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# **The link between COPD and coronary artery disease – implication for clinical practice**

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## **ABSTRACT**

Chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) are global epidemics that incur significant morbidity and mortality. The diseases are frequently found in combination, and they can also be found independent of the common causal factors, primarily smoking. Both conditions are systemic disorders with overlapping mechanisms and pathophysiologic processes. CAD has a strong effect on the severity and prognosis of COPD and vice versa, including acute exacerbations. Even the most recent practical clinical recommendations driven by Clinical Practice Guidelines still focus on one disease at a time, and do not provide advice for the management of patients with associated chronic conditions. COPD should be approached in a more comprehensive manner, including the treatment of cardiac comorbidities, particularly CAD. To focus treatment on these comorbidities might modify the natural course of the disease in patients with COPD who may not find relief from treatment of COPD alone.

**Key words:** Clinical Epidemiology, Cardiovascular diseases, COPD, Emphysema, Inflammation.

**Short title:** Clinical practice in complex COPD

## **INTRODUCTION**

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent, usually progressive airflow limitation and is associated with an enhanced chronic inflammatory response of the airways and the lung to noxious particles or gases.<sup>1</sup> Coronary artery disease (CAD, also known as atherosclerotic heart disease) is the end result of the accumulation of atheromatous plaques within the walls of the coronary arteries that supply the myocardium with oxygen and nutrients.

Both COPD and CAD are highly prevalent worldwide, and rates are sure to increase with the ageing of the population. The Global Burden of Disease project estimates that COPD causes the death of at least 2.9 million people annually: COPD was determined to be the sixth leading cause of death in 1990, has been the fourth since 2000, and is projected to be the third by 2020. These estimates are likely to be conservative, as they do not account for deaths to which COPD is a contributing factor, and the degree of misclassification can be high.<sup>2</sup> It is believed that, by 2030, COPD will be the direct underlying cause of 7.8% of all deaths and 27% of deaths related to smoking—only surpassed by 33% for cancer and 29% for cardiovascular disease.<sup>3</sup> Although mortality from CAD, both in middle life and at older ages, has been decreasing since 1970 in western Europe, it remains very high in central and eastern Europe. Furthermore, as survival after acute events improves, the incidence of CAD increases, especially in older women. The impact of COPD and CAD on health is therefore huge, and, given the relative frequency of the two diseases and their common causal factors, most notably smoking, the possibility that they are associated in the same patient is very high.

The relationship between COPD and CAD is far more complex than the simple coexistence of both diseases in the same individual. Airflow limitation is an important contributor to other common causes of morbidity and mortality. Large population-based studies suggest that patients with COPD are at two to three times greater risk for

cardiovascular mortality, which accounts for about 50% of the total number of deaths.<sup>4-6</sup> Indeed, although not generally recognized, poor lung function has been shown to be as powerful a predictor of cardiac mortality as established risk factors such as total serum cholesterol.<sup>7</sup> Here we examine the problems for clinical practice posed by the coexistence of COPD and CAD, through reviewing the prevalence and therapeutic and prognostic implications of COPD in patients with CAD and, conversely, of CAD in COPD patients.

### **PREVALENCE OF CAD IN PATIENTS WITH COPD**

Until recently, the prevalence of CAD in patients with COPD was investigated mainly in retrospective reports; only in the last few years have prospective, properly designed studies been performed to address the frequency, the type, and the role of CAD in COPD patients. Soriano et al.<sup>8</sup> conducted a descriptive analysis on the quantity and quality of cardiovascular comorbidities in newly diagnosed COPD patients enrolled in the General Practice Research Database, which includes about 6 million patients in the United Kingdom. In 1998, a total number of 2699 cases of COPD were identified and compared with cases not involving COPD. Among incident COPD patients, a frequency of >1% within the first year after diagnosis was observed for angina, myocardial infarction (MI), cataracts, osteoporosis, and respiratory infections, the highest being angina and MI. In a large retrospective cohort study involving 11 493 COPD patients, angina and acute MI were reported in 6.6% and 1.6% of patients, respectively.<sup>9</sup> Sin and Man,<sup>10</sup> analysing data from subjects >50 years of age who participated in the Third National Health and Nutrition Examination Survey, examined whether high levels of C-reactive protein (CRP) were present in participants with chronic airflow obstruction and if CRP was associated with cardiac injury. They observed that patients with moderate or severe airflow limitation had an increased incidence of ischemic changes on electrocardiograms, supporting not only the association between COPD and

CAD, but also the presence of a common underlying systemic inflammation based on CRP.<sup>10</sup> Finally, in a recent study properly designed to quantify the burden of comorbidities among COPD patients, Feary et al.,<sup>11</sup> using the Health Improvement Network, a large UK database of primary care medical records of a total of 1 204 110 patients aged >35 years, identified and analyzed the 2.5% of patients who had COPD. These patients (n = 29 870) were five times more likely to have a cardiovascular disease compared with those without COPD (n = 1 174 240). Moreover, in the follow-up analyses, after adjusting for confounding factors such as sex and smoking history and stratifying for age, the incidence of MI was greater in COPD patients than in those without COPD. Taken together, all these studies strongly suggest that CAD is common in COPD patients. Interestingly, this finding is also supported by studies designed for a different purpose, such as clinical trials. Indeed, COPD patients enrolled in ECLIPSE (Evaluation of COPD Longitudinally To Identify Predictive Surrogate Endpoints) showed an increased prevalence of ischemic heart disease compared to smoking and nonsmoking control subjects. This increase was independent of the severity of spirometric measurements.<sup>12</sup>

### **PREVALENCE OF COPD IN PATIENTS WITH CAD**

Estimates of COPD prevalence vary according to the population studied, diagnostic criteria applied, measurement tools, and surveillance systems.<sup>13</sup> Geographic variations are largely related to differences in population age structure and exposure to risk factors, primarily smoking.<sup>1, 13</sup> Most of the studies on the prevalence of COPD in patients with CAD have been conducted in cohorts hospitalized with acute coronary syndrome<sup>14, 15</sup> or enrolled in clinical trials.<sup>16</sup> No study has systematically examined pulmonary function in patients with stable CAD, and the percentage of those who have severe, reversible, or misdiagnosed airflow obstruction is not known.

Studies on the prevalence of COPD among patients with MI report discrepant results. The PREMIER registry<sup>17</sup> reported a prevalence of COPD that was more than double (15.6%) that reported in the SPRINT registry (7%).<sup>18</sup> The SPRINT study enrolled patients who survived the acute phase of MI, leading to a bias whereby COPD patients dying early were not enrolled, resulting in a lower prevalence of COPD among survivors. Conversely, the PREMIER registry, which also included MI survivors, used a less strict definition of COPD by including asthma. More recently, Bursi et al.<sup>19</sup>, by incorporating all individuals with a first MI and not including patients with asthma, documented a COPD prevalence of 12%. In this case, information on COPD status was obtained by review of the medical reports.

Regardless of the application of different COPD diagnostic criteria, the result of an increased COPD prevalence in patients with CAD in recent years may represent greater awareness of COPD, an ageing population, or increased age at onset of CAD. 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 CAD.<sup>19</sup> This has been further confirmed by the study of Soriano and coworkers<sup>20</sup>, who reported a prevalence as high as 33.6% of airflow limitation compatible with COPD in 119 patients with CAD who regularly visited a tertiary referral university hospital from October 2006 to June 2008. All the subjects underwent spirometry, and airflow limitation was defined according to the Global Initiative for Chronic Obstructive Lung Disease guidelines as a post-bronchodilator  $FEV_1/FVC < 0.7$ .<sup>21</sup>

Within patient populations with CAD, those with COPD were older and more often current or ex-smokers compared with those without COPD.<sup>15, 16, 19</sup> Also, patients with COPD had more comorbidities, such as chronic renal insufficiency, systemic hypertension, diabetes, dyslipidemia, and higher body mass index<sup>15, 16, 19</sup>, and they were more likely to present with atypical chest pain, palpitation, and dyspnoea than with typical chest pain.<sup>14</sup> These atypical

symptoms, mainly dyspnoea, could be misinterpreted as COPD exacerbation. In regard to gender difference, it has been reported that patients with COPD are more often women<sup>22</sup>, although this finding is not in agreement with the results of a previous study focused on the importance of COPD for prognosis and diagnosis of congestive heart failure in patients with acute MI.<sup>23</sup>

### **MECHANISMS LINKING COPD AND CAD**

Although COPD and CAD have common causal factors, primarily smoking, the increase of CAD in patients with COPD is independent of these known risk factors.<sup>24</sup> It has been convincingly argued that COPD is a major risk factor for atherosclerosis and development of CAD above and beyond its risk for, e.g., hypercholesterolemia or hypertension.<sup>7</sup>

The exact mechanism linking COPD to heart disease is not yet known, but systemic inflammation, oxidative stress, and hypoxemia are the major putative candidates. Of these, systemic inflammation is supported by the greatest amount of evidence. Low-grade systemic inflammation occurs in patients with clinically stable COPD and in many other chronic conditions, including CAD. Furthermore, in COPD, systemic inflammation persists after smoking cessation<sup>25</sup> and increases during the exacerbation of the disease. Notably, it is during exacerbations that patients with COPD have the highest risk of a cardiovascular event<sup>26</sup>. Given that the lungs of patients with COPD are chronically inflamed and that several inflammatory cytokines have been found to be elevated in the circulation of COPD patients<sup>27</sup>, systemic inflammation is mainly explained by the spread, or “spill-over,” of lung inflammatory mediators (Figure 1).<sup>28</sup> However, there is not a close correlation between the concentration of mediators in sputum and blood<sup>29</sup>, suggesting that other factors are also involved. Physical inactivity as a consequence of progressive dyspnoea may be an important element in promoting systemic inflammation. There is also increasing evidence that the

normal ageing process is associated with low-grade systemic inflammation.<sup>30, 31</sup> Both emphysema<sup>32</sup> and coronary atherosclerosis may represent diseases of accelerated ageing.

Along with systemic inflammation, oxidative stress and chronic hypoxia contribute to the pathophysiology of COPD, and they are crucial factors in the atherosclerotic disease process and progression of CAD. Topsakal et al.<sup>33</sup> nicely demonstrated that oxidative stress and inflammation in COPD are associated with intensity and severity of atherosclerosis in patients with established CAD, possibly through unfavourable effects on endothelial functions. Finally, it is worth noting the recent observation by Enriquez and colleagues<sup>34</sup> that patients with COPD who underwent a percutaneous coronary intervention had a greater mean number of significant atherosclerotic lesions, but the lesions were shorter and less likely to cause total occlusion of the involved vessels than were lesions found in patients without COPD. It is, therefore, probable that COPD patients belong to that subset of patients with CAD who have a diffuse disease which is less tractable with surgical or percutaneous catheter interventions and is associated with poor prognosis.<sup>35</sup>

## **TREATMENT OF CAD WITH AND WITHOUT COPD**

To address the complexity of the treatment of CAD, we examine 1) various levels of prevention strategy; 2) medical strategies to modulate the ischemic burden and to improve prognosis; and 3) coronary revascularization procedures, including percutaneous coronary angioplasty and coronary artery bypass grafting.

A fundamental premise that has to be taken into account is that no prospective, randomised efficacy study has ever been conducted to compare COPD patients with the general population or to investigate treatments or outcomes in an exclusively COPD population. Therefore, no evidence-based recommendation can be provided about the efficacy of treatment, because only indirect or deductive knowledge is available: Actually,

the guidelines available on prevention<sup>36</sup>, treatment<sup>37</sup> and revascularization<sup>38</sup> of CAD simply ignore this comorbidity except for the aspects related to beta-blocker tolerability. This is a major gap in our knowledge that warrants further investigation and tailored research.

## **Prevention strategies**

### *Primary prevention and strategies for individuals at risk*

At present, more than 90% of the total attributable risk of CAD worldwide is due to modifiable risk factors, including smoking, hypertension, obesity, unhealthy diet, abnormal lipids, and physical inactivity.<sup>39</sup> Some of these risk factors are also common in COPD. Unfortunately, the modernization of developing countries (e.g., the Far East and eastern Europe) is also leading to unhealthy lifestyles. Data from the recent EUROASPIRE survey conducted by the European Society of Cardiology<sup>40</sup> show that higher-risk profiles are also dramatically increasing in western Europe, even though there is increased consciousness of the burden of ischemic heart disease and increased use of drugs proven effective in secondary prevention. All of the scientific societies in the field share the vision that the most needed and dramatic improvement in the prevention of ischemic heart disease will be possible only with the implementation of healthy lifestyles and appropriate preventative measures<sup>36, 37, 40</sup>. Should this be possible, it will also have an impact on the prevalence of COPD.

### *Secondary prevention*

Over the last decade, pharmacologic treatments have been effective in reducing the rate of progression and the occurrence of complications (death or acute coronary syndromes) in established CAD or diabetic patients.<sup>37</sup> The modern treatment of these patients should include acetylsalicylic acid (or a tailored antiplatelet therapy), a statin, and an inhibitor of angiotensin-converting enzyme (ACE) (Figure 2). Aspirin acts mainly as an antiplatelet

agent, but statins and ACE inhibitors may provide an added benefit to COPD patients. Over the last couple of decades, statins have changed the natural history of CAD<sup>41</sup> by decreasing LDL (low-density lipoprotein) cholesterol and also likely through the so-called pleiotropic effects that are independent of statins' activity on circulating lipids. Among these effects, direct vascular protection seems of particular relevance in arterial disease, possibly because of the capacity of statins to upregulate the expression of nitric oxide synthetase and also to carry out a series of anti-inflammatory actions that lead to improved endothelial function. Recently, statin therapy has been associated with a decrease of pulmonary artery pressure in COPD patients, probably by enhanced local synthesis of nitric oxide.<sup>42, 43</sup> These experimental observations, plus other possible protective effects, have led to the concept that statins have considerable potential as an adjunct therapy in COPD.<sup>44-47</sup> Similarly, ACE inhibitors might have additional benefits for ischemic patients with COPD comorbidity<sup>44, 46, 48</sup> : Again, the well-known effect of this class of compounds is mediated by endothelial protection, but possible action on remodelling vessels and the interstitium in the lungs has also been suggested. However, as mentioned above, no prospective study with predefined end points has formally investigated these possibilities, or the possibility that statins and/or ACE inhibitors may ameliorate the coronary disease burden in COPD patients. Indirect evidence for this was provided by a case-control retrospective study on very large population-based cohorts at various cardiovascular risk levels.<sup>49</sup> In that study, statins and inhibitors of the renin angiotensin system reduced both cardiovascular (MI or death) and pulmonary outcomes, with the largest benefits obtained by combining the drugs. However, this finding has not yet been validated in tailored-outcome clinical investigations.

## **Medical strategies to modulate the ischemic burden and to improve prognosis**

The targets of pharmacologic treatment of CAD are the prognosis of the patient and improvement of the quality of life by reducing the severity and/or frequency of symptoms. Secondary prevention, as described above, is a cornerstone for improving prognosis in ischemic heart disease (Figure 2). Other pharmacologic approaches, including beta-blockers, calcium antagonists, ivabradine and nitrates, are effective in reducing symptoms but are not able to modify prognosis.<sup>37</sup> Beta-blockers are renowned for improving prognosis but only in patients with previous MI. The risk of cardiovascular death or MI was reduced by beta-blockers by some 30% in post-MI trials.<sup>50</sup> A meta-regression analysis of the effects of different beta-blockers on mortality found a significant 24% relative risk reduction in mortality with long-term secondary preventive treatment.<sup>51</sup> Even though this assumption is challenged by recent observations and based on studies conducted before the widespread use of reperfusion therapy in acute MI<sup>52</sup>, beta-blockers are the first-line therapy (Class IA), able to improve not only symptoms but also cardiac outcomes, and are mandatory, particularly in post-MI with reduced left ventricular function.<sup>37</sup> Unfortunately, COPD diagnosis is a strong predictor of beta-blocker underutilization in eligible patients because of a perceived contraindication and fear of inducing adverse reactions and bronchospasm.<sup>53, 54</sup> Actually, beta-blockers are well tolerated in patients with cardiac disease and concomitant COPD, and there is no evidence, in the large majority of patients, of worsening respiratory symptoms or FEV<sub>1</sub>: Consequently, before the decision is made to withhold beta-blockers, COPD and bronchodilator reversibility should be ascertained by pulmonary function testing.<sup>55, 56</sup> Underutilization of beta-blockers has been linked to poorer outcomes<sup>57</sup>, at least after MI or in patients with reduced left ventricular function. The cumulative evidence from trials and meta-analysis indicates that cardioselective beta-blockers should not be withheld in patients with reactive airway disease or COPD. Interestingly, retrospective cohort investigations on COPD

subjects with acute exacerbation seem to suggest that beta-blockade might even decrease mortality.<sup>58, 59</sup>

Particularly important in the treatment of CAD patients with COPD and complex comorbidities is the recent introduction of ivabradine, a compound able to selectively inhibit the  $I_f$  current of the sinoatrial node myocytes, thereby selectively reducing heart rate with no other effects on the cardiovascular system. Ivabradine is therefore able to decrease one of the major determinants of myocardial oxygen consumption, with consequent reduction of ischemic burden. Furthermore, ivabradine avoids the other effects of beta-blockers that are possibly undesirable in fragile patients, such as the unmasking of vasoconstrictive beta-adrenergic signalling, fatigue, hypertensive reactions, and sexual dysfunction,. Interestingly, ivabradine is able to reduce ischemia-related outcomes and prevent adverse remodelling in CAD patients.<sup>60-62</sup>

In regard to the treatment of COPD in patients with CAD: COPD should be treated as usual as there is no evidence that COPD should be treated differently in the presence of CAD. This statement is based on findings from large long-term studies in COPD<sup>63</sup> whereas no large long-term studies exist in this specific group of patients with both COPD and IHD. Although no studies on COPD medications in patients with unstable angina exist, it seems reasonable to avoid especially high doses of beta-agonists.

### **Coronary revascularization**

Myocardial revascularization has been a mainstay in the treatment of CAD for almost half a century. Coronary artery bypass grafting (CABG) has been used in clinical practice since the 1960s, but percutaneous coronary intervention (PCI) is now the most commonly used reperfusion procedure.<sup>38</sup> A detailed description of the two procedures is beyond the scope of this review, but some aspects are worth mentioning. Major technical differences exist

between the two procedures: CABG more often allows complete revascularization and ensures a good patency rate at follow-up, but imposes the added risk of sternotomy/thoracotomy and, usually, of extracorporeal circulation. PCI is less invasive with fewer acute complications, but has a higher restenosis rate (well above 10%) even using last-generation drug-eluting devices. Another clinical difference is that, although PCI is effective in reducing angina symptoms and improving quality of life, no study has been able to demonstrate any effect on occurrence of MI or of cardiovascular death. CABG, however, is effective in improving prognosis in high-risk groups (e.g., those with left main or three-vessel disease, or low ventricular function).

Given the risks involved in extracorporeal circulation, sternotomy and a very invasive surgical procedure, it is not surprising that any pulmonary comorbidity, including COPD, is a well-recognised risk factor for CABG and is included in every score used to quantify surgical risk. It is less obvious that COPD is an independent risk factor for long-term cardiac and cardiovascular death in patients with ischemic heart disease who undergo revascularization.

Nishiyama et al.<sup>64</sup> recently analysed 9877 consecutive patients who underwent their first elective PCI or CABG a decade previously, and found that COPD comorbidity was present in 2.4% of the subjects. After a 3-year follow-up, COPD significantly increased the adjusted risk for all-cause (+36%,  $P = 0.0003$ ) and cardiac (+48%,  $P = 0.003$ ) mortality. COPD's role as a predictor of poor long-term results of revascularization is not linked to reperfusion techniques: Selvaraj et al.<sup>65</sup> studied 10 994 patients treated with PCI only, and found that COPD was present in 11.3% of the subjects and led to an adjusted hazard ratio for long-term mortality of 2.16 (C.I. 1.81-2.56,  $P < 0.0001$ ). COPD comorbidity has also been shown to negatively influence the results of revascularization in the setting of PCI during acute MI.<sup>66</sup> These observations conclusively demonstrate that COPD patients in every clinical setting are at higher risk for suboptimal results of reperfusion therapy. The manner in

which COPD affects the incidence of long-term adverse cardiac events after coronary revascularization is not quite clear. Usually, COPD patients have a higher comorbidity profile and are treated suboptimally: Nevertheless, it is an intriguing possibility that COPD patients have an increased risk of acute atherothrombotic events, and that this increase is independent of smoking and other cardiovascular risk factors.

### **PROGNOSTIC IMPLICATIONS OF CAD IN PATIENTS WITH COPD**

COPD is the only major cause of death worldwide whose morbidity and mortality are increasing.<sup>1</sup> Data from multiple studies suggest that one of the most common, often unrecognized, causes of death is CAD. The Tucson Epidemiologic Study of Airways Obstructive Disease reported that cardiovascular disease is the primary cause of death in about 50% of patients with COPD, even in those with more severe airflow obstruction.<sup>4</sup> Hansell and coworkers,<sup>67</sup> recording all conditions listed on death certificates obtained in England and Wales for 1993-1999, noted that each one had at least one mention of chronic obstructive disease (COPD or asthma). The most frequent causes of death for all years studied and for both males and females were vascular diseases, in particular, CAD, followed by tumours and respiratory diseases. Sidney et al.<sup>69</sup> investigated the relationship between diagnosed and treated COPD and the incidence of hospitalization for cardiovascular disease (arrhythmia, acute MI, heart failure, and stroke) and mortality in a huge cohort of subjects entered in the Northern California Kaiser Permanente Medical Care Program. More than 45 000 COPD patients were identified, matched with an equal number of control subjects without COPD, matched for gender and age, and followed for about 3 years. The risk of hospitalization and mortality was higher in COPD patients than in control subjects for all cardiovascular diseases. Among the study end points, heart failure was the leading cause of hospitalization, followed by acute MI and stroke. While the risk of mortality did not differ by

gender, the association between COPD and cardiovascular disease was stronger in patients <65 years of age, and the risk of mortality was higher in patients 40 to 64 years of age, suggesting that cardiovascular disease should be recognized and treated earlier in younger COPD patients.<sup>68</sup> In a cohort of more than 20 296 subjects aged >45 years from the Atherosclerosis Risk Communities Study and the Cardiovascular Health Study, patients with more severe COPD (Global Initiative for Chronic Obstructive Lung Disease stages III and IV) were found to have a higher incidence of cardiovascular diseases (including MI, angina, transient ischemic attacks, stroke, and heart failure), higher risk of hospitalization, and higher risk of death than did patients with only mildly impaired lung function.<sup>24</sup>

In the TORCH (Towards a Revolution in COPD Health) study, of the 911 deaths reported in the 3 years of follow-up, 26% of COPD patients died from a cardiovascular disease, and the most common cause of death was sudden death, even though only a small proportion of patients (3%) had a documented diagnosis of acute MI. This is surprising, as sudden deaths are usually considered cardiovascular deaths (due to arrhythmia in patients with CAD, for example).<sup>69</sup> It is possible that these deaths were attributable to acute respiratory failure, since it can be difficult to distinguish the cause of death during or immediately after an acute COPD exacerbation.

It is well known that the natural history of COPD is characterized by exacerbations. Several studies have clearly established that acute exacerbations of COPD are a major driver of mortality, not only during and immediately after the acute event, but also long-term. Cardiovascular diseases seem to play an important role in the pathogenesis and prognosis of COPD exacerbations. Indeed, Donaldson et al.<sup>26</sup> showed that the risk of acute vascular events appears to be particularly high during exacerbations of COPD. After analyzing data from 25 857 patients with COPD entered in the Health Improvement Network Database over a 2-year period, the authors showed that the risk of MI 1 to 5 days after exacerbation

increased 2.3-fold. Retrospective studies suggest that concentrations of serum troponins are commonly raised in acute exacerbations of COPD; they also appear to reflect the severity of the exacerbation, even in the absence of a diagnosis of MI,<sup>70</sup> and to increase risk of death after hospital discharge.<sup>71</sup> These data have been recently confirmed in two prospective studies by Chang et al.<sup>72</sup> and Hoiseth et al.,<sup>73</sup> who reported that elevated serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T in patients hospitalized for an acute severe exacerbation were associated with increased early mortality independent of other known prognostic indicators. The effect was stronger in patients with tachycardia than in those with normal heart rate.

The link between severe COPD exacerbations, increased cardiac biomarkers, and acute cardiovascular events is not completely understood, but the increased systemic inflammation observed during an exacerbation would in part explain the association of these acute events. In a recent article, Maclay et al.<sup>74</sup> showed that patients with stable COPD have increased circulating platelet–monocyte aggregates compared with control subjects and that these aggregates increase even more during an acute exacerbation. This finding identifies a possible mechanism contributing to cardiovascular risk in patients with COPD.

Taken together, results of these studies suggest that patients admitted to hospital for a COPD exacerbation are at high risk for acute ischemic events that should be promptly recognized and treated.

## **PROGNOSTIC IMPLICATIONS OF COPD IN PATIENTS WITH CAD**

Studies focused on the prognosis of patients with CAD and concomitant COPD are few, are mainly limited to the impact of COPD on MI, and report sometimes inconsistent results.<sup>18, 19</sup>

In the SPRINT registry, although COPD patients had a higher incidence of in-hospital and long-term mortality, COPD was not an independent predictor of increased mortality.

However, COPD patients had a higher risk of developing chronic heart failure as well as paroxysmal atrial fibrillation and advanced atrioventricular block.<sup>18</sup> More recently, Hadi et al.<sup>14</sup> extended these findings in a larger group of patients from another part of the Middle East. They enrolled 8167 patients who were admitted with acute coronary syndrome; 71.3% were diagnosed with MI and 28.7% with unstable angina. Overall, 434 patients (5.3%) had a diagnosis of COPD. COPD was not independently associated with increased in-hospital mortality, but it was associated with a higher incidence of chronic heart failure. Conversely, Wakabayashi and colleagues<sup>15</sup> demonstrated that COPD is a strong and independent predictor of in-hospital death or cardiogenic shock in patients with acute MI.

The impact of COPD on the long-term outcome of MI is more clear than that of in-hospital results. In the PREMIER study, COPD was associated with a substantially greater risk of 1-year mortality and rehospitalisation.<sup>17</sup> Likewise, in a large community of patients with MI, survival was markedly reduced in patients with COPD compared with those without COPD after a follow-up of  $4.7 \pm 4.6$  years.<sup>19</sup> The survival curves diverged early, and this difference increased throughout the follow-up (Figure 3). At 5 years, survival was 46% among patients with COPD versus 68% in those without COPD. This equated to patients with COPD having an almost two fold increased risk of death. The association remained significant after adjustment for age, sex, smoking, hypertension, other comorbidities, biomarker levels, and treatment of MI. Lastly, Enriquez and colleagues,<sup>34</sup> using a large registry of patients who underwent a percutaneous coronary intervention, confirmed that patients with COPD had a significantly increased risk of death after 1 year, compared with patients without COPD.

Taken together, these findings indicate that in many models the prognostic significance of COPD approaches or exceeds that of traditional factors, including age, heart rate, left ventricular ejection fraction, diabetes, hypertension, and final creatinine.

## CONCLUSIONS AND RECOMMENDATIONS

CAD is a frequent comorbidity in patients with COPD and has a critical influence on severity and prognosis. Most of the studies performed, even in patients with severe COPD, do not include patients with chronic cardiovascular comorbidities, and thus even the most recent clinical treatment guidelines<sup>75</sup> provide little, if any, guidance for the practising physician in these complex cases.

Considering the frequency and the weight of cardiac comorbidities in patients with COPD, particularly CAD, and considering that the treatments available for COPD are effective only on symptoms and exacerbations but do not modify the natural history of the disease, we believe that patients with COPD should be treated in a more comprehensive manner, including the treatment of cardiac comorbidities, particularly CAD. The reason this is particularly relevant for CAD is that this disease has been shown to be eminently more treatable than COPD. Indeed, although the data are mainly derived from retrospective analyses, the treatment of cardiovascular comorbidities in COPD, particularly with statins, ACE inhibitors, angiotensin receptor blockers<sup>49</sup>, and beta-blockers,<sup>58, 76</sup> reduces morbidity, hospitalizations, and mortality in patients with COPD. In turn, it is important for specialists in nonpulmonary areas, including cardiology, to recognise that COPD commonly occurs in association with certain diseases in their speciality and to make the diagnosis using spirometry so that appropriate treatment may be instituted. Treatments already used in COPD might also be beneficial in some comorbid diseases, such as CAD.

In conclusion, patients with COPD, and those with concomitant chronic diseases, should be treated with multidrug regimens that are likely not only to improve the clinical conditions of the patient but also to modify the natural history of the disease.

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## Figure legends

### Figure 1

Patients with COPD have peripheral lung inflammation that may “spill over” into the systemic circulation, leading to skeletal muscle weakness and cachexia and an increasing propensity to cardiovascular, metabolic, and bone diseases, as well as depression. These patients have increased circulating cytokines, including IL-1 $\beta$ , IL-6, IL-18, and TNF $\alpha$ , as well as acute-phase proteins, such as CRP and serum amyloid A (SSA). The normal ageing process and reduced physical activity as a consequence of progressive dyspnoea cause low-grade systemic inflammation, which may contribute to comorbid diseases. Adapted from Barnes PJ, PLoS Med **2010**;16:7:e1000220.

### Figure 2

Algorithm for the medical management of chronic CAD. Adapted from reference 37.

### Figure 3

Kaplan-Meier survival curve after MI in patients with and without COPD.

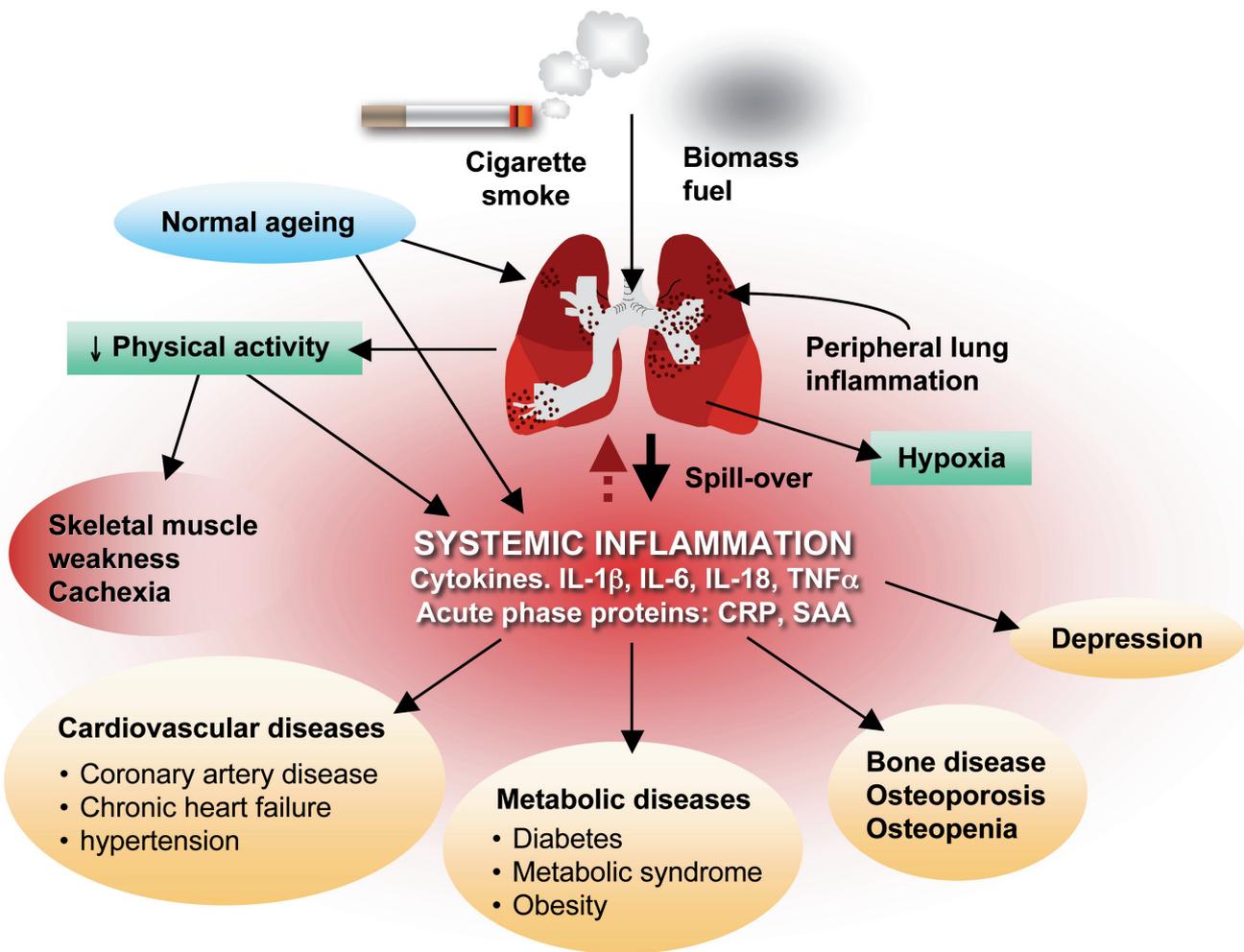
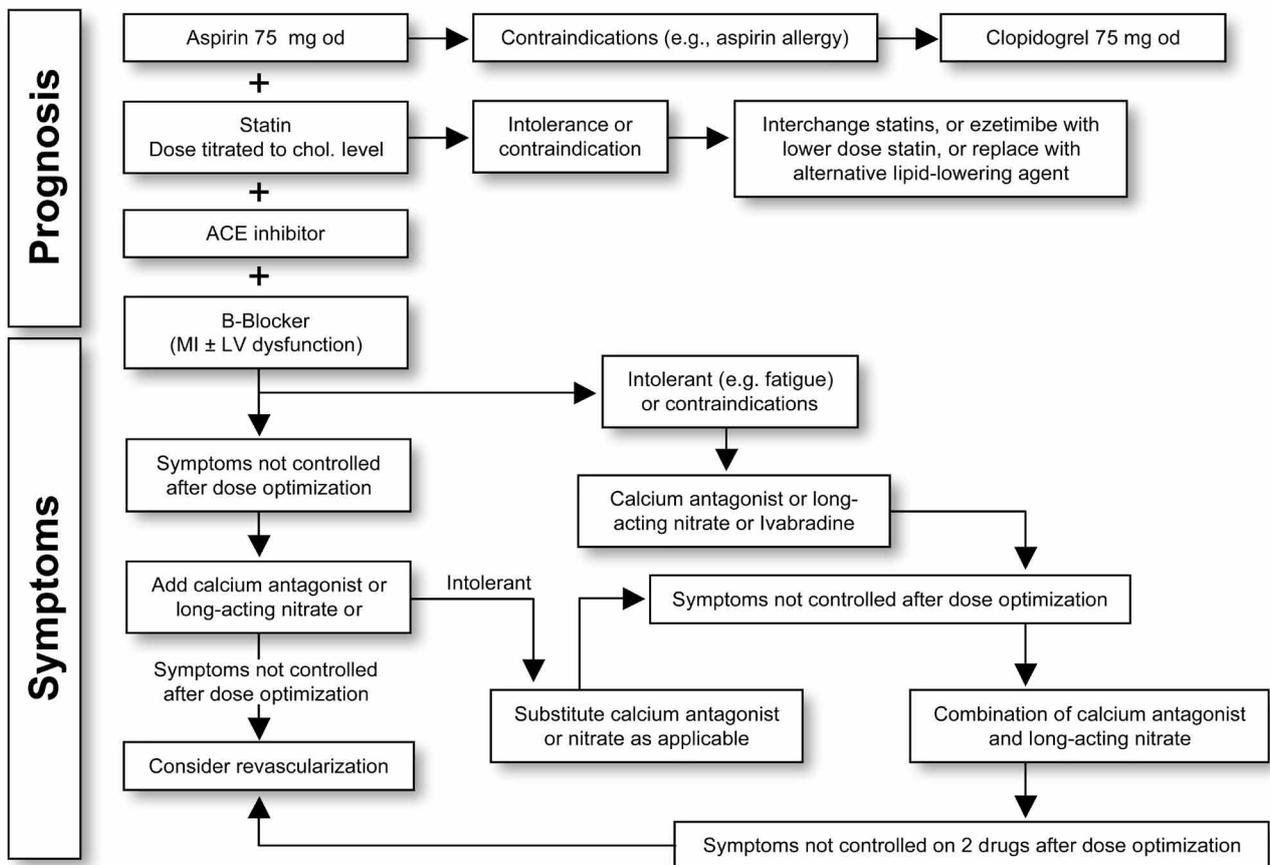


Fig.1

# Treatment of Chronic CAD



Adapted from. "Guidelines on the management of stable angina pectoris." *Eur. Heart J.* 2006; 27: 1341-1381

Fig.2

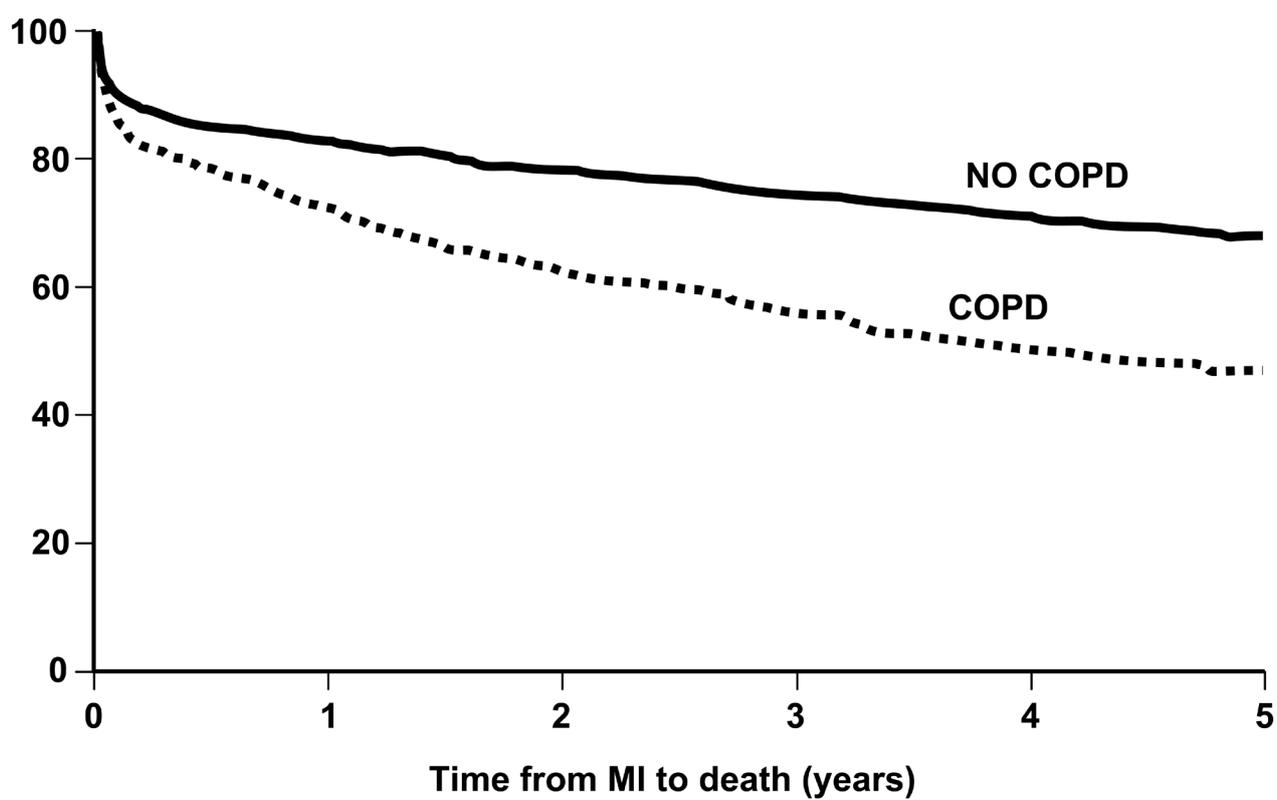


Fig.3