Chronic Obstructive Pulmonary Disease and Ischemic Heart Disease Comorbidity: Overview of Mechanisms and Clinical Management.

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Brief Title: COPD-IHD comorbidity.

Word count: abstract: 216; text: 3167; references: 2119.

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Keywords.

Chronic obstructive pulmonary disease; ischemic heart disease, myocardial infarction, comorbidity, mortality.

Abstract.

In the last few years, many studies focused their attention on the 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 the development of the COPD-IHD comorbidity, which therefore deserves special attention in early diagnosis and treatment. Patients with COPD-IHD comorbidity have a worst outcome, when 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. Taken together, these complications determine a significant increase in mortality. In most of cases death occurs for cardiovascular cause, soon after an acute exacerbation of COPD or a cardiovascular adverse event. Recent data regarding incidence, mechanisms and prognosis of this comorbidity, along with the development of new drugs and interventional approaches may improve the management and long-term outcome of COPD-IHD patients. The aim of this review is to describe the current knowledge on COPD-IHD comorbidity. Particularly, we focused our attention on underlying pathological mechanisms and we revise all treatments and strategies that may improve and optimize the clinical management of COPD-IHD patients.

Introduction.

Ischemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD) are major causes of morbidity and mortality worldwide [1-2]. There is a growing interest for the relationship between these two clinical entities [3-4]. This is principally due to their mutual interaction and clinical implications [1-4]. The aim of this overview is to analyze the literature in order to clarify current knowledge about: i) incidence and prevalence of COPD-IHD comorbidity; ii) mechanisms underlying IHD and COPD; iii) impact on the prognosis; iv) interventional and pharmacological treatments for COPD-IHD patients.

Research strategy.

To perform the present overview, we searched in MEDLINE and Google Scholar with MESH strategy. The terms used to start our research for relevant articles were: ("Myocardial Infarction" OR "Acute Coronary Syndrome" OR "Cardiovascular Diseases" OR "Myocardial Ischemia" OR “Heart Diseases”) AND ("Pulmonary Disease, Chronic Obstructive" NOT “Asthma”). Four independent reviewers (RP, MM, SM, SB) screened the bibliography, analyzing titles and abstracts and discussing when there were divergences. The articles selected were all full English papers. We limited the studies from 1990 to 2014. The search was further enhanced by analyzing references of selected articles or reviews. Articles were selected if they met the following criteria: (i) clinical trial (randomized or not), (ii) observational study, (iii) meta-analysis, (iv) review (systematic or not), (iv) international guidelines.

Chronic obstructive pulmonary disease.

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 [5]. The pooled prevalence of COPD was 7.6%, as estimated by a recent systematic review and meta-analysis of 37 studies [6]. Other studies showed prevalence ranging from 7.8% to 19.7%, but with a large amount of regional heterogeneity [7-8]. Prevalence is significantly higher in smokers or ex-smokers and males, and increases with age [1]. Current data suggest that by 2030, COPD will be the third-leading cause of death worldwide [9]. These data are alarming because the disease has a high prevalence worldwide but it is frequently under-diagnosed [1]. It is clearly recommended that the diagnosis of COPD could be established only with spirometry, which is the only reproducible and objective way to assess airflow limitation post-bronchodilator. The natural history of COPD is punctuated by recurrent episodes of acute exacerbations (AECOPD) which often require hospitalization and negatively affect patients quality of life, accelerate the rate of decline in lung function and are associated with significant mortality [1]. AECOPD carry a 10% risk of in-hospital mortality, which raises to 49% after 3 years [1].

COPD-IHD comorbidity.

- *Epidemiology.*

Both IHD and COPD are the result of cumulative exposure to risk factors over decades. Smoking history is a common risk factor for the two diseases, so it is not unexpected to find patients affected by IHD and COPD at the same time, especially in elderly. IHD is the most frequent comorbidity in COPD patients [1,3,10]. The risk to develop IHD, and particularly acute coronary syndrome (ACS), is significantly higher in COPD patients, if compared to general population [4]. Similarly, COPD is frequent in IHD patients, ranging from 4% to 18% [11-16]. This variability is due to different criteria used to define COPD (spirometry vs. medical records vs. patients' reported diagnosis) and/or intrinsic limitation of studies which *a priori* excluded patients with cardiovascular/respiratory comorbidity [11-16]. Moreover, the prevalence of COPD-IHD comorbidity is increasing over time [1,3,7], mainly because of implementation of diagnostic tests, ageing of the population and a growing awareness regarding COPD.

- *Underdiagnosis of COPD in IHD patients and vice-versa.*

Although the clinical/epidemiological association between COPD and IHD is well known and widely described, a consistent lack of diagnosis has been documented [17-18]. COPD resulted frequently undiagnosed in patients admitted to hospital for IHD [18]. Soriano et al. found that, despite its high prevalence, airway limitation was underdiagnosed in 60% of patients with cardiovascular disease (CVD) and in 87% of those with coronary artery disease (CAD) [18]. Similarly, in COPD patients, ACS may often occur with atypical symptoms (dyspnea instead of chest pain) [19]. ECG abnormalities (conduction abnormalities, especially left bundle branch block and right bundle branch block, higher heart rate and longer QTc) are common in COPD patients and may hinder the early detection of coexisting ACS [20].

- *Outcomes of IHD patients with concomitant COPD.*

COPD and IHD mutually exert a negative impact over disease progression, quality of life, short- and long-term outcomes. In IHD patients, several studies showed that the presence of concomitant COPD is associated with decreased short- and long-term survival compared to patients without COPD (Table 1) [11-15, 21-25]. Survival curve of COPD patients after myocardial infarction (MI) diverges early from that one of patients without COPD, and this difference continues to increase throughout the follow-up [12]. In the acute phase, in-hospital death or cardiogenic shock occurred more frequently in COPD patients (23.1% vs. 14.4% in patients without COPD, p<0.001) [26]. After multivariate analysis, COPD remained an independent predictor of hemodynamic compromise (OR 1.83, 95%CI 1.17-2.86) [26]. In the long-term follow-up, COPD patients admitted to hospital for ST-segment elevation MI and receiving primary PCI, are at higher risk of recurrent MI, heart failure and bleeding complications [15]. Similar findings were observed in COPD patients receiving coronary artery bypass graft (CABG) (Table 1) [21-25]. COPD patients undergoing surgical coronary revascularization are at higher risk of perioperative complications (acute renal failure, deep sternal wound infection, prolonged mechanical ventilation, atrial fibrillation) and early mortality [24].

- *Cardiovascular adverse events in COPD patients.*

In patients with COPD, up to a third of deaths are attributable to IHD [1]. For every 10% decrease in forced expiratory volume in one second (FEV_1), cardiovascular mortality raises by 28% [27-28]. The natural history of COPD includes recurrent episodes of exacerbation. A 2.3-fold increase in MI after AECOPD (95% CI, 1.1-4.7) has been documented [29]. In patients with previous STEMI and concomitant COPD, we observed an increased risk of recurrent MI after hospital admission for AECOPD (HR 2.1; 95% CI, 1.4-3.3) and a four-fold increased risk of death (HR, 4.2; 95% CI, 3.4-5.2) [15].

- *Cardiac markers increase during AECOPD and outcomes.*

The role of myocardial biomarkers in the setting of AECOPD is debated (Table 2) [30-40]. Retrospective studies showed that concentrations of serum cardiac troponin (the most sensitive marker of myocardial damage) are frequently raised during AECOPD [30-40]. Several causes, summarized in Figure 1, may explain the increase of this specific blood marker of cardiac injury during AECOPD [17,41-42]. Additionally, several concomitant factors may influence and contribute to cardiac troponin elevation (e.g. aortic valve disease, left ventricle hypertrophy, anaemia, heart failure, advanced age, renal failure, sepsis) [43]. Notably, troponin elevation has been associated with overall mortality after hospital discharge (Table 2) [30-40] and to higher risk of cardiac death and MI [40].

COPD-IHD comorbidity: underlying pathological mechanisms.

Despite the evidence of frequent clinical association, the underlying common biological and pathological mechanisms remain still largely unexplored.

- *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 in 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 frequently and simultaneously present in COPD and IHD [1,41]. 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 [44]. COPD patients showed persistent systemic inflammation and increased levels of acute phase proteins as interleukin-6 (IL-6), C-reactive protein (CRP) and fibrinogen [45]. Fibrinogen is involved in the atherosclerotic process, inducing plaque growing, stimulating the adhesion of platelets and white blood cells to the vessels wall and promoting muscle cell proliferation and migration [46]. High plasmatic levels of fibrinogen are directly related to risk of ACS [46]. 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 [47]. IL-6 may facilitate atherosclerotic plaque formation [41].

- *Platelet reactivity.*

COPD-related systemic inflammatory status may significantly affect also platelet reactivity (PR) and responsiveness to antiplatelet drugs. Indeed, as a result of inflammation, COPD patients have decreased platelet volume and increased platelet count [48]. High on-treatment PR is a strong

predictor of poor prognosis in patients undergoing PCI and stent implantation [49]. Recently, we showed that on-treatment PR is significantly higher in COPD patients [50]. This finding is independent to age, sex, cardiovascular risk factors and clinical presentation of IHD [50]. In COPD patients on dual antiplatelet therapy (aspirin + clopidogrel), we observed a lower drug responsiveness compared to patients without COPD [50]. The recently reported survival improvement of COPD patients after antiplatelet drug administration, may be considered a further indirect demonstration of the increased thrombotic risk in this population [51-52].

- *Arterial stiffness*

COPD is strongly related to increased arterial stiffness [53-54], because of 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 [53-55]. Moreover, matrix metalloproteinase (MMP)-2, MMP-9 and neutrophil elastase increase in COPD patients [56]. These proteases are implicated in a multitude of pathological processes, as atherosclerotic plaque formation, destabilization and rupture, thrombus formation [41,55], and change of the arrangement of wall vessel elastic fibers. Several studies showed a strong relationship between arterial stiffness and GOLD stage of COPD [53-54]. Patients in the GOLD stage III/IV showed a significantly higher arterial stiffness, which is an independent predictor of cardiovascular events and mortality [53-54].

- *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 [57-59]. Particularly, coronary artery calcifications are more severe in COPD patients [57-59]. Interestingly, in these patients a high Agaston score (indirect index of coronary calcium) is predictive for mortality [57].

- *Right ventricle morphology and function.*

A recent study of Hilde et al. showed the presence of initial signs of right ventricle remodeling (mild hypertrophy, dilatation or reduced systolic function) in COPD patients, even with normal pulmonary artery systolic pressure [42]. These findings suggested that COPD pathophysiological mechanisms induce a premature damage on right ventricle [42].

- *Abnormalities in coagulation cascade.*

Studies on thrombin generation profile of COPD patients 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 [60]. As a consequence, higher maximum thrombin levels, rates of thrombin generation and total thrombin formation are observed [60]. These findings may contribute to the altered thrombotic phenotype of COPD patients [60].

Clinical management of COPD-IHD comorbidity.

Frequently, the clinical management of COPD-IHD patients may be challenging. Randomized clinical trials on the topic are missing. Nevertheless, the analysis of prospective and retrospective registries may suggest several recommendations that are discussed below (Figure 2).

- *Diagnosis of COPD-IHD comorbidity.*

As COPD and IHD share several risk factors [1-4], physicians should identify patients at risk and investigate the possible concomitant disease. Particularly, patients admitted for ACS with a history of smoking (or exposure to occupational dusts or chemicals) should be considered at risk for having concomitant COPD. Spirometry is mandatory to confirm COPD diagnosis, but this test is not recommend in the early phase after ACS [1]. These patients should be referred to pulmonologists in the follow-up, for both evaluation and risk assessment. 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 important disease coexisting with COPD, so its assessment should be promptly considered [1].

- *Coronary revascularization.*

COPD patients undergoing PCI have a greater extent of coronary artery disease at angiography [57], compared to patients without COPD, and a significantly increased risk of death (HR 1.30, 95%CI 1.01-1.67) or repeat revascularization (HR 1.22, 95%CI 1.02-1.46) [14]. Nonetheless, observational studies showed that COPD patients hospitalized for acute MI are less likely to receive coronary revascularization (surgical or percutaneous) than patients without COPD (OR 0.64: 95%CI 0.54-0.77 for PCI and 0.46: 95%CI 0.32-0.66 for surgery) [19]. 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 [2]. Furthermore, patients with COPD who undergo PCI are less

likely to receive drug-eluting stent as compared to COPD-free subjects (14.4% vs. 11.6%) [15]. Also 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.

- *Access site for interventional procedures.*

COPD patients who undergo coronary artery angiography and PCI for ACS have a higher risk of major entry-site complications (6% vs. 4.3%) and access site bleeding requiring transfusion (2% vs. 1.4%), compared to patients without COPD [14]. In all-comers population, radial artery access for PCI showed to reduce significantly these bleeding complications as compared to femoral artery access [61].

- *Bleeding risk.*

Anemia emerged as determinant of poor outcome in COPD patients (HR 1.87; 95% CI 1.06-3.29) [62]. COPD patients have a higher prevalence of cerebral microbleeds (OR 1.7; 95% CI 1.1-2.5) [63] and of peptic ulcer bleeding (HR 1.91, 95% CI 1.7-2.2) [64]. Corticosteroid drugs, which are frequently prescribed in COPD patients, are associated with increased risk of gastrointestinal bleeding (OR 1.43; 95% CI 1.22-1.66 in a recently published systematic review and meta-analysis) [65]. Accordingly, proton-pump inhibitors should be considered to minimize the gastrointestinal bleeding risk [66].

- *IHD specific therapy: antiplatelet agents.*

A large observational study found that antiplatelet therapy reduced mortality in patients with oxygen-dependent COPD (HR 0.86; 95% CI 0.75-0.99) [51]. Recent data suggest an association between thrombocytosis and increased mortality at 1-year after AECOPD [52]. Antiplatelet therapy with aspirin or clopidogrel reduced 1-year mortality in COPD patients (OR 0.63; 95% CI 0.47-0.85) [52]. Current guidelines suggest, as first line treatment in patients with ACS, dual antiplatelet therapy with aspirin and new P2Y12 inhibitors (ticagrelor or prasugrel) [2]. A recent registry showed that clopidogrel administration (over prasugrel and ticagrelor) was more frequent in

asthma/COPD patients [67]. The increased risk of bleeding complications (both with prasugrel and ticagrelor) and/or dyspnea (with ticagrelor) may partially explain this finding [67].

- *IHD specific therapy: β-blockers.*

Historically, β-blockers were under-prescribed in COPD patients, principally for a supposed risk of bronchoconstriction secondary to the inhibition of β_2 adrenoreceptors [14,19]. On the contrary, the use of β-blockers is considered safe and should not be avoided because of COPD, neither during stable phase nor during exacerbations [1,68]. For their selective action over β_1 receptor, cardio-selective agents such as atenolol, bisoprolol, metoprolol and nebivolol should be preferred over other β-blockers [1,68]. Cardio-selective β-blockers produce no change in FEV_1 or respiratory symptoms compared to placebo [1,68]. Furthermore, cardio-selective β-blockers did not affect FEV_1 response to treatment with β_2-agonists, when used in association [1,68]. In MI patients with concomitant COPD, β-blockers improved survival (HR 0.50; 95% CI 0.36-0.69 for treatment started during hospital admission, HR 0.59; 95% CI 0.44-0.79 for patients already taking β-blockers before MI) [69].

- *IHD specific therapy: statins.*

Studies showed an immunomodulatory effect of statins over COPD and inhibition of both pulmonary and systemic inflammation [70]. In retrospective studies, the administration of statins reduced significantly the risk of COPD exacerbations [71]. On the contrary, in a large, multicenter, randomized placebo-controlled trial the administration of simvastatin at a daily dose of 40 mg did not affect exacerbation rates or time to first exacerbation in COPD patients at high risk for exacerbations (1.36±1.61 vs. 1.39±1.73 exacerbations and 223 vs. 231 days to the first exacerbation) [72]. Recent findings suggest no difference in statin prescription between patients with or without COPD after a myocardial infarction [15].

- *IHD specific therapy: ACE-inhibitors.*

A recent study demonstrated that, in smokers with a rapid FEV_1 decline (high risk for COPD), the use of ACE-inhibitors was protective against rapid decline (OR 0.55, 95%CI 0.33-0.93) and COPD

progression (0.34, 95%CI 0.15-0.78) [73]. ACE inhibitors modulate the recruitment of inflammatory and immune cells into the lung and thereby reduce lung function decline in cigarette smokers [73]. It is possible that the administration of ACE inhibitors may exert an unexpected beneficial effect on vascular endothelial dysfunction and lung parenchymal destruction [73].

- *COPD specific therapy.*

Corticosteroids are indicated in COPD to improve symptoms, quality of life and to reduce the frequency of exacerbations [1]. β_2-agonists antagonize bronchoconstriction, improving FEV_1 and respiratory symptoms, without affecting mortality [1,74]. Of note, β_2-agonists may induce tachycardia or precipitate cardiac rhythm disorders in susceptible patients, without increasing the risk of cardiovascular events [1,74]. Hence, concomitant IHD does not justify their avoidance.

- *Exercise training and pulmonary rehabilitation.*

Regular physical activity improves myocardial perfusion and retards disease progression in IHD patients [2]. A 12-months program of regular physical exercise in patients with stable coronary artery disease improved event-free survival and exercise capacity and reduced the number of hospital readmissions and repeat revascularizations [75]. By reducing basal sympathetic activity, enhancing vagal activity, restoring baroreflex sensitivity and improving endothelium-dependent vasodilation, exercise training might decrease blood pressure and reduce myocardial ischemia and arterial stiffness in COPD [53-55]. 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 [1]. Inspiratory muscle training leads to a reduction of dyspnea and to improvement in pulmonary function, respiratory muscle strength and functional capacity [76]. Furthermore, pulmonary rehabilitation increases FEV_1, delaying its progressive decline [77]. The presence of CAD determines significantly impaired cardiopulmonary exercise test responses with lower exercise capacity (peak oxygen consumption 42±16% vs. 53±19%) and impaired gas exchange (VE/VCO2 nadir 36±9 vs. 32±5), compared to COPD patients without CAD [78]. All these findings explain the relevance and potential positive prognostic influence of exercise

training and pulmonary rehabilitation in patients with COPD and IHD. COPD-IHD comorbidity should not be considered a limitation and/or contraindication for exercise training and pulmonary rehabilitation.

Future perspectives.

The link between COPD and IHD remains complex and largely unknown, with many issues that should be further addressed. Dedicated studies are desirable to improve current evidence and to guide physicians' decision. Some of the unanswered questions concern the diagnostic process, the early detection of comorbidity, screening strategies, the interpretation of troponin raise in AECOPD and the validation of pharmacological and interventional treatments tailored on COPD-IHD patients. With the ageing of population and the perspective of a dramatic raise in COPD-IHD prevalence, we are aware that this comorbidity will represent a major issue in daily clinical practice.

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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. IHD: ischemic heart disease. Myocardial infarction (MI) type 1: it is defined as spontaneous acute event related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries universal definition (universal definition of MI [43]). Myocardial infarction (MI) type 2: it is defined as MI secondary to ischemia due to either increased oxygen demand or decreased supply caused by conditions as coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension, sepsis, post-operative state (universal definition of MI [43]).

Figure 2. Clinical management of COPD-IHD patients.

COPD: chronic obstructive pulmonary disease. IHD: ischemic heart disease. CAD: coronary artery disease. TN: troponin. AECOPD: acute exacerbation of COPD. BB: beta-blockers. DES: drug eluting stent. MI: myocardial infarction. +: positive.

Table 1: Outcome of patients with IHD and concomitant COPD.

References	Study population	COPD Pts (%)	Follow-up	Mortality rate (COPD vs. no COPD)	COPD and mortality	Variables included in multivariable analysis	COPD and other outcomes
Bursi et al. [12]	3438 MI patients	415 (12%)	5 years	--	1.3 (95%CI 1.1-1.5)	Age, sex, smoking, hypertension, comorbidities, killip class, ACS	46% vs. 68%: 5-years survival rate
Berger at al. [11]	4284 PCI patients	183 (4%)	3 years	21% vs. 9%	2.1 (95%CI 1.5-3)	Age, HF, PVD, LVEF, smoking, diseased vessels	--
Selveraj et al. [13]	10994 PCI patients	1117 (10%)	33 months	24.4% vs. 10.4 % 2.9% vs. 1.2% (in-hospital)	2.1 (95%CI 1.8-2.5)	Age, heart rate, LVEF, diabetes, creatinine, ACS, haemoglobin, shock, procedural success	HR 2.5 (95%CI 1.4-4.3) for in-hospital death
Enriquez et al. [14]	10908 PCI patients	869 (8%)	1 year	2.2% vs. 1.1% (in-hospital)	1.3 (95%CI 1.1-1.6)	Age, sex, angiographic variables	HR 1.2 (95%CI 1.02-1.46) for repeated CR
Campo et al. [15]	11118 PCI patients	2032 (18%)	3 years	23.5% vs. 16%	1.4 (95%CI 1.2-1.6)	Age, diabetes, renal failure, shock, HF, red blood cell transfusion	HR 2.1 (95%CI 1.4-3.3) for MI HR 5.8 (95%CI 4.6-7.5) for HF HR 3 (95%CI 2.1-4.4) for SBE
Angouras et al. [21]	3760 CABG patients	550 (14.6%)	7.6 years	35% vs. 28.1%	1.28 (95%CI 1.1-1.5)	Age, urgency, LVEF, previous MI, PVD, HF, calcified aorta, smoking, immune deficiency	--
O'Boyle et al. [22]	13337 CABG patients	2742 (20.5%)	7 years	--	1.6 (95%CI 1.4-1.8)	Age, diabetes, LVEF, PVD, dialysis, EuroSCORE, CKMB	--
Leavitt et al. [23]	33137 CABG patients	2032 (18%)	3 years	23.5% vs. 16%	1.4 (95%CI 1.2-1.6)	Age, sex, obesity, previous CABG, LVEF, urgency, comorbidities, diseased vessels	COPD + other comorbidity HR 3.6 (95%CI 3.3-3.9) for death
Saleh et al. [24]	11217 CABG patients	2895 (26%)	30 days	3.2% vs. 1.7%	2.31 (95%CI 1.2-4.4)	Age, sex, LVEF, diseased vessels, urgency, PVD, diabetes, renal failure	
Manganas et al. [25]	322 CABG patients	221 (68%)	30 days	2.4% vs. 3%	---	---	Longer hospital stay and pulmonary infections more frequent

HR: hazard ratio. PCI: percutaneous coronary intervention. COPD: chronic obstructive pulmonary disease. ACS: acute coronary syndromes. MI: myocardial infarction. SBE: serious bleeding event. HF: heart failure. LVEF: left ventricle ejection fraction. PVD: peripheral vascular disease.

Table 2. Troponin increase during acute exacerbation of COPD.

References	Study design (pts)	Timing of Tn evaluation	Follow-up	Pts with high Tn (%)	Tn elevation and mortality (multivariable analysis)	Variables included in multivariable analysis	Tn elevation and other outcomes
Baillard et al. [30]	P (71)	Tn I admission and after 24h	Hospital stay	18%	HR 6.5 (95%CI 1.2–34.4) of in-hospital mortality	SAPS II	---
Brekke et al. [31]	P (897)	Tn T after 24h from the admission	1.9 years	---	HR 1.6 (95%CI 1.1–2.3) of all-cause mortality	creatinine, heart rate, PO2, PCO2, FEV1, WBC, CRP	---
Harvey et al. [32]	R (188)	Tn T/I admission	Hospital stay	25%	---	---	Longer hospital admissions
Kelly et al. [33]	R (252)	Tn I admission	Hospital stay	30%	HR 8.3 (95%CI 1.5–43.7) of in-hospital mortality.	pH, NIV	---
Marcun et al. [34]	P (127)	Tn T admission and before the dicharge	6 months	36%	---	age, sex , gold stage, BNP	HR 2.89 (95% CI 1.13–7.36) for hospital readmissions.
Martins et al. [35]	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.	sex, age, BNP, creatinine	---
McAllister et al. [36]	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. [37]	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.	Age, Lung Function, PO2, PCO2, CURB65, BAP65, BMI	---
Hoiseth et al. [38]	P (99)	hs Tn T admission	1,9 years	---	HR 8.9 (95% CI 2.4-32) for death	Age, CAD, HF, BNP, Hb	---
Fruchter et al. [39]	R (182)	Tn I in 24 h from admission	50 months	---	HR 1.3 for mortality	Age, IHD, PCO2	---

P: prospective. R: retrospective. Pts: patients. Tn: troponin. HR: hazard risk. CI: confidence interval. SAPS II: XXX. FEV1: forced expiratory volume at first second. WBC: white blood cell. CRP: C-reactive protein. NIV: not invasive ventilation. BNP: brain natriuretic peptide. BMI: body mass index. CAD: coronary artery disease. HF: heart failure. Hb: haemoglobin. IHD: ischemic heart disease.

Figure 1.

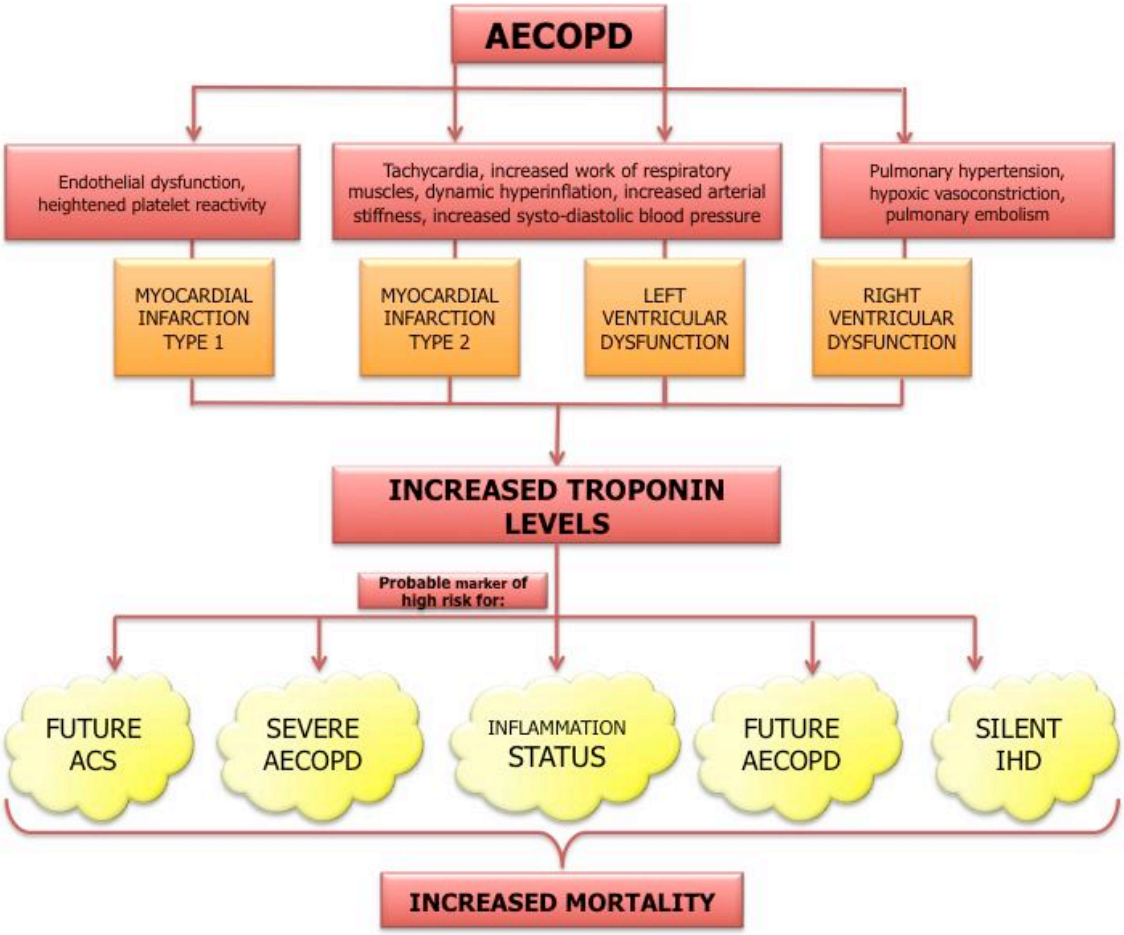
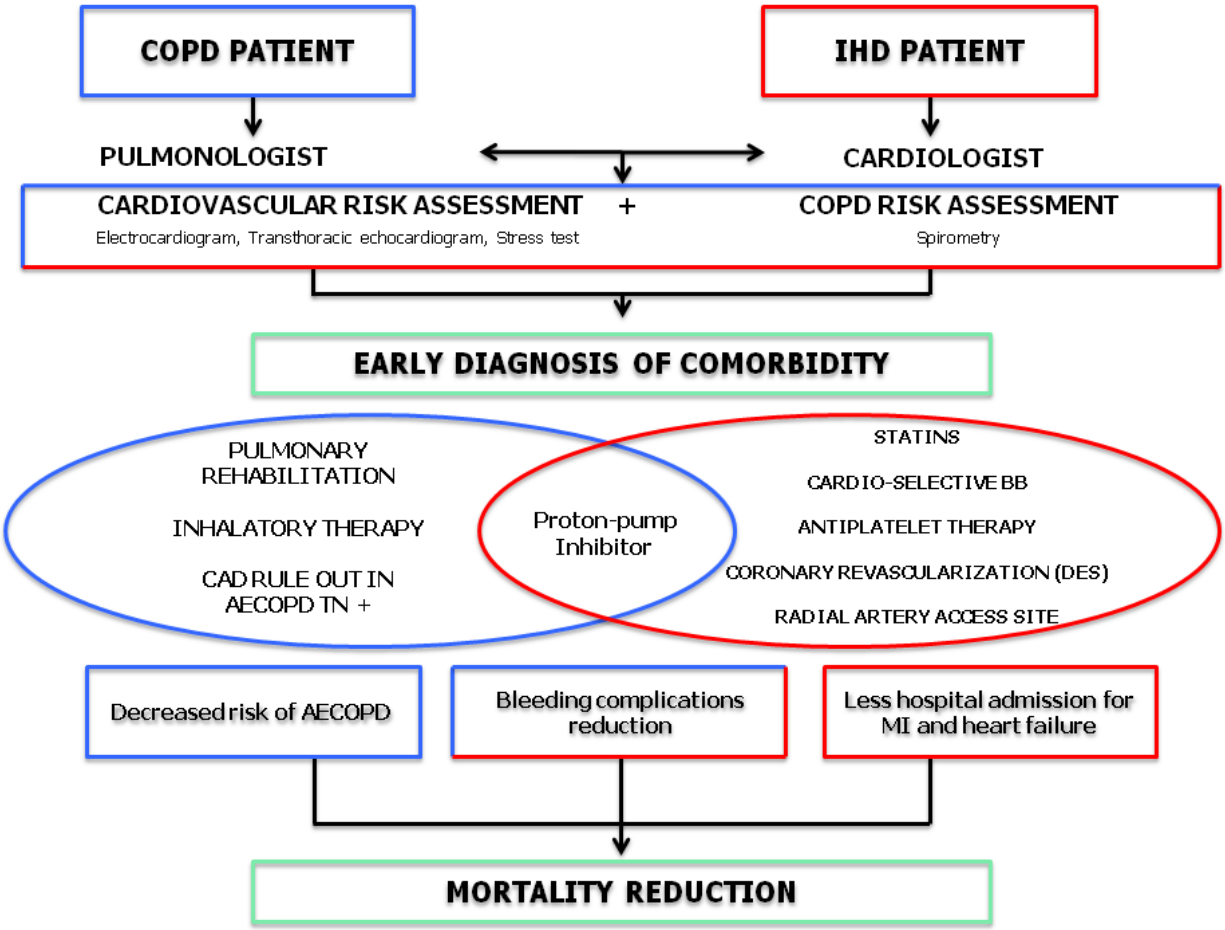

AECOPD
Endothelial dysfunction, heightened platelet reactivity
Tachycardia, increased work of respiratory muscles, dynamic hyperinflation, increased arterial stiffness, increased systo-diastolic blood pressure
Pulmonary hypertension, hypoxic vasoconstriction, pulmonary embolism
MYOCARDIAL INFARCTION TYPE 1
MYOCARDIAL INFARCTION TYPE 2
LEFT VENTRICULAR DYSFUNCTION
RIGHT VENTRICULAR DYSFUNCTION
INCREASED TROPONIN LEVELS
Probable marker of high risk for:
FUTURE ACS
SEVERE AECOPD
INFLAMMATION STATUS
FUTURE AECOPD
SILENT IHD
INCREASED MORTALITY

Figure 2.


COPD PATIENT
IHD PATIENT
PULMONOLOGIST
CARDIOLOGIST
CARDIOVASCULAR RISK ASSESSMENT +
Electrocardiogram, Transthoracic echocardiogram, Stress test
COPD RISK ASSESSMENT
Spirometry
EARLY DIAGNOSIS OF COMORBIDITY
PULMONARY REHABILITATION
INHALATORY THERAPY
CAD RULE OUT IN AECOPD TN +
Proton-pump Inhibitor
STATINS
CARDIO-SELECTIVE BB
ANTIPLATELET THERAPY
CORONARY REVASCULARIZATION (DES)
RADIAL ARTERY ACCESS SITE
Decreased risk of AECOPD
Bleeding complications reduction
Less hospital admission for MI and heart failure
MORTALITY REDUCTION