Chronic Obstructive Pulmonary Disease in Patients with Atherosclerosis

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PART IV MARKERS OF PROGNOSIS IN PATIENTS WITH COPD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and affects approximately 10% of the adults of 40 years and older.[1] It is currently the fifth leading cause of death and expected to be the third by 2020.[2] This is mainly driven by the continued use of tobacco, and the population aging. Worldwide, approximately 2.7 million deaths from COPD occurred in the year 2000.[2]

COPD is defined by the Global Initiative for Chronic Lung Disease (GOLD) as a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[3] This results in a chronic persistent low-grade inflammation in the lungs, and the intensity of the inflammation correlates with the severity of the disease. Importantly, the inflammatory state is not only restricted to the lungs but also extends systemically. This systemic inflammation is associated with the development of atherosclerosis and cardiovascular morbidity and mortality even after taken into account smoking status.[4]

Cardiovascular disease is a leading cause of mortality in patients with COPD and accounts for 20-25% of all deaths in COPD.[5, 6] In addition, for every 10% decrease of forced expiratory volume in 1 second (FEV_1), the risk of cardiovascular mortality increases with 14% and non-fatal acute coronary events with 20%.[7] Pulmonary complications contribute equally to postoperative morbidity, mortality as cardiac complications[8] and prolong hospital stay by an average of one to two weeks.[9]

PROGNOSIS

Although very poor lung function has been identified as a significant risk factor for post-operative pulmonary complications, the routine use of preoperative pulmonary function tests remains controversial. Accordingly, previous studies have generally excluded lung function measurements in the development of prediction models. The principal aim of **Chapter 1** was to investigate the relationship of preoperative pulmonary function to postoperative mortality for various surgical risk procedures in a large cohort of patients undergoing noncardiac surgery. Additionally, we aimed to develop a simple prognostic risk model including pulmonary function test results for the prediction of 30-day mortality following noncardiac surgery.

Contemporary management of COPD is focused largely on symptom relief and improving health-related quality of life (HRQL). HRQL is therefore increasingly used as an important outcome parameter in patients with COPD. Furthermore, impaired HRQL is known to be associated with increased mortality independent of pulmonary function and age.[10] In **Chapter 2** we studied the association between COPD severity and HRQL of life among vascular surgery patients. In addition, differences in HRQL between males and females were examined.

COPD AS A RISK FACTOR

COPD is associated with cardiovascular disease in people with normal kidney function.[11] Consequently, COPD may be associated with kidney disease (due to underlying vascular disease) independent of other covariates that might influence kidney function loss. Therefore we investigated in **Chapter 3** the relationship between COPD and chronic kidney disease in a large cohort of vascular surgery patients with peripheral arterial disease. Additionally, we assessed the association between COPD and mortality in patients with kidney disease.

Furthermore, COPD and heart failure are related comorbidities and often co-exist in the same patient independent of smoking status. Although this association has been previously

described, the co-existence between COPD and subclinical left ventricular dysfunction, without the presence of heart failure symptoms, is less well understood. **Chapter 4** determined the relationship and clinical relevance of COPD and subclinical left ventricular dysfunction in vascular surgery patients.

Besides cardiovascular mortality, cancer is another important leading cause of death in patients with COPD, especially lung cancer. This migh partly be explained by the underlying systemic inflammatory state in these patients. Previous studies suggested that statins might reduce the risk of cancer because of the anti-inflammatory properties, while others have suggested that statins may promote the development of new malignancies. In **Chapter 5** we sought to determine the relationship between COPD (and its severity) and risk of cancer mortality and whether the use of statins modified this relationship in surgical patients.

Obesity is a risk factor for many diseases, and especially cardiovascular disease. Despite this adverse association, numerous studies have documented an 'obesity paradox' in which overweight and obese patients with established cardiovascular disease, including peripheral arterial disease, have a better prognosis compared with normal weight patients. The highest mortality rates are observed in patients who are underweight. However, the presence of underlying COPD might explain the increased risk of mortality in the underweight patients. In **Chapter 6** we investigated the association between COPD and body mass index and mortality in a group of patients with peripheral arterial disease.

INTERVENTIONS IN PATIENTS WITH COPD AND ATHEROSCLEROSIS

Given the considerable amount of patients with COPD with concomitant cardiovascular disease, medical treatments that confer cardiovascular risk reduction, like statins and beta-blockers, may have a beneficial effect in reducing mortality in these patients. Because of the anti-inflammatory properties of statins, the drugs may have beneficial effects in patients with COPD. In **Chapter 7** we investigated the association between statins (and different dosing regimens) and short- and long-term outcome in patients undergoing surgery for their peripheral arterial disease.

In addition to statins, vascular surgery patients often require beta-blocker therapy. However, these drugs are frequently withheld from patients with COPD because of the concern that beta-blockers may induce bronchoconstriction. Additional concern of beta-blockers in COPD is the potential for insensitivity. COPD is associated with systemic inflammation, which may accelerate metabolism of beta-blockers, leading to reduced efficacy. In **Chapter 8** we studied the association between cardioselective beta-blockers and short- and long-term mortality in patients with COPD who underwent major vascular surgery. Furthermore we determine the relationship between low and intensified dosing regimens and mortality.

The long-term effects of beta-blockers on HRQL in patients with COPD are unknown. On one hand, beta-blockers may improve health status because of their beneficial effects on cardiac performance. On the other hand, beta-blockers may cause impaired physical, social and emotional functioning owing to their side effects and/or by causing worsening of lung function. In **Chapter 9** we studied the relationship between beta-blockers and HRQL of patients with peripheral arterial disease and COPD. Moreover, with the increase of COPD severity, patients often experience a progressive disability, which might lead to impaired HRQL.[12]

MARKERS OF PROGNOSIS IN PATIENTS WITH COPD

Aside from FEV_1, there are no established biomarkers in COPD that can assist clinicians in predicting which patients will and will not develop cardiovascular morbidity and mortality. This makes it difficult

for practicing clinicians to accurately risk-stratify patients and to intervene with cardioprotective interventions (e.g. statins and beta-blockers) in patients at increased risk. Therefore we determined in **Chapter 10** the relationship of carotid wall intima-media thickness, which is a marker for atherosclerosis, with COPD (and its severity) and with total as well as cardiovascular mortality in patients undergoing peripheral vascular surgery. In addition, N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a useful biomarker for risk-stratifying patients with heart failure in response to increased ventricular pressure and volume overload.[13] As NT-proBNP levels are also found to be elevated in patients with COPD[14], NT-proBNP may also be used to risk stratify patients with COPD. In **Chapter 11** we investigated the relationship between NT-proBNP and COPD severity and one-year mortality in vascular surgery patients with normal left ventricular function. In addition, **Chapter 12** describes the relationship between COPD and NT-proBNP as well.

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Part I

Prognosis

1

Does preoperative vital capacity predict postoperative survival in patients undergoing noncardiac surgery?

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ABSTRACT

BACKGROUND

As cardiac and pulmonary complications are the most common morbidities among patients undergoing major surgery, preoperative patient evaluation should consider both cardiac and pulmonary risks. We investigated the association between pulmonary function and postoperative mortality for noncardiac surgical procedures at various levels of surgical risk, and developed a prognostic risk model, including pulmonary function, and cardiac risk factors to estimate 30-day postoperative mortality.

METHODS

The study included 10,371 patients with a preoperative pulmonary function test who underwent elective noncardiac surgery between 1991 and 2008. Study endpoint was 30-day mortality. Using routinely obtained clinical data and spirometry, a prognostic risk model for 30 day mortality post-surgery was developed including forced vital capacity (FVC), age, gender, type of surgery, smoking status and revised cardiac risk index (ischemic heart disease, diabetes, renal insufficiency, cerebrovascular accident/transient ischemic attack, and heart failure).

RESULTS

For all types of surgical procedures, preoperative FVC was inversely related to 30-day mortality with highest mortality rates among patients undergoing high risk surgery. Compared to patients with normal FVC (i.e. ≥80% of the predicted value), those with FVC less than 40% of predicted had almost 8 fold increased risk of 30 day mortality (OR; 7.98; 95%CI, 3.42 to 18.65). A simple prognostic risk score derived from 6 variables predicts 30-day mortality postoperatively.

CONCLUSIONS

Preoperative FVC is associated with 30-day postoperative mortality, irrespective of the surgical risk classification, and after adjustment for well-known clinical determinants of postoperative risk. A simple risk score based on cardiac risk factors and pulmonary function predicts 30-day mortality with reasonable discrimination and precision.

INTRODUCTION

Nearly 5% of patients undergoing noncardiac surgery experience significant pulmonary complications, which are besides cardiac complications a major source of peri-operative morbidity and mortality[1, 2] and on average extend hospital stays by one to two weeks.[3] As cardiac and pulmonary complications are the most common morbidities among patients undergoing major surgery, the preoperative patient evaluation should therefore consider both cardiac and pulmonary risks.[2] However, to date, most of the focus has been on cardiac rather than pulmonary risk. Important risk factors for pulmonary complications include pulmonary function ,advanced age, smoking history, obesity, a positive cough test, and operative factors such as the site and duration of surgery.[4] Although very poor lung function has been identified as a significant risk factor for post-operative pulmonary complications[2, 5], the routine use of preoperative pulmonary function tests remains controversial. While some have suggested that pulmonary function testing could be useful to identify patients at risk for complications after surgery[6, 7] others have indicated that preoperative spirometry is of uncertain clinical value.[2] Accordingly, preoperative pulmonary function testing has not been used consistently in clinical practice.

Although previous studies aiming to develop risk models for perioperative complications have generally excluded lung function measurements[5, 8], it is well known that lung function decreases significantly during and following abdominal surgery.[2] Furthermore, modalities to increase lung function post-operatively such as deep breathing exercises, incentive spirometry or continuous positive airway pressure can significantly attenuate the risk of post-operative pulmonary complications.[9] For this and other reasons it could be useful to assess pulmonary function preoperatively. The principal aim of this study was to investigate the relationship of preoperative pulmonary function to postoperative mortality for various surgical risk procedures in a large cohort of patients undergoing noncardiac surgery. Additionally, we aimed to develop a simple prognostic risk model including pulmonary function test results for the prediction of 30-day mortality following noncardiac surgery.

METHODS

PATIENTS

Between January 1991 and December 2008, 10,371 patients with a preoperative pulmonary function test who underwent noncardiac surgery in the Erasmus Medical Center were included in the present study. Forced vital capacity (FVC) was determined pre and post-bronchodilator therapy. As recommended by the Global initiative for Obstructive Lung Disease (GOLD) committee[10], the post-bronchodilator values were used for the present study. The predicted FVC was calculated adjusted for age, gender and height according to the equation of Quanjer et al. which is recommended for European populations.[11] FVC% predicted was classified into severity using the following cutoffs: ≥80% predicted, 60-80% predicted, 40-60% predicted and <40% predicted.

SURGERY CLASSIFICATIONS

Based on the guidelines of the European Society of Cardiology[12], we classified the noncardiac surgical procedures into expected low cardiac risk (breast, dental, endocrine, eye, gynecology, orthopedic and reconstructive), intermediate cardiac risk (abdominal, ear-nose-throat, neurologic, pulmonary, renal, carotid and urologic), and high cardiac risk (aortic, peripheral vascular and other vascular).

CLINICAL DATA

Clinical data of all patients undergoing surgical procedures are routinely entered into a computerized hospital information system by trained administrative personnel. The following data were retrieved from this system; age, gender, smoking status (never/past smoker or current smoker) and cardiac risk index of Lee and colleagues[13] for major noncardiac surgery including history of myocardial infarction (MI), angina pectoris (AP), heart failure (HF) and cerebrovascular accident (CVA) and/or transient ischemic attack (TIA), diabetes mellitus (treatment with insulin and/or presence of fasting blood glucose of ≥7 mmol/l), and renal dysfunction (serum creatinine >2.0 mg/dl).

STUDY ENDPOINT

The primary endpoint was postoperative mortality defined as deaths (from any cause) occurring within 30 days of the date of surgery. Survival status of all patients was obtained from the hospital database and the civil registries. Within 30 days after surgery, 174 (1.7%) patients were lost to follow-up.

STATISTICAL ANALYSIS

The baseline characteristics across the FVC categories were compared using a chi-square test for categorical variables and analysis of variance for continuous variables. Mortality rates between the FVC groups were compared using a chi-square test and presented as percentages.

Data on smoking status was available in 8030 (77%) patients. In contrast to other risk factors such as history of myocardial infarction, smoking status, and especially history of smoking status, is not always reported in patients´ medical records. We used missing value analysis to impute the missing data (n=2341) on smoking status. Regression substititution was performed to predict the values for smoking using other variables without missing values (age, gender, CVA, MI, AP, HF, DM, renal insufficiency) and available data on smoking status. No outcome data was used to predict the missing data.

Logistic regression analysis was used to investigate the association between FVC and 30-day mortality. The estimated probability of 30-day mortality was calculated using a multivariate logistic regression model including the following risk factors which were entered simultaneously: FVC% of predicted value (which was divided into the following groups: <40% of predicted, 40-60% of predicted, 60-80% of predicted and ≥80% of predicted), age (in quartiles), surgical risk (as low, intermediate and high), gender, smoking status, and cardiac risk index[13] (as 0, 1, 2 or ≥3 cardiac risk factors (which included a history of MI, AP, HF, CVA/TIA, diabetes and renal insufficiency)). The final regression model included all significant risk factors as well as gender and smoking status for 30-day mortality. The predicted probability plot for 30-day mortality was created for predicted FVC% for all surgical risks adjusted for the above covariates.

To develop a parsimonious risk score for postoperative mortality, the coefficient of each risk factor was divided by 0.05 (the smallest beta coefficient in the model which was gender) and rounded to the nearest integer. These weighted scores were then assigned to each categorical predictor variable and the scores were summed together to produce a total score. The total scores were then used to generate 30-day survival probabilities for each risk score. Model discrimination between survivors and non-survivors was quantified by a c-statistic and its calibration was determined by the Hosmer-Lemeshow goodness-of-fit-test. Odds ratios (OR) were calculated along with their 95% confidence intervals (CI). For all tests, a 2-sided p-value of <0.05 was considered significant. All statistical analyses were performed using SPSS 15.0 for Windows.

RESULTS

BASELINE CHARACTERISTICS

There were 10,371 patients in this study. The mean age was 58 (±16) years and 6,144 (59%) were men. Table 1 shows the baseline characteristics in the various FVC% predicted categories. Significant differences were observed between the groups for age, gender, surgical risk, HF, CVA/TIA, DM, renal insufficiency, BMI and smoking status ($p<0.05$ for all). In total, 23% of the patients underwent low risk surgery, 65% intermediate risk, and 12% high risk surgery.

Table 1. Baseline characteristics

	FVC ≥80% predicted N=8,658	FVC 60-80% predicted N=1,304	FVC 40-60% predicted N=345	FVC <40% predicted N=64	p-value
Mean FVC% predicted (SD)	105(15)	72(6)	52(5)	31(8)	<0.001
Demographics					
Mean age in years (SD)	58(16)	58(16)	58(17)	44(18)	<0.001
Men (%)	59	63	62	55	0.01
Risk of surgery (%)					0.01
Low risk	15	17	17	17	
Low-intermediate risk	18	17	17	24	
Intermediate-high risk	66	65	66	59	
High risk	2	1	0	0	
Risk factors (%)					
Myocardial infarction	4	5	4	2	0.24
Heart failure	4	9	11	8	<0.001
Angina pectoris	8	10	8	5	0.08
Stroke or TIA	5	6	6	5	0.90
Diabetes Mellitus	36	44	43	45	<0.001
Renal insufficiency	3	7	6	5	<0.001
Current smoking*	38	34	32	14	<0.001

*2341 (23%) data obtained via missing value analysis

PULMONARY FUNCTION

Within 30-days after surgery, 360 (3.5%) patients died. The percentages were 3.0%, 5.3%, 8.6% and 10.9% for the decreasing FVC groups, respectively ($p<0.001$). Mortality rates varied significantly among the surgical risk groups within the different categories of FVC% predicted. In patients with normal pulmonary function (FVC ≥80% of predicted), 30-day mortality rates increased with increasing surgical risk from 0.8% for low risk surgery to 4.6% for high

risk surgery (Table 2). A FVC of 40% predicted was associated with higher mortality rates for 30-day mortality, ranging from 4.8% for low risk surgery to 33.3% for high risk surgery. FVC, as a continuous variable, was associated with reduced 30-day mortality (OR; 0.71; 95%CI, 0.64-0.78). After adjustment for other risk factors, the relationship remained significant (OR; 0.61; 95%CI, 0.54-0.70). The estimated risk for 30-day mortality increased with increasing surgical risk from 1.34% for patients with normal pulmonary function (FVC of 80% predicted) undergoing low risk surgery to 12.96% for patients with poor pulmonary function (FVC 40% predicted) undergoing high risk surgery (Figure 1).

Table 2. Risk of 30-day mortality according to FVC% predicted

Surgical risk	FVC 80% predicted	FVC 60% predicted	FVC 40% predicted
Low risk	0.8%	1.1%	1.5%
Low-intermediate risk	3.1%	4.3%	6.0%
Intermediate-high risk	5.8%	8.0%	10.9%
High risk	10.3%	14.0%	18.8%

Adjusted for age, gender, smoking status and cardiac risk index

Figure 1. The mean estimated risk of 30-day mortality for various surgical risk categories based on FVC% predicted

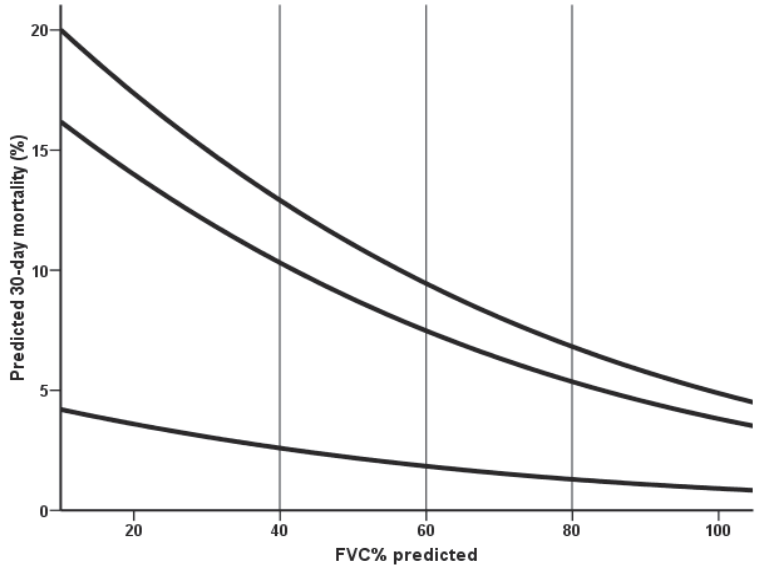


Table 3. Beta coefficient, odds ratio and score for the risk of 30-day mortality

	Beta coefficient	OR (95%CI)	Score
FVC percent predicted			
FVC ≥80% predicted	Reference	1.00	
FVC 60-80% predicted	0.582	1.79 (1.35-2.37)	8
FVC 40-60% predicted	1.169	3.22 (2.13-4.86)	16
FVC <40% predicted	2.062	7.86 (3.37-18.35)	27
Age group			
Age <47 yrs	Reference	1.00	
Age 47-60 yrs	1.139	3.12 (1.90-5.13)	15
Age 61-70 yrs	1.323	3.76 (2.30-6.12)	18
Age ≥71 yrs	1.732	5.65 (3.51-9.12)	23
Gender			
Male gender	0.073	1.08 (0.85-1.36)	1
Surgical risk			
Low risk surgery	Reference	1.00	
Low-intermediate risk surgery	1.255	3.51 (1.69-7.26)	17
Intermediate-high risk surgery	2.011	7.47 (3.81-14.64)	27
High risk surgery	2.046	7.74 (3.20-18.72)	27
Cardiovascular risk index (Lee)*			
0 cardiac risk factors	Reference	1.00	
1 cardiac risk factor	0.545	1.72 (1.35-2.20)	7
2 cardiac risk factors	0.813	2.26 (1.61-3.16)	11
≥3 cardiac risk factors	0.983	2.67 (1.66-4.31)	13
Current smoking	0.155	1.17 (0.94-1.46)	1

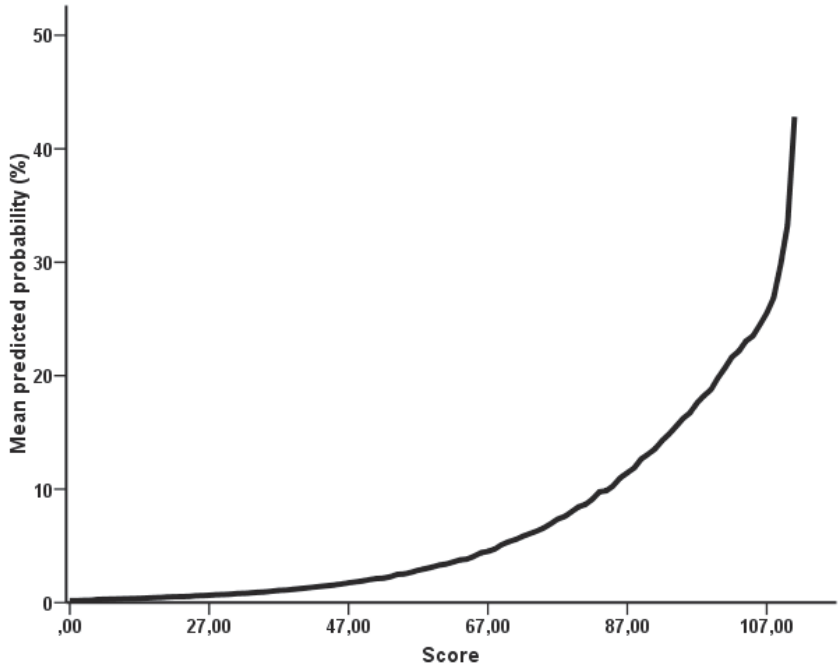
*Myocardial infarction, angina pectoris, heart failure, stroke or TIA, diabetes, renal insufficiency and current smoking

RISK MODEL

A risk model for 30-day mortality was developed using a logistic regression model which included 6 factors (FVC% predicted, surgical risk, age, gender, smoking status and cardiac risk index (Lee) (Table 3). In this multivariate model, those with FVC less than 40% predicted had almost 8 fold increased risk of 30 day mortality (OR; 7.98; 95%CI, 3.42 to 18.65) compared to patients with normal pulmonary function (FVC ≥80% of predicted) (Table 3). By summing the individual scores from the given predictors and using the total risk score, the patients´ probability of 30-day mortality can be estimated from Figure 2. The mean predicted probability for 30-day mortality was 0.3%

(2.8-2.9) for patients with a total score of 0-25, 1.0% (1.0-1.1) for score 25-50, 4.0% (3.9-4.0) for score 50-75 and 9.8% (9.6-10.0) for patients with a risk score equal to or more than 75 point. The c-statistic of the prognostic risk model was 0.73 (95% CI; 0.71-0.75). Calibration assessment with the use of the Hosmer and Lemeshow goodness-of-fit test produced a non-significant outcome (p=0.18). In addition, a complete case analysis was performed in which patients with unknown smoking status were excluded (n=2341). Similar results were found as in the main analysis.
We provide an example of how the risk index may be used. If a 67 year old smoking male patient, who is scheduled to undergo bilateral carotid endarterectomy (i.e. an intermediate risk surgery) with 2 cardiovascular risk factors, performs spirometry and produces a post-bronchodilator FVC of 50% of predicted, his total risk score would be 98. His 30-day mortality risk based on the current model would be 17% (Figure 2).

Figure 2. Prognostic risk model for predicted 30-day mortality



DISCUSSION

In this study we investigated the association between pulmonary function and postoperative mortality for different surgical risk procedures and developed a risk model including pulmonary function for the prediction of mortality within 30 days after noncardiac surgery.

To our knowledge, this is the first study in patients undergoing noncardiac surgery that investigated the relationship between FVC and postoperative mortality. Previous studies found forced expiratory volume in 1 second 14 and pulmonary dysfunction[15, 16] as significant predictors of poor operative outcome, however these studies included patients undergoing abdominal aortic aneurysm surgery only. We found that preoperative FVC was inversely related to postoperative mortality such that regardless of type of surgery and other factors, individuals with poor lung function had a much higher risk of post-operative mortality compared to those with normal lung function. As expected, the type of surgery modified this relationship. In patients with poor pulmonary function (FVC <40% predicted), 30-day mortality ranged from approximately 5% for low risk to 33% for high risk surgery. In intermediate risk surgery, the 30-day mortality rates varied from 3% in patients with normal FVC to 12% in those with very severe impairment in lung function. In patients with normal lung function, the 30-day mortality was less than 1% for low-risk surgery which increased to nearly 5% for high surgical procedures. Although routine preoperative pulmonary function testing is only recommended for patients undergoing high-risk procedures (i.e. thoracic, abdominal or lung resection surgery and coronary artery bypass surgery)[17], the results of the present study suggest that pulmonary function provide important prognostic information to patients undergoing even low or intermediate risk surgery. However, the results of preoperative pulmonary function testing should not be used to deny patients for surgery. It should guide physicians in the preoperative treatment of patients with reduced pulmonary function to minimize postoperative complications. For those with poor lung function, various intervention steps including smoking cessation, pulmonary rehabilitation, bronchodilator and corticosteroid therapy, and treatment of exacerbations may be taken preoperatively to enhance lung function. In addition, elective surgery could be postponed if acute exacerbation is present. Furthermore, as reduced pulmonary function is associated with increased risk of cardiovascular mortality compared to patients with normal pulmonary function18 these patients may require special preoperative cardiac risk assessment and treatment in addition to pulmonary measurements.

Postoperative pulmonary complications are common following non-thoracic surgery (due to reduced pulmonary function), ranging from 2% to 19%.[19] As Chetta and colleagues previously concluded, the effects of extra-thoracic or non resective thoracic surgery on pulmonary function rely on many factors such as advanced age, smoking habit, coexistence of pulmonary disease, surgical site, and the type of surgical procedure itself.[20] We therefore developed in the present study a simple prognostic risk model including pulmonary function as well as cardiac risk factors for the prediction of 30-day mortality following noncardiac surgery. Using preoperative pulmonary function tests in addition to other risk factors such as age, gender, type of surgical procedure and cardiac risk factors, it may be possible to identify patients who are susceptible for poor postoperative outcomes. The integration of these important clinical variables into a simple risk score facilitates their application to clinical practice. Additionally, some of the risk factors in the index are potentially modifiable which may reduce the risk for postoperative mortality. The strength of this risk score is that it can be calculated by using routine clinical data obtained on history and simple spirometry. Previous developed risk models for noncardiac surgery only focused on postoperative pulmonary complications[5, 8] or cardiac risk[13, 21] and did not include pulmonary function measurement. Although

both pulmonary function and cardiac risk factors are most important predictors of postoperative morbidity and mortality in noncardiac surgery patients[2], currently no prediction model exists in which these measurements are included.

There are some important limitations to the present study. First, the study was retrospective in nature and included only those who were referred to a pulmonary function laboratory which may limit generalizability to patients who do not have any pulmonary risk factors. Second, there is the possibility of residual confounding. Third, patients did not undergo full pulmonary function tests. Thus, we could not assess the importance of other lung function parameters such as total lung capacity, inspiratory capacity or gas transfer coefficient on post-operative mortality. Finally, we had missing data on smoking status. However, we believe that these patients should not be excluded to prevent any bias, and used established statistical methods to impute missing values (23%). It was assuring that in a sensitivity analysis which excluded cases which had missing values on smoking status, there were no significant differences in the results between this and the principal analysis.

In sum, the present study indicates that FVC is an important risk factor for post-operative mortality in patients undergoing noncardiac surgery. The risk was highest in patients with poor pulmonary function undergoing high risk surgery. FVC, along with data obtained on clinical history can be integrated into a simple clinical risk index that can predict 30-day mortality following surgery. This will better inform patients and clinicians regarding surgical risk and facilitate institution of interventions and therapies to optimally attenuate risk prior to surgery for certain patients.

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2

Health-related quality of life in vascular surgery patients with chronic obstructive pulmonary disease

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ABSTRACT

BACKGROUND

Health-related quality of life (HRQL) is increasingly used as an important outcome parameter in patients with chronic obstructive pulmonary disease (COPD). We investigated the association between COPD severity and HRQL among vascular surgery patients. In addition we examined the differences in HRQL between males and females.

METHODS

Of the original cohort of 3371 vascular surgery patients 1620 survived during long-term follow-up. These patients were sent the Short Form-36 (SF-36) health-related quality of life questionnaire, which was completed and returned by 1107 (68%) patients. Study endpoint was HRQL at follow-up.

RESULTS

COPD was present in 323 (30%) patients. Moderate and severe COPD were associated with impaired HRQL with odds ratios ranging from 1.6 to 3.6. Females scored worse on all domains of the SF-36 compared to males. HRQL decreased with increasing COPD severity among males on all SF-36 domains, this was not found among females.

CONCLUSION

Moderate to severe COPD is associated with impaired HRQL in vascular surgery patients. Furthermore, females tend to score worse on HRQL compared to males. However decreased HRQL with increasing COPD severity was only observed in males, not in females.

INTRODUCTION

To date, COPD is the fourth cause of morbidity and mortality in the developed world and is expected to be the third by 2020.[1] COPD is a progressive disease which results in lung function impairment with airway obstruction, dyspnea and cough.[2] With COPD condition decreasing, patients often experience a progressive disability, which might lead to an impairment in their health-related quality of life (HRQL).[3-5] Except for smoking cessation, no other intervention stops the rate of decline in lung function. The focus of COPD treatment should be on symptom relief to intercept the impairment of HRQL and even possible improve HRQL.[6] Furthermore, impaired HRQL is known to be associated with increased mortality independent of pulmonary function and age.[7]

HRQL assessment is often used for measuring the impact of chronic disease like COPD[8] and these instruments are increasingly used in clinical studies.[6] In Europe it is even required that clinical trials of new drugs for COPD should incorporate a symptomatic measure, such as a health status questionnaire, as a co-primary endpoint along with a measure such as the FEV_1.[9] Consequently, in recent years more and more research on the impact of disease on HRQL has been conducted in patients with COPD. However, to our knowledge, data are lacking in patients with peripheral artery disease (PAD) undergoing vascular surgery. This is also the case regarding research on gender differences.[10, 11] Therefore, the aim of the present study was to evaluate the association between COPD severity and HRQL in this group of vascular surgery patients. In addition we investigated whether HRQL differed between males and females.

METHODS

STUDY POPULATION

The study included 1620 patients of an original cohort of 3371 patients[12] with (PAD) who underwent elective vascular surgery (abdominal aortic surgery (AAA), carotid endarterectomy (CEA) or lower limb arterial reconstruction procedures (LLR) between 1990 and 2006 at the Erasmus Medical Center Rotterdam, The Netherlands. As described previously, in all patients we recorded demographic and clinical characteristics (Table 1) which were retrieved from the medical records.

At follow-up survival status was ascertained from the municipal civil registries. Subsequently all 1620 surviving patients were sent a self-administered HRQL questionnaire (see below) which was completed and returned by 1107 (68%) patients who were included in the study. Median follow-up was 6.9 years (interquartile range 3.6 to 11.6 years). Study endpoint was HRQL at follow-up.

PULMONARY FUNCTION TESTING

The diagnosis and classification of COPD was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines based on a post-bronchodilator test.[2] Patients without spirometry were classified based on presence of pulmonary symptoms (dyspnea, sputum production or cough) and use of COPD medications based on the GOLD guidelines as well. Mild COPD was defined as those who had symptoms and were using a short-acting bronchodilator when needed. Moderate COPD was defined as those with symptoms who required regular use with one or more bronchodilators. Severe COPD was defined as those with symptoms and were on regular treatment with one or more bronchodilators plus inhaled corticosteroids (for repeated exacerbations or persistent symptoms) or those patients who required domiciliary long-term oxygen

therapy. The disease severity was classified into 3 stages: I=mild COPD (FEV_1 FEV_1 /FVC <0.70 and FEV_1 ≥80% of the predicted FEV_1), II=moderate COPD (FEV_1 /FVC <0.70 and FEV_1 50% ≤FEV_1 <80% of the predicted FEV_1) and III=severe COPD (FEV_1 /FVC <0.70 and FEV_1 30% ≤FEV_1 <50% of the predicted FEV_1).[2]

SHORT FORM 36

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) has been widely accepted in recent years and is used in numerous studies including patients with COPD.[13-15] It contains 36 items divided into eight domains: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). Scores are calculated with a range from 0 to 100. A higher score on the SF-36 domains represents a better HRQL with a high score on the bodily pain scale indicating freedom from pain. The questionnaire has good reliability with Cronbach's alpha ranging from .65 to .96 for all domains.[16]

STATISTICAL ANALYSIS

Differences on baseline characteristics between the 4 groups (no COPD, mild COPD, moderate COPD and severe COPD) were compared using a chi-square test for dichotomous variables and are presented as percentages. Continuous data were compared using analysis of variance and presented as means and standard deviation (SD). A Bonferroni post-hoc correction was used to adjust for multiple comparisons. Univariate and multivariate logistic regression analyses were performed to assess the association between COPD severity and HRQL with no COPD used as reference. In the multivariate analyses, all potential confounders that might influence HRQL were simultaneously entered as covariates; age, gender, diabetes mellitus, renal dysfunction, current smoking, obesity, type of surgery (AAA, CEA, LLR), previous ischemic heart disease (myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention or angina pectoris), heart failure, history of cerebrovascular event (CVA) and/or transient ischemic attack (TIA), use of statins, aspirin, beta-blockers, corticosteroids and bronchodilators. To correct for the differential follow-up, adjustments were made for the number of follow-up years. A priori, the eight domains of the SF-36 were converted into tertiles for parsimony and subsequently dichotomized with the lowest tertile representing worst health status and the highest two tertiles representing best health status. All statistical tests were two-tailed. P <0.05 was used for all tests to indicate statistical significance. Odds ratios (OR) with 95% confidence intervals (CI) are reported.

RESULTS

PATIENTS

Baseline characteristics of the 1107 patients are presented in Table 1. Mean age was 63 ± 11 years, and 816 (74%) were men. A total of 332 (30%) patients had COPD: 177 (16%) had mild, 125 (11%) had moderate and 30 (3%) had severe COPD. Patients with COPD were more likely to have cardiovascular history and risk factors and to receive cardiac and pulmonary medical therapy. Patients who did not respond to the questionnaire were more likely to be women (32% vs 26%), were younger (61 yrs vs 63 yrs), had more frequent diabetes mellitus (19% vs 11%), and had a lower body mass index (25.5 kg/m^2 vs 26.2 kg/m^2), compared to the responding patients (p<0.05 for all) (data not shown). In addition, non-responding patients were more often smokers and used more frequent aspirin and corticosteroids (p<0.05 for all). No differences were observed for COPD (severity) between the patients who respond and did not respond to the questionnaire (p=0.18)

Table 1. Baseline characteristics according to COPD severity

	No COPD (N = 775)	Mild COPD (N = 177)	Moderate COPD (N = 125)	Severe COPD (N = 30)	p-value
Demographics (%)					
Mean age years (mean (SD))	62(11)	67(9)	65(10)	66(9)	<0.001
Male gender	71	82	79	70	<0.05
Cardiovascular history (%)					
Myocardial infarction	16	25	30	10	<0.001
Heart failure	3	6	4	0	0.13
Angina pectoris	13	23	19	13	<0.05
CVA/ TIA	40	22	29	27	<0.001
CABG	9	15	16	3	<0.05
PCI	8	12	10	3	0.15
Clinical characteristics (%)					
Diabetes Mellitus	10	11	18	7	0.051
Current smoking status	23	25	36	40	<0.001
Renal dysfunction	14	120	20	7	0.04
Body mass index (mean (SD))	26(4)	26(3)	26(4)	25(4)	0.21
Medication (%)					
Statins	32	45	41	47	<0.01
Beta-blockers	39	58	56	67	<0.001
Aspirin	54	53	49	33	0.14
Bronchodilators	0	7	13	20	<0.001
Corticosteroids	1	12	29	43	<0.001

*CVA: cerebrovascularaccident; TIA: transischemicattack; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention.

COPD SEVERITY AND HEALTH STATUS

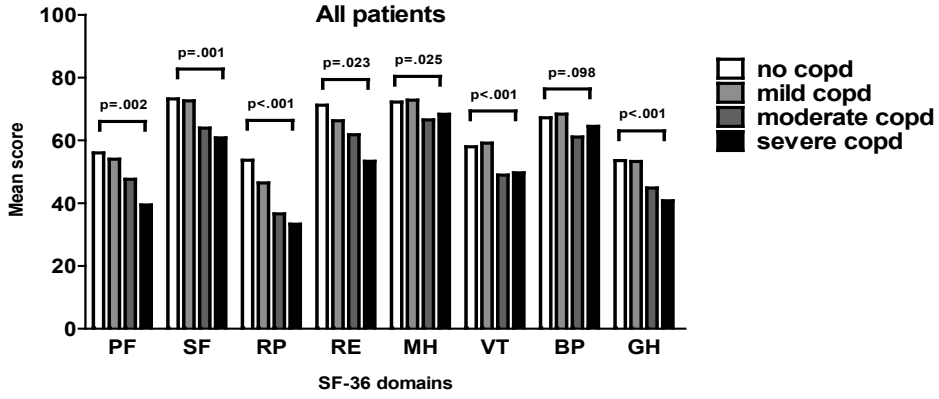
In all domains of the SF-36 except for the domain of bodily pain, HRQL scores decreased significantly with increasing COPD severity (Figure 1). As shown in the multivariate analyses, the significant signals in the domains of SF-36 were observed mostly among patients with moderate or severe COPD (Table 2). Mild COPD was generally not associated with impaired HRQL. Moderate COPD was significantly related with impaired HRQL in five of the domains with OR's varying between 1.5 and 2.0 as compared with patients without COPD. Among patients with severe COPD, impaired HRQL was observed in three of the domains with OR's ranging from 3.2 to 3.6.

Table 2. Association between COPD severity and HRQL

SF-36	PF		RP		BP		GH		VT		SF		RE		MH	
domains	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Univariate																
No COPD	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Mild COPD	1.3	[0.8-1.8]	1.4	[0.96-2.0]	1.2	[0.8-1.6]	1.1	[0.8-1.6]	1.0	[0.9-1.3]	1.0	[0.7-1.5]	1.3	[0.9-1.9]	1.1	[0.8-1.6]
Moderate COPD	1.6	[1.1-2.4]	2.3	[1.5-3.4]	0.8	[0.5-1.2]	2.3	[1.6-3.4]	1.8	[1.3-2.7]	2.1	[1.4-3.1]	1.5	[1.0-2.2]	1.9	[1.3-2.8]
Severe COPD	3.2	[1.5-6.9]	2.2	[1.0-4.7]	0.9	[0.4-2.0]	3.1	[1.4-6.6]	1.9	[0.9-4.0]	2.1	[1.0-4.5]	3.2	[1.4-7.1]	1.2	[0.5-2.6]
Multivariate																
No COPD	1.0		1.0		1.0		1.0		1.0		1.0		1.0		1.0	
Mild COPD	1.2	[0.8-1.7]	1.3	[0.9-1.9]	1.4	[0.97-2.1]	1.1	[0.7-1.6]	0.9	[0.6-1.4]	0.9	[0.6-1.3]	1.3	[0.8-1.9]	1.2	[0.8-1.7]
Moderate COPD	1.4	[0.9-2.3]	2.0	[1.2-3.2]	1.0	[0.6-1.6]	2.0	[1.3-3.1]	1.6	[1.04-2.5]	1.5	[1.0-2.4]	1.3	[0.8-2.2]	1.7	[1.1-2.7]
Severe COPD	3.3	[1.4-7.6]	2.1	[0.9-5.0]	1.1	[0.5-2.5]	3.2	[1.4-7.5]	1.7	[0.7-4.0]	1.7	[0.7-3.8]	3.6	[1.5-8.6]	1.1	[0.5-2.5]

PF = physical functioning; SF = social functioning; RP = role-physical; RE = role-emotional; MH = mental health; BP = bodily pain; VT = vitality; GH = general health.

Figure 1. Mean SF-36 domain scores according to COPD severity



HEALTH STATUS AND GENDER

Overall women scored worse on all HRQL domains compared to men ($p<0.05$ for all) (Figure 2). As observed in the total patient group, HRQL in men decreased with increasing COPD severity, however this was not seen among women (Figure 3a and 3b).

Figure 2. Mean SF-36 domain scores for male and females

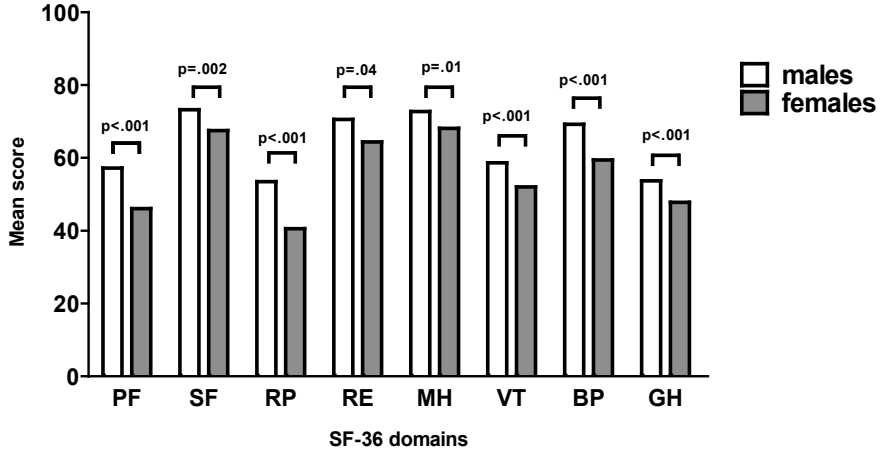
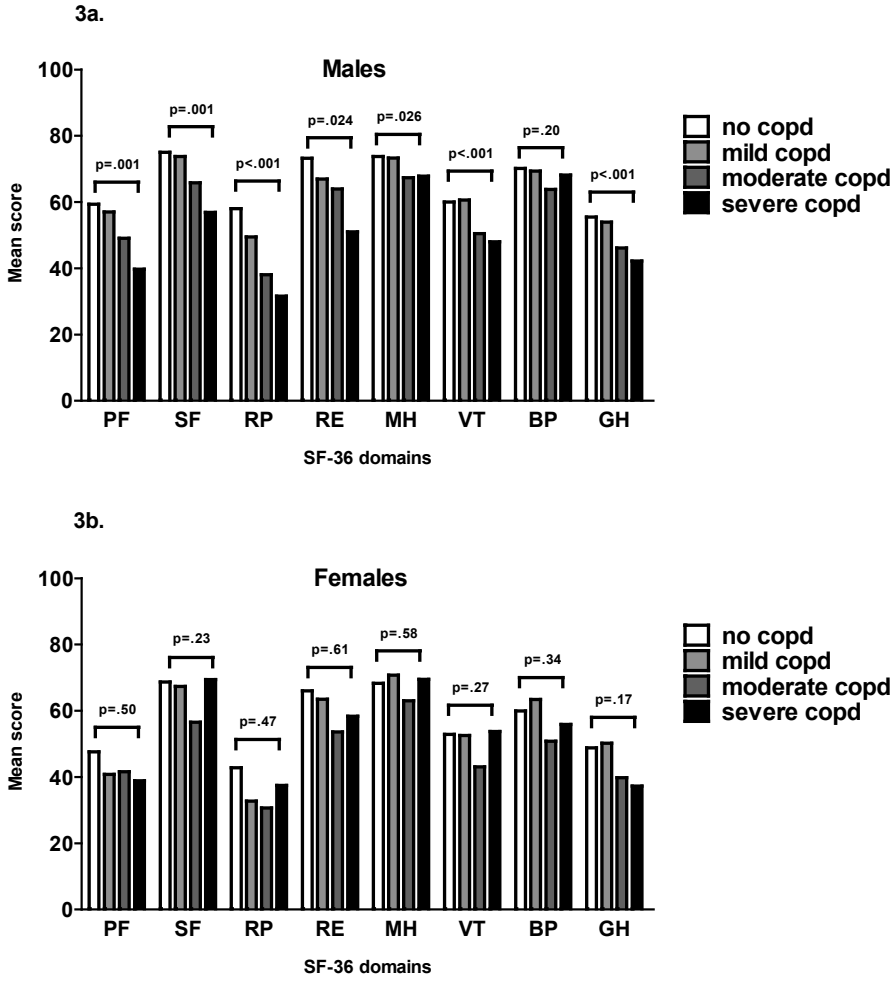


Figure 3. Mean SF-36 domain scores according to COPD severity among males and females



DISCUSSION

The results of the present study showed that severity of COPD affects HRQL in patients with peripheral artery disease who underwent vascular surgery. This is largely driven by patients with moderate to severe disease, mild COPD is not associated with significant changes in the SF-36 scores in any of the domains. In addition, females had worse HRQL compared to men, however HRQL did not decease with COPD severity as observed in males.

There have been several studies that have investigated the relationship between disease severity and HRQL in COPD but none in patients with vascular disease.[17-20] Our results are in general agreement with several studies who showed that HRQL decreases with increasing COPD disease severity[17, 20, 21] but only in those with moderate to severe disease. We did not found a significant reduction in HRQL in the mild stage of COPD. An explanation could be that patients with mild COPD (FEV_1 >80%) are often asymptomatic and consequently do not have as much complaints on their relatively good health profile compared to patients with moderate or severe COPD. Before patients note a change in exercise capacity (which is related with HRQL), the FEV_1 has to drop below about 85%.[22] In addition, when FEV_1 drops below 50% of the predicted FEV_1, essential activities of daily life become disturbed.[23] In contrast, Bridevaux et al. using a cohort of 6671 randomly selected adults, found an association between mild COPD and impaired HRQL, but the repeated lung function measures which were performed, may have overdiagnosed mild COPD.[18] Ferrer et al. also demonstrated that even patients in the mild stage show a HRQL reduction.[19] However, bias could have taken place whereas this study included only men.

Impairments in the domains of the SF-36 are related with COPD as well as with other comorbidities.[24] This is in line with our results which demonstrated that even patients without COPD scored below 80 which is known as normal score for almost all SF-36 domains.[25] We observed low overall scores as could be expected with underlying PAD.

In our study moderate COPD is associated with impaired health status on more SF-36 domains than severe COPD. This might be due to a lack of power. Another idea is that patients who are in the worst condition have learned coping strategies to deal with their bad overall health and are more positive towards their health status. A recent study found that COPD patients are able to choose suitable disease management techniques to prevent symptoms and complications.[26]

Data on gender differences in HRQL in COPD patients is scarce.[10, 11, 27, 28] We found worse scores on HRQL in females compared to males. Likewise, Osman et al. and also de Torres and co-workers both found females scoring worse on HRQL in COPD patients, however both used the SGRQ-questionnaire. In addition, a recent study found that higher perception of symptom control was associated with positive health ratings in females.[29] Furthermore we only found a significant decline in HRQL with worsening of COPD stage in males. This might be due to the lower percentage of females included in this study leading to a lack of power in the moderate and severe COPD groups.

Except for oxygen supplementation, most treatments have not been shown to improve survival.[6] Therefore, the most important goal of clinical management of COPD is to improve patients' HRQL. There are several interventions with positive effects on some or all HRQL components, including inhaled corticosteroids, inhaled bronchodilators, opioids, oxygen therapy, pulmonary rehabilitation, implementation of a disease-specific self-management program and lung volume reduction surgery.[6] Results of a previous study revealed that factors influencing health status of patients with COPD are dyspnoea and patients' physiological status, so a psychological assessment approach for improving the HRQL might be important in these patients.[30] This study

also concluded that in terms of improving health status, it may be reasonable to change medical interventions and therapeutic goals in accordance with the disease stage.[29, 30] Furthermore, teaching coping strategies should also be considered for improving HRQL of COPD patients.[31] Finally, smoking cessation halts the rate of decline in lung function, probably because smokers have not yet reached a more severe disease severity.[20] Treatment should therefore be aimed on symptom relief and smoking cessation.

There were several limitations to this study. Patients with both PAD and COPD differ mainly in comorbid conditions compared to those with only COPD. In this case we should suggest a randomized controlled trial to measure the HRQL. Due to the study design, there might be a possibility of confounding by unmeasured variables. Coherent on our long follow-up, HRQL was not measured at the same time for all patients and HRQL was only assessed in the surviving patients. In addition, we did not have HRQL at baseline and thus we were not able to investigate the impact of progression of COPD on HRQL during follow-up. Furthermore, we have used a generic questionnaire to measure HRQL, which is generally less sensitive then a disease specific tool. However, all patients included in the study also had PAD which could have affected their HRQL and may have been missed by a more disease-specific questionnaire. Moreover, the SF-36 is generally accepted and widely used in patients with COPD.[6, 13, 20, 32]

In conclusion, our results showed that moderate to severe COPD is associated with worse HRQL in patients undergoing vascular surgery. Although females experienced worse HRQL compared to males, deterioration of HRQL with increasing COPD severity was only observed in males.

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Part II

COPD as a risk factor

3

Association between chronic obstructive pulmonary disease and chronic kidney disease in vascular surgery patients

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ABSTRACT

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is recognized as a source of systemic inflammation and is associated with the development of cardiovascular disease. However, little is known about the association between COPD and chronic kidney disease (CKD). Therefore, we investigated the relationship between COPD and CKD and the association between COPD and mortality in patients with CKD.

METHODS

We conducted a cohort study of 3358 vascular surgery patients between 1990 and 2006. CKD was defined according to the Modification of Diet in Renal Disease equation as an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2. In addition, patients were divided into three categories based on the baseline estimated GFR: ≥90 mL/min/1.73m^2; 60-89 mL/min/1.73m^2; and <60 mL/min/1.73m^2. Multivariable logistic regression analysis was used to evaluate the independent association between prevalent COPD and CKD.

RESULTS

The prevalence of COPD was inversely related to kidney function. COPD was present in 47, 38 and 32% of patients with an estimated GFR <60, 60-89 and ≥90 mL/min/1.73 m^2, respectively. COPD was independently associated with CKD (OR 1.22; 95%CI 1.03-1.44; *P* = 0.03). This association was strongest in patients with moderate COPD (OR 1.33; 95%CI 1.07-1.65; *P* = 0.01). Both moderate and severe COPD were associated with increased long-term mortality in patients with CKD (HR 1.27; 95%CI 1.03-1.56; *P* = 0.03 and HR 1.61; 95%CI 1.10-2.35; *P* = 0.01, respectively), compared to patients without COPD.

CONCLUSIONS

Our findings indicate that COPD is moderately associated with CKD in a large cohort of vascular surgery patients. In addition, moderate and severe COPD are related to increased long-term mortality in patients with CKD.

INTRODUCTION

Chronic kidney disease (CKD) is a growing public health problem and affects a large number of individuals, ~13% of the US adult population.[1] This is mainly due to the increased prevalence of traditional cardiovascular risk factors such as diabetes, hypertension and obesity.[1, 2] In addition, the presence of cardiovascular disease is also important in the development and deterioration of kidney disease.[3] Previous studies have found underlying atherosclerosis, an inflammatory process,[4] to be associated with the pathogenesis of kidney disease.[5, 6] Hence, the relationship between cardiovascular disease and kidney function could also be due to an increased prevalence of other less well-examined cardiovascular risk factors, such as chronic obstructive pulmonary disease (COPD).

As with kidney disease, COPD is a major health care problem worldwide and is associated with cardiovascular disease as well. COPD is characterized by an abnormal inflammatory response of the lungs to noxious particles and gases.[7] However, the inflammation is not only restricted to the lungs but also extends systemically. Previous studies showed that this systemic inflammation might be the missing link between COPD and the development and progression of atherosclerosis and cardiovascular disease.[8] Consequently, given that a number of investigators[9-11] have shown that COPD is associated with cardiovascular disease in people with normal kidney function, it seems reasonable to propose that COPD in patients with vascular disease may also be associated with CKD independent of other covariates that might influence kidney function loss. Therefore, we investigated the relationship between COPD and CKD in a large cohort of vascular surgery patients with peripheral arterial disease. Moreover, we assessed the association between COPD and mortality in patients with kidney disease.

METHODS

STUDY POPULATION

The study included 3358 patients of an original cohort of 3371 patients who underwent elective vascular surgery [abdominal aortic surgery (AAA), carotid endarterectomy (CEA) or lower limb arterial reconstruction procedures (LLR)] between January 1990 and December 2006 in the Erasmus Medical Center, Rotterdam, The Netherlands.

EXPOSURES AND OUTCOMES

The primary exposure variable was a diagnosis of COPD at baseline. This diagnosis was based on a post-bronchodilator pulmonary function test, which was performed by 82% of the patients with a clinical diagnosis of COPD at baseline. Those participants without a pulmonary function test were given a clinical diagnosis of COPD according to a history of cough, dyspnea, sputum production and their pulmonary medication use. The severity of COPD was categorized according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria using the forced expiratory volume in 1 s (FEV_1)/ forced vital capacity (FVC) ratio and the percentage of the predicted FEV_1.[7] This approach is suggested by the American Thoracic Society (ATS) and the European Respiratory Society (ERS).[12] Further details of our study design have been previously described.[13]

The primary outcome variable was CKD. Serum creatinine was assessed in approximately all patients (n=3358, 99.6%) who were included in the analysis. CKD was defined as estimated glomerular filtration rate (GFR) <60 mL/min/1.73m^2 using the equation of the Modification of

Diet in Renal Disease (MDRD)[14]: 186.3 x (serum creatinine$^{-1.154}$) x (age$^{-0.203}$) x 0.742 (if female). Serum creatinine was measured in mg/dL, age in years and estimated GFR was expressed as mL/min/1.73 m^2. This cutoff was chosen on the basis of the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.[15] In addition, patients were divided into three categories based on the baseline estimated GFR: ≥90 mL/min/1.73m^2; 60 to 89 mL/min/1.73m^2 and <60 mL/min/1.73m^2.

Secondary endpoints included short-term (within 30 days after surgery) and long-term (within 10 years after surgery) mortality. Survival status was complete in 96% of all patients and ascertained from the municipal civil registry. The median follow-up was 5 years (interquartile range 2.0-9.1 years).

OTHER VARIABLES

In all patients, we recorded the following cardiovascular risk factors: age, gender, hypertension (defined as a blood pressure ≥140/90 mm Hg), diabetes mellitus (presence of fasting blood glucose of ≥140 mg/dL or treatment with insulin or oral hypoglycemic agents), hypercholesterolemia (total cholesterol of >200 mg/dl) and current smoking status. The patients' cardiovascular history was assessed including ischemic heart disease (previous myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention and/or angina pectoris), heart failure (defined according to the New York Heart Association classification) and stroke and/or transient ischemic attack.

STATISTICAL ANALYSIS

The baseline characteristics between the patients with and without CKD are described as means ± SD and percentages. Continuous variables were compared using the Student's *t*-test and dichotomous variables using chi-square tests. Univariable and multivariable logistic regression analyses were used to investigate the association between COPD and kidney disease. In addition, logistic regression analysis was used to examine the relationship between COPD and short-term mortality in a subgroup analysis including only patients with CKD (estimated GFR <60 mL/min/1.73m^2). Furthermore, Cox regression analysis was used to investigate this association during a 10-year period. In the multivariable analysis adjustments were made for age, gender, type of surgery, current smoking, previous heart failure, hypertension, diabetes and hypercholesterolemia. The final variables were chosen on the basis of biological plausibility. Odds ratios (OR) and hazard ratios (HR) are provided with their 95% confidence intervals (CI). Testing was two-sided and *P* values <0.05 were considered statistically significant. Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

BASELINE CHARACTERISTICS

The characteristics of the 3358 patients are presented in Table 1 based on the presence or absence of CKD. The mean serum creatinine concentration and estimated GFR in this population were 1.22 ± 1.15 mg/dL and 76 ± 30 mL/min/1.73m^2, respectively. In total, 918 (27%) patients had CKD defined by an estimated GFR <60 mL/min/1.73m^2 (mean estimated GFR 43 ± 15 mL/min/1.73m^2) (Table 1). Patients with CKD were older, were more likely to be female and had significantly higher proportions of hypertension, diabetes, COPD and cardiovascular disease. Importantly, CKD patients were less likely to be smokers and had a lower proportion of hypercholesterolemia. COPD was present in 1307 (39%) patients.

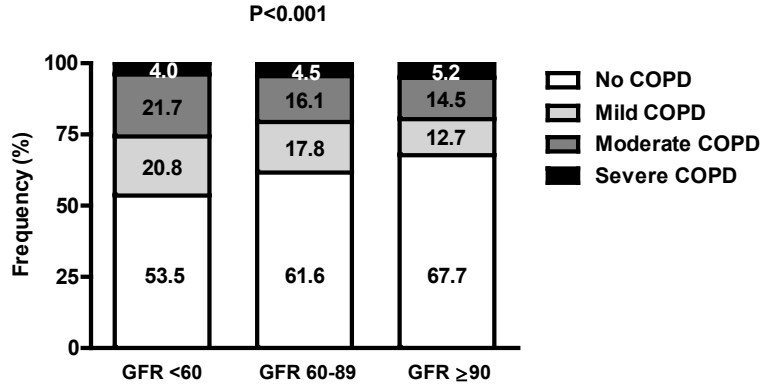
In addition to the 918 patients with an estimated GFR <60 mL/min/1.73m^2, 1500 and 940 patients had an estimated GFR level of 60-89 and ≥90 mL/min/1.73m^2, respectively. The distribution of the prevalence of COPD according to kidney function is presented in Figure 1. Across decreasing estimated GFR groups 32%, 38% and 47% had COPD (p <0.001).

Table 1. Baseline characteristics according to CKD

	Total (n=3358)	No CKD (GFR ≥60) (n=2440)	CKD (GFR <60) (n=918)	P value
Mean estimated GRF (SD)	76(30)	89(23)	43(15)	<0.001
Demographics				
Mean age (SD)	66(12)	64(12)	70(11)	<0.001
Male gender (%)	73	75	68	<0.001
Type of surgery (%)				<0.001
AAA[a]	36	33	40	
CEA[b]	24	28	15	
LLR[c]	40	39	45	
Cardiovascular history (%)				
Myocardial infarction	22	19	29	<0.001
Coronary revascularization[d]	16	15	19	<0.01
Heart failure	5	3	8	<0.001
Angina pectoris	14	13	18	<0.001
Stroke or TIA[e]	30	31	26	<0.01
COPD (%)				<0.001
No COPD	61	64	54	
Mild COPD	17	16	21	
Moderate COPD	17	15	22	
Severe COPD	5	5	4	
Clinical characteristics (%)				
Hypertension	38	34	50	<0.001
Diabetes Mellitus	15	14	17	<0.01
Hypercholesterolemia	18	19	15	<0.01
Current smoking status	28	30	24	<0.01

[a] AAA=Abdominal aortic surgery
[b] CEA=Carotid endarterectomy
[c] LLR=Lower limb arterial reconstruction procedures
[d] Coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)
[e] TIA=Transient ischemic attack

Figure 1. Percentages of COPD severity according to kidney function



CROSS-SECTIONAL RELATIONSHIP BETWEEN COPD AND CKD

Table 2 shows that COPD was associated with a higher risk of prevalent CKD. After adjustment for age, gender, type of surgery, current smoking, previous heart failure, hypertension, diabetes and hypercholesterolemia, patients with COPD had increased odds of CKD (adjusted OR 1.22 95% CI: 1.03 to 1.44; *P* = 0.03). This relationship was further explored by examining the association between COPD severity and CKD. A borderline significant relationship was observed for mild COPD while moderate COPD was independently associated with kidney disease (OR 1.23; 95%CI 0.99-1.53; *P* = 0.06 and OR 1.33; 95%CI 1.07-1.65; *P* = 0.01, respectively). No significant association was found between severe COPD and kidney disease (OR 0.80; 95%CI 0.54-1.20; *P* = 0.29) (Table 2).

Table 2. Association between COPD severity and CKD (estimated GFR <60 mL/min/1.73 m2)

	Univariable		Multivariable[a]	
	OR	[95% CI]	OR	[95% CI]
COPD	1.54	[1.32-1.80]	1.22	[1.03-1.44]
No COPD	1.00		1.00	
Mild COPD	1.57	[1.29-1.92]	1.23	[0.99-1.53]
Moderate COPD	1.67	[1.37-2.04]	1.33	[1.07-1.65]
Severe COPD	1.01	[0.69-1.49]	0.80	[0.54-1.20]

[a]Adjusted for age, gender, type surgery, current smoking, previous heart failure, hypertension, diabetes and hypercholesterolemia.

Table 3. Association between COPD and short- and long-term mortality in patients with CKD

	30-day mortality				10-year mortality			
	Univariable		Multivariable*		Univariable		Multivariable[a]	
	OR	[95% CI]	OR	[95% CI]	HR	[95% CI]	HR	[95% CI]
COPD	1.17	[0.74-1.85]	0.94	[0.58-1.54]	1.30	[1.11-1.53]	1.16	[0.98-1.38]
No COPD	1.00		1.00		1.00		1.00	
Mild COPD	1.25	[0.70-2.18]	1.00	[0.55-1.82]	1.08	[0.87-1.35]	0.98	[0.78-1.23]
Moderate COPD	1.12	[0.63-2.01]	0.91	[0.49-1.68]	1.43	[1.17-1.74]	1.27	[1.03-1.56]
Severe COPD	0.99	[0.29-3.35]	0.85	[0.24-2.96]	1.90	[1.31-2.76]	1.61	[1.10-2.35]

[a]Adjusted for age, gender, type surgery, current smoking, previous heart failure, hypertension, diabetes and hypercholesterolemia.

SHORT AND LONG-TERM OUTCOME IN PATIENTS WITH CKD

In total, 178 (5%) patients died within 30 days after surgery and 80 (9%) of those with CKD. No relationship between COPD and short-term mortality was observed in patients with CKD (adjusted OR 0.94 95% CI: 0.58 to 1.54; $P = 0.82$). During 10 years of follow-up, 1555 (46%) patients died. COPD was associated with a higher risk of long-term mortality (Table 3). After adjustments for demographics, type of surgery, current smoking, previous heart failure, hypertension, diabetes and hypercholesterolemia, moderate and severe COPD remained significantly associated with all-cause mortality in patients with CKD. (HR 1.27; 95%CI 1.03-1.56; $P = 0.03$ and HR 1.61; 95%CI 1.10-2.35; $P = 0.01$, respectively).

DISCUSSION

To date, several risk factors have been identified for the development and progression of CKD, e.g. older age, hypertension, diabetes, body mass index and cigarette smoking.[16] However, to our knowledge, the relationship between COPD and kidney disease as assessed in this study has not been previously reported. We demonstrated that the presence of COPD is moderately associated with CKD. Tobacco smoking plays an important role in both the development and progression of COPD and kidney disease.[17] However, the association between COPD and CKD persisted even after adjusting for smoking status. In addition, moderate and severe COPD were found to be independently associated with an increased risk of long-term mortality in patients with peripheral arterial disease and CKD.

COPD is generally recognized as a cause of systemic inflammation.[18] Pro-inflammatory cytokines, especially tumour necrosis factor-alpha (TNF-α), play an important role in the disease process.[19, 20] This systemic inflammatory state in patients with COPD is associated with increased risk of cardiac injury.[8] In addition to pulmonary inflammation, several other parts of the body are affected resulting in muscle wasting, weight loss, diabetes, osteoporosis and importantly atherosclerosis.[19, 20] A recent study by Iwamoto and colleagues found airflow limitation associated with increased mean carotid intima-media thickness in smokers compared to control smokers and never-smokers.[21] This suggests that airflow limitation, instead of smoking status, is independently related to subclinical atherosclerosis. Subsequently, atherosclerosis might affect the vasculature in the kidneys leading to kidney dysfunction. So the systemic inflammation seen in patients with COPD might explain the associations observed in our study. Moreover, it has been previously demonstrated that increased inflammation levels are present in patients with kidneydysfunction.

The Cardiovascular Health Study found kidney dysfunction to be independently associated with elevated levels of high-sensitivity C-reactive protein (hsCRP), fibrinogen and interleukin-6 in participants of 65 years and older.[22] This might suggest that the inflammatory response observed in patients with kidney disease might be exacerbated by concomitant COPD.

Another possible explanation of our findings might be pulmonary hypertension secondary to COPD, which has been associated with the progression of kidney disease. Patients with COPD have severe retention of salt and water, reduction in renal blood flow and glomerular filtration and neurohormonal activation.[23] However, as our study was not designed to examine the mechanisms responsible for the association between COPD and kidney disease, further studies are needed to elucidate the rationale behind these relationships.

The fact that we did not find severe COPD associated with kidney disease might be explained by the following: first, only patients who underwent vascular surgery were included in our study, so it might be possible that surgery was cancelled in those patients with a poor pulmonary function. Moreover, cardiovascular disease and cancer are major comorbidities in patients with COPD, with the inflammatory state as possible link. These comorbidities are the leading causes of death in patients with mild and moderate COPD, while in those with severe COPD respiratory failure is the predominant cause.[24] So it might be suggested that patients with severe COPD died because of their respiratory failure before they could develop kidney disease.

Given that early stages of impaired kidney function are associated with increased risk of death, cardiovascular events and hospitalization[25], it is important to identify and consequently treat these patients to improve prognosis. Adequate treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARB) is required in those patients to slow the progression of kidney disease. In addition, a recent meta-analysis of randomized controlled trials demonstrated that statin therapy significantly reduces lipid concentrations and cardiovascular endpoints in patients with prevalent cardiac disease and CKD.[26] Therefore, an important aspect of the treatment of patients with kidney disease is to control the underlying cause and management of cardiovascular risk factors. Hence, the observed association between moderate and severe COPD and increased long-term mortality in patients with CKD advocates the importance of the optimal management of COPD in patients with kidney disease as well.

Our study has some limitations as seen with retrospective studies. Unfortunately, we do not have any information on patients who were declined for surgery because of their pulmonary or kidney function that might explain the absence of a relationship between patients with severe COPD and kidney disease. Data on markers of inflammation were not available. Hence, the proposed mechanism that inflammation might be the underlying link between COPD and CKD could not be examined. In addition, due to the cross-sectional design of the study, the results need to be interpreted cautiously. As both pulmonary and kidney function are assessed at one time point, it is difficult to infer causality as the sequence of COPD and kidney disease could not be ascertained. Consequently, the results of our study need to be interpreted cautiously. Finally, only 5% of the cohort had advanced kidney disease (i.e. estimated GFR $\leq$30 mL/min/1.73m^2). Hence, the prevalence of COPD in this group of patients could not be examined.

In summary, mainly moderate COPD was found to be associated with kidney disease in vascular surgery patients with peripheral arterial disease. Furthermore advanced stages of COPD are associated with increased long-term mortality in patients with kidney disease. The presence of COPD might be responsible for the progression of atherosclerosis inducing further kidney disease. Further experimental and longitudinal studies are necessary to elucidate the role of COPD in the pathway by which kidney disease contributes to an increased risk of death.

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4

Co-existence of COPD and left ventricular dysfunction in vascular surgery patients

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ABSTRACT

BACKGROUND

The co-existence between chronic obstructive pulmonary disease (COPD) and heart failure has been previously described. However, the co-existence between COPD and subclinical left ventricular (LV) dysfunction, without the presence of heart failure symptoms, is less well understood. This study determined the relationship and clinical relevance of COPD and subclinical LV dysfunction in vascular surgery patients.

METHODS

1005 consecutive vascular surgery patients were included in which COPD was determined using spirometry and LV function using echocardiography. Mild COPD was defined as FEV_1 ≥80% of predicted + FEV_1/FVC-ratio <0.70. Moderate/severe COPD was defined as FEV_1 <80% of predicted + FEV_1/FVC-ratio <0.70. Systolic LV dysfunction was defined as LV ejection fraction <50% and diastolic LV dysfunction was diagnosed based on E/A-ratio, pulmonary vein flow and deceleration time. Multivariate regression analyses were used to evaluate the impact of COPD and LV dysfunction on all-cause mortality. The mean follow-up time was 2.2 ± 1.8 years.

RESULTS

Both, mild and moderate/severe COPD were associated with increased risk for subclinical LV dysfunction with odds ratio of 1.6 (95%-CI = 1.1-2.3) and 1.7 (95%-CI = 1.2-2.4), respectively. Mild- or moderate/severe COPD in combination with LV dysfunction was associated with increased risk for all-cause mortality (mild: hazard ratio 1.7; 95%-CI = 1.1-3.6, moderate/severe: hazard ratio 2.5; 95%-CI = 1.5-4.7).

CONCLUSIONS

COPD was associated with increased risk for subclinical LV dysfunction. COPD + subclinical LV dysfunction was associated with increased risk for all-cause mortality compared to patients with COPD + normal LV function. Echocardiography may be useful to detect subclinical cardiovascular disease and risk-stratify COPD patients undergoing vascular surgery.

INTRODUCTION

Every year, there are 100 million adults who undergo a noncardiac surgical procedure across the world.[1] This number is expected to increase by 25% by 2020.[2] The risk of perioperative complications increases in patients with comorbidities. There is increasing evidence that chronic lung disease, such as chronic obstructive pulmonary disease (COPD), and cardiovascular disease are common comorbidities in these surgical patients. Interestingly, it appears that these comorbidities are interrelated and often co-exist in the same patients, independent of age and smoking history.[3,4] These patients have extremely poor prognosis following surgery. With the increasing preoperative use of echocardiography and spirometry, it may now be possible to identify patients with mild COPD and subclinical left ventricular (LV) dysfunction prior to surgery, providing an opportunity to determine the clinical significance of mild COPD and subclinical LV dysfunction in patients undergoing noncardiac surgical procedures. In the current study, we determined the relationship of LV dysfunction to COPD and the impact that these comorbidities have, independently and collectively, on the risk of mortality in these patients. We hypothesized that COPD would be independently associated with LV dysfunction and that the presence of even subclinical LV dysfunction in patients with COPD would significantly increase the risk of mortality.

MATERIAL AND METHODS

STUDY POPULATION

The patient population consisted of 1005 consecutive patients undergoing surgery to repair lower extremity artery, abdominal aortic aneurysm, abdominal aortic stenosis or carotid artery. Both open and endovascular procedures were included. The study was performed at the department of vascular surgery of the Erasmus Medical Center in Rotterdam, the Netherlands, during the time period of 2002-2008. The study was approved by the hospitals' ethics committee and performed with informed consent of all patients.

BASELINE CHARACTERISTICS

Prior to surgery, a detailed history was obtained from every patient. Cardiac history was assessed and ischemic heart disease was defined as a history of angina pectoris, coronary revascularization or myocardial infarction. Additional clinical data included age, gender, cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke), abdominal aortic disease (defined as abdominal aortic aneurysm or stenosis), renal dysfunction (serum creatinine >2.0 mg/dL), diabetes mellitus (fasting blood glucose ≥7.0 mmol/l or requirement for insulin and/or oral antidiabetic medication), hypertension (defined as systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg in non-diabetics, systolic blood pressure ≥130mmHg, diastolic blood pressure ≥80mmHg in diabetics or the use of antihypertensive medication), hypercholesterolemia (defined as LDL cholesterol >3.5 mmol/l and/or the requirement of lipid-lowering medication) and smoking status. The use of the prescription medications was captured and included beta-blockers, statins, aspirin, oral anticoagulants, angiotensin-converting enzyme (ACE) inhibitors, diuretics, nitrates, corticosteroids and bronchodilators.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The diagnosis of COPD was based on preoperative postbronchodilator spirometry, which was performed in 95% of the patients according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Mild COPD was defined as forced expiratory volume in one second (FEV_1) 80% of predicted or greater in the presence of FEV_1/forced vital capacity (FVC) ratio of <0.70.[5] Moderate/severe COPD was defined as FEV_1/FVC <0.70 and FEV_1 <80% of the predicted. In those patients who did not have spirometry, the diagnosis of COPD was based on symptoms (dyspnea, sputum production, and/or cough) plus the use of a pulmonary medication such as bronchodilators and corticosteroids.

LEFT VENTRICULAR FUNCTION

Preoperatively, transthoracic echocardiography was performed in all patients using a handheld Acuson Cypress Ultrasound System (7V3c transducer). Standard parasternal and apical 2- and 4-chamber views were obtained during rest with the patient in the left lateral decubitus position as recommended.[6] Left ventricular end-systolic and enddiastolic volumes were determined and LV ejection fraction was calculated using the biplane Simpson's technique.[7] Systolic (S) and diastolic (D) pulmonary vein flow, deceleration time and mitral inflow E/A ratios of peak velocities (at early rapid filling E and late filling due to atrial contraction A) were determined in apical 4-chamber view as recommended by the American Society of Echocardiography.[8] Systolic LV dysfunction was defined as LV ejection fraction <50%.[9] Diastolic LV dysfunction was confirmed in patients with E/A-ratio <0.8 (impaired relaxation) or >2 (restrictive relaxation).[10] Abnormal pulmonary vein flow (S/D <1) was used to distinguish normal and pseudo-normal diastolic LV function in patients with E/A-ratio between 0.8 and 2.[11] Deceleration time >220 ms (impaired relaxation) or <140 ms (restrictive relaxation) defined diastolic LV dysfunction in patients with atrial fibrillation.[11] Patients with both systolic and diastolic LV dysfunction were classified as systolic LV dysfunction. The presence of LV dysfunction in combination with heart failure symptoms (shortness of breath, fatigue, exercise intolerance, signs of fluid retention[9]) defined symptomatic heart failure, confirmed in patients with New York Heart Association functional class ≥I.

FOLLOW-UP AND OUTCOME

Survival status was determined using municipal civil registries. The mean follow-up time was 2.2 - 1.8 years.

STATISTICAL ANALYSIS

Dichotomous data are described as numbers and percentages. Continuous variables are described as means ± standard deviation. Continuous data were compared using ANOVA and categorical data were compared using a Chi Square test. Cumulative long-term survival was determined using the Kaplan-Meier method. Univariate and multivariate Cox regression analyses were performed to evaluate the relationship of COPD and LV dysfunction with all-cause mortality. Multivariate regression analyses were adjusted for age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia and smoking status. A sub-analysis was performed to evaluate the prognostic value of COPD towards postoperative outcome, in addition to the Revised Cardiac Risk (RCR) Index.[12] Multivariate regression analyses were adjusted for RCR risk factors (high-risk type of surgery, symptomatic heart failure, ischemic heart disease, cerebrovascular disease, renal dysfunction and diabetes) next to age, gender hypertension, hypercholesterolemia and smoking status. We report both the

crude and the adjusted hazard ratios (HR) with their 95% confidence interval (95%-CIs). For all tests, a p-value <0.05 (2 sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, Illinois).

RESULTS

The baseline study population consisted of 1005 patients undergoing lower extremity artery (n = 356), abdominal aortic aneurysm or abdominal aortic stenosis (n = 411) or carotid artery repair (n = 238). Endovascular procedures comprised 36% of the surgical procedures. A majority of the patients were men (77%) and the mean age was 67 (standard deviation = 10) years.

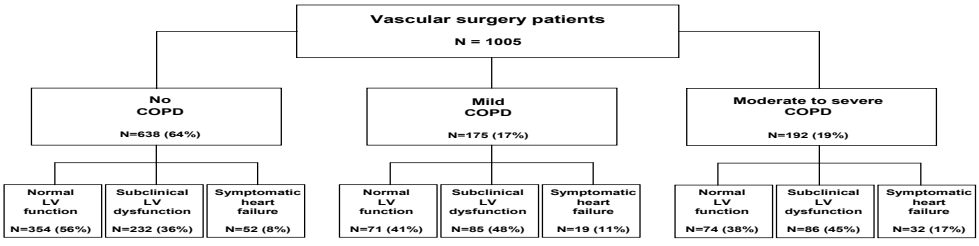
PREVALENCE OF COPD AND LV DYSFUNCTION

In total, 638 (64%) patients had no COPD and of the 367 (37%) with COPD; 175 (17%) had mild and 192 (19%) had moderate/severe COPD. At baseline, LV dysfunction was present in 506 (50%) patients. Of the 103 patients with symptomatic heart failure, 69 (67%) patients had LVEF ≤40 and 34 (33%) patients had a LVEF >40% + abnormal diastolic parameters. Of the 403 patients with subclinical LV dysfunction, 130 (32%) patients had LVEF ≤40%, 64 (16%) patients had LVEF >40-50% and 209 (52%) patients had LVEF >50% + abnormal diastolic parameters (177 patients with abnormal E/A-ratio and 32 patients with S/D <1 or abnormal deceleration time).

Of the patients with no COPD, 232/638 (36%) had subclinical LV dysfunction and 52/638 (8%) had symptomatic heart failure (Figure 1). In addition, subclinical LV dysfunction and symptomatic heart failure were present in 85/175 (48%) and 19/175 (11%) of the patients with mild COPD, respectively. Finally, of the patients with moderate to severe COPD, 86/192 (45%) had subclinical LV dysfunction and 32/192 (17%) had symptomatic heart failure.

Of the 171 patients with COPD and subclinical LV dysfunction, LVEF ≤40 was present in 60 (36%) of the patients. In addition, 32/51 (63%) of the patients with COPD + symptomatic heart failure had LVEF ≤40 (p <0.01).

Figure 1. Prevalence of chronic obstructive pulmonary disease and left ventricular dysfunction in vascular surgery patients



COPD = chronic obstructive pulmonary disease

BASELINE CHARACTERISTICS

Clinical parameters are listed in Table 1. Patients with 1) COPD, 2) LV dysfunction or 3) COPD + LV dysfunction were older, were likely to be men, had a higher prevalence of ischemic heart disease, abdominal aortic disease and were more likely to be treated with beta-blockers or diuretics compared to patients with normal pulmonary and normal LV function. Patients with COPD or COPD + LV dysfunction were also more often smokers and receiving corticosteroids and bronchodilators compared to patients with LV dysfunction or those with normal pulmonary and LV function. In addition, LV dysfunction with or without COPD was associated with increased risk of renal dysfunction, hypertension and use of oral anticoagulants and ACE inhibitors.

Table 1. Baseline characteristics

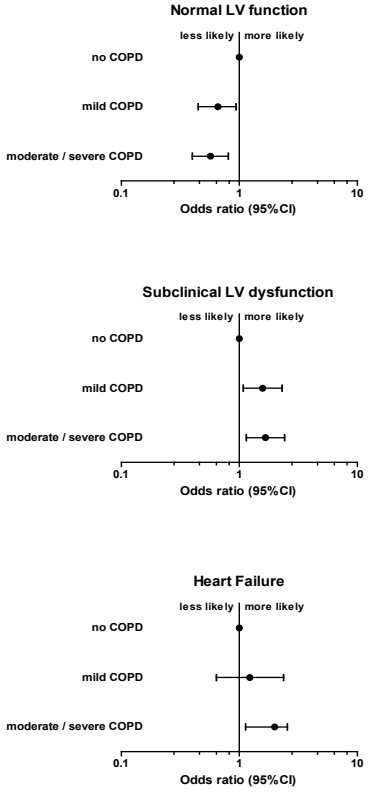
Baseline characteristics	No COPD and normal LV function [*N* = 354]		COPD [*N* = 145]		LV dysfunction [*N* = 284]		COPD + LV dysfunction [N = 222]		p-value
Demographics									
Age (± SD)	64	(11)	68	(8)	69	(10)	71	(9)	<0.01
Male (%)	245	(69)	118	(81)	214	(75)	192	(87)	<0.01
Medical history (%)									
Ischemic heart disease	104	(29)	61	(42)	141	(50)	124	(56)	<0.01
Cerebrovascular disease	134	(38)	35	(24)	122	(43)	62	(28)	<0.01
Abdominal aortic disease	112	(32)	71	(49)	116	(41)	134	(60)	<0.01
Renal dysfunction	44	(12)	18	(12)	61	(22)	56	(25)	<0.01
Diabetes mellitus	109	(31)	32	(22)	89	(31)	67	(30)	0.190
Hypertension	207	(59)	87	(60)	209	(74)	155	(70)	<0.01
Hypercholesterolemia	219	(67)	84	(60)	182	(67)	124	(57)	0.056
Smoker, current	145	(41)	80	(55)	99	(35)	96	(43)	0.001
Medication (%)									
Beta-blockers	246	(70)	122	(84)	220	(78)	190	(86)	<0.01
Statins	253	(72)	99	(68)	209	(74)	157	(71)	0.703
Aspirin	222	(63)	81	(56)	160	(56)	125	(56)	0.263
Oral anticoagulants	45	(13)	16	(10)	64	(23)	39	(18)	0.002
ACE inhibitors	90	(25)	39	(27)	108	(38)	73	(33)	0.004
Angiotensin receptor blockers	42	(12)	25	(17)	51	(18)	29	(13)	0.201
Diuretics	62	(18)	33	(23)	91	(32)	68	(31)	<0.01
Corticosteroids	17	(5)	39	(27)	21	(7)	47	(21)	<0.01
Bronchodilators	14	(4)	44	(30)	17	(6)	69	(31)	<0.01

COPD = chronic obstructive pulmonary disease, LV = left ventricular, ACE inhibitors = angiotensine-converting enzyme inhibitors.

ASSOCIATION BETWEEN COPD AND LV DYSFUNCTION

Patients with COPD were less likely to have normal LV function, with an odds ratio (OR) of 0.7 (95%-CI 0.5-0.9) for mild COPD and 0.6 (95%-CI 0.4-0.8) for moderate/severe COPD compared to patients with normal pulmonary function. Mild and moderate/severe COPD were both associated with subclinical LV dysfunction (mild: OR 1.6; 95%-CI 1.1-2.3, moderate/severe: OR 1.7; 95%-CI 1.2-2.4). Mild COPD was not significantly associated with heart failure (OR 1.2; 95%-CI 0.6-2.4). However, moderate/severe COPD was associated with heart failure with an OR of 2.0 (95%-CI 1.2-3.6). These results are demonstrated in Figure 2.

Figure 2. Association between chronic obstructive pulmonary disease and left ventricular function



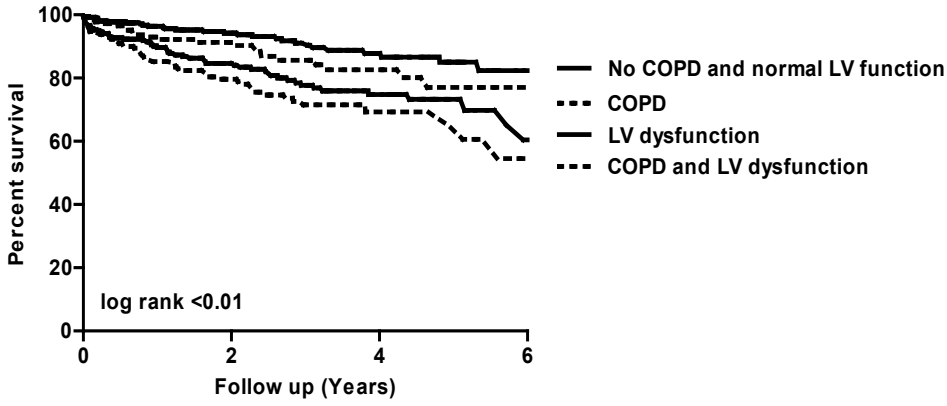
COPD = chronic obstructive pulmonary disease

ASSOCIATION BETWEEN COPD, LV DYSFUNCTION AND LONG-TERM FOLLOW-UP

During follow-up, 164 (16%) patients died of whom 77 (47%) had COPD. Mortality rates in patients with normal pulmonary + normal LV function was 8%; in those with COPD was 15%; in those with LV dysfunction was 20% and in patients with both COPD + LV dysfunction was 25% ($p < 0.01$). Cumulative 6-year survival rates according to pulmonary and LV function (log rank $p < 0.01$) are shown in Figure 3. Of the COPD patients who died during follow-up, 26 (34%) had mild COPD and

51 (66%) had moderate/severe COPD. A cardiovascular cause of death could be attributed in 54/77 (70%), 19/26 (73%) and 34/51 (67%) patients with no-, mild- or moderate to severe COPD, respectively (p = 0.351).

Figure 3. Cumulative 6-year survival



COPD = chronic obstructive pulmonary disease, LV = left ventricular.

MILD COPD

Patients with mild COPD + normal LV function did not have an increased risk for all-cause mortality (HR 1.0; 95%-CI 0.4-2.1), compared to patients with normal pulmonary and LV function. However, patients with mild COPD + subclinical LV dysfunction had an increased risk for all-cause mortality with an HR of 1.7 (95%-CI 1.1-3.6). Patients with mild COPD + overt heart failure had the highest risk for all-cause mortality with an HR of 2.7 (95% 1.2-5.9). These results are shown in Table 2.

MODERATE/SEVERE COPD

Patients with moderate/severe COPD had an increased risk for all-cause mortality, compared to patients with normal pulmonary function (HR 2.2; 95%-CI 1.3-4.5). HR was 2.5 (95%-CI 1.5-4.7) for patients with moderate/severe COPD and subclinical LV dysfunction and 3.8 (95%-CI 1.6-9.1) for patients with overt heart failure. These results are shown in Table 2.

Table 2. Association between chronic obstructive pulmonary disease, left ventricular function and long-term all-cause mortality

Characteristics		*N*	(%)	Univariable		Multivariable	
				Hazard ratio	[95% CI]	Hazard ratio	[95% CI]
No COPD	normal LV function [*N* = 354]	29	(8)	reference	-	reference	-
Mild COPD	normal LV function [*N* = 71]	7	(10)	1.2	0.5-2.6	1.0	0.4-2.1
	subclinical LV dysfunction [*N* = 85]	13	(15)	2.1	1.2-4.1	1.7	1.1-3.6
	heart failure [*N* = 19]	6	(32)	4.5	2.2-9.4	2.7	1.2-5.9
Moderate/ severe COPD	normal LV function [*N* = 74]	15	(20)	3.0	1.7-5.4	2.2	1.3-4.5
	subclinical LV dysfunction [*N* = 86]	23	(27)	3.3	1.8-6.0	2.5	1.5-4.7
	heart failure [*N* = 32]	13	(41)	6.1	2.8-13.4	3.8	1.6-9.1

Multivariable analysis adjusted for: age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia and smoking status. COPD = chronic obstructive pulmonary disease, LV = left ventricular.

COPD AND REVISED CARDIAC RISK INDEX

Multivariable analyses demonstrated that mild COPD was not associated with an increased risk for long-term all cause mortality (HR 1.0; 95%-CI 0.6-1.6) in addition to RCR Index risk factors. However, moderate/severe COPD was associated with an increased risk for long-term all cause mortality (HR 1.7; 95%-CI 1.2-2.5) in addition to the RCR Index risk factors.

DISCUSSION

The current study showed that both mild and moderate/severe COPD are associated with increased risk of LV dysfunction in vascular surgery patients. Approximately 1 out of 3 patients had COPD and in more than half of these patients, LV dysfunction was also present. In COPD patients with LV dysfunction, 3 out of 4 patients had subclinical LV dysfunction. Both mild and moderate/severe COPD patients, who had subclinical LV dysfunction, were at increased risk for all-cause mortality compared to COPD patients with normal LV function.

Several studies have been performed to evaluate the co-existence between moderate/severe COPD and heart failure. In 2005, Rutten et al. evaluated the prevalence of heart failure in COPD patients aged above 65 years during periods of clinical stability. They reported that heart failure was present in 20.5% of these moderate/severe COPD patients[3] and concluded that the prevalence of heart failure in stable COPD patients may be four times higher than in the general population of individuals over 65 years of age.[3, 13] In another observational study, Macchia et al. showed that 1 out of 4 patients with heart failure among a cohort of 1020 heart failure patients were also on treatment for COPD. In addition, the presence of COPD reduced the survival of these heart failure patients.[4] The prevalence of LV dysfunction in COPD patients may be increased

because both disorders share similar risk factors such as age, male gender and smoking[14] or because of systemic inflammation and oxidative stress associated with chronic lung disease.

While preoperative cardiac risk indices such as the widely used RCR Index, are used for more than 3 decades,[12, 15-17] the development and implementation of preoperative pulmonary risk indices has been complicated by conflicting results from multiple studies addressing this issue.[18-20] However, as stated in a systematic review of 'preoperative pulmonary risk stratification for non-cardiothoracic surgery' performed by Smetana et al., postoperative pulmonary complications are equally prevalent and contribute similarly to 1) morbidity, 2) mortality and 3) length of hospital stay of surgical patients, in comparison with cardiac complications.[21] Among 15 studies reported in this review article, 13 studies demonstrated that COPD was the most frequently identified risk factor for postoperative pulmonary complications.[21] In preoperative risk stratification of patients undergoing abdominal aortic aneurysm repair, both COPD and heart failure have been adapted as strong risk factors for adverse postoperative events.[22-24] One could therefore ask the question whether it is advisable to use separated cardiac and pulmonary risk indices. Especially, since it is known that COPD and heart failure often co-exist and, as we have shown in the current study that 1) mild COPD and subclinical LV dysfunction often co-exist as well, 2) the combination of these two is associated with an increased risk for long-term all-cause mortality and 3) moderate/severe COPD is an independently associated with increased risk for long-term all-cause mortality, in addition to the RCR Index. An important question remains if diagnosing and treatment of pulmonary and LV dysfunction will lead to improved long-term outcome. To address this issue, a randomized controlled trial of vascular surgery patients undergoing standard preoperative spirometry and echocardiography, could provide us with final answers addressing preoperative risk using an 'integrated cardio-pulmonary risk index'.

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective vascular surgery. Second, although two experienced investigators performed off-line assessments of the obtained ultrasound images, we cannot rule out inter-observer variability to have had minor influence on our results. Third, not all patients did have a preoperative pulmonary function test. In those patients who did not have a pulmonary function test, the diagnosis of COPD was based on symptoms and use of pulmonary medication.

The current study demonstrated that both mild and moderate/severe COPD were associated with an increased risk for subclinical LV dysfunction in patients undergoing vascular surgery. Patients with mild and moderate/severe COPD who had subclinical LV dysfunction were at increased risk for all-cause mortality, compared to COPD patients with normal LV function. These data suggest that pre-operative echocardiography may be useful to detect subclinical cardiovascular disease and risk-stratify COPD patients undergoing vascular surgery.

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5

COPD and cancer mortality: the influence of statins

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ABSTRACT

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is associated with an increased risk of lung cancer, independently of smoking. However, the relationship between COPD and total cancer mortality is less certain. A study was undertaken to investigate the association between COPD and total cancer mortality and to determine whether the use of statins, which have been associated with cancer risk in other settings, modified this relationship.

METHODS

The study included 3371 patients with peripheral arterial disease who underwent vascular surgery between 1990 and 2006; 1310 (39%) had COPD and the rest did not. The primary endpoint was cancer mortality (lung and extrapulmonary) over a median follow-up of 5 years.

RESULTS

COPD was associated with an increased risk of both lung cancer mortality (hazard ratio (HR) 2.06; 95% CI 1.32 to 3.20) and extra-pulmonary cancer mortality (HR 1.43; 95% CI 1.06 to 1.94). The excess risk was mostly driven by patients with moderate and severe COPD. There was a trend towards lower risk of cancer mortality among patients with COPD who used statins compared with patients with COPD who did not use statins (HR 0.57; 95% CI 0.32 to 1.01). Interestingly, the risk of extrapulmonary cancer mortality was lower among statin users with COPD (HR 0.49; 95% CI 0.24 to 0.99).

CONCLUSIONS

COPD was associated with increased lung and extrapulmonary cancer mortality in this large cohort of patients with peripheral arterial disease undergoing vascular surgery. The risk of lung cancer mortality increased with progression of COPD. Statins were associated with a reduced risk of extrapulmonary cancer mortality in patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a worldwide epidemic, affecting 10-15% of adults aged ≥40 years.[1] Over 80% of these patients have mild to moderately severe COPD (with forced expiratory volume in 1 s (FEV_1) >50% predicted) and, in these patients, the leading cause of mortality is cancer which accounts for >50% of all deaths.[2] Previous studies have shown that, while smoking is a shared risk factor for both COPD and lung carcinoma,[3] reduced lung function, independent of smoking, is another important risk factor for this type of cancer.[4-10] However, several important questions remain unanswered. First, previous studies in this area have focused primarily on the incidence of lung cancer rather than on lung cancer mortality per se. Since early stage lung cancers are potentially curable and since patients with COPD may have more radiographic investigations, ascertainment bias may have confounded the previous studies that have used lung cancer incidence rather than mortality as the primary outcome. Second, although it is known that extrapulmonary cancers account for approximately 20% of all deaths in stage 1 and stage 2 COPD,[11] the exact relationship between COPD (and its severity) and these cancers is not well known. Third, and most important from a clinical perspective, it is not known whether the risk of COPD and cancer mortality can be modulated by pharmacological treatment. Several studies suggest that statins (HMG-CoA reductase inhibitors) may reduce the risk of cancer including those in lungs, pancreas, prostate and colon.[12-15] On the other hand, some have suggested that statins may promote the development of new malignancies.[16] However, none of these studies has evaluated the effects of statins on cancer mortality in patients with COPD. In the present study we sought to determine (1) the relationship between COPD (and its severity) and the risk of total cancer mortality and (2) whether the use of statins modified this relationship.

METHODS

STUDY POPULATION

The patient population for this study has been described previously.[17] We used a cohort of 3371 patients who underwent elective noncardiac vascular surgery (abdominal aortic surgery, carotid endarterectomy or lower limb arterial reconstruction) between 1990 and 2006. COPD was defined according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[18] The COPD diagnosis was based on a post-bronchodilator FEV_1 to vital capacity ratio of 70% or less on spirometry (which was the case in 82% of the patients with COPD). Patients without spirometry were classified based on the presence of pulmonary symptoms (dyspnoea, sputum production or cough) and use of COPD medications based on the GOLD Guidelines for Management of stable COPD patients.[18] Mild COPD was defined as those who had symptoms and were using a short-acting bronchodilator when needed. Moderate COPD was defined as those with symptoms who required regular use of one or more bronchodilators. Severe COPD was defined as those with symptoms who were on regular treatment with one or more bronchodilators plus inhaled corticosteroids (for repeated exacerbations or persistent symptoms) or those patients who required domiciliary long-term oxygen therapy.

FOLLOW-UP AND ENDPOINTS

At time of follow-up the municipal civil registries were contacted to establish the survival status of all patients, which was completed in 96% of the patients during a median follow-up of 5 years (interquartile range (IQR) 2.0-9.1). The cause of death was ascertained by reviewing medical records, autopsy reports, contacting the referring physician, general practitioner or Statistics Netherlands. The primary endpoint of the study was total cancer mortality.

STATISTICAL ANALYSIS

Cancer mortality rates among the COPD severity groups were compared using a X^2 test. Cumulative long-term survival was determined by the Kaplan-Meier method and compared using a log-rank test. Univariate and multivariate Cox regression analyses were used to determine the association between COPD (severity) and cancer mortality. In these analyses, patients without COPD were used as the reference group. Cox regression analysis was also used to determine the relationship between statins and cancer mortality. In the multivariate analysis we adjusted for age, gender, type of surgery, diabetes, smoking status, hypercholesterolemia, corticosteroids, aspirin, statins and propensity score (for the association statins and cancer mortality). The proportional hazards assumption was verified by visual inspection of the log-log survival curves and by using the Schoefeld residuals. This propensity score was developed using a multivariate logistic regression model to adjust for the likelihood of receiving statins and included age, gender, COPD severity, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, obesity, type of surgery, year of surgery, cardiovascular history (Table 1), pulmonary medications (bronchodilators and corticosteroids) and cardiac medications (beta-blockers and aspirin).

RESULTS

CHARACTERISTICS OF STUDY COHORT

The baseline characteristics of the cohort are presented in Table 1. The mean (SD) age was 66 (12) years and 73% were men. There were 1310 patients (39%) with COPD; mild COPD (n = 578; 17%), moderate COPD (n = 579; 17%) and severe COPD (n = 153; 5%). Of the current smokers, 26% used statins whereas 23% of the never/ex-smokers were statin users (p = 0.20).

Table 1. Patient characteristics

	Total (n=3371)	Lung cancer (n=102)
Demographics (%)		
Mean (SD) age (years)	66 (12)	68 (7)
Men	73	76
Type of surgery		
AAA	36	41
CEA	24	18
LLR	40	41
COPD		
Mild COPD	17	19
Moderate COPD	17	29
Severe COPD	5	9
Cardiovascular history		
Myocardial infarction	22	17
Coronary revascularization*	16	14
Heart failure	5	3
Angina pectoris	14	8
Stroke or TIA	30	24
Clinical characteristics		
Diabetes Mellitus	15	10
Hypercholesterolemia	18	14
Smoking status		
Never/ex-smoking	72	64
Current smoking	28	36
Medication		
Corticosteroids	10	15
Statins	24	16
Aspirin	40	31

AAA, abdominal aortic surgery; CEA, carotid endarterectomy; COPD, chronic obstructive pulmonary disease; LLR, lower limb arterial reconstruction; TIA, transient ischaemic attack.
*Coronary artery bypass graft or percutaneous coronary intervention.

COPD AND CANCER MORTALITY

Over the follow-up period, 316 patients (9%) died from cancer. Patients with COPD had an increased risk of cancer mortality which was dependent on the severity of COPD. The risk of cancer mortality in patients with no COPD, mild, moderate and severe COPD was 8%, 10%, 14% and 12%, respectively ($p<0.001$). Overall, 102 patients (3%) died from lung cancer. The risk of lung cancer mortality in patients with no, mild, moderate and severe COPD was 2%, 3%, 5% and 6%, respectively ($p<0.001$).

The cancer-free survival curves stratified by COPD severity are shown in Figure 1 ($p<0.001$, log-rank test) (see Figure 1 in online supplement for lung cancer-free survival curves). COPD was independently associated with total cancer mortality (HR 1.61; 95% CI 1.25 to 2.06) (Table 2).

We tested the robustness of our findings by repeating the analysis following the exclusion of COPD patients without spirometry (see Tables 1 and 2 in online supplement). It was reassuring that these data were very similar to those from the main analyses. In addition, in a secondary analysis we created a new category of patients with a restrictive disorder (defined as FEV_1/FVC ratio >80% with FEV_1 <80% of predicted) and repeated the analysis. Patients with a "restrictive" defect had an increased risk of total cancer mortality as well as lung and extrapulmonary cancer mortality (see Table 3 in online supplement).

A non-significant trend was observed for mild COPD (HR 1.30; 95% CI 0.95 to 1.79), whereas patients with moderate or severe COPD had a significantly increased risk of cancer mortality (HR 1.92; 95% CI 1.43 to 2.58 and HR 1.95; 95% CI 1.14 to 3.31, respectively). A similar association with even higher HR was found between COPD and lung cancer mortality (HR 2.06; 95% CI 1.32 to 3.20). This association was largely driven by the group of patients with moderate and severe COPD, which were both strongly related to lung cancer mortality (HR 2.51; 95% CI 1.50 to 4.17 and HR 3.38; 95% CI 1.51 to 7.55, respectively).

A sensitivity analysis was performed in which patients who died of lung cancer were excluded from the analysis. COPD was still associated with an increased risk for non-pulmonary cancer mortality (HR 1.43; 95% CI 1.06 to 1.94). For patients with mild COPD the relationship was not significant (HR 1.22; 95% CI 0.83 to 1.79), but the relationship with moderate COPD was significant (HR 1.70; 95% CI 1.19 to 2.44). A significant association was not observed for severe COPD (HR 1.38; 95% CI 0.67 to 2.86), probably due to competing risks for mortality.

Table 2. Association between chronic obstructive pulmonary disease (COPD) and long-term cancer mortality

	Total cancer mortality				Lung cancer mortality				Extrapulmonary cancer mortality			
	Univariate		Multivariate*		Univariate		Multivariate*		Univariate		Multivariate*	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
COPD	2.03	1.63-2.53	1.61	1.25-2.06	2.76	1.86-4.08	2.06	1.32-3.20	1.76	1.34-2.30	1.43	1.06-1.94
No COPD	1.00		1.00		1.00		1.00		1.00		1.00	
Mild COPD	1.62	1.20-2.18	1.30	0.95-1.79	1.94	1.13-3.32	1.52	0.87-2.68	1.49	1.04-2.15	1.22	0.83-1.79
Moderate COPD	2.39	1.83-3.12	1.92	1.43-2.58	3.25	2.04-5.17	2.51	1.50-4.17	2.06	1.48-2.87	1.70	1.19-2.44
Severe COPD	2.42	1.49-3.95	1.95	1.14-3.31	4.54	2.21-9.34	3.38	1.51-7.55	1.64	0.83-3.25	1.38	0.67-2.86

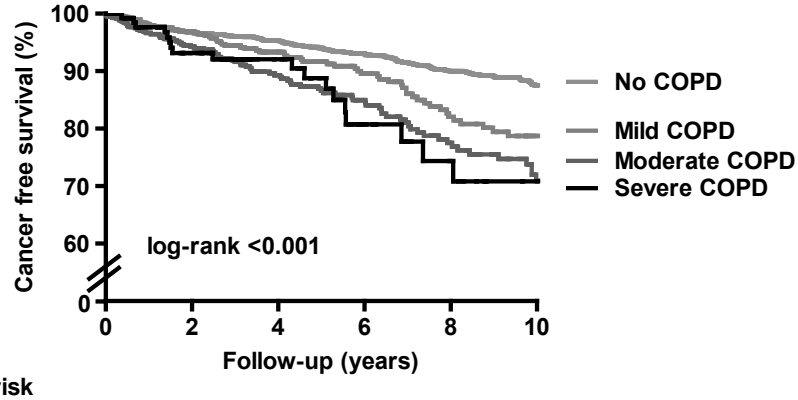
CI, confidence interval, HR, hazard ratio.
*Adjusted for age, gender, type surgery, diabetes, smoking, hypercholestrolemia, corticosteroids, statins and aspirin.

Table 3. Association between statins and cancer mortality

	Cancer mortality				Lung cancer mortality				Extrapulmonary cancer mortality			
	Univariate		Multivariate*		Univariate		Multivariate*		Univariate		Multivariate*	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All patients												
Statins	0.70	0.52-0.96	0.82	0.57-1.20	0.74	0.43-1.27	1.00	0.52-1.92	0.69	0.47-1.00	0.74	0.47-1.17
COPD patients												
Statins	0.52	0.32-0.84	0.57	0.32-1.01	0.46	0.20-1.07	0.75	0.28-2.05	0.56	0.31-1.00	0.49	0.24-0.99

ᶜAdjusted for age, gender, type surgery, diabetes, smoking, hypercholestrolemia, corticosteroids, aspirin and propensity score.

Figure 1. Long-term cancer-free survival according to severity of chronic obstructive pulmonary disease (COPD)



Number at risk						
No COPD	2061	1632	1292	1011	748	519
Mild COPD	578	420	295	201	135	92
Moderate COPD	579	401	284	189	122	71
Severe COPD	153	97	61	33	22	13

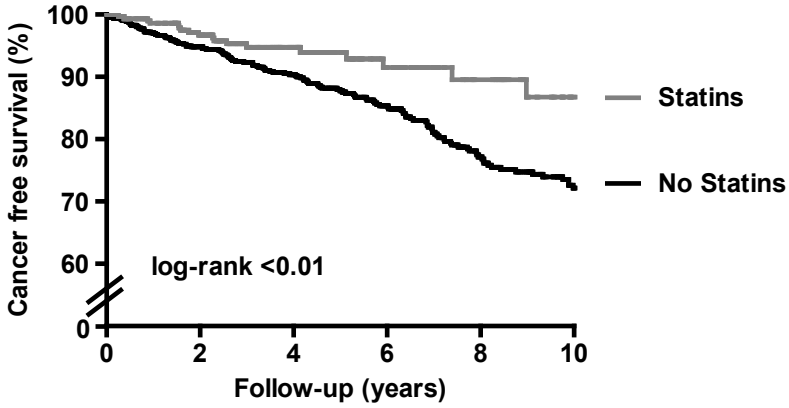
STATINS AND CANCER MORTALITY IN ALL PATIENTS

At baseline, 810 patients (24%) received statin therapy. Of the patients who received this treatment, 6% died from cancer during the follow-up period compared with 11% of the patients who did not use statins ($p<0.001$); 2% of the patients who used statins died from lung cancer compared with 3% of those who did not use statins ($p<0.05$). After excluding patients with lung cancer, extrapulmonary cancer was the cause of death in 4% of those who used statins and 7% of those who did not ($p<0.01$). After adjustments for potential confounding factors, statins were not significantly associated with total cancer mortality (HR 0.82; 95% CI 0.57 to 1.20), lung cancer mortality (HR 1.00; 95% CI 0.52 to 1.92) or extrapulmonary mortality (HR 0.74; 95% CI 0.47 to 1.17) (Table 3).

STATINS AND CANCER MORTALITY IN PATIENTS WITH COPD

Of the 1310 patients with COPD, 330 (25%) used statins at baseline. More patients who did not use statins died from cancer than those who used statins (14% vs 6%; $p<0.001$). Similar differences were noted when only lung cancer mortality (5% vs 2%; $p<0.01$) or extra-pulmonary cancer mortality (9% vs 4%; $p<0.01$) was considered. Figure 2 presents the long-term cancer-free survival curves of patients with COPD who did and did not use statins (see Figure 2 in online supplement for lung cancer-free survival curves). Of the patients who used a statin, 87% survived during the follow-up period compared with 72% of those who did not use statins at baseline ($p<0.01$, log rank test). After adjustments, the relationship was attenuated with borderline significance between statins and total cancer mortality (HR 0.57; 95% CI 0.32 to 1.01) and no significance between statins and lung cancer mortality (HR 0.75; 95% CI 0.28 to 2.05) (Table 3). However, in this subanalysis including only patients with COPD, statins were associated with reduced cancer mortality from sites other than the lungs (HR 0.49; 95% CI 0.24 to 0.99).

Figure 2. Long-term cancer-free survival according to statin use in patients with chronic obstructive pulmonary disease (COPD)



Number at risk						
No statins	980	681	512	356	235	153
Statins	330	236	124	65	43	23

DISCUSSION

This large study of patients with peripheral arterial disease demonstrates a significant relationship between COPD and cancer mortality. The risk rises sharply in patients with moderate to severe airflow obstruction (FEV_1 <80% predicted). Interestingly, both lung and extrapulmonary cancer deaths increased in patients with moderate COPD while, in those with severe COPD, lung cancer mortality predominated.

Our results confirm the findings of previous studies which investigated the association between COPD and lung cancer mortality. A severity-dependent association was found between the FEV_1 quintiles and risk for lung cancer mortality.[19-22] A similar relationship was observed in our study; however for the assessment of COPD severity we used the classifications as defined by the GOLD guidelines instead of FEV_1 quintiles. We found in particular that moderate and severe COPD were independent risk factors for lung cancer mortality. These findings are also in line with the results of three other studies which also investigated the relationship between the GOLD classifications of COPD severity and lung cancer. However, our results could not be compared directly with these studies as they examined the association with lung cancer incidence rather than lung cancer mortality.[7, 9, 23] Although the relationship between COPD and lung cancer is well known,[19-22] the association of COPD with extrapulmonary cancers is less well established. A study by Purdue et al. of construction workers failed to demonstrate a significant association between COPD and the risk of non-pulmonary carcinomas.[7] However, the study was limited by the small number of cancer events (3.7%) and the overwhelming predominance of men (96% of the cohort). By evaluating a group of high-risk patients (i.e., older, smoking history, comorbidities, mix of men and women), our study had sufficient power to demonstrate an independent association of COPD with extrapulmonary cancer mortality. On average, COPD increased extrapulmonary cancer mortality by more than 40%. Our study also suggests that extrapulmonary cancers are particularly

important causes of death in patients with moderate (but not mild or severe) COPD.[19-21, 24]

These data are consistent with previous reports by the Lung Health Study (LHS)[11] and TORCH (Towards a Revolution in COPD Health) groups.[25] LHS evaluated patients with mild to moderate COPD (average FEV_1 75% of predicted) whereas the TORCH trial studied patients with more severe diseases (FEV_1 44% of predicted). In the LHS 21% of deaths were from extrapulmonary cancers while, in the TORCH trial, extrapulmonary cancers only accounted for 7% of the total deaths. Thus, in severe COPD, other competing causes of mortality such as lung cancer and respiratory failure may be important.

The mechanism by which COPD increases cancer risk is largely unknown. Cigarette smoking is a shared risk factor for both COPD and solid organ cancers including lung, breast and colorectal cancer. However, in our analysis we adjusted for smoking and still found a significant relationship between COPD and cancer. Moreover, a recent study of lifelong never smokers found a significant relationship between COPD and lung cancer mortality.[8] Collectively, these data suggest that, in addition to cigarette smoking, other potential explanations should be considered. These include (1) shared genetic susceptibility,[26, 27] (2) delayed clearance of inhaled carcinogens because of airflow limitation;[28] and (3) chronic low-grade lung and systemic inflammation associated with COPD.[29] We have found previously that, in patients with COPD, systemic levels of C-reactive protein, a biomarker of systemic inflammation, is associated with future risk of cancer mortality including those related to extrapulmonary cancers.[30] Similarly, in the largest meta-analysis of its kind, Danesh and colleagues showed that plasma fibrinogen, another non-specific marker of systemic inflammation, is associated with both pulmonary and extrapulmonary cancers in smokers and in never smokers.[31]

Statins are lipid lowering drugs that also possess significant anti-inflammatory properties which may have beneficial effects not only on cardiovascular disease but on other comorbidities associated with COPD. The findings from the present study suggest that, in patients with COPD, statins may be effective in reducing deaths, especially from extrapulmonary cancers. The results of our study are consistent with previous epidemiological studies which have suggested that statins may lower cancer risk.[12-15, 32, 33] A study by Blais and collegues[34] found that patients using statins were less likely to be diagnosed with cancer than those using bile acid-binding resins, which indicates that the protective effect of statins is unlikely to be due to their lipid-lowering effect but is probably the result of other effects. The increased risk of cancer conferred by COPD might explain the increased benefit of statins observed in patients with COPD compared with patients with normal pulmonary function. Randomised controlled trials are needed to confirm our findings.

There are several limitations to this study. First, as the data were collected retrospectively, residual confounding by measured and unmeasured variables is possible. The results of this study should thus be interpreted cautiously and conservatively. Second, the study population consisted of patients who underwent vascular surgery. Since such patients are more likely to be smokers and to have additional risk factors for cancer than those of the general population, the findings of the present study may not be generalisable to the total population. Third, we did not have complete data on the primary site of the extrapulmonary cancer deaths. Of the 214 patients who died from extrapulmonary cancers, we were able to specify the site in 124 (58%) patients (see Figure 1 in online supplement for details). The impact of statins on different types and sources of extrapulmonary cancers therefore remains unknown. Fourth, statin use was categorised based on whether or not patients were treated with statins at the start of the follow-up period. We did not consider change in statin status during the follow-up period. This may have caused misclassification of statin status, which would have diluted the relationship. Our estimate of the potential effect of

statin on cancer mortality is therefore likely to be conservative.

In conclusion, COPD was associated with increased lung and extrapulmonary cancer mortality in this large cohort of patients with peripheral arterial disease undergoing vascular surgery. The risk of lung cancer mortality increased with severity of COPD, whereas the risk of extrapulmonary cancer was significant only in patients with moderate COPD, possibly because of competing risks for mortality in patients with severe COPD. Statins may modulate the risk of extrapulmonary cancer mortality in patients with COPD.

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6

The obesity paradox in patients with peripheral arterial disease

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ABSTRACT

BACKGROUND

Cardiac events are the predominant cause of late mortality in patients with peripheral arterial disease (PAD). In these patients, mortality decreases with increasing body mass index (BMI). COPD is identified as a cardiac risk factor, which preferentially affects underweight individuals. Whether or not COPD explains the obesity paradox in PAD patients is unknown.

METHODS

We studied 2,392 patients who underwent major vascular surgery at one teaching institution. Patients were classified according to COPD status and BMIs (i.e., underweight, normal, overweight, and obese), and the relationship between these variables and all-cause mortality was determined using a Cox regression analysis. The median follow-up period was 4.37 years (interquartile range, 1.98 to 8.47 years).

RESULTS

The overall mortality rates among underweight, normal, overweight, and obese patients were 54%, 50%, 40%, and 31%, respectively ($p < 0.001$). The distribution of COPD severity classes showed an increased prevalence of moderate-to-severe COPD in underweight patients. In the entire population, BMI (continuous) was associated with increased mortality (hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.94 to 0.98). In addition, patients who were classified as being underweight were at increased risk for mortality (HR, 1.42; 95% CI, 1.00 to 2.01). However, after adjusting for COPD severity the relationship was no longer significant (HR, 1.29; 95% CI, 0.91 to 1.93).

CONCLUSIONS

The excess mortality among underweight patients was largely explained by the overrepresentation of individuals with moderate-to-severe COPD. COPD may in part explain the "obesity paradox" in the PAD population.

INTRODUCTION

Cardiac events are the predominant cause of late mortality in patients with peripheral arterial disease (PAD).[1-3] Interestingly, in this population, unlike the situation in the general population, patients who are obese or overweight have better survival rates than those patients who are of normal weight.[4] Indeed, the greatest mortality rates are observed in patients who are underweight. This phenomenon has been referred to as the "obesity paradox".[4, 5] To date, the reasons underlying the obesity paradox have not been fully elucidated. Over the past decade, COPD has emerged as an independent risk factor for cardiovascular mortality.[6, 7] The effects of COPD on cardiovascular risk are amplified in the presence of another cardiac risk factor (*e.g.,* smoking, hypercholesterolemia, or PAD).[8] In this study, we investigated the influence of COPD on the relationship between body mass index (BMI) and mortality in a group of patients with PAD.[9]

MATERIALS AND METHODS

We studied 2,392 consecutive adult surgical patients admitted to the Department of Vascular Surgery of Erasmus University Medical Center (Rotterdam, the Netherlands), between January 1990 and November 2006. Patients were evaluated for the presence and severity of COPD prior to their surgical intervention using spirometry. Vascular surgical interventions included abdominal aortic surgery, carotid endarterectomy, or lower limb arterial revascularization procedures. BMI was measured during preoperative evaluation using standard procedures. Ethical approval for data collection and cohort evaluation were obtained from the Medical Ethics Committee of the hospital.

Baseline data included age, height, weight, and recorded medical history. The National Institutes of Health obesity classification[10] was used to divide the study population into the following four BMI categories: underweight (BMI <18.5 kg/m^2); normal weight (BMI, 18.5 to 24.9 kg/m^2); overweight (BMI, 25-29.9 kg/m^2); and obese (BMI ≥30 kg/m^2). The number of studied patients in each of these groups was 63 (2%), 1101 (33%), 956 (28%), and 272 (8%), respectively. We differentiated the patients according to whether they had COPD (n=1,110; 46.4%) or did not have COPD (n=1,282; 53.6%) based on the definition of the Global Initiative for Chronic Obstructive Lung Disease (or GOLD) Committee (FEV_1/FVC ratio less than 70% following therapy with bronchodilators and symptoms of cough or dyspnea, <70%). Mild COPD was defined as a FEV_1 of ≥80% predicted; moderate COPD was defined as an FEV_1 ≥50% to <80% predicted; and severe COPD was defined as an FEV_1 of <50% predicted.[11] We considered patients without COPD as those with normal pulmonary function tests, those without symptoms (i.e., without pulmonary complaints and/or pulmonary medications), and those who had normal arterial blood gases (Pco_2 <6.4 kPa, Po_2 >10.0 kPa) at the time of assessment.

Cardiac medical history included details of previous myocardial infarction, angina pectoris, heart failure (HF), and coronary artery revascularization (i.e., percutaneous coronary intervention or coronary artery bypass grafting). Comorbidities reported in the medical history included diabetes mellitus (DM), hypertension, smoking, dyslipidemia, and renal dysfunction. DM was defined as a fasting glucose concentration of ≥7.0 mmol/L or use of a hypoglycemic agent. Hypertension was defined as a BP of ≥140/90 mm Hg or the use of antihypertensive medications. A diagnosis of HF was considered if the patients had a history of shortness of breath on exertion or at rest, decreased physical ability, swelling of lower limbs on physical examination and echocardiographic signs consistent with cardiac decompensation.[12] Dyslipidemia was defined as a fasting serum

total cholesterol level of ≥5.5 mmol/L, a triglyceride level of ≥1.7 mmol/L, or a high-density lipoprotein cholesterol level of≤1.0 mmol/L at assessment or use of lipid-lowering agents. Renal dysfunction was defined as a serum creatinine level of >2.0 mg/dL (177 µmol/L) or a requirement for dialysis. In addition the cardiac risk score was determined for each patient using the Lee revised cardiac risk index, which included information about vascular operations, history of ischemic heart disease, HF, cerebrovascular accidents, insulin therapy for DM, and renal disease with a serum creatinine level of >2.0 mg/dL.[13] Patients were assessed for the use of cardiac medications including beta-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors, diuretics, aspirin, anticoagulants, nitrates and calcium channel blockers. The use of pulmonary medications, including bronchodilators and corticosteroids, was also captured.

STUDY ENDPOINTS

The endpoint of this study was all-cause mortality. The median duration of follow-up was 4.37 years (interquartile range 1.98 to 8.47 years). Information about death was obtained and verified by reviewing the hospital record and linking with the national civil registry.

STATISTICAL ANALYSIS

Categoric variables are expressed as percentages and were compared using a Pearson's X^2 test. Continuous variables are presented as mean (± SD) and were compared using analysis of variance. We performed univariate and multivariate analysis of survival times using a Cox proportional hazard model for all-cause mortality from which hazard ratios (HRs) and 95% confidence intervals (CIs) were derived. In the regression analyses, we used BMI both as a continuous variable and as a categoric variable. When the categoric BMI variable was included in the model, patients with normal weight were taken as the reference group. In the multivariate models, we adjusted for baseline characteristics including age, gender, cardiac risk score, current smoking status, COPD severity, year of surgery, and use of pulmonary medications. In addition we used stepwise regression models to investigate the association between the BMI categories and mortality, with stepwise adjustment made for clinical variables and subsequently for COPD severity and current smoking. Statistical significance was defined as a p-value of <0.05. All statistical analysis was performed using a statistical software package (SPSS, version 15.0 for Windows; SPSS; Chicago, IL).

RESULTS

In the population that we studied, we found a relatively homogenous distribution of BMI (mean BMI 25.4 ± 4.0 kg/m^2). Of the 2,392 patients, only 2.6% were underweight and 11.4% were obese, while the majority was either normal (46%) or overweight (40%). Patient characteristics according to BMI classifications are presented in Table 1. Current smokers were more prominent in the underweight group (p = 0.002). Moderate-to-severe COPD was more frequent among underweight patients (40%), while the frequencies of COPD in the overweight and obese groups were 25% and 22%, respectively (p <0.001). In contrast to the underweight group, patients in the obese group had more cases of hypertension, DM, and dyslipidemia and were more likely to be treated with beta-blockers, statins, aspirin, and ACE-inhibitors (p <0.05 for all).

During follow-up, 1,048 patients (43.8%) died; 56.8% of them had COPD. Mortality

among patients in different BMI categories included 34 patients (54%) in the underweight group, 550 patients (50%) in the normal group, 380 patients (40%) in the overweight group, and 83 (31%) in the obese group (p <0.001).

The relationships among BMI categories and COPD classifications are shown in Figure 1. The prevalence of COPD showed an inverse relationship with BMI; COPD was present more often in patients with lower BMI (p <0.001). The percentage of COPD was highest in patients who were underweight (51%), which was largely driven by the increased prevalence of severe COPD in this group. In the underweight category, 19% of the patients had severe COPD; whereas, in the obese category only 2% of the patients had severe COPD.

*Table 1. Baseline clinical characteristics of 2,392 patients according to BMI categories**

Variables	Total (n=2,392)	Underweight Group (n=63)	Normal-Weight Group (n=1,101)	Overweight Group (n=956)	Obese Group (n=272)	P Value
Demographics						
Age,† yr	66 (11)	64 (14)	67 (11)	67 (10)	63 (11)	<0.001
Male gender	1,782 (75)	34 (54)	823 (75)	749 (78)	176 (65)	<0.001
Type of surgery						<0.001
AAA	966 (40)	27 (43)	456 (41)	405 (42)	78 (29)	
CEA	561 (24)	6 (10)	217 (20)	254 (27)	84 (31)	
LLR	865 (36)	30 (47)	428 (39)	297 (31)	110 (40)	
Cardiac history						
Myocardial infarction	618 (26)	11 (18)	288 (26)	253 (27)	66 (24)	0.41
Revascularization‡	458 (19)	11 (18)	196 (18)	206 (22)	44 (16)	0.09
Heart failure	133 (6)	1 (2)	76 (7)	41 (4)	15 (6)	0.04
Angina	419 (18)	9 (14)	182 (17)	175 (18)	53 (20)	0.51
Clinical variables						
Hypertension	1042 (44)	10 (16)	442 (40)	449 (47)	141 (52)	<0.001
DM	362 (15)	0 (0)	127 (12)	155 (16)	80 (29)	<0.001
Current smoking status	781 (33)	26 (41)	395 (36)	288 (30)	72 (27)	0.002
Dyslipidemia	520 (22)	6 (10)	208 (19)	236 (25)	70 (26)	<0.001
BMI†	25 (4)	17 (1)	23 (2)	27 (1)	33 (4)	<0.001
Renal dysfunction	192 (8)	8 (13)	94 (9)	67 (7)	23 (9)	0.30
COPD						<0.001
None	1282 (53)	31 (49)	570 (52)	516 (54)	165 (61)	
Mild	481 (20)	7 (11)	231 (21)	197 (21)	46 (17)	

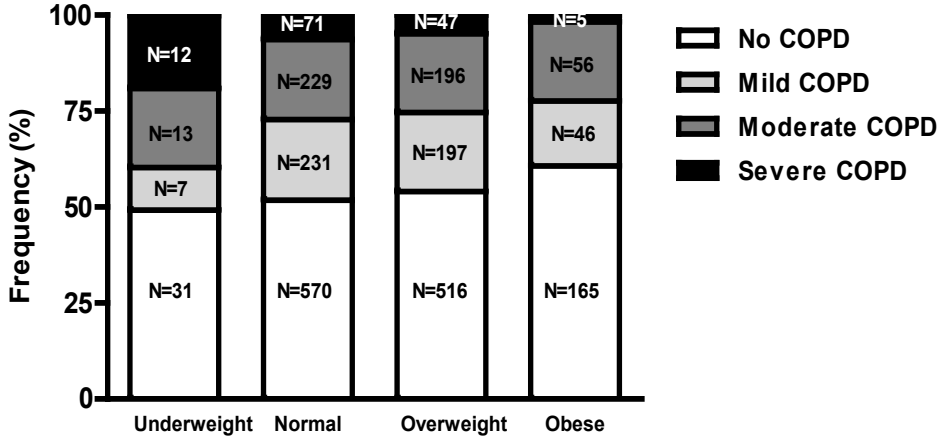
Moderate	494 (21)	13 (21)	229 (21)	196 (20)	26 (20)	
Severe	135 (6)	12 (19)	71 (6)	47 (5)	5 (2)	
Cardiac medication						
Statins	719 (30)	12 (19)	298 (27)	315 (33)	94 (35)	0.02
Beta-blockers	1026 (43)	15 (24)	457 (42)	408 (43)	146 (54)	<0.001
ACE inhibitors	640 (27)	11 (18)	264 (24)	278 (29)	87 (32)	0.004
Calcium antagonists	602 (25)	12 (19)	271 (25)	242 (25)	77 (28)	0.41
Diuretics	502 (21)	10 (16)	218 (20)	214 (22)	60 (22)	0.36
Aspirin	1021 (43)	18 (29)	434 (39)	432 (45)	137 (50)	<0.001
Anticoagulants	937 (39)	30 (48)	431 (39)	375 (39)	101 (37)	0.50
Nitrates	307 (13)	6 (10)	134 (12)	129 (14)	38 (14)	0.63
Pulmonary medication						
Bronchodilators	205 (9)	8 (13)	98 (9)	78 (8)	21 (8)	0.58
Corticosteroids	308 (13)	10 (16)	150 (14)	117 (12)	31 (11)	0.59

*Values are given as No. (%), unless otherwise indicated. AAA = abdominal aortic surgery; CEA = carotid endarterectomy; LLR = lower limb arterial reconstruction.

†Values given as mean (SD).

‡Previous coronary artery bypass graft or percutaneous coronary intervention.

Figure 1. The cross-relationship between COPD status and BMI in our population: COPD classifications among BMI categories



Moderate-to-severe COPD was independently associated with increased mortality (moderate COPD: HR, 1.67; 95% CI, 1.42 to 1.97; severe COPD: HR, 1.96; 95% CI: 1.50 to 2.55) [Table 2].

Table 2. Relationship between baseline risk factors and all-cause mortality

	Univariate analysis			Multivariate analysis*		
	HR	95% CI	p Value	HR	95% CI	p Value
COPD†						
Mild	1.45	1.23-1.71	<0.001	1.18	1.00-1.40	0.053
Moderate	2.21	1.91-2.56	<0.001	1.67	1.42-1.97	<0.001
Severe	2.52	1.99-3.18	<0.001	1.96	1.50-2.55	<0.001
BMI	0.95	0.94-0.97	<0.001	0.96	0.94-0.98	<0.001

*Adjustments were made for age, gender, cardiac risk score, current smoking status, year of surgery, and use of pulmonary medication.

†Classification of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (or GOLD) classification.[11]

*Table 3. Association between BMI (continuous and categories) and COPD severity and mortality**

Variables	Model 1	Model 2	Model 3	Model 4	Model 5
Cases, No.	2,387	2,387	2,387	2,387	2,387
Patients alive, No.	1,340	1,340	1,340	1,340	1,340
BMI	0.95 (0.94-0.97)	0.95 (0.94-0.97)	0.96 (0.94-0.97)	0.96 (0.94-0.97)	0.96 (0.94-0.97)
Underweight	1.38 (0.98-1.96)	1.44 (1.02-2.04)	1.30 (0.92-1.40)	1.42 (1.00-2.01)	1.29 (0.91-1.93)
Overweight	0.73 (0.64-0.83)	0.73 (0.64-0.83)	0.73 (0.64-0.84)	0.73 (0.64-0.84)	0.74 (0.65-0.84)
Obese	0.68 (0.54-0.85)	0.67 (0.53-0.85)	0.67 (0.53-0.85)	0.68 (0.53-0.86)	0.68 (0.54-0.86)
Mild COPD	1.19 (1.01-1.41)		1.19 (1.00-1.41)		1.18 (1.00-1.40)
Moderate COPD	1.81 (1.55-2.10)		1.69 (1.43-1.99)		1.67 (1.42-1.97)
Severe COPD	2.11 (1.67-2.68)		1.97 (1.51-2.57)		1.96 (1.50-2.55)

*Values are given as the HR (95% CI), unless otherwise indicated. Model 1 = adjusted for age and gender; Model 2 = multivariate analysis in which adjustments were made for age, gender, cardiac risk score, year of surgery, and pulmonary medication used; Model 3 = multivariate analysis in which adjustments were made for all of the variables in model 2 plus COPD severity; Model 4 = multivariate analysis in which adjustments were made for all of the variables in model 2 plus cigarette smoking; Model 5 = multivariate analysis in which adjustments were made for all of the variables in model 2 plus cigarette smoking and COPD severity.

BMI, on the other hand, was inversely associated with mortality. The risk of mortality increased by 4% for each 1 kg/m^2 reduction in BMI. After adjusting for the cardiac risk score, age, gender, year of surgery, current smoking status, and use of pulmonary drugs, patients who were underweight were 1.42 times more likely to die than individuals of normal weight (HR, 1.42; 95% CI, 1.00 to 2.01). In contrast, overweight and obese individuals had a reduced risk of mortality (overweight patients: HR, 0.73; 95% CI; 0.64 to 0.84; obese patients: HR, 0.68; 95% CI: 0.53-0.86) [Table 3, model 4]. When COPD severity was added to the multivariate model, the relationship between underweight status and mortality no longer remained statistically significant (HR, 1.29; 95% CI, 0.91 to 1.93). However, obesity and overweight remained significantly related to mortality (Table 3, model 5).

DISCUSSION

In this study, we examined a large cohort of patients with PAD and found a high prevalence of COPD (46.4%), especially among patients who were underweight. We observed an inverse relationship between BMI and mortality, which is consistent with the obesity paradox described previously. However, when we adjusted for COPD and its severity, the relationship between underweight and mortality no longer remained significant, indicating that a substantial proportion of the excess deaths in patients with low BMI occur in subjects with COPD. This raises the possibility that the excess deaths in patients with low BMI are related to the patients' underlying COPD. Our results are in accordance with those of Landbo et al.[14] They studied the prognostic association of BMI in a similar population of COPD patients and observed that underweight patients, especially those with severe COPD, had an increased risk of mortality.

Since spirometry is generally not part of a normal pre-operative assessment for patients undergoing major vascular surgery at many institutions, COPD may remain undiagnosed and untreated in this group of patients, resulting in excess morbidity and mortality. Indeed, even in our population, only 9% of the cohort was taking bronchodilators, though the overall prevalence of COPD was 47% and that for moderate-to-severe COPD was 27%. The findings in this study highlight the need for more aggressive use of spirometry and institution of COPD interventions (including smoking cessation, treatment of exacerbations and use of maintenance drugs) for patients with peripheral vascular disease.

The mechanisms responsible for the inverse relationship between BMI and mortality are uncertain. Previous studies[15, 16] have suggested that underweight patients demonstrate a higher metabolic rate, lower antioxidant capacity in skeletal muscles, and increased systemic inflammatory responses, which may contribute to excess weight loss and morbidity. Underweight status has also been associated with overt or occult malignancy. Our study findings suggest that in addition to the above factors, COPD may also be responsible for the obesity paradox (in the low BMI categories).

Our finding that overweight and obesity are associated with improved survival is consistent with the obesity paradox of survival in HF patients. Previous studies have clearly demonstrated that HF patients who have higher percentage of body fat[17,18] and elevated BMI[19,20] have lower mortality than those with normal or reduced BMIs. However, the mechanism(s) responsible for this observation remains elusive.[21, 22] Some investigators have suggested[23-25] that increased BMI may confer protection against endotoxin and inflammatory cytokines by increasing the production of "buffering" lipoproteins. HF may be diagnosed in obese patients at an earlier stage because they tend to be more symptomatic than HF patients with lean body mass. Thus, obesity may simply be a marker for less severe HF.

Our finding that nearly 50% of patients undergoing major vascular surgery for PAD had COPD highlights the importance of using screening spirometry in this population. Over half of these patients in the underweight category had moderate-to-severe COPD. These data support the notion of more aggressive "screening" and treatment for COPD before and after surgery to optimize the health outcomes of these patients.

There were certain limitations to the study. BMI has been recently questioned as a sensitive measure of body fatness.[26] Other anthropometric measurements of body fat such as waist circumference were not routinely performed preoperatively and, hence, could not be included in our analysis. We also did not have complete lung function measurements in the cohort. Knowledge regarding total lung and inspiratory capacity as well as diffusing capacity may provide incremental information on mortality. Moreover, because we did not directly interview patients, we could not

separate out purposeful from nonpurposeful weight loss.[27] Thus, the underlying reasons for the low BMI in our population are unknown. Finally, because smoking is a more powerful risk factor in PAD patients than in patients with HF, ischemic heart disease, or stroke, it is uncertain whether our current findings can be generalized to other cardiovascular populations.

We found that nearly 50% of patients with PAD undergoing a surgical procedure had evidence of COPD and that BMI was inversely related to long-term mortality. Importantly, there was a disproportionate overrepresentation of COPD in patients with low BMI. Patients with low BMI had an increased risk of mortality, while obese and overweight patients had a reduced risk of mortality compared to individuals of normal weight. Adjustments for the severity of COPD abolished the significant relationship between BMI and mortality in those patients who were underweight but not in those who were overweight or obese. These data suggest COPD is a highly prevalent condition in PAD patients who are undergoing surgical procedures, and that COPD may be responsible for the obesity paradox associated with reduced BMI and mortality in patients with PAD.

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Part III

Interventions in patients with COPD and atherosclerosis

7

Effect of statin therapy on mortality in patients with peripheral arterial disease and comparison of those with versus without associated COPD

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ABSTRACT

BACKGROUND

Chronic obstructive pulmonary disease (COPD) and peripheral arterial disease (PAD) are both inflammatory conditions. Statins are commonly used in patients with PAD and have anti-inflammatory properties, which may have beneficial effects in patients with COPD. The relationship between statin use and mortality was investigated in patients with PAD with and without COPD.

METHODS

From 1990 to 2006, we studied 3371 vascular surgery patients. Statin use was noted at baseline and, if prescribed, converted to <25% (low dose) and ≥25% (intensified dose) of the maximum recommended therapeutic dose. The diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease guidelines using pulmonary function test. Endpoints were short- (30-day) and long-term (10-year) mortality.

RESULTS

A total of 330 patients with COPD (25%) used statins, and 480 patients (23%) without COPD. Statin use was independently associated with improved short- and long-term survival in COPD patients (odds ratio 0.48, 95% confidence interval [CI] 0.23 to 1.00; hazard ratio 0.67, 95% CI 0.52 to 0.86, respectively). In patients without COPD, statins were also associated with improved short- and long-term survival (odds ratio 0.42, 95% CI 0.20 to 0.87; hazard ratio 0.76, 95% CI 0.60 to 0.95, respectively). In patients with COPD only an intensified dose of statins was associated with improved short-term survival. However, for the long-term, both low-dose and intensive statin therapy were beneficial.

CONCLUSIONS

In conclusion, statin use was associated with improved short- and long-term survival in patients with PAD with and without COPD. Patients with COPD should be treated with an intensified dose of statins to achieve an optimal effect on both the short- and long-term.

INTRODUCTION

We examined the relation between statins and mortality (both short- and long-term) in a group of patients who underwent surgery for peripheral arterial disease (PAD), and compared results in those with versus without associated chronic obstructive pulmonary disease (COPD).

METHODS

From 1990 to 2006, a total of 3,371 consecutive patients underwent elective vascular surgery at the Erasmus Medical Center, Rotterdam, The Netherlands. Surgical procedures included abdominal aortic surgery (AAA), carotid endarterectomy (CAE) or lower limb arterial reconstruction (LLR). Patients with AAA surgery underwent infrarenal AAA repair (aortic-to-aortic or aortic-bifurcation prostheses procedures, removal of infected prostheses, and other operations of the abdominal aorta). CEA surgery included reconstruction or desobstruction of the carotid artery and a LLR surgery included iliac-femoral, femoral-popliteal, and femoral-tibila artery bypass procedures, removal of infected prostheses, peripheral desobstruction, and other elective peripheral arterial surgical reconstructions. Patients with surgery for a ruptured abdominal aortic aneurysm or arterial reconstruction as a result of other surgical procedures or trauma were excluded.

Before surgery, a detailed cardiac history was obtained and patients were screened for hypertension (defined as a blood pressure ≥140/90 mm Hg and or antihypertensive treatment), hypercholesterolemia (total cholesterol of >5.2 mmol/L and/or cholesterol-lowering medication), diabetes mellitus (fasting blood glucose of ≥140mg/dl or treatment with insulin or oral hypoglycemic agents), serum creatinine renal dysfunction (baseline serum creatinine >1.5 mg/dl) current smoking status, body mass index calculated as weight divided by height squared (kg/m^2), presence of ischemic heart disease (previous myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, and angina pectoris), and previous heart failure (defined according to the New York Heart Association classification). Normal white blood cell count was defined as $<10 \times 10^9$/L and a value of $\geq 10 \times 10^9$/L was defined as increased. At baseline, cardiac medication was assessed including statins, beta-blockers, angiotensin-converting-enzyme inhibitors, diuretics, aspirin, anticoagulants, nitrates, and calcium channel blockers. Statins included fluvastatine, simvastatin, pravastatin, atorvastatin, and rosuvastatin. Bronchodilators and corticosteroids were considered pulmonary medications.

According to the Dutch pharmacotherapeutic recommendations, a maximum recommended therapeutic dose of 80 mg was used for atorvastatin, fluvastatin, simvastatin, and 40 mg was used for pravastatin and rosuvastatin. The dosage of statin therapy was converted to no dose, low dose (<25%), and intensified dose (≥25%) of the maximum recommended therapeutic dose.

Patients with a history of, for example, cough, dyspnea, sputum production and a positive pulmonary function test were suspected of having COPD. Eighty-two percent of patients with a COPD classification underwent a preoperative pulmonary function test. The guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) were used to diagnose COPD based spirometric values after bronchodilator use.[1] COPD was defined as a forced expiratory volume in 1 second/forced vital capacity ratio <0.70 and forced expiratory volume in 1 second <80% of predicted.[1] We used the prediction equation of Quanjer et al,[2] which has been previously validated.[3] The equation for men was 4.30 x length (m) – age x 0.029 – 2.49, and for women, 3.95 x height

(m) – age x 0.025 – 2.60.[2] Additionally, arterial blood gas values were obtained preoperatively on room air with the patient seated. Control patients (i.e., those without COPD) were defined as (1) those who did not meet the spirometric Global Initiative for Chronic Obstructive Lung Disease criteria and (2) those who did not undergo spirometry and did not have respiratory symptoms, were not on respiratory drug therapy, and showed normal arterial blood gas values on room air (Pco_2 <6.4 kPa, Po_2 >10.0 kPa).

Clinical information was retrieved from the medical records in our hospital. Survival status was obtained from the municipal civil registries and was completed in 96% of patients at the reference date of July 2007, with a median follow-up of 5 years. Endpoints were short- and long-term mortality, defined as death within 30 days and 10 years of follow-up, respectively.

Continuous data were expressed as mean ± SD and were compared using Student's *t*-test. Categorical data were presented as percentages and compared using chi-square test. Univariate and multivariate logistic regression analyses were used to evaluate the effect of statins on short-term mortality. Cumulative long-term survival was visualized using the Kaplan-Meier curve and compared using log-rank test. Hazard ratios (HRs) for long-term mortality between those who did and did not use statins were determined using a Cox proportional hazard regression model. In multivariate analysis, adjustments were made for age, gender, previous myocardial infarction, previous coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention), previous heart failure, previous angina pectoris, previous cerebrovascular accident or transient ischemic attack, hypertension, hypercholesterolemia, diabetes mellitus, impaired renal function, smoking status, body mass index, type of surgery (AAA, CEA or LLR), year of surgery, and use of beta-blockers, aspirin, bronchodilators and corticosteroids. Odds ratios (ORs) and HRs were provided with their 95% confidence intervals (CIs). All tests were 2 sided, and $p < 0.05$ was considered significant. All tests were performed using SPSS, version 12.0.1 (SPSS Inc., Chicago, Illinois) for Windows (Microsoft Corp., Redmond, Washington)

RESULTS

Baseline characteristics according to the presence of COPD and statin were listed in Table 1. Mean age of the 3,371 patients was 66 ± 13 years, and 73% were men. Overall, 24% (n = 810) were statin users. Of the total patients with COPD, 25% used statins, and of patients without COPD, 23%. Statins were more frequently prescribed to patients who underwent CEA and less frequent in patients who underwent LLR (both $p < 0.001$) in patients with and without COPD. Patients who received statins more often had a cardiovascular history, comorbidities (hypertension, diabetes mellitus, and dyslipidemia) and more frequently used concomitant cardiac medications compared with patients who did not use statins. Median follow-up was 5 years (range 6 months to 10 years). Within 30 days after surgery, 178 patients (5%) died, and 1,555 patients (46%) died during long-term follow-up.

Of patients with COPD on statin therapy, 12 (4%) died within 30 days compared with 72 (7%) without statins ($p = 0.016$). During long-term follow-up, 105 patients with COPD (32%) who received statins died, whereas 628 patients (65%) without statin therapy died ($p < 0.001$). Of patients without COPD who received statins, 11 (2%) died within 30 days compared with 83 (5%; $p = 0.006$). During the entire follow-up period, 110 patients (23%) with statins and 712 (45%) without statins died ($p < 0.001$). After adjusting for potential confounders, statin therapy was associated with improved survival at both the short- and long-term in patients with COPD (OR 0.48, 95% CI 0.23 to 1.00; HR 0.67, 95% CI

0.52 to 0.86, respectively; Table 2). These survival benefits were also observed in patients without COPD (OR 0.42, 95% CI 0.20 to 0.87; HR 0.76, 95% CI 0.60 to 0.95, respectively). Cumulative survival curves of the different groups are shown in Figure 1 (p <0.001).

Of patients with COPD using statins, 51% received a low dose and 49% received an intensified dose. In patients without COPD, 56% were treated with a low dose and 44% were treated with an intensive statin dose. Low dose had no beneficial effect on short-term mortality in patients with COPD (OR 0.77, 95% CI 0.34 to 1.74; Figure 2).

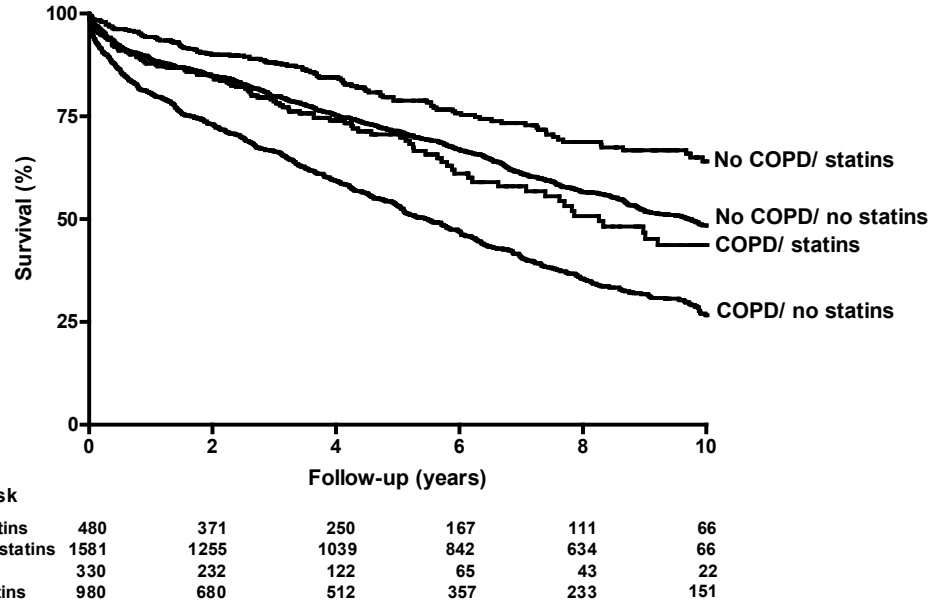
Table 1. Baseline characteristics according to statin use

	COPD (n=1,310)			No COPD (n=2,061)		
	Statins (n=330)	No statins (n=980)		Statins (n=480)	No statins (n=1,581)	p-value
Demographics						
Mean age (yrs)	69 (9)	69 (10)	0.40	64 (10)	64 (13)	0.78
Men	262 (79%)	772 (79%)	0.69	326 (68%)	1,091 (69%)	0.65
Type of surgery			<0.001			<0.001
AAA*	161 (48%)	465 (47%)		134 (28%)	433 (27%)	
CEA†	80 (24%)	102 (11%)		196 (41%)	440 (28%)	
LLR§	89 (27%)	413 (42%)		150 (31%)	708 (45%)	
Cardiovascular history						
Myocardial infarction	113 (34%)	228 (23%)	<0.001	131 (27%)	270 (17%)	<0.001
Revascularization‡	91 (28%)	158 (16%)	<0.001	114 (24%)	189 (12%)	<0.001
Heart failure	21 (6%)	49 (5%)	0.34	22 (5%)	61 (4%)	0.48
Angina	77 (23%)	144 (15%)	<0.001	102 (21%)	163 (10%)	<0.001
CVA/ TIA‖	107 (33%)	179 (18%)	<0.001	210 (44%)	514 (33%)	<0.001
Clinical variables						
Hypertension	161 (49%)	371 (38%)	<0.001	237 (49%)	513 (32%)	<0.001
Diabetes Mellitus	67 (20%)	116 (12%)	<0.001	97 (20%)	209 (13%)	<0.001
Current smoker	110 (33%)	331 (34%)	0.88	144 (30%)	366 (23%)	<0.05
Dyslipidemia**	138 (42%)	81 (8%)	<0.001	228 (48%)	153 (10%)	<0.001
Renal dysfunction	24 (7%)	89 (9%)	0.31	29 (6%)	91 (6%)	0.82
Body mass index (kg/m^2)	26 (4)	25 (4)	<0.05	26 (4)	25 (4)	<0.05
Cardiac medication						
Beta-blockers	242 (72%)	265 (30%)	<0.001	282 (56%)	352 (23%)	<0.001

ACE-inhibitors	110 (33%)	198 (20%)	<0.001	176 (37%)	294 (19%)	<0.001
Calcium antagonists	87 (26%)	227 (23%)	0.24	130 (27%)	301 (19%)	<0.001
Diuretics	93 (28%)	202 (21%)	<0.05	101 (21%)	211 (13%)	<0.001
Aspirin	187 (57%)	298 (30%)	<0.001	324 (68%)	554 (35%)	<0.001
Anti-coagulants	113 (34%)	359 (37%)	0.36	199 (42%)	669 (42%)	0.74
Nitrates	53 (16%)	121 (12%)	0.09	66 (14%)	148 (9%)	<0.05
Pulmonary medication						
Bronchodilators	47 (14%)	165 (17%)	0.27	0 (0%)	0 (0%)	0.08
Corticosteroids	92 (28%)	210 (21%)	<0.05	7 (2%)	10 (1%)	0.08

* Abdominal aortic surgery.
† Carotid endarterectomy.
§ Lower limb arterial reconstruction.
‡ Previous coronary artery bypass graft or percutaneous coronary intervention.
‖ Cerebrovascular accident/ transient ischemic attack.
** Total cholesterol >5.2 mmol/L and/or cholesterol-lowering medication.

Figure 1. Long-term mortality according to COPD and statin use



Number at risk

No COPD/ statins	**480**	**371**	**250**	**167**	**111**	**66**
No COPD/ no statins	**1581**	**1255**	**1039**	**842**	**634**	**66**
COPD/ statins	**330**	**232**	**122**	**65**	**43**	**22**
COPD/ no statins	**980**	**680**	**512**	**357**	**233**	**151**

Table 2. Effect of statins on 30-day and long-term mortality

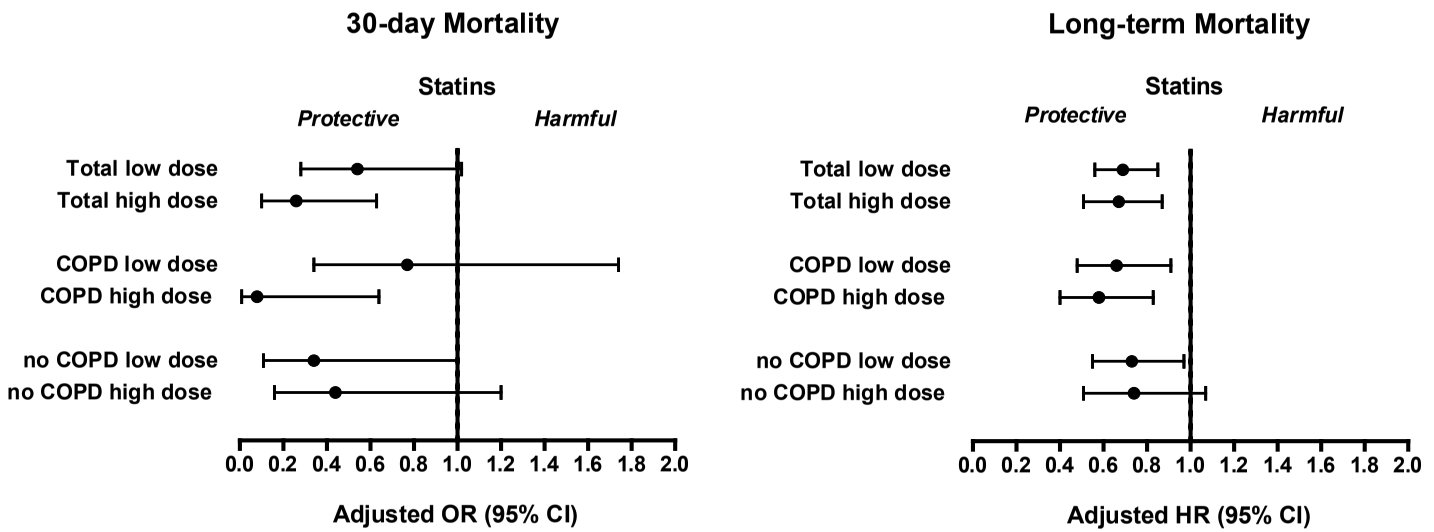
	30 day mortality				Long-term mortality			
	Univariate		Multivariate*		Univariate		Multivariate*	
	OR	[95% CI]	OR	[95% CI]	HR	[95% CI]	HR	[95% CI]
Statins								
Total	0.45	[0.29-0.70]	0.45	[0.27-0.75]	0.62	[0.53-0.71]	0.72	[0.60-0.85]
COPD	0.47	[0.25-0.88]	0.48	[0.23-1.00]	0.61	[0.49-0.74]	0.67	[0.52-0.86]
No COPD	0.42	[0.22-0.80]	0.42	[0.20-0.87]	0.63	[0.51-0.76]	0.76	[0.60-0.95]

*Adjusted for: age, gender, previous myocardial infarction, previous coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention), previous heart failure, previous angina pectoris, previous cerebrovascular accident or transient ischemic attack, hypertension, hypercholesterolemia, diabetes mellitus, impaired renal function, smoking status, body mass index, type of surgery (AAA, CEA or LLR), year of surgery, use of beta-blockers, aspirin, bronchodilators, and corticosteroids

However, an intensified dose was associated with improved short-term survival (OR 0.08, 95% CI 0.01 to 0.64). In subjects without COPD, there was no major difference in short-term survival between the 2 doses (low dose: OR 0.34, 95% CI 0.11 to 1.00; intensified dose: OR 0.44, 95% CI 0.16 to 1.20, respectively). During long-term follow-up, both low-dose and intensive statin therapy were associated with improved survival in patients with COPD (HR 0.66, 95% CI 0.48 to 0.91; HR 0.58, 95% CI 0.40 to 0.83, respectively). In patients without COPD, only a low statin dose was significantly associated with improved long-term survival (low dose: HR 0.73, 95% CI 0.55 to 0.97; intensified dose: HR 0.74, 95% CI 0.51 to 1.07, respectively; Figure 2).

In 651 patients (50%) with COPD, a preoperative white blood cell count was measured. Statin therapy seemed to have a large impact on reducing short-term mortality in patients with COPD with an increased white blood cell count (OR 0.16, 95% CI 0.03 to 0.99) compared with patients with a normal blood cell count (OR 0.38, 95% CI 0.10 to 1.42). In the long-term, statins were not significantly associated with improved survival in patients with COPD with a normal white blood cell count (HR 0.77, 95% CI 0.50 to 1.21), whereas they were associated with improved survival in patients with COPD with an increased white blood cell count (HR 0.40, 95% CI 0.18 to 0.88).

Figure 2. Effect of statin dose on short- and long-term mortality



*Adjusted for: age, gender, previous myocardial infarction, previous coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention), previous heart failure, previous angina pectoris, previous cerebrovascular accident or transient ischemic attack, hypertension, hypercholesterolemia, diabetes mellitus, impaired renal function, smoking status, body mass index, type of surgery (AAA, CEA or LLR), year of surgery, use of beta-blockers, aspirin,

DISCUSSION

Results of the present study confirmed the known beneficial effect of statins on short- and long-term mortality in patients with PAD and showed that this effect extended to patients with COPD. We found that intensive therapy was superior to low-dose therapy in reducing short- and long-term mortality in patients with COPD.

Consistent with our findings, several studies have showed that statin therapy reduced the mortality in patients with PAD undergoing vascular surgery.[5-8] We extended these findings by showing in patients with COPD that statins were associated with a 52% and 33% risk reduction on short- and long-term mortality, respectively. These data were in keeping with recent studies that reported similar relations in other COPD cohorts.[9-11] However, many of these studies used administrative databases and therefore did not have detailed spirometric or clinical data such as potential confounders as smoking or dyslipidemia, making them susceptible to biases and confounding.[10] Moreover, most studies had relatively short follow-up and no study examined the role of statins in patients with COPD with coexisting PAD who underwent vascular surgery. Because this group of patients is particularly vulnerable to cardiovascular disease morbidity and mortality, our findings are very salient.

Notably, we found that an intensified, but not low-dose therapy, was associated with improved short-term survival in patients with COPD, which raises the possibility that patients with COPD may have relative resistance to statins perioperatively (possibly owing to a large inflammatory load) and may require larger doses to achieve clinical benefits. These data were in keeping with those of Frost et al,[11] which suggested that the highest statin dose was most effective in reducing COPD deaths. Similarly, a recent study by Feringa et al[5] showed that higher statin doses were associated with better clinical outcomes than low doses in patients with PAD. These results confirmed the findings from recent clinical trials that showed superiority of intensive statin therapy over standard therapy in improving outcomes in patients with coronary heart disease.[12, 13]

Although our study was not designed to investigate the potential anti-inflammatory effects of statins on COPD, our results suggested that the beneficial effects of statins was larger in patients with COPD with an increased white blood cell count compared with those with normal counts. These findings were consistent with reported pleiotropic anti-inflammatory properties of statins and provided a plausible mechanism by which statins may have beneficial effects in patients with COPD.[14, 15]

The study had limitations, including the retrospective design, which might have led to underestimation of clinical risk factors. Furthermore, patients who received statin therapy had a different clinical risk profile compared with patients without statins, although the beneficial effect on mortality remained after adjusting for these risk factors. Also the follow-up period of 10 years may have been problematic because the prescription of statins increased exponentially over time. However, in multivariate analysis, we included the year of surgery to adjust for this potential bias and still found a survival benefit with statins. Finally, there might have been misclassification of COPD because a pulmonary function test was not performed in all patients. However, patients who did not undergo a pulmonary function test were free of symptoms and pulmonary medication. Of these patients, 98% had normal arterial blood gas results and were classified as having no COPD. Thus, it is unlikely that diagnostic misclassification could explain away the findings.

In conclusion, statin therapy at time of surgery was associated with improved short- and long-term survival in patients with PAD with and without COPD. An intensified dose of statins is recommended in patients with COPD to achieve the ultimate effect on both short- and long-term.

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8

The impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis

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ABSTRACT

BACKGROUND

Beta-blocker use is associated with improved health outcomes in patients with cardiovascular disease. There is a general reluctance to prescribe beta-blockers in patients with chronic obstructive pulmonary disease (COPD) because they may worsen symptoms. We investigated the relationship between cardioselective beta-blockers and mortality in patients with COPD undergoing major vascular surgery.

METHODS

We evaluated 3,371 consecutive patients who underwent major vascular surgery at one academic institution between 1990 and 2006. The patients were divided into those with and without COPD based on symptoms and spirometry. The major endpoints were 30-day and long-term mortality after vascular surgery. Patients were defined as receiving low-dose therapy if the dosage was less than 25% of the maximum recommended therapeutic dose; dosages higher than this were defined as intensified dose.

RESULTS

There were 1,265 (39%) patients with COPD of whom 462 (37%) received cardioselective beta-blocking agents. Beta-blocker use was associated independently with lower 30-day (odds ratio, 0.37; 95% confidence interval, 0.19-0.72) and long-term mortality in patients with COPD (hazards ratio, 0.73; 95% confidence interval, 0.60-0.88). Intensified dose was associated with both reduced 30-day and long-term mortality in COPD patients, whereas low dose was not.

CONCLUSIONS

Cardioselective beta-blockers were associated with reduced mortality in patients with COPD undergoing vascular surgery. In carefully selected patients with COPD, the use of cardioselective beta-blockers appears to be safe and associated with reduced mortality.

INTRODUCTION

During the last decade, beta-blocker therapy has become an increasingly important treatment in patients undergoing noncardiac surgery. Several studies have shown that peri-operative beta-blocker therapy can reduce the incidence of peri- and post-operative cardiac complications, including sudden death, angina and myocardial infarction in patients undergoing noncardiac vascular surgery.[1-5] Accordingly, the American College of Cardiology and the American Heart Association recommend the use of beta-blockers in patients undergoing major vascular surgery.[6] Many patients with cardiovascular disease (CVD) have co-existing chronic obstructive pulmonary disease (COPD) and vice versa possibly because they share the same risk factor, cigarette smoking.[7] In patients with COPD, approximately 30% of all deaths are from CVD.[8] Beta-blockers are, however, frequently withheld from COPD patients with co-existing CVD because of the concern that beta-blockers may induce bronchoconstriction from blockade of beta-2-adrenoreceptors. Although nonselective beta-blockers act on the beta-2-adrenoreceptors to inhibit bronchodilation,[9] there is substantial evidence that cardioselective beta-blockade is likely safe and beneficial in patients with COPD and CVD.[10-18] Additional concern regarding use of beta-blockers in COPD is the potential for insensitivity. COPD is associated with systemic inflammation, which may accelerate metabolism of beta-blockers, leading to reduced efficacy. Patients are particularly vulnerable to cardiac events during and after major vascular surgery.[19] The primary aim of the present study was to investigate the association between cardioselective beta-blockers and 30-day and long-term mortality in patients with COPD who undergo major vascular surgery. The secondary objective was to determine the relationship between low and intensified dosage and mortality. Some of the results of this study have been previously reported in the form of an abstract.[20]

METHODS

STUDY POPULATION

This observational retrospective study included 3,371 consecutive patients undergoing elective vascular surgery between 1990 and 2006 at the Erasmus Medical Center Rotterdam, The Netherlands. The surgical procedures included abdominal aortic surgery (comprising aortic-to-aortic or aortic-bifurcation prostheses procedures, removal of infected prostheses, and other operations of the abdominal aorta), carotid endarterectomy (including reconstruction or desobstruction of the carotid artery), and lower limb arterial reconstruction procedure (including iliac-femoral, femoral-popliteal, femoral-tibila artery bypass procedures, removal of infected prostheses, peripheral desobstruction and other elective peripheral arterial surgical reconstructions). Vascular reconstructions due to trauma and ruptured abdominal aortic aneurysms were excluded.

Abstracted variables included patient demographics (age and sex) and cardiac risk factors, including the following: hypertension (defined as a blood pressure ≥140/90 mm Hg), hypercholesterolemia (total cholesterol of >5.2 mmol/L), diabetes mellitus (presence of fasting blood glucose of ≥140mg/dl or treatment with insulin or oral hypoglycemic agents), serum creatinine renal dysfunction (baseline serum creatinine >1.5 mg/dl), current smoking status and body mass index (BMI) calculated as weight divided by height squared (kg/m^2). The patients' cardiovascular history was assessed and included the following: previous myocardial infarction, coronary revascularization (coronary artery bypass graft and/or percutaneous coronary intervention), heart failure (defined according to the New York Heart Association classification),

angina pectoris, stroke and/or transient ischemic attack. The use of bronchodilators and corticosteroids at baseline was captured. Cardiac medications at baseline were also evaluated. These included beta-blockers, statins, angiotensin-converting enzyme inhibitors, diuretics, aspirin, anticoagulants, nitrates and calcium channel blockers. Almost all (97%) of the prescribed beta-blockers were cardioselective beta-blocking agents: metoprolol, bisoprolol and atenolol. To evaluate the association of low and intensified beta-blocker dose with mortality, we converted the beta-blocker dosage at initial hospitalization. Low dose was defined as patients using less than 25% of the maximum recommended therapeutic dose, whereas intensified dose was defined as an average dose exceeding or equal to 25% of maximum recommended therapeutic dose. For metoprolol, a maximum recommended therapeutic dose of 400 mg was used, for bisoprolol 10 mg was used, and for atenolol 100 mg was used.

PULMONARY FUNCTION TESTING

A diagnosis of COPD was based on post-bronchodilator spirometric values in conjunction with a history of cough, sputum production and/or dyspnea. COPD was defined according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (FEV_1 to FVC ratio less than 70%[21]). Disease severity was classified into three groups: I = mild COPD (FEV_1/FVC <0.70 and FEV_1 ≥80% of the predicted FEV_1), II = moderate COPD (FEV_1/FVC <0.70 and FEV_1 50% ≤FEV_1 <80% of the predicted FEV_1), and III = severe COPD (FEV_1/FVC <0.70 and FEV_1 30% ≤FEV_1 <50% of the predicted FEV_1).[21] We used the equation of Quanjer and colleagues[22], adjusted for age, sex, and height, to calculate the predicted FEV_1 value, which has demonstrated to make an accurate prediction.[23] The equation for males is 4.30 x height (m) - age x 0.029 - 2.49 and for women is 3.95 x height (m) - age x 0.025 - 2.60.[22] In 82% of the patients with COPD, a preoperative spirometry was performed. The patients without a preoperative pulmonary function test were classified as having no COPD if they were free of pulmonary complaints (cough and dyspnea), and not currently receiving pulmonary medications (i.e., bronchodilators and corticosteroids) and demonstrated normal arterial blood gases on room air (Pco_2 <6.4 kPa and Po_2 >10.0 kPa).

FOLLOW-UP AND ENDPOINTS

Follow-up was complete in 96% of the study patients, with a median follow-up of 5 years. Survival status was obtained from the municipal civil registries. Clinical baseline characteristics were retrieved from the hospital medical records. Endpoints of the study were 30-day and long-term (10-yr) mortality regardless of the cause.

STATISTICAL ANALYSIS

Continuous data are presented as mean ± SD and compared using the Student's *t* test. Categorical variables among the patient groups are expressed as percentages and compared using χ^2 tests. Univariate and multivariate logistic regression analyses were used to determine the relationship of cardioselective beta-blockers and their dose with 30-day mortality. Cox proportional hazards models were used to analyze the impact of these drugs on long-term mortality, adjusted for salient covariates, including age, sex, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery, and cardiovascular history. In addition, a composite variable of statins, aspirin and angiotensin-concerting enzyme inhibitors was included. Patients who received non-selective beta-blockers (n=112; 3%) were excluded from the analysis. In addition, using a multivariate logistic regression model, we developed a propensity score to adjust for the likelihood of receiving beta-blockers in subjects with

COPD and non-COPD subjects. The variables in this model included: age, sex, COPD, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery, all variables on cardiovascular history, all cardiac and pulmonary medications (Table 1). The fit of the propensity score model was assessed using c-statistics and the Hosmer-Lemeshow goodness-of-fit-test. In all comparative analysis of beta-blockers, patients who were not on beta-blocker therapy were used as the reference group. Odds ratios (ORs) and hazard ratios (HRs) were calculated from these models along with their 95% confidence intervals (CIs). For all tests, a two-sided *P* value of less than 0.05 was considered significant. All statistical analyses were performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL).

Table 1. Baseline characteristics according to COPD and beta-blocker use

	COPD (n=1,265)			No COPD (n=1,994)		
	Beta-blocker (n=462)	No beta-blocker (n=803)	P value	Beta-blocker (n=567)	No beta-blocker (n=1,427)	P value
Demographics						
Mean age, yr (SD)	69 (9)	69 (10)	0.61	65 (11)	63 (13)	0.01
Male sex (%)	82	78	0.07	70	68	0.30
Type of surgery (%)			<0.001			<0.001
AAA	54	43		37	24	
CEA	15	13		31	31	
LLR	31	44		32	46	
Cardiovascular history (%)						
Myocardial infarction	33	21	<0.001	31	14	<0.001
Coronary revascularization*	25	14	<0.001	22	11	<0.001
Heart failure	7	5	0.22	5	4	0.29
Angina pectoris	26	11	<0.001	23	9	<0.001
Stroke or TIA	24	20	0.14	35	35	0.76
Clinical characteristics (%)						
Hypertension	49	36	<0.001	54	28	<0.05
Diabetes Mellitus	17	12	<0.05	18	14	0.08
Hypercholesterolemia	26	11	<0.001	28	14	<0.001
Renal dysfunction	9	8	0.43	10	4	<0.001
Body mass index (SD)	26 (4)	25 (4)	<0.05	26 (4)	25 (4)	<0.05
Current smoking status	35	33	0.41	27	24	0.21
Cardiac medication (%)						
Statins	49	11	<0.001	46	14	<0.001
ACE-inhibitors	31	19	<0.001	34	18	<0.001
Calcium antagonists	28	22	<0.05	33	16	<0.001
Diuretics	28	19	<0.05	23	11	<0.001

Aspirin	47	30	<0.001	58	37	<0.001
Anti-coagulants	32	38	<0.05	41	42	0.84
Nitrates	17	11	<0.05	18	7	<0.001
Pulmonary medication (%)						
Bronchodilators	13	18	<0.05	0	0	0.85
Corticosteroids	23	11	<0.001	1	1	0.88

Definition of abbreviations: AAA = abdominal aortic surgery; ACE = angiotensin-converting enzyme; CEA = carotid endarterectomy; COPD = chronic obstructive pulmonary disease; LLR = lower limb arterial reconstruction; TIA = transient ischemic attack.
*Coronary artery bypass graft or percutaneous coronary intervention.

RESULTS

BASELINE CHARACTERISTICS

Of the 3,371 patients (mean age 66 ± 12 yr; 73% male), 1,029 (31%) received cardioselective beta-blockers at their initial hospitalization (Table 1). The commonly used beta-blockers were bisoprolol at 50% (n=514), atenolol at 15% (n=151) and metoprolol at 32% (n=325). Patients with beta-blockers were more likely to have underlying history of cardiac disease, hypertension, and hypercholesterolemia (all p <0.001). The percentage of beta-blocker use was not significantly different among the COPD severity groups (mild COPD, 39%; moderate COPD, 35%; and severe COPD, 33%; *P* = 0.20).

ASSOCIATION BETWEEN CARDIOSELECTIVE BETA-BLOCKERS AND MORTALITY

Overall, there were 1,265 (39%) patients with COPD. Of these patients, 462 (37%) used cardioselective beta-blocking agents. In comparison, 567 (28%) of the patients who did not have COPD used beta blockers. Within 30 days of surgery, 16 (4%) patients with COPD who were receiving beta-blockers died. In contrast, 66 (8%) patients who did not use beta-blockers died during the same period of time (*P* = 0.001). Over the entire follow-up period, 184 (40%) patients with COPD who were and 532 (67%) were not on beta-blocker therapy died (p <0.001). Cardioselective beta-blockers were independently associated with reduced 30-day mortality in patients with (OR, 0.37; 95% CI, 0.19-0.72) and without COPD (OR, 0.34; 95% CI, 0.17-0.66) (Table 2). Over the entire follow-up period, cardioselective beta-blocking agents reduced long-term mortality in patients with COPD (HR, 0.73; 95% CI, 0.60-0.88). In the long-term, a trend was observed in patients without COPD, although it did not achieve statistical significance (HR, 0.84; 95% CI, 0.69-1.02).

A sensitivity analysis was performed using propensity score measurements for adjustment of various factors, including severity of disease to address the issue of confounding by indication. In this analysis, the relationship of cardioselective beta-blockade with mortality in patients with COPD was similar to the main analysis (OR, 0.41; 95% CI, 0.20-0.81 and HR, 0.75; 95% CI, 0.61-0.91). In patients without COPD, a significant association was found between beta-blocker use and 30-day mortality (OR, 0.36; 95% CI, 0.18-0.72). Similar to the main analysis, a trend was observed with the long-term mortality, although the relationship was not significant (HR, 0.88; 95% CI, 0.72-1.07).

The relationship between beta-blockers and mortality across different COPD severity groups is also summarized in Table 2. Even in moderate to severe group, beta-blocker therapy was associated with reduced mortality in the short and long-term.

Table 2. The association between cardioselective beta-blockers and mortality

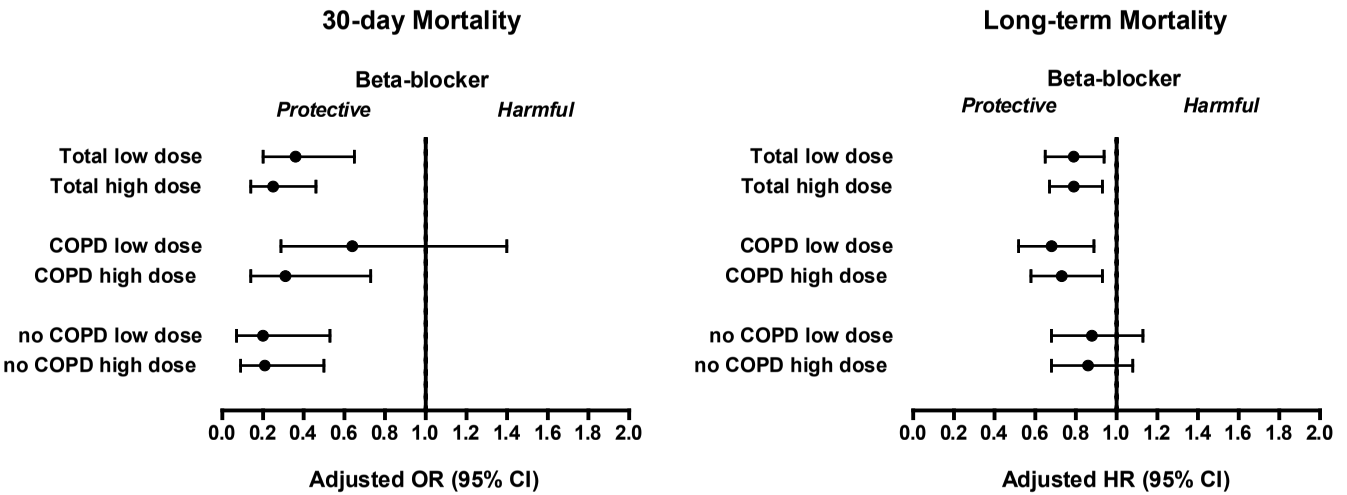
	30 day mortality				Long-term mortality			
	Univariate		Multivariate		Univariate		Multivariate	
	OR	[95% CI]	OR	[95% CI]	HR	[95% CI]	HR	[95% CI]
BBL								
Total	0.45	[0.30-0.66]	0.35	[0.22-0.57]	0.84	[0.74-0.95]	0.78	[0.68-0.89]
No COPD	0.46	[0.26-0.81]	0.34	[0.17-0.66]	0.86	[0.73-1.02]	0.84	[0.69-1.02]
COPD	0.40	[0.23-0.70]	0.37	[0.19-0.72]	0.74	[0.63-0.88]	0.73	[0.60-0.88]
Mild	0.45	[0.21-0.98]	0.46	[0.18-1.16]	0.70	[0.54-0.92]	0.68	[0.50-0.93]
Moderate/ severe	0.34	[0.15-0.78]	0.32	[0.12-0.85]	0.79	[0.64-0.98]	0.82	[0.64-1.05]

Definition of abbreviations: COPD = chronic obstructive pulmonary disease;
HR = hazard ratio; OR = odds ratio.

CARDIOSELECTIVE BETA-BLOCKER DOSE AND MORTALITY

Of the patients using cardioselective beta-blockers, 41% received low-dose beta-blocker therapy at the time of surgery and 59% received an intensified dose. These percentages were similar among patients with COPD, with 42% of the patients on a low-dose and 58% on an intensified dose. In patients with COPD, an intensified but not low-dose was associated with reduced 30-day mortality (OR, 0.26; 95% CI, 0.10-0.66) (Figure 1). However, in the long-term, both dosing regimens were associated with reduced mortality (low dose: HR, 0.70; 95% CI, 0.54-0.91 and intensified dose: HR, 0.76; 95% CI, 0.59-0.98). In patients without COPD, both low and intensified dosing regimens were associated with reduced 30-day mortality (OR, 0.30; 95% CI, 0.12-0.77 and OR, 0.36; 95% CI, 0.15-0.86, respectively). The relationships became insignificant for low-dose beta-blockers when long-term mortality was considered, although a trend for reduced mortality was still observed in non-COPD patients who were treated with an intensified dose (HR, 0.80; 95% CI, 0.62-1.03).

Figure 1. The association between low and intensified cardioselective beta-blocker dose and mortality



*Adjusted for age, sex, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery and cardiovascular history. CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OR = odds ratio.

DISCUSSION

The present study demonstrated that cardioselective beta-blockers were associated with reduced 30-day and long-term mortality in patients with COPD who underwent major vascular surgery. We also found that an intensified dosing regimen appeared to be superior to low-dose therapy in terms of its impact on 30-day mortality.

These findings are consistent with other studies that demonstrated the beneficial effects of beta-blockers in patients with COPD who recently experienced myocardial infarction[13, 15, 18]. A major limitation of the previous studies was that there was no or little information on lung function and as such the diagnosis of COPD could not be confirmed. We extend these findings by demonstrating among a large group of well-characterized patients with COPD, defined both clinically and spirometrically, that beta-blockers were safe and indeed beneficial in prolonging survival after major vascular surgery. There is evolving evidence showing that cardioselective beta-blockade probably does not induce bronchospasm in patients with COPD.[11, 12, 14, 16, 17] In addition, a meta-analysis of Salpeter and colleagues that evaluated the relationship between cardioselective beta-blockers and COPD found no significant differences in FEV_1 or respiratory symptoms between those who were treated with a cardioselective beta-blockers or those treated with placebo, even in patients with severe COPD.[24] In a study of patients with congestive heart failure, patients with and without COPD had similar rates of withdrawal from beta-blockers because of intolerance.[25] These data suggest that COPD does not increase the rate of adverse reactions to cardioselective beta-blockers (leading to withdrawal). In view of the observed beneficial effect of cardioselective beta-blockers in our study, we believe that cardioselective beta-blocking agents may be used cautiously in patients with COPD with underlying ischemic vascular disease. Because cardioselective beta-blocking agents have some (although minor) effects on the beta-2-adreneroreceptors, such patients should be monitored very closely for any adverse effects. Moreover, although we found that intensified dose was superior to low-dose therapy with regard to 30-day mortality, we believe that it may be prudent to initiate therapy at the lowest dose feasible and to gradually increase the dose to the target range over several weeks to ensure safety.

Why beta-blockers would be effective in COPD is largely unknown; however, it is well established that CVD is an important comorbidity in COPD. In the Lung Health Study, for instance, which studied 5,887 smokers, aged 35 to 60 years, with GOLD stage 1 and 2 disease (FEV_1 ≥50% predicted), CVDs were primarily responsible for 22% of all deaths[26] and cardiovascular events accounted for 42% of the first hospitalizations and 48% of the second hospitalizations.[27] The increased CVD risk in COPD may, in part, be related to excess adrenergic activity. Using microneurography of the peroneal nerve, Heindl and colleagues showed that patients with COPD have a marked increase in peripheral sympathetic discharge compared with control subjects[28], which was inversely related to the patients' oxyhemoglobin saturation (r = 0.54).[29] Patients with COPD also demonstrate reduced cardiac accumulation of meta-iodobenzylguanidine, an analog of guanetidine, a higher washout rate from the heart, and increased plasma norepinephrine levels than control subjects, indicating excess activity of the sympathetic nervous system with increased norepinephrine turnover than do control subjects.[30] In patients who demonstrate excess sympathetic nervous activity such as those with chronic heart failure or previous myocardial infarction, the use of beta-adrenoceptor blockers, which attenuate sympathetic nervous activity, improves cardiac function and reduces CVD morbidity and mortality.[31] In addition, beta-blockers may reduce peri- and postoperative cardiac complications by attenuating cardiac workload and myocardial ischemia through beta1-blockade. Beta1-blockade may also inhibit catecholamine-

induced necrosis and apoptosis of the myocardium, which may confer additional benefits to the stressed heart.[32]

Our finding that an intensified dosing regimen was superior to a low-dose regimen in reducing 30-day mortality is consistent with those from a previous study which examined the effect of low- and intensive-dose therapy in vascular surgery patients.[19] It is also consistent from the findings of the MOCHA (Multicenter Oral Carvedilol Heart Failure Assessment), SENIORS (Study of the Effects of Nebivolol Intervention on Outcome and Rehospitalization in Seniors with Heart Failure), and the COMET (Carvedilol or Metoprolol European Trial) trials, which also demonstrated a dose-related reduction in mortality.[33-35] Conversely, the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure) trial and the CIBIS (Cardiac Insufficiency Bisoprolol Study) II trail failed to demonstrate this dose-dependent effect.[36, 37] However, all these trials were conducted in patients with heart failure and should therefore be carefully compared with our study. Unfortunately, in most of these trials, patients with COPD were excluded because of concerns about bronchoconstriction, which makes cross-comparisons difficult. To our knowledge, the present study is the first of its kind to investigate the dose-dependent association between beta-blockers and mortality in vascular surgery patients with COPD.

There were limitations to the study. First, we could not fully rule out the possibility that some individuals with COPD also had asthma. However, although bronchial hyper-responsiveness is more common (and more severe) in asthma than in COPD, over 70% of patients with COPD also demonstrate bronchial hyperresponsiveness. Thus, in reality, a clear separation is not always possible in clinical practice.[38] Second, this was an observational study and not a clinical trial, which raises the possibility of confounding. To mitigate this possibility, we carefully collected salient clinical and demographic information and used sophisticated statistical modelling and inclusion of lung function measurements. We calculated a propensity score for beta-blocker use and included this propensity score in the multivariable analysis to correct for the conditional probability of receiving the medication. We found that this made no material difference to the overall results. Although we cannot entirely rule out confounding by reverse indication, the adjustments of these factors including spirometric data suggest that these findings are not spurious and unlikely due to treatment selection. Nevertheless, additional prospective studies are needed to validate these early findings. Third, the prescription of beta-blockers increased during 10 years of follow-up. To minimize the effect of this potential bias, we adjusted for the year of surgery in the analysis. Moreover, although we found that beta-blocker therapy was associated with both short- and long-term survival, our measure of beta-blocker exposure occurred at one-time point. We did not have follow-up data on beta-blocker use, which may have led to exposure misclassification. However, it is likely that patients who were prescribed beta-blockers at baseline were more likely to have received similar therapy in subsequent periods of follow-up.[39] Thus, the long-term benefits of beta-blocker therapy are likely on the basis of ongoing use of these medications as an outpatient.

In summary, our results suggest that cardioselective beta-blockers are beneficial in patients with COPD undergoing vascular surgery, with an intensive dose being most effective in the reduction of 30-day mortality. Therefore, cardioselective beta-blocking agents should not be withheld from patients with COPD undergoing vascular surgery.

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9

Beta-blockers and health-related quality of life in patients with peripheral arterial disease and COPD

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ABSTRACT

BACKGROUND

Beta-blockers are frequently withheld in patients with cardiovascular disease who also have chronic obstructive pulmonary disease (COPD) because of concerns that they might provoke bronchospasm and cause deterioration in health status. Although beta1-selective beta-blockers are associated with reduced mortality in COPD patients, their effects on health status are unknown. The aim of this study was to investigate the relationship between beta-blockers and health-related quality of life (HRQL) in patients with peripheral arterial disease and COPD.

METHODS

Of the original cohort of 3371 vascular surgery patients, 1310 had COPD of whom 469 survived during long-term follow-up. These COPD patients were sent the Short Form-36 (SF-36) health-related quality of life questionnaire, which was completed and returned by 326 (70%) patients.

RESULTS

No significant differences in any of the SF-36 domains were observed between COPD patients who did and did not use beta-blockers ($p > 0.05$ for all). Furthermore, beta-blockers were not associated with any impairment in HRQL among patients with COPD.

CONCLUSIONS

Beta-blockers had no material impact on the HRQL of patients with peripheral arterial disease who also had COPD. This suggests that beta-blockers can, in most circumstances, be administered to patients with COPD without impairment in HRQL.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) often have or develop co-existing cardiovascular diseases including congestive heart failure, ischemic heart disease and hypertension.[1] Beta-blockers are indicated in most of these conditions, as they improve heart function, symptoms and survival.[2, 3] However, there is under-utilization of beta-blockers in cardiovascular patients with COPD because of concerns that these drugs may induce bronchoconstriction and worsen symptoms.[4] Although the data are mixed, the totality of evidence suggests that beta1-selective beta-blockers (at least in the short-term) do not worsen pulmonary function[5-10] and are associated with reduced mortality in patients with cardiovascular disease who have COPD.[11-13] The long-term effects on health status and health-related quality of life (HRQL) of beta-blockers in COPD are unknown. On one hand, beta-blockers may improve HRQL because of their beneficial effects on cardiac performance; on the other hand, beta-blockers may cause impaired physical, social and emotional functioning owing to their side effects and/or by causing worsening of lung function. The latter may partly explain the sub-optimal prescription rate of these drugs for patients with COPD. We thus sought to determine the relationship between beta-blockers and HRQL of patients with peripheral arterial disease, who also had COPD.

METHODS

PATIENTS

The study is based on a subgroup of the original cohort of vascular surgery patients, that has been described previously.[13] Briefly, a detailed cardiac history, in addition to clinical and demographic characteristics, were obtained in all patients undergoing a peripheral vascular operative procedure prior to their surgery. Their survival status was ascertained at long-term follow-up (up to 10 years) using the municipal civil registry. HRQL of patients was determined at follow-up using a self-administered questionnaire that was mailed to all eligible subjects (see below). In this mailing, we also obtained information regarding the use of beta-blockers using a short questionnaire.

COPD

The diagnosis of COPD was based on spirometric evidence for fixed airflow obstruction as assessed by a post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of less than 0.70 and FEV_1 of <80% of predicted, which was obtained at baseline prior to their original vascular surgery.[14] Patients who did not undergo spirometry were categorized as not having COPD if they did not complain of cough, dyspnea or sputum production, were not taking any pulmonary medication (bronchodilators or corticosteroids) and demonstrated normal arterial blood gases on room air defined by arterial carbon dioxide tension (Pco_2) <6.4 kPa and oxygen tension (Po_2) >10.0 kPa. Patients without spirometry who met any one of these criteria were classified as having COPD.

HEALTH-RELATED QUALITY OF LIFE

For the assessment of HRQL, the Dutch version of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used.[15, 16] SF-36 is a widely used generic questionnaire to measure patients' health status and has been used previously in patients with COPD.[17-19] The questionnaire contains 36 items covering 8 domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). The domains scores range from 0 to 100, with higher scores indicating better HRQL.

STATISTICAL ANALYSIS

The primary exposure variable was the use of beta-blockers at baseline and the primary endpoint of the present study was HRQL at follow-up. The baseline categorical variables of the patients who did and did not use a beta-blocker were compared using a chi-square test for dichotomous variables and a Student's t-test for continuous variables. Dichotomous variables are presented as percentages, while continuous variables are presented as mean ± standard deviation (SD). The domains of the SF-36 were converted into tertiles for parsimony and subsequently dichotomized,[20, 21] with the lowest tertile indicating worst health status and the highest two tertiles representing best health status. Univariate and multivariate logistic regression analyses were used to determine the association between beta-blocker use and health status. In the multivariate analysis, adjustments were made for all baseline characteristics that might reasonably affect HRQL including age, gender, diabetes mellitus, hypertension, hypercholesterolemia, renal dysfunction, current smoking, obesity, type of surgery (abdominal aortic surgery (AAA), carotid endarterectomy (CEA), or lower limb arterial reconstruction procedures (LLR)), year of surgery, previous ischemic heart disease (myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention or angina pectoris), heart failure, cerebrovascular event (CVA) or transient ischemic attack (TIA), statins, aspirin, corticosteroids and bronchodilators. To correct for the differential follow-up, adjustments were made for the number of follow-up years. Additionally, a propensity score was added as a covariate to the model to adjust for the likelihood of receiving beta-blockers. This propensity model contained all variables which were included in the logistic regression analysis, except for the number of follow-up years. Odds ratios (OR) are presented as risk estimates with 95% confidence intervals (CI). For all tests, a 2-sided p-value of <0.05 was considered significant. All tests were performed using SPSS 15.0 for Windows.

RESULTS

PATIENTS

In total, 1310 (39%) of the original 3371 patients had COPD. Of these patients, two had moved abroad, 28 were lost to follow-up and 469 (36%) survived during the follow-up period. The median follow-up time was 6.4 years with an interquartile range of 2.9 to 9.3 years. All 469 patients were sent the SF-36 questionnaire at follow-up, which was completed and returned by 326 (70%) patients. An overview of the patient inclusion for this study is presented in Figure 1.

Clinical baseline characteristics are presented in Table 1. Of the 326 patients with peripheral arterial disease and COPD, 59% (n = 191) received beta-blockers. The mean age was 66 ± 10 years and 80% (n = 262) were men. Patients on beta-blockers were older and were more likely to have had a previous myocardial infarction, coronary revascularization, angina pectoris, diabetes mellitus, renal dysfunction and hypercholesterolemia compared with those who were not on beta-blockers (all p-values <0.05). These patients also received more often other medications like statins, aspirin and corticosteroids ($p<0.05$). Only two differences were found in baseline characteristics between the COPD patients who filled out the questionnaire and those who did not respond. The non-responding patients were more likely to be women and had more frequent history of renal dysfunction ($p<0.05$).

BETA-BLOCKERS AND COPD

Of the 326 responding COPD patients, 191 (59%) patients used beta-blockers at baseline. Of these, 174 (91%) received a beta1-selective beta-blocker (i.e., bisoprolol, metoprolol or atenolol). Of the 191 patients who had received beta-blockers at baseline, 31 (16%) had discontinued its use (by self-report) at follow-up. All of these patients were probed to ascertain the cause for the discontinuation; in no case was worsening of pulmonary symptoms noted. The distribution of beta-blocker discontinuation between those with and without COPD was similar (of the patients who had discontinued, 54% did not have COPD and 46% had COPD). At baseline 135 COPD patients were not treated with beta-blockers, however at follow-up, 72 (53%) of these patients had initiated beta-blocker therapy. In total, 232 (71%) patients were using beta-blockers by the end of follow-up. Of these, 204 (88%) used beta1-selective beta-blockers (Figure 1).

Figure 1. Patient flowchart

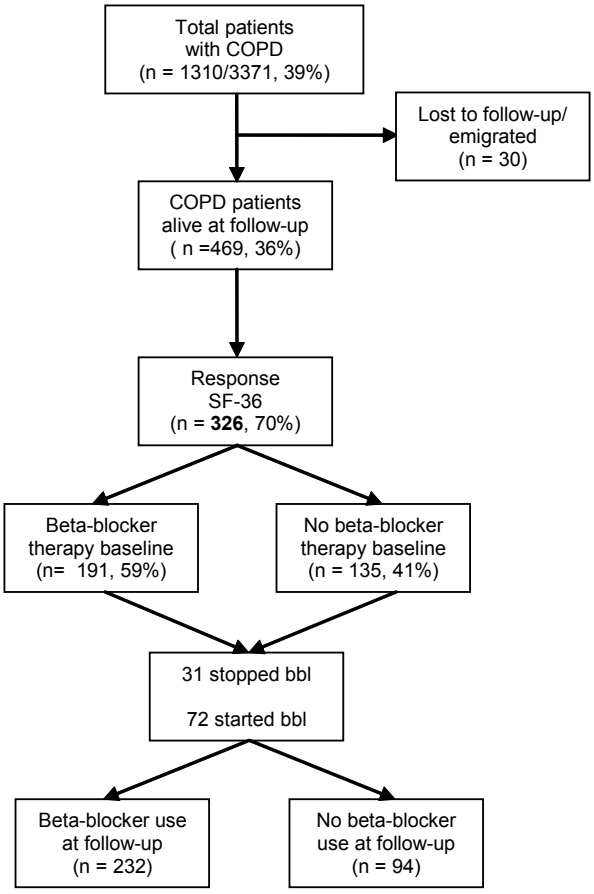
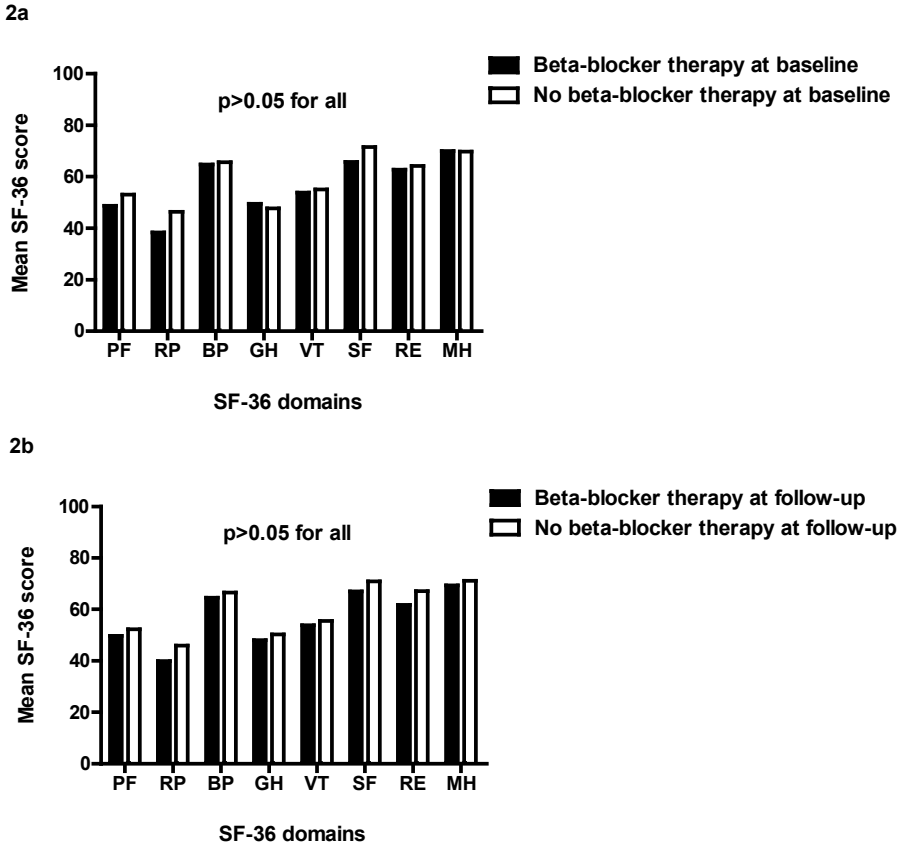


Table 1. Baseline characteristics of the study patients

	Total (n = 326)	Beta-blockers[a] (n = 191)	No beta-blockers (n = 135)	p-value
Demographics				
Mean age years (mean (SD))	66(10)	68(9)	64(11)	<0.001
Male gender	80%	81%	79%	0.67
Type of surgery				0.28
AAA	50%	53%	44%	
CEA	21%	20%	23%	
LLR	29%	27%	33%	
Cardiovascular history				
Myocardial infarction	26%	33%	16%	<0.01
Coronary revascularization[b]	23%	28%	15%	<0.01
Heart failure	5%	4%	5%	0.67
Angina pectoris	20%	29%	8%	<0.001
Stroke or TIA	25%	25%	25%	0.91
Clinical characteristics				
COPD				0.43
Mild COPD	54%	54%	53%	
Moderate COPD	37%	36%	40%	
Severe COPD	9%	11%	7%	
Hypertension	43%	46%	39%	0.26
Diabetes Mellitus	14%	20%	4%	<0.001
Hypercholesterolemia	23%	28%	16%	<0.01
Renal dysfunction	19%	23%	12%	0.01
Body mass index (mean (SD))	26(4)	26(4)	26(4)	0.81
Current smoking status	31%	32%	29%	0.56
Medication				
Statins	44%	58%	23%	<0.001
Aspirin	49%	56%	39%	<0.01
Bronchodilators	10%	11%	10%	0.98
Corticosteroids	15%	19%	10%	0.04

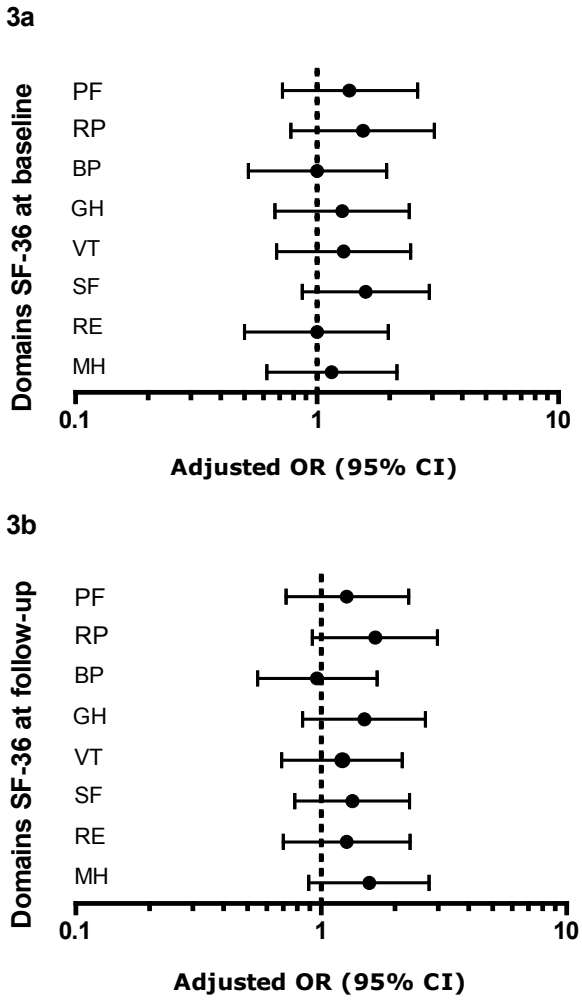
[a]Use at baseline.
[b]Coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI).
Abbreviations: AAA, abdominal aortic surgery; CEA, carotid endarterectomy; LLR, lower limb arterial reconstruction; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease.

Figure 2. Mean SF-36 scores



A) Mean SF-36 scores of COPD patients with beta-blocker therapy at baseline; B) Mean SF-36 scores of COPD patients with beta-blocker therapy at follow-up.
Abbreviations: PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

Figure 3. The association between beta-blocker therapy and health-related quality of life (HRQL)



A) The adjusted association between beta-blocker therapy at baseline and HRQL; B) The adjusted association between beta-blocker therapy at follow-up and HRQL. Adjusted for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, renal dysfunction, current smoking, obesity, type of surgery, previous ischemic
heart disease, heart failure, cerebrovascular event or transient ischemic attack, statins, aspirin, corticosteroids, bronchodilators, year of surgery, number of follow-up years (for Figure 3b) and propensity score.
Abbreviations: PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; OR,odds ratio; CI, confidence interval.

HEALTH-RELATED QUALITY OF LIFE

The mean scores on the SF-36 domains according to beta-blocker use are presented in Figure 2a. There were no significant differences in HRQL scores between those who were and were not taking beta-blockers (p >0.05 for all). Multivariate analyses also showed no significant associations between beta-blockers and the individual domains of the SF-36 in patients with COPD: (PF: OR 1.36; 95% CI 0.72-2.61, RP: OR 1.55; 95% CI 0.78-3.06, BP: OR 1.00; 95% CI 0.52-1.94, GH: OR 1.27; 95% CI 0.67-2.41, VT: OR 1.29; 95% CI 0.68-2.44, SF: OR 1.59; 95% CI 0.87-2.92, RE: OR 1.00; 95% CI 0.50-1.97, MH: OR 1.15; 95% CI 0.62-2.14) (Figure 3a).

We also evaluated the impact of beta-blocker use at follow-up on HRQL. Again, there were no significant differences in mean HRQL scores between patients who were and were not treated with beta-blockers (Figure 2b). Beta-blocker therapy at follow-up was not associated with impaired health status (PF: OR 1.27; 95% CI 0.72-2.27, RP: OR 1.66; 95% CI 0.92-2.98, BP: OR 0.96; 95% CI 0.55-1.69, GH: OR 1.50; 95% CI 0.84-2.66, VT: OR 1.22; 95% CI 0.69-2.14, SF: OR 1.34; 95% CI 0.78-2.29, RE: OR 1.27; 95% CI 0.70-2.30, MH: OR 1.57; 95% CI 0.89-2.75) (Figure 3b).

DISCUSSION

In the present study we investigated the relationship between beta-blockers and HRQL in patients with peripheral arterial disease and COPD. Our findings indicate that beta-blocker therapy does not impair HRQL in this patient population.

These data are similar to a recent review and meta-analysis in patients with chronic heart failure, which demonstrated that beta-blocker therapy did not impair HRQL.[22] We extend these findings by demonstrating a similar relationship in COPD patients. The results of our study are also consistent with those reported by Mascarenhas and colleagues[23] who in a cohort of patients with heart failure and COPD, found a low withdrawal rate of beta-blockers because of adverse effects among those who used these drugs.

Although clinicians are reluctant to prescribe beta-blockers to COPD patients for fear of provoking bronchospasm and exacerbating lung dysfunction, there is compelling evidence to indicate that the benefits (related to cardiovascular morbidity and mortality) are likely to outweigh the potential risk of adverse events in patients with COPD, especially when beta1-selective beta-blockers are used.[11-13, 24] Previous studies suggest that beta1-selective beta-blockers can be given safely to patients with COPD and do not worsen pulmonary function at least in the short-term when used cautiously.[5-10] We have also observed previously that intensified doses of beta-blockers were superior to low-dose therapy in reducing mortality in patients with COPD, which suggests that although it is reasonable to initiate beta-blockers at a low dose, if possible, the dose should be titrated upwards judiciously and slowly to the therapeutic doses in these patients.[13]

Besides survival and adverse effect, it is also important to study the impact of medical treatment on patients' perspective of their health status. To date, HRQL is often used as a secondary endpoint. However, as the focus of COPD management is to improve HRQL, it is important that HRQL is not adversely affected by medical therapy that potentially prolongs survival, e.g., by the treatment with beta-blockers. Moreover, knowledge of the patients' perception of the effect of therapy is essential for the physicians' treatment decisions. Importantly, the results of our study indicate that beta-blocker therapy does not impair patients' health status and could be used in patients with cardiovascular disease and COPD.

The study has some limitations. First, our study was not a randomized controlled trial. As such, although adjustments were made for known covariates, there is the possibility of confounding

by unmeasured variables. In addition, beta-blockers were not randomly assigned and therefore subject to confounding by indication. However, propensity analysis was performed to adjust as much as possible for this type of bias.[25] We did not have accurate information on the duration of beta-blocker exposure and non exposure. A more detailed analysis of the relationship between the duration of beta-blocker exposure (or non-exposure) at follow-up and HRQL was therefore not possible (e.g., a time-dependent covariate analysis). For these and other reasons, a randomized controlled trial is needed to validate these early findings. Furthermore, during follow-up, a number of patients stopped using beta-blockers. It was reassuring that patients did not report worsening of their lung condition or respiratory symptoms for the discontinuation. Nevertheless, a more detailed assessment of long-term pulmonary on and off beta-blockers, using patient-based symptoms questionnaire and lung function testing, would be helpful to better understand why certain patients with COPD discontinue beta-blocker therapy during follow-up.

In sum, although beta-blockers are often indicated in patients with cardiovascular disease, clinicians are reluctant to prescribe these drugs to patients with co-existing COPD for fear of inducing bronchospasm and worsening their health status. The findings of the present study suggest that general health status is not materially affected by these drugs. In view of their potential life-preserving effects in patients with cardiovascular disease, these results suggest that beta-blockers can in most circumstances be judiciously administered to patients with COPD without impairing their HRQL.

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Part IV

Markers of prognosis in patients with COPD

10

Association of COPD with carotid wall intima-media thickness in vascular surgery patients

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ABSTRACT

BACKGROUND

There is increasing evidence that non-invasive imaging modalities such as ultrasonography may be able to detect subclinical atherosclerotic lesions, and as such may be useful tools for risk-stratification. However, the clinical relevance of these observations remains unknown in patients with COPD. Therefore we investigated the association between COPD and carotid wall intima-media thickness (IMT) in patients undergoing vascular surgery and its relationship with mortality in these patients.

METHODS

Carotid wall IMT was measured in 585 patients who underwent lower extremity, aortic aneurysm or stenosis repair. Primary study endpoint was increased carotid wall IMT which was defined as IMT ≥1.25 mm. Secondary study endpoints included total and cardiovascular mortality over a mean follow-up of 1.5 years.

RESULTS

Thirty-two percent of patients with mild COPD and 36% of the patients with moderate/severe COPD had increased carotid wall IMT, while only 23% had an increased carotid wall IMT in patients without COPD ($p < 0.01$). COPD was independently associated with an increased carotid wall IMT (OR 1.60; 95% CI 1.08-2.36). Among patients with COPD, increased carotid wall IMT was associated with an increased risk of total (HR 3.18 95% CI 1.93-5.24) and cardiovascular mortality (HR 7.28, 95% CI 3.76-14.07).

CONCLUSIONS

COPD is associated with increased carotid wall IMT independent of age and smoking status. Increased carotid wall IMT is associated with increased total and cardiovascular mortality in patients with COPD suggesting that carotid wall measurements may be a good biomarker for morbidity and mortality in these patients.

INTRODUCTION

There is a growing body of literature that indicates that chronic obstructive pulmonary disease (COPD) is an independent risk factor for cardiovascular disease.[1] For every 10% decrease in lung function (as measured by forced expiratory volume in 1 s, FEV_1) cardiovascular mortality increases by nearly 30%.[2] However, aside from FEV_1, there are no established biomarkers in COPD that can assist clinicians in predicting which patients will and will not develop cardiovascular morbidity and mortality, as these patients (even with established ischemic heart disease) often have normal lipid profile.[3] This makes it difficult for practicing clinicians to accurately risk-stratify patients and to intervene with cardioprotective interventions (e.g. statins) in patients at increased risk. There is increasing evidence that non-invasive imaging modalities such as ultrasonography may be able to detect subclinical atherosclerotic lesions, and as such may be useful tools for risk-stratification.[4] Using B-mode ultrasonography, previous studies have shown that reduced lung function is related to increased intima-media thickness (IMT) of the common carotid artery.[5-9] However, the clinical relevance of these observations remains unknown as previous studies did not evaluate the impact of increased IMT on hard outcomes such as morbidity and mortality in these patients. In this report, we determined the relationship of carotid wall IMT with COPD (and its severity) and with total as well as cardiovascular mortality in patients undergoing peripheral vascular surgery.

METHODS

PATIENTS

The study population was derived from an ongoing study of patients undergoing vascular surgery involving lower extremity artery, abdominal aortic aneurysm, abdominal aortic stenosis or carotid artery repair.[10] Beginning 2004, carotid wall IMT measurements were performed on all patients. In this paper, we report on 585 consecutive patients who had this measurement beginning 2004 to May of 2009. We excluded patients who underwent carotid artery repair. Prior to surgery we obtain baseline characteristics in all patients from their medical records. Abstracted variables included age, gender, body mass index (weight divided by height squared (kg/m^2)), current smoking status, diabetes mellitus (known diabetes, fasting blood glucose ≥7 mmol/l or requirement for insulin and/or oral anti-diabetic medication), hypercholesterolemia (known hypercholesterolemia or LDL cholesterol >3.5 mmol/l), renal dysfunction (creatinine >1.5 mg/dl or known renal dysfunction), stroke and ischemic heart disease (myocardial infarction, angina pectoris and/or coronary revascularization). The Medical Ethics Committee of the hospital was informed about the study and no official approval was requested per institutional practice.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The diagnosis of COPD was based on preoperative post-bronchodilator spirometry which was obtained in 95% of the COPD patients. COPD was defined according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD): predicted FEV_1 <80% of the predicted FEV_1 and FEV_1 / forced vital capacity (FVC) ratio <0.70.[11] COPD severity was classified into mild COPD (FEV_1/FVC <0.70 and FEV_1 ≥80% of the predicted FEV_1), and moderate/severe COPD (FEV_1 /FVC <0.70 and FEV_1 <80% of the predicted FEV_1). In patients who did not have a pulmonary function test, the diagnosis of COPD was based on symptoms (dyspnea, sputum production, and/or cough) and use of pulmonary medication (bronchodilators and corticosteroids).

CAROTID WALL INTIMA-MEDIA THICKNESS

Preoperatively, the carotid wall IMT was measured according to the 'Mannheim Carotid Intima-Media Thickness Consensus' scanning and interpreted according to protocol recommendations.[12] Measurements were taken at least 10 mm proximal to the carotid bifurcation, in the near and far wall of the left and right common carotid artery. Repeated measurements were performed along a minimum of 10 mm length. Four measurements were taken from both the left and right common carotid artery (two in the near and two in the far wall). The maximal measurement from these eight measurements was used for analysis. Plaques were excluded from the measurements. Two sonographers, unaware of the clinical information for each patient, performed the measurements. The inter-observer correlation was 96.2%. Using a receiver operating characteristics (ROC) analysis, an optimal predictive cutoff value of carotid wall IMT for total and cardiovascular mortality was determined to be 1.25 mm. Accordingly patients were categorized into two classes based on this cutoff and those with IMT ≥1.25 mm were deemed to have increased IMT.

FOLLOW-UP AND OUTCOME

Information on vital status was obtained from the municipal civil registries. Follow-up was completed in all patients with a mean follow-up of 1.5 years. Endpoints were total and cardiovascular mortality 5 years after surgery. Mortality was considered cardiovascular unless evidence of a non-cardiovascular cause could be ascertained on review of medical records or electronic patient files.

STATISTICAL ANALYSIS

The differences in baseline characteristics between patients with and without increased carotid wall IMT were assessed using the Student's *t*-test for continuous variables and a Chi-square test for categorical variables and were presented as means and percentages, respectively. Mean carotid IMT values of patients without COPD, mild COPD and moderate/ severe COPD were compared using analysis of variance. To assess the relationship between COPD severity (independent variable) and increased IMT (dependent variable) we used logistic regression analysis. We determined the relationship between increased carotid wall IMT and mortality in patients with COPD by employing a Cox regression analysis in which adjustments were made for age, gender, diabetes, hypercholesterolemia, hypertension, renal dysfunction, body mass index, smoking status, previous ischemic heart disease and stroke. Odds ratios (OR) and hazard ratios (HR) were provided with their 95% confidence intervals (CI). All tests were two-sided and *p*-values <0.05 were considered statistically significant. Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA) for Windows.

RESULTS

PATIENTS

Baseline characteristics of the 585 patients are shown in Table 1. In total 164 (28%) patients had increased carotid wall IMT. COPD was present in 267 (46%) patients; mild (21%), moderate (20%) and severe COPD (5%). Patients with increased carotid wall IMT were more likely to be older and to be male. COPD, renal dysfunction and history of stroke were also more often present in patients with increased carotid wall IMT ($p < 0.05$ for all).

COPD AS RISK FACTOR FOR INCREASED CAROTID WALL IMT

The mean carotid wall IMT of the entire population was 1.07 mm. Of the patients without COPD, 23% demonstrated increased carotid wall IMT whereas 32% of patients with mild COPD and 36% of the patients with moderate/severe COPD had increased IMT (p <0.01) (Fig 1). The mean carotid wall IMT values of these groups were 1.03 mm, 1.11 mm and 1.13 mm, respectively (p <0.01). Moreover, intimal thickness was compared between COPD patients with spirometry (95%) and those with clinical diagnosis of COPD (5%). The mean carotid wall IMT of these patients was 1.12 mm and 1.09 mm, respectively (p = 0.78) indicating no significant difference in IMT between the two subgroups.

Table 1. Baseline characteristics of the study population

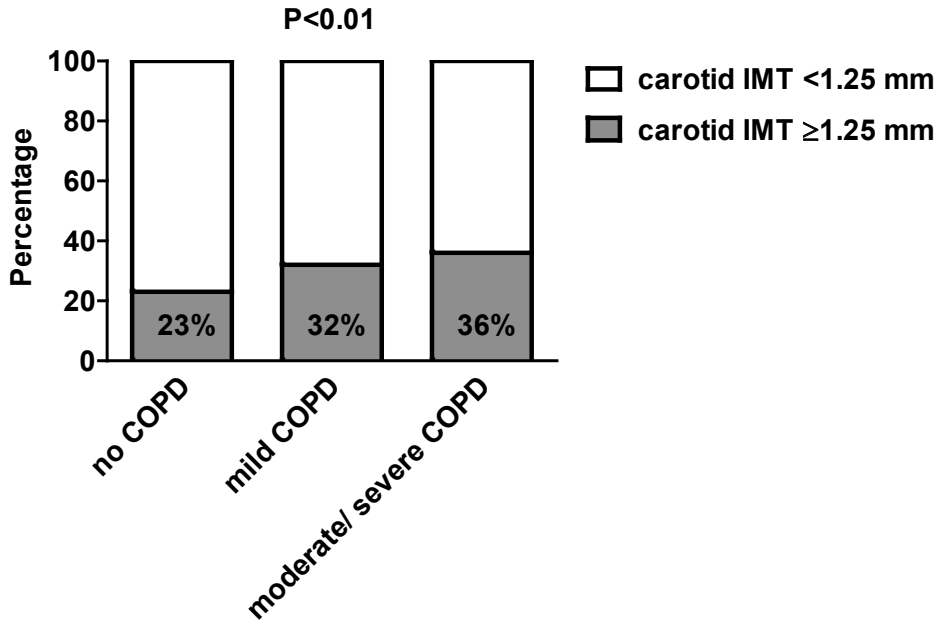
	carotid wall IMT <1.25 mm (n=421)	carotid wall IMT ≥1.25 mm (n=164)	p-value
Demographics			
Mean age (years ± SD)	67 (11)	70 (10)	<0.01
Male gender (%)	75	84	<0.05
Clinical characteristics			
Diabetes mellitus (%)	33	34	0.80
Glucose (mmol/l ± SD)	6.0 (2.0)	5.7 (2.0)	0.14
Hypercholesterolemia (%)	65	67	0.63
Total cholesterol (mmol/l ± SD)	4.8 (1.2)	4.7 (1.3)	0.37
LDL cholesterol (mmol/l ± SD)	2.8 (1.1)	2.9 (1.1)	0.73
HDL cholesterol (mmol/l ± SD)	1.3 (0.4)	1.2 (0.5)	0.83
Hypertension	64	71	0.09
Renal dysfunction (%)	20	28	<0.05
Body mass index (SD)	26 (4)	26 (3)	0.65
Smoking status (%)			0.91
Never smoker	21	19	
Current smoker	43	44	
Past smoker	36	37	
Cardiovascular history			
Ischemic heart disease* (%)	43	46	0.50
Stroke (%)	12	26	<0.001
COPD (%)			<0.01
Mild COPD	20	23	
Moderate/severe COPD	22	32	

* Myocardial infarction, angina pectoris and/or coronary revascularization

After adjusting for other risk factors, COPD was significantly associated with increased carotid wall IMT (OR 1.60 95% CI 1.08-2.36). This association was mainly driven by patients with moderate/severe COPD (OR 1.70 95% CI 1.08-2.68). Mild COPD, on the other hand, was not significantly related to increased IMT (OR 1.48 95% CI 0.90-2.42). In a sensitivity analysis, we excluded patients who experienced a previous stroke (n = 93) and repeated the analysis. The

relationship of COPD with increased carotid wall IMT was similar to those from the main analysis (OR 1.82 95% CI 1.18-2.82); for mild COPD the OR was 1.64 (95% CI 0.95-2.83) and the OR for moderate/severe COPD was 1.99 (95% CI 1.19-3.31). Furthermore a sensitivity analysis was performed excluding patients with a clinical diagnosis of COPD instead of spirometry. The results of this analysis were comparable to the original analysis as well (OR 1.68 95% CI 1.13-2.49); for mild COPD (OR 1.62 95% CI 0.99-2.68) and for moderate/severe COPD (OR 1.73 95% CI 1.09-2.73).

Figure 1. Percentage increased carotid wall IMT according to COPD severity



ASSOCIATION CAROTID WALL IMT AND MORTALITY IN PATIENTS WITH COPD

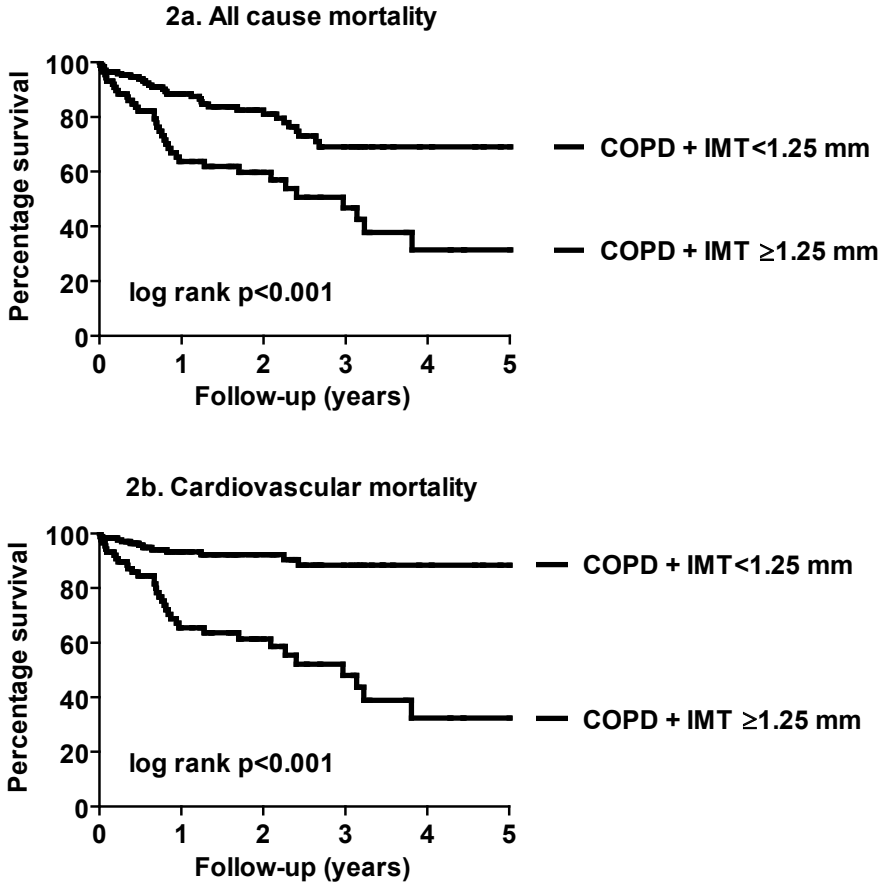
Of the patients with COPD (n = 267), 72 (27%) died during the follow-up period (Table 2). The cumulative 5-year survival curves (total and cardiovascular mortality) of the COPD patients with and without increased carotid wall IMT are presented in Fig 2. After adjusting for possible confounding factors, among patients with COPD, increased carotid wall IMT was associated with an increased risk of total mortality compared with COPD patients without increased IMT (HR, 3.18 95% CI 1.93-5.24) (Table 2). When cardiovascular mortality was considered, a significant relationship was even more striking (HR 7.28, 95% CI 3.76-14.07).

Table 2. Association between carotid wall IMT and mortality in patients with COPD

	Death N (%)	HR	[95% CI]
All-cause mortality	72 (27)		
COPD, IMT <1.25 mm	33 (19)	1.00	
COPD, IMT ≥1.25 mm	39 (43)	3.18	[1.93-5.24]
Cardiovascular mortality	51 (19)		
COPD, IMT <1.25 mm	14 (8)	1.00	
COPD, IMT ≥1.25 mm	37 (41)	7.28	[3.76-14.07]

Adjusted for age, gender, smoking status, previous ischemic heart disease, stroke, renal insufficiency, hypertension, diabetes, hypercholesterolemia and body mass index.

Figure 2. Kaplan-Meier survival curves for long-term outcome in patients with COPD



DISCUSSION

It is now well recognized that cardiovascular disorders are the leading cause of morbidity and mortality in patients with moderate COPD. However, there is a paucity of validated biomarkers that can be used in clinical practice to accurately risk stratify such patients for early and aggressive interventions. We found that irrespective of smoking status and other comorbidities, moderate to severe COPD was independently associated with increased IMT of the common carotid artery and COPD patients with increased IMT, independent of their lung function, had increased risk of total and cardiovascular mortality compared to COPD patients with normal IMT.

Our results are consistent with previous studies, conducted largely in healthy subjects, which have demonstrated an association between reduced lung function and increased carotid wall IMT.[5, 7-9, 13] However, these studies were limited in that two studies included only men[5, 9], one did not adjust for smoking status[8] and one assessed atherosclerosis by determining carotid atherosclerotic plaques instead of carotid wall IMT[7] and most importantly, none related the IMT with long-term mortality.

The mechanism for the association of COPD with increased carotid wall IMT is not well known. It is generally recognized that systemic inflammation exists in COPD and is associated with increased cardiovascular morbidity and mortality.[3] However, a previous study indicated that systemic inflammatory biomarkers such as C-reactive protein, were not associated with the progression of carotid wall IMT,[14] suggesting that other potential mechanisms are involved. Another possibility could be shared risk factors between COPD and carotid disease such as smoking. In our analysis, however, we adjusted for smoking status and still found a significant relationship between COPD and increased carotid wall IMT arguing against this theory. In addition, a recent study showed that mean carotid IMT in male smokers with airflow obstruction was greater than that of control smokers and never smokers, suggesting that airflow limitation rather than smoking per se is associated with atherosclerosis.[5]

Whatever the mechanism, our study indicates that carotid IMT is a surrogate for future mortality of patients with COPD. Since IMT measurements are non-invasive, reproducible, accessible (in most vascular laboratories) and can be performed quickly and relatively inexpensively, these data suggest that carotid IMT is a very promising biomarker to risk-stratify patients with COPD for mortality and in particular for cardiovascular mortality, which affects 30 to 50% of COPD patients.[15, 16]

There are some limitations to this study. Our study was conducted in patients who underwent surgery for their peripheral arterial disease and were at increased risk of cardiovascular mortality. Secondly, the cross-sectional design of the study precludes attribution of causality between COPD and IMT. Thirdly, as we did not measure serum or plasma biomarkers of inflammatory or oxidative pathways, we could not assess the importance of these pathways in the relationship of COPD with carotid wall IMT. Fourthly, COPD was not confirmed spirometrically in 5% of the patients. However, inclusion or exclusion of such patients makes little difference to the overall results.

In conclusion, the results of this study showed that, after adjustment for other important risk factors such as smoking, COPD was associated with increased carotid wall IMT. In addition, increased carotid wall IMT was related with increased all-cause and cardiovascular mortality in patients with COPD. These data raise the possibility of using carotid wall IMT for risk-stratification in patients with COPD.

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11

Predictive value of NT-proBNP invascular surgery patients with COPD and normal left ventricular systolic function

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ABSTRACT

BACKGROUND

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is commonly used to identify a cardiac cause of dyspnoea. However, patients with chronic obstructive pulmonary disease (COPD) may also have increased plasma NT-proBNP levels because of right-sided myocardial stress caused by pulmonary hypertension. We investigated the relationship between COPD and elevated NT-proBNP levels as well as the impact of elevated NT-proBNP levels on mortality in vascular surgery patients with normal left ventricular systolic function.

METHODS

Prior to vascular surgery, NT-proBNP levels, pulmonary function and left ventricular ejection fraction (LVEF) were assessed in 376 patients. Only patients with a LVEF >40% were included; n=261. Elevated NT-proBNP levels were defined as ≥500 pg/ml. Firstly, we assessed the relationship between COPD and NT-proBNP levels. Secondly, we investigated the association between elevated NT-proBNP levels and one-year mortality.

RESULTS

COPD was independently associated with elevated NT-proBNP levels (OR 3.36, 95%CI 1.30-8.65) with significant associations found for mild and severe COPD. Elevated NT-proBNP levels were associated with increased one-year mortality in patients with (HR 7.73, 95%CI 1.60-37.43) and without COPD (HR 3.44, 95%CI 1.10-10.73).

CONCLUSIONS

COPD was associated with elevated NT-proBNP levels in patients with a normal LVEF undergoing vascular surgery. Elevated NT-proBNP levels independent of other well-established risk factors were associated with increased one-year mortality. NT-proBNP may be a useful biomarker to risk-stratify patients with COPD.

INTRODUCTION

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted in the cardiac ventricles in response to increased ventricular pressure and volume overload and is a useful biomarker for the diagnosis of heart failure and for risk-stratifying patients with heart failure.[1, 2] Moreover, recent studies indicate that NT-proBNP levels associate with postoperative cardiac events and mortality following vascular surgery.[3, 4] Patients with COPD may also have elevated NT-proBNP levels, though the levels are lower than those observed in heart failure[5] and correlate with pulmonary arterial pressures, and hypoxaemia.[6-10] Importantly, NT-proBNP levels increase during exacerbations and fall during the recovery phase and independently predict which patients during exacerbations will require stays in the intensive care unit.[11] NT-proBNP may thus be a good biomarker in COPD. However, before this notion can be accepted, several questions regarding NT-proBNP need to be answered. First, it is not known whether NT-proBNP levels associate with COPD disease severity in patients with normal left ventricular ejection fraction (LVEF) independent of established risk factors such as smoking. Second, it is not known whether NT-proBNP levels are associated with mortality in COPD patients with normal LVEF. In the present study, we sought to determine the relationship between NT-proBNP and COPD severity and one-year mortality in vascular surgery patients with normal left ventricular function.

MATERIALS AND METHODS

PATIENTS

We used data from 376 consecutive patients who underwent major vascular surgery (abdominal aortic surgery (AAA), carotid endarterectomy (CEA) or lower limb arterial reconstruction (LLR)) between June 2004 and March 2008 and who had preoperative left ventricular ejection fraction (LVEF) assessed by the Simpson's biplane disc method.[12] All of these patients also underwent spirometry prior to surgery and based on these data were then classified as COPD or non-COPD. Only patients who had normal left ventricular systolic function defined as LVEF ≥40% were included in the present analysis (N=261 patients). The study was approved by the Medical Ethics Committee of the Erasmus Medical Center. Prior to surgery, age, gender and clinical risk factors including hypertension (blood pressure ≥140/90 mmHg and/or treated for hypertension), diabetes mellitus (fasting glucose level ≥7.0 mmol/L and/or treatment with insulin or oral hypoglycemic agents), renal dysfunction (defined as estimated glomerular filtration rate (GFR) <60 mL/min/1.73m^2 using the equation of the Modification of Diet in Renal Disease (MDRD)) and current smoking status (non smoker/current smoker/ex smoker) were captured. The patient database also included information regarding the patient's prior history of cardiovascular disease (defined as previous myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention, cerebrovascular accident or transient ischemic attack, heart failure or the presence of stable angina pectoris or a positive cardiac stress test).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

All patients underwent a preoperative post-bronchodilator spirometry from which the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) were assessed. COPD was defined according to the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines.[13] COPD severity was classified into 3 stages: I=mild COPD (FEV_1/FVC <0.70 and FEV_1 ≥80% of the

predicted FEV_1), II=moderate COPD (FEV_1 /FVC <0.70 and FEV_1 50% ≤FEV_1 <80% of the predicted FEV_1) and III=severe COPD (FEV_1 /FVC <0.70 and FEV_1 30% ≤FEV_1 <50% of the predicted FEV_1).[13] The predicted FEV_1 was calculated, adjusting for gender, age and height, using the regression equation of Quanjer et al.[14] which has been previously validated.[15] The equation for males was 4.30 * height (m) – age * 0.029 – 2.49 and for women 3.95 * height (m) – age * 0.025 – 2.60.[14]

NT-PROBNP

Peripheral blood samples were collected using standard venipuncture techniques from which plasma was prepared. NT-proBNP measurements were performed preoperatively. Plasma NT-proBNP concentration was determined using an electrochemoluminescence assay on an Elecsys 2010 (Hoffman-La Roche, Basel, Switzerland). Elevated NT-proBNP levels were defined as ≥500 pg/ml as suggested by others.[16]

FOLLOW-UP AND ENDPOINT

Survival status at follow-up was obtained from the hospitals electronic database including patients' medical records. Study endpoint was one-year all-cause mortality and the mean follow-up was 0.5 years. As a sensitivity analysis, we assessed the relationship of pro-BNP levels and total mortality over 3 years of follow-up.

STATISTICAL ANALYSIS

Differences in baseline characteristics between non-elevated and elevated NT-proBNP levels were assessed using the Student's t-test for continuous variables and a Chi-square test for categorical variables. Data are presented as percentages unless otherwise indicated.

To assess the relationship between pulmonary function (independent variable) and NT-proBNP levels (dependent variable) we used the following analyses. Linear regression analysis was used for the association between percentage predicted FEV_1 and log-NT-proBNP plasma levels. For this analysis, NT-proBNP levels were log-transformed to achieve normality. In the multivariable analyses we adjusted for potential confounding factors including gender, age, diastolic dysfunction (defined as the ratio of the early to atrial peak filling velocities, i.e. e/a ratio, <0.75 or >2.0), surgery site, renal dysfunction (GFR <60 mL/min/1.73^2), hypertension, smoking status and the revised cardiac risk index[17] (including previous ischemic heart disease, heart failure, diabetes mellitus, renal dysfunction, cerebrovascular accident and/or transient ischemic attack). In addition, logistic regression analysis was used to examine the association between COPD severity and NT-proBNP plasma levels ≥500 pg/ml using the non-COPD patients as the referent.

To assess the relationship between elevated NT-proBNP levels and one-year mortality we used Cox proportional hazard modelling. In the multivariable analysis we adjusted for the risk factors mentioned above as well as for severity of COPD. In addition, cumulative one-year survival curves for COPD patients with and without elevated NT-proBNP levels were determined by the Kaplan-Meier method and compared using the log-rank test. Odds ratios (OR) and Hazard ratios (HR) are presented as risk estimates with 95% confidence intervals (CI). For all tests, a 2-sided p-value of <0.05 was considered significant. All tests were performed using SPSS 15.0 for Windows.

RESULTS

PATIENTS

The mean age of the study population (n=261) was 68 ± 10 years, and 79% were men (Table 1). A total of 217 patients had non-elevated NT-proBNP levels (<500 pg/ml), while 44 had elevated levels (≥500 pg/ml). Patients with elevated NT-proBNP levels were older, and more likely to have had previous myocardial infarction, coronary revascularization, heart failure, COPD, diabetes and renal dysfunction compared to patients with low levels (all p<0.05). COPD was diagnosed in 144 (55%) patients: 83 (32%) had mild COPD, 48 (18%) had moderate COPD and 13 (5%) had severe COPD. Diastolic dysfunction was present in 34% of the patients without COPD, 46% in mild COPD, 33% in moderate COPD and 58% in severe COPD (p=0.18). The median NT-proBNP levels among the no COPD, mild, moderate and severe COPD patients were 125, 212, 170 and 352 (pg/ml), respectively. The percentage of patients with COPD increased as the plasma NT-proBNP levels also increased. COPD was present in 52% of the patients with non-elevated NT-proBNP levels, while 73% of those with elevated NT-proBNP levels had COPD (p<0.05). The distribution of the COPD severity groups in patients with non-elevated and elevated NT-proBNP levels is presented in Figure 1.

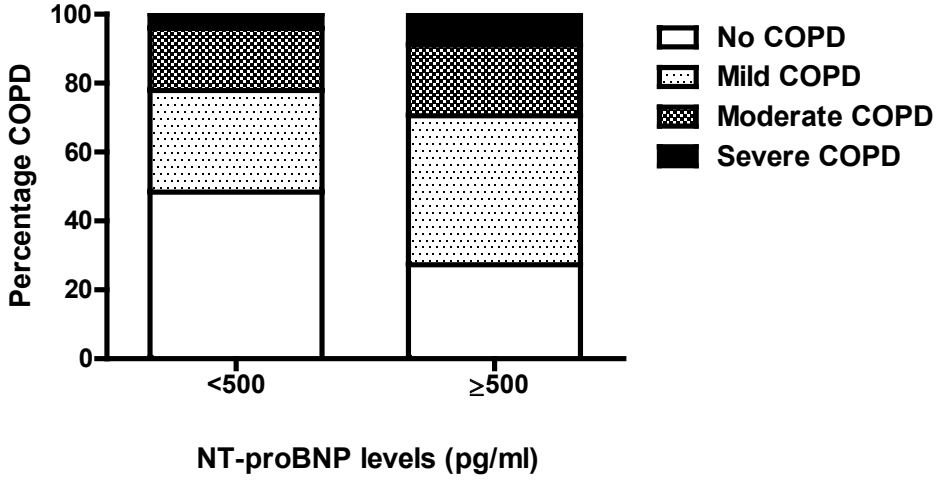
Table 1. Baseline characteristics

	Total (n=261)	Non-elevated NT-proBNP levels (<500 pg/ml) (n=217)	Elevated NT-proBNP levels (≥500 pg/ml) (n=44)	P-value
Demographics				
Mean age (SD)	68(10)	67(10)	72(9)	<0.01
Male gender (%)	79	79	77	0.82
Cardiovascular history (%)				
Myocardial infarction	28	24	46	<0.01
Coronary revascularization[1]	17	15	27	<0.05
Heart failure	4	2	14	<0.001
Angina pectoris	20	19	30	0.10
Stroke/TIA	38	38	39	0.89
Clinical variables (%)				
COPD[2]	55	52	73	<0.05
No COPD	45	48	27	
Mild COPD	32	30	43	0.05
Moderate COPD	18	18	21	
Severe COPD	5	4	9	
Mean FEV_1[3]	2.6(0.8)	2.7(0.8)	2.2(0.7)	<0.001
Diastolic dysfunction[4]	39	37	48	0.21
Hypertension	51	51	52	0.89
Diabetes Mellitus	21	18	34	<0.05
Renal dysfunction[5]	21	16	46	<0.001
Smoking status				0.53

Non smoker	18	18	21	
Current smoker	31	30	36	
Ex smoker	51	53	43	
Body mass index (SD)	26(4)	26(4)	26(5)	1.00
Site of surgery				0.93
AAA[6]	51	51	52	
CEA[7]	27	28	25	
LLR[8]	22	21	23	

[1] Previous coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)
[2] COPD defined according to the GOLD guidelines
[3] Forced vital capacity in 1 second
[4] Defined as e/a ratio <0.75 or >2.0
[5] GFR <60 mL/min/1.73m^2
[6] Abdominal aortic surgery
[7] Carotid endarterectomy
[8] Lower limb arterial reconstruction

Figure 1. COPD severity in elevated and non-elevated NT-proBNP levels



COPD AND NT-PROBNP LEVELS

The percentage predicted FEV_1 was inversely related to NT-proBNP levels (Figure 2). The beta coefficient for log-NT-proBNP for every one percent increase in the predicted FEV_1 was -0.20 ($p<0.01$). After adjustment for other risk factors the beta coefficient was -0.20 ($p<0.001$).

Additionally, compared to non-COPD patients, patients with COPD had increased risk for elevated NT-proBNP levels (OR 3.36, 95%CI 1.30-8.65). There was a significant relationship between mild and severe COPD severity and elevated (≥500 pg/ml) NT-proBNP levels (mild COPD: OR 3.42, 95%CI 1.21-9.96 and severe COPD: OR 6.89, 95%CI 1.33-35.62) (Table 2). However no significant association was found for moderate COPD (OR 2.04, 95%CI 0.58-7.12).

Figure 2. Regression line percentage predicted FEV_1 and log-NT-proBNP levels

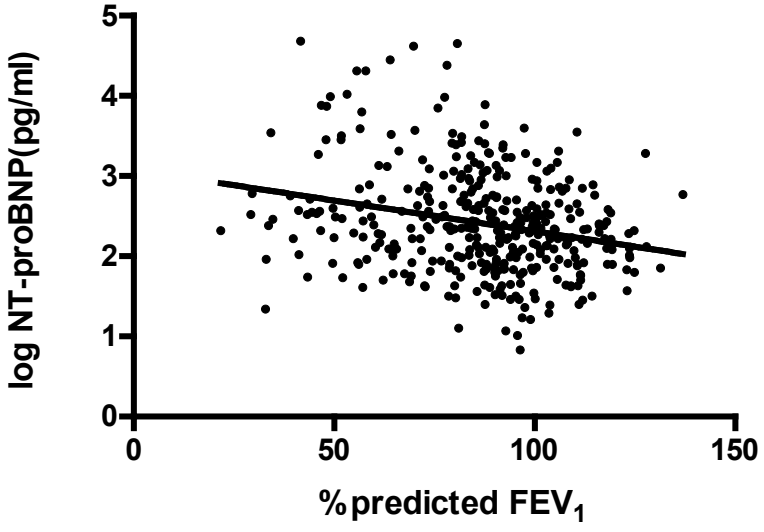


Table 2. Association between COPD severity and elevated NT-proBNP levels

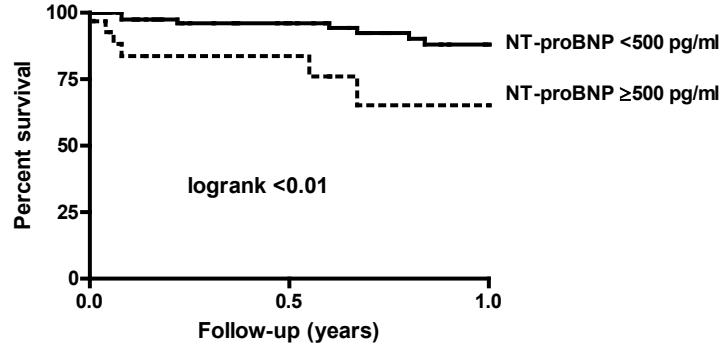
	Univariate		Multivariate*	
	OR	[95% CI]	OR	[95% CI]
No COPD (n=117)	1.00		1.00	
Mild COPD (n=83)	2.60	[1.18-5.71]	3.42	[1.21-9.69]
Moderate COPD (n=48)	2.02	[0.79-5.17]	2.04	[0.58-7.12]
Severe COPD (n=13)	3.89	[1.04-14.57]	6.89	[1.33-35.62]

*Adjusted for age, gender, type of surgery, revised cardiac risk index, smoking status, renal dysfunction, hypertension and diastolic dysfunction

NT-PROBNP AND MORTALITY

During one-year follow-up 23 (9%) patients died of whom 13 (57%) had COPD. Elevated NT-proBNP levels were associated with one-year mortality following vascular surgery in all patients (univariable analysis, HR 3.91, 95%CI 1.69-9.07 and multivariable analysis HR 3.44, 95%CI 1.10-10.73) as well as in the sub-analysis including only those with COPD (univariable analysis, HR 4.48, 95%CI 1.48-13.51 and multivariable analysis HR 7.73, 95%CI 1.60-37.43). The cumulative one-year survival rates in COPD patients with non-elevated and elevated NT-proBNP levels were 88% and 65%, respectively (log rank $p<0.01$) (Figure 3). The findings were not materially changed when follow-up was extended to 3 years. Elevated pro-BNP was associated with increased total mortality in all patients (multivariable HR 3.21, 95% CI 1.19-8.68) and in patients with COPD (multivariable HR 5.60, 95% CI 1.38-22.74).

Figure 3. Kaplan-Meier estimate of one-year survival for elevated and non-elevated NT-proBNP levels in patients with COPD



Numbers at risk			
NT-proBNP <500 pg/ml	112	58	37
NT-proBNP ≥500 pg/ml	32	12	4

DISCUSSION

The present study demonstrates that COPD is associated with elevated plasma NT-proBNP levels in vascular surgery patients with a normal left ventricular systolic function. We found that even patients with mild COPD were three times more likely to have had elevated NT-proBNP levels than those without COPD, while those with severe disease were approximately six times more likely to have had elevated NT-proBNP levels. Importantly, elevated NT-proBNP levels were associated with increased risk of death in COPD patients independent of well-established risk factors such as smoking status and age.

These data are consistent with those of Leuchte et al. who showed in 176 patients with various lung disorders that elevated plasma NT-proBNP levels were associated with mortality. However, they did not separate COPD from other end-stage lung disorders.[18] We extend these data by demonstrating in well-characterized COPD patients that elevated plasma NT-proBNP levels are associated with increased one and three year mortality. Moreover, we have demonstrated that even mild COPD is associated with elevated plasma NT-proBNP levels. Our finding that NT-proBNP levels are elevated in COPD and inversely related to FEV_1 and FEV_1 to FVC ratio is consistent with those of previous studies.[10, 19] We extend these findings by demonstrating a significant relationship of elevated NT-proBNP with total mortality in patients with COPD.

Our study was not designed to answer the critical question of mechanisms. Previous studies suggest that plasma NT-proBNP levels relate to the pulmonary arterial pressure of COPD patients. In these studies, plasma BNP levels increased as pulmonary arterial pressure increased and with the occurrence of right ventricular dysfunction.[6, 8, 9, 20-23] Other studies suggest that plasma BNP levels may also relate to patient's arterial hypoxemia.[7] Our observation that even patients with mild COPD, who are unlikely to have severe pulmonary hypertension, right ventricular dysfunction and arterial hypoxemia have increased plasma pro-BNP levels suggest that other mechanisms may also be involved.

Whatever the mechanism is, our study findings indicate that elevated plasma NT-proBNP increases the risk of one-year mortality by seven-fold in this select group of high-risk patients with COPD. This suggests that plasma NT-proBNP may be a potential biomarker for risk-stratification in these patients. In congestive heart failure, BNP and NT-proBNP levels are used to guide therapy and this approach (of using BNP or NT-proBNP levels) has been shown to improve health outcomes.[24] Moreover, in chronic heart failure, there are several drugs that can modify BNP or NT-proBNP levels including valsartan[25] and spironolactone.[26] Beta-blockers may be most beneficial in patients with elevated BNP levels.[27] Whether a similar approach can be taken in COPD is uncertain. Provocatively, we have shown previously that 3 month treatment with non-invasive mechanical ventilation nocturnally in patients with severe COPD was associated with a reduction in pro-BNP and pro-atrial natriuretic peptide levels.[28] The effect of other anti-COPD interventions on these neurohormones is unknown.

This study has several limitations. First, the retrospective nature of data analysis may have led to an underestimation of the impact of clinical variables on the relationship. Second, we did not have objective measurements of pulmonary arterial pressure. Thus, we could not determine whether patients with elevated NT-proBNP had pulmonary hypertension. Given the results of our study and the reason mentioned above, we believe it is likely that the observed associations are due to increased pulmonary pressure instead of other factors. Third, NT-proBNP might be elevated due to ischemic heart disease. However, in the multivariable analysis we adjusted for possible confounding factors including ischemic heart disease suggesting other possible causes. Fourth, the sample size of the present study was relatively modest, which might explain the lack of a significant association between moderate COPD and elevated NT-proBNP levels. Fifth, we did not have arterial blood gas measurements on room air and as such we could not determine the contribution of arterial hypoxemia to the relationship between COPD and NT-proBNP levels. However, since most of these patients were not on domiciliary oxygen therapy, it is highly unlikely that chronic arterial hypoxemia could explain away the findings.

In conclusion, COPD in vascular surgery patients with normal left ventricular systolic function is associated with elevated NT-proBNP, which in turn is associated with increased one-year mortality. These data raise the possibility that NT-proBNP could be an important biomarker for risk-assessment and prognostication in patients with COPD.

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12

Elevated N-terminal pro-B-type natriuretic peptide levels: the effect of chronic obstructive pulmonary disease

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We read with great interest the recent article by Daniels et al.[1] in which the investigators reported that detectable cardiac Troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were both associated with increased all-cause and cardiovascular death in healthy older adults.

NT-proBNP was previously identified as a prognostic cardiac risk marker and associated with increased mortality. NT-proBNP is released by cardiac myocytes in response to wall stress in conditions associated with volume overload as in heart failure and chronic kidney disease, pressure overload as in patients with heart valve abnormalities, and ischemia owing to coronary disease. In the present study, the association remained even after participants with baseline coronary heart disease were excluded, which was 30% of the subjects with elevated (≥450 pg/ml) NT-proBNP levels.

However, the authors might have overlooked the effect of chronic obstructive pulmonary disease (COPD) on NT-proBNP levels. COPD is associated with cardiovascular disease and is an independent risk factor for cardiovascular morbidity and mortality.[2] We recently investigated the relationship between COPD, both the presence and severity, and NT-proBNP levels in 376 patients. To mitigate the influence of heart failure, chronic kidney disease, and myocardial ischemia, we adjusted for history of angina pectoris, myocardial infarction, heart failure and renal function. In addition, all patients had resting left ventricular function of more than 40% using echocardiography. The severity of COPD was assessed using pulmonary function tests with the GOLD (Global Initiative for Chronic Obstructive Lung Disease) classification. We found COPD as an independent risk factor for increased NT-proBNP levels, and the levels increased with the severity of COPD.

The underlying mechanism is likely to be pulmonary hypertension and right ventricular dysfunction caused by pulmonary arterial pressure overload.[3] COPD may induce wall stretching, ventricular dilation, and/or increased vascular pressures, which may promote the secretion of the neurohormone NT-proBNP. Because COPD is common in the elderly population (affecting nearly 35% of this population)[4], the addition of spirometric data to the analysis by Daniels et al. would have been very interesting and informative. The less severe forms of COPD are often asymptomatic and therefore frequently underestimated, especially in the elderly. Thus, the presence of underlying COPD might have contributed to the observed correlation between NT-proBNP and outcome in this elderly population.

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SUMMARY AND DISCUSSION

PROGNOSIS

Pulmonary complications contribute equally to perioperative morbidity and mortality as cardiac complications, however, pulmonary function measurements are generally not included in risk models for perioperative complications. In a large cohort of patients undergoing noncardiac surgery we have shown that the risk of 30 day mortality increases sharply in patients with poor pulmonary function, for different surgical risk categories (**Chapter 1**). Even in patients undergoing low to intermediate risk procedures, preoperative spirometic testing is likely of significant value in risk-classifying patients. Although currently routine preoperative pulmonary function testing is only recommended in patients at high risk of postoperative (pulmonary) complications (i.e. thoracic, abdominal or lung resection surgery and coronary artery bypass surgery), the results of our study suggest that pulmonary function testing could also be important in patients undergoing other surgical procedures. Using preoperative pulmonary function tests in addition to other risk factors such as age, gender, type of surgical procedure and cardiac risk factors, it may be possible to identify patients who are susceptible for poor postoperative outcome. The integration of these important clinical variables into a simple risk score facilitates their application to clinical practice. The strength of the developed risk score is that it can be calculated by using routine clinical data obtained on history and simple spirometry.

As the main goal for COPD management is to relief symptoms and improve health-related quality of life (HRQL), more research on the impact of disease on HRQL has been conducted last years in patients with COPD. In **Chapter 2** we evaluated the association between COPD severity and HRQL in patients undergoing vascular surgery. Patients with COPD had worse HRQL scores compared to patients without COPD and decreased significantly with increasing COPD severity. Mild COPD was generally not associated with impaired HRQL which might be explained by the fact that these patients are often asymptomatic. In addition, women scored worse on all HRQL domains compared to men.

COPD AS A RISK FACTOR

Like COPD, chronic kidney disease is a growing public health problem as well and affects a large number of individuals, approximately 13% of the adult population in the United States.[1] The risk of perioperative morbidity and mortality after surgery increases in patients with comorbidities. **Chapter 3** shows that the presence of COPD is associated with kidney disease in vascular surgery patients and those with both diseases have highest risk for long-term mortality. This may (partly) be explained by the systemic inflammation seen in patients with COPD. The presence of COPD might be associated with the progression of atherosclerosis affecting the vasculature in the kidneys leading to kidney dysfunction. So the inflammatory response observed in patients with kidney disease might be exacerbated by concomitant COPD. An important aspect of the treatment of patients with kidney disease is to control the underlying cause and management of cardiovascular risk factors. Besides adequate treatment with cardiovascular drugs as ACE inhibitors or angiotensin-II receptor blockers (ARB), optimal management of COPD is important in these patients as well.

In addition to kidney disease, heart failure is another important comorbid condition which is common in patients with COPD. In **Chapter 4** we demonstrated that COPD is associated with increased risk for subclinical left ventricular dysfunction. Patients with COPD and subclinical left ventricular dysfunction have an increased risk for all-cause mortality compared to patients with COPD who have normal left ventricular function. These data suggest that pre-operative

echocardiography may be useful to detect subclinical cardiovascular disease and risk-stratify COPD patients undergoing vascular surgery.

Cancer is one of the leading causes of death in patients with COPD. In **Chapter 5** we demonstrated a significant relationship between COPD and cancer mortality in a large number of patients with peripheral arterial disease. The risk rises sharply when patients demonstrate moderate to severe airflow obstruction. Interestingly, in moderate COPD, both lung and extra-pulmonary cancer deaths increased while, in severe COPD, lung cancer mortality predominated. Although cigarette smoking is a shared risk factor for both COPD and cancer, also other explanations should be considered including shared genetic susceptibility, delayed clearance of inhaled carcinogens because of airflow limitation[2] and chronic low-grade lung and systemic inflammation associated with COPD. Furthermore, the anti-inflammatory properties of statins may have beneficial effects not only on cardiovascular disease but on other comorbidities associated with COPD as well. The findings from our study suggest that in patients with COPD statins may be effective in reducing deaths from especially extra-pulmonary cancers. The increased risk of cancer conferred by COPD might explain the increased benefit of statins observed in these patients compared to patients with normal pulmonary function. However, further studies are needed to confirm our findings.

In contrast to the general population, patients with cardiovascular disease who are obese or overweight have better survival rates than those patients who are of normal weight or underweight. As COPD is associated with excess weight loss, COPD might explain the 'obesity paradox' in these patients. An inverse relationship was found between BMI and mortality in our cohort of patients with peripheral arterial disease undergoing vascular surgery (**Chapter 6**). However, when we adjusted for COPD and its severity, the relationship between underweight and mortality no longer remained significant, indicating that a substantial proportion of the excess deaths in patients with low body mass index occur in subjects with COPD. This raises the possibility that the excess deaths in patients with low body mass index are related to underlying COPD. Underweight patients might demonstrate with a higher metabolic rate, lower antioxidant capacity in skeletal muscles, and increased systemic inflammatory responses, which may contribute to excess weight loss and morbidity. In addition, underweight has also been associated with overt or occult malignancy. These results highlight the need for more frequently use of spirometry and institution of COPD interventions (including smoking cessation, treatment of exacerbations and use of maintenance drugs) for vascular surgery patients with low body mass index.

INTERVENTIONS IN PATIENTS WITH COPD AND ATHEROSCLEROSIS

Since 22% of the patients with COPD die from a cardiovascular disease related cause, medical treatment that confer cardiovascular risk reduction, like beta-blockers and statins, are frequently used in these patients. In atherosclerotic patients without COPD, these drugs are associated with improved outcome after vascular surgery.[3, 4] Consequently, the beneficial effects might extend to vascular surgery patients with COPD.

Of the currently available cardiovascular drugs, statins are particularly appealing as they not only lower serum lipids but also have significant anti-inflammatory properties. These drugs have been unequivocally demonstrated to improve cardiovascular outcomes in different settings of cardiovascular patients. We have demonstrated that the known beneficial effect of statins on 30-day and long-term mortality in patients with peripheral arterial disease extends to patients with COPD (**Chapter 7**). Interestingly, we found superiority of intensive statin therapy over low-dose therapy in reducing 30-day mortality in COPD patients. It might be possible that patients with COPD require a larger dose to achieve clinical benefits because of the increased inflammatory state.

Beta-blocker therapy is frequently withheld from COPD patients with co-existing cardiovascular disease because of the concern that beta-blockers may induce bronchoconstriction from blockade of beta-2-adrenoreceptors. Nevertheless, there is substantial evidence that cardioselective beta-blockers can be used in COPD patients without provoking bronchospasm and pulmonary deterioration.[5, 6] In **Chapter 8** we demonstrated in a cohort of patients with peripheral arterial disease, of whom 39% had COPD, that cardioselective beta-blockers are associated with reduced 30-day and long-term mortality after vascular surgery. A possible mechanism might be the reduced sympathetic nervous activity due to beta1-blockade which is previously observed in patients with chronic heart failure or previous myocardial infarction.[7] Another explanation might be the reduced cardiac workload and myocardial ischemia as a result of beta-blocker use. Furthermore beta-blockers may modulate inflammatory status and could therefore improve outcome in patients with COPD. In addition, we found an intensified dosing regimen to be superior to low-dose therapy in terms of their impact on 30-day mortality. However, as cardioselective beta-blocking agents have slight effects on the beta-2-adreneroreceptors, these drugs still need to be used cautiously in patients with COPD. Beta-blockers should be initiated at a low dose and, if tolerated well, carefully increased to the target dose. Given that beta-blockers are associated with reduced mortality in patients with COPD, these drugs should not be withheld from these patients with underlying cardiovascular disease.

As the focus of COPD management is to improve HRQL, it is important that HRQL is not adversely affected by medical therapy that potentially prolongs survival. As described above, beta-blockers are often withdrawn in patients with COPD because of fear of pulmonary worsening. Consequently, there is under-utilization of beta-blocker use in cardiovascular patients with COPD. We investigated in **Chapter 9** the association between beta-blockers and HRQL in patients with both peripheral arterial disease and COPD and found that beta-blockers do not impair HRQL in these patients. Knowledge of patients' perception of the effect of therapy is essential for the physicians' treatment decisions. The results of our study indicate that beta-blocker therapy does not impair patients' health status and could be used in patients with cardiovascular disease and COPD.

MARKERS OF PROGNOSIS IN PATIENTS WITH COPD

COPD is a systemic inflammation which is associated with the development and progression of cardiovascular disease, independent of smoking status. In **Chapter 10** we found that, irrespective of smoking status and other comorbidities, moderate to severe COPD was independently associated with increased intima-media thickness (IMT) of the common carotid artery in vascular surgery patients, suggesting that impaired pulmonary function is related to atherosclerosis. Importantly, COPD patients with increased IMT had increased risk of total and cardiovascular mortality compared to COPD patients with normal IMT. Since IMT measurements are non-invasive, reproducible, accessible and can be performed quickly and relatively inexpensively, these measurements might be used for risk-stratification of patients with COPD. Another marker that might be helpful to risk-stratify vascular surgery patients with COPD is N-terminal pro-B-type natriuretic peptide (NT-proBNP). Elevated NT-proBNP levels are demonstrated to be associated with increased risk of death in COPD patients independent of well-established risk factors such as smoking status and age (**Chapter 11-12**). In patients with congestive heart failure, NT-proBNP levels are used to guide therapy which has been shown to improve health outcomes.8 Angiotensin-converting enzyme (ACE) inhibitors, diuretics and beta-blockers can modify NT-proBNP levels in these patients. However, further studies are needed to investigate whether a similar approach can be taken in patients with COPD.

CONCLUSION

COPD is an important cardiovascular risk factor and associated with poor prognosis. COPD frequently co-exist in patients with peripheral arterial disease resulting in worse outcome after vascular surgery. Treatment with beta-blockers and statins is associated with reduced mortality in these atherosclerotic patients with concomitant COPD. In addition to cardiovascular risk assessment, preoperative pulmonary risk assessment, using spirometry, might be useful to identify patients at increased risk for adverse outcome. Pulmonary function along with data obtained on clinical history can be integrated into a simple clinical risk index that can predict postoperative outcome. This will better inform patients and clinicians regarding surgical risk and facilitate institution of interventions and therapies to optimally attenuate risk prior to surgery.

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SAMENVATTING EN DISCUSSIE

PROGNOSE

Pulmonale complicaties dragen gelijkwaardig bij aan perioperatieve morbiditeit en mortaliteit als cardiale complicaties. Desondanks worden longfunctie waarden over het algemeen niet opgenomen in risico modellen voor het voorspellen van perioperatieve complicaties. In een groot cohort van niet cardiale chirurgie patiënten, hebben we laten zien dat preoperatieve longfunctie omgekeerd gerelateerd was met 30-dagen mortaliteit onafhankelijk van operatie type en andere risicofactoren (**Hoofdstuk 1**). Dat wil zeggen, patiënten met een verslechterde longfunctie hadden een aanzienlijk hoger risico voor postoperatieve sterfte dan patiënten met een normale longfunctie. Zoals verwacht, het risico van de chirurgische procedure beïnvloedde deze relatie. In patiënten met een slechte longfunctie varieerde het sterfte percentage van ongeveer 5% voor een laag risico operatie tot 33% voor een hoog risico operatie. Hoewel momenteel het preoperatief testen van de longfunctie alleen is aanbevolen in patiënten met een hoog risico op postoperatieve complicaties (o.a. thoracale, abdominale of longresectie chirurgie en coronaire arterie bypass chirurgie), laten de resultaten van onze studie zien dat het preoperatief testen van de longfunctie ook belangrijk zou kunnen zijn in patiënten die een procedure met laag of gemiddeld risico ondergaan. In patiënten met een slechte longfunctie kunnen preoperatief verscheidene interventies gestart worden om de longfunctie te verbeteren, waaronder stoppen met roken, pulmonale revalidatie, behandeling met bronchodilatoren en het behandelen van exacerbaties.

Door preoperatieve longfunctie waarden toe te voegen aan andere risicofactoren zoals leeftijd, geslacht, risico van chirurgische procedure en cardiale risicofactoren, kunnen patiënten met een verhoogd risico op een verslechterde postoperatieve uitkomst geïdentificeerd worden. Het transformeren van deze belangrijke klinische variabelen naar een eenvoudige risicoscore, maakt het gebruik in de klinische praktijk mogelijk. Het voordeel van de ontwikkelde risicoscore is dat het berekend kan worden aan de hand van klinische gegevens die routinematig verkregen worden en het gebruik in combinatie met het gebruik van een eenvoudige longfunctie test. Belangrijk is dat een deel van de risicofactoren die in het model zijn opgenomen, behandeld kunnen worden wat de postoperatieve mortaliteit kan reduceren.

Het speerpunt van de behandeling van chronisch obstructieve longziekte (COPD) is het bestrijden van symptomen en het verbeteren van de gezondheidsstatus. De laatste jaren wordt er dan ook steeds meer onderzoek verricht naar de kwaliteit van leven in patiënten met COPD. In **Hoofdstuk 2** hebben we de relatie tussen de ernst van COPD en kwaliteit van leven onderzocht in een groep patiënten met perifeer vaatlijden. Patiënten met COPD bleken een slechtere kwaliteit van leven te hebben, vergeleken met patiënten zonder COPD en de kwaliteit van leven daalde aanzienlijk wanneer de ernst van de ziekte toenam. Een milde vorm van COPD was over het algemeen niet geassocieerd met een verminderde kwaliteit van leven wat verklaard zou kunnen worden door het feit dat deze patiënten vaak asymptomatisch zijn. Verder scoorden vrouwen slechter op kwaliteit van leven dan mannen.

COPD ALS RISICOFACTOR

Chronisch nierfalen is net als COPD een toenemend gezondheidsprobleem en treft ongeveer 13% van de volwassen van de Verenigde Staten.[1] Het risico op perioperatieve morbiditeit en mortaliteit na chirurgie stijgt in patiënten met co-morbiditeiten. **Hoofdstuk 3** laat zien dat de aanwezigheid van COPD geassocieerd is met nierfalen in patiënten met perifeer vaatlijden. Patiënten met beide ziekten hebben daarbij het hoogste risico op lange termijn mortaliteit. De relatie tussen COPD en

nierfalen zou (deels) verklaard kunnen worden door de systemische inflammatie die aanwezig is in COPD patiënten. De aanwezigheid van COPD is geassocieerd met de progressie van atherosclerose wat de vaten in de nieren kan aantasten en kan lijden tot nierfalen. De inflammatoire reactie die zich voordoet in patiënten met nierfalen zou dus verergerd kunnen worden door de aanwezigheid van COPD. Een belangrijk aspect in de behandeling van patiënten met nierfalen is het onderdrukken van onderliggende cardiovasculaire risicofactoren. Naast adequate behandeling met cardiovasculaire medicatie zoals angiotensine-converterend enzym (ACE) inhibitors of angiotensine-II receptor blokkers is het tevens van belang om COPD optimaal te behandelen.

Een andere belangrijke en veel voorkomende co-morbiditeit in patiënten met COPD is hartfalen. In **Hoofdstuk 4** laten we zien dat COPD gerelateerd is met een verhoogd risico op subklinische linker ventrikel dysfunctie. Patiënten met COPD en subklinische linker ventrikel dysfunctie hebben een verhoogd risico voor totale mortaliteit vergeleken met COPD patiënten met een normale linker ventrikel functie. Deze data suggereert dat het gebruik van preoperatieve echocardiogram bruikbaar kan zijn voor het opsporen van subklinische cardiovasculaire ziekte en risicostratificatie van vaatchirurgische patiënten met COPD.

Een van de belangrijkste doodsoorzaken in patiënten met COPD is kanker. **Hoofdstuk 5** geeft een significante relatie weer tussen COPD en het overlijden aan kanker in een groot aantal patiënten met perifeer vaatlijden. Het risico neemt aanzienlijk toe wanneer er sprake is van een gemiddelde tot ernstige luchtweg obstructie. Interessant hierbij is dat zowel sterfte als gevolg van longkanker als sterfte als gevolg van maligniteiten buiten de longen toeneemt in patiënten met een gemiddelde vorm van COPD terwijl in patiënten met ernstig COPD longkanker sterfte overheerst. Hoewel roken een gemeenschappelijk risicofactor is voor COPD en kanker, moeten ook andere verklaringen overwogen worden zoals genetische factoren, vertraagde verwijdering van geïnhaleerde carcinogenen als gevolg van de luchtweg obstructie en de chronisch inflammatoire status in patiënten met COPD.[2] De resultaten van ons onderzoek laten tevens zien dat het gebruik van statines effectief zou kunnen zijn in het reduceren van sterfte in patiënten met COPD, met name sterfte als gevolg van maligniteiten anders dan van de longen. Het verhoogde risico op kanker veroorzaakt door COPD zou dit gunstige effect van statines in patiënten met COPD mogelijk kunnen verklaren. Echter, verder onderzoek is nodig om onze bevindingen te bevestigen.

Er zijn verschillende studies die aan hebben getoond dat cardiovasculaire patiënten met overgewicht of obesitas, in tegenstelling tot de algemene bevolking, een betere overleving hebben dan patiënten met een normaal of ondergewicht. Aangezien COPD geassocieerd is met gewichtsafname, zou COPD misschien verantwoordelijk kunnen zijn voor deze 'obesitas paradox'. Een omgekeerde relatie was gevonden tussen body mass index en mortaliteit in een cohort van patiënten met perifeer vaatlijden die een vaatoperatie ondergaan (**Hoofdstuk 6**). Patiënten met een hoger gewicht hadden een lager risico op sterfte en patiënten met ondergewicht hadden een verhoogd risico op lange termijn sterfte na de operatie. Maar de associatie tussen ondergewicht en mortaliteit was niet langer significant wanneer gecorrigeerd werd voor COPD, wat suggereert dat een aanzienlijk deel van het toegenomen aantal sterfgevallen in patiënten met een laag lichaamsgewicht plaatsvindt in de patiënten met COPD. Patiënten met ondergewicht hebben mogelijk een hoger metabolisme, een verminderde antioxidatieve capaciteit van de spieren en een verhoogde systemische inflammatoire status wat kan resulteren in gewichtsverlies en morbiditeit. Ook is ondergewicht geassocieerd met het voorkomen van maligniteiten. Deze bevindingen benadrukken de behoefte voor het gebruik van preoperatieve longfunctie test en optimale behandeling van COPD in vaatchirurgische patiënten met een lage body mass index.

INTERVENTIES IN PATIËNTEN MET COPD EN ATHEROSCLEROSE

Gezien 22% van de patiënten met COPD overlijdt als gevolg van een cardiovasculair gerelateerde oorzaak, is een behandeling met cardiovasculaire medicatie, zoals beta-blokkers en statines, vaak noodzakelijk. Deze medicatie zorgt voor betere uitkomst na een vaatchirurgische ingreep in patiënten met atherosclerose zonder COPD.[3, 4] Derhalve zouden deze gunstige effecten zich tevens kunnen manifesteren in patiënten met COPD.

Van de op dit moment beschikbare cardiovasculaire medicatie, zijn in het bijzonder statines erg aantrekkelijk. Statines verlagen niet alleen de serum lipiden maar hebben daarnaast ook anti-inflammatoire eigenschappen. We hebben laten zien dat statines ook geassocieerd zijn met verminderde mortaliteit binnen 30 dagen en op lange termijn in COPD patiënten met atherosclerose die een vaatoperatie ondergaan (**Hoofdstuk 7**). Interessant hierbij is dat een intensieve dosering effectiever bleek te zijn in het reduceren van 30-dagen mortaliteit dan een lage dosering. Het zou mogelijk kunnen zijn dat patiënten met COPD een hogere dosering nodig hebben om een hetzelfde klinische effect te behalen door de toegenomen systemische inflammatoire status die aanwezig is in deze patiënten.

Het gebruik van beta-blokkers wordt vaak weerhouden van cardiovasculaire patiënten met COPD gezien de kans op bronchoconstrictie als gevolg van blokkade van de beta-2-receptoren. Echter, er is aanzienlijk bewijs dat cardioselectieve beta-blokkers gebruikt kunnen worden in patiënten met COPD zonder bronchospasmen en pulmonale verslechtering te veroorzaken.[5, 6] In **Hoofstuk 8** hebben we in patiënten met perifeer vaatlijden, waarvan 39% COPD had, aangetoond dat cardioselectieve beta-blokkers geassocieerd zijn met verminderde sterfte binnen 30 dagen na een vaatoperatie en tevens sterfte op lange termijn reduceert. Een mogelijke verklaring zou de verminderde activiteit van het sympatische zenuwstelsel door beta-1 blokkade kunnen zijn, wat eerder is aangetoond in patiënten met chronisch hartfalen of myocard infarct.[7] Een andere verklaring kan de verminderde cardiale belasting en myocard ischemie zijn als gevolg van beta-blokker gebruik. Daarnaast zouden beta-blokkers de inflammatoire status in patiënten met COPD mogelijk kunnen onderdrukken en daardoor postoperatieve uitkomst verbeteren. Wederom vonden we een intensieve dosering superieur aan een lage dosering met betrekking tot het effect op mortaliteit. Echter, cardioselectieve beta-blokkers hebben een geringe invloed op beta-2-adrenoreceptoren en moeten daarom met zorg gebruikt worden in patiënten met COPD. Beta-blokkers moeten gestart worden in de vorm van een lage dosering en, wanneer de medicatie goed verdragen wordt, kan de dosering voorzichtig opgehoogd worden naar de beoogde dosering. Gezien het feit dat beta-blokkers een reductie van mortaliteit teweegbrengen in patiënten met COPD, zou deze medicatie niet weerhouden moeten worden van COPD patiënten met onderliggend cardiovasculair lijden.

Zoals hierboven eerder beschreven, is de focus van COPD management het verminderen van symptomen en het verbeteren van de kwaliteit van leven. Daarom is het belangrijk dat dit laatste niet negatief beïnvloed wordt door medicamenteuze behandelingen die als doel hebben het leven te verlengen zoals beta-blokkers. In **Hoofdstuk 9** hebben we de relatie tussen beta-blokker gebruik en kwaliteit van leven bestudeerd in patiënten met zowel perifeer vaatlijden als COPD en hebben gevonden dat beta-blokkers de kwaliteit van leven niet beïnvloeden. De perceptie van patiënten met betrekking tot de effecten van een bepaalde behandeling is belangrijk voor de keuzes van de behandelend arts. De resultaten van onze studie laten zien dat beta-blokkers de kwaliteit van leven niet beïnvloeden en dus gebruikt kunnen worden in patiënten met COPD die deze medicatie behoeven ten gevolge van onderliggend cardiovasculair lijden.

MARKERS VOOR PROGNOSE IN PATIËNTEN MET COPD

COPD is een systemische inflammatie die geassocieerd is met het ontstaan en de ontwikkeling van cardiovasculaire ziekte, onafhankelijk van roken. In **Hoofdstuk 10** hebben we gevonden dat gemiddeld tot ernstig COPD, onafhankelijk van andere risicofactoren, geassocieerd is met een toegenomen intima-media dikte (IMT) van de halssalagader in vaatchirurgische patiënten. Dit suggereert dat een verminderde longfunctie gerelateerd is met atherosclerose. Patiënten met zowel COPD als een toegenomen IMT hadden een verhoogd risico op totale en cardiovasculaire mortaliteit vergeleken met COPD patiënten waarbij geen toegenomen IMT gevonden was. Gezien IMT metingen niet invasief, reproduceerbaar en toegankelijk zijn en tevens relatief snel en goedkoop uitgevoerd kunnen worden, zouden deze metingen gebruikt kunnen worden voor de risicostratificatie van patiënten met COPD. Een andere marker die gebruikt zou kunnen worden in vaatchirurgische patiënten met COPD is N-terminal pro-B-type natriuretic peptide (NT-proBNP). Verhoogde NT-proBNP waarden zijn, wederom onafhankelijk van andere welbekende risicofactoren zoals roken en leeftijd, geassocieerd met een verhoogd risico op mortaliteit in COPD patiënten (**Hoofdstuk 11-12**). In patiënten met congestief hartfalen, worden NT-proBNP bepalingen gebruikt voor het afstemmen van de juiste behandeling wat vervolgens geassocieerd is met verbeterde gezondheidsuitkomsten.[8] Hoewel ACE inhibitors, diuretica en beta-blokkers NT-proBNP waarden in deze patiënten kunnen verlagen, is verder onderzoek nodig om te kijken of een zelfde benadering gebruikt kan worden in patiënten met COPD.

CONCLUSIE

COPD is een belangrijke risicofactor voor atherosclerose en cardiovasculaire comorbiditeiten in patiënten met perifeer vaatlijden. Patienten met zowel cardiovasculaire comorbiditeiten als COPD hebben een verhoogd risico op postoperatieve sterfte na een vaatoperatie. Patiënten met perifeer vaatlijden en COPD die een vaatchirurgische ingreep ondergaan, hebben baat bij het gebruik van beta-blokkers en statines gezien het korte en lange termijn mortaliteit reduceert. Verder is het preoperatief identificeren van risicofactoren en een optimaal preoperatief beleid van uiterst belang. Markers zoals IMT metingen en NT-proBNP bepalingen zouden gebruikt kunnen worden voor de preoperatieve risicostratificatie van patiënten met COPD. Daarnaast is preoperatieve longfunctie een belangrijke voorspeller voor postoperatieve mortaliteit in patiënten die niet cardiale chirurgie ondergaan. Met behulp van preoperatieve longfunctie waarden gecombineerd met overige risicofactoren kan een risicoscore berekend worden wat het risico op postoperatieve mortaliteit kan voorspellen. Dit zal patiënten en clinici beter informeren omtrent het operatieve risico en bijdragen aan het instellen van interventies en therapieën waardoor het risico zo veel mogelijk beperkt kan worden.

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* Award winning presentation

CURRICULUM VITAE

Yvette Regina Bernardina Maria was born on March 7, 1981 in Tilburg, the Netherlands. She graduated secondary school in 1999 at the Cobbenhagencollege in Tilburg. In 2003 she obtained her bachelor degree of education in biology at Fontys Hogeschool Tilburg. Subsequently, she studied health sciences at the VU University in Amsterdam and obtained her master degree in public health research in 2006. After that she started a PhD traineeship at the Erasmus Medical Center in Rotterdam under supervision of prof.dr. Don Poldermans.

PHD PORTFOLIO

Name PhD student: Yvette RBM van Gestel Erasmus MC Department: Anesthesiology Research School: COEUR	PhD period: 2006-2010 Promotor(s): Prof dr D Poldermans Supervisor:

1. PhD training	Year	Workload (ECTS)
General courses		
- Scientific Writing in English	2003	3
- Ethics in Public Health	2003	3
Specific courses (e.g. Research school, Medical Training)		
- COEUR, PhD courses	2007-2009	9
- Scientific Health Research I	2003	5
- Scientific Health Research II	2004	6
- Advanced Methods in Public Health	2004	6
Seminars and workshops		
- Consultation Center for Patient Oriented research (CPO)	2007-2008	1.5
- COEUR, Research seminars	2006-2007	1.2
- Journal Club	2006-2010	1
Presentations		
- National conferences	2008	1
- International conferences	2009	1
(Inter)national conferences		
- European Society of Cardiology Congress, annual	2007-2009	3

2. Teaching	Year	Workload (Hours/ECTS)
Supervising practicals and excursions, Tutoring		
- COEUR 'Cardiovascular research'	2007-2010	3
- MolMed 'Basic introduction course on SPSS'	2009	1
Supervising Master's theses		
- MSc students EUR (Cihan Simsek, Han Witteveen, Verart Hüzeir)	2008-2010	4

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