement in the survival of very severe COPD patients after antiplatelet drug administration may be considered a further indirect demonstration of their increased thrombotic risk [47].

- *Arterial stiffness*

The increase in vasoconstriction, oxidative stress and ageing in COPD are factors that act together inducing an important increase in arterial stiffness. The higher arterial stiffness observed in COPD patients is due to several factors: increased blood pressure (systolic and diastolic), severity of inflammation, increased coronary artery calcium, older age, imbalance between protease and anti-protease, severity of hypoxia, chronic hyperglycaemia [48-50]. MMP-2, -9 and neutrophil elastase increase in COPD patients. These proteases are implicated in the following processes: pathogenesis

of atherosclerotic plaque, change of the arrangement of wall vessel elastic fibers, destabilization of the atherosclerotic plaque with promotion of its rupture and thrombus formation [49-50]. Several studies showed a strong relationship between arterial stiffness measure and GOLD stage of COPD [51]. Patients in the GOLD stage III/IV showed a significantly higher arterial stiffness, that is an independent predictor of cardiovascular events and mortality [51].

- *Extension of coronary artery disease.*

Preliminary angiographic studies showed worse atherosclerotic burden and atherosclerotic lesion properties in patients with COPD as compared to those without [13]. Particularly, coronary artery calcifications are more severe. Interestingly, in COPD patients a higher Agaston score (indirect index of coronary calcium) is predictive for total and cardiovascular mortality, even if it is not related to the severity of airflow obstruction [48].

- *Right ventricle morphology and function.*

Lung hyperinflation, systemic inflammation and endothelial dysfunction act all together in COPD patients, resulting in a direct and negative impact on the right ventricle. Indeed a recent study of Hilde et al. revealed that in COPD patients even if pulmonary artery systolic pressure is normal, initial signs of remodelling of right ventricle, such as mild hypertrophy, dilatation or reduced systolic function are present, suggesting that all patho-physiological mechanisms characterizing the chronic inflammatory state of COPD patient induce a premature damage on right ventricle [52].

- *Abnormalities in coagulation cascade and bleeding risk.*

In a prospective, multinational study of 8167 patients hospitalized for ACS, thrombolytic therapy

and glycoprotein IIb/IIIa inhibitors were less likely to be administered to COPD population because of the increased bleeding risk [53]. The increased bleeding risk is confirmed by data from REAL (Registro Angioplastiche dell'Emilia-Romagna) registry, which showed that COPD emerged as a strong independent risk factor for serious bleeding events [13]. Reasons for an increased bleeding risk are several, starting from the higher risk of arrhythmia, such as atrial fibrillation, which requires an anticoagulation therapy. Similarly, a recent finding reported that COPD patients, as compared to subjects with normal lung function, have a higher prevalence of cerebral microbleeds detected at magnetic resonance imaging [54]. Also a significant higher risk of peptic ulcer bleeding is reported [55]. Studies on thrombin generation profiles in COPD patients, as compared to healthy subjects, showed increased levels of prothrombin, coagulation factors II, V, VII, VIII and IX and lower level of free tissue factor pathway inhibitor, as well as higher maximum thrombin levels, rates of thrombin generation and total thrombin formation. These findings may contribute to the altered thrombotic phenotype in COPD patients [56].

COPD-IHD comorbidity: considerations for its clinical management.

Currently, clinical studies tailored on the management of COPD-IHD patients are not available. Nevertheless, the analysis of prospective and retrospective registries may suggest several recommendations that are discussed below (Figure 3).

- *Early diagnosis of COPD-IHD comorbidity.*

The early diagnosis of concomitant pathology, which may worse prognosis, is relevant both for concomitant IHD in COPD patients and concomitant COPD in IHD patients. Being well known that COPD and IHD share several risk factors, physicians should identify patients at risk and investigate the possible concomitant disease. Particularly, patients admitted for ACS who are elderly and with a history of smoking (or exposure to occupational dusts or chemicals) should be considered at risk for having concomitant COPD. Therefore, clinical suspicion needs to be assessed by spirometry to confirm the presence of persistent airflow limitation. On the other hand, patients referring to physician's attention with a confirmed diagnosis of COPD should be assessed for their cardiovascular risk profile. GOLD guidelines point out that cardiovascular disease is probably the most frequent and most important disease coexisting with COPD, so its assessment should be considered promptly [1]. Another subset of patients deserving special attention is that including patients hospitalized for AECOPD. Current data suggest that the elevation of two cardiac markers as troponin and pro-BNP predict strongly worse prognosis. It is important to measure these biomarkers in any patient hospitalized for AECOPD. The correct interpretation of this biomarker is a clinical challenge as it may reflect the severity of the exacerbation or an ACS, which anyway necessitate prompt treatment and whose recognition is crucial.

- *Improving the diagnosis of ACS in COPD patients.*

During ACS, COPD patients are more likely to present atypical symptoms such as non-typical chest pain, palpitation and dyspnea than typical chest pain. The misleading clinical presentation causes a significant delay in diagnosis and treatment, which exerts a negative impact over prognosis [53]. Furthermore, ECG abnormalities are common in COPD patients and may hinder the early detection of coexisting ACS [57]. Elevated values of cardiac troponin, as we have seen before, may be of uncertain interpretation. Considering that an early diagnosis is crucial for the correct management of ACS, special attention should be paid to patients with a history of COPD when they present to physician's attention, to avoid delay in diagnosis and treatment.

- *Optimization of the antiplatelet treatment.*

The enhanced platelet reactivity of COPD patients and the evidence that antiplatelet therapy improves survival in patients with oxygen-dependent COPD [47], may suggest that concomitant presence of COPD in ACS patients could request drugs providing the strongest platelet inhibition. Contemporaneously, a recent registry showed that presence of asthma/COPD is an independent predictor favoring the use of clopidogrel over prasugrel and ticagrelor [58]. Patients with COPD may have an increased absolute risk of experiencing dyspnea with ticagrelor, the mechanism of which has not been elucidated (interaction between ticagrelor and adenosine generation may be responsible). The symptom usually resolves without need for treatment discontinuation and rarely requires ticagrelor to be stopped. As a general recommendation, patients with COPD in the setting of an ACS should be treated with dual antiplatelet therapy, with a combination of aspirin and ticagrelor rather than aspirin and clopidogrel, exactly as any other patient with ACS should be [5-6].

- *Access site for coronary revascularization.*

COPD patients who undergo coronary artery angiography and PCI for ACS have a higher risk,

compared to patients without COPD, of experiencing major entry-site complications and access site bleeding requiring red blood cell transfusion [12]. The use of radial artery as access site for the procedures showed to reduce significantly these bleeding complications. For this reason in COPD patients may be preferable the radial artery access site as compared to femoral artery, to obtain a significant reduction of bleeding complications.

- *Optimization of the coronary revascularization.*

Observational studies showed that COPD patients hospitalized for ACS are less likely to receive coronary revascularization (surgical or percutaneous) than patients without COPD [53]. As showed by Enriquez et al. COPD patients undergoing PCI are more likely to have high-risk demographic features and to have a greater extent of coronary artery disease at angiography [12]. It is important to underline that a conservative approach finds no evidence-based recommendation, so myocardial revascularization should not be denied or delayed in patients affected by ACS, regardless of whether they have COPD or not [5-6]. Finally patients with COPD who undergo PCI are less likely to receive drug-eluting stent compared with COPD-free subjects [13]. This practice finds no evidence-based validation and should be discouraged, as the whole presence of COPD does not represent for itself a contraindication to prolonged dual antiplatelet therapy. So, as a general recommendation, implantation of drug eluting stent should be preferred over bare metal stent [5-6].

- *Optimization of COPD specific therapy.*

Is debated if corticosteroids alone reduce mortality in COPD patients and modify the long-term decline in lung function. Their use is indicated to improve symptoms, reduce the frequency of exacerbations and improve quality of life [1]. The preferred route of administration is inhalation because oral corticosteroids have numerous side effects [59]. Moreover, oral corticosteroids may further increase the risk of bleeding complications [60]. Then, awaiting future trials evaluating the impact of steroid administration over cardiac outcomes, inhaled corticosteroids are recommended,

when indicated. Beta$_2$-agonists improve FEV$_1$ and symptoms. Their use does not increase the risk of cardiovascular events, so they should not be avoided because of IHD. In general, there is no evidence that COPD should be treated differently from usual in presence of concomitant IHD [1,19].

- *Exercise training and pulmonary rehabilitation in COPD-IHD patients.*

Regular physical activity improves myocardial perfusion and retards disease progression in IHD patients. As described by Hambrecht et al., a 12-months program of regular physical exercise in patients with stable coronary artery disease improved the event-free survival, the exercise capacity and reduced the number of hospital readmissions and of repeat revascularizations [61]. Exercise training by reducing basal sympathetic activity, enhancing vagal activity, restoring baroreflex sensitivity, improving endothelium-dependent vasodilation, might decrease blood pressure and reduce myocardial ischemia and arterial stiffness [51]. Similar findings are obtained in COPD patients by the pulmonary rehabilitation. Pulmonary rehabilitation includes exercise training, education and behavior changes, with the objective to improve the physical and psychological condition of people with chronic respiratory disease. Inspiratory muscle training leads to a reduction of dyspnoea and to an improvement in pulmonary function, respiratory muscle strength, and functional capacity. A larger longitudinal study confirmed the ability of pulmonary rehabilitation in reducing dyspnoea and increasing exercise tolerance [62]. It has been demonstrated that pulmonary rehabilitation may increase FEV$_1$, delaying its progressive decline [63]. At the same time, as demonstrated by Thirapatarapong et al., IHD-COPD patients have significantly impaired cardiopulmonary exercise test responses with lower exercise capacity and impaired gas exchange compared to COPD patients without IHD [64]. All these findings explain the relevance and potential positive prognostic influence of exercise training and pulmonary rehabilitation in patients with COPD-IHD comorbidity. COPD-IHD comorbidity should not be considered a limitation and/or contraindication for exercise training and pulmonary rehabilitation. On the contrary,

although specific prospective studies are lacking, exercise training and pulmonary rehabilitation in COPD-IHD patients should be early started to improve dyspnoea, angina, health-related quality of life, cardiovascular response at exercise and finally long-term prognosis.

- *Optimization of IHD specific therapy: beta-blockers.*

Historically, beta-blockers were under-prescribed in COPD patients [12,65]. This was principally due to the risk of bronchoconstriction secondary to the inhibition of beta 2 adrenoreceptors. Current evidences suggest that, when indicated, the use of beta-blockers brings benefits considerably larger than the potential risks even in patients with irreversible bronchial obstruction. The use of beta-blockers is considered safe and should not be avoided because of COPD, neither during stable phase nor during exacerbations. For their selective action over $beta_1$ receptor, cardio-selective agents such as atenolol, bisoprolol, metoprolol and nebivolol should be preferred over other beta-blockers for their minor effect over bronchial muscle. Cardio-selective beta-blockers produce no change in FEV_1 or respiratory symptoms compared to placebo. Furthermore, cardio-selective beta-blockers did not affect FEV_1 response to treatment with $beta_2$-agonists, when used in association [1,66].

- *Optimization of IHD specific therapy: statins.*

Statins represent the cornerstone of the IHD treatment. Recently, preliminary studies showed that statins are able to exert an immunomodulatory effect on COPD and to inhibit both pulmonary and systemic inflammation [67]. In retrospective studies the administration of statins reduced significantly the risk of COPD exacerbations [68]. This key point has been prospectively investigated in the randomized placebo-controlled trial of simvastatin in the prevention of COPD exacerbations (STATCOPE) [69]. In the STATCOPE trial, the administration of simvastatin at a daily dose of 40 mg did not affect exacerbation rates or the time to a first exacerbation in patients with COPD who were at high risk for exacerbations [69]. Nevertheless, considering the well-known

benefit of statins in IHD patients, the prescription of statins in patients affected by COPD-IHD comorbidity is recommended. Accordingly, recent evidences suggest the absence of differences in the rate of statin's prescription between patients with or without concomitant COPD [13].

- *Optimization of IHD specific therapy: ACE-inhibitors.*

A recent study demonstrated that, in smokers (n=1170) with a rapid FEV_1 decline (high risk for COPD), the use of angiotensin-converting enzyme (ACE) inhibitors was protective against rapid decline and COPD progression [70]. This was particularly evident among smokers with concomitant cardiovascular disease, hypertension, or diabetes. The anti-inflammatory action of ACE inhibitors, due to the blockage of the pro-inflammatory effect of angiotensin II, is well known. They are able to modulate the recruitment of inflammatory and immune cells into the lung and thereby to reduce lung function decline in cigarette smokers. It is possible that the administration of ACE inhibitors to subjects with a clinical indication for its use may exert an unexpected beneficial effect on vascular endothelial dysfunction and lung parenchymal destruction [70]. Starting from the well known protective effect of ACE-inhibitors in IHD patients, the discovery of an additional protective role of ACE-inhibitors in reducing the decline in FEV_1, makes mandatory to early prescribe this drug in COPD-IHD patients.

- *Management of the increased bleeding risk.*

Dual antiplatelet therapy and steroids (both frequently prescribed in COPD-IHD patients) increase the risk of gastrointestinal bleeding. The administration of proton-pump inhibitors reduces this risk [5-6,71]. Particular care should be used in managing revascularization strategies and medical therapy in COPD patients, including stent type (e.g. second generation DES), arterial access site and type and length of dual antiplatelet therapy. Special attention deserves COPD-IHD patients with atrial fibrillation (concomitant use of oral anticoagulation) and/or those in oral corticosteroids.

The chronic use of proton-pump inhibitors is mandatory in these patients. In patients requiring oral anticoagulation, new anticoagulant agents (dabigatran, apixaban, rivaroxaban) with a more favorable risk profile as compared to warfarin should be preferred [72-74].

Conclusions.

The link between COPD and IHD is very complex and it still not fully understood. In daily clinical practice, the principal aim should be the adoption of the better treatment of each singular disease. Future studies are clearly on demand to validate pharmacological and interventional treatments tailored on COPD-IHD patients. These studies should improve our ability in the early diagnosis of the presence and risk of COPD-IHD comorbidity and should suggest treatments able to improve the long-term outcome.

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Figure legend.

Figure 1. Relationship between acute exacerbation of COPD and troponin levels.
AECOPD: acute exacerbation of chronic obstructive pulmonary disease. ACS: acute coronary syndromes.

Figure 2. From pathological mechanisms to clinical manifestations in COPD-IHD comorbidity.
PR: platelet reactivity. CAD: coronary artery disease. RV: right ventricle. COPD: chronic obstructive pulmonary disease. IHD: ischemic heart disease.

Figure 3. Clinical management of COPD-IHD patients.
COPD: chronic obstructive pulmonary disease. IHD: ischemic heart disease. ECG: electrocardiogram. TT ECHO: transthoracic echocardiography. CAD: coronary artery disease. TN: troponin. AECOPD: acute exacerbation of COPD. PPI: proton pump inhibitor. BB: beta-blockers. DES: drug eluting stent. HA: hospital admission. HF: heart failure. MI: myocardial infarction. +: positive.

Table 1: Prognostic impact of COPD comorbidity in patients with-IHD.

References	Study population	COPD Pts n° (%)	Diagnosis of COPD	Follow-up	Mortality rate in COPD patients vs controls without COPD	HR of mortality in COPD population	Other outcomes in COPD population
Berger at al. [9]	4284 patients underwent PCI	183 (4%)	Requirement of chronic bronchodilator therapy or a FEV_1 < 75% of the predicted value or a room air pO2 <60 or a pCO2 >50.	3 years	21% vs. 9%	2.15 (95%CI 1.53-3.02)	--
Selveraj et al. [11]	10994 patients underwent PCI	1117 (10%)	Clinical history, COPD marked as comorbidity in database.	33 months	24.4% vs. 10.4 % 2.9% vs. 1.2% (in-hospital)	2.16 (95%CI 1.81-2.56)	in-hospital death HR 2.5 (95%CI 1.45-4.35)
Enriquez et al. [12]	10908 patients underwent PCI	869 (8%)	History or presence of physician-diagnosed COPD and chronic pharmacologic therapy and/or have an FEV_1 <75% of predicted value.	1 year	2.2% vs. 1.1% (in-hospital)	1.30 (95%CI 1.01-1.67)	repeated CR HR 1.22 (95%CI 1.02-1.46)
Bursi et al. [10]	3438 patients with MI	415 (12%)	Medical records	5 years	--	1.30 (95%CI 1.10-1.54)	5-year survival rate: 46% (95%CI 41-52) vs. 68% (95%CI 66-70) in COPD vs. no COPD patients
Campo et al. [13]	11118 patients underwent PCI	2032 (18%)	Documented history of hospital admission for COPD or treatment with pharmacologic therapies specific for COPD	3 years	23.5% vs. 16%	1.4 (95%CI 1.2-1.6)	reMI HR 2.1 (95%CI 1.4-3.3) HF HR 5.8 (95%CI 4.6-7.5), SBE HR 3 (95%CI 2.1-4.4)

HR: hazard ratio. PCI: percutaneous coronary intervention. COPD: chronic obstructive pulmonary disease. CR: coronary revascularization. MI: myocardial infarction. SBE: serious bleeding event. HF: heart failure. FEV_1: forced expiratory volume at 1 second.

Table 2. Troponin increase during acute exacerbation of COPD.

References	Study design (pts)	Troponin dosage timing	Follow-up	% of pts with increased troponin	Data on mortality related to increased troponin	Other outcomes related to increased troponin
Baillard et al. [30]	P (71)	Tn I admission and after 24h	Hospital stay	18%	HR 6.52 (95%CI 1.23–34.47) of in-hospital mortality.	---
Brekke et al. [26]	P (897)	Tn T after 24h from the admission	1,9 years	---	HR 1.64 (95%CI 1.15–2.34) of all-cause mortality.	---
Harvey et al. [24]	R (188)	Tn T/I admission	Hospital stay	25%	---	Longer hospital admissions
Kelly et al. [31]	R (252)	Tn I admission	Hospital stay	30%	4.4% in hospital mortality in Tn increased group (95%CI 2.5–7.7); HR 8.3 (95%CI 1.58–43.7) of in-hospital mortality.	---
Marcun et al. [32]	P (127)	Tn T admission and before the dicharge	6 months	36%	---	HR 2.89 (95% CI 1.13–7.36) for hospital readmissions.
Martins et al. [33]	R (173)	Tn I in 48 h from admission	18 months	70%	No significant differences for in-hospital mortality Higher 18th month mortality in pts with high troponin.	---
McAllister et al. [34]	P (242)	Tn I/T in 48 h from admission	Hospital stay	10%	---	No association between chest pain and ECG changes in patients with increased troponin
Chang et al. [28]	P (241)	Tn T in 24 h from admission	One months	17%	HR 6.3 (95% CI 2.4-16.5) for 30 days mortality.	---
Hoiseth et al. [29]	P (99)	hs Tn T admission	1,9 years	---	HR 4.5 (95%CI 1.2-16) for death among pts with hs-cTnT levels 14.0-39.9 HR 8.9 (95% CI 2.4-32) for death among pts with hs-cTnT >40 ng/l	---
Fruchter et al. [35]	R (182)	Tn I in 24 h from admission	50 months	---	HR 1.3 for mortality	---

P: prospective. R: retrospective. Pts: patients. Tn: troponin. HR: hazard risk. CI: confidence interval.

Figure 1

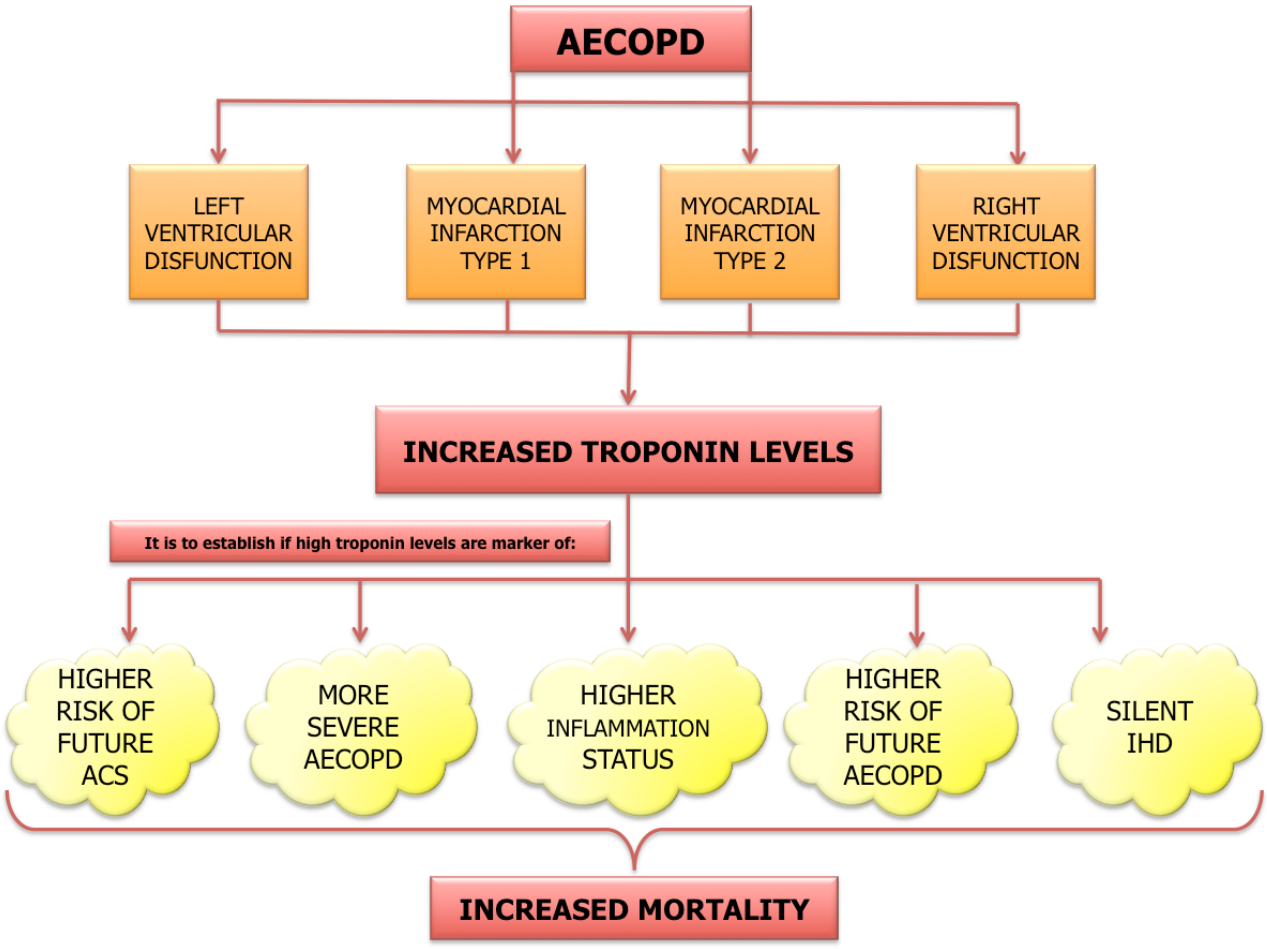

AECOPD
LEFT VENTRICULAR DISFUNCTION
MYOCARDIAL INFARCTION TYPE 1
MYOCARDIAL INFARCTION TYPE 2
RIGHT VENTRICULAR DISFUNCTION
INCREASED TROPONIN LEVELS
It is to establish if high troponin levels are marker of:
HIGHER RISK OF FUTURE ACS
MORE SEVERE AECOPD
HIGHER INFLAMMATION STATUS
HIGHER RISK OF FUTURE AECOPD
SILENT IHD
INCREASED MORTALITY

Figure 2

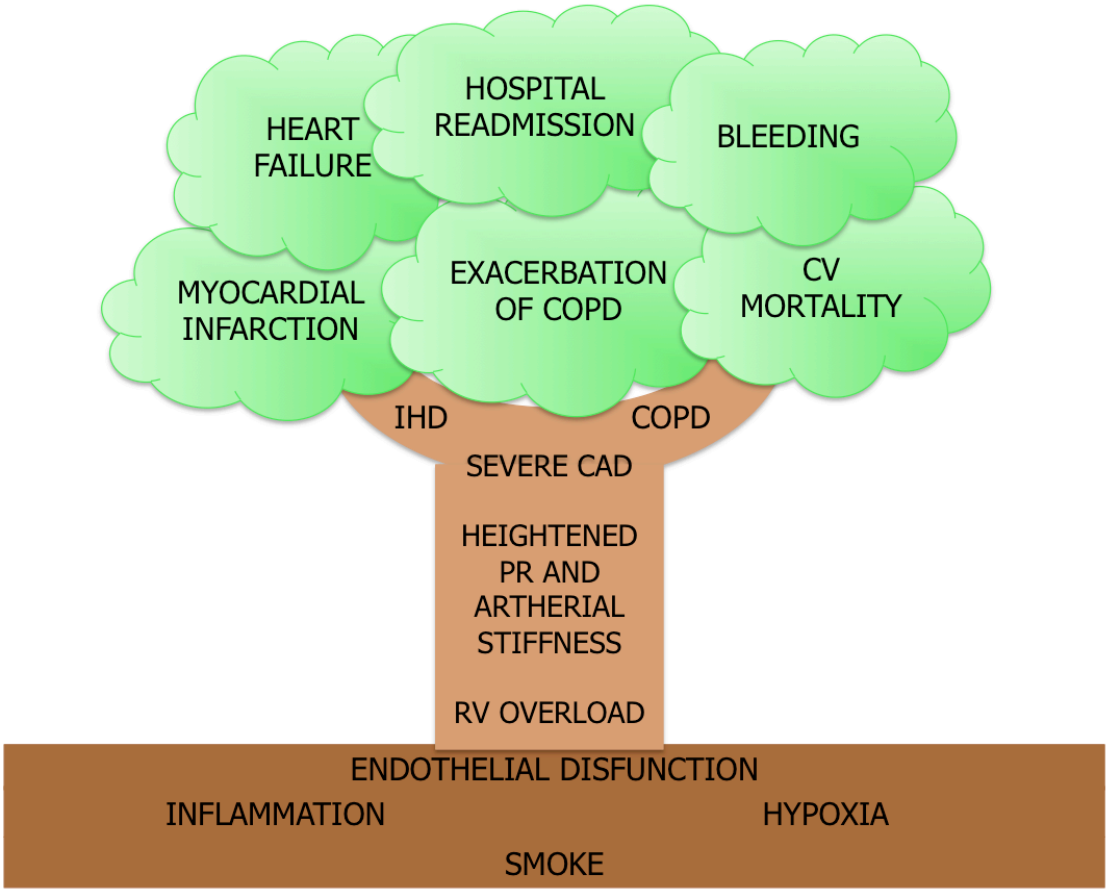
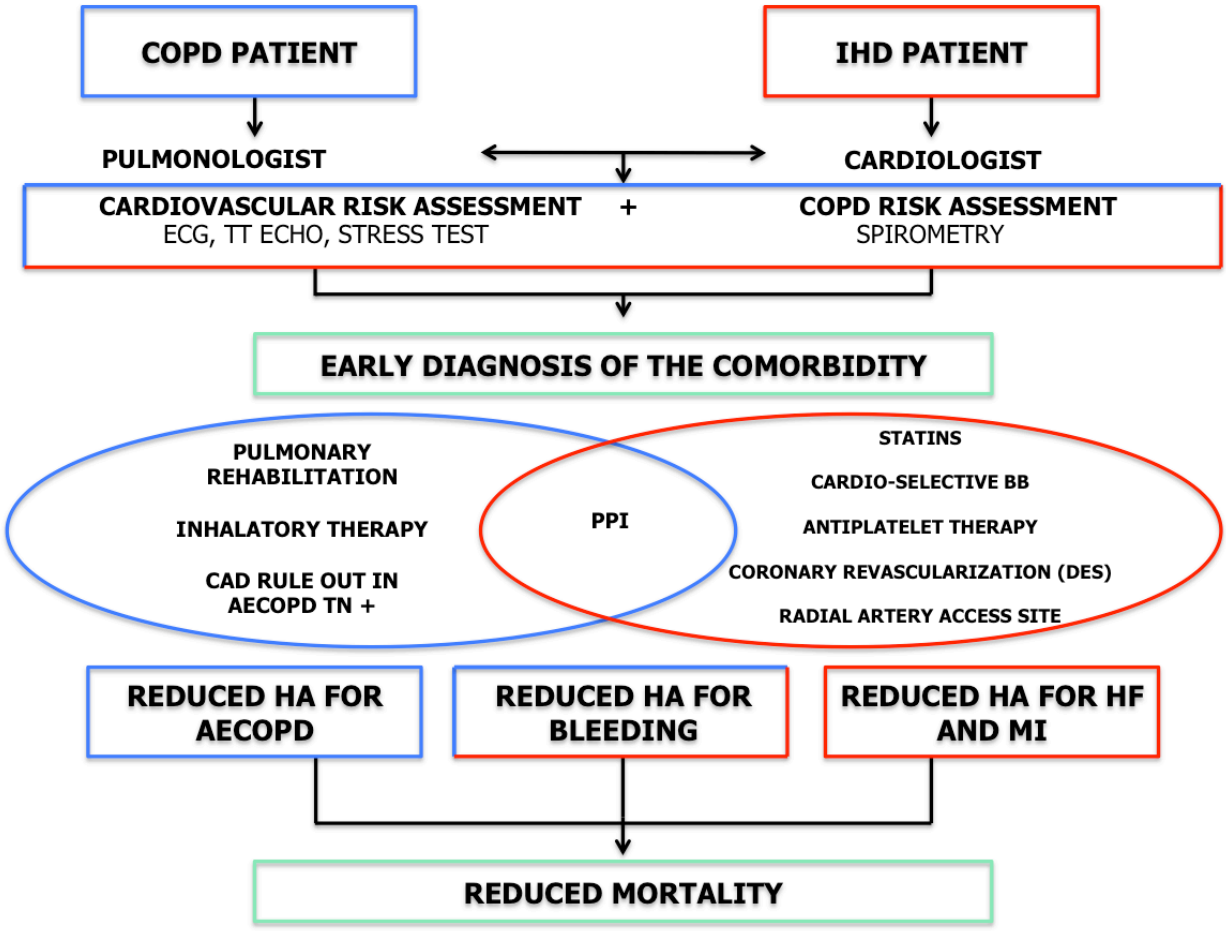

HEART FAILURE
HOSPITAL READMISSION
BLEEDING
MYOCARDIAL INFARCTION
EXACERBATION OF COPD
CV MORTALITY
IHD
COPD
SEVERE CAD
HEIGHTENED PR AND ARTHERIAL STIFFNESS
RV OVERLOAD
ENDOTHELIAL DISFUNCTION
INFLAMMATION
HYPOXIA
SMOKE

Figure 3


COPD PATIENT
IHD PATIENT
PULMONOLOGIST
CARDIOLOGIST
CARDIOVASCULAR RISK ASSESSMENT
ECG, TT ECHO, STRESS TEST
+
COPD RISK ASSESSMENT
SPIROMETRY
EARLY DIAGNOSIS OF THE COMORBIDITY
PULMONARY REHABILITATION
INHALATORY THERAPY
CAD RULE OUT IN AECOPD TN +
PPI
STATINS
CARDIO-SELECTIVE BB
ANTIPLATELET THERAPY
CORONARY REVASCULARIZATION (DES)
RADIAL ARTERY ACCESS SITE
REDUCED HA FOR AECOPD
REDUCED HA FOR BLEEDING
REDUCED HA FOR HF AND MI
REDUCED MORTALITY